Published in final edited form as:

Technol Cancer Res Treat. 2015 June ; 14(3): 305–314. doi:10.1177/1533034614547454.

Clinical Assessment of 2D/3D Registration Accuracy in 4 Major Anatomic Sites Using On-Board 2D Kilovoltage Images for 6D Patient Setup

Guang Li, PhD¹, T. Jonathan Yang, MD², Hugo Furtado, PhD^{3,4}, Wolfgang Birkfellner, PhD^{3,4}, Åse Ballangrud, PhD¹, Simon N. Powell, MD, PhD², and James Mechalakos, PhD¹

¹ Department of Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

² Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

³ Center of Medical Physics and Biomedical Engineering, Medical University Vienna, Wien, Austria

⁴ Christian Doppler Laboratory for Medical Radiation Research for Radiation Oncology, Medical University Vienna, Wien, Austria

Abstract

To provide a comprehensive assessment of patient setup accuracy in 6 degrees of freedom (DOFs) using 2-dimensional/3-dimensional (2D/3D) image registration with on-board 2-dimensional kilovoltage (OB-2DkV) radiographic images, we evaluated cranial, head and neck (HN), and thoracic and abdominal sites under clinical conditions. A fast 2D/3D image registration method using graphics processing unit GPU was modified for registration between OB-2DkV and 3D simulation computed tomography (simCT) images, with 3D/3D registration as the gold standard for 6DOF alignment. In 2D/3D registration, body roll rotation was obtained solely by matching orthogonal OB-2DkV images with a series of digitally reconstructed radiographs (DRRs) from simCT with a small rotational increment along the gantry rotation axis. The window/level adjustments for optimal visualization of the bone in OB-2DkV and DRRs were performed prior to registration. Ideal patient alignment at the isocenter was calculated and used as an initial registration position. In 3D/3D registration, cone-beam CT (CBCT) was aligned to simCT on bony structures using a bone density filter in 6DOF. Included in this retrospective study were 37 patients treated in 55 fractions with frameless stereotactic radiosurgery or stereotactic body radiotherapy for cranial and paraspinal cancer. A cranial phantom was used to serve as a control. In all cases, CBCT images were acquired for patient setup with subsequent OB-2DkV verification. It was found that the accuracy of the 2D/3D registration was 0.0 ± 0.5 mm and $0.1^\circ \pm 0.4^\circ$ in phantom. In patient, it is site dependent due to deformation of the anatomy: 0.2 ± 1.6 mm and

Reprints and permission: sagepub.com/journalsPermissions.nav

Corresponding Author: Guang Li, PhD, DABR, Department of Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA. lig2@mskcc.org.

Authors' Note

T. Jonathan Yang is the cofirst author.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

$-0.4^{\circ} \pm 1.2^{\circ}$ on average for each dimension for the cranial site, 0.7 ± 1.6 mm and $0.3^{\circ} \pm 1.3^{\circ}$ for HN, 0.7 ± 2.0 mm and $-0.7^{\circ} \pm 1.1^{\circ}$ for the thorax, and 1.1 ± 2.6 mm and $-0.5^{\circ} \pm 1.9^{\circ}$ for the abdomen. Anatomical deformation and presence of soft tissue in 2D/3D registration affect the consistency with 3D/3D registration in 6DOF: the discrepancy increases in superior to inferior direction.

Keywords

image registration; rotational correction; patient setup; image-guided radiotherapy

Introduction

Image-guided radiotherapy has substantially improved the accuracy of patient setup, resulting in greater confidence in tumor dose coverage and in many instances, reducing the treatment margin and sparing more normal tissue.^{1,2} In-room 2-dimensional kilovoltage (2DkV) imaging systems, which provide high-contrast images of bony structures, implanted fiducials, and even soft tissues, are essential for localizing and positioning an internal target. A gantry-mounted kV system, such as Varian On-board Imager (Varian Medical Systems, Palo Alto, California) and the Elekta Synergy system (Elekta Inc, Stockholm, Sweden), provides orthogonal on-board 2DkV (OB-2DkV) images and/or half/full rotational scan around the linac isocenter for cone-beam computed tomography (CBCT) images.^{3,4} The 3-dimensional (3D)/3D registration between CBCT and simulation CT (simCT) images yields 6 degrees of freedom (DOFs), while the 2-dimensional (2D)/2D registration between orthogonal OB-2DkV image pair and digitally reconstructed radiograph (DRR) images can produce 5DOF, including 2 in-plane rotations (Yaw and Pitch), leaving roll rotation undetected. In conventional-fractionation radiotherapy, translational alignment is of primary importance, whereas residual rotations are often uncorrected. In frameless stereotactic radiosurgery (fSRS) or stereotactic body radiotherapy (SBRT), however, correction of residual rotation becomes more important, as it can improve treatment accuracy, especially for targets with asymmetric shape and next to a critical structure.

Full 6DOF can be obtained from orthogonal 2DkV images using 2D/3D image registration and has been used by Cyber-Knife (Accuray Inc, Sunnyvale, California) and ExacTrac (BrainLab, AG Feldkirchen, Germany) to correct body rotation using a 6-dimensional (6D) couch.⁵⁻⁹ These room-mounted imaging systems produce orthogonal, oblique 2DkV images, and 3 rotational alignments can be achieved by matching the 2DkV with a variety of DRRs generated with small rotation intervals. In rigid anatomy, the accuracy of 2D/3D registration in 6DOF has improved from 1.5 to 0.75 mm, approaching the accuracy of 3D/3D registration.^{3,9-13} However, these 2D/3D registration programs can only handle system-specific 2DkV images acquired from their own systems. Neither of the 2 systems can perform registration using OB-2DkV images.

Recently, the 2D/3D image registration method has been reported for an isocentric linac system and was validated using artificial and animal phantoms.¹⁴⁻¹⁶ A registration accuracy of 1.0 mm was achieved based on fiducial registration error (FRE)¹⁴ and performance was

enhanced using a graphics processing unit (GPU).¹⁷ In this article, we assess the accuracy of 2D/3D registration in 6DOF using OB-2DkV in 4 anatomical sites under clinical conditions. Thirty-seven patients treated in single- or hypofraction SRS or SBRT were studied. The CBCT was acquired for patient setup and OB-2DkV images were acquired for setup verification after CBCT shift. A head phantom experiment was conducted to evaluate the intrinsic registration accuracy as a control. The registration of CBCT/simCT was used as the gold standard to evaluate 2D/3D registration in 6DOF using OB-2DkV at 4 sites in the body, including the brain, head and neck (HN; clavicle [C-]spine), thorax (thoracic [T-]spine), and abdomen/pelvis (lumbar [L-]spine).

Materials and Methods

Patient and Phantom Image Acquisition and 2D/3D Registration

Two patient data sets were used: orthogonal OB-2DkV images and CBCT images. Between the orthogonal OB-2DkV imaging (brief as 2DkV afterward), there was 15 to 20 seconds time interval to rotate the gantry by 90°. Between CBCT for setup shift and 2DkV for setup verification, the time interval was within 5 to 10 minutes, including image acquisition, manual registration, and setup approval. Frameless stereotactic immobilization devices, which restrict motion within 1.0 mm,^{18,19} were used for all patients who were treated with fSRS or SBRT.

The treatment sites included cranial (brain) and paraspinal (C-spine, T-spine, and L-spine) regions, covering the entire axial skeleton. Bony landmarks were used for alignment. The image data sets of 37 patients (55 fractions) were studied, including 17 cranial patients (19 fractions), 7 C-spine (10 fractions), 5 T-spine (11 fractions), and 8 L-spine (15 fractions). A head phantom was also studied. Full-fan CBCT was usually acquired with 2-mm slice thickness, although half-fan CBCT was also used for thoracic and abdominal sites. The orthogonal 2DkV images were acquired at different combinations of gantry angles: 22 (270° and 0°), 5 (0° and 90°), 12 (315° and 45°), and 16 (135° and 225°). The CBCT/simCT (3D/3D) registration was used as the gold standard to evaluate 2DkV/DRR (2D/3D) registration.

The 2D/3D registration program was written in C++ (GCC 4.6) with GPU (NVIDIA CUDA toolkit v4.0 under Ubuntu 12.04, a LINUX operating system) parallel processing. A laptop computer (Intel i7 CPU—Q720 at 1.6 GHz, 8 GB RAM, in 64bit Windows 7 with NVIDIA Quadro FX 880M) was used for the 2D/3D registration. The normalized mutual information was applied as the metric with 16 bins for the joint histogram, and Powell newoua derivative-free algorithm (InitRhoStart = 2 for controlling initial step size) was used as the optimizer with 2000 maximum iterations and a 1×10^{-6} function tolerance as stop criteria. Multi-resolution approach was applied. The window/level (W/L) setting is image specific, aiming for optimal view of the bones.

Coordinate System for 2D/3D Image Registration

The OB-2DkV imaging (camera) coordinate system (CS) was set differently from the megavoltage treatment beam (room) CS.¹⁴ The origin of the 2DkV CS was set at the center

of the 2D imager, which was 500 mm away from the machine isocenter. The position of the x-ray imaging source was set 1000 mm from the treatment isocenter and 1500 mm from the imager panel in the direction of the foot (Figure 1). The 2 orthogonal imaging positions were 90° apart clockwise. In brief, the relationship between a 3D point $\mathbf{w}$ of the volume in the room CS and its projected 2D point $\mathbf{n}$ in the 2DkV image CS can be described as:

$$\mathbf{n} = \mathbf{P}_{camera}^{image} \mathbf{T}_{room}^{camera} \mathbf{w} \quad (1)$$

where $\mathbf{P}_{camera}^{image}$ is a perspective projection matrix and $\mathbf{T}_{room}^{camera}$ is a rigid transformation matrix from the CS of the room to the image. These 2 matrices are expressed as:

$$\mathbf{P}_{camera}^{image} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & -1/f & 1 \end{bmatrix} \quad (2)$$

where f (=1500 mm) is defined as the distance between the x-ray source and imager plane.

$$\mathbf{T}_{room}^{camera} = \begin{bmatrix} C_\beta C_\gamma & C_\gamma S_\beta S_\alpha - S_\gamma C_\alpha & C_\gamma S_\beta C_\alpha + S_\gamma S_\alpha & t_x \\ C_\beta S_\gamma & S_\gamma S_\beta S_\alpha + C_\gamma C_\alpha & S_\gamma S_\beta C_\alpha - C_\gamma S_\alpha & t_y \\ -S_\beta & C_\beta S_\alpha & C_\beta C_\alpha & t_z \\ 0 & 0 & 0 & 1 \end{bmatrix} \quad (3)$$

where C and S denote cosine and sine functions, respectively, and α , β , and γ are the Euler angles of the Cartesian axes in the x, y, and z directions, respectively; t_x , t_y , and t_z are the elements of translational vector: $\mathbf{T} = (t_x, t_y, t_z)^T$. The rotation matrix $\mathbf{R}$ is the first 3 rows and columns:

$$\mathbf{R} = \mathbf{R}_z \mathbf{R}_y \mathbf{R}_x \quad (4)$$

where $\mathbf{R}_z$, $\mathbf{R}_y$, and $\mathbf{R}_x$ are the 3×3 rotation matrices for rotation around the z-, y-, and x-axes.

Initial Guess for Automatic 2D/3D Image Registration

The ideal alignment position was used as the initial guess for 2D/3D registration by aligning the planning isocenter in simCT (a point within the image volume) with the machine isocenter for 2D (at the center of the image plane) and 3D (at the center of the image volume) on-board imaging. In simCT images, the isocenter coordinate relative to the center (x_{ctr} , y_{ctr} , and z_{ctr}) of the image volume, or field of view (FOV), was calculated based on Digital Imaging and COmmunication in Medicine (DICOM) information, including the image position (x_0 , y_0 , z_0), pixel size (a , b), slice thickness (c), image size ($512 \times 512 \times N$; N = number of slices), and the isocenter coordinate (x_{iso} , y_{iso} , and z_{iso}). So the new coordinate of the isocenter (x'_{iso} , y'_{iso} , and z'_{iso}) relative to the center of the FOV represented the ideal translational alignment:

$$\begin{bmatrix} x'_{iso} \\ y'_{iso} \\ z'_{iso} \\ 1 \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 & x_{iso} - x_{ctr} \\ 0 & 1 & 0 & y_{iso} - y_{ctr} \\ 0 & 0 & 1 & z_{iso} - z_{ctr} \\ 0 & 0 & 0 & 1 \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 & x_{iso} - (x_0 + 512 \times a/2) \\ 0 & 1 & 0 & y_{iso} - (y_0 + 512 \times b/2) \\ 0 & 0 & 1 & z_{iso} - (z_0 + N \times c/2) \\ 0 & 0 & 0 & 1 \end{bmatrix} \quad (5)$$

The initial rotations of the 2DkV images were set as shown in Figure 1. Nonideal initial guesses with $\sim \pm 5$ mm away from the ideal alignment position were tested in the phantom case.

Image Preprocessing and Post-registration Verification

An in-house MatLab program was developed to process 2DkV before 2D/3D registration (1) adjusting the W/L to optimally visualize bony structures in both 2DkV images and DRRs and the new pixel grayscale was saved for registration and (2) drawing masks for 2DkV images and DRRs to exclude moving anatomy and foreign objects from the registration. For instances, the arm and diaphragm were excluded from the region of interest (ROI). After registration was completed, it was checked using chessboard (multi-split windows) visualization.

The FOV of the simCT images was cropped to eliminate peripheral air voxels and the grayscale was rescaled to 0 to 255 using ANALYZE (AnalyzeDirect, Inc, Overland Park, Kansas). The center of the FOV of the simCT images was preserved, and the final voxel size, using tri-linear interpolation, was $1.0 \times 1.0 \times 1.0 \text{ mm}^3$.

Rotational Conversion From Imaging System to Couch System

The rotation results from 2D/3D registration refer to the OB imager CS, which was converted to couch CS to determine patient shifts in 6DOF. Four imaging positions (Figure 1) were used, including anterior-posterior (AP, $Y = 0^\circ$), right lateral (RL, $Y = 90^\circ$), right anterior oblique (RAO, $Y = 45^\circ$), and left posterior oblique (LPO, $Y = -135^\circ$). The rotation matrix ($\mathbf{R}'$) in the couch CS was calculated based on the rotation of the gantry CS ($\mathbf{R}$) along the Y-axis (longitudinally):

$$\mathbf{R}' = \mathbf{R}'_z(\phi) \mathbf{R}'_y(\theta) \mathbf{R}'_x(\psi) = \mathbf{R} \cdot \begin{bmatrix} \cos Y & 0 & \sin Y \\ 0 & 1 & 0 \\ -\sin Y & 0 & \cos Y \end{bmatrix} \quad (6)$$

$$\begin{bmatrix} a' \\ b' \\ c' \end{bmatrix} = \begin{bmatrix} \cos Y & 0 & \sin Y \\ 0 & 1 & 0 \\ -\sin Y & 0 & \cos Y \end{bmatrix} \begin{bmatrix} a \\ b \\ c \end{bmatrix} \quad (7)$$

where $\mathbf{R}$ is defined in Equation 4, the Euler angles (ϕ , θ , and ψ) are defined in the $\mathbf{R}'$ CS, and C and S denote cosine and sine functions, respectively. Using Equations 6 and 7, the Euler angles and the translational shift vector (a' , b' , and c') in the couch CS were calculated.

3D/3D (CBCT/simCT) Image Registration

The registration of CBCT and simCT images was automatic with a bone density filter (200-1700 HU) in 6DOF using ARIA Offline Review (Varian Medical, Palo Alto, California). The autoregistration results were visually verified. Since clinical CBCT images that were saved in the ARIA database represent final patient setup position, the result of 3D/3D registration reflects the difference between manual 3DOF and automatic 6DOF registrations. The discrepancy between 2D/3D and 3D/3D registrations was used to assess the accuracy of 2D/3D registration in 6DOF.

Results

Table 1 shows the results comparing 2D/3D and 3D/3D image registration (with a bone density filter) for 4 anatomic sites, including the brain (head), C-spine (HN), T-spine (thorax), and L-spine (abdomen/pelvis). In each dimension of translation and rotation, the average differences were 0.7 ± 2.0 mm and $-0.2^\circ \times 1.4^\circ$ for all sites, and these averages increased from superior to inferior sites. Without motion and deformation, the phantom results showed 0.0 ± 0.5 mm and $0.1^\circ \pm 0.4^\circ$ using the ideal alignment as initial guess but 0.4 ± 1.1 mm and $0.2^\circ \pm 0.3^\circ$ using 6 nonideal alignments (with $\sim \pm 5$ mm from the ideal position) as initial guesses. Table 2 shows 6DOF results for all 4 anatomic sites; no consistent difference was observed among the 3 rotations. Figure 2 shows the distribution of the differences in all patients. The retrospective automatic 3D/3D ignored in 3D/3D registration in 6DOF produces some noticeable differences from the online manual image registration in 3DOF (Table 3).

Head Image Registration

Figure 3 shows the chessboard evaluation of the registration results in a brain cancer case, and Figure 2A shows the distribution of the discrepancy between 2D/3D and 3D/3D image registrations in each dimension of the translations and rotations in cranial cases. All patients for cranial cancer underwent fSRS, which used both head molds and mouth bites to immobilize the head; motion between CBCT and 2DkV is within 1.0 mm.¹⁹ In addition, minimal deformation was expected in images of the head, especially for registration with a bone density filter, which eliminates the contribution from soft tissue in 3D/3D registration. Soft tissue pixels are present in 2D/3D image registration, although W/L was adjusted to enhance bony structure and suppress soft tissue. The discrepancy between 2D/3D and 3D/3D registration in patients is 0.2 ± 1.6 mm and $-0.4^\circ \pm 1.2^\circ$ in each DOF. For rigid head phantom, the registration discrepancy is 0.0 ± 0.5 mm and $0.1^\circ \pm 0.4^\circ$, smaller than those in patient cases.

Head and Neck Image Registration

The discrepancy between 2D/3D and 3D/3D registration in HN patients is 0.7 ± 1.6 mm and $0.3^\circ \pm 1.3^\circ$. The difference in C-spine curvature between setup and simulation is visible in both 2D and 3D images, resulting in a slightly higher discrepancy than that found in cranial images. Possible patient motion in CBCT and 2DkV imaging may also contribute to the discrepancy. Figure 4A shows that soft tissue alignment is registration due to the use of a bone density filter, whereas it is present in 2D/3D registration.

Thoracic Image Registration

Figure 4B also shows 3D/3D thoracic (T-spine) image registration that ignores patients' arms because of a limited FOV and ignores soft tissue (including the diaphragm) because of the use of a bone density filter. In 2D/3D registration, these moving anatomical elements were avoided by drawing a mask to exclude them from the ROI, as shown in Figure 5. Respiration-induced motion reduces registration accuracy, resulting in a higher discrepancy of 0.7 ± 2.0 mm and $-0.7^\circ \pm 1.1^\circ$ between 2D/3D and 3D/3D registration.

Abdominal and Pelvic Image Registration

The 2D/3D image registration in abdominal and pelvic sites (L-spine) has the highest discrepancy, when compared with 3D/3D registration: 1.1 ± 2.6 mm and $-0.5^\circ \pm 1.9^\circ$, primarily resulting from different degrees of soft tissue involvement, deformation, and bone positioning variation.

Discussion and Conclusion

In this retrospective study, we have demonstrated that OB-2DkV images can be used via 2D/3D registration to provide 6DOF for patient setup at the 4 major sites. Although on-board imaging can produce CBCT images for a 6DOF setup, CBCT imaging exposes patients to a much higher dose of radiation and has a smaller FOV than orthogonal 2DkV imaging.

We evaluated 37 patients, 55 treatments, and 4 different anatomic sites, and the discrepancy between 2D/3D and 3D/3D image registration was found to increase slightly from cranial to C-spine to T-spine to L-spine sites. As Table 3 shows, patient rotation is present within a range (2s) of $\sim 3^\circ$ in extracranial cases and $\sim 1^\circ$ in intracranial cases using manual adjustment. Residual rotation can lead to potential adverse effects in dose delivery for tumor with irregular shape and/or a nearby critical structure. In the presence of rotation, manual registration relies on local bony structure for target localization, but this is subjective and user dependent.

Assessment of 2D/3D Registration Using 3D/3D Registration as Gold Standard

Despite the restrictive fSRS or SBRT immobilization devices, inter- and intrafractional and voluntary (within 1.0 mm) and involuntary (respiratory and digestive) motions are expected to occur between 2 imaging acquisitions. Therefore, possible anatomical differences between 2DkV and CBCT images are expected under clinical conditions, resulting in 2D/3D and 3D/3D registrations, as shown in Tables 1 and 2 and Figure 2. So these results more likely represent the upper limits of uncertainty of the 2D/3D registration under the clinical conditions. In prospective studies, orthogonal image projections could be obtained from the CBCT scans to minimize the time gap to within 1 minute between imaging; however, such projections are lost in a retrospective study as the raw scanning data are not saved after 48 hours.

The result from head phantom data as a control shows a better registration result in the absence of deformation (0.0 ± 0.5 mm and $0.1^\circ \pm 0.4^\circ$). It also illustrates that the importance

of using the ideal alignment as initial guess in 2D/3D registration, as the accuracy and uncertainty are degraded to 0.5 ± 1.1 mm in translation while similar ($0.2^\circ \pm 0.3^\circ$) in rotation, suggesting that a locally optimal result could occur.

There is an intrinsic difference between 2D/3D and 3D/3D image registration: that is, the contribution from soft tissue, which is more likely to be deformable. In 3D/3D registration, a bone density filter (200-1700 HU) was applied so that only bony structures were used for alignment, whereas 2D/3D registration is not equipped with such a filter. Although the W/L of both 2DkV and DRRs is manually adjusted for optimal visualization of the bony structure, some soft tissues are included in the registration, as shown in Figures 3 and 5. Soft tissue, which comes with dramatic contrast and possible motion, such as air in the bowels, heart–lung and diaphragm–lung interfaces, and skin surface, would deviate 2D/3D registration from bony alignment. In fact, we observed that the difference between 3D/3D registrations with and without the bone density filter is around 0.2 ± 0.2 mm or $0.1^\circ \pm 0.1^\circ$ on average. This effect is patient and site dependent. Similar observations were reported earlier.²⁰⁻²²

Deformation within the ROI plays a significant role in both 2D/3D and 3D/3D image registration. The head phantom results show the intrinsic uncertainty of the 2D/3D registration (0.5 mm and 0.3°), which are better than patient results in the cranial site (1.6 mm and 1.2°). Because whole head is used as ROI in both phantom and patient cases, inclusion of lower jaw (Figure 3) elevates uncertainty from the differences in jaw position and associated soft tissue deformation in patient cases. Selective ROI definition can improve the accuracy.^{22,23}

Furthermore, both 2D/3D and 3D/3D registrations are rigid, and they are therefore not accurate in handling images deformed between simCT and pretreatment CBCT or 2DkV. Thus, 3D/3D registration itself may not be completely reliable and accurate. In fact, the precision of 3D/3D registration is 1.0 mm. So using CBCT/simCT registration as the gold standard has an uncertainty of at least 0.5 mm (half of the precision) in deformable anatomy. Although the deformation effect has been minimized as much as possible by masking out specific mobile structures, such as the arm and diaphragm (Figure 5), deformation is inevitable and will affect registration in both methods, causing patient-related discrepancies that go beyond method-related discrepancies.²⁴ This could explain the increasing discrepancy in sites from the head to abdomen/pelvis, as shown in Table 1.

Finally, the imaging isocenter between 2DkV and CBCT differs by 0.5 mm in our Trilogy machine, based on the Winston-Lutz test. Therefore, this intrinsic discrepancy also affects the difference between 2D/3D and 3D/3D registration, since the 2 imaging isocenters were not perfectly aligned.

Different Uncertainties in 2D/3D Registration for Different Anatomical Sites

In a previous study,^{14,15} a pig's head with fiducial markers was used as a nonrigid phantom to assess this 2D/3D image registration and its accuracy was assessed based on FRE. A mean FRE of 1.3 mm was reported, showing the absolute accuracy for fiducial matching. Although a different end point for comparison was chosen in this study, the standard

deviation in head registration (0.2 ± 1.6 mm and $-0.4^\circ \pm 1.2^\circ$ for cranial anatomy) is roughly on the same level.

Head motion is minimized since the frameless stereotactic immobilization system was used to fix the patient for fSRS treatment,¹⁹ restricting head motion within a millimeter. For other treatment sites, SBRT immobilization utilizing a body cradle and an indexed box²⁵ was used. As the body immobilization decreases and mobility increases, the motion plays an increasing role from HN to the thorax and to the abdomen, which was observed from this registration study, as shown in Table 1. Previously, we evaluated volumetric image registration in the thoracic and abdominal regions and observed a similar trend of increasing uncertainty in the direction of superior to inferior.^{22,26,27}

Drawing a mask to eliminate interference objects, including movable tissue and foreign devices, is essential for an accurate 2D/3D image registration, especially the nonaxial bones and moving diaphragm. The registration dependency on ROI selection has been reported.^{22,23} In the thorax, the spine and rib cage have a fixed geometric relationship, except for slight breathing motion at anterior sides. Movable tissues, such as the humeral bone and diaphragm, were excluded from both 2DkV and CBCT images using masking and a small FOV, respectively, as shown in Figures 4 and 5. In the abdomen, the spine and iliac crest bone could be slightly twisted from the simulation position, causing more deformation. Moreover, air in the digestive tract produces high contrast and introduces substantial image variations,²⁴ which cannot be easily eliminated from 2DkV images. In addition, unlike the thorax where the lung density is low, the organs in the abdomen/pelvis are dense and contribute more pixel intensity in 2D/3D registration. Therefore, the difference between the 2D/3D and 3D/3D registrations in the abdominal site produced the largest deviations among all 4 sites (Table 1).

Potential for Using OB-2DkV Imaging for 6DOF Patient Setup

This study shows that the accuracy of 2D/3D registration is dependent on anatomic sites, due to the degree of deformation at each site and the inability of current 2D/3D registration to eliminate the contribution of pixel intensity from soft tissue. This deformation includes higher potential body motion in the body than cranial case, since the SBRT body cradle is less stringent than the fSRS immobilization device. The current 2D/3D registration is sensitive to the W/L of 2DkV images, which determines bone-to-soft-tissue contrast used in the registration. In the 2D/3D registration program, the CT grayscale was scaled down to 1 byte (0-255) from 2 bytes (0-4095) to match that of 2DkV. Further study toward implementing a pseudobone density filter for 2DkV imaging may be a key to improve the consistency between 2D/3D and 3D/3D registrations, while automasking could be implemented to automatically determine the ROI.²⁸ Deformation in the bony landmarks, however, is an intrinsic uncertainty for any rigid image registration and cannot be easily corrected.

It is worthwhile to compare manual 3DOF and automatic 6DOF results (Table 3). The noticeable difference between these 2 results suggests for the importance of rotational adjustment. In addition, under our clinical setup procedure for stereotactic treatment, the rotation factor is generally limited to within 3° on average in the 4 sites. Clinically, it is

desirable to further minimize patient rotation at setup, and 2D/3D registration using OB-2DkV has the potential to provide an imaging guidance alternative to CBCT for patient rotation correction.

The current 2D/3D registration assumes that patient does not move between 2 orthogonal 2DkV imaging, which is 15 to 20 seconds apart. Respiratory motion will likely produces 2 2DkV images at different respiratory phases. Such involuntary motion affects soft tissues mostly, with some impacts on the anterior ribs, which are not fully accounted for in 2D/3D registration. In addition, it is critical to have automation in the 2D/3D registration pipeline, replacing the current manual preparation, to facilitate clinical workflow.

This study has demonstrated that OB-2DkV images can be used to achieve 6DOF image registration with an uncertainty of 1.5 mm and 1.2° for cranial anatomy in patients. A quantified difference between phantom and patient results demonstrates elevated magnitude of uncertainty in clinical patient setup using 2D/3D registration. For the 4 anatomical sites, the uncertainty of 2D/3D registration increases from the superior to inferior sites, primarily due to patient anatomy. On-board 2DkV could be used to control the 6D couch for 6DOF patient setup via 2D/3D image registration, although there is room for further improvement.

Acknowledgments

The authors would like to thank Ms S. Fontenla for her assistance in querying patient database for this retrospective study and Mr M. Sullivan for his assistance in setup research ARIA Offline Review (version 10) for this retrospective registration study.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The research was in part supported by Memorial Sloan Kettering Cancer Center; the Austrian Federal Ministry of Economy, Family, and Youth; the Austrian National Foundation for Research, Technology, and Development; and the Austrian Science Foundation (FWF project L 503).

Abbreviations

DOF	degree of freedom
OB-2DkV	on-board 2-dimensional kilovoltage
FRE	fiducial registration error
GPU	graphics processing unit
simCT	simulation computed tomography
CBCT	cone-beam computed tomography
C-spine	clavicle spine
T-spine	Thoracic spine
L-spine	Lumbar spine
fSRS	frameless stereotactic radiosurgery
SBRT	stereotactic body radiotherapy

IGRT	image-guided radiotherapy
FOV	field of view
CS	coordinate system
ROI	region of interest
MI	mutual information
RC	Rank correlation
HU	Hounsfield Unit
W/L	window/level
AP	anterior-posterior
RL	right lateral
RAO	right anterior oblique
LPO	left posterior oblique

References

1. Jaffray D, Kupelian P, Djemil T, Macklis RM. Review of image-guided radiation therapy. *Exp Rev Anticancer Ther.* 2007; 7(1):89–103. doi:10.1586/14737140.7.1.89.
2. Li, G.; Mageras, G.; Dong, L.; Mohan, R. *Image-Guided Radiation Therapy*. 3rd. Lippincott Williams & Wilkins; Philadelphia, PA: 2011. p. 229-258.
3. Kim J, Jin JY, 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. doi:10.1016/j.ijrobp.2010.05.052. [PubMed: 20832184]
4. Peng LC, Kahler D, Samant S, et al. Quality assessment of frameless fractionated stereotactic radiotherapy using cone beam computed tomography. *Int J Radiat Oncol Biol Phys.* 2010; 78(5): 1586–1593. doi:10.1016/j.ijrobp.2010.02.011. [PubMed: 20646859]
5. Murphy MJ. An automatic six-degree-of-freedom image registration algorithm for image-guided frameless stereotaxic radiosurgery. *Med Phys.* 1997; 24(6):857–866. doi:10.1118/1.598005. [PubMed: 9198019]
6. Adler JR Jr, Murphy MJ, Chang SD, Hancock SL. Image-guided robotic radiosurgery. *Neurosurgery.* 1999; 44:1299–1306. discussion 1306-1297. [PubMed: 10371630]
7. 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 kilo-voltage cone-beam CT. *Radiother Oncol.* 2009; 93(3):602–608. doi:10.1016/j.radonc.2009.09.009. [PubMed: 19846229]
8. Lei S, Piel N, Oermann EK, et al. Six-dimensional correction of intra-fractional prostate motion with cyberknife stereotactic body radiation therapy. *Front Oncol.* 2011; 1:48. doi:10.3389/fonc.2011.00048. [PubMed: 22655248]
9. Ackerly T, Lancaster CM, Geso M, Roxby KJ. Clinical accuracy of ExacTrac intracranial frameless stereotactic system. *Med Phys.* 2011; 38(9):5040–5048. doi:10.1118/1.3611044. [PubMed: 21978048]
10. Wurm RE, 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. doi:10.1080/02841860600919233. [PubMed: 16982554]

11. Jin JY, Yin FF, Tenn SE, Medin PM, Solberg TD. Use of the BrainLAB ExacTrac X-Ray 6D system in image-guided radiotherapy. *Med Dosim.* 2008; 33(2):124–134. doi:10.1016/j.meddos.2008.02.005. [PubMed: 18456164]
12. Verbakel WF, Lagerwaard FJ, et al. The accuracy of frameless stereotactic intracranial radiosurgery. *Radiother Oncol.* 2010; 97(3):390–394. doi:10.1016/j.radonc.2010.06.012. [PubMed: 21047692]
13. Kim J, Wen N, Jin JY, 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. doi:10.1120/jacmp.v13i3.3729. [PubMed: 22584170]
14. Pawiro SA, Markelj P, Pernus F, et al. Validation for 2D/3D registration. I: a new gold standard data set. *Med Phys.* 2011; 38(3):1481–1490. [PubMed: 21520860]
15. Gendrin C, Markelj P, Pawiro SA, et al. Validation for 2D/3D registration. II: the comparison of intensity- and gradient-based merit functions using a new gold standard data set. *Med Phys.* 2011; 38(3):1491–502. [PubMed: 21520861]
16. Birkfellner W, Wirth J, Burgstaller W, et al. A faster method for 3D/2D medical image registration—a simulation study. *Phys Med Biol.* 2003; 48(16):2665–2679. [PubMed: 12974581]
17. Spoerk J, Bergmann H, Wanschitz F, Dong S, Birkfellner W. Fast DRR splat rendering using common consumer graphics hardware. *Med Phys.* 2007; 34(11):4302–4308. [PubMed: 18072495]
18. Yenice KM, Lovelock DM, Hunt MA, et al. CT image-guided intensity-modulated therapy for paraspinal tumors using stereotactic immobilization. *Int J Radiat Oncol Biol Phys.* 2003; 55(3):583–593. doi:S0360301602039421. [PubMed: 12573745]
19. Li G, Ballangrud A, Kuo LC, et al. Motion monitoring for cranial frameless stereotactic radiosurgery using video-based three-dimensional optical surface imaging. *Med Phys.* 2011; 38(7):3981–3994. [PubMed: 21858995]
20. Boswell S, Tome W, Jeraj R, Jaradat H, Mackie TR. Automatic registration of megavoltage to kilovoltage CT images in helical tomotherapy: an evaluation of the setup verification process for the special case of a rigid head phantom. *Med Phys.* 2006; 33(11):4395–404. [PubMed: 17153418]
21. Forrest LJ, Mackie TR, Ruchala K, et al. The utility of megavoltage computed tomography images from a helical tomotherapy system for setup verification purposes. *Int J Radiat Oncol Biol Phys.* 2004; 60(5):1639–1644. doi:10.1016/j.ijrobp.2004.08.016. [PubMed: 15590196]
22. Li G, Xie H, Ning H, et al. A feasibility study of image registration using volumetrically classified, motion-free bony landmarks in thoracic 4DCT images for image-guided patient setup. *Int J Biomed Eng Tech.* 2012; 8(2/3):259–273. doi:10.1504/IJBET.2012.046084.
23. Ren L, Godfrey DJ, Yan H, Wu QJ, Yin FF. Automatic registration between reference and on-board digital tomosynthesis images for positioning verification. *Med Phys.* 2008; 35(2):664–672. [PubMed: 18383688]
24. Kim J, Kumar S, Liu C, et al. A novel approach for establishing benchmark CBCT/CT deformable image registrations in prostate cancer radiotherapy. *Phys Med Biol.* 2013; 58(22):8077–8097. doi:10.1088/0031-9155/58/22/8077. [PubMed: 24171908]
25. Lovelock DM, Hua C, Wang P, et al. Accurate setup of paraspinal patients using a noninvasive patient immobilization cradle and portal imaging. *Med Phys.* 2005; 32(8):2606–2614. [PubMed: 16193791]
26. Li G, Xie H, Ning H, et al. A novel 3D volumetric voxel registration technique for volume-view-guided image registration of multiple imaging modalities. *Int J Radiat Oncol Biol Phys.* 2005; 63(1):261–273. doi:10.1016/j.ijrobp.2005.05.008. [PubMed: 16024179]
27. Li G, Ning H, Brown A, et al. Image guided, motion-free patient body setup using 3D volumetric image registration of classified stable bony landmarks. *Int J Radiat Oncol Biol Phys.* 2008; 72:S535. doi:10.1016/j.ijrobp.2008.06.072.
28. Steininger P, Neuner M, Weichenberger H, et al. Auto-masked 2D/3D image registration and its validation with clinical conebeam computed tomography. *Phys Med Biol.* 2012; 57(13):4277–4792. doi:10.1088/0031-9155/57/13/4277. [PubMed: 22705709]

Figure 1.

Coordinate system transformation from imaging system to linac isocenter system: (A) translational shift of imaging coordinate system from the center of the imager to isocenter; (B) rotation along x-axis, 90° from interior to anterior; and (C) rotation along y-axis, 90° to right lateral (RL) imaging position (90°, 90°, and 0°). In this case, the orthogonal image pair is the anterior-posterior (AP) image (90°, 0°, and 0°), 90° clockwise from the RL image. For other orthogonal pairs, different rotations along the y-axis were applied.

Figure 2.

Distribution of the error of 2D/3D registration using 3D/3D registration as the gold standard: (A) head (0.2 ± 1.6 mm and $-0.4^\circ \pm 1.2^\circ$) and (B) all anatomic sites (0.7 ± 2.0 mm and $-0.2^\circ \pm 1.4^\circ$). 2D indicates 2-dimensional; 3D, 3-dimensional.

Figure 3. Chessboard display of 2D/3D image registration results of an orthogonal of x-ray images to orthogonal digitally reconstructed radiographs (DRRs) in (A) right lateral (RL) view and (B) anterior-posterior (AP) view. 2D indicates 2-dimensional; 3D, 3-dimensional.

Figure 4.

Motions (arrows in sagittal view) and natural avoidance of movable body parts (arrows in coronal and axial views) in the full-fan CBCT scan for 3D/3D registration. 3D indicates 3-dimensional.

Figure 5.

An example of a mask drawn to define the region of interest (ROI) for 2D/3D image registration. Note that the arm and diaphragm are excluded from registration. Images in the top row are 2 orthogonal 2DkV x-ray radiographic images with individual masks. Right anterior oblique (RAO: 90°, 315°, and 0°) and left anterior oblique (LAO: 90°, 45°, and 0°). The chessboard (bottom row) is just for demonstration purposes, while in 2D/3D registration, the mask was applied for both 2DkV images and digitally reconstructed radiographs (DRRs). 2D indicates 2-dimensional; 3D, 3-dimensional.

Table 1

The Mean and Standard Deviation Between 2D/3D Registration and 3D/3D Registration for Each of the Translational and Rotational Degrees of Freedom at Different Anatomical Sites.

Anatomic Site	No. of Patient (No. of Fraction)	Translation, mm		Rotation, °		Time, seconds	
		Avg	St dev	Avg	St dev	Avg	St dev
Phantom	1 (3)	0.0	0.5	0.1	0.4	5.4	0.3
	Test ^a	0.4	1.1	0.2	0.3		
Head	17 (19)	0.2	1.6	-0.4	1.2	5.8	0.6
C-spine	7 (10)	0.7	1.6	0.3	1.3	6.0	2.2
T-spine	5 (11)	0.7	2.0	-0.7	1.1	6.7	1.1
L-spine	8 (15)	1.1	2.6	-0.5	1.9	8.2	1.0
All sites	37 (55)	0.7	2.0	-0.2	1.4	6.6	1.9

Abbreviations: avg, average; C-spine, clavicle spine; L-spine, lumbar spine; st dev, standard deviation; T-spine, thoracic spine; 2D, 2-dimensional; 3D, 3-dimensional.

^aRegistration was started 6 arbitrary positions with ~+5 mm from the ideal alignment.

Table 2Difference Between 2D/3D Registration and 3D/3D Registration in 6DOF.^a

Anatomic Site	Analysis	Translation, mm			Rotation, °		
		X	Y	Z	Pitch	Roll	Yaw
Head	Avg	-0.2	0.3	0.5	-1.0	-0.6	0.5
	St dev	1.8	1.3	1.6	1.2	0.7	1.1
C-spine	Avg	0.1	1.2	0.7	-0.1	0.8	0.0
	St dev	1.5	1.9	1.4	1.4	1.3	1.0
T-spine	Avg	1.7	0.4	0.1	-1.2	-0.5	-0.3
	St dev	1.9	1.8	2.0	1.2	1.0	1.1
L-spine	Avg	2.1	-0.1	1.3	-0.1	-1.4	0.1
	St dev	2.7	1.7	2.8	1.7	2.0	1.7
All sites	Avg	0.9	0.5	0.6	-0.6	-0.4	0.1
	St dev	2.2	1.6	1.9	1.4	1.5	1.2

Abbreviations: avg, average; C-spine, clavicle spine; DOF, degree of freedom; DRR, digitally reconstructed radiograph; L-spine, lumbar spine; st dev, standard deviation; T-spine, thoracic spine; 2D, 2-dimensional; 3D, 3-dimensional.

^aThe 3D/3D registration uses a bone density filter (200-1700 HU) for intensity range selection for registration. The roll rotation is only calculated from different DRRs With minute rotation variation away from the theoretical roll rotation. For C-spine and L-spine cases, the average and standard deviation for roll rotation are higher than that for pitch and yaw, whereas in the brain and T-spine, all three rotations have similar accuracy and uncertainty.

Table 3

Difference Between Clinical Manual Registration in 3DOF and Retrospective Autoregistration in 6DOF.^a

Anatomic Site	Analysis	Translation, mm			Rotation, °		
		X	Y	Z	Pitch	Roll	Yaw
Head	Avg	0.1	0.1	-0.1	0.6	0.2	0.0
	St dev	0.6	0.7	1.0	0.7	0.2	0.4
C-spine	Avg	-0.3	-0.3	0.1	0.2	-0.5	0.5
	St dev	0.6	0.5	0.5	1.0	0.9	1.1
T-spine	Avg	0.3	-0.3	-0.1	0.5	0.4	0.0
	St dev	1.2	1.1	1.3	0.6	0.7	1.0
L-spine	Avg	1.2	-1.1	-0.2	0.9	0.3	0.2
	St dev	2.9	2.8	1.6	1.1	1.4	1.0
All sites	Avg	0.3	-0.4	-0.1	0.5	0.1	0.2
	St dev	1.1	1.1	0.4	0.2	0.5	0.3

Abbreviations: avg, average; C-spine, clavicle spine; DOF, degree of freedom; L-spine, lumbar spine; st dev, standard deviation; T-spine, thoracic spine; 2D, 2-dimensional; 3D, 3-dimensional.

^a Clinical manual registration focuses on local structure and compensates for rotational difference using translational shift. The retrospective 3D/3D registration uses a bone density filter (200-1700 HU) for intensity range selection for registration. The shifts shown here are from 3D/3D registration based on stored manual registration positions.