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PROSTATE INTRAFRACTION MOTION ASSESSED BY SIMULTANEOUS KV FLUOROSCOPY AT MV DELIVERY I: CLINICAL OBSERVATIONS AND PATTERN ANALYSIS

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Abstract

Purpose—To describe prostate intrafraction motion using kV fluoroscopy at treatment delivery for a hypofractionated radiotherapy protocol.

Methods and Materials—KV images were acquired during treatment delivery as well as pre and post-treatment Cone Beam Computed Tomography (CBCT) for each fraction of 30 patients, totaling 571 fractions for analysis. We calculated population statistics, evaluated correlation between interfraction and intrafraction motion, evaluated effect of treatment duration, classified whether motion resolved by post-treatment CBCT, and compared motion magnitude on a per patient basis.

Results—The elapsed time between pre- and post-CBCTs was (18.6±4.5) minutes. The population mean of motion measured by kV fluoroscopy was (−0.1, 0.5, −0.6) mm, the systematic was (0.5, 1.3, 1.2) mm, and random was (0.9, 1.9, 2.0) mm in the right-left, anterior-posterior, and superior-inferior axes, respectively. The probability of motion increased with treatment duration, with the mean increasing to (0.0, 1.0, −0.9) mm, and the systematic to (0.6, 1.7, 1.5) mm when measured using post-treatment CBCT. For any motion ≥2mm, ~75% did not resolve by post-treatment CBCT. Motion magnitude varied considerably among patients, with the probability of a 5mm displacement ranging from 0.0% to 58.8%.

Conclusions—Time dependency of intrafraction motion should be considered to avoid bias in margin assessment, with post-treatment CBCT slightly exaggerating the true motion. The patient-specific nature of the intrafraction motion suggests a patient-specific management approach may be beneficial.

Keywords

Prostate Cancer; Intrafraction; Organ Motion; Radiation Therapy; CBCT

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Introduction

Advances in image-guided radiotherapy have made daily correction of interfractional uncertainties possible for prostate cancer treatment. Many clinics now have the capability of some form of online image guidance, leading decreased target positioning uncertainty and reduced treatment margins. With the correction of interfractional uncertainties, accurate quantification of intrafraction motion and residual setup error has become increasingly important for prostate cancer radiotherapy.

The general characteristics of prostate intrafraction motion have been presented in a number of publications. From these, we know the general probability of motion for a typical radiotherapy fraction (1–3), that motion is largest and is correlated in the anterior-posterior (AP) and superior-inferior (SI) axes (1,4,5), and that the probability of motion depends upon elapsed time (1,3,6). Intrafraction motion has also been characterized according to patient diet (7), treatment setup orientation (5,8), rectal filling status (3,9,10), and when rectal balloons are used (11).

In treatment planning intrafraction motion is often compensated using additional margins. Methods for determining adequate margins include recipes from descriptive statistics (12) and reconstruction of delivered dose taking into account the motion (13,14). Both methods assume the measured motion is representative of the actual probability of motion at treatment delivery. However, because the probability of motion increases with treatment duration, differences in the measurement acquisition schedule and treatment delivery schedule could potentially lead to discrepancies between the measured probability of motion used for margin calculation and actual probability of motion at treatment delivery. For example, a post-treatment localization using Cone Beam Computed Tomography (CBCT) or ultrasound is often performed for motion evaluation. Because this localization is always made after treatment delivery, a systematic difference in motion magnitude may be introduced. Indeed, although only prostate motion occurring during Mega-Voltage (MV) delivery will be of dosimetric consequence, most reported measurements consist of pre- and post-treatment measurements only, are not synchronized with treatment delivery, or do not involve treatment delivery at all.

At our clinic we recently demonstrated feasibility of measuring prostate intrafraction motion using a gantry mounted kV imager and synchronizing the measurement with treatment delivery (15,16). This technique can provide an estimate of the 3D prostate position at the time of MV beam delivery and is potentially applicable to the large number of clinics with gantry mounted kV imager technology installed. We have applied this technique in conjunction with pre- and post-CBCT acquisitions to measure the intrafraction motion for 30 hypofractionated radiotherapy patients, for a total of 571 fractions of treatment. In this paper we describe the prostate intrafraction motion at treatment delivery for this group of patients.

Methods and Materials

Protocol

At William Beaumont Hospital, 30 patients were enrolled in an institutional review board approved protocol for hypofractionated prostate radiotherapy. Patients had 3 gold coils (Visicoil, IBA, Bartlett TN) implanted into the prostate gland via ultrasound guidance, and Magnetic Resonance Image (MRI) and Computed Tomography (CT) images acquired of the prostate region for treatment planning. The treatment plan consisted of Intensity Modulated Radiation Therapy (IMRT) using 6 or 15 MV photons delivered at 5–7 gantry angles, and treatment was delivered in 20 fractions of 3.2 Gy per fraction. Ten patients were treated with

a 7 beam arrangement (235°, 285°, 335°, 25°, 75°, 125°, 180°), three patients with 5 beams (230°, 300°, 15°, 90°, 155° or 195°, 270°, 335°, 50°, 120°), and seventeen patients with 6 beams (220°, 280°, 330°, 30°, 80°, 140°). Patients were given dieting instructions similar to those described by Smitsmans *et al.* (7) and were instructed to take Gas-X and 30cc of Milk of Magnesia daily, but were not instructed to void bladder or rectum before treatment.

At each fraction the patient was aligned on the treatment couch to skin marks in supine position and a pre-treatment CBCT (CBCT₁) was acquired of the treatment area. CBCT₁ was reconstructed online and a 6-degree registration was performed based on the position of the coils relative to the planning CT (17). While the registration included rotations, the applied correction did not, the effect of which was investigated by Murphy (18). To minimize errors, the 6-degree registration was first converted to a couch translation (ignoring rotation) within the clinical software and was approved by the operator, after which the couch was shifted. Treatment was delivered afterwards using step-and-shoot IMRT and kV fluoroscopy images were acquired at 5.5 Hz at each beam beginning at treatment beam initialization and lasting throughout MV delivery with a maximum duration of ~38s per beam. After treatment delivery a second CBCT (CBCT₂) was acquired. The mean ($\pm$ standard deviation) of the elapsed time between midpoint of CBCT₁ and initiation of the first kV fluoroscopy acquisition was 5.8 minutes ($\pm$ 2.0 min), with the mean elapsed time between midpoint of CBCT₁ and completion of the final kV fluoroscopy acquisition being 14.9 minutes ($\pm$ 2.0 min). The elapsed time between midpoint of CBCT₁ and midpoint of CBCT₂ was 18.6 minutes ($\pm$ 4.5 min).

Intrafraction Motion Evaluation

The intrafraction motion evaluation has been previously described in detail (15); here we give a brief summary. We use MV scatter incident on the kV imager to detect the turning on and off of the MV beam. Although it is possible to detect intra-beam motion by analyzing each fluoroscopy frame, we averaged the fluoroscopy images acquired during Multi-Leaf Collimator (MLC) movements between step-and-shoot segments to obtain one localization per gantry angle. While it is possible to use frames acquired during MV delivery, this does little to improve the 3D localization accuracy for monoscopic imaging (16).

Image processing included smoothing to reduce noise and applying a gradient across the image to emphasize small high contrast objects (15). The fluoroscopy images were registered automatically to a template image derived from CBCT₂ which consisted of a Digitally Reconstructed Radiograph (DRR) of the coils only, and the registration was verified visually. We estimated the prostate 3D trajectory throughout the fraction by assuming the shortest path satisfying all 2D localizations (one per gantry angle) and ending at CBCT₂ (6), the error of which was investigated previously and was shown to be typically <1.5mm for 95% of localizations (16). We also estimated the 3D trajectory assuming the shortest path without taking into consideration CBCT₂, and compared it to the situation assuming the shortest path ending at CBCT₂.

We evaluated intrafraction motion at each fraction for which CBCT and kV fluoroscopy images were acquired. In some cases there were fewer than 20 fractions per patient because fluoroscopy and/or CBCT₂ were not available for various reasons. Overall, the analysis included 571 fractions with 3112 point measurements from kV fluoroscopy and 552 localizations from CBCT₂. CBCT₁ was used as the reference (accounting for the online correction) in the motion evaluation of the 19 fractions for which CBCT₂ was not acquired.

Analysis

We report the motion characteristics for our treatment protocol and group of patients. Our analysis included calculating population descriptive statistics, evaluating correlation between interfraction and intrafraction motion, evaluating the effect of treatment duration on motion magnitude, classifying motion based on whether it resolved by CBCT₂, comparing motion magnitude on a per patient basis, and comparing target uncertainty before online correction and during treatment delivery.

We calculated population statistics of (1) intrafraction motion measured by kV fluoroscopy, (2) intrafraction motion measured by CBCT₂, and (3) prostate uncertainty before the couch correction (interfractional & setup error) measured by CBCT₁. The difference between descriptive statistics calculated using kV fluoroscopy and CBCT₂ represents bias between intrafraction motion measured using post-treatment localization and the actual motion at treatment delivery.

For each patient we define $\mu_{i,j}$ and $\sigma_{i,j}$ as the mean and standard deviation in each axis of all intrafraction positions obtained from shortest path analysis between fractions i and j , with positive values corresponding to displacements from the treatment plan in the right, posterior, and superior directions. We describe the patient specific mean (M_p), systematic (Σ_p), and random (RMS_p) errors in each axis as:

$$M_p = \sum_{j=1}^F \frac{\mu_{j,j}}{F} \quad (1)$$

$$\Sigma_p = \sqrt{\sum_{j=1}^F \frac{(\mu_{j,j} - M_p)^2}{F - 1}} \quad (2)$$

$$RMS_p = \sqrt{\sum_{j=1}^F \frac{\sigma_{j,j}^2}{F - 1}} \quad (3)$$

where F is the total number of fractions for the patient. We calculate the global mean (M_T) systematic (Σ_T), and random (RMS_T) errors, defined as:

$$M_T = \sum_{i=1}^N \frac{M_{pi}}{N} \quad (4)$$

$$\Sigma_T = \sqrt{\sum_{i=1}^N \frac{(M_{pi} - M_T)^2}{N - 1}} \quad (5)$$

$$RMS_T = \sqrt{\frac{\sum_{i=1}^N \frac{\Sigma_{P_i}^2 + RMS_{P_i}^2}{N-1}}{N-1}} \quad (6)$$

where N is the total number of patients, M_{P_i} is the mean, Σ_{P_i} is the systematic, and RMS_{P_i} is the random error for patient i . Because CBCT₁ and CBCT₂ each consists of only one measurement per fraction, the values of $\sigma_{j,j}$ and RMS_P are zero when calculating descriptive statistics for these cases. We also calculated the probability of displacement from the treatment plan for kV fluoroscopy, CBCT₁, and CBCT₂.

It is possible that patients with large interfraction motion will also have large intrafraction motion, which may be useful in deciding the optimal treatment protocol for a particular patient. We tested this hypothesis by measuring the correlation between patient specific interfractional (from CBCT₁) and intrafractional (from kV fluoroscopy) systematic errors (Σ_P) for each axis.

Many methods of margin calculation and evaluating the dosimetric consequences of intrafraction motion assume a constant probability of motion throughout each fraction; however recent studies have shown that prostate intrafraction motion is dependent on elapsed treatment time (1,3,6). We evaluated the positional uncertainty as a function of elapsed time from CBCT₁ by sorting prostate position measurements (both kV fluoroscopy and CBCT₂) by elapsed time from CBCT₁ and binning them into 2 minute intervals. For each interval we calculated the probability of a vector displacement from the plan greater than 1, 2, 3, and 5mm, as well as the probability of a 3mm displacement in each axis. Insufficient data was available for calculations <4 and >26 minutes. For kV fluoroscopy acquisitions, elapsed time was measured from midpoint of CBCT₁ to midpoint of the kV fluoroscopy acquisition. For CBCT₂ acquisitions, elapsed time was measured from midpoint of CBCT₁ to midpoint of CBCT₂.

To assess how often the prostate reverses its direction of motion during treatment, we evaluated the percentage of fractions that motion did and did not resolve by CBCT₂. For a given threshold, we classified each fraction as having resolved, having not resolved, or having no motion above the threshold. Fractions were classified as having resolved if the threshold was exceeded during the fraction but the final displacement (CBCT₂) was below the threshold. Fractions were classified as having not resolved if the threshold was exceeded during the fraction, and remained at or above the threshold at CBCT₂.

If intrafraction motion varies significantly between patients, it may be best managed on an individual basis, and adaptive strategies applied for interfraction motion (19) may also be applicable for intrafraction motion. To evaluate the potential of adaptive strategies for prostate intrafraction motion we computed descriptive statistics for each patient, including the probability of vector displacement from the plan after online correction.

Results

Table 1 shows the values of M_T , Σ_T , and RMS_T calculated from kV fluoroscopy, CBCT₁, and CBCT₂. Observed prostate motion from kV fluoroscopy was greatest in AP and SI, and posterior and inferior motion were correlated with a correlation coefficient (cc) of 0.53 ($p < 0.0001$). RL-axis motion was generally of smaller magnitude, having little correlation with other axes. The value of M_T increased in AP and SI between the kV fluoroscopy and CBCT₂, indicating a global drift throughout the fraction in the posterior and inferior directions. No such drift was observed in the RL-axis. Interfraction motion was correlated

with intrafraction motion with $cc = 0.57, 0.54$, and 0.48 in RL, AP, and SI, respectively ($p_{RL} = 0.001$, $p_{AP} = 0.002$, $p_{SI} = 0.008$).

The probability of vector displacement from the plan is plotted in Figure 1 for kV fluoroscopy, CBCT₁, and CBCT₂. For kV fluoroscopy the probability of displacement greater than 3, 5, 7, and 10mm was 31.6%, 11.2%, 4.5%, and 0.5%, respectively. For CBCT₂ this increased to 38.0%, 15.6%, 8.2%, and 1.5%, and the probability was largest for CBCT₁, at 80.4%, 50.2%, 25.7%, and 8.8%. Also shown for comparison is the localization error for the kV fluoroscopy technique measured in a previous study (16), and the average probability of displacement greater than 3, 5, 7, and 10mm measured by Langen *et al.* using electromagnetic transponders for 17 patients (550 tracks, mean treatment duration = 10 min) (1). In both Table 1 and Figure 1 the probability of displacement for CBCT₁ was considerably larger than for kV fluoroscopy, showing an overall reduction in prostate position uncertainty from online image guidance. Also, the measured intrafraction motion from CBCT₂ was systematically larger than the measured motion from kV fluoroscopy. Differences in prostate trajectories were minimal when assuming the shortest path ending at CBCT₂ and when CBCT₂ was not taken into consideration, with the mean $\pm$ standard deviation of the difference being 0.0 ± 0.1 mm in both RL and AP.

Figure 2 shows the time dependency of the motion. In 2A the probability of displacement from the planning CT greater than 1, 2, 3, and 5mm is plotted versus elapsed time from CBCT₁, showing an overall increase in probability of motion over time. In 2B, the probability of displacement >3 mm is plotted for each axis. All three axes generally showed increasing probability of motion, with the RL-axis motion being of smaller magnitude. Measurements were used from both kV fluoroscopy and CBCT₂, with the total number of measurements in each interval shown in 2C.

Figure 3A shows the percentage of all fractions classified as having resolved by CBCT₂, not having resolved by CBCT₂, and having no motion greater than the threshold during kV fluoroscopy, as a function of the threshold. Figure 3B shows the percentage of fractions with motion above the threshold classified as having resolved and not having resolved. For a threshold of 2 and 4mm, 21% and 25% of fractions with motion above this threshold were classified as having resolved by CBCT₂. From Figure 3B we see that above ~ 2 mm, the percentage of fractions with motion above the threshold classified as having resolved was fairly constant at $\sim 25\%$ for all thresholds. This signifies that for any displacement measured during treatment delivery ≥ 2 mm, there is a $\sim 25\%$ probability that the prostate will return to below the threshold by CBCT₂, and $\sim 75\%$ probability that the prostate displacement will remain above the threshold throughout CBCT₂. To put it another way, CBCT₂ alone is unable to detect the intra-fraction motion for 25% of cases.

The probability of vector displacement from the plan exceeding a threshold during treatment delivery is plotted for each patient in Figure 4. The motion varied considerably between patients, with the median vector displacement per patient ranging from 1.1-5.4mm, and the 95th percentile of the vector displacements (red dashed horizontal line in Fig. 4) ranging from 2.4-10.5mm. The probability of a 2mm and 5mm displacement ranged from 11.8% to 97.6%, and from 0.0% to 58.8%, respectively. These results indicate that the prostate motion varies considerably on a per patient basis, and that patient specific compensation strategies for intrafraction motion may be worthwhile.

Figure 5 shows an evaluation of the online correction for the 5 patients with the largest 95th percentile error. Plotted for each patient is the probability of vector displacement greater than a threshold as measured by CBCT₁, kV fluoroscopy, and CBCT₂. In comparison to

probability of motion during kV fluoroscopy, the probability of displacement at CBCT₁ ranged from being much greater (A) to no apparent difference (E).

Discussion

Previous studies have shown that prostate intrafraction motion is dependent on treatment duration. Langen *et al.* used prostate motion tracks from electromagnetic transponders and showed that the likelihood of displacement increased with time elapsed after patient positioning (1). Kotte *et al.* used portal imaging at each gantry angle, and showed the probability of motion increased at each beam (6). Ghilezan used cine-MRI to calculate the probability of displacement versus time for various abdominal points of interest, and showed increasing probability with time for prostate (3). Our analysis also shows the probability of displacement increasing with elapsed time. This is quite reasonably the cause of the difference in magnitude measured using CBCT₂ vs. kV fluoroscopy shown in Table 1 and Figure 1. In our case, using CBCT₂ rather than measurements during treatment delivery exaggerated M_T and Σ_T in the AP and SI axes on the order of ~0.5mm. Similar bias will likely be introduced for other protocols where motion measurement and treatment delivery do not occur over the same timeframe.

In comparison to other studies, the systematic and random errors reported by Kotte *et al.* are approximately half the magnitude of the values reported here (6). One explanation is that their measurements were relative to the first beam angle with a delivery time of 5–7 minutes, while both increased delivery time and residual setup error are included in our error. Also, the average probability of displacement measured by Langen *et al.* (shown in Figure 1) was somewhat smaller in magnitude than our measured values, which may also be caused by the time dependency of the motion. Although mean treatment durations were similar, in our case treatment delivery and kV fluoroscopy acquisition were typically initiated 5–6 minutes after CBCT₁, and the probability of displacement before this period can be expected to be of smaller magnitude. However another possible cause is that our protocol may include greater residual setup error because in their case the electromagnetic transponders are used to verify the correction online. Overall our results suggest that the timeframe of the motion measurement is not irrelevant, and because of this we recommend that any intrafraction motion measurement used for margin assessment be of a similar timeframe as treatment delivery.

Langen *et al.* observed two types of intrafraction motion: slow posterior and inferior drifting that does not resolve spontaneously, and sudden transient motion that often resolves spontaneously (1). Kotte *et al.* also observed that a reversal of motion direction occurs for many patients (6). In comparison, we found that when displacement above any threshold >2mm occurred during treatment delivery, the prostate will return to below the threshold by CBCT₂ in ~25% of cases. We also observed a global posterior and inferior drift, which is most likely caused by bladder filling (20). Although this drift was small in magnitude, a global drift will result in translation rather than blurring of the dose and hence may have non-negligible dosimetric consequences. Therefore further investigation involving dose reconstruction is warranted. One expectation is that the posterior prostate drift may lead to increased bladder and decreased rectum dose.

Our observation that intrafraction motion varies considerably per patient agrees with previous studies (1,3). While this suggests that patient specific margins would be worthwhile, it has yet to be shown that they may be estimated with sufficient accuracy within the first few fractions. We investigate the feasibility of adaptive strategies for prostate intrafraction motion in further detail in a companion paper (21).

Ideally the online correction should eliminate interfractional uncertainties and result in much smaller magnitude of motion; however for some patients with large intrafraction motion we observed target uncertainty during treatment delivery to be similar in magnitude to before online correction. While it appears from this data that the online correction may be less effective for some patients, these results should be considered cautiously for a number of reasons. First, the target uncertainty for CBCT₁ does not account for added intrafractional uncertainties that would be present in a protocol without image guidance. Second, our measurement of interfractional motion magnitude may be biased because of the fact that in anticipation of the online correction, therapists may not perform the initial setup as carefully as possible.

The results presented here should be considered together with the limitations of our kV fluoroscopy measurement technique. Because we perform only one localization per beam angle we do not detect higher frequency motion. Also to obtain a 3D trajectory we assume the shortest path ending at CBCT₂, which will also introduce some error (95% within ~1.5mm) (16), however in our analysis we found little difference whether CBCT₂ is included in the shortest path reconstruction. We also did not evaluate rotations; previous studies measured intrafractional rotations to be $\leq 1.8^\circ$ for all axes, and interfractional rotations to be 6.8–8.0° about the RL-axis and $\sim 3^\circ$ in other axes (22,23).

In conclusion, we have evaluated prostate intrafraction motion for a hypofractionated prostate radiotherapy protocol using kV fluoroscopy during treatment delivery. The probability of prostate motion increased with treatment duration, which this should be considered in margin assessment to avoid bias. The measurement by post-treatment localization exaggerates the true intrafraction motion. A global drift was observed in the posterior and inferior directions, with ~75% of motion being classified as not having resolved by CBCT₂. Motion magnitude varied considerably from patient to patient, suggesting a patient specific approach to compensating intrafraction motion may be beneficial.

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Figure 1. Probability of vector displacement from planning CT for kV fluoroscopy, CBCT₁, and CBCT₂. Also shown is the average probability of motion measured by Langen *et al.* (1) and the kV fluoroscopy localization error (16).

A

B

C

Figure 2.

(A) Probability of vector displacement greater than 1, 2, 3, and 5mm versus elapsed time from CBCT₁. (B) Probability of 3mm displacement in the right-left (RL), anterior-posterior (AP), and superior-inferior (SI) axes versus elapsed time from CBCT₁. (C) Number of measurements in each 2-minute interval.

Figure 3.

(A) Percentage of fractions classified as having resolved by CBCT₂, not having 5 resolved by CBCT₂, and having no motion greater than the threshold. (B) Percentage of motion during treatment delivery greater than a threshold that resolved and did not resolve by CBCT₂.

Figure 4. Probability of vector displacement from plan exceeding a threshold at treatment 10 delivery measured by kV fluoroscopy, each line represents one patient. The red horizontal dashed line indicates the 95th percentile error.

Figure 5. Probability of displacement from plan measured by kV fluoroscopy, CBCT₁, and CBCT₂ for the 5 patients with the largest 95th percentile of motion.

Table 1

Descriptive statistics of population calculated using CBCT₁, kV fluoroscopy, and CBCT₂. RL=Right-Left, AP=Anterior-Posterior, SI=Superior-Inferior. RMS=Root-Mean-Square.

data set	RL (mm)			AP (mm)			SI (mm)		
	M _T	Σ _T	RMS _T	M _T	Σ _T	RMS _T	M _T	Σ _T	RMS _T
CBCT ₁	-0.5	2.3	2.6	2.2	3.3	2.8	0.5	1.8	2.1
kV fluoroscopy	-0.1	0.5	0.9	0.5	1.3	1.9	-0.6	1.2	2.0
CBCT ₂	0.0	0.6	0.8	1.0	1.7	2.1	-0.9	1.5	2.0