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A Systematic Analysis of Errors in Target Localization and Treatment Delivery for Stereotactic Radiosurgery Using 2D/3D Image Registration

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Abstract

Purpose: To determine the localization uncertainties associated with 2-dimensional/3-dimensional image registration in comparison to 3-dimensional/3-dimensional image registration in 6 dimensions on a Varian Edge Linac under various imaging conditions. **Methods:** The systematic errors in 6 dimensions were assessed by comparing automatic 2-dimensional/3-dimensional (kV/MV vs computed tomography) with 3-dimensional/3-dimensional (cone beam computed tomography vs computed tomography) image registrations under various conditions encountered in clinical applications. The 2-dimensional/3-dimensional image registration uncertainties for 88 patients with different treatment sites including intracranial and extracranial were evaluated by statistically analyzing 2-dimensional/3-dimensional pretreatment verification shifts of 192 fractions in stereotactic radiosurgery and stereotactic body radiotherapy. **Results:** The systematic errors of 2-dimensional/3-dimensional image registration using kV–kV, MV–kV, and MV–MV image pairs were within 0.3 mm and 0.3° for the translational and rotational directions within a 95% confidence interval. No significant difference ($P > .05$) in target localization was observed with various computed tomography slice thicknesses (0.8, 1, 2, and 3 mm). Two-dimensional/3-dimensional registration had the best accuracy when pattern intensity and content filter were used. For intracranial sites, means $\pm$ standard deviations of translational errors were -0.20 ± 0.70 mm, 0.04 ± 0.50 mm, and 0.10 ± 0.40 mm for the longitudinal, lateral, and vertical directions, respectively. For extracranial sites, means $\pm$ standard deviations of translational errors were -0.04 ± 1.00 mm, 0.2 ± 1.0 mm, and 0.1 ± 1.0 mm for the longitudinal, lateral, and vertical directions, respectively. Two-dimensional/3-dimensional image registration for intracranial and extracranial sites had comparable systematic errors that were approximately 0.2 mm in the translational direction and 0.08° in the rotational direction. **Conclusion:** The standard 2-dimensional/3-dimensional image registration tool available on the Varian Edge radiosurgery device, a state-of-the-art system, is helpful for robust and accurate target positioning for image-guided stereotactic radiosurgery.

Keywords

image guided, image registration, 2D/3D, 3D/3D, systematic error, Edge

Abbreviations

ANOVA, analysis of variance; AP, anterior–posterior; CBCT, cone beam computed tomography; CI, confidence interval; CT, computed tomography; DOF, degrees of freedom; 4D, 4 dimensional; GI, gastrointestinal; IGRT, image-guided radiation therapy; LAT, lateral; LNG, longitudinal; ROI, regions of interest; SBRT, stereotactic body radiotherapy; SEM, standard errors of the mean; simCT, simulation computed tomography; 6D, 6 dimensions; SD, standard deviation; SRS, stereotactic radiosurgery; 2D/3D, 2 dimensional/3 dimensional; VRT, vertical

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Introduction

Online image-guided radiation therapy (IGRT) is an effective tool designed to reduce potential systematic and random errors in radiation oncology.[1] Uncertainties arise due to position change, tissue deformation, and breathing motion and may

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result in undesired dose delivery to patient.[2] Consequently, accurate target localization is crucial for IGRT to deliver highly conformal dose to the treatment site for optimum treatment outcome.

Two-dimensional/3-dimensional (2D/3D) image registration is an image-guided procedure[3] that aligns 2D image data to 3D image data such as alignment of 2 X-ray images to corresponding digitally reconstructed radiographs (DRRs) generated from simulation computed tomography (simCT). Besides 2D/3D image registration, 3D/3D image registration is also used in IGRT to register different sets of tomographic images such as magnetic resonance imaging/computed tomography (CT) and cone beam CT (CBCT)/CT. These registrations provide rigid transformation to align anatomic structures at the treatment position with those used for treatment planning in the 3 dimensions (x, y, and z) and rotations about 3 perpendicular axes (pitch, roll, and yaw), that is, in 6 degrees of freedom (6DOF).[4] The rigid alignment can be achieved accurately using a robotic treatment couch, which allows up to 6DOF.[5,6] The 2D/3D image registration has been used in the ExacTrac (BrainLab AG, Feldkirchen, Germany) system[7] and CyberKnife (Accuray Inc, Sunnyvale, California) system.[8] Different image registration methods have different performances in terms of target localization. For image registration, the best match of images is estimated by similarity measures. Intensity-based similarity measures such as mutual information, cross-correlation, and pattern intensity are mainly used for 2D/3D image registration.[9-13] The 2D/3D image registration can be used for treatment sites in the head, spine, and others.[14] The accuracy of 2D/3D registration has been improved to submillimeter for rigid structures,[15-21] which is required for stereotactic radiosurgery (SRS). The Edge (Varian Medical Systems, Palo Alto, California), the latest Linac-based SRS platform, has a comprehensive imaging package designed for treatment localization of various disease sites, including CBCT and stereoscopic X-ray imaging with advanced 2D/3D image registration tool. In SRS treatments, image registration of planning CT images and pre-/during-treatment images is crucial to allow precise patient positioning. The CBCT provides 3D volumetric information to better visualize anatomical structures and soft tissue. The CBCT images are registered to the planning CT images using 3D/3D image registration method. However, it takes longer to acquire/reconstruct the images and review the registration results. The 2D/3D image registration utilizes 2 X-ray projection images to register the planning CT images. It can provide fast patient setup based on the bony structures and can monitor patient motions during the treatment by taking snapshot images. Therefore, 3D/3D image registration based on the CBCT is best suited for initial patient localization, whereas 2D/3D image registration based on the X-ray projections is best suited for position verification and motion monitoring. This study is designed to evaluate the localization uncertainty of 2D/3D image registration on the Edge system by comparing 3D/3D image registration in 6 dimensions (6D).

Methods and Materials

Evaluation of 2D/3D Image Registration

A study of CBCT localization accuracy on the Edge showed that the deviation between imaging isocenter and radiation isocenter was 0.2 ± 0.1 mm in terms of mean $\pm$ standard deviation (SD).[22] The daily end-to-end test on the Edge using CBCT localization also showed that the mean and SD of the absolute average deviation and maximum deviation of radiation isocentricity were 0.20 ± 0.03 mm and 0.66 ± 0.18 mm, respectively, which were consistent and within the SRS/stereotactic body radiotherapy (SBRT) tolerance (0.75 mm average and 1.0 mm maximum) recommended by the American Association of Physicists in Medicine Task Group 142 and the American Society for Radiation Oncology quality and safety guidelines.[23-25] Therefore, 3D/3D image registration was used as the gold standard in our study. The residual deviations between 2D/3D and 3D/3D registrations were used to evaluate the localization uncertainty of 2D/3D registration in 6D.

Image Acquisition

The 2D kV image and kV-CBCT were acquired from On-Board Imager (OBI) kV imaging system (Varian Medical Systems), which is gantry mounted. The 2.5-MV portal images were acquired by an electronic portal imaging device.

Phantom Study of 2D/3D Image Registration

Image pair. The first test was designed to evaluate the localization uncertainty of 2D/3D image registration with different orthogonal image pairs. A Rando head phantom (RSD, Long Beach, California) embedded with radiopaque targets (metal ball bearings) was scanned using a CT slice thickness of 0.8 mm. It was positioned on the 6DOF robotic couch with random setup deviations within the range of ± 5 mm in the translational direction and $\pm 2°$ in the rotational direction. Three kinds of orthogonal image pairs (kV–kV, MV–kV, and MV–MV) were acquired at the same gantry angles (0° and 270°). The image pairs were automatically registered with DRRs using 2D/3D image registration. Without applying correction shifts from 2D/3D image registration to the couch, kV-CBCTs of the phantom were acquired for 3D/3D image registration. The residual deviations were calculated by subtracting correction shifts of 3D/3D image registrations from those of 2D/3D image registrations. The entire test was repeated to confirm statistically consistent results.

Computed tomography slice thickness. The purpose of the second test was to statistically evaluate the localization uncertainty of automatic 2D/3D image registration with different CT slice thicknesses (0.8, 1.0, 2.0, and 3.0 mm). The procedure used for this test was similar to that used for the first test. The head phantom was placed on the couch with random setup deviations in 6DOF. Two orthogonal kV images acquired at the gantry angles of 0° and 270° were used for 2D/3D image registration. The correction shifts from 2D/3D image registrations were obtained for each simCT. Corresponding residual deviations were calculated.

Parameter set. The third test was designed to evaluate the impact on the localization uncertainty from different parameters using the automatic 2D/3D image registration tool. Similarly, random deviations were used for the head phantom setup in 6DOF. Orthogonal kV image pairs were acquired. The parameter set of the 2D/3D image registration tool has 3 options for similarity measures (mutual information, cross-correction, and pattern intensity) and 4 image filters options (Laplacian of Gaussian, Gaussian smoothing, content filters, and none). Various options were combined such that there were 12 parameter sets used, in total, for 2D/3D image registration. No parameter was changed in the 3D/3D image registration tool. No manual adjustment was applied in any test. By repeating measurements with different setups, residual deviations were calculated and analyzed for statistical significance.

Couch angle. Because treatment beams are delivered at different couch angles to improve tumor conformality, an evaluation was performed to determine whether automatic 2D/3D image registration is reliable for monitoring intrafractional motion of patient at different couch angles. As the head phantom had a subglobose shape, there was not an appreciable difference in the beam's eye view of simCTs at different couch angles. Consequently, an anthropomorphic pelvic phantom was adopted for evaluation. The pelvic phantom was positioned on the couch with random setup deviations in 6DOF at couch angles of 30°, 45°, and 60° for 2D/3D image registration. The KV-CBCT was acquired at the couch angle of 0° and registered with the simCT using 3D/3D image registration. Measurements of residual deviations were repeated for each couch angle.

Imaging peak kilovoltage (kVp) in the lateral direction. The fifth test was designed to evaluate the impact of imaging kVp in the lateral (LAT) direction on localization uncertainty of automatic 2D/3D image registration. Since attenuation of the photon beam can affect image quality, imaging energy may be increased to improve image quality, particularly for large-body sizes. The appropriate imaging kVp is needed for adequate 2D/3D image registration. Dimensions of the anthropomorphic pelvic phantom are 21 cm in the anterior–posterior (AP) direction and 30 cm in the LAT direction. The AP imaging tube default voltage is 75 kV for imaging pelvis on the Edge system. In the LAT direction, the tube voltage of the OBI was increased from 100 to 125 kV, with 5 kV increments to acquire the LAT image. Automatic 2D/3D image registration was performed with different LAT imaging kVps. Residual deviations were calculated after 3D/3D image registration for the corresponding imaging energies. Measurements were repeated with random phantom setups.

Patient Study of 2D/3D Image Registration

Pretreatment verification shifts from 88 patients were evaluated, including 40 intracranial SRS (61 fractions), 16 spine (22 fractions), 26 lung (88 fractions), and 6 other SBRT (21 fractions). For intracranial SRS, patients were immobilized using the Encompass mask system (QFix Inc, Avondale, Pennsylvania), as shown in Figure 1. Elekta full BlueBAG BodyFIX vacuum cushion (Medical Intelligence, Schwabmünchen, Germany) was used for spine SBRT (Figure 2). The Encompass mask system was also used together with BodyFIX system for immobilization of vertebrae from C1 to T4. Patient immobilization for SBRT of the lung, abdomen, and pelvis was accomplished by the BodyFIX system or full-body Alpha Cradle (Smithers Medical Products Inc, North Canton, Ohio).

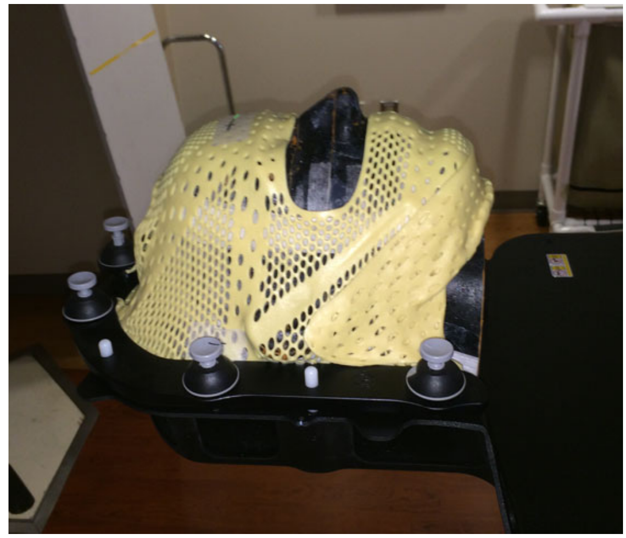

Figure 1. QFix Encompass mask system.

Figure 2. Elekta full BlueBAG BodyFIX vacuum cushion.

For intracranial SRS and spine SBRT in which breathing motion was not a consideration, the process of patient setup was as follows (illustrated in Figure 3): 3D CBCT was acquired, and 3D/3D image registration was used for patient setup and target localization. The patient was aligned based on bony landmarks with the 6DOF robotic couch. Orthogonal MV–kV image pairs were acquired after couch adjustment. The 2D/3D image registration was used for pretreatment verification. The verification shifts met the tolerance criteria: translational deviations were <1 mm and rotational deviations were <1°. This criterion defining the action limits was based on clinical experience. If the shifts from pretreatment verification were <1 mm and 1°, patients were treated based on the 3D/3D

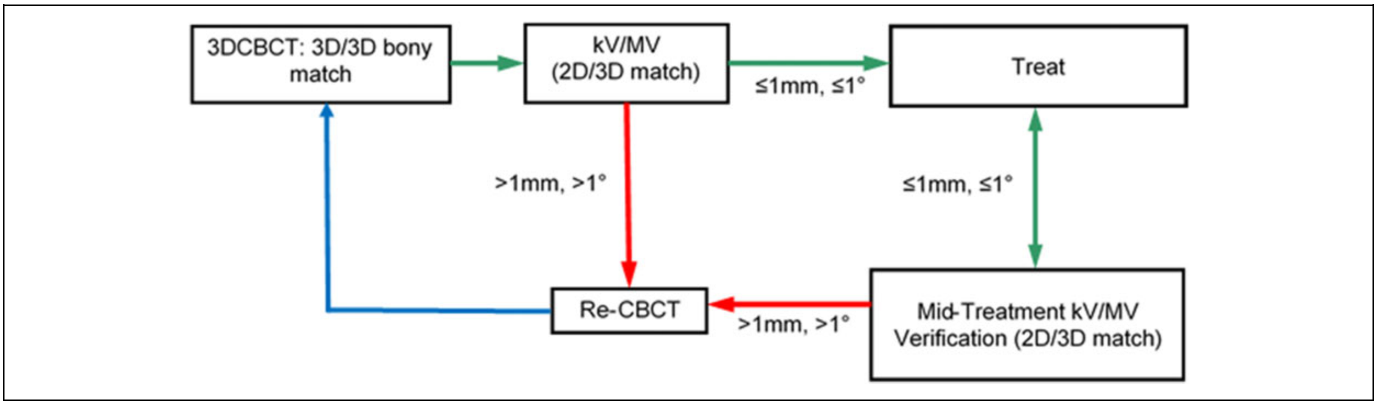

Figure 3. Flowchart for intracranial and spine stereotactic radiosurgery (SRS).

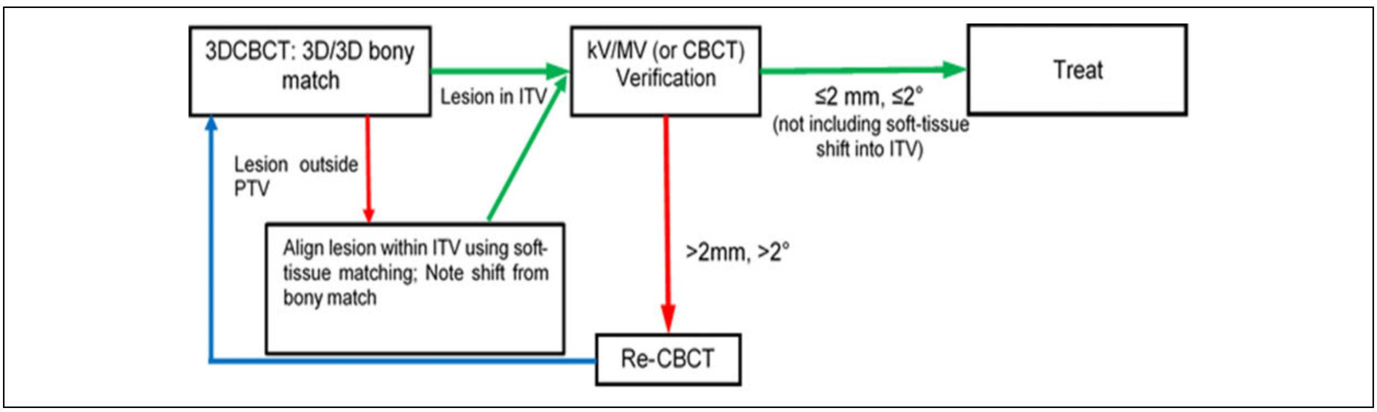

Figure 4. Flowchart for lung and other stereotactic body radiotherapy (SBRT).

image registration results. If the deviation was out of tolerance, patient setup would be repeated and the results reconsidered.

Patient motion management was carefully considered for the lung and abdomen SBRT, and consequently, the patient setup process (Figure 4) was different from that for intracranial SRS and spine SBRT. The treatment process was as follows: 3D CBCT was acquired and matched with simCT using 3D/3D image registration for the patient setup and target localization. The patient was aligned based on bony landmarks with robotic couch adjusted in 6DOF. If the lesion observed in 3D CBCT was within the internal target volume (ITV), orthogonal MV–kV image pairs were acquired for pretreatment verification using 2D/3D image registration. The tolerances for these SBRT verification shifts were 2 mm transitionally and 2° rotationally. If pretreatment verification shifts were within the limits, the treatment continued.

Pretreatment verification shifts determined the residual deviations of target localization between 2D/3D image registration and 3D/3D image registration for corresponding treatment sites. They were analyzed to evaluate the localization uncertainty of 2D/3D image registration.

Statistical Analysis

The 3D/3D image registration was used as the gold standard to evaluate the localization uncertainty of 2D/3D image registration. Measurements were repeated 6 times for each test. Each test was made individually at approximately monthly intervals. All tests were completed within 8 months. An assumption of a normal distribution of the data was made. Random translational and rotational setup deviations were in the range of ±5 mm and ±2°, respectively. The means ± SDs of residual deviations were calculated. Means and standard errors of the means (SEM) are shown in each figure. The means of residual deviations showed the systematic errors of 2D/3D image registration. The mean values being negative or positive did not indicate which kind of registration was superior. Since 3D/3D image registration was used as the gold standard, positive mean values meant that 2D/3D image registration would have a tendency to generate larger correction shifts in the same directions than those from the 3D/3D image registration and vice versa. The SEM represented the reliability of the systematic error measurement. The 95% confidence interval (CI) was also calculated to evaluate the reliability of the systematic error measurement. A paired Student *t* test was used to measure the significance of the difference between 2 image registration algorithms under the same conditions. One-way analysis of variance (one-way ANOVA) was used to compare differences in systematic errors under different conditions. Comparisons with $P < .05$ were considered to reach statistical significance.

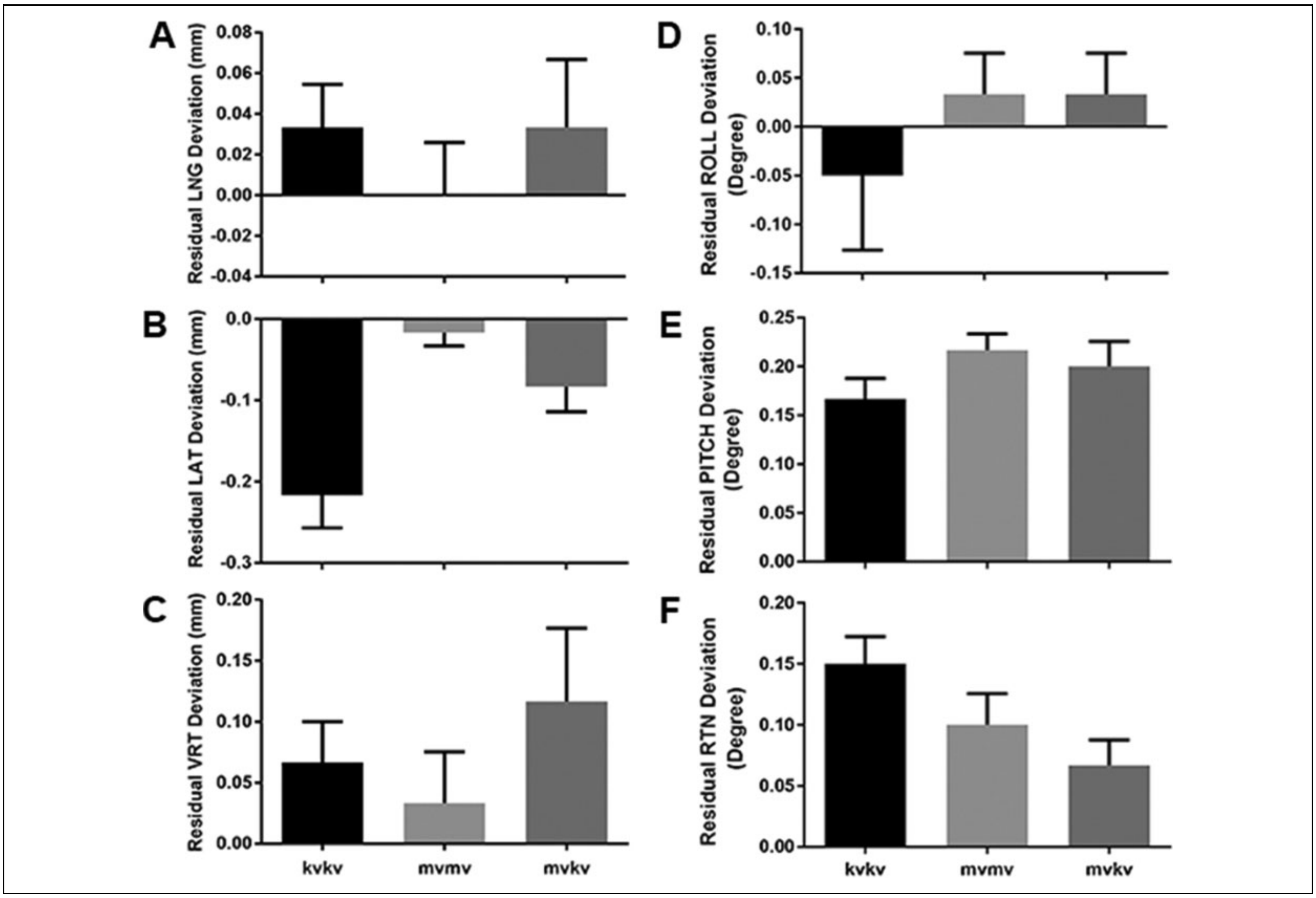

Figure 5. Two-dimensional/3-dimensional (2D/3D) image registration residual deviations versus image pairs. The column represents the mean of residual deviations for each image pair (kV–kV, MV–MV, and MV–kV), and the error bar above the column is standard error of the mean (SEM) in each figure of corresponding direction (A: longitudinal [LNG], B: lateral [LAT], C: vertical [VRT]; D: roll, E: pitch, F: rotation [RTN]).

Results

Phantom Results

Image pairs. Figure 5 shows the residual deviations between 2D/3D image registration and 3D/3D image registration using different orthogonal image pairs. At the 95% CI level, the systematic errors using kV–kV, MV–kV, and MV–MV image pairs were all within 0.3 mm and 0.3°. In longitudinal (LNG), vertical (VRT), and roll directions, the systematic errors were not statistically significant for any image pairs. But in the pitch and RTN (yaw is shown as rotation [RTN] in the Edge system) rotations, systematic errors were statistically significant (pitch: $P_{\text{kV-kV}} = .0005$, $P_{\text{MV-MV}} < .0001$, $P_{\text{MV-kV}} = .0006$ and RTN: $P_{\text{kV-kV}} = .0011$, $P_{\text{MV-MV}} = .0117$, $P_{\text{MV-kV}} = .0250$ by Student *t* test). In the LAT direction, the systematic error using MV–MV image pairs was not statistically significant. But systematic errors from kV–kV and MV–kV image pairs were statistically significant ($P_{\text{kV-kV}} = 0.0029$ and $P_{\text{MV-kV}} = 0.0422$ by Student *t* test).

Computed tomography slice thickness. The systematic errors for using different CT slice thicknesses (0.8, 1.0, 2.0, and 3.0 mm) in 2D/3D image registration are shown in Figure 6. In the LNG direction, the systematic errors were 0.05, 0.08, 0.05, and 0.03 mm, respectively. The systematic errors in the LAT direction were −0.20, −0.08, −0.20, and −0.08 mm, respectively. Vertically, the systematic errors were −0.05, 0.05, 0.00, and 0.05 mm for the corresponding CT slice thicknesses. In the roll direction, the systematic errors were 0.05°, 0.03°, 0.10°, and 0.03°, respectively. In the pitch direction, the systematic errors were 0.2°, 0.2°, 0.3°, and 0.3°, respectively. In the RTN direction, the systematic errors for corresponding CT slice thicknesses were 0.15°, 0.20°, 0.18°, and 0.20°, respectively. These changes were not statistically significant ($P = .6119$, .2115, and .2102 for the LNG, LAT, and VRT directions, respectively; $P = .4004$, .2089, and .7402 for roll, pitch, and RTN rotations, respectively, by one-way ANOVA).

Similarity measure and image filter. The results of applying 3 similarity measures combined with 4 image filters in 2D/3D image registration are shown in Table 1. Residual deviations are shown as means ± SDs. There were some cases that the images were still mismatched after automatic 2D/3D image registration or systematic errors exceeded limits (1 mm and 1°). Those residual deviations are shown as "not working properly."

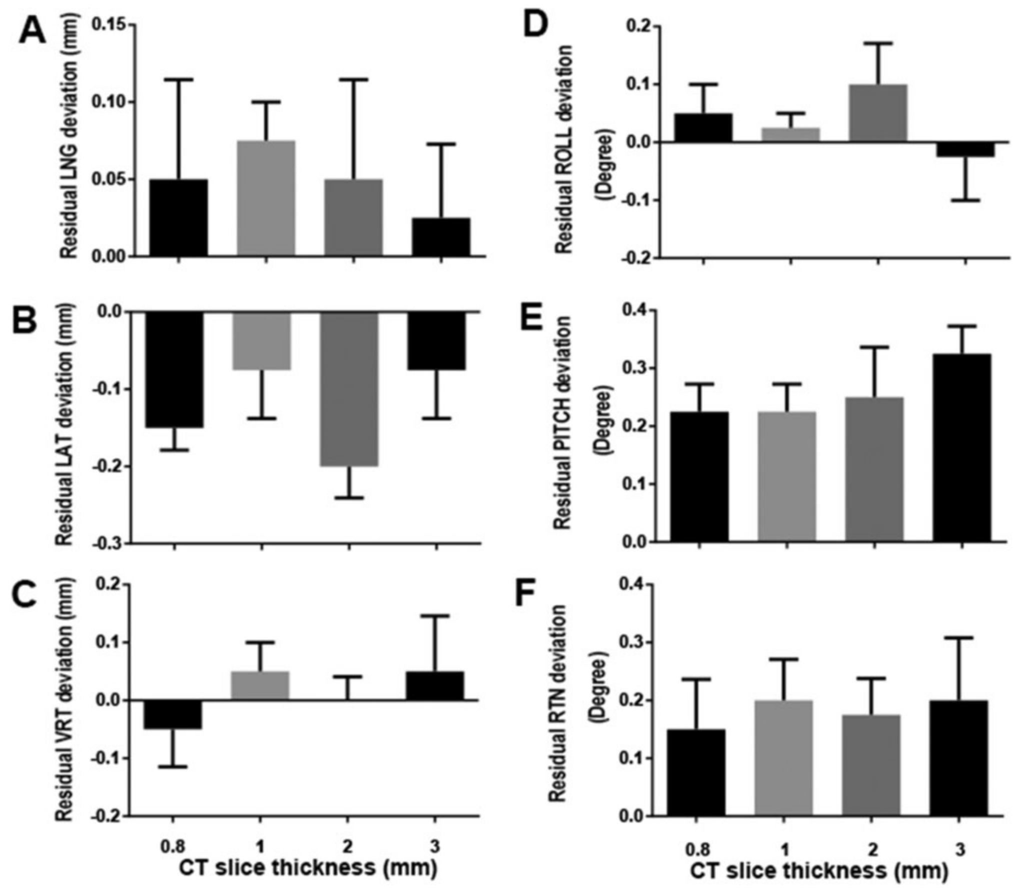

Figure 6. Two-dimensional/3-dimensional (2D/3D) image registration residual deviations versus computed tomography (CT) slice thicknesses. Mean and standard error of the mean (SEM) of residual deviations are shown for corresponding CT slice thickness (0.8, 1, 2, and 3 mm) in each direction (A: longitudinal [LNG], B: lateral [LAT], C: vertical [VRT]; D: roll, E: pitch, F: rotation [RTN]).

Table 1. Residual Deviations of 2D/3D Image Fusion Using Different Similarity Measures (SM) and Image Filters (IF).[a]

		Residual Translations, Mean ± SD, mm			Residual Rotations, Mean ± SD, degree		
SM	IF	LNG	LAT	VRT	Roll	Pitch	RTN
MI	GS	Not working properly					
MI	LG	Not working properly					
MI	CT	0.32 ± 0.36	−0.28 ± 0.21	−0.17 ± 0.6	−0.05 ± 0.43	0.32 ± 0.31	0.00 ± 0.23
MI	W/O	0.57 ± 0.12	−0.35 ± 0.10	−0.62 ± 0.09	−0.27 ± 0.50	0.32 ± 0.12	0.03 ± 0.18
CC	GS	Not working properly					
CC	LG	Not working properly					
CC	CT	Not working properly					
CC	W/O	Not working properly					
PI	GS	Not working properly					
PI	LG	Not working properly					
PI	CT	0.02 ± 0.11	−0.23 ± 0.16	0.18 ± 0.16	−0.12 ± 0.19	0.03 ± 0.15	0.12 ± 0.09
PI	W/O	−0.15 ± 0.19	−0.27 ± 0.12	0.25 ± 0.26	0.03 ± 0.38	−0.07 ± 0.12	−0.08 ± 0.17

Abbreviations: CT, computed tomography; 2D/3D, 2 dimensional/3 dimensional; LAT, lateral; LNG, longitudinal; SD, standard deviation; VRT, vertical.
[a]Similarity measures tested were mutual information (MI), cross-correlation (CC), and pattern intensity (PI). Images were processed with Laplacian of Gaussian filter (LG), Gaussian smoothing filter (GS), content filter (CF), and without filter (W/O). Residual deviations are shown as means ± SDs.

Couch angle. The 2D/3D image registration had different systematic errors at couch angles of 30°, 45°, and 60° (Table 2). But the couch angle did not change the systematic error significantly in any direction ($P = .2066$, .7726, and .8185 for the LNG, LAT, and VRT directions, respectively; $P = .4103$, .1835, and .4226 for roll, pitch, and RTN rotations,

Table 2. Residual Deviations of 2D/3D Image Registration at Different Couch Angles.

	Residual Translations, Mean ± SD, mm			Residual Rotations, Mean ± SD, degree		
Couch Angle, degree	LNG	LAT	VRT	Roll	Pitch	RTN
30	−0.07 ± 0.12	−0.10 ± 0.17	0.20 ± 0.24	0.03 ± 0.12	0.03 ± 0.15	−0.03 ± 0.06
45	−0.03 ± 0.23	0.10 ± 0.26	0.17 ± 0.14	0.10 ± 0.20	−0.10 ± 0.10	0.03 ± 0.06
60	0.30 ± 0.26	0.20 ± 0.36	0.17 ± 0.10	−0.10 ± 0.30	−0.17 ± 0.06	0.07 ± 0.06

Abbreviations: 2D/3D, 2 dimensional/3 dimensional; LAT, lateral; LNG, longitudinal; SD, standard deviation; VRT, vertical.

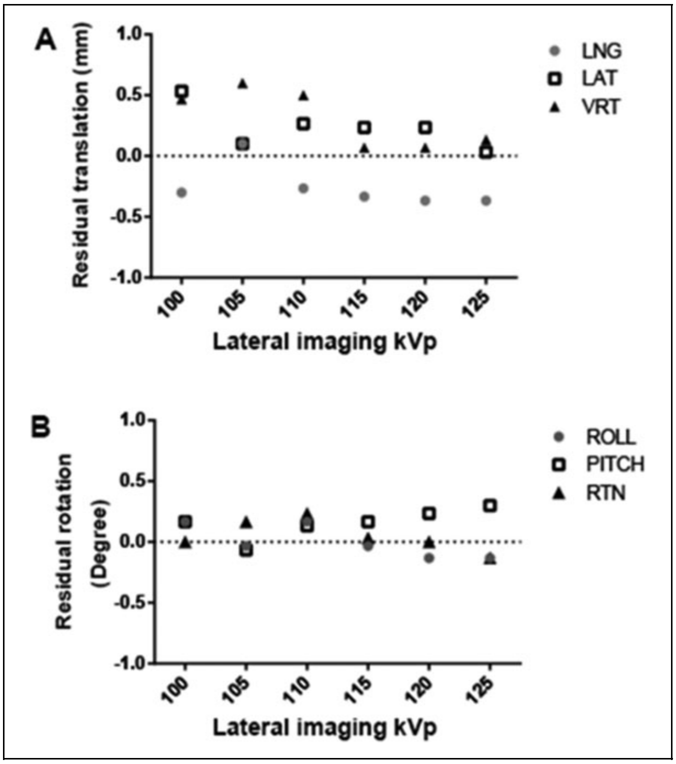

Figure 7. Two-dimensional/3-dimensional (2D/3D) image registration residual deviations versus imaging kVp in the lateral (LAT) direction. Imaging kVps were increased from 100 to 125 kV in the LAT direction. A, Mean of translational residual deviations. B, Mean of rotational residual deviations.

respectively, by one-way ANOVA). Compared to the 3D/3D image registration, systematic error of 2D/3D image registration was significant at the couch angle of 60° in the pitch direction ($P = .0377$ by Student t test).

Imaging kVp in the LAT direction. Figure 7 shows the localization errors of 2D/3D image registration with different LAT imaging kVps for the pelvic phantom. The imaging kVp in the LAT direction did not change the systematic error significantly in 6DOF from 100 to 125 kV ($P = .4314$, .1865, and .0813 for the LNG, LAT, and VRT directions, respectively; $P = .2674$, .5324, and .4645 for the roll, pitch, and RTN rotations, respectively, by one-way ANOVA). The absolute values of the systematic errors in the translational directions were around 0.3 mm and around 0.1° in rotational directions.

Patient data. Figure 8 shows the results of the patient study. The systematic errors only varied significantly for roll rotations ($P = .0454$ by one-way ANOVA). The mean and SEM of verification shifts are summarized in Table 3. For intracranial and extracranial target localization, 2D/3D image registration had comparable systematic errors that were around 0.2 mm in the translational direction and 0.08° in the rotational direction.

Discussion

Jin *et al*[18] indicated that 2D/3D image registration could improve the localization accuracy compared to the 2D/2D image registration, since 2D/3D image registration could correct setup deviations that were correlated with the rotational shifts. From the present head phantom study, the discrepancy between 2D/3D and 3D/3D image registrations using different image pairs was found to be quite small (0.3 mm and 0.3°) for the Edge system. We demonstrated that there was no clinically significant impact of using different image pairs for 2D/3D image registration. Ma *et al*[26] also showed that 2D/3D image registration in the ExacTrac system had 0.3 mm residual translational error and 0.3° residual rotational error in phantom setup. The systematic errors between kV–kV image pairs and MV–MV image pairs were significantly different in the LAT direction ($P = .0066$). The deviation between the LAT correction shifts from kV–kV and MV–MV image pairs was 0.2 ± 0.1 mm (mean ± SD). The MV–MV image pairs resulted in the smallest systematic error of 2D/3D image registration in the LAT direction, which was −0.02 ± 0.08 mm. Pattern intensity was used in the test. Wu *et al*[27] reported that pattern intensity had the best accuracy if using MV images for 2D/3D image registration. From the IsoCal data performed in the past, the offsets between the MV imager center and the treatment isocenter were 0.06 mm in the IsoCal verification, whereas the kV imager offsets were 0.14. The IsoCal software analyzes the offset of the MV/kV imager panels relative to the treatment isocenter at various gantry angles and applies the correction to the imaging panels as a function of gantry angle. Therefore, the 0.2 ± 0.1 mm deviation in the LAT direction is attributable to the IsoCal calibration.

Considering 3D/3D image registration as the gold standard, the systematic errors of 2D/3D image registration were not affected by changes in the CT slice thickness. There would be no difference using simCT with 0.8, 1.0, or 2.0 mm CT slice thickness for 2D/3D or 3D/3D image registration. Fox *et al*[28] also reported no difference between 0.625 and 2 mm CT slice

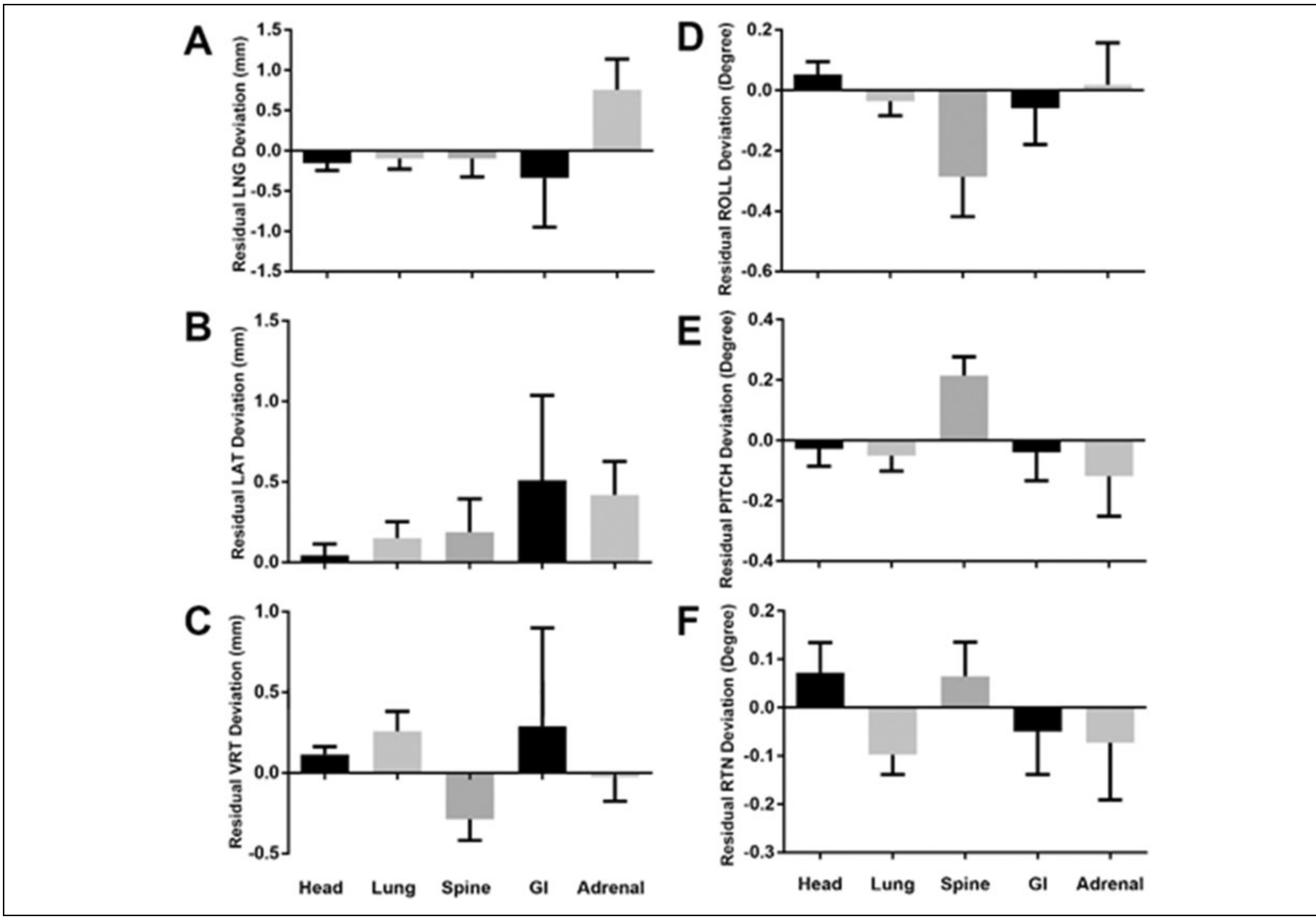

Figure 8. Residual deviations from 2-dimensional/3-dimensional (2D/3D) pretreatment verification versus treatment sites. Mean and standard error of the mean (SEM) of residual deviations are shown for corresponding treatment sites (head, lung, spine, gastrointestinal [GI], and adrenal gland) in each direction (A: longitudinal [LNG], B: lateral [LAT], C: vertical [VRT]; D: roll, E: pitch, F: rotation [RTN]).

Table 3. Patient 2D/3D Residual Deviations for Different Treatment Sites.

		Residual Translations, Mean ± SD, mm			Residual Rotations, Mean ± SD, degree		
Site	Fx	LNG	LAT	VRT	Roll	Pitch	RTN
Intracranial	61	−0.2 ± 0.7	0.04 ± 0.5	0.1 ± 0.4	0.04 ± 0.3	−0.03 ± 0.4	0.07 ± 0.5
Lung	88	−0.1 ± 1	0.2 ± 1	0.3 ± 1	−0.04 ± 0.5	−0.05 ± 0.5	−0.1 ± 0.4
Spine	22	0.1 ± 1	0.2 ± 1	−0.3 ± 0.6	−0.3 ± 0.6	0.2 ± 0.3	0.06 ± 0.3
GI	10	−0.3 ± 2	0.5 ± 2	0.3 ± 2	−0.06 ± 0.4	−0.04 ± 0.3	−0.05 ± 0.3
Adrenal	11	0.8 ± 1	0.4 ± 0.7	−0.03 ± 0.5	0.02 ± 0.5	−0.1 ± 0.4	−0.07 ± 0.4
Extracranial	131	−0.04 ± 1	0.2 ± 1	0.1 ± 1	0.08 ± 0.5	−0.05 ± 0.5	−0.06 ± 0.4

Abbreviations: 2D/3D, 2 dimensional/3 dimensional; GI, gastrointestinal; LAT, lateral; LNG, longitudinal; SD, standard deviation; VRT, vertical.

thicknesses for positioning accuracy. But in the LNG direction, a 0.5-mm deviation was found in the correction shift between 1 and 3 mm CT slice thicknesses from 2D/3D image registration. From 3D/3D image registration with 1 and 3 mm CT slice thicknesses, the correction shift deviation was 0.6 mm. The impact of 3 mm CT slice thickness on image registration in the LNG direction was significant ($P < .05$). For a CT slice thickness of 3 mm, Murphy[29] reported poor accuracy of the head localization and also found that the accuracy was improved by a factor of 2 using 1 mm CT slice thickness. The 0.5-mm deviation could be a result of image blurring, which brought geometrical uncertainties in the image registration. Although slabs of the head phantom were tightly assembled, there were still air gaps between slabs paralleled along the LNG direction in the simCT. These gaps had sharp local intensity gradients. The image pixels on the interfaces between different materials in the phantom were more blurred in the simCT with 3 mm CT slice thickness. Uncertainties of bony structure boundaries in the simCT could provide less accurate information in the DRRs for image registration at lower CT resolution. The uncertainty of determining the metal ball bearing center in the simCT with 3-mm-slice thickness could also result in 0.4 mm LNG error as reported by Jin *et al*.[30]

Twelve parameter sets were tested to evaluate the automatic 2D/3D image registration. Each parameter set had 2 steps. The image filter was applied only in the first step to reduce the time of the optimization process. Table 1 shows that only 4 parameter sets were robust. Without image filters, cross-correlation was less accurate than the mutual information or the pattern intensity. However, Wu *et al*[27] and Penney *et al*[11] showed better accuracy of localization with cross-correlation. Since the cross-correlation is sensitive to the noise and large variation in intensities, it may not always work properly. A large data set of clinical images may be further tested to evaluate the overall performance of the cross-correlation. With Laplacian of Gaussian filter or Gaussian smoothing filter, none of the parameter sets functioned properly. The background or some features of the original image were altered with the implementation of image filters. When using intensity-based similarity measures such as mutual information and cross-correlation for image registration, the pixel intensity change could result in undesirable matches. Gaussian smoothing filter or Laplacian of Gaussian filter had the potential to change intensity values in an image. These filters could induce errors in the image registration as assessed by intensity-based similarity measures. Among the tested similarity measures, only pattern intensity takes spatial information into consideration. Since the neighborhood information is involved, the effect of intensity variation outside the neighborhood is reduced. Soft tissues have lower spatial frequencies in the image than those of bones. With similarity measures of pattern intensity, soft tissue information can be filtered out by a proper sensitivity value and then bony structures are used for the registration. The parameter set of the 2D/3D image registration using pattern intensity and content filter achieved the best accuracy in the phantom study. This parameter set is recommended for clinical use of 2D/3D image registration. The phantom study indicates that with the parameter set recommended above, planar kV images from the OBI kV imaging system have good image quality for robust image registration. Neither the Laplacian of Gaussian filter nor the Gaussian smoothing filter was needed for the 2D/3D image registration using OBI.

The systematic error of the 2D/3D image registration varied slightly with couch angles. Although the systematic error in the pitch direction was significant at the couch angle of 60°, the 95% CI was smaller than 0.3°. In other directions, the systematic errors were close to 0 and negligible. When the couch rotated, the simCT also rotated with the same angle in the software. Corresponding DRRs were then generated with the same couch angle. The 3D/3D image registration was used as the gold standard to evaluate 2D/3D image registration without couch kick. The deviations from the 2D/3D image registration included the registration errors and the isocentric uncertainty due to the couch rotation. End-to-end tests were used to evaluate the coincidence of the gantry, collimator, and couch axes with the radiation isocenter. The radiation isocenter accuracy at a combination of gantry, collimator, and couch angles was 0.34 ± 0.18 mm. The couch rotation offset was 0.17 mm.[23] The change in systematic error at different couch angles could also come from regions of interest (ROIs) used in 2D/3D image registration. Considering that the pelvic phantom was simple and rigid, different ROIs in the phantom did not change systematic error significantly. The systematic error was very small and not clinically significant at each couch angle. Consequently, the results indicate that the 2D/3D image registration is reliable for verification at different couch angles.

Imaging energy may be increased to get better image quality for larger size patients. In the pelvis imaging setting, the default energy in the LAT direction is 100 kVp for small patients and 120 kVp for extra-large patients. So, to evaluate the impact of energy change on image quality, the range in imaging energy chosen was from 100 to 125 kVp, with an increment of 5 kVp. The performance of the 2D/3D image registration was consistent when the imaging energy of the OBI was increased for the LAT image acquisition. Imaging kVp did not change the systematic error significantly in either the translational or the rotational directions. Considering displacements of the 3D vectors from the residual deviations, the means of displacements were 0.9, 0.6, 0.6, 0.5, 0.5, and 0.4 mm at corresponding kVps from 100 to 125 kV with 5 kV increment. At 125 kV, which was also used for CBCT, the mean of displacement was the smallest (0.4 mm). However, the mean of displacement did not vary significantly with kVps ($P = .231$ by one-way ANOVA). From the test results, the systematic errors did not show significant variation in the rotational directions ($P > .05$ by one-way ANOVA). So, the 2D/3D image registration was robust within the range of imaging energy tested.

In the phantom study, the systematic errors of the 2D/3D image registration could be statistically significant but were not clinically significant since the deviation was submillimeter. In the patient study, 2D/3D pretreatment verification shifts of intracranial sites showed minimal residual deviations. This was mainly due to the strict immobilization of patient head with the mask system and bony landmarks inside the head. The residual deviations observed from the intracranial sites were comparable to those from the head phantom study. The residual deviations between the intracranial and extracranial sites were also comparable. For lung patients, motion encompass method was applied to manage breathing motion. Four-dimensional (4D) CT was used to scan patients in the simulation, and ITV was created to cover all possible tumor motions induced by breathing. Therefore, verification shifts in the translational directions were small. The verification shifts for gastrointestinal (GI; pancreas) had the largest random errors in the translational directions. Since breathing artifacts degrade image quality, they could induce errors in the image registration of GI. Additionally, GI motility such as peristalsis could not be captured in the 4D CT images. These errors were random and could lead to potentially large deviations. Systematic errors of 2D/3D image registration for intracranial and extracranial sites were <1 mm in the translational directions and <1° in the rotational directions. This may indicate that for target localization, 2D/3D image registration could perform as well as 3D/3D image registration does. For radiosurgery with the Edge system, MV–kV image pairs were usually used for patient setup verification. However, MV image is known to have relatively poor contrast resolution.[31] Pisani *et al* also concluded that kV image-based correction was qualitatively more effective than MV image-based correction.[32] The Edge system uses 2.5 MV portal imaging instead of 6 MV portal imaging. The 2.5 MV portal imaging has advantages in terms of high- and low-contrast resolutions and contrast-to-noise ratio. Due to the fact that 2.5 MV photon beam has higher photoelectric effect than 6 MV photon beam, 2.5 MV portal imaging has better bone–soft tissue contrast and improved image registration. Based on the results presented, the 2D/3D image registration with kV images can achieve the same level of localization accuracy of the CBCT-based registration for bony structure alignment. The 2D/3D image registration using only kV images could have comparable accuracy as 3D/3D image registration. However, the image quality of kV planar imaging degraded sharply for large patient. The 2.5 MV portal imaging would be recommended for target localization and setup verification with the 2D/3D image registration when the patient has a large body size.

Conclusion

The Edge system offers a 2D/3D image registration tool with high robustness and accuracy for target localization using different imaging modalities, CT slice thicknesses, and couch angles. Pattern intensity and content filter are recommended for the use of this 2D/3D image registration tool. The 2D/3D image registration is reliable for setup verification in SRS and SBRT when the bony landmarks are used for alignment.

Declaration of Conflicting Interests

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References

1. Dawson LA, Jaffray DA. Advances in image-guided radiation therapy. *J Clin Oncol*. 2007;25(8):938-946.
2. Gierga DP, Chen GT, Kung JH, Betke M, Lombardi J, Willett CG. Quantification of respiration-induced abdominal tumor motion and its impact on IMRT dose distributions. *Int J Radiat Oncol Biol Phys*. 2004;58(5):1584-1595.
3. Yaniv Z, Cleary K. *Image-Guided Procedures: A Review. Technical Report*. Washington, DC: Computer Aided Interventions and Medical Robotics, Imaging Science and Information Systems Center; 2006.
4. Bansal R, Staib LH, Chen Z, et al. A novel approach for the registration of 2D portal and 3D CT images for treatment setup verification in radiotherapy. In: Wells WM, Colchester A, Delp S, eds. *Medical Image Computing and Computer-Assisted Intervention—MICCAI'98*. Connecticut, USA: Springer; 1998: 1075-1086.
5. Meyer J, Wilbert J, Baier K, et al. Positioning accuracy of cone-beam computed tomography in combination with a HexaPOD robot treatment table. *Int J Radiat Oncol Biol Phys*. 2007; 67(4):1220-1228.
6. Guckenberger M, Meyer J, Wilbert J, Baier K, Sauer O, Flentje M. Precision of image-guided radiotherapy (IGRT) in six degrees of freedom and limitations in clinical practice. *Strahlenther Onkol*. 2007;183(6):307-313.
7. Jin J-Y, Ryu S, Rock J, et al. Evaluation of residual patient position variation for spinal radiosurgery using the Novalis image guided system. *Med Phys*. 2008;35(3):1087-1093.
8. Ho AK, Fu D, Cotrutz C, et al. A study of the accuracy of cyberknife spinal radiosurgery using skeletal structure tracking. *Neurosurgery*. 2007;60(2 suppl 1):ONS147-ONS156.
9. Lemieux L, Jagoe R, Fish D, Kitchen N, Thomas D. A patient-to-computed-tomography image registration method based on digitally reconstructed radiographs. *Med Phys*. 1994;21(11): 1749-1760.
10. Maes F, Collignon A, Vandermeulen D, Marchal G, Suetens P. Multimodality image registration by maximization of mutual information. *IEEE Trans Med Imaging*. 1997;16(2):187-198.
11. Penney GP, Weese J, Little J, Desmedt P, Hill DL, Hawkes DJ. A comparison of similarity measures for use in 2-D-3-D medical image registration. *IEEE Trans Med Imaging*. 1998;17(4):586-595.
12. Pluim JP, Maintz JA, Viergever M. Mutual-information-based registration of medical images: a survey. *IEEE Trans Med Imaging*. 2003;22(8):986-1004.
13. Hipwell JH, Penney GP, Cox TC, Byrne JV, Hawkes DJ. 2D-3D intensity based registration of DSA and MRA—a comparison of similarity measures. In: Dohi T, Kikinis R, eds. *Medical Image Computing and Computer-Assisted Intervention—MICCAI 2002*. London, UK: Springer; 2002:501-508.
14. Markelj P, Tomazevic D, Likar B, Pernus F. A review of 3D/2D registration methods for image-guided interventions. *Med Image Anal*. 2012;16(3):642-661.
15. Kim J, Jin J-Y, Walls N, et al. Image-guided localization accuracy of stereoscopic planar and volumetric imaging methods for stereotactic radiation surgery and stereotactic body radiation therapy: a phantom study. *Int J Radiat Oncol Biol Phys*. 2011;79(5): 1588-1596.
16. Takakura T, Mizowaki T, Nakata M, et al. The geometric accuracy of frameless stereotactic radiosurgery using a 6D robotic couch system. *Phys Med Biol*. 2010;55(1):1-10.
17. Wurm R, Gum F, Erbel S, et al. Image guided respiratory gated hypofractionated stereotactic body radiation therapy (H-SBRT) for liver and lung tumors: initial experience. *Acta Oncol*. 2006; 45(7):881-889.
18. Jin JY, Yin FF, Tenn SE, Medin PM, Solberg TD. Use of the BrainLAB Exac Trac X-Ray 6D system in image-guided radiotherapy. *Med Dosim*. 2008;33(2):124-134.

19. Verbakel WF, Lagerwaard FJ, Verduin AJ, Heukelom S, Slotman BJ, Cuijpers JP. The accuracy of frameless stereotactic intracranial radiosurgery. *Radiother Oncol*. 2010;97(3):390-394.
20. Kim J, Wen N, Jin J-Y, et al. Clinical commissioning and use of the Novalis Tx linear accelerator for SRS and SBRT. *J Appl Clin Med Phys*. 2012;13(3):3729.
21. Li G, Yang TJ, Furtado H, et al. Clinical assessment of 2D/3D registration accuracy in 4 major anatomic sites using on-board 2D kilovoltage images for 6D patient setup. *Technol Cancer Res Treat*. 2015;14(3):305-314.
22. Huang Y, Zhao B, Chetty IJ, Brown S, Gordon J, Wen N. Targeting accuracy of image-guided radiosurgery for intracranial lesions: a comparison across multiple linear accelerator platforms. *Technol Cancer Res Treat*. 2015;15(2):243-248.
23. Wen N, Li H, Song K, et al. Characteristics of a novel treatment system for linear accelerator-based stereotactic radiosurgery. *J Appl Clin Med Phys*. 2015;16(4):5313.
24. Klein EE, Hanley J, Bayouth J, et al; Task Group 142, American Association of Physicists in Medicine. Task Group 142 report: quality assurance of medical accelerators. *Med Phys*. 2009;36(9):4197-4212.
25. Solberg TD, Balter JM, Benedict SH, et al. Quality and safety considerations in stereotactic radiosurgery and stereotactic body radiation therapy: executive summary. *Pract Radiat Oncol*. 2012;2(1):2-9.
26. Ma J, Chang Z, Wang Z, Jackie Wu Q, Kirkpatrick JP, Yin FF. ExacTrac X-ray 6 degree-of-freedom image-guidance for intracranial non-invasive stereotactic radiotherapy: comparison with kilovoltage cone-beam CT. *Radiother Oncol*. 2009;93(3):602-608.
27. Wu J, Kim M, Peters J, Chung H, Samant SS. Evaluation of similarity measures for use in the intensity-based rigid 2D-3D registration for patient positioning in radiotherapy. *Med Phys*. 2009;36(12):5391-5403.
28. Fox TH, Huntzinger C, Johnstone PA, Ogunleye T, Elder ES. Performance evaluation of an automated image registration algorithm using an integrated kV imaging and guidance system. *J Appl Clin Med Phys*. 2006;7(1):97-104.
29. Murphy MJ. The importance of computed tomography slice thickness in radiographic patient positioning for radiosurgery. *Med Phys*. 1999;26(2):171-175.
30. Jin J-Y, Ryu S, Faber K, et al. 2D/3D image fusion for accurate target localization and evaluation of a mask based stereotactic system in fractionated stereotactic radiotherapy of cranial lesions. *Med Phys*. 2006;33(12):4557-4566.
31. Zhang L, Garden AS, Lo J, et al. Multiple regions-of-interest analysis of setup uncertainties for head-and-neck cancer radiotherapy. *Int J Radiat Oncol Biol Phys*. 2006;64(5):1559-1569.
32. Pisani L, Lockman D, Jaffray D, Yan D, Martinez A, Wong J. Setup error in radiotherapy: on-line correction using electronic kilovoltage and megavoltage radiographs. *Int J Radiat Oncol Biol Phys*. 2000;47(3):825-839.