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PHYSICS CONTRIBUTION

ASSESSMENT OF PLANNING TARGET VOLUME MARGINS FOR INTENSITY-MODULATED RADIOTHERAPY OF THE PROSTATE GLAND: ROLE OF DAILY INTER- AND INTRAFRACTION MOTION

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Purpose: To determine planning target volume margins for prostate intensity-modulated radiotherapy based on inter- and intrafraction motion using four daily localization techniques: three-point skin mark alignment, volumetric imaging with bony landmark registration, volumetric imaging with implanted fiducial marker registration, and implanted electromagnetic transponders (beacons) detection.

Methods and Materials: Fourteen patients who underwent definitive intensity-modulated radiotherapy for prostate cancer formed the basis of this study. Each patient was implanted with three electromagnetic transponders and underwent a course of 39 treatment fractions. Daily localization was based on three-point skin mark alignment followed by transponder detection and patient repositioning. Transponder positioning was verified by volumetric imaging with cone-beam computed tomography of the pelvis. Relative motion between the prostate gland and bony anatomy was quantified by offline analyses of daily cone-beam computed tomography. Intratreatment organ motion was monitored continuously by the Calypso® System for quantification of intrafraction setup error.

Results: As expected, setup error (that is, inter- plus intrafraction motion, unless otherwise stated) was largest with skin mark alignment, requiring margins of 7.5 mm, 11.4 mm, and 16.3 mm, in the lateral (LR), longitudinal (SI), and vertical (AP) directions, respectively. Margin requirements accounting for intrafraction motion were smallest for transponder detection localization techniques, requiring margins of 1.4 mm (LR), 2.6 mm (SI), and 2.3 mm (AP). Bony anatomy alignment required 2.1 mm (LR), 9.4 mm (SI), and 10.5 mm (AP), whereas image-guided marker alignment required 2.8 mm (LR), 3.7 mm (SI), and 3.2 mm (AP). No marker migration was observed in the cohort. **Conclusion:** Clinically feasible, rapid, and reliable tools such as the electromagnetic transponder detection system for pretreatment target localization and, subsequently, intratreatment target location monitoring allow clinicians to reduce irradiated volumes and facilitate safe dose escalation, where appropriate. © 2010 Elsevier Inc.

Fiducial markers, Image guidance, Prostate cancer, Target setup, Organ motion.

INTRODUCTION

Radiotherapy for localized prostate cancer currently utilizes conformal techniques to improve survival rates, local control rates, and toxicity rates. The use of intensity-modulated radiotherapy, in particular, may enable even greater sparing of organs at risk, making dose escalation a realistic option

or permitting a further reduction of treatment-related side effects. Nevertheless, accurate target (prostate) localization remains a crucial factor for optimal target dosing and normal tissue avoidance.

Traditionally, target localization has relied on skin marks to infer prostate position, in conjunction with periodic pelvic

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bony anatomy portal imaging for verification. However, this technique neither takes into account the fact that bony anatomy and skin marks are not reproducibly related, nor does it take into account the fact that the prostate gland moves relative to both skin marks and bony anatomy (1). Although interfraction motion can be reduced using daily image guidance and custom immobilization devices, intrafraction motion continues to occur, and its mitigation has proven quite difficult to quantify. Nonetheless, systems have been used to quantify intrafraction motion, including megavoltage portal imaging (2), magnetic resonance imaging (3, 4), kilovoltage radiographs (5), transabdominal ultrasound (6), and electromagnetic tracking systems (7). Currently, a technique of growing interest is the use of intraprostatic fiducial markers (8, 9) to serve as a surrogate of prostate position. With two-dimensional and three-dimensional (3D) imaging now an integral component of contemporary linear accelerators, fiducial-based image guidance has become a well-established technique not only for patient positioning and repositioning but also for target motion assessment during the course of treatment, albeit snapshots in time.

In the present study, the magnitude of interfraction motion was assessed using four daily localization techniques: three-point skin mark alignment, volumetric imaging with bony landmark registration, volumetric imaging with fiducial marker registration, and patient repositioning with implanted electromagnetic transponders. Intrafraction motion was also assessed by real-time motion tracking using the Calypso System (10) (Calypso Medical Technologies, Inc., Seattle, WA). The planning target volume (PTV) margins needed to deliver 95% of the prescription dose to 95% of the clinical target volume (CTV) for 90% of the patients (11) were computed for all four alignment techniques.

METHODS AND MATERIALS

Patient cohort and treatment planning

A cohort of 14 patients with histologically confirmed clinical Stage I–III adenocarcinoma of the prostate gland formed the basis of the present retrospective study. Each patient had three electromagnetic transponders implanted within the prostate gland under transrectal ultrasound guidance at least 1 week before treatment planning simulation (12). With the patient in the supine position, simulation computed tomographic imaging (CT) was performed on a dedicated 16-slice helical big-bore simulator (Philips Medical Systems, Cleveland, OH), with 1 mm slice thickness through the transponders and 3 mm elsewhere. Simulation CT studies were transferred to a 3D dosimetric planning platform (Pinnacle³ v7.6; Philips Medical Systems, Andover, MA) for structure segmentation and treatment planning. The prostate gland was considered the CTV. The PTV was defined by an asymmetric 3D expansion of the CTV: 7 mm in the right/left/superior/anterior directions and a tighter 4 mm in the posterior/inferior directions (to limit the volume of irradiated rectum). Treatment consisted of step-and-shoot intensity-modulated radiotherapy of 6-MV photons, delivered at seven different gantry angles: 0°, 51°, 95°, 153°, 207°, 265°, and 309°, in a course of 39 fractions.

Daily target localization protocol

Daily pretreatment setup was based on laser and skin marks established during simulation. Per clinical protocol, each patient was repositioned by translational table positioning of the centroid of the implanted transponders in appropriate correspondence with the isocenter of the linear accelerator (7, 13). Calypso-based patient repositioning was subsequently validated by a 2.5 mm slice width volumetric cone-beam CT (CBCT; Varian Medical Systems, Palo Alto, CA) (14, 15) through an online manual seed registration process with a 3 mm action threshold. Like the Calypso System, the origin of the CBCT system was defined as a point in space identified by the initial isocenter from simulation. Using a 3D Cartesian coordinate system, this spatial location was designated as a “zero point” with X, Y, Z coordinates of 0, 0, 0. Hence, software-derived shifts from the Calypso System and from physician-approved manual CBCT/planning CT comparison were characterized as lateral (left–right [LR] or X), vertical (anterior–posterior [AP] or Y), and longitudinal (superior–inferior [SI] or Z) coordinates. For the purpose of this study, –X, –Y, –Z coordinates defined motion to the left, posterior, and inferior directions of the zero point, respectively.

Intratreatment motion analysis

Intratreatment motion of the prostate gland was monitored in real time through a 10-Hz nominal frequency update of the X, Y, Z displacement of the reference isocenter from its zero point using the Calypso System. Per clinical protocol, a corrective intervention, put in place to ensure accurate targeting of the PTV, required that reference transponder centroid deviation >4 mm in any translational direction lasting >1 s necessitated treatment interruption and subsequent patient realignment. Transient deviations, unlike sustained gradual displacements >4 mm, lasting <1 s were ignored.

Offline image registration and analysis

An offline automatic CBCT/planning CT bony anatomy–based registration process was performed on a dedicated image registration platform (VelocityAI v2.2; Velocity Medical Solutions, Atlanta, GA). For the purpose of this study, automatic image registration was based strictly on pelvic bony anatomy with no consideration of the femoral heads. The 3D coordinates of each transponder’s location on pretreatment CBCTs were independently recorded by three investigators (C.M.K., R.G.M., and P.A.S.) for each patient and for each day of treatment. For the purpose of this study, the location of the centroid of the three implanted transponders was used as a surrogate for the position of the prostate gland relative to pelvic bony anatomy. The daily displacement of the prostate gland relative to its position at the time of simulation was computed using Eq. 1 below:

$$\Delta\text{Centroid} \begin{pmatrix} X, Y, Z \end{pmatrix} = \left[\sum_1^n (\bar{X}_i - \bar{X}_{i,iso}), \sum_1^n (\bar{Y}_i - \bar{Y}_{i,iso}), \sum_1^n (\bar{Z}_i - \bar{Z}_{i,iso}) \right], \quad (1)$$

where $\bar{X}, \bar{Y}, \bar{Z}$ represent the average of corresponding transponder coordinate values recorded by investigators C.M.K., R.G.M., and P.A.S.; i represents a transponder; iso indicates corresponding transponder coordinates defined at the time of simulation; and Σ is the summation operator.

Quality assurance

An anthropomorphic pelvic phantom (RANDO; Phantom Laboratory, Salem, NY) was used to assess the positioning accuracy of

the Calypso System relative to the CBCT system. The phantom was also used to validate the accuracy of the image fusion algorithm used for bony anatomy registration. As in patient cases, three transponders were implanted into the phantom; transponders were orthogonally oriented and spaced approximately 3.5 cm from each other, with their long axes approximately parallel to each other. The phantom was subjected to both the daily target localization protocol and the offline image registration and analysis procedures outlined above a total of 14 times on 14 consecutive days.

Clinical implications: Error estimation and margin computation

Systematic and random error components for the cohort were assessed with the van Herk *et al.* margin formula (16). The systematic error component, Σ , was calculated as the standard deviation of the mean setup correction for each individual patient. The random error component, σ , was determined by computing the root mean square of the series' standard deviation of individual patient setup error. Both systematic and random error components were computed for skin-mark localization, volumetric imaging localization with bony landmark registration, volumetric imaging localization with fiducial marker registration, and patient positioning with implanted electromagnetic transponders. Clinically usable margins were subsequently computed according to the van Herk *et al.* (16) formulation with a minimum cumulative CTV dose of at least 95% of the prescribed dose for 90% of the patient population (see Eq. 2 below):

$$\text{Margin}_{\text{PTV}} = 2.5 \sqrt{\sum_{s,\text{Inter}}^2 + \sum_{\text{Intra}}^2} + 0.7 \sqrt{\sigma_{s,\text{Inter}}^2 + \sigma_{\text{Intra}}^2}, \quad (2)$$

where the subscripts “s, Inter” and “Intra,” respectively, denote setup intertreatment motion and intratreatment motion. It is worth noting that this margin does not account for penumbra near the collimator leaf or block edge.

Electromagnetic transponder migration assessment

Analyses of intertransponder distances from daily image guidance were used as a proxy for transponder migration. Allowing the origin to be the isocenter, the root mean square value of the intertransponder distances on both daily CBCTs and simulation CTs were computed using Eq. 3, below:

$$\text{Dist}_{st} = \sqrt{(X_s - X_t)^2 + (Y_s - Y_t)^2 + (Z_s - Z_t)^2}, \quad (3)$$

where s and t are any two transponders. Transponder migration was quantified as the standard deviation of the average differences between daily intertransponder distances and their reference distance, measured at the time of simulation, over each patient's course of treatment.

RESULTS

Quality assurance

For the 14 phantom measurements, the average differences between the measured Calypso offset and the calculated CBCT shift were 0.4 ± 0.4 mm, 0.2 ± 0.3 mm, and 0.4 ± 0.3 mm in the LR, SI, and AP directions, respectively. The accuracy of the bony anatomy registration algorithm (VelocityAI) was better than 0.5 mm (0.07 ± 0.41 mm), a value that included intrauser variability and the effects of fusion CT images of different thickness.

Interfraction prostate motion

Table 1 summarizes interfraction motion as a function of three alignment techniques. The range of prostate interfraction movement for skin mark alignment relative to the Calypso System alignment was less in the LR and SI directions (-1.06 ± 2.85 mm and -1.45 ± 4.43 mm, respectively) than in the in the AP direction (8.76 ± 6.53 mm). Like skin mark alignment, the range of prostate interfraction movement for implanted marker alignment relative to the Calypso System alignment was less in the LR and SI directions (-0.12 ± 1.25 mm and 0.34 ± 1.51 mm, respectively) than in the in the AP direction (0.51 ± 1.75 mm). Finally, bony anatomy interfraction movement showed the same trend as skin mark alignment, although the difference was less obvious: -0.08 ± 0.69 mm, 0.77 ± 3.51 mm, and 0.30 ± 3.96 mm in the LR, SI, and AP directions, respectively.

Intratreatment movement

The time interval for the intratreatment motion assessment ranged between 8 and 16 min. Table 2 summarizes intratreatment motion in the cohort. The observed intrafraction movement was as much as 4.8 mm in the RL, 9.1 mm in the AP, and 8.6 mm in the SI directions, respectively. As expected, motion in the lateral direction was smaller than in the AP and SI directions.

PTV margins

The results of seven scenarios are summarized in Table 3. With the assumption that interfraction motion is “zero” with Calypso-based alignment and continuous intratreatment tracking, LR, SI, and AP margins of 1.4, 2.7, and 2.3 mm, respectively, are required. When aligning the target volume to isocenter immediately before each treatment fraction by use of skin marks alone, and assuming no intratreatment motion, LR, SI, and AP margins of 7.3, 10.9, and 16.0 mm, respectively, are required. Inclusion of the measured intratreatment motion increased the LR, SI, and AP margins to 7.5, 11.4, and 16.3 mm, respectively. If markers are aligned to isocenter before each treatment fraction, the required margins (LR, SI, and AP) from these simulations are 2.5, 2.6, and 2.3 mm, and increase to 2.8, 3.7, and 3.3 mm with the inclusion of intratreatment motion. Finally, if bony anatomy is used for alignment, the required margins (LR, SI, and AP) from these simulations are 1.6, 8.9, and 10.2 mm, and increase to 2.2, 9.4, and 10.5 mm with the inclusion of intratreatment motion.

Marker migration

A total of 1680 intermarker distances (1638 from daily pretreatment CBCTs and 42 from simulation CTs) were assessed for the cohort. Of the 1638 daily intermarker distances, 59.3% and 80.7% varied ≤ 1 mm and ≤ 2 mm, respectively, from their corresponding reference values. No overall diminishing pattern in the difference between reference and daily intermarker distances was observed; an indication of nonperceivable gland shrinkage during the course of treatment for the cohort. However, Table 4 indicates daily variation in the intermarker distances from their reference values, ranging

Table 1. Average, SD of the average, and SD of marker setup error in each direction, when each supine patient was aligned by skin marks and lasers, markers using CBCT, and bony anatomy using CBCT

Parameter	Skin marks (mm)			Implanted marker (mm)			Bony anatomy (mm)		
	LR	AP	SI	LR	AP	SI	LR	AP	SI
Mean	-1.06	8.76	1.45	-0.12	0.51	0.34	-0.08	0.30	0.77
1 SD	2.85	6.53	4.43	1.25	1.75	1.51	0.69	3.96	3.51
Range	-9.60	-6.20	-5.25	-10.0	-6.00	-6.00	-1.62	-12.4	-11.3
	+6.25	+24.1	+18.1	+10.0	+7.00	+7.00	+1.58	+11.4	+9.72
Σ_{Inter}	2.47	5.47	3.92	0.59	0.47	0.64	0.51	3.36	2.93
σ_{Inter}	1.67	3.34	1.60	1.40	1.57	1.37	0.41	2.50	2.29

Abbreviations: SD = standard deviation; CBCT = cone-beam computed tomography; LR = left–right; AP = anterior–posterior; SI = superior–inferior; – = motion to the left/posterior/inferior directions about isocenter.

from -4.9 mm to +3.9 mm (with 95% confidence), attributable in part to transponder migrations and/or prostate gland deformation induced by bladder/rectal fillings.

DISCUSSION

Linear accelerator and multileaf collimator technology has evolved to the point that radiation doses can be delivered to target volumes with high accuracy and precision. However, the accuracy of these technologies is limited by uncertainty in treatment parameters, including organ motion and setup errors. Therefore, knowledge of these treatment errors, their characteristics and causes, in addition to techniques necessary for their control or mitigation, is an increasingly important component of the clinical radiotherapy process.

Traditional setup techniques have relied on skin marks aligned to room-based lasers or on the alignment of bony anatomy to digitally reconstructed radiographs or volumetric CT, using corresponding landmarks as surrogates for target volume position. The “true isocenter” is considered reproducible with the assumption that there is no deviation in patient body habitus between simulation and treatment; that is,

bony anatomy and soft tissue remain in the same position with zero prostate displacement relative to the pelvis. However, it is well known that prostate displacement occurs independently from bony anatomy, resulting in both systematic and random deviations, of which the point-in-time CT acquisition at simulation is only one of many. Results from the present study confirm the presence of significant variability in prostate position. As such, in the absence of information on the position of soft tissue(s) within the target volume, setup accuracy based on these techniques is limited, making frequent setup corrections during radiotherapy a futile process. With skin mark alignment in particular, almost all of the fractions in the present cohort were >2 mm from the “true isocenter.” Positioning in the AP dimension was the most variable, owing in part to variable and nonreproducible daily filling of the bladder and rectum, variable positioning of the pelvis within the immobilization device, and the suppleness of skin. Furthermore, overall prostate displacements favored the anterior direction (88.6% vs. 10.0%), a plausible consequence of rectum filling during the treatment course surpassing the rectum filling at simulation. Additionally, the position of the prostate favored a more left (62.9% vs.

Table 2. Intrafraction preparation and treatment errors determined with the Calypso System

Patient no.	Mean (mm)			SD (mm)			Range (mm)		
	LR	AP	SI	LR	AP	SI	LR	AP	SI
1	-0.05	-0.48	0.34	0.50	1.03	0.69	[-1.54, 2.97]	[-2.77, 3.06]	[-5.77, 3.97]
2	0.56	0.86	1.50	0.74	1.57	1.37	[-2.01, 4.66]	[-2.02, 6.05]	[-4.03, 7.63]
3	-0.36	0.26	0.07	0.59	1.66	1.15	[-3.82, 2.89]	[-3.83, 5.06]	[-7.98, 8.61]
4	0.05	-0.43	0.16	0.61	0.77	0.68	[-2.04, 2.26]	[-2.48, 3.26]	[-2.99, 3.49]
5	0.05	-0.43	0.16	0.60	0.77	0.68	[-3.71, 2.26]	[-2.48, 3.26]	[-2.99, 3.49]
6	-0.37	-0.16	0.43	0.92	1.16	0.62	[-2.49, 4.49]	[-2.90, 3.26]	[-4.71, 3.92]
7	0.34	-0.88	0.36	0.58	1.29	1.28	[-4.78, 3.01]	[-5.20, 5.48]	[-5.17, 6.04]
8	0.31	-0.07	-0.50	0.60	1.62	1.53	[-4.58, 2.73]	[-5.89, 5.34]	[-5.14, 7.26]
9	0.58	0.10	0.52	0.92	1.05	1.03	[-4.40, 3.75]	[-2.28, 4.88]	[-4.02, 4.95]
10	0.04	-1.15	-1.34	1.02	1.80	2.06	[-3.50, 2.13]	[-7.95, 5.98]	[-5.80, 4.51]
11	0.22	0.16	0.82	0.76	1.14	1.37	[-3.87, 3.55]	[-9.13, 8.98]	[-4.39, 4.77]
12	0.66	-0.83	-0.32	1.08	2.25	1.83	[-3.12, 3.78]	[-6.56, 4.12]	[-7.93, 7.44]
13	0.13	0.08	0.36	0.83	1.37	1.64	[-2.52, 3.88]	[-4.72, 4.84]	[-4.52, 4.97]
14	-0.24	-0.19	1.15	0.57	0.97	0.96	[-4.07, 2.24]	[-1.86, 4.83]	[-4.80, 3.49]
Intrafraction parameters	M_{LR}	M_{AP}	M_{SI}	Σ_{LR}	Σ_{AP}	Σ_{SI}	σ_{LR}	σ_{AP}	σ_{SI}
	0.12	-0.22	0.26	0.33	0.52	0.70	0.76	1.38	1.29

Abbreviations as in Table 1.

Table 3. Margins required for setup error computed using the van Herk *et al.* formulation*

Target volume alignment technique	Margins (mm)		
	LR	AP	SI
Skin marks without intrafraction motion	7.34	16.0	10.9
Skin marks with intrafraction motion	7.52	16.3	11.4
CBCT-based marker alignment without intrafraction motion	2.46	2.28	2.56
CBCT-based marker alignment with intrafraction motion	2.81	3.23	3.68
CBCT-based bony anatomy alignment without intrafraction motion	1.57	10.2	8.92
CBCT-based bony anatomy alignment with intrafraction motion	2.13	10.5	9.36
Calypso-based alignment	1.36	2.28	2.64

Abbreviations as in Table 1.

* $2.5\Sigma + 0.7\sigma$ (16).

33.7%) and superior (54.4% vs. 42.8%) position than at simulation. These findings are in agreement with results in the literature (2, 17–21) but contradict results by Altholf *et al.* (22) and Rudat *et al.* (23), who showed the largest displacement to be in the SI direction.

Because the prostate is not attached directly to bony anatomy, and as data in the present study show (Table 1), prostate displacement relative to bony anatomy is large. With the exception of lateral displacements, patient repositioning using bony anatomy only slightly improves target positioning over skin-mark alignment, making bony anatomy a poor surrogate for prostate position, with potentially little to no role in ensuring adequate dose delivery to the target volume. This is consistent with findings by Beltran *et al.* (2) and O'Daniel *et al.* (17), respectively. As such, both online and offline approaches could be implemented for patient alignment. However, although offline correction protocols aim at reducing systematic errors, online correction protocols have the potential to reduce both systematic and random errors at the expense of increasing treatment time per fraction.

Unlike bony anatomy fusion, daily online pretreatment image guidance with use of implanted markers provides a surrogate for soft-tissue target volume positioning that limits the effects of interfraction motion on treatment precision. The use of intraprostatic markers, however, assumes that the markers are fixed within the prostate and act as a reliable sur-

rogate for the position of the prostate gland. This is corroborated by data in the present study that indicate an average intermarker movement of <5 mm (with 95% confidence). Nonetheless, there still is temporal variability in target localization based on fiducial markers. This is attributable in part to intratreatment sources of motion because the relative positioning error of the CBCT and Calypso systems used in the present study is assessed to be 1 mm at worst. As such, required margins, though significantly smaller when compared with skin mark and/or bony anatomy alignments, could be as large as 2.7 mm (SI) without taking intrafraction motion into account. Furthermore, unlike skin mark and bony anatomy alignments, for which the range of interfraction motion proved to be significantly larger than the range of intrafraction displacement, this is not the case for marker-based image guidance. In the latter technique, the mean intrafraction displacement is comparable to, and in some directions larger than, the mean interfraction displacement. This is of significant magnitude because whereas intrafraction motion only plays a marginal role in determining PTV margins for patient positioning by skin marks and/or bony anatomy, it does play a crucial role for marker-based alignment.

Nevertheless, because image-guidance techniques (CBCT in the present study) require several minutes for data acquisition and processing for patient alignment, their temporal resolution makes them neither practical nor accurate for the assessment of intratreatment organ motion, which is nontrivial (Table 2). It is noteworthy to mention that daily online pretreatment image guidance with CBCT in the absence of fiducial markers, although challenging, is also feasible. Although soft-tissue matching has been used at our institution on patients who were not candidates for invasive placement of fiducial markers, it is known to have greater observation uncertainties when compared with marker matching, as has been shown by Mosley *et al.* (24). Hence, our preference is to use calcifications as surrogate markers, if present within the prostate gland, because they have been demonstrated by Zeng *et al.* (25) to be stable throughout the course of treatment.

A real-time tracking system like the Calypso transponder system with adaptive treatment may be able to reduce the PTV margins even further (see Table 3) with prebeam position corrections and continuous monitoring and the use of an action threshold to mitigate the effects of large intratreatment motions.

Limitations

Despite the comprehensive nature of this study, there are some important limitations that are worth reporting. First, an important shortcoming of the margin recipe used in the present study is its lack of adequate incorporation of rotational and/or deformation errors. Although fiducial markers are an excellent surrogate of prostate position, they do not define the shape and volume of the prostate gland. To the credit of the present study, even if rotations were measured, the magnitudes of rotational corrections of prostate position are generally very small, with standard deviations in the range

Table 4. Marker migration computed as the difference between reference intertransponder distance (at the time of simulation) and daily intertransponder distance (from daily CBCTs)

Alignment technique	Mean \pm SD (mm)		
	Apex–left base	Right base–left base	Apex–right base
CBCT	0.44 \pm 1.78	0.15 \pm 1.54	–0.52 \pm 2.25

Abbreviations as in Table 1.

of 0.9°–4.0°, with the greatest amount of rotation seen in the left–right axis (26–28), and may be impractical to perform. Second, characterization of rotation and/or deformation errors is beyond the scope of the present work. Consequently, LR discrepancies between Calypso-based alignment and CBCT-based bony anatomy alignment with intrafraction motion observed in Table 3 (potentially due to the fact that whereas repositioning based on the Calypso System is a 3-degree-of-freedom process, the other is a 4-degree-of-freedom process) are not adequately addressed. Third, as a consequence of perceived directionality (at least for skin mark localization) in overall prostate displacement, use of the van Herk *et al.* formulation (16) may not be adequate to compensate for asymmetric movements (28, 29). Fourth, sustained intratreatment displacements exceeding our clinically predetermined threshold typically occurred gradually. As such, inter- and intrafield breaks were used to reposition patients who were trending toward the threshold;

consequently, large sustained excursions were rare. Finally, the margin findings in the present study are based on a cohort of 14 institution-specific patients and may not provide adequate coverage for patients with excessive prostate mobility. This is especially important because at present there is no accurate method for segregating patients into small vs. excessive prostate motion.

CONCLUSIONS

Increasing both the prescribed radiation dose and the PTV margins yields the risk of increased treatment-related toxicity. Small increases in PTV margin expansions may greatly increase the volume of tissue irradiated to the prescription dose. Clinically feasible, rapid, and reliable tools to monitor target location during a radiotherapy treatment, like the Calypso System, allow clinicians to reduce the irradiated volume and facilitate safe dose escalation, where appropriate.

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