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Validating a Predictive Atlas of Tumor Shrinkage for Adaptive Radiotherapy of Locally Advanced Lung Cancer

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Abstract

Purpose: To cross-validate and expand a predictive atlas that can estimate geometric patterns of lung tumor shrinkage during radiation therapy using data from 2 independent institutions and to model its integration into adaptive radiation therapy (ART) for enhanced dose escalation.

Methods and Materials: Data from 22 patients at a collaborating institution were obtained to cross-validate an atlas, originally created with 12 patients, for predicting patterns of tumor shrinkage during radiation therapy. Subsequently, the atlas was expanded by integrating all 34 patients. Each study patient was selected via a leave-one-out scheme and was matched with a subgroup of the remaining 33 patients based on similarity measures of tumor volume and surroundings. The spatial distribution of residual tumor was estimated by thresholding the superimposed shrinkage patterns in the subgroup. A Bayesian method was also developed to recalibrate the prediction using the tumor observed on the midcourse images. Finally, in a retrospective predictive treatment planning (PTP) study, at the initial planning stage, the predicted residual tumors were escalated to the highest achievable dose while maintaining the original prescription dose to the remainder of the tumor. The PTP approach was compared isotoxically to ART that replans with midcourse imaging and to PTP-ART with the recalibrated prediction.

Results: Predictive accuracy (true positive plus true negative ratios based on predicted and actual residual tumor) were comparable across institutions, 0.71 versus 0.73, and improved to 0.74 with an expanded atlas including 2 institutions. Recalibration further improved accuracy to 0.76. PTP increased the mean dose to the actual residual tumor by an averaged 6.3Gy compared to ART.

Conclusion: A predictive atlas found to perform well across institutions and benefit from more diversified shrinkage patterns and tumor locations. Elevating tumoricidal dose to the predicted residual tumor throughout the entire treatment course could improve the efficacy and efficiency of treatment compared to ART with midcourse re-planning.

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Summary

We generated a predictive atlas that can estimate the spatial distribution of residual tumor in response to radiation therapy and validated the atlas across independent institutions. Treatment planning guided by the prediction and by the recalibration of the prediction based on imaging surveillance can provide relevant dose escalation to the actual residual tumor. It can also improve efficacy compared with the adaptive midcourse replanning approach.

Introduction

Lung cancer continues to account for the most deaths among patients with cancer in the United States, far exceeding other common cancers (1). Despite advances in treatment technologies, 5-year survival is poor in patients with locally advanced non-small cell lung cancer (2). Better mechanistic understanding of how lung tumors respond to radical radiation therapy, both anatomically and metabolically, is essential to improve the standard of care and to discover new dosing paradigms such as adaptive radiation therapy (ART) (3). Previously, we developed a novel geometrical atlas (4, 5) that can capture the spatial patterns of lung tumor shrinkage commonly seen during the course of radiation therapy (6–11) and that can predict the spatial distribution of residual tumor after radiation therapy. This information then guides predictive treatment planning (PTP) that escalates dose to the predicted residual tumor while maintaining a baseline dose to the rest of the original tumor and without compromising the sparing of organs at risk (OARs). When the atlas performs well, the hot spots in the dose distribution align well with the actual residual tumor, resulting in significantly increased mean dose conforming to the subportion of the tumor associated with possible resistance or recurrence. This selective dose escalation strategy is more favorable than boosting dose to the entire tumor, which may cause higher toxicities to the surrounding OARs. In addition, the atlas can also be used to systemically analyze the spatial patterns of resistant tumors in a longitudinal imaging study.

To expand the scope of the predictive atlas, originally composed of 12 patients from our institution (Inst1), we recruited 22 patients with lung cancer from a collaborative institution (Inst2). Equipped with a much larger set of patients, the new atlas covers more diversified tumor shrinkage patterns and becomes more representative of the general population of patients with locally advanced lung cancer. The expanded atlas provides new opportunities to cross-validate the predictive algorithm between 2 independent institutions, improve the algorithm for better predictive accuracy, and analyze the behavior of the predictive atlas with more statistical power. Furthermore, because we monitor patients with weekly cone beam computed tomography (CBCT), recalibration of the prediction using the observed imaging data becomes increasingly critical. The updated prediction can determine the timing of triggering a replanning process that improves tumor coverage or lowers OAR toxicities in the context of ART. We address the developments of these emerging research issues.

Methods and Materials

Patient populations

This retrospective longitudinal imaging study of lung cancer included patients who had planning computed tomography (CT) and consecutive weekly CBCT acquired during the course of conventional radiation therapy lasting 5 to 7 weeks (12, 13). The prescription in Inst1 is 56 to 70 Gy (median 60 Gy) with 2 Gy/fraction, versus 48 to 66 Gy (median 66 Gy) with 1.8 to 3 Gy/fraction (median 2.75 Gy/ fraction) in Inst2. Parenchymal and mediastinal lung tumors were segmented by the radiation oncologists on all imaging sets. To better assess the spatial and temporal changes of tumors at the voxel level, rigid 3-dimensional image registrations aligning the spine and outer lung were performed to transfer the contours of gross tumor volume (GTV) on the weekly CBCTs to the planning CT. Thirty-four patients with more than 20% tumor shrinkage, defined as the difference in tumor volume seen on the planning CT and last weekly CBCT divided by tumor volume on the planning CT, were selected to construct and evaluate the predictive atlas.

The characteristics of investigated lung tumors are listed in Table 1. Tumors of patients from Inst2 present a wider range of volume, location, and shrinkage than those of patients from Inst1, making the expanded atlas more diversified. The atlas is biased toward tumor shrinkage because it excludes patients whose tumor grew or did not shrink noticeably (<20%) and who are reported to account for 50% to 60% of the patient population receiving chemotherapy or radiation therapy (14, 15).

Predictive atlas

Predictive algorithm—The design details of the predictive algorithm were described in our previous papers (4, 5). The spatial shrinkage patterns from GTV on the planning CT (GTV_{orig}) to the actual residual tumor on the last weekly CBCT (GTV_{resd}) were modeled using their relative scores for the 3 principal components. Given a test patient, patterns from patients in the atlas were superimposed to form a prior probability map of potential residual tumors. Voxel by voxel, the prior probability map was projected onto GTV_{orig} of the test patient according to the relative scores of principal components. Subsequently, a binary prediction of the residual tumor (GTV_{pred}) was derived by thresholding the probability map. By comparing the predicted and actual residual tumor, we calculated model properties, including the sensitivity, specificity, accuracy (portion of true positives and true negatives inside the original tumor), Dice coefficient, and root mean square of the distance between the 2 objects.

Cross-validation between 2 institutions—The first objective of this study is to test whether an atlas composed of patients from one institution can predict tumor shrinkage in a cohort of patients from another independent institution. In this scenario, we use all 12 patients from Inst1 to predict the shrinkage patterns of the 22 patients from Inst2, and vice versa, and cross-checked the accuracies.

Expansion of the atlas—The second objective of this study is to integrate all patients from 2 institutions into a unified predictive atlas. The more diversified shrinkage patterns

presented challenges to the predictive consistency and accuracy. For example, mediastinal tumors on either side of the lung tend to shrink toward the central mediastinum. Predicting the shrinkage pattern of a left-sided mediastinum tumor using patterns of right-sided tumors therefore introduces positional errors. Intuitively, matching an incoming patient to a subgroup in the atlas with similar shrinkage patterns would mitigate this problem. As an attempt to reduce errors, we developed an algorithm to group patients based on a unified measure of similarity that considers tumor volume and surrounding environment.

To quantify the environment surrounding a specific tumor, we developed the concept of a density map of surrounding tissues (DMST). We first expanded GTV_{orig} on the original planning CT with a uniform 1 cm margin to form a 3-dimensional rind. We then projected the rind from Cartesian to polar coordinates centered at the center of gravity of GTV_{orig} , where voxels in the rind were grouped into subregions according to their azimuth and inclination angles with a 1° resolution. Finally, we calculated a ratio of mean Hounsfield units between the subregion and tumor:

$$DMST(\varphi, \theta) = \text{mean}[HU(\varphi, \theta)_{\text{rind}}] / \text{mean}(HU_{GTV})$$

The DMST illustrates how a tumor is situated. In the example (patient 19) shown in Fig. 1a, the bottom of the DMST (inclination angle $>90^\circ$) has very low intensities, corresponding to the lung tissue inferior to GTV_{orig} , whereas the higher intensity at the top corresponds to adjacent mediastinum or chest wall.

We defined a similarity measure between a test patient i and a patient j in the atlas as a linear combination of volume match and cross-correlation between 2 DMSTs:

$$SIM_{ij} = \text{corr}(DMST_i, DMST_j) + \lambda \min(Vol_i/Vol_j, Vol_j/Vol_i)$$

where λ weights the relative influence of tumor volume and DMST. After sorting the similarity, we selected the top N patients to form a matched subgroup and subsequently used it for prediction.

We investigated the impact of the patient-matching process on predictive accuracy. Following the leave-one-out assessment scheme, we applied the similarity filter (varying λ from 0 to 1 with a step size of 0.2) to match the test patient to a subgroup of N patients (varying from 1 to 33) within the entire atlas. After calculating predictive accuracies for each composition in this 2-dimensional search space, we determined the optimal N and λ corresponding to the maximal resultant accuracy. Subsequently, we compared the maximal derived accuracy with the resultant accuracy from using all available patients ($n = 33$) in the atlas and evaluated the improvement in a statistical Wilcoxon signed-rank test.

We also assessed the sensitivities of the model parameters N and λ . Each testing patient has an individual optimal list, which includes the top N matching patients resulting in the maximal accuracy at a particular λ . When varying λ , this list changes. The turnover rate, defined as the portion of patients changed compared with the optimal list around the optimal

λ and N , was calculated to assess the sensitivity of patient selection to λ . In addition, the accuracy gradient around the optimal N and λ was calculated for evaluation.

Bayesian-based recalibration

PTP is a feed-forward paradigm, but it can also benefit from the feedback collected via imaging surveillance similar to other ART paradigms. We emulated a midcourse (3–4 weeks into radiation therapy) replanning protocol commonly used in ART (16), used the observations of GTV_{mid} (on the midcourse CBCT) to recalibrate GTV_{pred} , and developed a strategy to replan given the updated prediction (GTV_{pred}').

Starting with the recalibration process, we built a prior probability map that correlates the spatial distribution of GTV_{mid} with GTV_{resd} for all patients in the atlas. Given a GTV_{mid} , we first applied a 3-dimensional Euclidean distance transform on a resampled isotropic grid (ie, peeling the object layer by layer by 1 voxel thicknesses and labeling each layer with a distance value ranging from 0 at the boundary and increasing to the highest value at the innermost point). Similarly, we expanded GTV_{mid} by 2 layers and assigned a negative distance value of -1 and -2 , respectively. We then correlated each voxel inside each layer of GTV_{mid} to the corresponding voxel inside the GTV_{resd} of this particular patient and formed a lookup table that linked the Euclidean distance to the probability of coinciding with actual residual tumor for each layer. To be comparable across patients, we normalized the Euclidean distance to the maximum number of inner layers of each individual patient. After superimposing all the patient data, we formed a unified coincidence probability curve (Fig. 2).

By comparing the spatial distribution of GTV_{pred} with GTV_{mid} , we modified the original prediction of each individual patient and generated a corrected version, GTV_{pred}' , following Bayesian rules: (1) voxels inside GTV_{pred} but outside GTV_{mid} were removed from the prediction because the probability of being actual residual tumor outside GTV_{mid} is very low ($<5\%$); and (2) voxels outside GTV_{pred} and inside GTV_{mid} , but with a normalized Euclidean distance higher than 0.4, were added to the prediction because the probability of being actual residual tumor was high ($>75\%$). By comparing GTV_{pred}' with GTV_{resd} , we assessed the improvement of such a correction over predictions with GTV_{pred} or GTV_{mid} . Note that the GTV_{mid} used in the current model is a result of clinical treatment with uniform dosing and would be a conservative (larger) estimation of a PTP plan with simultaneously integrated boost potentially causing more shrinkage.

Predictive treatment planning

We have demonstrated that PTP, a simultaneously integrated boost technique escalating dose to the predicted residual target, is beneficial as measured by higher dose to the actual residual tumor and poses less work burden compared with the conventional midcourse ART (4). In this study, we focus on demonstrating the feasibility of adapting the original PTP plan given the updated prediction (ART-PTP). In the replanning process, we first expanded GTV_{orig} , GTV_{pred} , GTV_{pred}' , and GTV_{resd} with 1 cm margin and formed PTV_{orig} , PTV_{pred} , PTV_{pred}' , and PTV_{resd} , respectively, to account for setup and respiratory uncertainties. We treated the original PTP plan as a pre-existing dose and escalated dose to PTV_{pred}' as high as

possible while not reducing dose to PTV_{orig} or increasing OAR toxicities benchmarked by the original PTP plans. The general toxicity guidelines are to constrain the lung mean dose to less than 20 Gy and the cord maximal dose to less than 45 Gy. To simulate the dose of the entire delivery, we generated a unified plan, ART-PTP, as a sum of the equally weighted adaptive and original PTP plan. As a control, we also simulated the conventional midcourse ART, represented by an equally weighted sum of a clinical plan prescribing a uniform dose to PTV_{orig} , and an adaptive plan prescribing the highest achievable dose to PTV_{mid} . We investigated the dosimetric advantages of ART-PTP over PTP and ART by evaluating the accumulative dose to PTV_{resd} .

Results

In the design of matching a test patient to a better-suited subgroup for prediction, the maximal predictive accuracy averaged across the atlas was reached at $\lambda = 0.6$ and $N = 9$. After reaching the maximum, the averaged accuracy rapidly leveled off with respect to number of patients included in the subgroup. The turnover rate averages 9% when λ changes ± 0.2 around its optimal value, resulting in a reduction of 0.002 in predictive accuracy. Around the optimal value, the gradient of accuracy with respect to N is 0.008. Density maps of surrounding tissues and matching results are shown in Fig. 1b. In this example, although correlation of DMST between patient 21 and the testing patient 19 is high, the mismatch between the volumes (52 cm^3 vs 159 cm^3) lowers the rank.

Table 2 summarizes characteristics of predictions using Inst1 to predict Inst2 and vice versa, using the entire atlas (33A) and the top 9 matched patients (9M). Performance of predictions between institutions is comparable, indicating the feasibility of predicting shrinkage patterns from one cohort to another with the presence of moderate heterogeneities in patient characteristics. 9M is statistically significantly better than 33A ($P < .01$, Wilcoxon signed-rank test), although the absolute improvements in accuracy and the Dice coefficient are modest, around 0.02 on average and 0.08 at maximum. The smaller root mean square of the distance indicates fewer spatial deviations from the actual residual tumor, which is essential for relevant dose escalation. Smaller deviation from the actual shrinkage also indicates the higher consistency and reliability of 9M. As illustrated in Fig. 3a (patient 19 from Inst2), the prediction from 9M (magenta) had a higher accuracy when evaluated by the actual residual tumor (blue color wash), 0.85 versus 0.80, than was 33A (green). Similar observations made with patient 14 are illustrated in Fig. 3b.

As shown in Table 2, the midcourse correction improved all predictive properties over GTV_{pred} and GTV_{mid} ($P < .05$). Varying the threshold in converting probabilities to binary predictions, the receiver operating characteristic curves of midcourse correction, 9M, and 33A were generated, with an area under the curve of 0.85, 0.79, and 0.76, respectively. GTV_{mid} was, on average, 27% bigger than GTV_{resd} , resulting in predictions with high sensitivity but low specificity and in large spatial errors because the shrinkage at the middle of the radiation therapy was not fully realized. As illustrated in Fig. 3c (patient 6 from Inst1), GTV_{pred} differs from GTV_{mid} because it is expanded in the superior and lateral directions and shrunken at the posterior edge, yielding an increased agreement with GTV_{resd} . Similar observations made with patient 8 are illustrated in Fig. 3d.

Four of the 34 patients had more than 63% (mean + standard deviation) shrinkage. The predictive accuracies (using 9M) of these patients averaged 0.65, trending lower ($P = .12$) compared with the 0.75 averaged across the rest of patients, indicating that the performance of the atlas may suffer when the tumor shrinks significantly compared with the atlas patients. In fact, the worst performance of 9M occurred for a patient who had an extreme shrinkage of 89% and an irregular shrinkage pattern to a corner of the original tumor; this resulted in an accuracy of 0.48, the only case in the atlas beyond the range of 2 standard deviations of the predictive accuracies. Even a midcourse CBCT scan could not identify this outlier early and improve the predictive accuracy. Because the residual tumor was only 18 cm³ in this case, a reirradiation of the residual tumor via stereotactic body radiation therapy can be applied to control the tumor, if necessary.

In a retrospective planning study of Inst1, which can be used for direct comparison with the previously published planning study (5), the PTP, adaptive PTP (ART-PTP), and conventional ART plans had the same prescription dose to PTV_{orig} and indistinguishable lung mean dose and cord maximal dose. Because PTP escalated dose from the beginning of radiation therapy with SIB, it raised the mean dose to PTV_{resd} by 6.3 ± 1.8 Gy compared with ART; meanwhile, ART-PTP was able to further escalate 1.5 ± 0.3 Gy over PTP because of its improved prediction.

Discussion

We have demonstrated that a predictive atlas can work on a large number of patients and across independent institutions. Furthermore, a patient-matching process and a recalibration using the midcourse image surveillance can modestly improve the predictive accuracy. The predictive algorithm can capture a significant portion of the actual residual tumors among patients with noticeable differences in tumor geometries, locations, shrinkage patterns, and radiation therapy dosing schemes. As we gradually accumulate more patients in our atlas across institutions, we envision empowering the atlas with other clinical variables (eg, tumor pathologic and physiologic properties, heterogeneous dose and fractionation schemes) and systemically assessing the limitations of the atlas. These efforts will hopefully improve the predictive accuracy and expand the applicability of the atlas and better facilitate the design of radiation therapy.

In the context of adaptive treatment planning, in addition to patient anatomy, the ability of adaptation to provide useful dose escalation relies on 2 factors: (1) the accuracy with which the boost target is defined and (2) the timing of replanning within the treatment course. The conventional approach that prescribes a uniform dose to the entire tumor for the full radiation therapy course is not adequate because the accuracy of using GTV_{orig} to predict GTV_{resd} is low. Adaptive planning based on a midcourse scan improves predictive accuracy but at best takes advantage of only half of the prediction because the plan designed for the larger GTV_{orig} already has used up part of the OAR tolerance. Additionally, GTV_{mid} is in general larger than GTV_{pred}, thus limiting its dose escalation ability given the same constraints on toxicity. PTP is effective because of its excellent accuracy and timing. ART-PTP can modestly raise the level of dose escalation further, and, if using PTP, a midcourse CT provides patient-specific evidence to justify continuing with the initial planned

inhomogeneous dose distribution. In the scenario in which improvement from ART-PTP is not significant, the replanning process can be waived, giving PTP an efficiency advantage because the burdens of additional planning and quality assurance are removed. Based on the promising performance of the predictive atlas in this retrospective study, we are forming a prospective clinical protocol and will test the predictive power of the atlas in a routine clinical setting.

As a population-based approach, the predictive algorithm works well when the characteristics of an individual patient fall into the statistical range of the cohort. Our atlas has a selection bias toward considerable tumor shrinkage. Although the atlas has an impact on a significant number of patients, its applicability is limited to 40% to 50% of the patients receiving chemotherapy and radiation therapy by excluding patients whose tumor grows or shrinks very little. Studies using clinical data and radiomics (17–19) have demonstrated that quantitative image features extracted from pretreatment scans can be used to predict tumor response (eg, volume shrinkage) to chemotherapy and radiation therapy, thereby identifying patients who may not benefit from PTP in advance of radiation therapy. However, even if the stratification of patients to PTP is wrong, the simultaneous integrated boost to the target predicted by PTP becomes a randomly located hot spot within the initial PTV, which would either not affect TCP or, more likely, would increase it without increasing OAR toxicity because of the isotoxic design of PTP compared with the standard uniform dosing approach. Additional metabolic information acquired from pre- and midtreatment PET scans may help us detect outliers because PET focuses on tumor characteristics of metabolism other than geometry. We are developing a PET/CT-based biological model to study the trajectory of tumor response throughout radiation therapy (20, 21). By combining our geometrical atlas with the PET-based model, we might be able to improve the predictive accuracy and dose escalate more effectively to relevant parts of the tumor. Furthermore, longitudinal imaging studies of dose escalation to PET-avid regions (22, 23) can help us understand tumor responses to inhomogeneous dose distributions at different dose levels and can provide relevant data for the recalibration of the predictive model. At least 2 prospective protocols acquiring such data are under way (16–24).

Our dosimetric analysis is limited by the approach of rigid registration on spine and outer lung. The model could be updated by using alternative registration strategies such as tumor alignment. Analysis of deformed tumor would need deformable registration for dose accumulation. In the complicated scenarios in which trajectories of tumor shrinkage play a critical role, the gain of PTP needs to be carefully explored; however, it should still exist with accurate dose delivery because tumor eventually would morph to the spatial location where PTP creates a high dose bath. A more comprehensive planning study evaluating these scenarios will follow.

Conclusions

A predictive atlas was found to perform well across institutions and to benefit from more diversified shrinkage patterns and tumor locations. Elevating tumoricidal dose to the predicted residual tumor throughout the entire treatment course could improve the efficacy and efficiency of treatment compared with the adaptive replanning approach.

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Fig. 1.

(a) Construction of a patient-specific density map of surrounding tissues (DMST) (patient 19). (b) The rank of similarity matching patient to #19 decreases from left to right and from top to bottom. The top 9 patients (9M) are selected for prediction.

Fig. 2. Coincidence probability of being inside the actual residual tumor given normalized Euclidean distances of the gross tumor volume (GTV) observed on a midcourse cone beam computed tomography. Normalized distance greater than 0.4 (green zone) indicates high coincidence probability and is used as a criterion for correction. (A color version of this figure is available at <https://doi.org/10.1016/j.ijrobp.2018.05.056>.)

Fig. 3.

(a) Prediction from 9M (magenta) had a higher accuracy as evaluated by the actual residual tumor (blue color wash), 0.85 versus 0.80, than did 33A (green) for patient 19. (b) Prediction from 9M improves spatial accuracy for patient 14 compared with 33A. (c) and (d) Example (patients 6 and 8) of improving the original prediction based on midcourse observation. (A color version of this figure is available at <https://doi.org/10.1016/j.ijrobp.2018.05.056>.)

Table 1

NSCLC tumor characteristics

Atlas	No. of patients	Shrinkage		Original GTV (cm ³)		Location	
		Mean ± SD (%)	Range (%)	Median	Range	Parenchymal	Mediastinal
Inst1	12	43 ± 8	(26–59)	54	(4–401)	6	6
Inst2	22	50 ± 17	(28–89)	138	(22–851)	10	12
Inst1 + Inst2	34	48 ± 15	(26–89)	116	(4–851)	16	18

Abbreviations: GTV = gross tumor volume; Inst1 = institution 1; Inst2 = institution 2; NSCLC = non-small cell lung cancer; SD = standard deviations.

Table 2

Characteristics of predictions using Inst1 to predict Inst1 (Inst1→Inst1), Inst1 to predict Inst2 (Inst1→Inst2), and vice versa, using 33A, 9M, observations on Mid-CBCT, and recalibration of prediction based on Mid-corr

Atlas	Accuracy	Sensitivity	Specificity	DICE	RMSD(mm)	Shrinkage difference (%)
Inst1→Inst1	0.74 ± 0.04	0.73 ± 0.08	0.76 ± 0.10	0.75 ± 0.04	3.2 ± 1.4	6 ± 13
Inst1→Inst2	0.71 ± 0.07	0.73 ± 0.11	0.74 ± 0.11	0.69 ± 0.13	3.1 ± 1.3	-0 ± 17
Inst2→Inst2	0.71 ± 0.08	0.74 ± 0.10	0.72 ± 0.11	0.70 ± 0.13	3.0 ± 1.4	2 ± 17
Inst2→Inst1	0.73 ± 0.05	0.70 ± 0.12	0.79 ± 0.17	0.74 ± 0.05	3.6 ± 1.5	-9 ± 16
33A	0.72 ± 0.07	0.70 ± 0.10	0.77 ± 0.11	0.71 ± 0.11	3.5 ± 1.5	-5 ± 16
9M	0.74 ± 0.07	0.74 ± 0.09	0.76 ± 0.10	0.73 ± 0.11	3.1 ± 1.4	-2 ± 13
Mid-CBCT	0.69 ± 0.11	0.96 ± 0.04	0.37 ± 0.20	0.70 ± 0.13	3.6 ± 2.5	-27 ± 13
Mid-corr	0.76 ± 0.07	0.77 ± 0.09	0.76 ± 0.09	0.76 ± 0.12	2.0 ± 0.9	-0 ± 12

Abbreviations: 9M = top 9 matched patients from the atlas; 33A = entire atlas; CBCT = cone beam computed tomography; Inst1 = institution 1; Inst2 = institution 2; Mid-CBCT = midcourse cone beam computed tomography; Mid-corr = midcourse observations; RMSD = root mean square deviation.

The shrinkage difference is between observed and predicted final shrinkages.