

# Daily patient setup error in prostate image guided radiation therapy with fiducial-based kilovoltage onboard imaging and conebeam computed tomography

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**Background:** This study examined the interfraction setup error in patients undergoing prostate radiotherapy using fiducial markers and on-board imaging.

**Methods:** Patients (n=53) were aligned to the treatment isocenter by laser followed by orthogonal kilovoltage (kV) radiographs to visualize bony anatomy and implanted fiducial markers. The magnitude and direction of couch shifts for isocenter correction required was determined by image registration for bony anatomy and fiducial markers. Twice weekly, 25 of the 53 patients also underwent conebeam computed tomography (CBCT) to measure any residual error in patient positioning. Based on individual coordinate shifts from CBCT, a net three-dimensional (3D) residual shift magnitude vector  $R$  was calculated.

**Results:** The average couch shifts were 0.26 and 0.40 cm in inferior direction and 0.25 and 0.33 cm in superior direction for alignments made with bony anatomy and fiducial markers, respectively ( $P < 0.0001$ ). There were no significant differences noted in the vertical or lateral planes between the two image registration methods. In subset of 25 patients, no residual shift from fiducial plain film set up was required with CBCT matching in 66.5%, 52.4% and 57.9% of fractions for longitudinal, vertical and lateral planes, respectively, with majority (79%) of patients having a net residual 3D shifts of  $< 0.3$  cm. The use of CBCT increased average treatment time by approximately 6 min compared to kV radiographs alone.

**Conclusions:** The residual setup errors following daily kV image guided localization, as determined by CBCT, were small, which demonstrates high accuracy of kV localization when fiducial markers are present.

**Keywords:** Conebeam computed tomography (CBCT); fiducial markers; image guided radiation therapy (IGRT); prostate cancer

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## Introduction

Since the field's inception over a century ago, radiation oncology has been faced with the fundamental challenge of delivering radiotherapy to malignant tissue while sparing surrounding healthy organs. In order to address this issue, researchers have delved into image-guided radiation therapy (IGRT), which refers to the integration of radiation planning, patient positioning, and treatment delivery with

new and emerging image-based tumor definition methods (1). While advances in tumor volume delineation and the practice of IGRT have led to more precise treatments, the need for increased accuracy in beam targeting remains (2). Greater accuracy would allow conforming of the planning target volume (PTV) more closely to the clinical target volume (CTV), which would reduce the volume of healthy tissue irradiated. In turn, this could allow radiation dose escalation resulting in better local control with decreased

associated morbidity. The benefit of dose escalation with conformal radiation delivery has already been well-demonstrated in the treatment of prostate cancer (3).

One of the commonly practiced method for verifying interfraction changes involves the comparison of megavoltage (MV) X-ray portal images to the reference kilovoltage (kV) X-ray images obtained during computed tomography (CT) simulations or to digitally reconstructed radiographs (DRRs) (4). To circumvent the poorer resolution of MV imaging, a number of studies have been conducted implementing planar and volumetric kV imaging (5,6). The On-Board Imager™ (OBI) has been commonly used to provide this type of imaging. It consists of a diagnostic X-ray tube and kV flat-panel imager mounted on the treatment machine gantry via robotic arms that operate along three axes of motion. In recent years, the OBI has been used to verify patient positioning via two dimensions—planar orthogonal kV radiographs, and via three dimensions—kV conebeam CT (CBCT).

kV CBCT allows for the reconstruction of a three-dimensional (3D) CT image from data collected during a single gantry rotation around a stationary patient (7). Such an imaging system has been shown to be capable of producing soft tissue images with excellent spatial resolution in a seamless, efficient manner (8). Thus, it has often been used preferentially over paired orthogonal kV images in cases where 3D soft tissue detail is important for patient position verification (5). It has also been used when treating small targets without fiducial markers, when using a small number of treatment fractions, and when performing adaptive radiotherapy (5). Still, while kV CBCT provides better soft tissue contrast, its use could be limited by the increase in radiation session length it requires as well as the greater dose it delivers to the patient in comparison to planar imaging (9).

In cases of prostate cancer, both of these image registration methods have provided daily image guidance in an attempt to more accurately deliver radiation (4,6). The location and mobility of the prostate makes its accurate localization using external markers such as skin tattoos and bony anatomy difficult. While ultrasound has also been widely utilized for localization of the prostate, it was found to be less accurate than kV imaging with fiducial markers (10). Fiducials—radioopaque typically gold, cylindrical seeds—are implanted into the prostate via needle under transrectal ultrasound guidance (11). Imaging techniques using fiducials located within the prostate allows for more accurate targeting of the mobile organ and reduces interfractional variation

of radiation. Greer *et al.* reported offline bony anatomy systematic errors of 1.6, 2.5 and 4.4 mm in the right-left (RL), superior-inferior (SI), and anterior-posterior (AP) directions, respectively (12). McNair *et al.* reported offline bony anatomy systemic errors of 1.3, 1.9, and 2.5 mm and online fiducial systemic errors of 0.9, 1.1, and 1.0 mm in the RL, SI, and AP directions, respectively (13). Both studies also calculated the margins to account for set-up error for each technique which was of 6, 9, and 13 mm (12) and 4.7, 6.3, and 8.4 mm (13) in the RL, SI, and AP directions with bony anatomy and 2, 4, and 5 mm (12) and 1.3, 1.2, and 1.2 mm (13) in these directions with online fiducial markers.

Because of the accuracy of kV planar imaging with fiducials, the necessity for CBCT has been questioned (12,13). The purpose of this study was to compare interfraction patient setup error in prostate radiotherapy using planar kV radiographs with patient anatomy, planar kV radiographs with fiducial markers, and CBCT with fiducial markers. With this frame of reference, the utility of CBCT was also assessed.

## Materials and methods

### Simulation

A total of 53 patients with prostate cancer undergoing radiation therapy were included in this study. All of the patients had three radioopaque fiducial markers implanted in their prostate 1-2 weeks prior to their treatment planning session, allowing for post-implantation seed migration. At the time of simulation, no special bowel preparation was performed and patients were instructed to have an empty bladder for both simulation and treatment. Patients were instructed to remove all clothing from the waist down to minimize displacement from the garments.

Immobilization and alignment consisted of supine positioning, indexed F roll under the head, hands folded on chest, and a leg-immobilization device encompassing the foot and separating the legs. Patients were straightened visually using the sagittal laser and prepared for scanning. A CT scan was performed using a Phillips Brilliance Big Bore scanner employing the pelvis protocol. Orthogonal scout films were obtained to check for pelvic rotation and tilt and patients were aligned accordingly. Patient were scanned from L1 vertebral body to below the lesser trochanter using 3 mm slices assuring all three fiducials were visible. Anterior, right and left lateral tattoos were placed at the isocenter coordinates. Following CT simulation and

treatment planning, all patients were treated on a Varian iX<sup>®</sup> or Trilogy<sup>®</sup> linear accelerator equipped with on-board kV imaging capabilities.

### *Positioning and OBI*

On days of treatment, patients were placed in the same position as the simulation and aligned to their three skin tattoos using treatment room sagittal and transverse lasers. An OBI (Varian Medical Systems) was utilized to take an orthogonal film pair. Visual confirmation of matching bony anatomy was performed to identify potential patient rotation, and, if discovered, the patient was realigned and re-imaged. Patient rotation was checked on the initial OBI films by examining the pelvic brim and obturator foramen for rotational displacement. If discovered, the patient was asked to raise and lower their pelvis and visually examined for rotation and straightness and setup again to tattoos and coordinates. This practice took care of all rotational misalignments we experienced.

During this process, implanted fiducial markers were also contoured on the anterior and lateral projections of the DRRs, and the kV images were overlaid onto them using the Varian<sup>®</sup> OBI matching program then manipulated in the inferior-superior, AP and left-right directions. Both automatic and manual matching was employed and implanted seeds were moved to the center of the DRR contour. If all three contours were misaligned, the patient would be repositioned and reimaged. When fiducials were matched, corresponding shifts were also sent electronically to the linear accelerator and the treatment table was moved to the desired location. All OBI film movements were reviewed and approved by the physician post treatment, or, pre-treatment if there was any question regarding patient or fiducial positioning.

### *Conebeam CT image acquisition*

Twenty-five of the 53 patients in this study also underwent CBCT guided positioning in addition to orthogonal films. Twice a week, a 360° CBCT was performed immediately after fiducial matching shifts were carried out with the Varian kV OBI system, version 9. Scans were acquired using the pelvis protocol, 512 by 512 pixels and half-bowtie fan mount. After acquisition and reconstruction, the CBCT was matched in the transverse, sagittal and coronal planes to the fiducials in the original CT simulation scan and residual movements were performed and recorded for study

purposes. All CBCT scans were reviewed and approved by the physician post treatment.

### *Treatment*

Treatment was delivered by a Varian iX<sup>®</sup> or Trilogy<sup>®</sup> linear accelerator using 6 MV photons as prescribed in an intensity modulated radiation therapy treatment plan produced using Phillips Medical Systems, Pinnacle 3 (version 8.0 m) treatment planning system. Fractionation of 44 treatments to a total dose of 7,920 cGy was administered daily.

### *Statistical analysis*

Descriptive statistics were calculated for shifts recorded using planar kV radiographs with bony anatomy and fiducial markers for all 53 prostate cancer patients. The Chi-square test was used to compare frequencies of shifts in longitudinal (SI), vertical (AP) and lateral (RL) planes. A “No shift” was defined as required movement of less than 1 mm (<0.1 cm). The difference in mean shifts in each direction was compared using a repeated measures ANOVA analysis using Proc MIXED in SAS 9.1 system (SAS Institute, Cary, NC, USA). The analysis allows modeling of variance-covariance matrix among repeated shifts recorded for each patient over the course of radiation treatment period.

In a subset of 25 patients who also underwent CBCT guided positioning residual set-up shifts were recorded and descriptive statistics and frequencies were calculated for each direction. Based on individual coordinate shifts, a net 3D residual shift magnitude vector “*R*” was calculated for each fraction according to following equation:

$$R = \sqrt{(X)^2 + (Y)^2 + (Z)^2}$$

where *R* is the net residual 3D shift while *X*, *Y* and *Z* are residual shifts recorded in left-right, inferior-superior and AP directions, respectively. The frequencies of occurrence of residual 3D shifts were calculated for the CBCT subset. We regarded the residual 3D shift magnitude *R* as a useful figure of merit when considering the difference between planar imaging and CBCT for patient alignment. This is because PTV margins in conformal radiotherapy are generated in a 3D manner; therefore any discussion of the adequacy of setup precision is best framed in 3D terms as well. In addition, basing the analysis on the residual 3D shift *R* leads to an essential finding that is more compact and more easily communicated than is possible when

**Table 1** Comparison of mean shifts (cm) recorded with kV radiographs using bony anatomy and fiducial markers among 53 prostate cancer patients

Shift direction	Bony anatomy				Fiducial markers				P value
	n	Mean	SE	Range	n	Mean	SE	Range	
Longitudinal									
Inferior	1,323	0.26	0.02	0.10-1.6	1,425	0.40	0.02	0.10-2.2	<0.0001
Superior	691	0.25	0.04	0.10-3.0	682	0.33	0.04	0.10-2.4	<0.0001
Vertical									
Anterior	965	0.38	0.02	0.10-2.2	1,000	0.37	0.02	0.10-1.6	0.333
Posterior	1,133	0.37	0.02	0.10-2.1	1,118	0.36	0.02	0.10-2.1	0.322
Lateral									
Left	1,091	0.46	0.02	0.10-2.2	1,107	0.46	0.02	0.10-2.2	0.845
Right	1,069	0.46	0.02	0.10-2.2	1,047	0.46	0.02	0.10-2.4	0.721

kV, kilovoltage; n, number of directional shifts; SE, standard error.

each coordinate axis is examined separately. A two-sided hypothesis was used for all tests, and a probability value of less than 0.05 was considered statistically significant.

## Results

Fifty-three patients underwent a total of 2,334 radiation treatment fractions. The mean shifts made by alignment with fiducial markers were significantly greater in the inferior and superior directions compared to alignment with bony anatomy alone (0.40 *vs.* 0.26 cm and 0.33 *vs.* 0.25 cm with  $P < 0.0001$ , respectively). There were no statistically significant differences in mean shifts between bony anatomy and fiducial markers in different directions of vertical or lateral planes. A comparison of mean couch shifts (cm) recorded with kV radiographs using bony anatomy and fiducial markers is presented in *Table 1*.

### *Bony anatomy vs. fiducials on kV images*

*Table 2* presents a comparison of the frequency with which couch shifts were required in those 53 patients following alignment to bony anatomy *vs.* fiducial markers. There was a significantly greater frequency of shifts in the inferior direction using fiducial markers compared to bony anatomy (61.1% *vs.* 56.7%,  $P < 0.002$ ). In addition, alignment to bony anatomy in the longitudinal plane more often resulted in no shift following initial patient setup when compared to fiducial marker alignment (13.7% *vs.* 9.7%,  $P < 0.0001$ ). There were no statistically significant differences in

frequencies of shifts made in the vertical or lateral planes between these two image registration methods.

### *kV image vs. CBCT*

In the subset of 25 patients (with 439 treatment fractions), once patient alignment and shifts were completed using kV images to fiducial markers, CBCT was done to match the fiducial markers to assess the need for any additional shifts. The residual shifts were recorded between the kV image-guided fiducial alignment and CBCT-guided fiducial alignment in *Table 3*. No residual shift was recorded in 66.5%, 52.4% and 57.9% of fractions for longitudinal, vertical and lateral planes, respectively. The mean residual shift was 0.17, 0.17, 0.16, 0.21, 0.15 and 0.15 cm in inferior, superior, anterior, posterior, left and right direction respectively. For net residual 3D shift *R*, the percentage of total treatment fractions requiring no shift, 0.1-0.3 cm shift, 0.3-0.5 cm shift, 0.5-0.7 cm shift, and greater than a 0.7 cm shift are presented in *Figure 1*. The majority (79%) of treatments required less than a 0.3 cm shifts or no shift using CBCT imaging after pre-alignment based on fiducials using kV imaging.

### *Treatment time*

An analysis of randomly selected one-third of the study participants who received CBCTs along with OBI and their treatment, revealed patients having a CBCT were on the table about 14 min, whereas non-CBCT treatments were slightly over 8 min, which includes OBI seed matching. The

**Table 2** Comparison of frequency of shifts recorded with kV radiographs using bony anatomy and fiducial markers among 53 prostate cancer patients

Shift direction	Bony anatomy (N=2,334), n (%)	Fiducial markers (N=2,334), n (%)	P value
Longitudinal			
No shift	320 (13.7)	227 (9.7)	<0.0001
Inferior	1,323 (56.7)	1,425 (61.1)	0.002
Superior	691 (29.6)	682 (29.2)	0.773
Vertical			
No shift	236 (10.1)	216 (9.3)	0.322
Anterior	965 (41.4)	1,000 (42.8)	0.300
Posterior	1,133 (48.5)	1,118 (50.0)	0.310
Lateral			
No shift	174 (7.5)	180 (7.7)	0.740
Left	1,091 (46.7)	1,107 (47.4)	0.639
Right	1,069 (45.8)	1,047 (44.9)	0.518

"No shift" defined as less than 1 mm (<0.1 cm) shift. kV, kilovoltage; N, total shifts; n, number of directional shifts.

**Table 3** Descriptive statistics for residual shifts (cm) recorded with CBCT over fiducial marker position among 25 prostate cancer patients with 439 treatment fractions

Shift direction	n (column %)*	Mean	SE	Median	Range
Longitudinal					
Inferior	69 (15.7)	0.17	0.01	0.10	0.10-0.70
Superior	78 (17.8)	0.17	0.01	0.10	0.10-0.70
No shift	292 (66.5)			Not applicable	
Vertical					
Anterior	27 (6.2)	0.16	0.01	0.10	0.10-0.40
Posterior	182 (41.5)	0.21	0.01	0.20	0.10-0.80
No shift	230 (52.4)			Not applicable	
Lateral					
Left	69 (15.7)	0.15	0.01	0.10	0.10-0.40
Right	116 (26.4)	0.15	0.01	0.10	0.10-0.60
No shift	254 (57.9)			Not applicable	

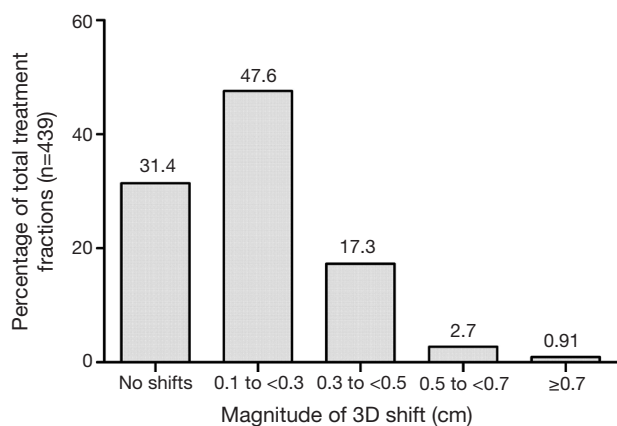
\*, Number and percentage of subjects with directional or no shift (<1 mm) out of 439 total treatment fractions. CBCT, conebeam computed tomography; SE, standard error.

difference was statistically significant ( $P < 0.05$ ) using *t*-test. These calculations were retrospectively performed using the documented beginning of the OBI film session and the time the last field was treated.

## Discussion

Similar to the studies by Greer *et al.* and McNair *et al.*, our data also suggest that kV imaging with alignment to fiducial

markers is superior to alignment using bony anatomy alone (12,13). Mean shifts in the inferior and superior directions were significantly greater, whereas AP and left-right shifts did not differ. The larger daily shifts with fiducial markers are reflective of the fact that prostate is an internal organ that can move with respect to the skin markings and bony anatomy, requiring more shifts to account for the location variability. The reason for greater shifts required in the inferior-superior direction is unclear but review of



**Figure 1** Histogram of the magnitude of 3D shifts required based on CBCT after patient positioning with plain fiducial marker kV radiographs. Based on 439 treatment fractions from 25 prostate cancer patients. “No shift” defined as less than 1 mm (<0.1 cm) shift. 3D, three-dimensional; CBCT, conebeam computed tomography; kV, kilovoltage.

literature suggests that this trend is not universal (12-15). One possible explanation is the daily prostate position shift caused by nearby organs such as the rectum and the bladder. Patients did not undergo daily bowel preparation prior to treatment and the amount of stool and gas in the rectum can certainly affect prostate positioning. In addition, patients were instructed to empty their bladder prior to simulation and treatment, but there is no effective way to standardize the post-void residual volume prior to simulation and treatment, especially considering many patients have enlarged prostates and voiding difficulties. A small study have investigated the bladder volume and prostate position changes using CBCT in patients who were instructed to keep their bladder full and found the bladder dimension to differ significantly in the inferior-superior direction but no significant shift in the target position (16). Further studies are needed to investigate the inter-fraction variability in size and shape of these surrounding organs that may explain our observation.

Fiducial-based imaging does not add any more time, radiation dose, or resources that are required for bony anatomy based imaging during a radiation treatment session. There have even been small studies that have reported on fiducial based imaging and its ability to reduce PTV margins (17). We believe that, in prostate radiotherapy, bony anatomy based alignment has inherent and significant limitations in localizing a soft tissue organ that is mobile

with respect to the nearby bony structures, and it is therefore reasonable to replace this alignment technique with fiducial based imaging. According to the American College of Radiology (ACR) Appropriateness criteria, daily localization of the prostate with implanted markers is more appropriate than bony anatomy for external beam radiation therapy for patients with localized prostate cancer (18). Our results continue to support the mounting evidence of improved target localization afforded by fiducial based imaging. However, larger studies with follow-up data are needed to assess if the benefit of target localization with fiducial markers actually translates into better clinical outcomes.

Prostate localization using CBCT has the theoretical advantage of providing better soft tissue delineation and accurately localizing fiducial markers in 3D view, which cannot be accomplished by kV imaging. This is potentially important when the patient’s bladder and rectum sizes vary significantly on certain days of treatment. However, in the present study, we found only marginal benefit of CBCT for the alignment of implanted fiducials compared to kV radiographs. Residual mean shifts guided by CBCT were relatively small compared to kV imaging alignment (majority less than 0.3 cm). This small discrepancy in fiducial localization is to be expected due to the difference in target visualization between the two image registration methods and subtle patient motion while imaging is being obtained on treatment table and may not necessarily result in truly more accurate radiation delivery to the target organ. Shi *et al.* compared CBCT software-automated alignment to soft tissue markers *vs.* CBCT manual alignment to implanted fiducials, concluding that alignment to fiducials was the more accurate method (15). Barney *et al.* investigated CBCT-guided manual soft tissue alignment, comparing it to kV portal image-guided fiducial alignment (14). Although their data revealed that 60% of shift differences between these two methods were greater than 3.0 mm, the authors endorsed fiducial alignment based on CBCT-related increases in treatment times and the need for physician input for soft tissue alignment.

The greater length of time required for CBCT acquisition is likely not inconsequential, as studies have shown that the required margins for intrafractional motion increase with treatment time (19). In our study, the treatment time also significantly differed between the two groups, with CBCT patients taking on average 6 more minutes per treatment. Furthermore, CBCT increases overall patient exposure to ionizing radiation. Kan *et al.* reported that standard kV CBCT resulted in an effective dose of 22.7 mSv per scan to

the pelvis and that if used daily could increase the secondary cancer risk by up to 2% to 4% (20).

Because of the propensity for the prostate to shift within the pelvis, an imaging localization modality that identifies the organ itself appears to be superior and can potentially result in smaller margins to account for errors. While fiducial markers are a good way to localize the prostate, their use is not universal in practice of radiation oncology. In addition, insertion of the markers is not without its own set of complications and this should be taken into consideration (11). When fiducials are not present, Palombarini *et al.* found that, compared to bone alignment with CBCT, soft tissue alignment resulted in larger degree of AP shifts due to random shifts in prostate position. The authors concluded that CBCT's ability to see not only bony landmarks but also soft tissue gray scale allows for better localization of prostate in daily treatments and may reduce the PTV margins (21). This is especially important as the field starts moving towards more hypofractionated treatment, such as stereotactic body radiation therapy. In addition, CBCT imaging can offer the advantage of much better resolution of the pelvic structures, such as intra- or peri-prostatic calcifications, compared to plain films, which can be used as natural markers in select patients without the need to undergo invasive marker placement (22). Thus, CBCT may be more valuable in such cases where fiducials are not utilized. Large scale study directly comparing the use of fiducials in CBCT IGRT is warranted to further clarify which technique results in better outcome.

In interpreting the results of this study, several limitations must be addressed. Due to time constraints and resources available, CBCT was not universally done to all of the patients. This reduced the amount of data available in the CBCT group. As mentioned earlier, one of the advantages of CBCT is in its soft tissue resolution, allowing for assessment of not only prostate location but shape of surrounding anatomy, more frequent CBCT (daily with or without fiducial markers) could potentially provide more accurate treatment delivery. Another limitation of the study is its lack of clinical outcome with respect to disease control and toxicities. Future studies can potentially compare objective clinical findings and patient reported outcome to different target localization in order to assess the degree of benefit in more accurate treatments.

## Conclusions

In conclusion, the results of this study indicate that

daily prostate localization using fiducial markers in kV radiographs during radiation therapy for prostate cancer may offer better target localization compared to patient bony anatomy alone. The addition of CBCT to did not seem to provide significant additional benefit if fiducials are already in use but is associated with increased treatment time and radiation exposure to the patients. CBCT may be more useful in cases where fiducials have been lost and there are less than three present, or in patients who are medically unable to undergo fiducial placement.

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All authors contributed to the design of the study. JC Ye was involved in all aspects of the study and co-wrote the paper. MM Qureshi performed the data analysis and was involved in interpretation of results along with assisting in writing the paper. P Clancy and LN Dise were involved in carrying out the treatment and collection of data. J Willins designed the method to calculate 3D shift and was involved in editing the manuscript. AE Hirsch supervised this study and was involved in all aspects of the study from study design to data interpretation and co-wrote paper.

## Footnote

*Conflicts of Interest:* Presented in part at the 52<sup>nd</sup> Annual Meeting of the American Society for Radiation Oncology, Oct 31-Nov 4, 2010, San Diego, CA, USA.

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