A block matching-based registration algorithm for localization of locally advanced lung tumors

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Purpose: To implement and evaluate a block matching-based registration (BMR) algorithm for locally advanced lung tumor localization during image-guided radiotherapy.

Methods: Small (1 cm^3), nonoverlapping image subvolumes (“blocks”) were automatically identified on the planning image to cover the tumor surface using a measure of the local intensity gradient. Blocks were independently and automatically registered to the on-treatment image using a rigid transform. To improve speed and robustness, registrations were performed iteratively from coarse to fine image resolution. At each resolution, all block displacements having a near-maximum similarity score were stored. From this list, a single displacement vector for each block was iteratively selected which maximized the consistency of displacement vectors across immediately neighboring blocks. These selected displacements were regularized using a median filter before proceeding to registrations at finer image resolutions. After evaluating all image resolutions, the global rigid transform of the on-treatment image was computed using a Procrustes analysis, providing the couch shift for patient setup correction. This algorithm was evaluated for 18 locally advanced lung cancer patients, each with 4–7 weekly on-treatment computed tomography scans having physician-delineated gross tumor volumes. Volume overlap (VO) and border displacement errors (BDE) were calculated relative to the nominal physician-identified targets to establish residual error after registration.

Results: Implementation of multiresolution registration improved block matching accuracy by 39% compared to registration using only the full resolution images. By also considering multiple potential displacements per block, initial errors were reduced by 65%. Using the final implementation of the BMR algorithm, VO was significantly improved from $77\% \pm 21\%$ (range: 0%–100%) in the initial bony alignment to $91\% \pm 8\%$ (range: 56%–100%; $p < 0.001$). Left-right, anterior-posterior, and superior-inferior systematic BDE were 3.2, 2.4, and 4.4 mm, respectively, with random BDE of 2.4, 2.1, and 2.7 mm. Margins required to include both localization and delineation uncertainties ranged from 5.0 to 11.7 mm, an average of 40% less than required for bony alignment.

Conclusions: BMR is a promising approach for automatic lung tumor localization. Further evaluation is warranted to assess the accuracy and robustness of BMR against other potential localization strategies. © 2014 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4867860>]

Key words: nonsmall-cell lung cancer, image registration, image-guided radiation therapy

1. INTRODUCTION

Online image guidance is an established and powerful tool for reducing geometric uncertainties in radiotherapy.¹ For example, interfractional errors resulting from patient setup variability can be mitigated by acquiring images of the patient immediately prior to each treatment fraction (referred to herein as “on-treatment” images).^{2,3} With the advancement of volumetric on-treatment imaging such as computed tomography (CT) on rails, megavoltage CT, and cone beam CT (CBCT), direct visualization of primary tumors has enabled more accurate and robust localization, particularly for lung tumors. Precision in patient setup is essential for modern treatment techniques that utilize narrow margins, steep dose gradients, and hypofractionated treatment regimens.

Direct localization of primary lung tumors is possible using both manual^{4,5} and automatic^{6–8} registration techniques. However, these approaches predominantly apply to stereotactic body radiation therapy (SBRT), where targets are generally small and well-defined. Furthermore, with treatments

lasting only 1–2 weeks, changes in pathology and surrounding anatomy are generally limited,⁹ resulting in more straightforward target localization. This is not the case for locally advanced lung tumors, where tumor shrinkage over time and pulmonary conditions such as atelectasis or pleural effusion introduce substantial geometric variability throughout treatment.¹⁰ These pathoanatomical changes present a major challenge to manual and automatic rigid registration algorithms^{11,12} as well as commonly available deformable registration algorithms.¹³ A more robust registration technique is needed to improve the reliability of target localization for locally advanced lung cancer patients.

The current study explores the feasibility of an automatic block-matching-based registration (BMR) algorithm as an alternative for improved lung tumor localization. This registration technique is carried out in three steps.^{14,15} First, small image subvolumes, termed “blocks,” are identified and distributed on the planning CT to prioritize the registration of distinct features on and near the tumor surface. Each block is then independently registered to the on-treatment image

FIG. 1. Workflow for block-matching-based registration. (a) Blocks are placed on the reference (planning) image at the surface of the initial gross tumor volume (solid contour). (b) Each block is independently registered to the moving image using an exhaustive search over all translations in a predefined window. The blocks in this center image show the registered location of the blocks from the left image; two additional blocks registered into the current image plane. The weekly physician contour is provided as a dashed line for reference. (c) The resulting transform vectors are aggregated to obtain the global image registration. This corresponds to the couch shift required for patient setup correction.

using an automatic rigid transform. Finally, the displacement vectors from each separate block registration are reduced to a global registration of the on-treatment image, representing a couch shift for patient setup corrections.

This registration strategy offers several key advantages to its novel application of target localization. Because this algorithm relies on the rigid alignment of many small, nonoverlapping image blocks, BMR ideally requires fewer voxels than rigid registration of the entire target volume or the whole image, and in that sense may be more efficient for target localization.^{16,17} Furthermore, because each block is registered independently, complex deformations such as shearing and tissue topology changes can be recovered. Finally, the set of block displacement vectors can be regularized or filtered to reduce the impact of misregistrations on the final image alignment.^{18–20}

The block-matching algorithm in this study was implemented based on an existing open-source framework (Insight Segmentation and Registration Toolkit²¹ version 4.2.0) that benefited from parallel execution and block placement using both image intensity features and a binary mask.¹⁵ However, because the existing tool was designed for general-purpose deformable registration, many developments were necessary to tailor the algorithm to the specific task of lung tumor localization. The purpose of this study is to implement and evaluate a block-matching algorithm specifically for the localization of locally advanced lung tumors. The accuracy and robustness of block-matching is assessed for several different BMR implementations, including a new algorithm based on the identification of multiple-candidate registrations (MCR) for each individual block.

2. Methods

2.A. Algorithm implementation

Modification of the existing block-matching framework was carried out by separately addressing each of the three BMR steps: block placement, block registration, and global

image registration. This is summarized in Fig. 1 and discussed in Secs. 2.A.1–2.A.3.

2.A.1. Block placement

In general, as an important requirement for reliable target localization, the surface of the on-treatment target must be well-aligned with (or, in the case of shrinking targets, entirely within) the surface of the planning target. Surface alignment was prioritized by placing blocks in close proximity to existing target contours [Fig. 1(a)]. Although this algorithm required target contours on the planning CT, this condition is easily met in the context of image-guided radiation therapy. Contours were converted to a binary image mask, which was then dilated by 2 mm to provide a larger region near the tumor surface in which distinct image subvolumes could be identified. Blocks were then distributed such that the center voxel was contained within the dilated mask region. The resulting block distribution was intended to capture the high contrast gradients commonly observed between lung tumors and the surrounding lung parenchyma, increasing the potential accuracy of block registrations. This distribution was also intended to avoid block placement inside the lung tumor, where limited tissue contrast may reduce registration accuracy.

In general, smaller blocks may fail to reliably match corresponding intensity features between two images, whereas larger blocks may capture regions containing substantial deformations that complicate the local rigid registration.²² A nominal block size of 1 cm³ represented the best tradeoff between these competing factors, as determined in a preliminary analysis. The voxel size was 1.2×1.2 mm² axially with a slice thickness of 2.0 mm for images in this study.

To improve block registration accuracy, it was desirable to begin placing blocks in the most distinct regions along the tumor surface. Further preliminary analysis compared several different image features for this purpose.²³ The feature with the highest positive predictive value (i.e., high values of the image feature best predicted accurate block

registrations) was the minimum eigenvalue of the local intensity gradient. This particular feature highlighted regions with strong intensity gradients in three orthogonal directions, representative of corner-like structures. Blocks containing a corner-like structure tended to register more accurately than blocks with edge-based features such as the gradient magnitude or the local intensity variance. The registration of blocks along smooth edges is known to be degenerate.²⁴

After placing the initial blocks in the most distinct regions along the tumor surface, remaining blocks were placed according to decreasing values of the minimum gradient eigenvalue. This process continued until no more nonoverlapping blocks could be added to the tumor surface. The final block distribution was likely to contain both distinct and indistinct regions, but this configuration prevented blocks from clustering in portions of the GTV surface, thereby preventing a corresponding bias in the final tumor registration.

2.A.2. Block registration

Each block was individually registered from the planning CT to a predefined window region in the on-treatment image [Fig. 1(b)]. Block similarity between planning and on-treatment images was computed using the symmetric correlation ratio (SCR) defined by Lau *et al.*¹⁸ In initial tests, a search radius of 2.5 cm was necessary to capture the displacement of the tumor surface for all patients in the current study population. However, for more general clinical application, a search radius exceeding 3–4 cm may be necessary to account for target shape and volume variability and positional uncertainties (e.g., initial setup errors, respiratory motion, etc.).²⁵ Registrations were performed using an exhaustive search over all possible translations within the window region. For efficiency, only whole-voxel translations were used to avoid image interpolation, and rotations were excluded.

Initial data analysis revealed that large block displacements were correlated with large block misregistrations. To reduce the impact of these large errors, a multiresolution pyramid registration scheme was employed. Sequential registrations were performed for images downsampled by factors of 4, 2, and 1, with block sizes of 4, 2, and 1 cm, respectively. As a result of downsampling, blocks contained the same number of voxels at each physical dimension. The window regions spanned 8, 4, and 2 cm, respectively, in the on-treatment image and also contained the same number of voxels due to downsampling. This improved the efficiency of the exhaustive search strategy without sacrificing a large initial search space.

After registering all blocks at a single resolution, the resulting displacement vectors were regularized using a median filter.¹⁸ The median displacement was computed separately for each Cartesian axis within small neighborhoods of immediately adjacent blocks. Specifically, the neighborhood $\mathcal{N}(b_i)$ for the block centered at point b_i was defined to include all blocks centered at points less than twice the block size of 1 cm from b_i

$$\mathcal{N}(b_i) = \{b_j | \|b_j - b_i\| < 2 \cdot \text{BlockSize}\}.$$

FIG. 2. Block-matching with multiple-candidate registrations. (a) Using an exhaustive search, registrations are obtained that maximize the SCR within the search space of each block. However, the resulting displacement vectors may not adequately represent the “true” registration of the tumor surface. (b) Registration criteria are relaxed such that a single block may have one or more promising registrations (the “candidates”), represented here by multiple displacement vectors originating from the same point. (c) Because each block should only have one “true” registration, a postprocessing step extracts the single most likely displacement per block. (d) Median filtering yields the final displacement vector field, which better captures the registration of the tumor surface. Steps (b)–(d) are performed at each resolution in the pyramid registration scheme.

This definition was necessary to account for the nonuniform block distribution employed in this study. After regularization, the final displacements were used to initialize the position of the window region for subsequent registrations at finer resolutions.

A second major development in the current BMR algorithm addressed blocks that were registered with a high similarity value, but that were not matched to their expected location near the tumor surface [Fig. 2(a)]. These blocks often contained degenerate features such as edges or planes that matched at multiple locations within the window region. In many cases, it was possible to recover the expected displacement using a two-step regularization procedure termed MCR. First, the “candidate” registrations were defined for a given block as the set of promising displacements having a maximum or *near*-maximum correlation ratio. Then, the single most likely displacement was selected from among these candidates, as explained in more detail below.

To obtain all promising registrations for each block, a three-dimensional similarity map of the SCR was generated for every translation in the exhaustive search space. The maximum SCR was obtained during this process. Additional candidate registrations were then identified in

order of decreasing SCR according to the following heuristic constraints:

- i. the SCR was at least 95% of the global maximum for the given block,
- ii. the SCR was greater than 0.75, and
- iii. the distance between candidate registrations was greater than half the block size.

The first constraint ensured that only near-optimal displacements were considered as potential candidate registrations. The second constraint was based on preliminary data that associated a lower SCR with less accurate block registrations. Finally, the third constraint limited the identification of degenerate block registrations along smooth, planar tissue surfaces. These constraints were determined heuristically such that one or more reasonable candidate registrations per block could be obtained [Fig. 2(b)]. However, constraints were still sufficiently strict to limit the total number of candidate registrations, thus only including the most promising displacement vectors.

Since blocks should only have one “true” registration, a postprocessing step was necessary to extract the single most likely displacement for each block. This relied on the assumption that neighboring blocks along the tumor surface should have very similar registrations. By extension, block displacement vectors that better aligned a portion of the tumor surface were expected to have a lower variance. Therefore, the most likely registration for an individual block minimized the variance of displacement vectors within its own neighborhood as well as the neighborhoods of all surrounding blocks. The net result was a more regular set of displacement vectors with a smaller percentage of gross block misregistrations [Fig. 2(c)]. The MCR technique was always applied prior to median filtering, which provided a final degree of regularization to the displacement vector field [Fig. 2(d)].

2.A.3. Global image registration

The sparsely sampled displacement vector field provided an estimate of the true underlying changes in pathology and local anatomy between the planning and on-treatment images. To compute the optimal rigid transform between images for setup correction, a Procrustes analysis was implemented. Briefly, translational corrections were given by the mean of the displacement vectors in each cardinal direction. To determine rotational corrections, it was first necessary to compute the covariance matrix between the center coordinates of blocks from the initial and registered distributions. Singular value decomposition of the covariance matrix yielded a rotation matrix that optimally oriented the two block distributions. This final, global transform was applied to on-treatment images for analysis [Fig. 1(c)].

2.B. Analysis

According to a protocol approved by the local institutional review board, weekly breath-hold CT scans were acquired for 18 locally advanced lung cancer patients throughout

4–7 weeks of conventionally fractionated radiotherapy.^{10,26} One patient presented with two tumors that were registered and analyzed separately. The primary gross tumor volume (GTV) was delineated by a physician on each image. Prior to automatic block-matching, manual bony-anatomy registrations were performed to align all weekly CTs with the planning CT.

2.B.1. Block registration errors (BRE)

The implementation and development of the current BMR algorithm was assessed using the week 4 CT for a randomly selected subset of 12 patients. The week 4 CT was selected (1) for consistency, as not all patients had images acquired after this week of treatment, and (2) to provide an intermediate degree of variability in tumor shape and volume and in pathoanatomical conditions (PAC) such as atelectasis or pleural effusion.¹²

Because blocks were distributed along the surface of the primary tumor, physician contours were used to compute block registration errors. No point-to-point correspondence existed between contoured targets from the planning and weekly CTs, so an inhouse deformable mesh registration tool was used to estimate the transform between target surfaces.²⁷ The BRE was then computed as the magnitude of the difference between the estimated displacement $\mathbf{d}_{\text{mesh}}(b_i)$ and the observed block displacement $\mathbf{d}_{\text{BMR}}(b_i)$,

$$\text{BRE}(b_i) = \|\mathbf{d}_{\text{mesh}}(b_i) - \mathbf{d}_{\text{BMR}}(b_i)\|$$

for the block centered at point b_i . Large discrepancies between block-matching-based registration and deformable mesh registration were a strong indicator of poor block registration quality. In contrast, better agreement between these two registration techniques indicated a more reliable registration of blocks between the target surfaces.

Contouring variability inherently limited the accuracy of deformable mesh registration as a validation tool for BMR. To circumvent this problem, BMR was also evaluated for a set of artificially deformed images. These images were previously generated for the current study subpopulation²⁸ using the small deformation, inverse consistent linear elastic (SICLE) algorithm.²⁹ The deformed images thus provided a reasonable simulation of the actual internal changes for these patients. Block registration errors were computed in this case as the difference between the known deformation $\mathbf{d}_{\text{SICLE}}(b_i)$ and the observed block displacement,

$$\text{BRE}(b_i) = \|\mathbf{d}_{\text{SICLE}}(b_i) - \mathbf{d}_{\text{BMR}}(b_i)\|.$$

Unlike the block registration errors defined for weekly image registrations, these errors were not affected by delineation uncertainties.

Given that a limited number of blocks were used to register the smallest target volumes, a statistical power analysis was performed to determine the smallest detectable BRE using a significance level (α) of 0.05 and a power ($1-\beta$) of 80%,

$$\text{BRE}_{\min} = \sqrt{\frac{\sigma_{\text{BRE}}^2}{n}}(z_{\alpha/2} + z_{\beta}),$$

where σ_{BRE}^2 is the variance of the BRE. The values of $z_{\alpha/2}$ and z_{β} were obtained from the two-tailed and one-tailed normal cumulative probability distributions, respectively. The BRE_{min} was computed separately in each direction, then averaged over all directions.

Finally, the mean and standard deviation of the magnitude of block registration errors were computed for each patient. To determine population statistics, the group mean (G) was computed as the average over all individual patient means; systematic error (Σ) was defined as the standard deviation over all individual patient means; and random error (σ) was defined as the root-mean-square of the individual patient standard deviations.

2.B.2. Registration errors of the target volume

Using the multiresolution pyramid technique with multiple-candidate registrations, the final block-matching algorithm was used to register all 18 patients and all available weekly images, for a total of 93 registrations. Registration errors for the entire GTV were determined by comparing the physician-delineated GTV from the planning CT ($\text{GTV}_{\text{Planning}}$) with the physician-delineated GTV from the registered on-treatment image ($\text{GTV}_{\text{Registered}}$). Volume overlap (VO) was computed as the intersection of planning and registered target volumes divided by the registered target volume,

$$\text{VO} = \frac{\text{GTV}_{\text{Planning}} \cap \text{GTV}_{\text{Registered}}}{\text{GTV}_{\text{Registered}}} \cdot 100\%.$$

The VO from the initial bony alignment and BMR was statistically compared using a Wilcoxon sign-rank test.

Border displacement errors (BDE) were computed as the distance between the extents of $\text{GTV}_{\text{Planning}}$ and $\text{GTV}_{\text{Registered}}$ in the left, right, anterior, posterior, superior, and inferior directions.^{26,30} The distance was scored as positive if a border from $\text{GTV}_{\text{Registered}}$ was shifted outside the corresponding border from $\text{GTV}_{\text{Planning}}$, as this would require a margin to compensate. In contrast, the distance was scored as negative for registered target borders that were shifted inside the planning target, in which case adequate coverage is likely for that portion of the GTV. The error distributions from opposing target borders were combined to quantify the border reproducibility in each cardinal direction [left-right (LR), anterior-posterior (AP), and superior-inferior (SI)]. The group mean (G) and the systematic (Σ) and random (σ) variability were computed separately in each direction,³¹ from which the required margins were also determined.³²

Because patient setup uncertainties may be influenced by PAC such as atelectasis or pleural effusion,¹⁰ VO and BDE were recomputed separately for patient subpopulations with and without the presence of PAC. Patients with these conditions were referred to as the PAC-positive group ($N = 7$; 35 registrations), while patients without these conditions were referred to as the PAC-negative group ($N = 11$; 58 registrations).

3. RESULTS

3.A. Block registration accuracy

Figures 3–5 highlight the accuracy of block-matching for 12 of the 18 patients in the current study population, listed in order of increasing tumor size. Between 13 and 181 distinct blocks were registered for each patient. For patients

FIG. 3. Mean and standard deviation of the magnitude of block matching errors from registration of artificially deformed images. Results are shown for the initial BMR implementation, MCR, multiresolution pyramid registration with median filtering, and the combined effect of pyramid registration, MCR, and median filtering. The final group (“All”) represents the group mean (G) and random error (σ) for these 12 patients. Differences between BMR algorithms were not statistically significant.

FIG. 4. Mean and standard deviation of the magnitude of discrepancies between block-matching-based registration of weekly CT images and deformable mesh registration. Results are shown for the initial BMR implementation, MCR, multiresolution pyramid registration with median filtering, and the combined effect of pyramid registration, MCR, and median filtering. The final group ("All") represents the group mean ($\bar{G}$) and random error (σ) for these 12 patients. Asterisks denote significant error reductions between BMR algorithms.

1–7, the GTV ranged from 0.6 to 46.6 cm³ initially and from 0.6 to 32.0 cm³ by the fourth week of treatment. These targets regressed by an average of 35% (range: 0%–64%) during this period. For patients 8–12, the initial GTV ranged from 58.3 to 241.9 cm³, with the week 4 GTV ranging from 35.6 to 181.5 cm³. Mean target volume regression was 37% (range: 25%–45%). Two PAC-positive patients were included in this subpopulation, one of which (patient 2) had a pleural effusion that progressed throughout treatment and another (patient 8) with atelectasis that resolved by the fourth week of treatment.

Figure 3 shows the average magnitude of BDE after registration of the artificially deformed images. The initial BMR implementation resulted in mean block displacement errors of 4.1 mm for all patients ($\Sigma = 4.4$ mm, $\sigma = 7.8$ mm). The MCR modification reduced group mean errors to 2.5 mm ($\Sigma = 3.0$ mm, $\sigma = 4.7$ mm). With pyramid registration and median filtering, group mean errors were 1.7 mm ($\Sigma = 1.2$ mm, $\sigma = 1.8$ mm) without MCR and 1.7 mm ($\Sigma = 0.8$ mm, $\sigma = 1.3$ mm) with MCR. Differences in mean BRE between BMR algorithms were not significant for this subpopulation of 12 patients ($p = 0.08$) according to Friedman's test, a nonparametric version of ANOVA for repeated measures analysis.

Figure 4 shows the magnitude of discrepancies resulting from comparison between block-matching of weekly CTs and deformable mesh registration. The initial BMR implementation resulted in mean block displacement errors of 11.5 mm ($\Sigma = 4.9$ mm, $\sigma = 10.0$ mm). Using MCR, mean errors were reduced to 7.6 mm ($\Sigma = 4.0$ mm, $\sigma = 6.5$ mm). Both pyramid registration methods significantly improved block-matching accuracy compared to the initial BMR algorithm according to Friedman's test ($p < 0.001$). The pyramid algorithm

without MCR resulted in errors of 5.2 mm ($\Sigma = 2.2$ mm, $\sigma = 3.1$ mm), and the final algorithm (pyramid + MCR + median) resulted in errors of 4.8 mm ($\Sigma = 1.9$ mm, $\sigma = 2.6$ mm). The final algorithm also demonstrated a significant improvement over registration with MCR alone. Note that statistics were computed over the mean errors from all patients in Fig. 4 and not for individual patients.

Figure 5 demonstrates the impact of MCR on block registration errors. Results are shown only for the fraction of block displacements that changed after applying the MCR technique. Beneath each subfigure, the top row provides the patient index ("All": patients 1–12), and the bottom row provides the number of MCR-modified blocks divided by the total number of blocks for each patient. The fraction of modified blocks depended on the number of initially misregistered blocks, either in the original BMR algorithm [Fig. 5(a)] or the final stage of the pyramid BMR algorithm [Fig. 5(b)]. It also depended on the identification of more than one promising displacement vector for each misregistered block. Because these factors differed between the initial and pyramid algorithms, the fraction of modified blocks differs between top and bottom figures.

According to Fig. 5(a), between 7% and 62% of block displacements were modified by the MCR technique. For this subset of blocks, median filtering and MCR resulted in block registration errors of 7.9 ± 4.9 and 7.8 ± 4.9 mm, respectively. The combined approach of MCR with median filtering reduced registration errors to 6.2 ± 3.5 mm. In Fig. 5(b), one patient did not have any block displacements modified by MCR. The remaining patients had between 4% and 57% of block displacements modified using the MCR technique. For this subset of blocks, the smallest registration errors of

FIG. 5. The effect of the MCR regularization technique on block-matching accuracy for weekly CT images. Beneath each subplot is the patient index (top row) and the fraction of blocks with modified displacements after MCR (bottom row). Registration errors are shown only for this fraction of blocks. The final group ("All") represents the group mean ($\bar{G}$) and random error (σ) for these 12 patients. (a) Comparison of MCR against the initial block-matching implementation. (b) Comparison of MCR against the final stage of pyramid registration. The additional effects of median filtering are also included in both cases.

6.2 ± 3.5 mm were again provided by the combined approach of MCR with median filtering.

For the final block-matching algorithm, the standard deviation over all BRE vectors for all patients was 3.3, 3.6, and 3.4 mm in the left-right, anterior-posterior, and superior-inferior directions, respectively. A statistical power analysis revealed a minimum detectable BRE averaging 3.4 mm for 10 blocks, 2.0 mm for 30 blocks, and 1.1 mm for 100 blocks (Fig. 6). Note that this does not necessarily represent a lower limit on registration errors for the target volume.

3.B. Target localization accuracy

Figure 7 shows the VO of targets after bony alignment and BMR. BMR significantly improved the overall VO of PAC-negative patients by an average of $10\% \pm 12\%$ (range: -3% to 45% ; $p < 0.001$), with 49 of 56 registrations resulting in better overlap. Of these registrations, initial VO of $81\% \pm 14\%$ was increased to $93\% \pm 7\%$. The remaining seven reg-

istrations reduced the VO from $88\% \pm 6\%$ to $87\% \pm 6\%$. For PAC-positive patients, VO was also significantly improved by an average of $20\% \pm 32\%$ (range: -19% to 98% ; $p = 0.003$). Bony alignment resulted in one patient with no target overlap for three weeks of treatment. Block-matching improved the VO in 21 of 33 registrations from an initial average of $59\% \pm 31\%$ to $94\% \pm 5\%$. The 12 remaining registrations reduced the VO from $89\% \pm 8\%$ to $83\% \pm 12\%$.

Table I lists the border errors and setup margins for bony anatomy alignment and BMR. The negative group means indicated that target borders were predominantly shifted inward toward the tumor centroid, and that tumor volumes generally regressed throughout treatment for the study population. Compared to bony alignment, BMR reduced systematic and random border errors by 1.2–2.4 and 0.5–0.9 mm, respectively, for all patients. For PAC-negative patients, BMR reduced systematic and random border errors by 0.4–1.1 and 0.3–0.8 mm, respectively. Corresponding error reductions for PAC-positive patients were 1.5–4.0 and

FIG. 6. Minimum detectable BRE with a statistical significance (α) of 0.05 and a power ($1-\beta$) of 80%. Results are shown for the initial BMR implementation, MCR, multiresolution pyramid registration with median filtering, and the combined effect of pyramid registration, MCR, and median filtering.

0.8–1.1 mm, respectively. These reductions translated to improvements in the required margins ranging from 3.5 to 6.9 mm (all patients), 1.9 to 3.1 mm (PAC-negative), and 4.4 to 11.4 mm (PAC-positive).

4. DISCUSSION

A block-matching-based registration algorithm has been implemented to improve the localization of locally advanced lung tumors. Eventually, such an algorithm could be used to automate registration of on-treatment imaging for image-guided setup correction. By concentrating blocks near the surface of tumors, this algorithm prioritizes surface align-

TABLE I. Mean (G), systematic (Σ), and random (σ) border displacement errors (in millimeters), along with required margins (M) in the LR, AP, and SI directions. Results are shown for all patients, for the subgroup without PAC-negative, and for the subgroup with PAC-positive.

	All patients			PAC-negative			PAC-positive		
	LR	AP	SI	LR	AP	SI	LR	AP	SI
Bony alignment									
G	-2.2	-2.0	-1.2	-2.1	-1.7	-0.6	-2.3	-2.3	-2.1
Σ	4.4	4.8	6.1	4.7	3.3	4.7	4.0	6.6	7.7
σ	2.9	2.9	3.6	2.7	2.4	3.3	3.1	3.6	4.0
M	10.7	11.9	16.7	11.2	7.7	13.5	9.7	16.9	20.5
BMR									
G	-2.2	-1.9	-1.0	-2.2	-1.6	-0.5	-2.1	-2.4	-1.7
Σ	3.2	2.4	4.4	3.6	2.2	4.3	2.5	2.6	4.6
σ	2.4	2.1	2.7	2.4	1.8	2.5	2.3	2.5	2.9
M	7.2	5.0	11.7	8.2	4.6	11.6	5.3	5.5	11.5
Difference: Bony – BMR									
G	0.0	-0.1	-0.2	0.1	-0.1	-0.1	-0.2	0.1	-0.4
Σ	1.2	2.4	1.7	1.1	1.1	0.4	1.5	4.0	3.1
σ	0.5	0.8	0.9	0.3	0.6	0.8	0.8	1.1	1.1
M	3.5	6.9	5.0	3.0	3.1	1.9	4.4	11.4	9.0

ment as an important requirement for target localization, and it exploits the high-contrast gradients commonly observed between lung tumors and the surrounding lung tissue. Accurate and robust block-matching was possible using multiresolution pyramid registration in conjunction with our multiple-candidate registrations technique. This reduced the population systematic and random border errors and improved the average target VO, with similar trends noted for both PAC-positive and PAC-negative subpopulations.

The accuracy of block registrations was first evaluated using artificially deformed images. Because the deformed images were generated directly from the weekly CTs, they provided a reasonable approximation of the pathological and

FIG. 7. Cumulative histograms of the volume overlap between planned and treatment GTV after bony anatomy alignment and block-matching-based registration. Results are shown for patients stratified according to the presence of PAC such as atelectasis and pleural effusion.

anatomical changes demonstrated by these patients. Comparison of block displacement vectors with the expected transform from deformable image registration yielded an error metric impacted solely by inaccuracies in the block-matching process. However, because deformed images may not represent the full extent of irregular target volume changes (e.g., abrupt changes in the tumor surface or dissolving of the tumor interior), these errors potentially underestimated block-matching accuracy for the weekly patient images. In general, any changes between planning and weekly CTs that could not be modeled by pure deformation would likely increase the block-matching errors shown in Fig. 3.

For registration of the weekly patient CT images, a ground truth for block-matching accuracy did not exist. Instead, tumor surface alignment was estimated using a deformable mesh registration method with an accuracy of 2–3 mm.²⁷ By itself, mesh registration was not considered a feasible solution for online guidance. It required contoured target volumes on the weekly images (which are generally unavailable at the time of radiation delivery), and registrations lasted 5–25 min depending on the number of mesh vertices. The BMR algorithm in this work did not require on-treatment target delineation and executed in less than 15 s on a 16 core work station. Because the endpoints of both registration techniques involved tumor surface alignment, deformable mesh registration provided an effective bronze standard for block registration accuracy. Gross block misalignments were easily detected by large discrepancies with mesh registration; however, registration errors in Fig. 4 included both mesh registration uncertainty and target delineation variability. This implies that uncertainties arising solely from block-matching may be less than the errors actually reported in this case. Furthermore, the random orientation of block-matching error vectors in the LR, AP, and SI directions likely diminishes the aggregate target localization errors.

The initial BMR algorithm in this work was based on an existing open-source framework.¹⁵ For individual block registration, key aspects of this initial algorithm included (1) feature detection for block placement and (2) an exhaustive search strategy that relied on an established image similarity metric. Despite fine-tuning algorithm parameters such as block-size, the initial BMR algorithm demonstrated large BRE. This was primarily attributed to the substantial degree of variability in lung tumor shape and volume throughout treatment. One potential solution was to vary the block size to better match the scale of nearby image features, similar to the adaptive saliency method of Zhang.³³ However, it was determined in a preliminary analysis that 1 cm³ blocks provided the best balance between accuracy and computational efficiency. Other published BMR algorithms relied on block placement and block-matching designs consistent with our initial implementation.^{14,16} These alternatives were therefore not expected to improve upon our initial results. Instead, the existing framework was redesigned for improved robustness through regularization of the block displacement vectors.

Regularization strategies were implemented under the assumption that neighboring blocks along the tumor surface should have similar displacement vectors. Although this as-

sumption may not apply to general-purpose BMR algorithms, the two different regularization techniques in this work contributed to substantial improvements in BRE. First, pyramid registration was employed to better capture both coarse and fine details in the registration. Downsampling by a factor of 4 enabled a large initial window region of 8 cm in the moving image, which was sufficient for the registration of images with target volume regression, respiratory excursion, or slight initial misalignment. Pyramid registration also provided the opportunity for data regularization between resolution levels using a median filter. Initial block matching errors could thus be corrected before they were propagated to subsequent registrations at finer resolutions.

The second regularization technique was MCR, in which large block misregistrations could be corrected by searching for other promising displacements (i.e., having near-maximal SCR scores) that were more consistent with tumor surface alignment. Although block misregistrations were not guaranteed to be corrected, Fig. 5 demonstrates that the new block displacements were more consistent on average with changes in the target surface (as determined by deformable mesh registration). Furthermore, when combined with pyramid registration and median filtering, the regularization provided by MCR resulted in the smallest systematic and random block-matching errors from a population standpoint (Figs. 3 and 4). For some patients, the combination of pyramid registration, MCR, and median filtering caused a slight increase in mean block registration errors. This was partly attributed to regularization with the median filter, which provided a somewhat variable degree of improvement on the final registration results.

The final block-matching algorithm led to substantial gains in target localization compared to bony anatomy alignment. However, required margins still ranged from 5.0 to 11.7 mm after block-matching-based registration. These relatively large margins resulted from the combined effects of localization error, delineation uncertainty, and target volume variability (i.e., changes in tumor shape and size). This implies that even with high-quality target registration, purely rigid shifts have a limited ability to correct for all sources of uncertainty throughout treatment. To further reduce margins, strategies to manage target volume variability (such as adaptive radiation therapy) and delineation error are required.

Yeung *et al.*³⁴ conducted a similar study for lung cancer patients also receiving conventionally fractionated radiotherapy. In their retrospective review, automatic rigid registration of the spine was compared against automatic soft-tissue-based registration of the planning target volume. Variations in the relative treatment couch shifts were used to formulate margins, which were shown to decrease by 5–14 mm after direct tumor registration. However, these margins did not account for potential residual errors in the tumor registration. More modest gains ranged from 3.5 to 6.9 mm for patients in the current study, likely because registration error of the GTV was directly assessed for both registrations.

Larger improvements in systematic and random BDE and margin size were noted for the sub-population of PAC-positive patients than for the subpopulation of PAC-negative

patients. PAC-positive patients demonstrated larger variations between planning and on-treatment CTs due to changes in tumor volume, atelectasis, and pleural effusion.¹⁰ This led to larger initial GTV registration errors from bony anatomy alignment and larger potential corrections after BMR. For PAC-positive patients, BMR provided an average reduction in systematic and random border errors of 46% and 28%, respectively. This resulted in a 52% overall decrease in margin size.

The current study sought to establish block-matching as an accurate and robust registration technique for locally advanced lung tumors. To date, this has been demonstrated using CT-CT registration for images acquired with an active breath-hold protocol. Further evaluation of this tool for CT-CBCT registration is pending. The SCR similarity metric is suitable for multimodality registration and should not impact the results of CT-CBCT registrations. The presence of additional noise, potential image artifacts, and respiratory motion in CBCT images may all impact the accuracy reported in this study. However, BMR is anticipated to be robust against these complications due to the independent registration of image subvolumes. Misregistration of a reasonably small number of blocks could be corrected through a combination of pyramid registration, the multiple-candidate registrations technique, and median filtering, potentially leading to robust target localization and reduced patient setup uncertainties.

Future work will also consider the simultaneous registration of multiple treatment targets, as direct tumor alignment may result in poor localization of other lesions such as metastatic lymph nodes.³⁵ Furthermore, direct tumor alignment may increase the dose delivered to nearby risk structures.⁷ Because block-matching provides local displacements of the entire tumor surface, it may be possible to adapt the final tumor registration in order to better localize other lesions or better spare risk structures.

5. CONCLUSION

A block-matching-based registration algorithm has been implemented specifically for the localization of locally advanced lung tumors. Through a combination of regularized pyramid registration and a new multiple-candidate registrations strategy, substantial improvements were demonstrated relative to an initial bony anatomy alignment in systematic and random border errors, margin sizes, and target volume overlap. Accurate and robust registrations were observed for patients both with and without the presence of pathoanatomical conditions such as atelectasis or pleural effusion. Future work is warranted to evaluate block-matching against other potential localization strategies for routine image-guidance.

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