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CLINICAL INVESTIGATION **Prostate**

AN ASSESSMENT OF PTV MARGIN DEFINITIONS FOR PATIENTS UNDERGOING CONFORMAL 3D EXTERNAL BEAM RADIATION THERAPY FOR PROSTATE CANCER BASED ON AN ANALYSIS OF 10,327 PRETREATMENT DAILY ULTRASOUND LOCALIZATIONS

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Introduction: We have assessed the planning target volume (PTV) margins required for adequate treatment of the prostate in the absence of daily localization imaging based on the statistical analysis of a large data set obtained from 5 years of use of a two-dimensional ultrasound pretreatment localization device.

Methods and Materials: Data from 387 prostate patients were analyzed retrospectively. Every patient in the study received daily pretreatment localization resulting in a total of 10,327 localizations, each comprising an isocenter displacement in three directions: anteroposterior, right-left lateral, and superior-inferior. The mean displacement for each direction for each patient was computed from daily treatment records, and a mean of the means was used in the analysis.

Results: The mean displacements required to shift the target to the required position were 6.1 mm posterior (4.4 mm SD), 2.1 mm superior (4.5 mm SD), and 0.5 mm right (3.6 mm SD). The 6.1-mm shift posterior is indicative of a systematic uncertainty. Differences in planning conditions between the computed tomography simulation and the treatment room may account for this discrepancy.

Conclusion: Our study has revealed systematic intertreatment uncertainties that would have required a nonuniform PTV margin ranging in dimensions between 2.7 mm anterior, 14.9 mm posterior, 7.7 mm right, 6.7 mm left, 11 mm superior, and 7 mm inferior to encompass the prostate for 95% of our sample if the ultrasound localization system were not used. In the absence of systematic uncertainties, a uniform PTV margin of 9 mm would suffice. © **2007 Elsevier Inc.**

Prostate cancer, Daily ultrasound target localization, Setup uncertainty, PTV margin, Conformal radiotherapy.

INTRODUCTION

In conformal radiotherapy, an assumption is made that the target location is well-known and that variations in position because of treatment time localization uncertainties and setup errors are accounted for by a planning margin. The margin added to the target volume compensates for a combined uncertainty from systematic and random errors. The International Commission on Radiation Units and Measurements reports 50 and 62 (1, 2) define target structures for use in radiotherapy treatment planning as the gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV). Although the GTV and CTV are anatomic concepts, the PTV is a geometric construct, containing the CTV and a sufficiently large margin around it to account for uncertainties during treatment setup and delivery, as well as inter- and intrafraction organ motion. Interfraction organ motion occurs between treatment fractions and is significant when the target location is different from its position during treatment planning. Intrafraction motion occurs during the actual treatment of the patient.

Organ motion is of particular concern when treating prostate cancer because the prostate is mobile and its position can vary between treatment fractions (3–5). Although other factors, such as setup errors, uncertainties in treatment time localization, and changes in the patient geometry contribute to the PTV, it is the interfraction organ motion that leads to the largest uncertainty in daily target position. The PTV margins of up to 2 cm are commonly used in the absence of daily treatment localization to account for this motion in an effort to ensure complete target coverage.

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With this in mind, in an effort to reduce PTV margins, several pretreatment imaging systems have been developed to localize the prostate position before treatment. These systems not only allow the user to image the prostate and other relevant organs, but also provide information as to how to shift the patient to correct the position on the treatment couch to fully cover the original target. There are four types of systems available commercially: ultrasound (US) based systems (6–8); fiducial marker-based systems using electronic portal imaging device (EPIDs) (9–11); cone-beam computed tomography (CT) (12), and, more recently, megavoltage CT based systems (13). Byrne *et al.* have compiled a comprehensive literature review of prostate motion and daily localization during radiation therapy (4).

Recently, studies have shown the US-based systems to be less accurate than fiducial marker-based systems, but still useful for radiotherapy localization (14–16). The discrepancies between systems, which are in the order of 3 mm, can of course be accounted for by the PTV at treatment time, meaning that the PTV margin used when US localization is used would be larger than that when fiducial marker systems are implemented.

Ultrasound systems are in widespread use in the radiotherapy community, and our intent is to report on 5 years of use of a two-dimensional US system used for the daily pretreatment localization of the prostate gland in prostate cancer patients undergoing conformal radiotherapy at our facility, with the idea to examine if various commonly used PTV margin dimensions are adequate for target coverage in the absence of US localization. Several collaborative multi-institutional protocols allow the use of tight treatment margins around the prostate without the use of pretreatment localization, and frequently the PTV dimensions are defined in terms of critical organ location and toxicity without regard to target motion.

METHODS AND MATERIALS

We have analyzed data from 387 patients treated for localized prostate cancer between 2001 and 2005. Each patient underwent a series of pretreatment US localizations during daily setup.

All patients underwent CT simulation with full bladder and no guidelines regarding rectal filling. The patients were placed in the supine position with a triangle sponge placed under their knees, and a Styrofoam block placed between their ankles. The CT scans were performed with a dedicated radiotherapy CT simulator using a standard pelvic scanning protocol, with 5-mm slice thickness and spacing. A urethrogram was performed on each patient using between 10 and 20 mL of contrast media. Three fiducial markers defining a reference isocenter were placed on each patient. After the scan, the patients were tattooed at the locations of the fiducial markers, and the data were transferred to the treatment planning system for organ outlining and target definition. The CTV was defined as the prostate gland as visible on the CT scan. A uniform PTV margin of 7 mm around the prostate was added for all patients accounting for intrafraction prostate motion and uncertainties in the use of the US system. The rectum, bladder, femoral heads, and penile bulb were also contoured for each patient. The 387 patients received a variety of doses ranging from 50 Gy to 79.2 Gy with conventional daily fractionation in 25 to 44 fractions. The patients were typically planned and treated with a conformal, coplanar five-field technique using 18 MV photons, and the dose distributions were generated to conform with International Commission on Radiation Units and Measurements guidelines (1, 2) for target coverage and dose homogeneity.

The treatment isocenter was defined at the geometric center of the PTV, and its coordinates were defined with respect to the reference isocenter in terms of anteroposterior (AP), right-left (RL), and superior-inferior (SI) shifts. On the first day of treatment, the patients were positioned with the treatment room lasers aligned with the tattoos defining the reference isocenter position. The patients were subsequently shifted to the treatment isocenter as defined from the treatment plan, and were initially setup at this point for all subsequent fractions.

A commercially available two-dimensional US system (BAT system, NOMOS Corporation, Cranberry Township, PA) was used for daily target localization. The system uses a transabdominal probe that acquires single images in the sagittal or coronal planes, is able to track the probe position in three dimensions, and relates its position to the treatment room isocenter. Contours of the CTV and critical organ structures, typically bladder and rectum, previously outlined on a three-dimensional radiation therapy planning system are imported into the software running the US system. The contours, whose position relative to the treatment isocenter is known from the three-dimensional radiation therapy planning system, are reformatted and superimposed on the images acquired with the system. The user can then "shift" the contours on screen until the CTV position matches the position of the prostate as seen on the US image. This shift is performed on both the sagittal and coronal views, and the system calculates a shift in three dimensions (AP, SI, and RL) by which the patient should be moved to align the target center to the treatment machine isocenter. After the shift is performed, the magnitude and direction of the shifts are recorded by the system and in the treatment chart.

For patients in this study, the mean shifts in the three directions and standard deviations were calculated for the entire treatment course for each patient. The data were tested for normality using a Shapiro-Wilk test (17) to validate the correlation between the means and standard deviations of the data, and systematic and random errors respectively. The overall mean shift was calculated by computing the mean shift in each direction for each patient first, and then averaging those means for all of the patients in each direction. The statistical significance of the results where subsets of the data were compared was calculated using Student's t test (18).

RESULTS

A total of 387 patients were included in this study for a total of 10,327 US localizations resulting in 30,981 shifts (AP, SI, and RL). All patients that received daily US localization for at least four consecutive fractions of their treatment were included in the study. On average, each patient underwent 27 localizations (median, 23) ranging between a minimum of 4 and maximum of 41. Although an effort was made to provide pretreatment localization to all eligible patients for all fractions, this was not always possible for various reasons, such as mechanical breakdowns of the

Table 1. Statistical results from 10,327 ultrasound localizations

Axis of displacement measurement	Mean shift and direction (mm)	Median shift (mm)	SD (σ) (mm)	Range (mm)
AP	6.1 posterior	5.7 posterior	4.4	27.1 posterior; 9.1 anterior
SI	2.1 superior	2.3 superior	4.5	16.7 superior; 14.7 inferior
RL	0.5 right	0.4 right	3.6	13.2 right; 9.4 left

The shift direction indicates the direction of target displacement with respect to the isocenter, as indicated by the ultrasound localization software.

Abbreviations: AP = anteroposterior; RL = right-left; SI = superior-inferior.

localization system or linear accelerator. Also, depending on the treatment regimen, some patients received pretreatment localization for the boost phase of their plan only.

Table 1 contains the statistical results from the shifts with respect to direction. For a normal (Gaussian) distribution, the mean may be considered representative of systematic uncertainties and the standard deviation (SD) representative of random uncertainties. The data were tested for normality using a Shapiro-Wilk test (17), and all data were found to be normally distributed to a 0.05 significance level ($W = 0.9881$, $p = 0.8432$, 95% CI). The largest mean shift was reported in the AP direction, 6.1 mm posterior, with an SD of 4.4 mm. A mean shift of 2.1 mm with an SD 4.5 mm was found in the superior direction, and along the lateral axis a mean shift of 0.5 mm to the right with an SD 3.6 mm was computed. Histograms for each group of shifts are presented

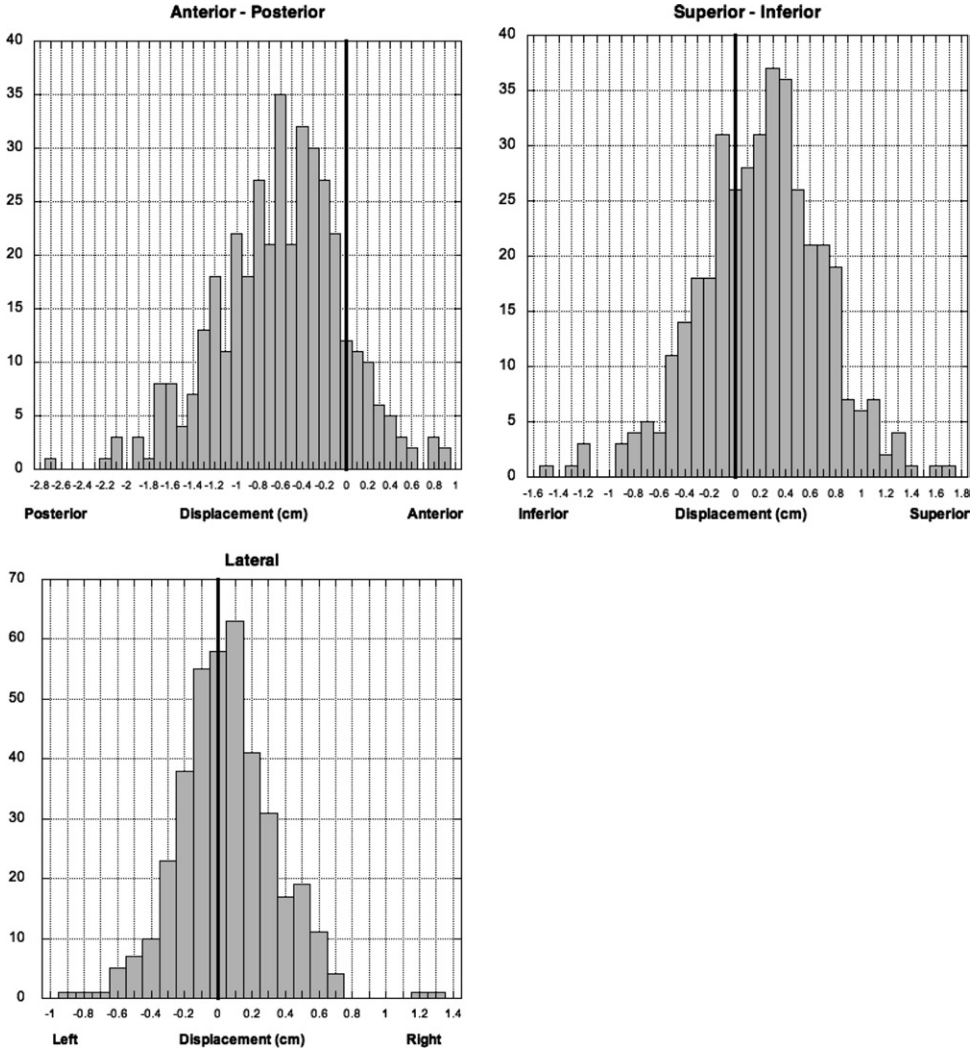

Fig. 1. Frequency histograms of prostate displacement calculated for each axis of motion based on the mean shift in each direction (anteroposterior, superior-inferior, right-left) for each patient.

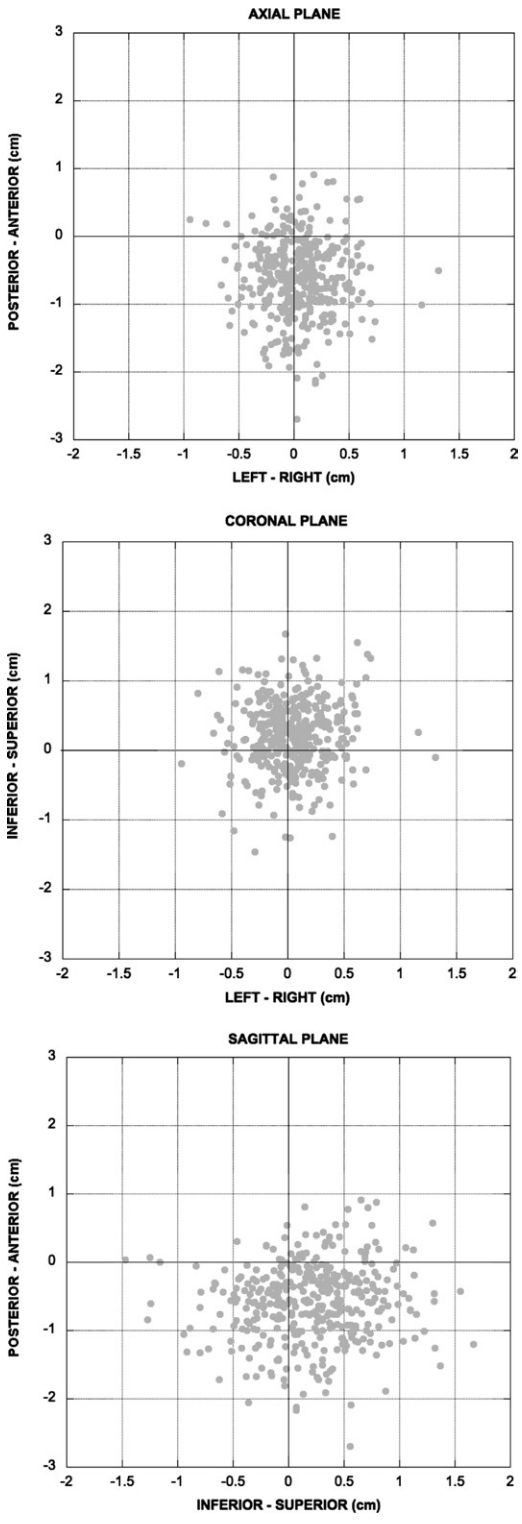

Fig. 2. Scatter plots illustrating the mean displacement from isocenter (0, 0) for each patient in the axial, coronal, and sagittal planes.

in Fig. 1. Scatter plots of the mean displacements for each patient are shown for the axial, coronal, and sagittal planes in Fig. 2. To assess any trends in the data with respect to time, the mean displacements in the three directions as well as their respective SDs are plotted as a function of time (represented chronologically by patient number) in Fig. 3.

To investigate the possibility that patient discomfort during the initial CT scan affected the prostate position at time of scanning, data from a cohort of 32 randomly selected patients were examined. Mean displacements were calculated in the posterior direction for the first week (6.9 mm) and last week (6.4 mm) of treatments. A Student's *t* test was used to evaluate the statistical significance of difference between the means. The result showed that the means were not significantly different within the 95% confidence interval ($\alpha = 0.05$, $t = 1.960$, $t = 0.29279$).

An assessment of the PTV margin required to encompass the prostate for 95% of all displacements if US localization was not available was carried out. The results are shown in Table 2. The margin dimensions were calculated by adding $\pm$ 2 SD to the mean shift for each direction, the mean value representing the overall systematic uncertainty, and the 2 SD representing the random uncertainty. Notwithstanding the systematic errors (means equal to zero), PTV margins of 7.2, 8.8, and 9.0 mm (RL, AP, and SI, respectively) would be required for coverage in 95% of instances. When the mean displacement is considered, margins of 7.7 and 6.7 mm (RL), 2.7 and 14.9 mm (AP), and 11.1 and 6.9 mm (SI) are required.

A further analysis was conducted detailing the number of instances the prostate would have remained within a PTV of specified dimensions if US localization were not available. The results are shown in Table 3. A PTV margin of 5 mm would have only contained the prostate 93, 54, and 71% of the time in the RL, AP, and SI directions, respectively. The target coverage increases with increasing PTV margin, and for a 15 mm PTV margin the prostate would have been contained 100, 95, and 100% of the time in the RL, AP, and SI directions, respectively.

DISCUSSION

An examination of the data in Table 1 shows the existence of non-negligible mean displacements both in the posterior direction (6.1 mm) and superior direction (2.1 mm). It would be reasonable to expect that for such a large sample of patients, the mean displacements in each direction would be close to zero. The overall results of our study were compared with those found in the literature for users of the same localization system and similar study sample size. Chandra *et al.* (19) compiled data for 147 patients and 3,509 localizations. Their figures for interfraction SD (4.9 mm AP, 4.4 mm SI, 2.8 cm RL) compare well with the results of our work (4.4 mm AP, 4.5 mm SI, 3.6 mm RL). Similarities are also found when comparing the median shifts (3 mm post, 2.5 mm superior, and 1.1 mm right) from the aforementioned study, vs. 5.7 mm post, 2.3 mm superior, and 0.4 mm right obtained from our data set. The means of the studies were not directly comparable as different methods of calculation were used. The differences in the medians, and for that matter the means, are greater than the differences observed with the SD. Another recent study by Fung *et al.* (20)

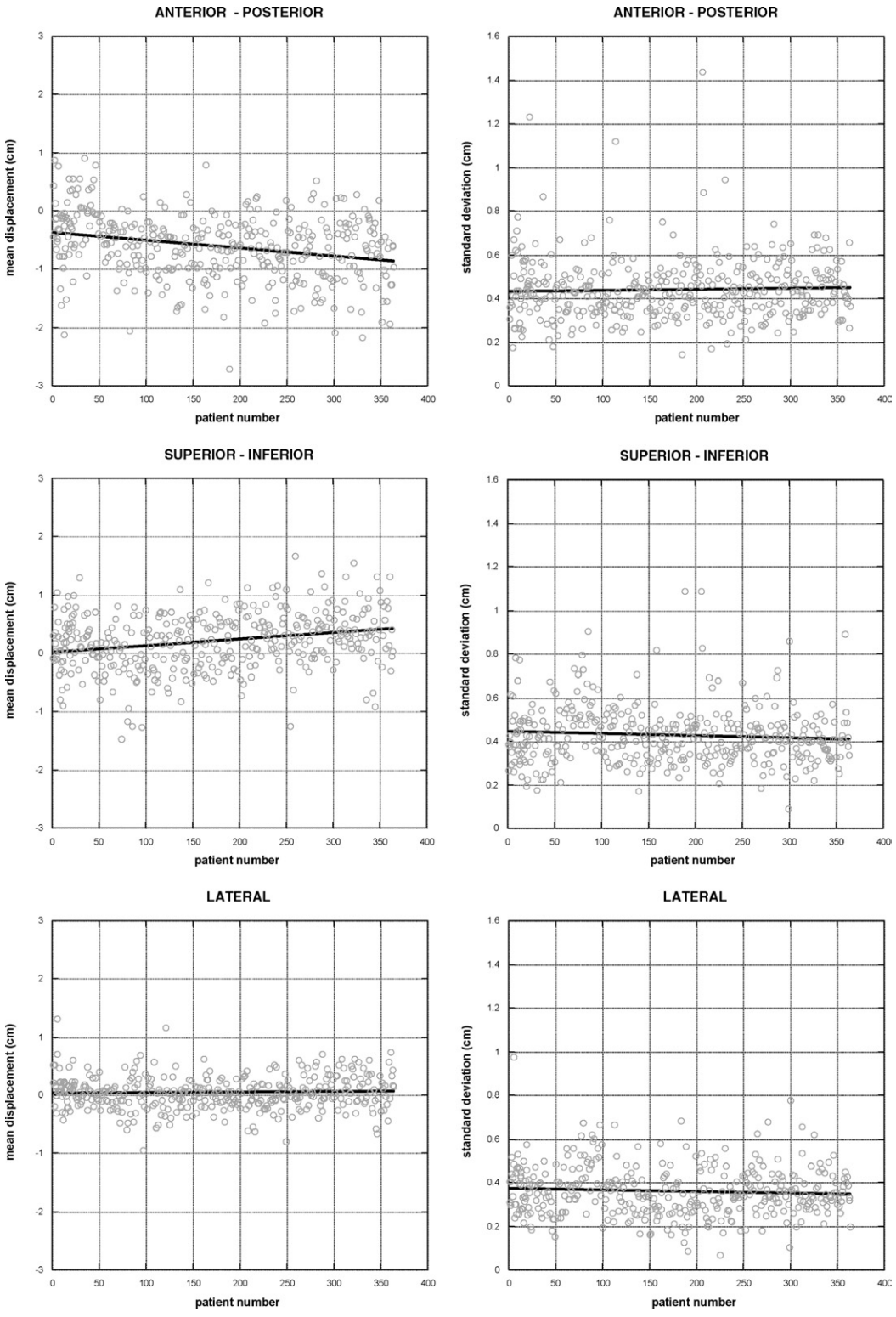

Fig. 3. Plots of mean displacements and SD for the three major axes as a function of patient number. The first patients were treated in 2001 and the last in 2005.

also yielded similar results to ours in terms of average shift (1.3 mm post, 2.5 mm superior, 0.3 mm right). In all directions but AP, the results of the three studies match to within 1 mm. The differences in the AP axis may be attributable to systematic uncertainties inherent to each institution's procedures with respect to the use of the US localization system, CT simulator, and patient treatment time setup.

To rationalize the systematic shifts in the AP and SI directions, an effort was made to try to identify the main

Table 2. PTV margin required to contain the prostate displacements in 95% of localizations if daily ultrasound localization was not available

Direction of displacement	2 SD (mm)	Mean shift data (mm)	PTV margin required to contain 95% of our study sample (mm)
Right	7.2	0.5 (right)	7.7
Left			6.7
Anterior	8.8	6.1 (posterior)	2.7
Posterior			14.9
Superior	9.0	2.1 (superior)	11.1
Inferior			6.9

Abbreviations: PTV = planning target volume; SD = standard deviation.

The 2 SD value in the table represents the margins required notwithstanding the systematic error (mean shifts).

differences between the CT simulator environment and procedures, and the treatment room US localization conditions to see if these differences could account for the results of our study. The first source of uncertainty arises from the fact that the system compares contours drawn on a CT scan projected together with isocenter information on the two-dimensional US images. The integrity of the data transfer is verified through a quality assurance procedure by which a dedicated phantom is CT scanned, outlined, and the information sent to the US system. The phantom is then placed on the treatment couch and the US localization calibration procedure is applied. Our departmental policy (which follows the manufacturer's guidelines) is that the system must be fully recalibrated if the calibration is off by more than 2 mm in any direction. A review of the calibration procedure and results was carried out as part of this work and no systematic displacements were found after the calibration procedure. With respect to uncertainties related to the general system usage and US image acquisition and interpretation, an audit of the quality of the US evaluation is commissioned on an annual basis at our department as part of the clinical quality assurance program. Thirty patients are chosen at random, and the localization images are retrieved for five fractions of each patient treatment. A US specialist repeats the localization procedure on the saved images of the patients, compares his results to what was done at treatment time, and scores the localization as acceptable or unacceptable. Using this quality assurance procedure, we have found less than 2% of localizations to be unacceptable, and, in fact, have found no systematic misinterpretations of the images.

The entire process of two-dimensional US localization hinges on the fact that the patient is CT scanned and treated in the same position, and that any differences in target position on a daily basis are due to natural organ motions and setup errors. There are, however, a few differences between the planning and treatment conditions that may introduce the systematic displacements we see in our data. The systematic shifts in the posterior direction may be attributed to: the pressure exerted by the user while using the US probe; differences in construction and rigidity of the treatment couch and the CT simulator couch; the use of contrast via urethra for planning purposes; and the general anxiety and nervousness of patients on the day of their CT scan. Several authors (21, 22) have demonstrated that probe pressure can produce a prostate displacement in the posterior direction in the order of several millimeters. Others (23, 24) have shown that for patients receiving retrograde urethrography for treatment planning purposes, there exist systematic shifts in prostate position of the order of 1–2 mm in both the posterior and superior directions as a direct result of the procedure.

The patient's anxiety and nervousness on the day of CT planning was also considered with the thought that these feelings may manifest themselves in physiologic reactions, such as muscle contractions, that may compromise the treatment planning process by changing the position of the relevant anatomy during the planning scan, or during the first few treatments. As treatments progress, the patients will invariably feel more comfortable and relaxed and this may also be reflected in US localization displacements. Mean displacements were calculated in the posterior direction for the first week (6.9 mm) and last week (6.4 mm) of treatments for 32 randomly selected patients. A Student's *t* test was used to show that the means were not significantly different within 95% confidence interval ($\alpha = 0.05$, $t = 1.960$, $t = 0.29279$), and that the difference of the means is in fact a casual occurrence. Therefore, although a small difference in means was observed, this does not contribute significantly to the mean displacements found for the entire patient population.

Another source of systematic displacement in the posterior direction may be the design and construction of the treatment machine couch. The patients considered in this study were all treated on the same linac, and simulated on the same CT simulator. The CT simulator has a flat graphite tabletop, which exhibits no sag across (left to right) the table in the posterior direction, although there may be a considerable couch sag in the longitudinal direction. The linac on which the patients were treated has a metal couch with a "tennis racket" insert allowing for posterior beam orientations. Even when first strung, these rackets exhibit a sag

Table 3. Percentage of total shifts in each axis of displacement (10,327) in which the prostate would have remained within a specified uniform PTV margin if daily pretreatment ultrasound localization was not used

Size of uniform	% Prostate displacements within the PTV		
PTV margin (mm)	RL (%)	AP (%)	SI (%)
5	93.2	51.4	71.0
7	98.6	66.4	84.7
10	99.5	81.0	95.0
12	99.7	88.0	98.0
15	100	95.0	100.0

Abbreviation: AP = anteriorposterior; PTV = planning target volume; RL = right-left; SI = superior-inferior.

(right to left) when a patient is on them, and we have measured this sag on such an insert to be in the order of 5–10 mm (depending on the weight of the patient) even when the patient is treated on a Styrofoam board placed on the insert. The sag results in a posterior displacement of the prostate with respect to the isocenter that is not observed at the time of CT. Examining the data illustrated in Fig. 3, we note a steady increase in the mean displacement in the posterior direction as a function of time, consistent with the racket insert becoming stretched as a result of continuous long-term use without replacement or repair. The data shown in Fig. 3 indicate essentially no change in the SDs calculated for each axis of displacement over the duration of the study, demonstrating a consistent random uncertainty throughout the study. This result also indicates the prostate position at treatment time would have been on average 6 mm below what was seen at the planning stage, and that without daily US localization this couch sag problem may have gone uncorrected or even unnoticed.

A notable systematic shift (mean, 2.1 mm) was found in the superior direction as well. This shift may be partly due to the urethrogram effect discussed earlier, and also from the way the target is defined using the CT scan. There have been numerous studies detailing the shortcomings of CT with regard to prostate volume definition, with the consensus being that CT-defined volumes overestimate the prostate volume (25, 26). Typically, our patients are scanned with a 5-mm slice thickness and separation, and because the apex of the prostate is difficult to identify on a CT scan even with urethral and bladder contrast, there may be a tendency to "overdraw" the prostate especially in the superior direction from volume effects from the scan parameters used. A sagittal view of this contour is projected on the US system screen as the reference image at the time of localization, and this exaggerated contour may suggest to the user that a superior displacement of the target toward the contour boundaries is required. We estimate that this alone could introduce displacements in the range of 0–5 mm (one CT slice thickness) in the superior direction.

Random uncertainties in prostate displacement can be assessed from the SDs calculated from measured displacements. These uncertainties are a manifestation of random patient setup errors, inconsistencies in the US system calibration, and random changes in the patient's anatomy. The changes in the patient anatomy between fractions (interfraction) may be a function of bladder or rectal fill, as well as patient position. It is important to assess these uncertainties as they can help define the PTV dimensions if a daily localization system is not available for use. The SDs were found to be 4.4 mm, 4.5 mm, and 3.6 mm in the AP, SI, and RL directions, respectively. Knowing that our shift distribution is Gaussian, we can surmise that 2 SDs would include 95% of our sample. Thus, in the absence of systematic errors, a PTV margin of 8.8 mm AP, 9 mm SI, and 7.2 mm RL, would contain the prostate 95% of the time regardless of daily localization. These results are very similar to those found by Fung *et al.* (20) who suggested margins of 10 mm AP, 9 mm SI, and 8 mm in the LR direction. For our particular situation with significant systematic errors represented by the nonzero means of our displacement distributions, larger margins would have been required to adequately treat the prostate if no daily localization was used. The PTV margin required to contain the prostate 95% of the time would have been nonuniform across the major axes and ranged between 2.7 and 14.9 mm depending of the direction. Table 2 contains the relevant data. Of note is that the largest margin required would extend posterior 14.9 mm into the rectum, arguably the most critical structure relevant in a typical prostate treatment plan. For our study sample, a uniform 15 mm PTV margin would have encompassed the prostate more than 95% of the time, if two-dimensional US localization had not been used.

The data in Table 3 represent the percentage of all shifts, whose magnitude in any axis of displacement is less than the margin uniformly defined for PTVs of various dimensions. A relatively small PTV margin of 5 mm would, for instance, only contain the prostate for 93%, 51%, and 71%, of the time in the RL, AP, and SI directions, respectively. The data also confirm the findings in Table 2, indicating that a 15-mm uniform PTV margin will encompass the target at least 95% of the time (100%, 95%, and 100%, for the RL, AP, and SI directions, respectively). Even ignoring the systematic errors found at our clinic, a 5-mm posterior PTV margin would encompass the CTV less than 75% of the time in this direction. There exist several large multi-institutional protocols such as the Radiation Therapy Oncology Group P0126, which allow margins as small as 5 mm even in the absence of daily localization, and it is quite common for practitioners to actually reduce the PTV margin in the posterior aspect for reasons of rectal sparing regardless of daily localization.

CONCLUSIONS

Daily US localization is a useful and worthwhile procedure that can reduce setup uncertainties and may result in a more accurate and precise treatment. At our institution, a two-dimensional US-based system has been available for daily setup verification of prostate cancer patients receiving external beam radiotherapy since 2001. Data from 387 patients, amounting to 10,327 pretreatment localizations, were collected and analyzed. The measured displacements in the RL, AP, and SI directions were found to be normally (Gaussian) distributed. Nonnegligible mean displacements in the superior (2.1 mm) and posterior (6.1 mm) directions are representative of systematic uncertainties in the treatment planning and patient setup procedures. The SDs representing random intrafraction uncertainties of 4.4, 4.5, and 3.6 mm in the AP, SI, and RL directions, respectively, were found. If daily localization is not available, the data support the use of a nonuniform PTV margin ranging in dimensions between 2.7 mm in the anterior aspect to 14.9 mm in the posterior aspect, 7.7 mm to the right, 6.7 mm to the left, 11 mm superior, and 7 mm inferior of the prostate. A

15-mm uniform PTV margin would encompass the prostate 95% (2 SD) of the time when US localization is not accessible. Similarly, in the absence of systematic displacements, a PTV margin of 9 mm dimension in the AP and SI axes and of 7 mm in the RL axis would be adequate for coverage of the prostate in 95% of instances.

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