## ORIGINAL ARTICLE

# Calculating interfractional prostate motion during radiation therapy course using fiducial markers

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## Summary

*Purpose:* In this study we evaluated the day to day prostate displacement during radiation therapy by using implanted radiopaque fiducials and daily image guided position verification.

*Methods:* The data of 10 patients that received radiation therapy to the prostate were analyzed. Three fiducial markers were implanted in the prostate before treatment initiation for everyday verification of the target's position. Daily X ray images (kilovolt/KV films) of the pelvis were acquired for verification and were matched with baseline images produced during treatment preparation using bony structures and fiducials as landmarks. We calculated the mean difference between the two methods and the prostate displacement derived from these measurements.

*Results:* A total of 208 KV films were obtained. Our results showed a non-uniform prostate motion, with most of the displacements observed in the caudal direction followed by anterior, posterior, cranial, right and left. The mean target motion in each of the above directions was 3.5 mm, 3.5 mm, 3.3 mm, 3.9 mm, 2 mm and 2.4 mm. Based on the cumulative frequency of the target's displacement, a margin of 8 mm, 7mm, 5 mm, 4 mm, 9 mm and 7 mm in the anterior, posterior, left, right, cranial and caudal direction respectively would account for 95% of prostate's motion, provided that every day KV image guidance is performed.

*Conclusion:* A non-isotopic margin of 8 mm, 7mm, 5 mm, 4 mm, 9 mm and 7 mm around the prostate can be considered safe for treatment delivery.

*Key words:* fiducials, interfractional motion, prostate, radiotherapy

## Introduction

Radiation therapy is among the most commonly used treatments for prostate cancer with disease control rates comparable to radical prostatectomy for all stages [1–3]. Additionally, modern radiotherapy techniques such as volumetric arc therapy (VMAT), have significantly reduced toxicity leading to excellent tolerability of the treatment by the patients [4–11]. Historically, safety margins were applied around the target (Planning Target Volume, PTV) in order to account for everyday variability of the patient's positioning on the linear accelerator as well as for the day to day displacement of the prostate (interfractional movement) due to bladder and rectum filling [12–19]. The PTV margins reassure that the target will not be missed but they lead to more toxicity by increasing the size of radiation fields [20–23]. Advances in radiological imaging, have allowed for daily image guidance (Image Guided Radiation Therapy, IGRT) in order to verify the position of the prostate before treatment and thus

reduce the PTV margins. The variation in prostate's position during treatment is of great importance specifically in cases where port films or KV (kilovoltage) images are used for the verification since prostate is not visible and bone structures are used as landmarks. In this study we intended to evaluate interfractional prostate movement and propose PTV margins to adjust for this target displacement.

## Methods

This trial included patients with biopsy proven localized prostate cancer (cT1c-cT3bN0M0) that received radiation therapy only to the prostate (lymph node irradiation was not permitted), were 40 to 85 years old and had WHO performance status 0-2. Patients with a calculated risk of lymph node involvement ≥5% [24] were excluded from the study, as were those with PSA level > 40 ng/ml, T3 disease and GS ≥8, T3 disease and PSA ≥10 ng/ml and those with GS ≥8 and T3-T4 disease or PSA level ≥10 ng/ml. Any previous operations to the prostate or urinary bladder (history of prostatectomy, transurethral resection of bladder tumor (TURBT)), inflammatory bowel disease, hip replacement, previous irradiation of the pelvis were not allowed. All patients were staged with digital examination, prostate biopsy, PSA evaluation, and CT of the pelvis and abdomen. Pelvic MRI and bone scan were prescribed for patients with T3-T4 stage, PSA >20 ng/ml or GS 8-9 or for those with symptoms.

In case of hormone therapy (androgen deprivation therapy, ADT), an LHRH analogue combined with initial anti androgen to reduce testosterone flair was given 2 months before initiation of radiotherapy. Patients received ADT for 6 months of 2-3 years according to risk group. Under transrectal ultrasound guidance, three radiopaque markers (fiducials) were implanted in the prostate, one in the apex and two in the base. The fiducials should be placed in such an arrangement that they are all visible in frontal (0 degrees) and lateral (90 degrees) X ray imaging. The day before implantation, patients were instructed to use an enema and receive 1000 mg of Kinolone. In case of use of anticoagulants, the medicine should be stopped 5 days before and replaced by heparin injections.

CT simulation was performed at least 5 days after fiducials placement by acquiring a 3 mm slice CT of the pelvis from L4 vertebra up to the ischial tuberosities. The patients were instructed to use an enema the night before simulation and the same day they should empty their bladder and drink 500 ml of water 45 min before CT scan (bladder filling protocol). The prostate with or without the seminal vesicles (SV) and normal tissues (organs at risk, OAR) were delineated. Decision on if and to which extend the SV would be treated was made according the calculated risk of involvement [25]. If the estimated risk was <10%, the prostate alone would be treated to a total dose of 72 Gy (2.25 Gy per fraction in 32 fractions), while for a calculated risk between 10-25%, the prostate together with the proximal 1 cm of the SV received the prescribed dose and the rest of the SV were treated to lower dose of 58.9 Gy (1.84 Gy/fr). Finally, if the risk was above 25% the prostate and the proximal

2 cm received 72 Gy. OAR included the femoral heads, penile bulb, bladder, bowel bag and rectum and mandatory dose constraints for these organs were defined. A planning target volume (PTV) of 10 mm in all directions and 5 mm posteriorly was used. To ensure minimum interfractional prostate motion, patients were instructed to follow the bladder filling protocol every day before treatment and received instructions regarding dietary management, fluid intake and laxative use.

Patients' position was evaluated daily before treatment by acquiring two X ray images (KV) of the pelvis in 0 and 90 degrees and two methods were used to match the KV images with the digitally reconstructed images (DRR) produced by the initial CT scan simulation. First, the matching was performed using bony landmarks of the pelvis and then a second registration followed using the fiducials before proceeding to treatment. The couch shifts in three axes (vertical, lateral and longitudinal) produced by the fiducials protocol relative to bone match were documented. The prostate motion was calculated by translating the couch shifts as follows: a positive shift in the vertical, lateral and long axes indicated a displacement in the anterior, left and cranial direction while negative values were indicative of posterior, right and caudal displacement.

Frequencies of the couch shifts in the three axis (vertical, long, lateral) were presented using percentages. The shifts were dichotomized into a new variable (shifts observed vs no shifts observed) and McNemars's test was used to compare frequencies between vertical, long and lateral axis. The level of significance was set to a= 0.05. The calculated significance level of McNemar's test was adjusted using the Bonferroni's correction. Descriptive statistics of the displacements (in mm) in the anterior, posterior, cranial, caudal, left and right direction were presented using mean value with 95% confidence interval, range and standard deviation. For all 6 directions, the value of the empirical cumulative distribution function was calculated at the 95th percentile, providing an estimate of the margin around the target needed to cover 95% of displacements. Statistical analysis was performed using SPSS version 25. Therapy was delivered using the volumetric arc therapy (VMAT) technique. All patients provided written informed consent.

## Results

Ten patients with localized prostate cancer were included in the study and a total of 208 KV films were taken. The most common couch correction using the fiducials protocol was observed in the vertical axis (87.5% of total cases) followed by long (64%) and lateral (34.6%) (Table 1). The frequency distribution of couch shifts in each axis is presented in Figure 1. McNemar's test showed a statistically significant difference in the shift frequency between vertical and lateral (p< 0.001) or long and lateral (p< 0.001), while no difference was observed between vertical and long (p= 0.154). The mean couch correction by fiducial usage relative to

bone match in the vertical, lateral and long axis was 0.51 MM (confidence intervals (CI) -0.1–10.2), -0.15 MM (CI (-) 3.6–(-)0.6) and -0.65 MM (CI (-)12.3–(-)0.7), respectively. The most common target displacement was towards the caudal direction (52.4%) followed by anterior (49.5%), posterior (38%), cranial (30.3%), right (22.1%) and left (12.5%) (Table 2). After considering only those cases that any motion was observed, the calculated mean displacement was 3.5 mm (CI 3.1-3.9) in the anterior direction, 3.3 mm posteriorly (CI 2.8-3.8), 2.4 mm left (CI 1.9-2.9), 2 mm right (CI 1.6-2.5), 3.9 mm cranially (CI 3.1-4.7) and 3.5 mm caudally (CI 2.9-4.1). Distributions are seen in Figure 2. Extremes of motion were rare in the anterior and posterior direction, with only 1% and 1.3% of cases respectively presenting a target movement of ≥1 cm. In the cranial and caudal direction, the corresponding values were higher with 3.2% and 2.7% of cases presenting a displacement of ≥1.3 cm and 0.8 cm respectively. The highest rates of extremes were observed in the left (7.6% ≥0.5 cm displacement) and right direction (6.5% ≥0.4 cm displacement). Based on the cumulative frequency of the displacements observed, a margin of 8 mm, 7 mm, 5 mm, 4 mm, 9 mm and 7 mm in the anterior, posterior, left, right, cranial and caudal direction would be required in order to cover 95% of the interfractional motion

**Table 1.** Descriptive statistics of table shifts difference between bone match and fiducials in each axis

|  | *N(%)* | *Mean (mm)* | *95% CI* | *SD* | *Range* |
|---|---|---|---|---|---|
| Vertical | 182 (87.5) | 0.51 | (-)0.1– 10.2 | 3.76 | 20 |
| Longitudinal | 172 (64) | -0.65 | (-)12.3 – (-)0.7 | 4.25 | 35 |
| Lateral | 72 (34.6) | -0.15 | (-)3.6 – (-)0.6 | 1.51 | 17 |

N: displacement count observed in the corresponding axis (number in parenthesis represents percentage of total observations), Mean represents the mean difference between the two matching protocols, CI: confidence intervals, SD: standard deviation
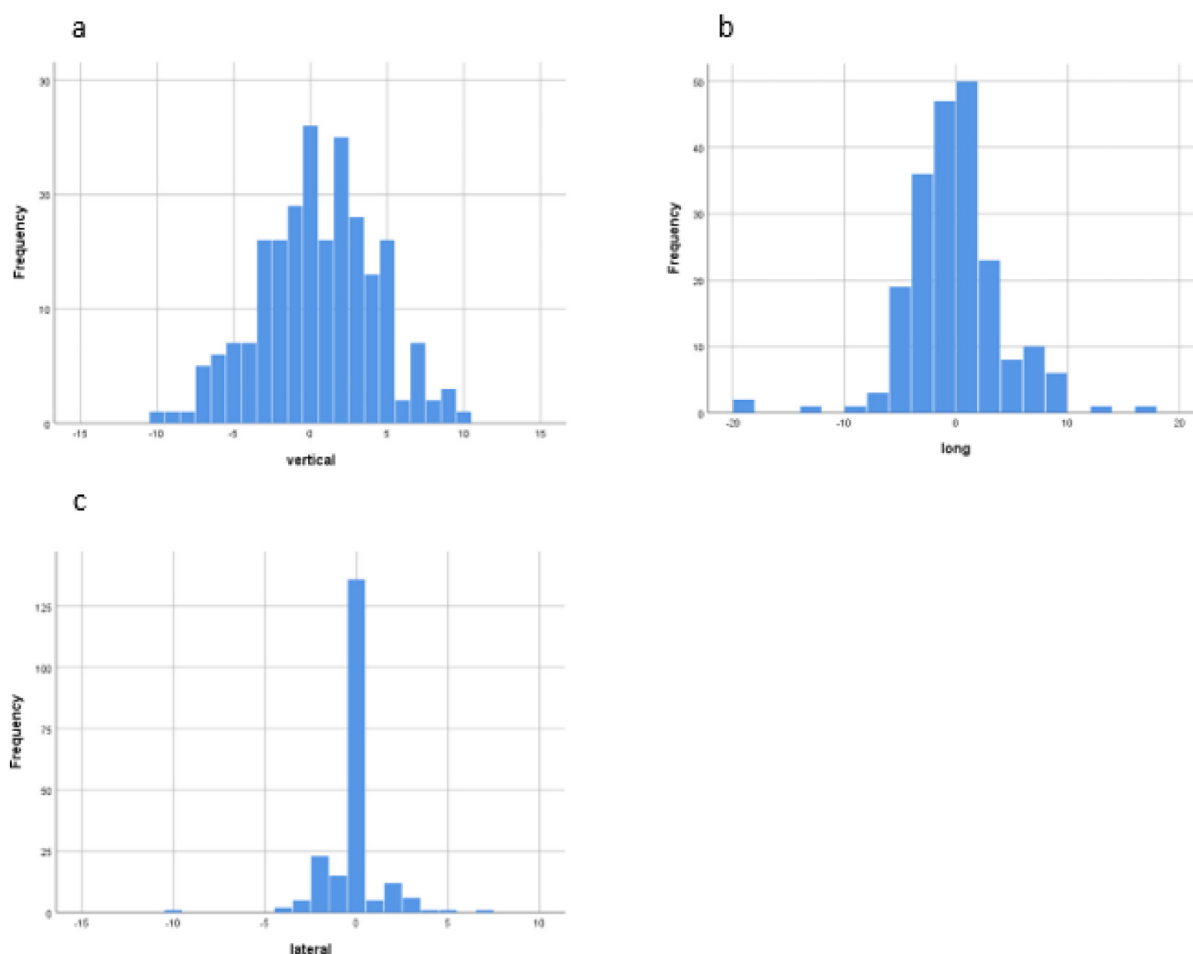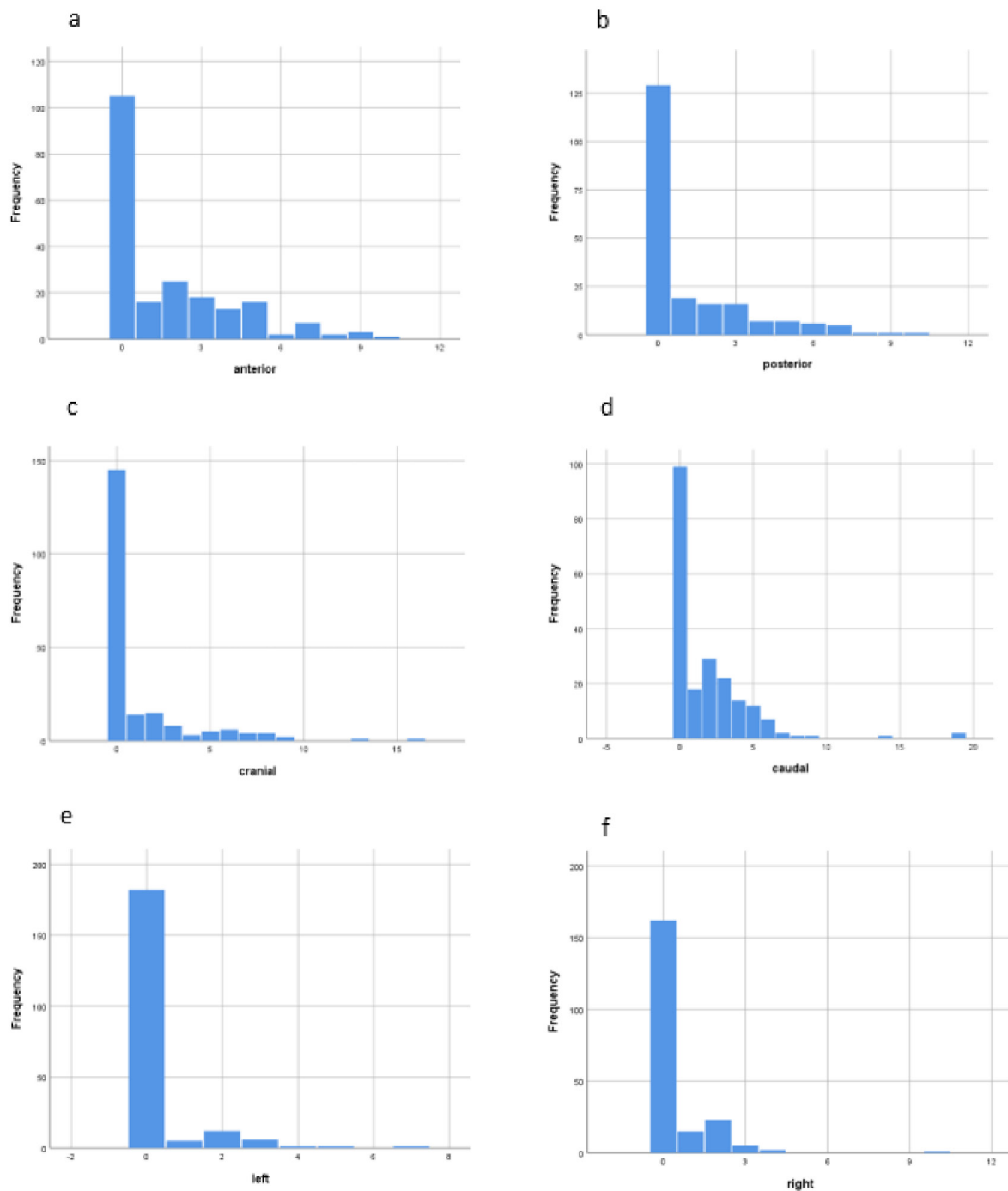


**Figure 1.** Frequency distribution of the displacements in **(a)** vertical, **(b)** long and **(c)** lateral axis.

**Table 2.** Descriptive statistics of prostate displacement in each direction

| | N (%) | Mean (mm) | 95% CI | SD | Range |
|---|---|---|---|---|---|
| Anterior | 103 (49.5) | 3.55 | 3.13-3.97 | 2.15 | 9 |
| Posterior | 79 (38) | 3.29 | 2.81-3.78 | 2.16 | 9 |
| Cranial | 63 (30.3) | 3.94 | 3.15-4.72 | 3.1 | 15 |
| Caudal | 109 (52.4) | 3.51 | 2.96-4.07 | 2.92 | 18 |
| Left | 26 (12.5) | 2.42 | 1.89-2.96 | 1.33 | 6 |
| Right | 46 (22.1) | 2.04 | 1.62-2.47 | 1.43 | 9 |

N: displacement count observed in the corresponding direction (number in parenthesis represents percentage of total observations), CI: confidence intervals, SD: standard deviation



**Figure 2.** Frequency distribution of the displacements in **(a)** anterior, **(b)** posterior, **(c)** cranial, **(d)** caudal, **(e)** left and (f) right direction.

## Discussion

In this study we found a mean prostate displacement of 3.5 mm, 3.3 mm, 3.9 mm, 3.5 mm, 2.4 mm and 2 mm in the anterior posterior, superior, inferior, left and right direction respectively. After comparing bone match and fiducials methods for image matching during setup verification, we found a mean difference in the table shifts between the two methods of 0.51 mm, -0.65 mm and – 0.15 mm in the vertical, longitudinal and lateral axis, respectively. This study was conducted to estimate the interfractional motion of prostate and propose safety margins around the target to account for these displacements.

Modern radiotherapy and imaging methods have evolved dramatically allowing radiation oncologists to safely increase dose without harming the surrounding normal tissues [4–11]. This is particularly important since there are data in the literature supporting that dose escalation leads to better disease control [26–32]. Additionally, modern techniques have led to significantly less toxicity, while larger margins around the target volume and larger radiation fields have been associated with higher toxicity rates [20–23]. Consequently, defining PTV margins is of great importance in order to safely delivery radiation therapy. Balance should be kept though between minimizing toxicity and ensuring target coverage. Today, IGRT combined with high doses of IMRT therapy is the standard of care and verification protocols, including CT scans or Xray images (Kilovoltage Imaging, KV) of the pelvis are used. The latter is frequently combined with fiducials markers to identify the target's position since prostate is not visible on those images. Some departments face difficulties in employing fiducial usage in every day clinical practice (lack of human or financial resources, difficulties in cooperation between departments) in which case, defining margins becomes a real challenge since bony landmarks are used as a surrogate for prostate position. Knowing the amplitude of prostate displacement between treatments is of great importance in order to safely apply margins and ensure target coverage. The margins proposed in this study would cover most of prostates interfractional motion, given that everyday image guided radiation therapy with bone match is performed to account for day to day setup variation.

Some other studies in the literature have found similar results. Schallenkamp et al followed a similar methodology to our study by implanting fiducials to track prostate motion and found that the mean displacement in the superior-inferior, anterior-posterior and right-left direction was 2.5 mm, 3.7 mm and 1.9 mm respectively [33] . In another study, larger target movement was observed,

with mean values of 5.6 mm and 5.9 mm in the posterior and inferior direction respectively [34]. Additionally, a displacement bigger than 1 cm in the posterior and inferior direction was observed in 30% and 11% of the total cases, much higher than the rates observed in our study. The authors attributed this result to bladder and rectum filling and subsequent distension of those organs.

The important role of bladder and rectum filling to interfactional movement has been verified in a number of studies [35-38]. Schild et al [36] found a prostate displacement of up to 0.8 cm (median 0.2 cm) posteriorly due to bladder distension, while Ten Haken et al [35] observed that rectal distension with 60 cc of contrast resulted in an anterior-superior shift of the prostate of 0.5 cm mean value (range 0-2 cm). In another report by Melian et al [37], instillation of 30 cc of air into the rectum led to shifts in target of up to 30 cm anteriorly and superiorly and 1.5 cm laterally. This highlights the importance of keeping consistent rectal and bladder volumes as much as possible throughout the course of radiation therapy. We followed a strict protocol of bladder filling and dietary instructions which probably led to less frequent extremes of motion as well as to relatively small prostate displacements.

This study has limitations. We only used KV portals for imaging and not cone beam CT. Such an approach would offer us more accurate information on prostate movement as well as on target rotation. Moreover, we only observed fiducials shifts relative to bone match to define prostate motion, while other studies have also used the center of mass (COM) as a landmark. COM was defined as the center of a triangle created by the three fiducials. This method offers additional information regarding fiducials migration during treatment course and rotational shifts of the target due to bladder and rectal dilatation. Yet, our findings are consistent with other reports in the literature [34,39-42] and we believe they can be considered safe.

To conclude, Interfractional movement is an important factor for target coverage which should always be considered when planning the radiation therapy treatment for prostate cancer. The PTV margins applied around the target account for both interfractional movement and every day setup errors. To eliminate the latter, daily KV imaging with bone match should be performed. In that case a margin of 8 mm, 7mm, 5 mm, 4 mm, 9 mm and 7 mm in the anterior, posterior, left, right, cranial and caudal direction would cover 95% of prostate displacements.

## Conflict of interests

The authors declare no conflict of interests.

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