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CLINICAL INVESTIGATION **Prostate**

POTENTIAL FOR HIGHER TREATMENT FAILURE IN OBESE PATIENTS: CORRELATION OF ELEVATED BODY MASS INDEX AND INCREASED DAILY PROSTATE DEVIATIONS FROM THE RADIATION BEAM ISOCENTERS IN AN ANALYSIS OF 1,465 COMPUTED TOMOGRAPHIC IMAGES

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Purpose: Recent clinical outcome studies on prostate cancer have reported the influence of patient's obesity on the biochemical failure rates after various treatment modalities. In this study, we investigated the effect of patient's physical characteristics on prostate shift in external beam radiotherapy (EBRT) and hypothesized that there maybe a correlation between patient physique and tumor shift.
Methods and Materials: A retrospective analysis was performed using data for 117 patients who received image-guided radiation therapy (IGRT) for prostate cancer between January 2005 and April 2007. A total of 1,465 CT scans were analyzed. The standard deviations (SDs) of prostate shifts for all patients, along with patient weight, body mass index (BMI), and subcutaneous adipose-tissue thickness (SAT), were determined. Spearman rank correlation analysis was performed.
Results: Of the 117 patients, 26.5% were considered normal weight, 48.7% were overweight, 17.9% were mildly obese, and 6.9% were moderately to severely obese. Notably 1.3%, 1.5%, 2.0%, and 21.2% of the respective shifts were greater than 10 mm in the left–right (LR) direction for the four patient groups, whereas in the anterior–posterior direction the shifts are 18.2%, 12.6%, 6.7%, and 21.0%, respectively. Strong correlations were observed between SAT, BMI, patient weight, and SDs of daily shifts in the LR direction ($p < 0.01$).
Conclusions: The strong correlation between obesity and shift indicates that without image-guided radiation therapy, the target volume (prostate with or without seminal vesicles) may not receive the intended dose for patients who are moderate to severely obese. This may explain the higher recurrence rate with conventional external beam radiation therapy. **© 2009 Elsevier Inc.**

Obese, Shift CT-on-rails, IGRT.

INTRODUCTION

Recently, three studies have suggested that obesity might be an independent predictor of clinical recurrence or biochemical failure (based on rising prostate-specific antigen [PSA] levels after conventional external radiation therapy) among patients treated with external beam radiotherapy (EBRT) (1–3). In these studies, the patients were treated with conventional non–image guided radiation therapy. Obese patients were found to have a higher biochemical failure rate. However, this phenomenon was not observed for those patients who were treated with radioactive seed implants (brachytherapy). Merrick *et al.* analyzed the biochemical progression-free survival in a population of 686 patients after brachytherapy, and found no statistically significant impact of patient's obesity on the biochemical failure rates (4, 5). The impact of patient's obesity degree on outcome for patients who underwent radical prostatectomy is controversial. In two independent studies, both Freedland *et al.* (6) and Amling *et al.* (7) reported that in prostate cancer patients undergoing radical prostatectomy (RP), an increased BMI was associated with a greater risk of biochemical progression based on the analysis of two large independent patient samples (>2,700 for each) treated with anatomical RP. However, in another study of patients with prostate cancer treated with radical prostatectomy, Siddiqui *et al.* (8) analyzed the results of 5,313 patients treated by RP between 1990 and 1999 and found that obesity (as indicated by their body mass index (BMI)) had no impact on biochemical progression. Although Strom *et al.* suggested that there may be intrinsic reason for obesity and failure (3), we believe that this difference in

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outcome may be secondary to the modalities used for the treatment. For example, it is conceivable that setup uncertainties in very obese patients may lead to external beam treatment uncertainties, and in turn lead to increased failure rates. In fact, Millender *et al.* had reported significant mean left–right (LR) setup error (11.4 mm) measured with an electronic portal image device (EPID) on three severely obese patients (BMI >40) who underwent EBRT with the help of implanted fiducial markers (9). As such, the influence of obesity on clinical outcome might therefore be modality dependent (brachytherapy, radical prostatectomy, and EBRT). In this study, we test the hypothesis that prostate target shift uncertainty existing in fractionated radiotherapy may play an important role in the correlation between obesity and biochemical failure rate after EBRT. In addition, we sought to validate that patient obesity or similar body parameters (body mass index [BMI], patient weight, and local obesity) may have direct a impact on prostate shift during EBRT.

Multiple prostate motion studies (10–13) have shown that the uncertainty of setup adjustment in terms of x-, y-, z-shift (referred to as ‘‘shift’’) against planning position varies from patient to patient. In other words, some patients might have minor shifts (<5mm) while others have large shift (>10mm) during their EBRT. As a logical response to this issue, clinical interventions against prostate shifts should be patient dependent. This is extremely important for those patients who have a higher probability of large shifts. The correlation of patient's shift magnitude and certain body parameters such as body mass index (BMI), weight in kilograms, or subcutaneous adipose-tissue thickness (SAT) may help to identify characteristics of those patients with higher probabilities of large shifts (>10 mm).

METHODS AND MATERIALS

Patient characteristics and treatment

Body mass index is a key index for relating a person's body weight to his/her height which is defined as body weight in kilograms (kg) divided by the square of the height in meters (m). The National Institutes of Health (NIH) defines normal body weight as a BMI value of 20 to ≤25, overweight 25 to ≤30, mildly obese 30 to ≤35, and moderately to severely obese as >35. The 117 patients examined were thus categorized according to their BMI values into the four subgroups of normal weight (31 patients), overweight (57), mildly obese (21), and moderately to severely obese (8). Correspondingly, 395, 715, 255, and 100 daily shifts were further analyzed in the three orthogonal directions for these four patient subgroups.

Because BMI describes the body weight relative to height, it correlates strongly in adults with the total body fatty tissue content. In this study, we test the hypothesis that the amount of fatty tissue in the pelvic region may have direct impact on prostate shifts during radiation treatment; this is because, conventionally, the positioning of the target or the prostate gland is delineated by marks (usually tattoo) placed on the patient's skin. These marks define the treatment isocenter. With an obese patient, these marks may move from day to day because of the movement of the skin, and we assume that with increasing obesity, the movement increases mostly because of the inconsistency of setup ball bearings from fraction to fraction. These bearings are used to mark the tattoo marks that delineate the treatment isocenter; the metallic ball bearings are used because they are easily identifiable by the CT imaging.

In this study, the ‘‘subcutaneous adipose-tissue thickness’’ or SAT is defined as the distance (measured in centimeter) measured at the isocenter from the skin to the underlying muscle of bone. In the case of the anterior tattoo mark delineating the isocenter, the SAT is measured from the skin at the isocenter mark to the anterior portion of the rectus abdominus muscle overlying the symphsis pubsis (Fig. 1). In this work, we decided to call this anterior isocenter distance to SAT because it is much thicker than the distance at the LR isocenter marks, and thus, much more subjected to possible daily shifts, and is therefore the subject of this study. However, it should be noted that this concept of measuring SAT may be generalized to treatment of other sites. We believe that with increasing SAT, there maybe a higher chance of skin shifting from side to side, and thus the uncertainty of radiation delivered from fraction to fraction. The characteristics of BMI, SAT, and body weight for the entire patient population and each of BMI categories are summarized in Table 1. Our data indicate that approximately 70% of patients are either overweight or obese which is very close to the statistics (66.3%) from a national survey (14)

Treatment planning and shift measurements

The use of patient data was approved by the institutional review board of Atlantic Health. The study subjects included 117 patients who had primary prostate cancer. All patients were planned with ADAC Pinnacle 7.4f (Madison, WI) 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. Planning target volume (PTV) was formed by adding a 10-mm margin around the clinical target volume (CTV) except the posterior direction at PTV to CTV distance was reduced to 5 mm to reduce rectal dose. The plan was then optimized per in-house designed constraints. Using 15-MV photons, these patients received 77.4 Gy (primary prostate cancer) in 43 fractions consisting of either 15 or 10 fractions with image guidance.

As shown in Fig. 2, image guidance in our department is referred to as Fusion of the CT and Linac (FOCAL). It is performed in the initial phase of the treatment in which only the prostate gland (or prostate bed) is irradiated. In the second phase, the prostate gland and the seminal vesicle are irradiated. The margins used in the

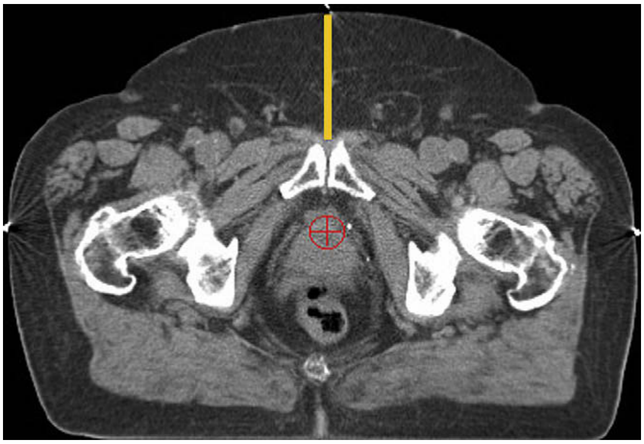

Fig. 1. Measurement of subcutaneous adipose-tissue thickness (SAT) as indicated by the yellow line.

Table 1. Distribution of patients in four groups according to body mass index (BMI)

Category	Normal weight (BMI ≤25)	Overweight (BMI 25 to ≤30)	Mildly obese (BMI 30 to ≤35)	Severely obese (BMI>35)	Total
No. of patients	31(26.5%)	57(48.7%)	21(17.9%)	8 (6.8%)	117
BMI	23.3 ± 1.7	27.4 ± 1.5	32.3 ± 1.6	42.4.± 4.9	28.3 ± 5.3
SAT (cm)	4.5 ± 1.2	5.7 ± 1.4	7.7 ± 1.8	11.8 ± 3.5	6.2 ± 2.5
Weight (kg)	73.4 ± 8.4	86.4 ± 7.7	104.4 ± 8.8	135.5 ± 29.5	89.6 ± 19.3

Abbreviation: SAT = subcutaneous adipose-tissue thickness.

second phase are based on the shifts determined in the first phase of the image-guided radiation therapy (IGRT) treatments, thus they are patient specific. Detailed description of the IGRT treatment technique and the determination of the target shifts have been reported elsewhere (11, 15, 16). Very briefly, three metallic ball bearings on the central axis plane are used to guide the initial setup. The treatment couch is rotated 180° for CT scanning. A fusion of this pretreatment CT and the planning CT is performed from which the daily movement of the prostate gland in the anterior–posterior (AP), left–right (LR), and cephalic–caudal (SI) directions can be determined. The placement of the isocenter inside the patient is accordingly adjusted and the treatment is delivered. A total of 1,465 pretreatment CT scans were obtained during 10 IGRT fractions for 58 patients and 15 fractions for 59 patients were analyzed, and the corresponding shifts in the AP, LR, and SI directions formed the basis of this investigation.

Data statistics and correlation analysis

For each patient subgroups (normal weight, over weight, mildly obese and severely obese), the measured interfraction prostate displacements in each direction (AP, LR, and SI) or shifts were described by SDs of 10 to 15 shifts obtained during their IGRT treatment. The daily radius shift is defined as the root-sum-square of daily shift in three orthogonal directions (AP, LR, and SI), it quantifies the overall prostate displacement from planning position regardless of anatomical direction. The frequency (%) of large shifts (>10 mm) in each patient subgroups were also studied and compared among various BMI patient groups.

For each patient, the variation of individual prostate shift in each observed directions (AP, LR, and SI) measured during IGRT treatment was described by the SD (σ_{AP}, σ_{LR}, σ_{SI}) of the daily prostate displacements. The σ_{AP}, σ_{LR}, σ_{SI} values represent the magnitude of shift or the random component of the shifts (RCS) in direction AP, LR, and SI for each patient, respectively. To verify that RCS is associated with certain body parameters, a nonparametric Spearman correlation (17) study between RCS and patient weight, BMI, and SAT was further performed. The Spearman correlation coefficient is then used to measure the correlation strength between RCS and three body parameters.

RESULTS

Figure 3 (a–c) plots the cumulative probability of daily shift as a function of shift magnitude for the four patient groups in AP, LR, and their radius direction, respectively. Our shift data reveal that the frequencies of shift measuring at least 10 mm in the LR direction for the four patient subgroups are 1.3%, 1.5%, 2.0%, and 23.0%, respectively, and the frequencies of shift of at least 10 mm in the AP direction are 18.2%, 12.6%, 6.7%, and 21.0%, respectively. The frequency of large shifts in the SI direction for the four groups are insignificant (<1%) and thus will not be considered further. The SDs of the shifts in AP, LR, and SI directions for four groups are summarized in Table 2.

As shown in Table 2, BMI increased from <25 to >35. There was a progression of the SDs of the shifts in the LR direction, from 3.0 mm (normal body weight), to 3.4 mm (overweight), to 3.8 mm (mildy obese), and finally to 8.9 mm (severely obese). On the other hand, for the AP direction, the corresponding SDs of the isocenter shifts are 7.0 mm, 6.1 mm, 4.7 mm, and 7.4 mm, respectively, which basically means no clinically relevant difference among the various groups. Similarly, for the SI direction, the corresponding SDs of the isocenter shifts are 2.2 mm, 1.4 mm, 1.1 mm, and 2.3 mm, respectively, indicating minimal differences are not clinically relevant.

Figures 4, 5, and 6 plot the SDs of shifts in the AP and LR directions for each patient as a function of SAT, BMI, and weight, respectively. There was a trend evident that the LR shift increased with the obesity degree (SAT, BMI, or weight), whereas the AP shift tended to decrease with the various parameters that correlated with obesity, namely, SAT, BMI, or weight (Figs. 4–6; Table 2). Spearman correlation coefficients between SD of shift and the three body parameters (SAT, BMI, and patient weight) are summarized in Table 3. The correlation coefficients indicate that all three of these body parameters are negative correlated with the SD of AP

Fig. 2. Siemens Primatom at Morristown Memorial Hospital, Morristown, NJ.

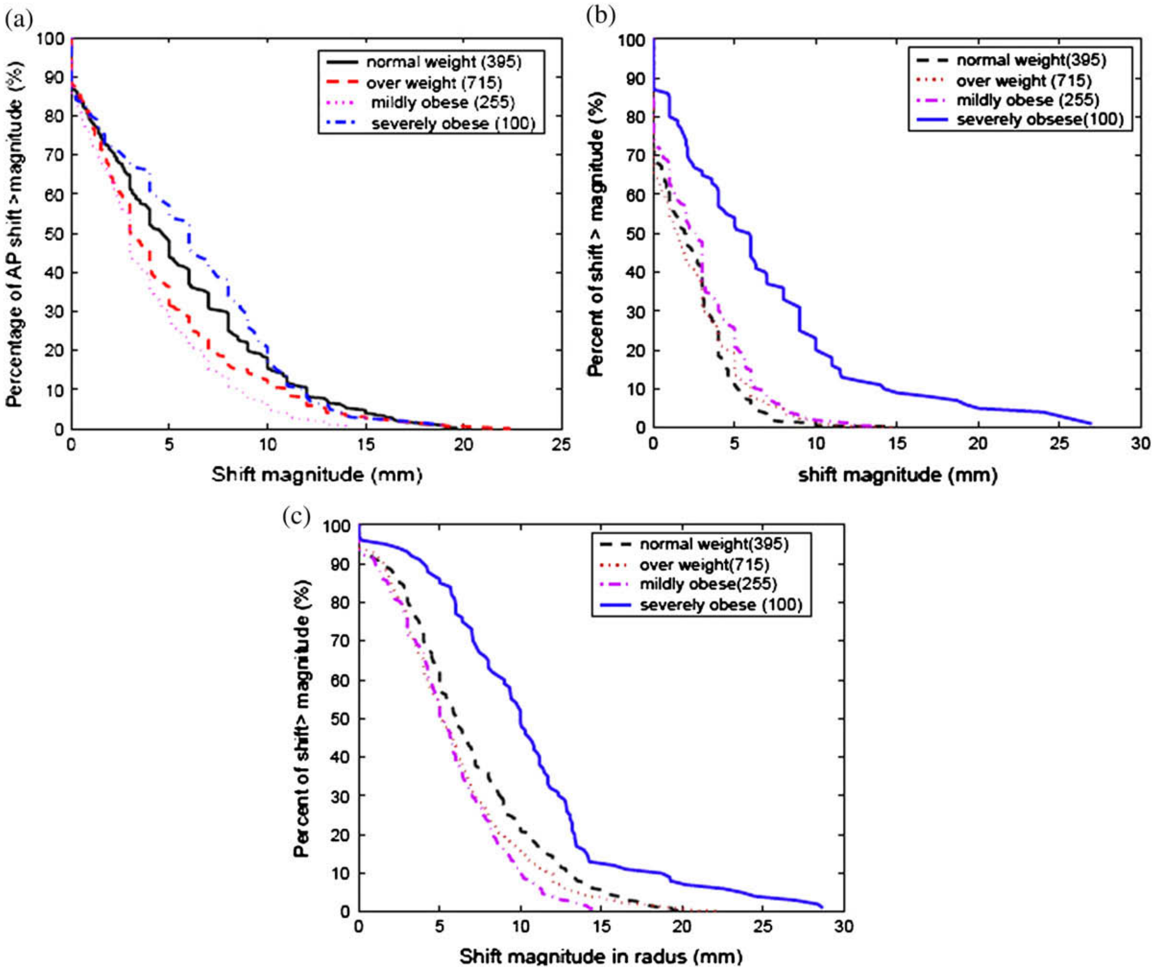

Fig. 3. (a) Percent anterior–posterior (AP) shift in magnitude for the four patient groups. (b) Percent left–right (LR) shift in magnitude for the four patient groups. (c) Percent radius shift in magnitude for the four patient groups.

direction. In contrast, the parameters are positively correlated with SD of the patient's LR shift. These three body parameters are all statistically significantly associated with the patient's LR shift ($p < 0.01$).

DISCUSSION

Several studies have been performed to understand the nature and magnitude of the prostate shift during radiation treatment (10, 18–21). These studies either emphasize the interfractional or the intrafractional prostate motion. Image-guided techniques (11, 22, 23) using modalities such as computed tomography (CT)–on-rails, Tomotherapy, or cone-beam CT have become a mainstay of treatment of prostate cancers. The IGRT technique allows correction of target displacements from the planned position before the actual radiation delivery. As such, it is not necessary to use a wider treatment margin to compensate for the target displacement. On the other hand, the extra cost, extra radiation dose delivered secondary to image acquisitions, and time involvements for the IGRT are drawbacks of this technique. However these current drawbacks may have diminishing impacts with improved technologies in the future. As mentioned earlier, the magnitude of prostate displacement during EBRT is

Table 2. Standard deviation (SD) of the target displacement from their planned position for each patient group

Direction	Normal weight (BMI ≤25) *N* = 31	Overweight (BMI 25 to ≤30) *N* = 57	Mildly obese (BMI 30 to ≤35) *N* = 21	Severely obese BMI >35 N=8	Entire population *N* = 117
AP	7.0 mm	6.1 mm	4.7 mm	7.4 mm	6.3
LR	3.0 mm	3.4 mm	3.8 mm	8.9 mm	4.0
SI	2.2 mm	1.4 mm	1.1 mm	2.3 mm	1.7

Abbreviations: AP = anterior–posterior; BMI = body mass index; LR = left–right; SAT = subcutaneous adipose-tissue thickness; SI = cephalic–caudal.

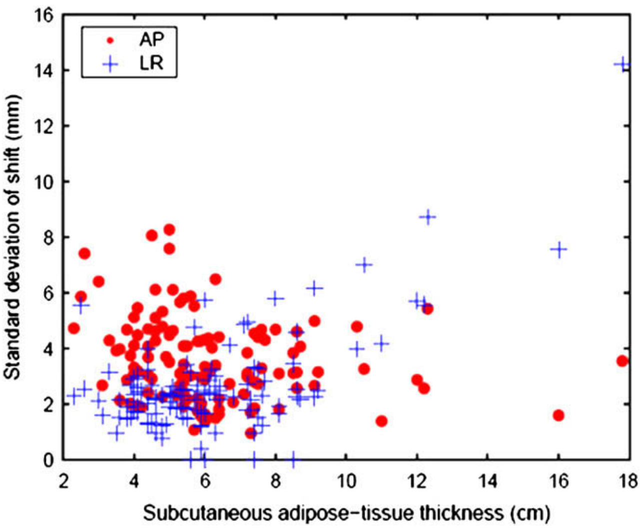

Fig. 4. Scatter plot of subcutaneous adipose-tissue thickness (SAT) and standard deviation (SD) of prostate shift. AP = anterior–posterior; LR = left–right.

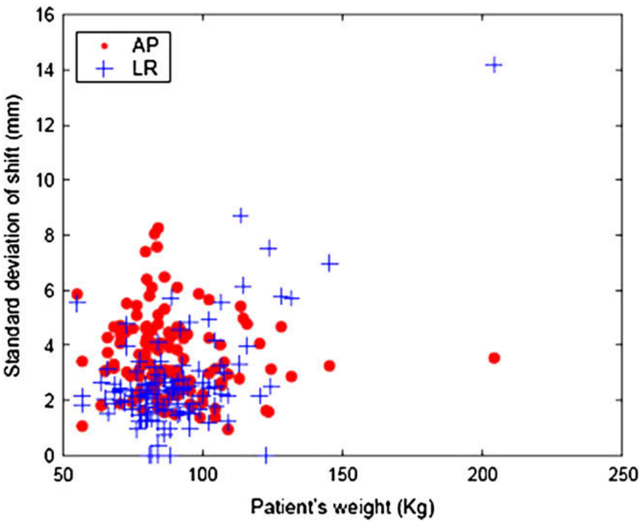

Fig. 6. Scatter plot of patient weight and standard deviation (SD) of prostate shift. AP = anterior–posterior; LR = left–right.

dependent on the patient and on the anatomical direction. Some patients have insignificant shifts throughout their treatment courses, whereas others have large target shifts almost on a daily basis. In this study, we examined patient BMI, body weight, and SAT in relationship to the prostate shifts. We found that patients with large BMI values (*i.e.,* BMI >35) tended to have a greater magnitude of prostate shift in the LR direction (σ_{LR} = 8.9 mm for the severely obese group) compared with those in the other three groups (range, 3.0–3.8 mm). Similar to the finding of Millender *et al.* (9), our data indicate that the LR shift of the prostate is significantly influenced by the patient's body parameters, whereas the shifts in the other two directions (AP and SI) do not seem to be much affected by these parameters.

The treatment of large patients with prostate cancer is challenged by the support tolerance and the width of the treatment couch. The common physical characteristic of patients with BMI >35 is a large abdominal girth. When lying flat on the treatment couch, the anterior and the LR skin marks of these patients may not remain stationary relative to the alignment lasers in the treatment room. This is especially true for the anterior marker because of the large amount of fatty tissues in the abdomen. Thus daily setup in the LR direction is difficult and results in large day-to-day variation of skin markers relative to bony structure. On the other hand, the AP variations of the isocenter are caused by the intrinsic rectal expansion/movements and skin movements. This second component of the skin movements would result in ''inaccurate'' laser alignments of the isocenter in the AP direction and are determined by the ''tattoo marks'' at the left and right LR portions of the patient's body. As can be seen in Fig. 1, the thickness of the fatty tissues immediately adjacent to the left and right tattoo marks are much thinner than the thickness of the fatty tissue underneath the anterior tattoo marks. If it is true that the setup deviations or uncertainties is a function of such subcutaneous fatty tissue thickness, then the difference in the tissue thickness as seen in Fig. 1 may explain why only the LR shifts of the prostate gland is significantly affected by the body parameters. Although not investigated for this study,

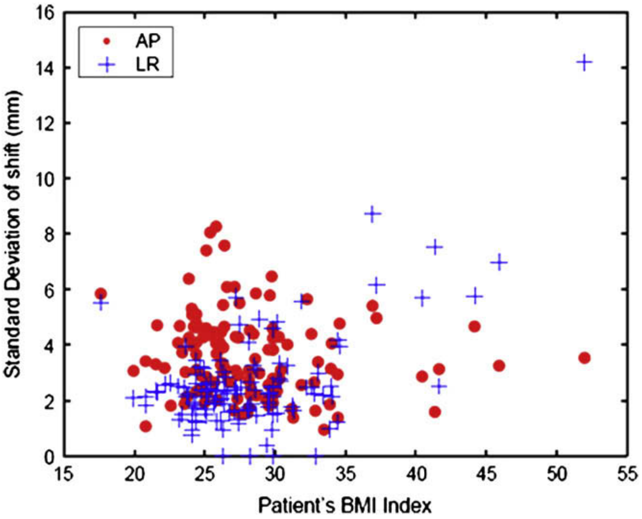

Fig. 5. Scatter plot of body mass index (BMI) and standard deviation (SD) of prostate shift. AP = anterior–posterior; LR = left–right.

Table 3. Correlation strength between standard deviation (SD) of each patient's shift (σ_{LR} and σ_{AR}) and the body parameters of subcutaneous adipose-tissue thickness (SAT), body mass index (BMI), and weight

SD of prostate shift	Body parameter	Correlation strength, Rs(p)
σ_{LR}	SAT	0.30 (0.001)
σ_{AP}	SAT	−0.25 (0.007)
σ_{LR}	BMI	0.24 (0.01)
σ_{AP}	BMI	−0.18 (0.05)
σ_{LR}	Weight	0.25 (0.007)
σ_{AP}	Weight	−0.18 (0.05)

it is possible that the fatty tissue thickness at the anterior portion of the abdominal–pelvic girth increases more than the fatty tissue thickness at the LR portion when the patient gains more weight.

Most current image-guided techniques are not suitable for these large patients. Ultrasonographic guidance is limited by its poor image quality associated with increased distance from the abdominal surface to the bladder (24). Tomotherapy currently does not have a large bore to perform pretreatment CT for prostate cancer patients of large size such as those in the present study. Onboard imaging devices (such as Kilo-Voltage CT and MegaVoltage CT, Electronic Portal Imaging Device) produce adequate images for patients with normal and overweight BMI, but the image qualities deteriorate with increasing BMI. For patients with higher BMI, the onboard imaging devices may require the use of implanted fiducial markers to detect any shifts of the target secondary to image degradation. IGRT using the CT-on-rails system, especially with a large-bore diagnostic CT scanner (84 cm) produces superb image quality even for patients with high BMI values. Using such a system, we could easily observe the significant shift differences among the various BMI patient groups.

Data from Strom *et al*. (3) showed that the probability of 10-year biochemical failure-free survival after EBRT for obese patients is 20–25% lower than that for the normal weight, over weight, and mildly obese patient groups (62%~65%). However, the cause of this phenomenon was not explicitly concluded in the study by Strom *et al*. Our analysis indicates that obese patient generally tend to have large (>10 mm) shifts in prostate position. As shown in Fig. 3c, the frequency of large radius shift for severely obese patients (50%) is significantly higher than that for three other groups (8–18%). Without correcting these target shifts, the delivered dose to the prostate gland will be less than the prescribed dose, and may lead to a high treatment failure. As an example, we have recently treated a prostate patient whose weight was 450 lb, BMI was 45, and SAT was 17.8 cm. The patient received daily pretreatment CT for setup verification. Daily target displacement of the patient is plotted in Fig. 7. The magnitude of setup error in 13 of 40 fractions was found to be more than 10 mm in the LR direction. Had this patient been treated with the conventional three-dimensional conformal technique, whereby a uniform margin of 10 mm was commonly chosen for prostate cancer, the LR shift would imply that a portion of the prostate target volume might be underdosed up to 30%. For the other three groups, the frequency of large shift in the LR direction was relatively small (<2% of the entire treatment course) and might result in approximately 2% underdosage with use of the same three-dimensional conformal technique.

It is thus highly conceivable that the higher biologic/biochemical failure observed for obese patients is simply a result of target miss, as those patients were treated with EBRT without image guidance. In our correlation analysis between the three body parameters and SD of daily prostate shifts, we found that all three parameters had strong associations with the SDs of the daily shifts in the LR direction. For the severely obese patients (BMI>35, SAT >10 cm), the SD of prostate shift was 8.9 mmm which is two times greater than those for the three other patient subgroups (SD, 3.0–3.8 mm). Thus image guidance for the treatment of obese patients is desirable because it can correct target displacement before radiation delivery. Although one may attempt to offset the effect of large shifts in the LR directions by increasing the LR margin of treatment, this would likely result in an increase in rectal dose since oblique fields are often used for treatment. Moreover, as shown in Table 2, there is significant shift of the prostate gland in the AP direction (with an average SD of 6.3 mm for the entire population and 7.0 mm for patients who are of normal weight). With such significant shifts in the AP directions regardless of patient body parameters, and the increased LR shifts with increasing body weight, it maybe prudent to use IGRT for obese patients, for example in the form of implanted fiducial markers or, as in our situation, using CT-on-rails IGRT.

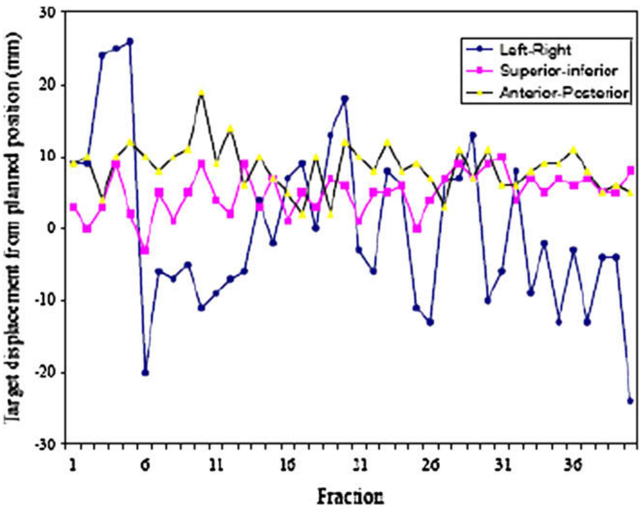

Fig. 7. Daily prostate shifts measured for a patient weighing 450 lb (see text for details).

CONCLUSION

In summary, patients with large (>10 mm) displacement in prostate position require more frequent IGRT treatments such as those using the Siemens Primatom (Concord, CA), Tomotherapy (Madison, WI), and onboard cone-beam CT. We found that patient BMI, SAT, and weight were the effective predictors in the identification of patient subpopulation that have large shifts in prostate position. By comparing daily prostate displacement for the four different BMI patient groups, we have observed that the moderately or severely obese patients (BMI >35) tend to have large shifts in prostate position in the LR direction direction, whereas the changes in magnitude in the SI and AP directions are less correlated with increasing body weight. Nevertheless, in the AP direction, the SD of the prostate shift is not small for the entire population at 6.3 mm . This AP shift, when added on to the increased

LR shifts as seen in patients with increasing body weight, can produce a significant spatial (three dimensional) shift of the prostate gland and lead to increase treatment failures if not corrected. By using modern IGRT technology, such shifts may be corrected easily and thus may lead to improved control rates.

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