

CLINICAL INVESTIGATION

Prostate

INTERFRACTIONAL PROSTATE SHIFTS: REVIEW OF 1870 COMPUTED TOMOGRAPHY (CT) SCANS OBTAINED DURING IMAGE-GUIDED RADIOTHERAPY USING CT-ON-RAILS FOR THE TREATMENT OF PROSTATE CANCER

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Purpose: To review 1870 CT scans of interfractional prostate shift obtained during image-guided radiotherapy.
Methods and Materials: A total of 1870 pretreatment CT scans were acquired with CT-on-rails, and the corresponding shift data for 329 patients with prostate cancer were analyzed.

Results: Of the 1870 scans reviewed, 44% required no setup adjustments in the anterior–posterior (AP) direction, 14% had shifts of 3–5 mm, 29% had shifts of 6–10 mm, and 13% had shifts of >10 mm. In the superior–inferior direction, 81% had no adjustments, 2% had shifts of 3–5 mm, 15% had shifts of 6–10 mm, and 2% had shifts of >10 mm. In the left–right direction, 65% had no adjustment, 13% had shifts of 3–5 mm, 17% had shifts of 6–10 mm, and 5% had shifts of >10 mm. Further analysis of the first 66 consecutive patients divided into three groups according to body mass index indicates that the shift in the AP direction for the overweight subgroup was statistically larger than those for the control and obese subgroups ($p < 0.05$). The interfractional shift in the lateral direction for the obese group (1 SD, 5.5 mm) was significantly larger than those for the overweight and control groups (4.1 and 2.9 mm, respectively) ($p < 0.001$).

Conclusions: These data demonstrate that there is a significantly greater shift in the AP direction than in the lateral and superior–inferior directions for the entire patient group. Overweight and obese patient groups show a significant difference from the control group in terms of prostate shift. © 2008 Elsevier Inc.

Prostate cancer, Interfractional shift, Review, Overweight.

INTRODUCTION

Several clinical studies have demonstrated a correlation between local control and the total dose delivered (1–3) for prostate cancer. Zelefsky *et al.* (3) have shown that there is a statistically significant difference in prostate-specific antigen relapse-free survival in patients who receive ≥ 75.6 Gy compared with those who received ≤ 64.8 Gy. Unfortunately, the ability to escalate dose to the prostate without causing normal tissue complications (e.g., rectal bleeding) may be compromised by a variety of geometric uncertainties spanning the entire process of prostate irradiation, including true target definition (4–6), inter- and intrafractional patient motion, organ motion (7, 8), and daily setup error (9, 10). Here, we assume that the linear accelerator and simulator geometric uncertainties (laser alignment and field shaping device) (11), the dosimetric uncertainties in beam characterization and machine output calibration, and treatment-planning quality

assurance are all handled diligently by the physicist(s) within each institution. Among all treatment geometric errors, organ motion (12) and patient setup variation (13) are two major concerns during radiation delivery for prostate cancer because they lead to shift of the target from its reference frame (as delineated in the treatment-planning CT). Depending on the treatment margins, uncorrected target shifts may lead to under-dosage of the prostate, thus potentially decreasing local tumor control, or over-dosage to the rectum, thus increasing rectal complications.

Intensity-modulated radiotherapy (IMRT) is now accepted as the standard of treatment for prostate cancer for its ability to deliver a clinically desired high dose to the target without increasing treatment morbidity (14). However, its advantage may be offset by treatment geometric errors during the treatment course. Without a clear indication of the target location, dose escalation with IMRT may cause more harm than good.

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Understanding the interfractional target shifts due to interfractional target motion and daily setup error and their management becomes a critical issue for prostate cancer IMRT. The application of image-guided IMRT (referred to here as IG-IMRT or IGRT) overcomes this weakness by correcting interfractional organ shifts before radiation delivery with image guidance.

As one of the first several centers in the United States to implement IG-IMRT for prostate cancer, the Department of Radiation Oncology at the Carol G. Simon Cancer Center, Morristown Memorial Hospital (Morristown, NJ) has performed more than 3000 treatments of IG-IMRT since its inception in June 2000. A comprehensive review of the vast clinical data may provide specific advice for further improvements in IGRT (e.g., the issue of relatively low patient throughput), as well as for conventional IMRT without image guidance (e.g., the clinical basis for planning target volume [PTV] margin formation, and patient-dependent intervention strategies).

METHODS AND MATERIALS

Study population, treatment planning, and delivery

In this study, CT studies from a total of 329 prostate patients who were treated from May 2000 to August 2005 were obtained just before radiation treatments. These patients had either primary prostate cancer or rising prostate-specific antigen levels after radical prostatectomy. Treatment management included conventional IMRT and IG-IMRT. The IG-IMRT consisted of 5–10 consecutive fractions with pretreatment CT scans in the cone-down phase or in the initial part of the radiation course. The pretreatment CTs were obtained using a CT-on-rails (Siemens Primatom; Siemens Medical Solutions, Concord, CA), from which the target shifts were determined. A total of 77.4 Gy was delivered with 15-MV X-rays in 43 fractions.

All patients were either planned with the ADAC Pinnacle 7.4f (Madison, WI) or the Helax TMS (Nucletron, Veenendaal, The Netherlands) with a five-beam setup (gantry position at 180°, 260°, 350°, 220°, and 140°). The target volume (prostate with or without seminal vesicles), rectum, and bladder were contoured by radiation oncologists in the department. The PTV was formed by adding a 10-mm margin around the clinical target volume except in the posterior direction, which was 5 mm to reduce rectal complication. The plan was then optimized using in-house-designed dose-volume constraints.

CT-on-rails-based IGRT procedure and shift measurements

In our department, the treatment of prostate cancer with image guidance is referred to as FOCAL (fusion of the CT and LINAC). A detailed description of FOCAL treatment and the determination of the target shifts has been reported elsewhere (15, 16). In general, our CT-on-rails-based IGRT starts from the acquisition of a planning CT. To obtain the treatment-planning CT the patient is set up in the treatment position. Metallic ball bearings (BBs) are placed on the patient's anterior and lateral skin marks that define the central axis plane of the prostate gland; the planning isocenter can be triangulated from the three BB positions. Once the optimized plan is completed, the planning CT scan, along with the planning isocenter and organ contours, are then exported to the image fusion software. Just before each treatment fraction the patient is set up in the treat-

ment position, and the BBs are again placed on the anterior and lateral skin marks that are assumed to best define the axial plane of the prostate gland containing the planning isocenter for that particular fraction. Using a CT-on-rails (Primatom) the treatment couch is reversed 180°, and the patient is positioned for the daily verification CT scan. This CT scan is then sent to the fusing software, where it is manually fused to the initial planning CT scan. Once the prostate gland is aligned on both scans the target shift defined by the distance between the planning isocenter and the daily isocenter triangulated from verification CT can be measured. The treatment couch is returned to the original position, and the specific shifts detected during the IGRT procedure are corrected by adjusting the position of the treatment table. As an example, Fig. 1 shows the CT images of prostate and rectum positions of a patient on 2 different days (planning and treatment day). It can be seen from the figure that there are significant variations of the prostate and rectal positions.

When the IGRT procedure was initially developed at Morristown Memorial Hospital in 2000, the purpose was to accurately boost radiation dose to the prostate gland in the last five consecutive treatment fractions. The IGRT procedure took approximately 45 min (compared with conventional non-IGRT delivery, which took approximately 10–15 min). As we passed our learning curve we have become more efficient. The total time has been reduced to 20–25 min from the verification CT scanning to the finishing of radiation delivery. With the Siemens Sensation 16-slice CT scanner and the Siemens AT fusion software, the entire IGRT procedure, from CT scanning (which alone takes approximately 30 s) to image fusion and physician approval takes <10 min. As we gained more experience in IGRT, since 2004 the procedure has further evolved into what is now known as *adaptive therapy* in the radiation oncology community. In the first 10–15 fractions, each prostate cancer patient receives image-guided RT, from which both the systematic and random components of shifts can be observed. Subsequently in the second phase of treatment (non-IGRT), the systematic shift can be corrected, and the random component of shifts is accounted for with a patient-dependent treatment margin. As reported previously (17), we have found that the residual systematic error can be minimized well with 10 IGRT fractions.

The prostate shifts during 10 FOCAL treatments for 45 patients and 5 FOCAL treatments for the other 284 patients were measured in the three orthogonal directions: left–right (LR), anterior–posterior (AP), and superior–inferior (SI). In total, 1870 CT scans were collected, and 5610 interfractional prostate shifts were reviewed. The shift data were analyzed from different perspectives: (1) the patient population as a whole, (2) the systematic and the random components in the shifts, and (3) patient physical characteristics.

RESULTS

Analysis of the magnitude of the interfractional target shift

Of the 1870 CT scans reviewed, 44% required no setup adjustments in the AP direction (if the shift of target from planned position is <3 mm, no adjustment is performed), 14% had shifts of 3–5 mm, 29% had shifts of 6–10 mm, and 13% had shifts of >10 mm. In the SI direction, 81% had no setup adjustments (ie, shift <3 mm), 2% had shifts of 3–5 mm, 15% had shifts of 6–10 mm, and 2% had shifts of >10 mm. In the LR direction, 65% had no setup adjustment, 13% had shifts of 3–5 mm, 17% had shifts of 6–10 mm, and 5% had shifts of >10 mm. In particular, the incidences of a shift in the posterior direction (treatment couch

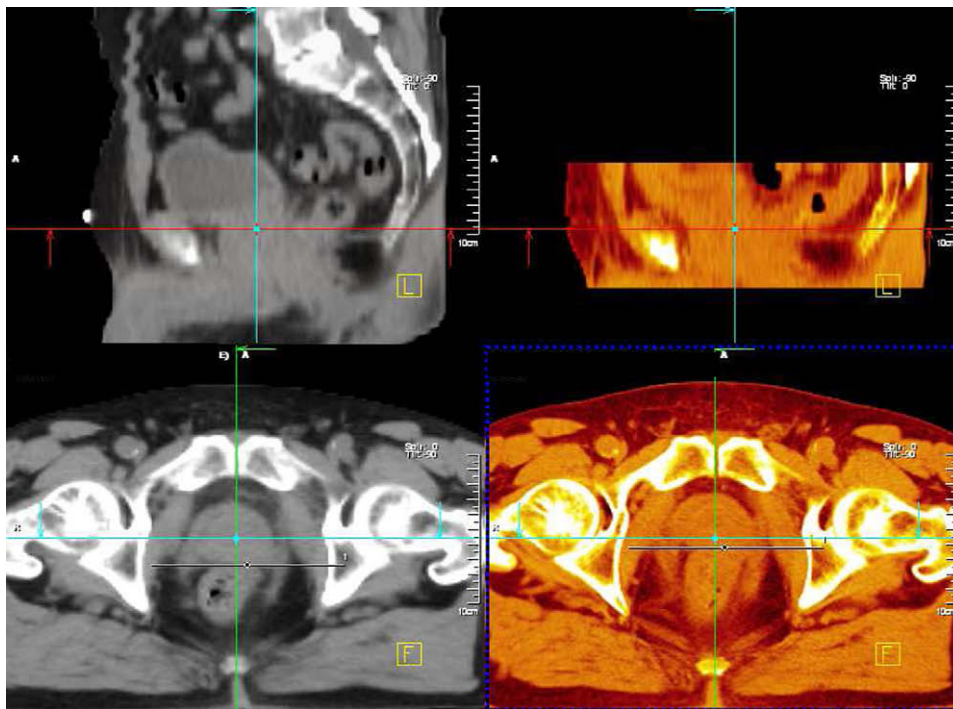


Fig. 1. Side-by-side comparison between a slice in pretreatment (gray) and planning CTs (red).

raised) were as follows: 21% ≥ 4 mm, 12% ≥ 6 mm, and 3% >10 mm. The distribution of the setup adjustments in the three orthogonal directions along with the maximum and minimum setup adjustment are shown in Table 1. In the extreme case, a shift of up to 27 mm of the target from its planned position in the lateral direction was observed. Obviously, the current treatment margin is not sufficient to compensate for such large shifts. Not correcting the target shifts could lead either to under-dosage of the target or to increased dosage to the normal tissue involved.

Analysis of isocenter shift

The interfractional prostate shift data were further analyzed according to the method of Yan and Lockman (18). The daily shift for each patient comprised a random and a systematic component. The individual systematic shift for a patient is calculated to be the mean of the daily prostate shift, whereas the individual random shift is defined as the deviation of the daily target shifts from their mean for each patient. Subsequently, the distribution of the individual systematic shift over the entire patient group (329 samples in our study),

referred to as *treatment preparation uncertainty* in the literature, is defined as the SD of the systematic shifts, whereas the distribution of random shift, referred to as *delivery uncertainty*, is calculated to be the SD of random shifts of 1870 measurements.

Of the 329 patients for whom data were reviewed, 54% required no clinical interventions (mean shift <3 mm, readjustment or isocenter shift in the second phase of treatment) in the AP direction, 24% had mean shifts of 3–5 mm, 20% had mean shifts of 5–9 mm, and 1.5% had shifts of >10 mm. In the SI direction, 87% did not require clinical interventions, 11% had mean shifts of 3–5 mm, 2% had mean shifts of 6–10 mm, and no mean shift exceeded 10 mm. In the LR directions, 82% had mean shifts of <3 mm, 12% had mean shifts of 3–5 mm, 5% had mean shifts of 6–10 mm, and 1% had mean shifts of >10 mm. The preparation and delivery uncertainties in the three orthogonal directions for all patients are listed in Table 2.

Analysis of shifts for different patient groups

To examine the target shift data according to patient-specific characteristics, three patient subgroups were sampled from our patient pool (329) according to individual body

Table 1. Summary of mean and SD of setup adjustment over 1870 shift measurements

Direction	Average shift (mm)	SD (mm)	Maximum (mm)	Minimum (mm)
AP	0.4	5.5	23.0	-20.0
SI	0.0	2.6	15.0	-10.0
LR	0.9	3.7	25.0	-27.0

Abbreviations: AP = anterior–posterior; SI = superior–inferior; LR = left–right.

Table 2. Summary of treatment preparation and delivery uncertainties: data for 329 patients

Direction	Preparation (mm)	Delivery (mm)
AP	4.3	3.9
SI	1.7	2.3
LR	2.3	3.2

Abbreviations as in Table 1.

mass index (BMI): a control group ($n = 16$, BMI <25 kg/m²), an overweight group ($n = 29$, BMI 25–30 kg/m²), and an obese group ($n = 21$, BMI >30 kg/m²). The mean and SD of interfractional prostate shifts in the AP, LR, and SI directions for the three patient subgroups are summarized in Table 3. Our data indicate that the interfractional prostate shift in the AP direction for the overweight subgroup (1 SD = 5.3 mm) was statistically larger than those for the control (4.1 mm) and obese patient subgroups (4.1 mm) ($p < 0.05$, F test). On the other hand, the interfractional prostate shift in the lateral direction for the obese patient subgroup (5.5 mm) was significantly larger than for the overweight and control subgroups (4.1 mm and 2.9 mm, respectively; $p < 0.001$, F test).

The random component of interfractional prostate shift was defined earlier in the text as the SD of target shift for each patient. To validate whether the random component of prostate shift is associated with patient weight, a correlation study between random prostate shift and patient weight was performed. Figure 2 is a scatterplot of SD of prostate shift and patient weight. The correlation between shift and body weight was calculated to be 0.14, 0.52, and 0.005 in the AP, LR, and SI directions, respectively. The shift in the lateral direction was significantly correlated with patient weight. Details of our findings regarding obese and overweight patients will be reported elsewhere.

DISCUSSION

In this study we reviewed 1870 pretreatment CT scans for our prostate cancer patients treated between May 2000 and August 2005. This is perhaps one of the largest and longest series of prostate patients clinically treated with IGRT in the United States. The use of a diagnostic CT scanner in our IGRT system provides superior image quality compared with other imaging modalities, such as megavoltage cone-beam or even kilovoltage cone-beam CT. Thus, accurate measurement of daily prostate shifts through side-by-side planning and pretreatment CT comparisons can be achieved with ease. The direct application of this study is in the determination of an appropriate tumor margin for prostate irradiation. The treatment margin to form a PTV from the clinical target volume depends not only on the interfractional prostate shift but also on the different treatment techniques, such as three-dimensional conformal RT, IMRT, or IG-IMRT. In theory, IG-IMRT (e.g., our FOCAL treatment technique) requires the smallest treatment margin because interfractional target shifts can be corrected before radiation delivery in each

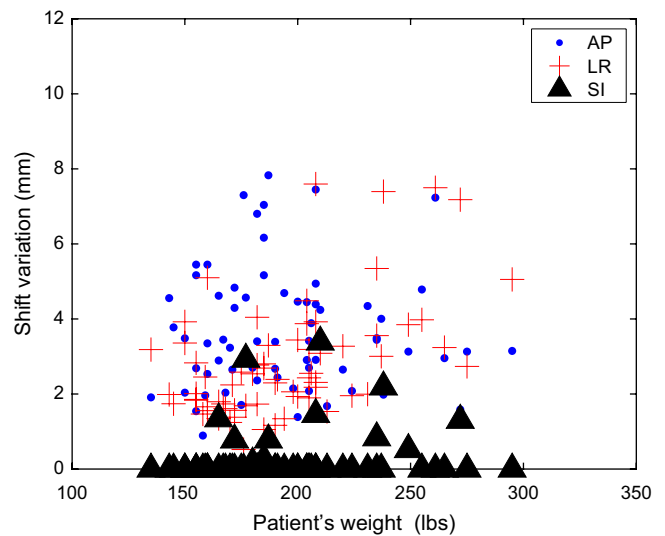


Fig. 2. Scatterplot of the random component of target shift and patient weight.

fraction with the help of image guidance from localization CT. As stated earlier, target shift constitutes two components: one source is the target movement due to the day-to-day filling status of the rectum and bladder, and the other source is the daily setup error due to patient body characteristics and human error (e.g., misalignment of the skin markers and in-room lasers). The residual error after image guidance comprises intrafractional prostate motion and volume change and the inherent uncertainty (e.g., image resolution and thickness of CT slice) in the IGRT technique that cannot be corrected with image guidance itself. A reasonable treatment margin for IG-IMRT needs to address the residual errors to achieve full dose coverage. The overall residual uncertainty (1 SD) is then estimated to be in the range of 1.5–2.1 mm by Dehnad *et al.* (19). Correspondingly, the treatment margin for IG-IMRT will be in the range of 5 to 6 mm according to the margin recipe of van Herk *et al.* (20). Several investigators suggested a very tight treatment margin (e.g., 3 or 5 mm) for IG-IMRT techniques (21, 22), to decrease rectal complications. However, with such a tight margin, the overall residual error cannot be fully addressed and may result in tumor control failure.

As an important component of overall residual error, prostate deformation and its dosimetric impact are concerned in prostate irradiation. The superior image quality of the CT-on-rails provides a unique opportunity to assess target deformation over the IGRT treatment course. To illustrate one such application, target deformation can be evaluated in patients with significant calcification in the prostate. After fusion of the verification CT with the planning CT, the location difference of prostate calcifications between the two CT studies can be used to describe target deformation. On the basis of our experience with prostate IGRT, this difference is caused by a combination of patient rotation, variable rectal and bladder filling status, and interfractional prostate rotation. Because most linear accelerators cannot address target rotation (or deformation), deformation measured as a shift in the (x , y , z)

Table 3. Summary of interfraction prostate shift for three patient subgroups

	Control	Overweight	Obese
Fractions	143	320	232
AP shift (mm)	0.3 ± 4.1	−0.1 ± 5.3	0.7 ± 4.1
LR shift (mm)	0.5 ± 4.1	1.1 ± 2.9	−0.3 ± 5.5
SI shift (mm)	0.0 ± 0.4	−0.1 ± 0.8	−0.2 ± 1.1

Abbreviations as in Table 1.
Values are mean ± SD.

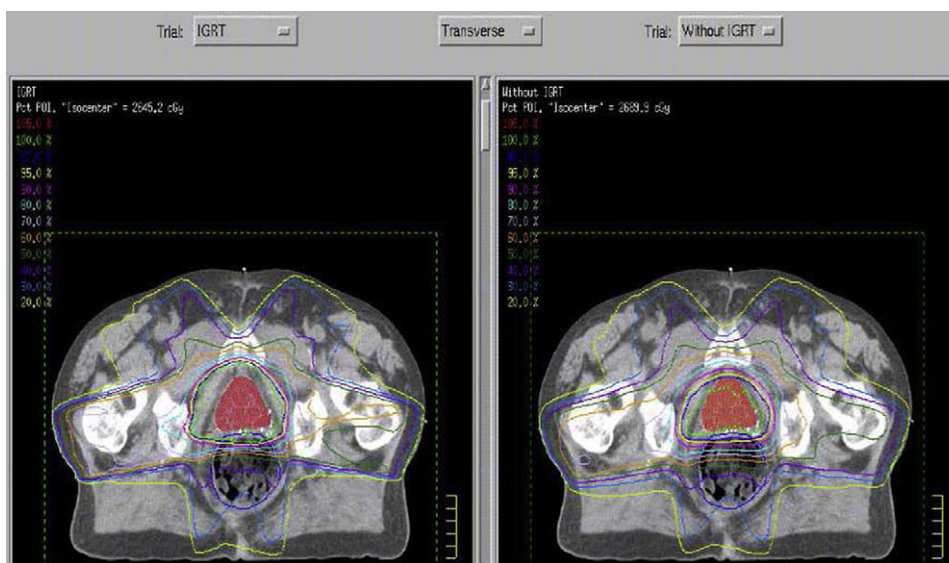


Fig. 3. Dose comparison of treatment with vs. without image-guided intensity-modulated radiotherapy (IGRT).

direction may not be accurate. A study is presently being performed to evaluate prostate deformation for those patients with calcifications, and sufficient patient samples will warrant our conclusions on this issue.

The treatment of prostate cancer with conventional IMRT without image guidance requires a relatively wider treatment margin than that required by IG-IMRT. The treatment margin for conventional IMRT not only needs to address uncorrected residual errors but also interfractional prostate movement that can only be corrected with pretreatment image guidance. Using our interfractional prostate shift data (Table 2) in the van Herk margin recipe (20), treatment margins of 13.5, 6.0, and 8.0 mm are required for conventional IMRT treatment practice in the three orthogonal directions (AP, SI, and LR), respectively, without the benefit of image guidance.

The dosimetric consequences of daily target shift for prostate have been intensively studied by different investigators, considering the effect of systematic and random target shifts (18, 23, 24). In these previous studies, the actual dose was estimated by shifting the planned dose distribution based on the target position sampled from the shift bank and summing the shifted distribution. Alternately, it is calculated by the convolution of planned dose distribution with the probability density function of the observed target shift. We further simulated the effect of target shift by a composite plan to include all 15 daily target shifts into the dose calculation. Figure 3 compares the composite dose distributions for a prostate irradiation with and without IGRT. The composite dose distribution is calculated with the Philips Pinnacle treatment-planning system by summing dose distributions over 15 fractions with beam shifts simulating corresponding target shifts. As shown in the figure, the dose gradient at the interface between rectum and prostate is sharp with IGRT, whereas without correcting for target shifts the dose gradient becomes broader, and more rectal volume could be irradiated with a high dose.

Data from the Centers for Disease Control and Prevention show that the overweight and obese population in the United

States has increased steadily in the past 20 years, and the most recent statistics indicate that 34.5% and 30% of the population belongs to these two groups, respectively. Several studies have reported the difficulties in imaging in diagnostic radiology (ultrasound, CT, and MRI) and in treatment for patients with weight problems (25). A recent study from the M. D. Anderson Cancer Center suggested that obese patients have a higher probability of clinical or biochemical recurrence (26). However, the correlation of patient weight or BMI with treatment accuracy and the subsequent clinical impact are still unknown. By comparing the obese and overweight patient groups with the control patient group, we have observed that patient weight does correlate with treatment accuracy, in particular in the lateral and AP directions. We have also found that interfractional prostate movement for obese patients is significantly different in the lateral direction from that of the control group, whereas interfractional organ motion in the AP direction for the overweight patient group is statistically larger than in the other two groups. Millender *et al.* (27) reported a similar result, that obese patients tended to have large shifts in the lateral direction, and concluded that the shift is due to setup variation rather than prostate motion. It seems that appropriate clinical interventions are required for these two patient groups, otherwise the local tumor control for these patients may be compromised. On the basis of our analysis, a generous treatment margin is recommended for the obese patient group because local tumor control is more of a concern than normal tissue complications. On the other hand, frequent image guidance should be given to overweight patients because a generous margin can not be applied owing to possible rectal complications.

CONCLUSIONS

A review of patient shift data from 1870 scans demonstrated that there is a significantly greater target shift in the

AP direction than in the lateral and SI directions. Without correcting for interfractional prostate movement, local control failure or an undesirably high dose to the rectum are likely. The overweight and obese patient groups (according

to BMI) showed a significant difference from the control group in terms of interfractional prostate movement. It is suggested that image guidance should be performed frequently for these two patient groups.

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