Validation of an algorithm for the nonrigid registration of longitudinal breast MR images using realistic phantoms

Xia Li

Institute of Imaging Science, Vanderbilt University, Nashville, Tennessee 37232

Benoit M. Dawant

Institute of Imaging Science, Vanderbilt University, Nashville, Tennessee 37232 and Department of Electrical Engineering and Computer Science, Vanderbilt University, Nashville, Tennessee 37232

E. Brian Welch

Institute of Imaging Science, Vanderbilt University, Nashville, Tennessee 37232 and MR Clinical Science, Philips Healthcare, Cleveland, Ohio

A. Bapsi Chakravarthy

Department of Radiation Oncology, Vanderbilt University, Nashville, Tennessee 37232

Lei Xu

Department of Biostatistics, Vanderbilt University, Nashville, Tennessee 37232

Ingrid Mayer

Department of Medical Oncology, Vanderbilt University, Nashville, Tennessee 37232

Mark Kelley

Department of Surgical Oncology, Vanderbilt University, Nashville, Tennessee 37232

Ingrid Meszoely

Department of Medical Oncology, Vanderbilt University, Nashville, Tennessee 37232

Julie Means-Powell

Department of Surgical Oncology, Vanderbilt University, Nashville, Tennessee 37232

John C. Gore

Institute of Imaging Science, Vanderbilt University, Nashville, Tennessee 37232; Department of Radiology and Radiological Sciences, Vanderbilt University, Nashville, Tennessee 37232; Department of Physics and Astronomy, Vanderbilt University, Nashville, Tennessee 37232; Department of Biomedical Engineering, Vanderbilt University, Nashville, Tennessee 37232; and Department of Molecular Physiology and Biophysics, Vanderbilt University, Nashville, Tennessee 37232

Thomas E. Yankeelov^{a)}

Institute of Imaging Science, Vanderbilt University, Nashville, Tennessee 37232; Department of Radiology and Radiological Sciences, Vanderbilt University, Nashville, Tennessee 37232; Department of Physics and Astronomy, Vanderbilt University, Nashville, Tennessee 37232; Department of Biomedical Engineering, Vanderbilt University, Nashville, Tennessee 37232; and Department of Cancer Biology, Vanderbilt University, Nashville, Tennessee 37232

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Purpose: The authors present a method to validate coregistration of breast magnetic resonance images obtained at multiple time points during the course of treatment. In performing sequential registration of breast images, the effects of patient repositioning, as well as possible changes in tumor shape and volume, must be considered. The authors accomplish this by extending the adaptive bases algorithm (ABA) to include a tumor-volume preserving constraint in the cost function. In this study, the authors evaluate this approach using a novel validation method that simulates not only the bulk deformation associated with breast MR images obtained at different time points, but also the reduction in tumor volume typically observed as a response to neoadjuvant chemotherapy.

Methods: For each of the six patients, high-resolution 3D contrast enhanced T_1 -weighted images were obtained before treatment, after one cycle of chemotherapy and at the conclusion of chemotherapy. To evaluate the effects of decreasing tumor size during the course of therapy, simulations were run in which the tumor in the original images was contracted by 25%, 50%, 75%, and 95%, respectively. The contracted area was then filled using texture from local healthy appearing tissue. Next, to simulate the post-treatment data, the simulated (i.e., contracted tumor) images were coregistered to the experimentally measured post-treatment images using a surface registration. By comparing the deformations generated by the constrained and unconstrained version of ABA, the authors assessed the accuracy of the registration algorithms. The authors also applied the two algorithms on experimental data to study the tumor volume changes, the value of the constraint, and the smoothness of transformations.

Results: For the six patient data sets, the average voxel shift error (mean $\pm$ standard deviation) for the ABA with constraint was 0.45 ± 0.37 , 0.97 ± 0.83 , 1.43 ± 0.96 , and 1.80 ± 1.17 mm for the 25%, 50%, 75%, and 95% contraction simulations, respectively. In comparison, the average voxel shift error for the unconstrained ABA was 0.46 ± 0.29 , 1.13 ± 1.17 , 2.40 ± 2.04 , and 3.53 ± 2.89 mm, respectively. These voxel shift errors translate into compression of the tumor volume: The ABA with constraint returned volumetric errors of $2.70 \pm 4.08\%$, $7.31 \pm 4.52\%$, $9.28 \pm 5.55\%$, and $13.19 \pm 6.73\%$ for the 25%, 50%, 75%, and 95% contraction simulations, respectively, whereas the unconstrained ABA returned volumetric errors of $4.00 \pm 4.46\%$, $9.93 \pm 4.83\%$, $19.78 \pm 5.657\%$, and $29.75 \pm 15.18\%$. The ABA with constraint yields a smaller mean shift error, as well as a smaller volume error ($p=0.031$ 25 for the 75% and 95% contractions), than the unconstrained ABA for the simulated sets. Visual and quantitative assessments on experimental data also indicate a good performance of the proposed algorithm.

Conclusions: The ABA with constraint can successfully register breast MR images acquired at different time points with reasonable error. To the best of the authors' knowledge, this is the first report of an attempt to quantitatively assess in both phantoms and a set of patients the accuracy of a registration algorithm for this purpose. © 2010 American Association of Physicists in Medicine. [DOI: [10.1118/1.3414035](https://doi.org/10.1118/1.3414035)]

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I. INTRODUCTION

Neoadjuvant or preoperative chemotherapy, which was once reserved for patients with locally advanced breast cancer, is now being used in the management of earlier stages of disease. It not only allows patients the option of breast conserving surgery, but also allows an *in vivo* evaluation of tumor response. Despite its increasing use, there are as yet no reliable methods of quantitatively measuring tumor response. Current methods of monitoring treatment response rely on frank changes in tumor size as measured by physical exam, mammography, and/or ultrasound, which unfortunately are frequently unreliable.¹ Although serial biopsies can be obtained to monitor tumor response, these are invasive and therefore can only be obtained infrequently. They also provide very poor spatial sampling and may prove to be misleading.²⁻⁵ The most widely used radiological method of measuring tumor response is based on the Response Evaluation Criteria in Solid Tumors (RECIST), which was introduced by an international working group in 2000.⁶⁻⁸ RECIST criteria offer a simplified, practical method for extracting the salient features of anatomical imaging data. After obtaining high-resolution anatomical images via computed tomography or magnetic resonance imaging (MRI), measurable lesions representative of the involved organs are identified as "target lesions." The sum of the longest diameter for all target lesions is then computed and changes in the baseline sum longest diameter is then used to assess response. While RECIST is a practical tool, it has several well-recognized deficiencies including that the criteria for response is based on 1D changes which are downstream manifestations of underlying pathophysiology. Alternative methods are needed to characterize the underlying pathophysiological changes. One possible approach is to obtain functional imaging data [e.g., dynamic contrast enhanced MRI (DCE-MRI)] at multiple time points throughout treatment and then coregister such data so that tumor character-

istics can be quantitatively compared on a voxel-by-voxel basis. Such methods have been developed for the brain,⁹ but currently there are no techniques available for breast cancer data.

We have recently presented a method for the registration of breast MR images obtained at different time points throughout the course of neoadjuvant chemotherapy.¹⁰ The challenging problem is that, in general, registration of breast images acquired before and after therapy with intensity-based methods will result in the deformation of both normal and cancerous tissue. Since tumors typically change shape and volume during treatment, common algorithms may compress or expand tumors during the registration process and therefore provide results that are misleading in regard to tumor response. The method we proposed is an extension of the adaptive bases algorithm (ABA) which employs a constraint to control the compression or expansion of a tumor. We showed how this technique can be used to register high-resolution anatomical images and then lower resolution physiological parameter maps (e.g., the volume transfer constant K^{trans} and the extravascular extracellular volume fraction v_e) obtained from sequential DCE-MRI exams. Using this method, such parameters can be compared on a voxel-by-voxel basis throughout therapy.¹⁰ To the best of our knowledge, there has only been one other approach for registering longitudinal breast MR, the method proposed by Chittineni *et al.*¹³

Although we have shown qualitatively that our approach was satisfactory, a more quantitative evaluation would increase the confidence we have in the results we generate. This is, however, a challenging task because of the lack of ground truth. Schnabel *et al.*^{11,12} have proposed a technique based on finite element methods for the validation of breast image registration algorithms. If the material properties of the tissues can be measured, these models can be used to simulate the response of the breast to various types of boundary conditions such as regional displacement, point puncture,

or one-sided and two-sided contacts. However, it is difficult to measure tissue properties and label structures and substructures on an individual basis. Furthermore, the tumor will almost certainly have different mechanical features before and after therapy. As a result, this approach typically leads to approximate breast models with plausible deformations. We have proposed an alternative approach.¹⁰ We are also interested in generating phantoms that represent plausible cases, which provide a “gold standard” in which to test our registration algorithm. Specifically, we are interested in modeling bulk breast motion and deformation caused by (1) possibly large differences in position when scanning a patient over many weeks and (2) tumor response to therapy. The approach we use relies on patient volumes acquired longitudinally. Using these volumes, we simulate realistic bulk breast deformations with a surface-based registration method. We also simulate tumor response by shrinking the tumors and filling in the void with texture estimated from the surrounding area. This provides us with realistic pairs of pretreatment and post-treatment images for which the deformation field is known. These can thus be used to validate quantitatively our registration algorithm and its sensitivity to parameter settings.

In our earlier work, we used a single data set. Here, we expand this study to six data sets with tumors and breasts of various shapes and size. We study the effect of tumor segmentation, which is required in our approach, on our simulated images. Using our phantoms, we compare statistical results obtained with the constrained and unconstrained versions of our algorithm. We also compare deformation fields obtained with and without constraints for the six patient data sets. Furthermore, clinical and biological observations are presented to support the simulation and validation approaches.

II. MATERIALS AND METHODS

II.A. Data acquisition

Six patients with localized breast cancer, stages IIA to IIIB, were enrolled in the study. Patients signed a protocol-specific consent that was approved by our Institutional Review Board. Each patient underwent DCE-MRI on a Philips 3.0 T Achieva MR scanner (Philips Healthcare, Best, The Netherlands) prior to initiating neoadjuvant chemotherapy. A four-channel receive double-breast coil covering both breasts was used for all imaging (Invivo Inc., Gainesville, FL). Data for a T_1 map and DCE-MRI were acquired as previously reported.¹⁰ A catheter placed within an antecubital vein delivered 0.1 mmol/kg of the contrast agent Magnevist (Bayer Healthcare Pharmaceuticals, Germany) over 20 s (followed by a saline flush). Following the dynamic scan, a 3D T_1 -weighted high-resolution isotropic volume examination (THRIVE) scan was acquired with a fat-nulling inversion pulse and the following parameters: TR/TE/ α = 6.98/3.6 ms/10° and NSA = 1. The THRIVE scan resolution was 400 × 400 × 129 reconstructed to 512 × 512 × 129 over a 170 × 170 × 129 mm³ axial field of view with a SENSE factor of two so that the scan required 2.7 min.

Each patient was scanned at three time points: Within one week before the onset of neoadjuvant chemotherapy, within one week of completion of the first cycle, and after completion of all cycles of neoadjuvant chemotherapy but prior to surgery. The treatment regimen was left to the discretion of the treating medical oncologist.

II.B. Registration algorithms

Details for this algorithm have been presented elsewhere.¹⁰ Briefly, a rigid body registration algorithm is applied to T_1 -weighted breast MR images first.¹⁴ The non-rigid registration method we used for the longitudinal breast MR image registration relies on an intensity-based registration algorithm, which we call ABA for adaptive bases algorithm.¹⁵ The ABA method measures normalized mutual information¹⁶ (NMI) and calculates the deformation field through maximizing the value of NMI. The deformation field is modeled by a linear combination of radial basis functions¹⁷ to register the source and target images.

As previously mentioned, tumors before and after neoadjuvant chemotherapy frequently change shape and volume. Generally, an intensity-based nonrigid registration algorithm will tend to match the tumors in the source and target image, leading to the compression or expansion of the tumors in the source image in order to match the target image. If the goal is to compare, on a voxel-by-voxel basis, the parametric maps of tumor status, this compression or expansion will result in an inaccurate analysis of response within the tumor voxels. Therefore, we incorporate a constraint term proposed by Rohlfing *et al.*¹⁸ to minimize the deformation of the tumors. This constraint term is added in the similarity measure in ABA and the new cost function becomes

$$f_{\text{cost}} = -\frac{H(A) + H(B)}{H(A, B)} + \alpha \cdot \frac{\sum_x |\log(J(x))|}{M}, \quad (1)$$

where $H(A)$ and $H(B)$ are the marginal entropy of image A and B , $H(A, B)$ is the joint entropy, x is the coordinate vector of a voxel in the tumor area, M is the total number of voxels in the area, and $J(x)$ is the Jacobian determinant that measures the extent of deformation in the current voxel. α is a parameter used to control the weight of the constraint term, which is set at 0.15 empirically.¹⁰ Based on our experiments, this setting leads to a good compromise between reorienting the tumor and preserving the tumor volume for most experimental data (see more comments on the selection of α in Sec. III). In theory, the constraint we have used above preserves volume. It should thus permit tissue deformation. In practice, however, this term acts as a strong regularization term. The higher the weight for this term, the “stiffer” (i.e., more rigid) the transformation is. Using this term over the entire image volume leads, in our experience, to transformations that preserve the tumor volume but that also cannot register the rest of the image. The tumor is, in general, stiffer than the breast adipose and glandular tissues. Limiting the effect of the Jacobian term to tumor area permits the properties of the transformation to adapt spatially, i.e., it leads to

transformations that preserve the volume of the tumor while permitting deformation of breast as a whole. Hence, as opposed to the original application of this approach,¹⁸ we apply the constraint term only to the tumor area.

The tumor needs to be segmented before the modified ABA is applied to the breast images. Depending on the tumor to healthy tissue contrast available in a given slice, we used two methods. When the contrast between tumor and normal tissues is relatively high, a semiautomatic segmentation tool¹⁹ is used to segment the tumor. First, a region of interest (ROI) which contains the tumor is defined manually. The contours of objects in the ROI are generated with various thresholds and the threshold that yields the most accurate segmentation (as assessed visually) of the tumor is chosen. Next, this threshold is applied to the ROI and the voxels whose intensity is lower than the threshold are eliminated. The connected region which has the largest area is saved and the other small detected regions within the ROI are eliminated. In slices where the contrast between tumor and healthy tissue was not sufficient, simple manual segmentation was applied. We acknowledge that there is a mature literature on breast tumor segmentation,^{20–22} but we do not need to apply these methods here. While more advanced methods will certainly yield a more accurate, and faster, segmentation, inaccuracy in tumor delineation is not a major issue here because (1) we use the integral of the Jacobian constraint over the entire tumor volume and (2) the transformations produced by the ABA vary smoothly. There is thus no abrupt change in the transformation characteristics at the boundary of the tumor. As a consequence, a segmentation error of a few pixels does not affect the results in a substantial way, and the segmentation methods outlined above are sufficient to allow for the accurate performance of the registration algorithm. Figure 1 demonstrates the robustness of the proposed algorithm by showing the effect of tumor segmentation on registration results. Panels a–c show green contours that illustrate examples of tumor undersegmentation, accurate segmentation, and oversegmentation, respectively. Using these three different regions to compute the Jacobian constraint the images are registered to the image shown in panel g. Results obtained for each case are shown in panels d–f. As shown in these panels, results obtained with all three tumor contours are undistinguishable, thus indicating that the algorithm we propose is not sensitive to tumor delineation. Panel h shows the results obtained without any constraint. Here, the shape of the tumor has been drastically altered, thus showing the need for the Jacobian constraint.

II.C. Validation approach for simulated data

In a clinical trial, tumor response is typically divided into four general categories: Complete response, partial response, stable disease, and progressive disease.⁶ A comprehensive review by Sahoo *et al.*²³ states that tumor size will be reduced in neoadjuvant therapy for most patients and tumor growth after neoadjuvant chemotherapy is unlikely. Moreover, while the exact statistics differ by tumor stage, breast cancer subtype, and treatment regimen, several studies^{24–26}

FIG. 1. The tumor is segmented differently (panels a–c) and the registration results (panels d–f) are similar, indicating the registration algorithm is robust to the tumor delineation. Compared to the tumor in the target image (panel g), the tumor in the deformed image is preserved successfully. Moreover, without the constraint, the tumor is substantially compressed (panel h).

indicate that progressive disease (i.e., tumor expansion) occurs only in only a small fraction of patients. Thus, while expansion could certainly be considered, we have focused our efforts on the situation of tumor reduction, which accounts for the overwhelming majority of situations seen clinically. It is also certainly possible to observe a complete response in some patients;^{23–26} thus, we also consider this situation in our validation approach.

Figure 2 shows a flow chart for the phantom creation and validation procedures we propose. There are four main steps in the process: Data acquisition, simulation, transformation, and comparison. To simulate the post-treatment MR images, the tumor in the original pretreatment images is segmented using the strategy described in Sec. II B and contracted by an arbitrary amount using one of the fundamental operations in morphological image processing: Erosion.²⁷ The contracted area is filled using texture from nearby healthy appearing tissue. The healthy appearing tissue is selected as follows (shown in Fig. 3): For every voxel v_i within the contracted area, the closest point p_i on the contour of the area is found. The mirror voxel v'_i is found in the normal tissue areas through connecting the two points v_i and p_i and extending the vector $\overrightarrow{v_i p_i}$ such that $|\overrightarrow{v_i p_i}| = |\overrightarrow{p_i v'_i}|$. Then the intensity of v'_i is smoothed by a $3 \times 3 \times 3$ Gaussian filter with a standard deviation of 1 voxel, and the voxel v_i is filled using the filtered intensity of v'_i . This step can be conducted automatically on both 2D and 3D images. It is worth noticing that the way we fill in the contracted tumor area is close to clinical observation. Pathologic studies following neoadjuvant therapy show that in most cases, scar tissue replaces the tumor tissue that was there previously. More specifically, the

FIG. 2. The flow chart of the validation procedure, which includes data acquisition, simulation, transformation, and comparison. The tumor in the pretreatment image is contracted to generate the simulated image A_s in the simulation step. The RPM algorithm is then applied to coregister A_s and the true post-treatment image. This step produces the simulated post-treatment image with known deformation, allowing comparison of the original and modified ABAs on a voxel-by-voxel basis.

tumor bed is characterized by an area of hyalinized vascular stroma with stromal edema and fibroelastosis.²³ The stroma may be infiltrated by foamy histiocytes and aggregates of lymphocytes.²³ Areas of tumor necrosis may leave nodules of histiocytes and cholesterol clefts.²³ It is therefore reasonable to assume that tumor “erosion” is taking place.

Figure 4 shows the original pretreatment images (top row) from four different patients, the corresponding images after the simulation in which the tumor is contracted by different

FIG. 3. The contracted area is filled using texture from nearby healthy appearing tissue in a postcontrast, fat-suppressed THRIVE image. For each voxel v in the contracted area, the closest point p on the tumor contour is detected and used to find the voxel v' in the healthy tissue. The voxel v is then filled using the intensity of v' .

FIG. 4. The original pretreatment, postcontrast, fat-suppressed THRIVE images from four different patients (upper row), the simulated image with tumor contracted by different percentages (middle row), and the close-up views of the tumor regions (lower row). Note that even when the tumor is fully contracted (first column), the simulated image still appears realistic.

percentages (middle row), and the close-up view of the simulated regions (bottom row). Notice that although the tumor is considerably different in shape, size, and texture, the simulated images with contracted tumor appear realistic and can be used in the next step which is to simulate breast deformation caused by patient repositioning and generate the simulated post-treatment images. A complete removal of the tumor, as displayed in Fig. 4, also displays the efficiency and feasibility of the simulation approach.

To simulate breast deformation caused by repositioning, the breast surfaces are first segmented automatically from the actual pretreatment and post-treatment images. The contrast between the breast and the background is high due to the relatively high signal-to-noise ratio of the data, allowing a single threshold to segment the boundary easily. Once the surfaces of the breast in the pretreatment and post-treatment images are segmented, they are downsampled to create two sets of points. In each slice in the volumes, the contour points are downsampled by a factor of 30. This number was arrived at empirically and was found to provide enough surface coverage for registration. There are approximately 15–30 points after the downsampling for each slice. The two point sets are then coregistered using a robust point matching²⁸ (RPM) algorithm. This algorithm iteratively computes both a correspondence between two sets of points and a smooth nonrigid transformation based on thin-plate splines (TPSs), which registers the two image volumes. The correspondence is calculated using the softassign technique,^{29–31} in which each point in the source image is assigned to each point in the target image with a weight between 0 and 1. The weight is the element of a fuzzy correspondence matrix

$$m_{ij} = \frac{1}{T_M} \exp \left(- \frac{(y_j - f(x_i))^T (y_j - f(x_i))}{2T_M} \right), \quad (2)$$

where f is the TPS transformation. T_M is the temperature parameter used to simulate the physical annealing and x_i and

FIG. 5. (a) The original postcontrast, fat-suppressed THRIVE breast image, (b) the corresponding simulated image with tumors shrunk by $\sim 50\%$, (c) the simulated post-treatment image after the breast deformation is simulated using the robust point matching algorithm, and (d) the true post-treatment image.

y_j are the points in the source and target point sets, respectively. T_M is set as 0.5 initially (recommended in the original paper²⁸) and decreased gradually after each iteration. A virtual correspondence $\bar{y}_i$ to the source point x_i is generated by assigning $\bar{y}_i = \sum_{j=1}^N m_{ij} y_j$, with N equal to the total number of target points. This fuzzy assignment allows the construction of a virtual correspondence automatically, thereby allowing the cardinality of two sets of points to be unequal. At each iteration, after the virtual correspondence is determined, a thin-plate spline based nonrigid transformation is computed, and a new correspondence can be calculated based on the generated transformation. Finally, the two sets of points are aligned and the final transformation T_{RPM} is generated for the whole breast volume. Once computed, the transformation is applied to the image with the contracted tumor to generate the simulated post-treatment image.

The RPM is a reasonable approach to not only simulate breast deformation without compressing the tumor, but also generate realistic post-treatment images with known deformation fields. To model the deformation field, the RPM algorithm employed here uses TPSs, which have infinite support, instead of compactly supported positive radial basis functions of Wu¹⁷ which are used in the ABA. Furthermore, the control points in the RPM are placed only on the breast surface, while in the ABA the control points are located in areas of the images over which registration is inaccurate.¹⁵ The methods we use to generate the deformation fields and to estimate these deformation fields are thus substantially different, as desired when generating test sets to evaluate a particular registration method.

Figure 5 displays an example after this transformation step. One original breast MR image is shown in Fig. 5(a) and the corresponding simulated image with the tumor contracted by approximately 50% is displayed in Fig. 5(b). Then the

breast deformation is simulated using the RPM algorithm, and the simulated post-treatment image [Fig. 5(c)] is generated. This figure shows how the RPM algorithm deforms the image in Fig. 5(b) to match the contour of the true post-treatment image [Fig. 5(d)], without using the tumor to drive the registration. Hence, this algorithm provides a smooth transformation to simulate bulk breast deformation without compressing the tumor.

To validate and compare the ABA with and without constraint using this scheme quantitatively, the pretreatment and post-treatment images from six patients were acquired, and the tumor in the pretreatment images is contracted by approximately 25%, 50%, 75%, and 95%, respectively. The simulated post-treatment images with different tumor sizes are generated using the scheme just described. The original and constrained ABAs are then applied to align the pretreatment images to the simulated post-treatment images to generate the transformations T_{ABA} and T_{ABA_CON} , respectively. Finally, the deformation fields estimated with the original and the modified version of the ABAs are compared to the known deformation fields to study the effect of the constraint scheme. In particular, for each voxel x_i in the tumor area, the displacement after each registration algorithm can be found and the mean registration error can be computed and compared voxel-by-voxel

$$\text{error}_{ABA} = \frac{\sum_{i=1}^M |T_{RPM}(x_i) - T_{ABA}(x_i)|}{M},$$

$$\text{error}_{ABA_CON} = \frac{\sum_{i=1}^M |T_{RPM}(x_i) - T_{ABA_CON}(x_i)|}{M}, \quad (3)$$

where M is equal to the total number of voxels in the tumor area.

II.D. Validation approach for experimental data

In the experimental data, tumor deformation resulting from the registration process is assessed both qualitatively and quantitatively. We evaluate the registration algorithms (1) by visually inspecting the deformation fields, (2) by computing the tumor volume changes, (3) through the value of the constraint expressed in Eq. (1), and (4) through the smoothness of the deformation fields. The smoothness can be measured by the bending energy,^{32,33} which has the following form:

$$E_{\text{bending}} = \frac{1}{V} \int \int \int ((\partial^2 T / \partial x^2)^2 + (\partial^2 T / \partial y^2)^2 + (\partial^2 T / \partial z^2)^2 + 2(\partial^2 T / \partial x \partial y)^2 + 2(\partial^2 T / \partial x \partial z)^2 + 2(\partial^2 T / \partial y \partial z)^2) dx dy dz, \quad (4)$$

where T denotes the transformation in 3D images, and V is the tumor volume. It is well known that the smoother the transformation, the smaller the bending energy.

TABLE I. The mean errors (mm) and standard deviations of ABA with and without constraint over the tumor area when the tumors are contracted by different percentages for six patients. Note that the mean voxel shift errors were calculated through averaging over all voxels of the tumor area from all patients instead of directly averaging the mean shift error of each patient. The nonparametric Wilcoxon signed rank test is applied to each simulated case.

Patients	Methods	25%	50%	75%	95%
1	ABA_CON	0.22 ± 0.11	0.87 ± 0.53	1.04 ± 0.67	1.24 ± 0.73
	ABA	0.35 ± 0.16	1.17 ± 0.67	2.14 ± 1.47	3.09 ± 2.31
2	ABA_CON	0.32 ± 0.25	0.99 ± 0.93	0.87 ± 0.67	1.01 ± 0.57
	ABA	0.36 ± 0.23	1.77 ± 1.65	3.37 ± 2.57	2.64 ± 1.70
3	ABA_CON	0.73 ± 0.50	1.40 ± 0.64	1.91 ± 0.57	2.28 ± 0.67
	ABA	0.51 ± 0.28	0.84 ± 0.60	2.33 ± 1.66	3.00 ± 1.94
4	ABA_CON	0.47 ± 0.29	1.08 ± 1.01	1.96 ± 1.13	2.48 ± 1.45
	ABA	0.55 ± 0.39	1.39 ± 1.34	4.51 ± 3.30	5.38 ± 4.04
5	ABA_CON	0.19 ± 0.10	0.17 ± 0.08	0.37 ± 0.18	0.40 ± 0.24
	ABA	0.37 ± 0.15	0.39 ± 0.18	0.70 ± 0.42	0.85 ± 0.64
6	ABA_CON	0.46 ± 0.27	0.52 ± 0.34	1.48 ± 0.93	2.27 ± 0.96
	ABA	0.49 ± 0.22	0.53 ± 0.26	1.70 ± 1.08	4.33 ± 2.27
Mean	ABA_CON	0.45 ± 0.37	0.97 ± 0.83	1.43 ± 0.96	1.80 ± 1.17
	ABA	0.46 ± 0.29	1.13 ± 1.17	2.40 ± 2.04	3.53 ± 2.89
<i>p</i> values		0.4375	0.3125	0.031 25	0.031 25

III. RESULTS

III.A. Validation results for simulated data

Table I shows the mean registration errors $\text{error}_{\text{ABA}}$ and $\text{error}_{\text{ABA_CON}}$ over the tumor area when the tumors are contracted by different percentages for six patients. The average voxel shift error for the ABA with constraint was 0.45 ± 0.37 , 0.97 ± 0.83 , 1.43 ± 0.96 , and 1.80 ± 1.17 mm for the 25%, 50%, 75%, and 95% contraction simulations, respectively. Note that the mean voxel shift errors were calculated through averaging over all voxels of the tumor area from all patients, instead of directly averaging the mean shift error of each patient. In comparison, the unconstrained ABA

returned errors of 0.46 ± 0.29 , 1.13 ± 1.17 , 2.40 ± 2.04 , and 3.53 ± 2.89 mm, respectively. The nonparametric Wilcoxon signed rank test was applied to each simulated case, instead of the commonly used Student's *t*-test. The nonparametric Wilcoxon signed rank test is a more robust method for small sample sizes (as it does not require a normal population distribution), and we therefore use it to report the *p* values for all the following tables. The *p* values in Table I imply that the proposed method leads to significantly smaller mean errors, when the tumors were contracted by 75% and 95%, compared to the unconstrained ABA. In particular, when the tumor is contracted by 95% in the simulated post-treatment

TABLE II. The tumor volume changes using ABA with and without constraint when the tumors are contracted by different percentages for six patients. Note that tumor is compressed notably using the unconstrained ABA compared to the constrained ABA.

Patients	Methods	25% (%)	50% (%)	75% (%)	95% (%)
1	ABA_CON	0.18	10.58	12.26	15.27
	ABA	0.37	16.51	24.76	30.35
2	ABA_CON	3.40	9.79	8.28	7.63
	ABA	4.70	10.72	19.61	16.46
3	ABA_CON	0.24	2.25	2.29	2.94
	ABA	1.69	7.94	21.73	25.73
4	ABA_CON	10.64	13.27	15.96	19.82
	ABA	12.43	14.38	24.82	31.15
5	ABA_CON	0.37	4.95	13.41	13.84
	ABA	0.97	5.44	18.19	16.90
6	ABA_CON	1.39	3.02	3.47	19.63
	ABA	3.86	4.58	9.57	57.88
Mean	ABA_CON	2.70	7.31	9.28	13.19
	ABA	4.00	9.93	19.78	29.75
<i>p</i> values		0.031 25	0.031 25	0.031 25	0.031 25

images, the original ABA considerably compresses the tumor in the pretreatment images in order to match it to the contracted tumor in the post-treatment images, leading to much larger registration errors. Although there are no significant differences showing in p values for the first two cases (25% and 50%), the proposed registration algorithm can preserve the tumor volume significantly better ($p=0.031$) than the unconstrained ABA (see Table II).

Another observation in Table I is that as the contracted percentage increases, the mean shift errors of both algorithms increase. For the ABA, the more the tumor is contracted in the simulated image, the more the tumor in the source image is compressed during registration, and the larger the error. It should be noted that for the ABA with constraint, we use the same value of the weight parameter, $\alpha=0.15$, for all the simulated cases, in order to make the comparison under the exactly same parameter setting (see more comments on the selection of α below).

Figure 6 provides an example of how the registration errors are distributed, through displaying the histogram of errors resulting from the original and modified ABA registrations when the tumors are contracted by 95% for six patients. For all the patients, the ABA with constraint leads to more compact error distributions, compared to the original (unconstrained) ABA, indicating that the proposed algorithm has a smoother deformation over tumor areas. Figure 7 shows one example of this in which the color-coded errors have been superimposed over one postcontrast THRIVE slice of tumor when the tumor is contracted by 95% for one patient. The maximum shift error by ABA in this slice is 7.01 mm, which is considerably larger than that produced by the ABA with constraint (2.71 mm).

The voxel shift errors translate into compression of the tumor volume. Table II shows the significantly reduced percentages of the tumor volumes ($p=0.031$ via the nonparametric Wilcoxon signed rank test) after registration for four simulated cases: The ABA with constraint returned volumetric errors of $2.70 \pm 4.08\%$, $7.31 \pm 4.52\%$, $9.28 \pm 5.55\%$, and $13.19 \pm 6.73\%$ for the 25%, 50%, 75%, and 95% contraction simulations, respectively, whereas the unconstrained ABA returned volumetric errors of $4.00 \pm 4.46\%$, $9.93 \pm 4.83\%$, $19.78 \pm 5.657\%$, and $29.75 \pm 15.18\%$. When the tumors are contracted by 95% in the simulated images, the tumor volume can be compressed up to $\sim 57\%$ (patient #6) by the original algorithm. However, with the constraint, the proposed method displays nearly three times less compression. Moreover, as in Table I, we use the same constraint parameters for all cases in this table, in order to make a fair comparison. We believe a larger constraint parameter value α will lead to an even smaller registration error and tumor volume change for the proposed algorithm when the tumor is contracted more. The value of α is fixed at 0.15 for all studies, though this value is not optimal for all data sets. Unfortunately, the automatic selection of this value is difficult. A value that is too small cannot constrain the tumor volume sufficiently; a value that is too large leads to transformations that are too stiff and can even affect the reorientation of the

FIG. 6. The histogram of errors of ABA with and without constraint when the tumors are contracted by 95% for six patients. Note that the constrained ABA leads to more compact error distributions, with considerably smaller maximum errors.

tumor. This may appear counterintuitive but it is caused by the way the algorithm currently works. It is very difficult to produce a transformation that remains rigid (i.e., a transformation that would not be penalized by the Jacobian constraint) through iterations. Although the final transformation may be close to rigid, i.e., a square remains a square, the square will typically go through deformations when the algorithm iterates. When the Jacobian constraint is high, the algorithm is not able to deform the square and cannot escape from local minima. A similar tradeoff between the volume preservation and registration is also mentioned in the work of Rohlfing *et al.*¹⁸ Further works will investigate the selection and optimization of the α value for an individual patient.

III.B. Validation results for experimental data

For the six patients used in the study, the translation computed with the rigid body registration is up to approximately 22 mm, and the rotation is up to approximately 10° . Figure 8 shows an example of an original source image, the image

FIG. 7. One central slice of tumor contracted by 95% with the color-coded errors (voxel shifts in mm) superimposed on a postcontrast, fat-suppressed THRIVE. In this slice, the original ABA leads to errors up to 7.01 mm, while the ABA with constraint results in errors only up to 2.71 mm.

after the rigid body registration, and the image after both the rigid and nonrigid registration, respectively. The green contour is segmented from the target image and copied onto the following images for comparison. This image shows that while the rigid registration roughly aligns the images pretreatment/post-treatment, it is not accurate. The constrained nonrigid registration then refines the alignment by aligning the normal tissues while preserving the tumor volume.

Figure 9 shows registration results obtained on the 3D high-resolution MR images of one of the patients. In this figure, the slices with the same index in the volumes acquired at time t_1 (pretreatment), t_2 (post one cycle of treatment), and t_3 (post all neoadjuvant chemotherapy) are displayed at different registration stages. Green contours are drawn to facilitate visual assessment. Notice that without the constraint, the ABA compresses the tumor regions substantially, although the breast contours are aligned accurately. However, the modified algorithm matches the breast contours as well as healthy tissues, while preserving the tumor shape and volume from being distorted.

The corresponding deformation fields shown in Fig. 9 also indicate the modified algorithm preserves the tumor volume better. In the fourth row of Fig. 9, the first two panels are the deformation fields registering the image at t_1 and t_3 , without and with the constraint, respectively. The last two panels are the deformation fields registering the image at t_2 and t_3 . By visual inspection, it can be seen that the proposed algorithm leads to a smoother deformation field. The bending energy value of the transformations [based on Eq. (4)] computed with the unconstrained and constrained ABA are 0.049 and 0.0091, respectively, also indicating that transformations obtained with the proposed algorithm are smoother than those obtained with the original one. The mean constraint

FIG. 8. The original source image (left panel), the image after the rigid body registration (middle panel), and the image after both the rigid and nonrigid registration (right panel), respectively. The green contour is segmented from the target image (not shown) and copied onto the following images for comparison.

values over the tumor area [described by Eq. (1)] are 0.6273 and 0.1492 for the unconstrained and constrained ABA, respectively, indicating better volume preservation by the constrained ABA. The statistical analysis of the constraint values and the smoothness of transformation for all patients are described below (Table III).

Table III shows the validation results through computing the tumor volume changes, the constraint values, and the bending energy. The first two columns in Table III show the

FIG. 9. Three axial, postcontrast, fat-suppressed THRIVE slices at three different time points after rigid body registration (column 1), after nonrigid registration without the constraint (column 2), and with the constraint (column 3). In the fourth row, the zoom-in deformation field without and with the constraint at t_1 (the first and second panels) and t_2 (the third and fourth panels) are shown, respectively. It is clear that the rigid registration can only provide an approximate registration result, and the original ABA compresses the tumor significantly, although the normal tissues are registered accurately. The modified ABA can perform well on both normal tissues and the tumor.

TABLE III. The tumor volume changes, the constraint values, and the bending energy are calculated for the experimental data, after the registration using ABA with and without constraint, respectively. The nonparametric Wilcoxon signed rank test is applied to all data and the p values are listed. The results of all the three validation approaches show that the ABA with constraint leads to significantly smaller tumor volume changes, constraint values, and bending energies, indicating the efficiency of the constraint term.

Patients	The tumor volume changes ($p=0.031$)		The constraint values ($p=0.031$)		The bending energy ($p=0.031$)	
	ABA_CON (%)	ABA (%)	ABA_CON	ABA	ABA_CON	ABA
1	0.30	25.10	0.6771	1.2901	0.0085	0.089
2	7.90	35.80	0.1878	0.4843	0.0028	0.1764
3	4.40	66.30	0.1492	0.6273	0.0091	0.0491
4	6.10	17.80	0.0992	0.5978	0.01	0.2091
5	2.00	87.10	0.0253	0.6948	0.001	0.2318
6	8.20	49.10	0.0831	0.689	0.0031	0.1482
Mean	4.80	46.90	0.2036	0.7301	0.0058	0.1506

reduced percentages of the tumor volumes after applying the two registration algorithms. The original ABA compresses the tumor by 46.9%, while the modified algorithm reduces the tumor by only 4.8%. Using the exactly same parameters, the original ABA compresses the tumor significantly ($p=0.031$ obtained by applying the nonparametric Wilcoxon signed rank test to the data of the first two columns in Table III) more than the proposed algorithm.

We also detect the extent of the voxel volume change over tumor areas as described in Eq. (1) to validate the algorithms quantitatively. In Eq. (1), the constraint term is measured by the logarithm of the Jacobian determinant, whose value will be equal to zero if there is no compression or expansion during the transformation. Hence, the smaller the constraint value, the less compression or expansion caused by the voxel deformation over tumor areas. The third and fourth columns in Table III display the constraint values for the experimental data. The p value of 0.031 via the nonparametric Wilcoxon signed rank test applied to the constraint values in Table III indicates the modified ABA leads to better preservation of voxel volumes than the unconstrained ABA.

The last two columns in Table III list the bending energies of transformations generated by the two algorithms over tumor area. The much smaller mean energy value of 0.0058 by the constrained ABA represents the considerably smoother transformation, compared to the value of 0.15 by the unconstrained ABA. We applied the nonparametric Wilcoxon signed rank test to the energy values in Table III to compare the two algorithms, and the p value of 0.031 shows a significant difference between the two algorithms.

IV. CONCLUSIONS

An accurate registration algorithm would allow for the quantitative assessment of tumor response to treatment on a voxel-by-voxel basis. In a previous study,¹⁰ we presented a registration algorithm for breast MR images acquired at different time points. We modified the adaptive bases algorithm and added a tumor-volume preserving constraint in the cost function. In this study, we expanded upon our novel valida-

tion approach developed to simulate the tumor deformation caused by, e.g., treatment response and the breast deformation caused by patient reposition. Through coregistering the pretreatment images and the simulated post-treatment images, we have complete knowledge of the deformation applied to the pretreatment images to construct the post-treatment images, thereby allowing quantitative assessment on simulated data sets. We generated simulated data with different tumor sizes and compared the original and constrained ABAs. The validation results show that the constrained ABA leads to a statistically smaller registration error.

We also noticed that in Table I, the original ABA led to smaller errors than the proposed one for patient 3 when the tumor was contracted by 25% and 50%. We believe that in this patient, the proposed algorithm most likely did not converge to the right solution under the current parameter setting. The additional constraint term in the cost function increases the complexity of the optimization procedure. Ongoing work is investigating this problem.

In addition to the simulations, we have also validated our algorithm on experimental data. Visual assessment demonstrates the proposed algorithm yields smoother deformation fields and leads to more accurate registration results. Quantitative assessment on experimental data includes the detection of the tumor volume change, the extent of voxel compression or expansion, and the smoothness of transformation over tumor areas. The results also show that ABA with constraint regularizes the transformation better and preserves tumor volume efficiently.

Although the influence of the Jacobian-based constraint on the tumor volume preservation may be predictable, the phantom images we have generated permit the study of the sensitivity of this algorithm to the value of the weighing coefficient. We have shown that one value leads to good results for the majority of the cases but may need to be adjusted for others. As we gain more experience with this type of images, it is possible that different alpha values could be associated with different image characteristics (e.g., type

of tumor, breast density, or patient response). One could, for instance, categorize patients based on RECIST and assign an alpha value to each of these categories. Our results also show that registering longitudinal breast MR volume is achievable. This is of clinical importance because only after registering longitudinal scans accurately can we assess response to treatment on a voxel-by-voxel basis.

To the best of our knowledge, this is the first report to quantitatively evaluate in both phantoms and a set of patients the accuracy of a registration algorithm for this special and clinically relevant purpose. Future efforts will apply the proposed registration method to dynamic contrast enhanced and diffusion weighted MRI data³⁴ obtained during the course of treatment to see if assessing voxel changes in pharmacokinetic parameters, as enabled by this approach, leads to a more sensitive indicator of treatment response than currently used measures of tumor response including mammograms, ultrasounds, MR imaging, and physical examination.

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^{a)} Author to whom correspondence should be addressed. Electronic mail: thomas.yankeelov@vanderbilt.edu

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