



Fiducial Markers, Saline, and Balloons to Locate and Stabilize the Prostate during Proton Therapy

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Abstract

Purpose: To determine the value of fiducials in daily image-guided prostate targeting for proton therapy (PT), to compare intrafraction motion between two stabilization strategies (rectal saline and balloon), and to determine the respective impacts of these combined strategies on planning target volume (PTV) expansions and smearing margins.

Materials and Methods: Forty patients were randomly selected from a pool of low-risk prostate cancer patients with intraprostatic fiducials treated with proton therapy between 2006 and 2012, including 20 with intrarectal saline or 20 with endorectal balloons for daily prostate stabilization. Daily pre- and post-treatment orthovoltage (kV) films and digitally reconstructed radiographs (DRRs) were analyzed to determine prostate interfraction displacement, intrafraction motion, daily residual setup error in three axial dimensions (anterior-posterior, superior-inferior, and left-right), necessary population PTV expansions using van Herk's formula ($2.5\Sigma + 0.7\sigma$), and smearing margins.

Results: Interfraction displacement population means did not differ significantly in either treatment group. Intrafraction displacement population means in the anterior-posterior direction were significantly smaller with balloons than with saline. With fiducial markers to account for interfraction motion, PTV margins could be reduced by 4.0, 4.2, and 2.3 mm in the anterior-posterior, superior-inferior, and left-right directions, respectively, in saline-treated patients, and by 6.3, 6.8, and 0.8 mm in each direction, respectively, in balloon-treated patients. With fiducials, PTV margins were smaller using rectal balloons compared with saline: 2.3 vs. 3.6 mm in the anterior-posterior direction, 2.7 vs. 3.4 mm in the superior-inferior direction, and 1.1 vs. 2.0 mm in the left-right direction. The maximum smearing margin in balloon patients were 10.7 mm.

Conclusions: Fiducial markers are valuable for reducing the PTV expansion necessary to account for interfraction displacement. Rectal balloons were more effective than saline in decreasing intrafraction prostate motion, thereby permitting smaller PTV expansions to reduce the amount of normal tissue included in the target volume.

Keywords: proton therapy; prostate cancer; fiducial markers

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Introduction

In external-beam radiation therapy, the accuracy of tumor targeting and treatment delivery affect both the likelihood of tumor control and the likelihood of treatment complications related to normal tissue damage. Internal tumor targets may vary in position within the body on a daily basis (interfraction motion); for example, within the pelvis the degree of bladder and bowel filling may affect the location of the prostate relative to the bony pelvis and pelvic skin surface. In addition, because the prostate sits atop the urogenital diaphragm and adjacent to the rectum, non-rigid structures subject to both voluntary and involuntary motion, the location of the prostate within the pelvis may change during radiation delivery (intrafraction motion). An expansion (the planning target volume or PTV) beyond the actual target volume identified on 3-dimensional simulation imaging must be planned to account for both prostate interfraction and intrafraction motion to assure accurate targeting and treatment delivery, particularly with highly conformal radiation techniques such as x-ray-based intensity-modulated radiation therapy (IMRT) or proton therapy. Minimizing the PTV expansion required for accuracy is key to minimizing treatment complications. The purpose of the study reported herein is to evaluate the current strategy used at the University of Florida Health Proton Therapy Institute (UFHPTI, Jacksonville, FL) to account for interfraction motion, to compare two strategies used for minimizing intrafraction motion, and to determine the adequacy of the current PTV expansion policy used in the prostate cancer program at UFHPTI.

Materials and Methods

Patients

Forty patients were randomly selected from a population enrolled in an institutional review board-approved outcome tracking protocol ongoing since 2006 at the UFHPTI. Patients had pathology-confirmed low-risk prostate adenocarcinoma.

Patient Simulation and Setup

Prior to treatment simulation and planning, all patients had 3 to 4 visicoil intraprostatic fiducial markers placed in the prostate to permit daily image-guided localization of the target. Each marker was 5 mm in length and 0.75 mm in diameter. Thirty minutes before simulation and daily treatments, each patient voided, drank 420 cm³ of water for bladder stabilization, and was positioned in a customized vacuum-body mold. Twenty patients had 100–200 cm³ of saline instilled into the rectum. Typically, a volume of 100 cm³ was used unless rectal expansion and gas expulsion was deemed inadequate at computed tomography (CT) simulation, in which case an additional 100 cm³ was added. The volume of saline used at simulation was repeated each day with treatment. Another 20 patients had an endorectal balloon inserted into the rectum, then inflated with 80–100 cm³ saline. CT simulation images were then obtained with a Philips Brilliance CT Big Bore simulator (Philips Healthcare, Andover, MA). Magnetic resonance (MR) imaging was acquired immediately after CT using a Philips Panorama 0.23T open-MR imaging system. Using the Philips Pinnacle AcQSim3 virtual simulation workstation, CT and MR images were fused and the prostate target was delineated on the fused CT-MR image set before being imported into the Varian Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA). The target volume was expanded (PTV) to account for intrafraction and interfraction motion. Apertures were designed to shape the radiation dose distribution perpendicular to the beam path and compensators were fabricated to modify the path length of protons passing through the aperture to create a conformal dose distribution with the distal shape of the target. To account for potential slight changes in radiologic path length related to intrafraction and interfraction motion, a range compensator “smearing” margin of 19 mm was added. Additional distal and proximal margins along the beam direction were added for each treatment field to mitigate the effect of beam-range uncertainties.

Fiducial markers were identified in the treatment planning CT image set and marked in the digitally reconstructed radiographs (DRRs). During daily treatment set-up, the patient was aligned on the table with a room laser, pre-treatment orthogonal kV film pairs were acquired, and fiducial locations were marked on the kV images. Using digital positioning image registration software (DIPS, IBA, Belgium), the locations of fiducials on daily acquired images were compared to their locations on the DRR simulation image. The DIPS program calculated translational corrections necessary to replicate the prostate location at simulation relative to the beam axis. The patient position was then manually corrected by shifting the treatment couch along the cephalad-caudad (superior-inferior), horizontal (right-left), and vertical (anterior-posterior) axes. A maximum of 2 mm of setup “residual error” was allowed in any axis; table shifts and refilming were repeated each day until the residual error in all axes was within the 2-mm requirement. Post-treatment orthogonal kV film pairs were acquired following every

treatment fraction for the first 10 treatments and once per week thereafter to assess intrafraction motion and thus the adequacy of the PTV margin.

Data Analysis

The range of prostate interfraction motion in 3 axes was estimated by calculating differences in prostate position (as represented by the location of fiducials relative to bony anatomy) on each of 39 daily pretreatment x-ray images compared to the simulation DRR, with the DRR fiducial position used as the reference. Similarly, intrafraction motion in the three axes was estimated by calculating the difference between pre- and post-treatment prostate positions for all treatments in each patient. The mean, minimum, and maximum values and standard deviations for interfraction motion, intrafraction motion, and pretreatment setup residual errors were calculated for the saline and rectal balloon treatment cohorts. The Wilcoxon signed-rank test was performed to evaluate differences between the mean values of the saline versus balloon treated groups in the anterior-posterior (AP), superior-inferior (SI), and left-right (LR) directions for interfraction motion, intrafraction motion, and setup residual errors. Two-sample *F*-test was performed to evaluate differences between the balloon and saline groups in variances for interfraction motion, intrafraction motion, and setup residual errors in each axial direction.

To determine the systematic and random components of the interfraction motion, intrafraction motion and pretreatment

setup residuals, the following equations were used: $\bar{L}_j = \left(\frac{1}{M_j}\right) \sum_{i=1}^{M_j} L_{ij}$ for the *j*th patient error (equation 1), $\bar{L} = \left(\frac{1}{N}\right) \sum_{j=1}^N \bar{L}_j$ for

the population-averaged error (equation 2), $\Sigma = \sqrt{\left(\frac{1}{N}\right) \sum_{j=1}^N (\bar{L}_j - \bar{L})^2}$ for the standard deviation of the systematic error

distribution (equation 3), and $\sigma = \sqrt{\left(\frac{1}{N}\right) \sum_{j=1}^N \left[\left(\frac{1}{M_j}\right) \sum_{i=1}^{M_j} (L_{ij} - \bar{L}_j)^2\right]}$ for the standard deviation of the random error distribution

(equation 4).

For patients $j \in \{1, 2, \dots, N\}$ and for each patient's treatment session $i \in \{1, 2, \dots, M_j\}$, L_{ij} is defined as either a vector of prostate intrafraction motion error, interfraction motion error, or setup residual error. PTV margins necessary to account for intrafraction motion and setup residual errors were calculated according to the van Herk formula of $2.5\Sigma + 0.7\sigma$, in which Σ is the total systematic error and σ is the total random error for both prostate intrafraction motion and setup residual errors [1].

The range compensator (bolus) smearing margins that were necessary to account for changes in radiologic path length related to interfraction and intrafraction motion were calculated as the quadratic summation of target motion (TM, sum of the maximally acceptable interfraction and intrafraction shifts) as well as target depth (TD) and bolus thickness (2 mm). The distal target position and bolus thickness averaged 280 mm. The following formula was used [2]:

$$BE = \sqrt{(IM + SM)^2 + (0.03x(\text{distal CTV depth} + \text{bolus thickness}))^2}$$
 (equation 5) where BE is bolus expansion (smearing

margin), IM is internal organ motion radius occurring orthogonally to the beam axis, and SM is setup error occurring orthogonally to the beam axis.

JMP software was used for statistical analysis (SAS Institute, Cary, NC). Paired differences between saline and balloon for each patient were attained and Wilcoxon's signed rank sum test was used to assess statistical differences in either the anterior-posterior, superior-inferior, or left-right directions for interfraction motion, intrafraction motion, and setup residual error. For all of these comparisons, an *F* test for equality of variances was also applied to the same paired differences.

Results

Table 1 shows the interfraction displacement population mean, minimum, maximum, and standard deviation in the three axial directions within each treatment group. Interfraction motion means were not significantly different between the two treatment groups as indicated by the Wilcoxon signed-rank test (*p* values were 0.20, 0.86, and 0.31 in the AP, SI, and LR directions, respectively). An *F* test revealed that balloons non-significantly increased population standard deviations in the AP (from 2.0 to 2.8 mm; *p*=0.16) and SI directions (2.1 to 3.1 mm; *p*=0.09) but led to a significant reduction in the LR direction (1.2 to 0.5 mm;

Table 1. Interfraction motion statistics in all three axial directions for saline- and balloon-treated populations in millimeters.

	Anterior-posterior direction			Superior-inferior direction			Left-right direction		
	Saline	Balloon	P value	Saline	Balloon	P value	Saline	Balloon	P value
Mean ^a	-1.4	-0.2	0.20	-0.3	0.3	0.86	-0.1	-0.5	0.31
SD ^b	2.0	2.8	0.16	2.1	3.1	0.09	1.2	0.5	0.0002
Minimum	0.0	0.0		0.0	0.0		0.0	0.0	-
Maximum	10.1	11.3		9.1	11.8		12.8	3.45	-

^aWilcoxon signed-rank sum test.

^b2-Sample F test.

$p = 0.0002$). Ranges were similar in the saline and balloon groups for the AP axis with 10.1 versus 11.3 mm, respectively, and for the SI axis with 9.1 vs. 11.8, respectively, but worse with saline than balloons for the LR axis with 12.8 versus 3.45 mm, respectively.

Table 2 demonstrates the intrafraction motion and setup residual error population mean, minimum, maximum, and standard deviation in each axis direction for the saline and balloon groups. Population means in the AP direction were significantly lower in the balloon group than in the saline group: -0.2 vs. 0.4 mm ($p = 0.02$), trending lower in the SI direction: 0.1 vs. 0.6 mm ($p = 0.08$), and not differing in the LR direction ($p = 0.41$). The F test showed significantly higher population standard deviations with saline compared to balloons: 0.9 to 0.6 mm ($p = 0.04$) in the AP axis, 0.3 to 0.1 mm ($p = 0.0003$) in the LR axis, and 0.9 to 0.6 mm ($p = 0.12$) in the SI axis. The observed setup residual error means were not statistically different between saline and balloons in the AP or LR directions, but setup errors in the SI direction were significantly lower in the balloon population compared with the saline group (0 vs. 0.3 mm, respectively; $p = 0.002$). The F test showed significantly higher population standard deviations with saline compared to balloons only in the LR direction with 0.4 vs. 0.2 mm ($p = 0.003$).

Table 3 lists the calculated systematic and random error components of interfraction motion, intrafraction motion, and setup residual errors for saline and rectal balloons as indicated by equations 3 and 4 described above.

Table 4 shows the intrafraction components, the setup residual error components, and the total PTV expansion values calculated using van Herk's formula ($2.5\Sigma + 0.7\sigma$), including and excluding the interfraction component for saline and rectal balloon subjects. The use of fiducials to account for interfraction motion reduced the necessary PTV margins with saline prostate stabilization by 4.0 , 4.2 , and 2.3 mm, respectively, in the AP, SI, and LR axes; with balloons, fiducials reduced the PTV margins by 6.3 , 6.8 , and 0.8 mm, respectively, in the AP, SI, and LR axes. Compared with saline, rectal balloons reduced the PTV expansions from 3.6 to 2.3 mm in the AP direction, 3.4 to 2.7 mm in the SI direction, and 2.0 to 1.1 mm in the LR direction.

Other potential errors include beam alignment, x-ray delineation, and table positioning errors. These errors contributed less than an additional 0.06 mm in uncertainty and were therefore considered inconsequential to our final PTV margins and not included in the reported calculations.

Table 2. Intrafraction motion and setup residual error population statistics in each axial direction for both treatment groups in millimeters.

	Anterior-posterior direction			Superior-inferior direction			Left-right direction		
	Saline	Balloon	P value	Saline	Balloon	P value	Saline	Balloon	P value
<i>Intrafraction motion</i>									
Mean ^a	0.4	-0.2	0.02	0.6	0.1	0.08	0.1	0.0	0.41
SD ^b	0.9	0.6	0.04	0.9	0.6	0.12	0.3	0.1	0.0003
Min	0.0	0.0	-	0.0	0.0	-	0.0	0.0	-
Max	7.6	4.9	-	5.8	7.1	-	4.4	1.9	-
<i>Setup residual errors</i>									
Mean ^a	-0.1	0.0	0.61	0.3	0.0	0.002	-0.1	0.0	0.74
SD ^b	0.3	0.2	0.09	0.3	0.4	0.46	0.4	0.2	0.003
Min	0.0	0.0	-	0.0	0.0	-	0.0	0.0	-
Max	2.3	2.0	-	2.3	2.0	-	2.4	2.0	-

^aWilcoxon signed-rank sum test.

^b2-Sample F test.

Table 3. Systematic (Σ) and random (σ) error components of intrafraction motion and setup residual errors for saline and rectal balloon populations in millimeters.

	Anterior-posterior direction		Superior-inferior direction		Left-right direction	
	Saline	Balloon	Saline	Balloon	Saline	Balloon
Inter						
Σ	2.0	2.8	2.1	3.1	1.2	0.5
σ	2.4	1.8	2.3	1.9	1.3	0.6
Intra						
Σ	0.9	0.6	0.9	0.6	0.3	0.1
σ	1.5	1.0	1.2	1.1	0.6	0.4
Setup						
Σ	0.3	0.2	0.3	0.4	0.4	0.2
σ	0.6	0.7	0.7	0.5	1.0	0.6

Based on actual interfraction displacement errors and intrafraction motion calculated for balloon patients in this study, new smearing margin calculations showed that the initial smearing margins used by our institution (19 mm) [3] could be reduced to 10.3 mm, 10.7 mm, and 8.5 mm in the AP, SI, and LR axes, respectively.

Discussion

Clinical data suggest a strong correlation between dose-volume histogram (DVH) parameters and rectal toxicity [4–6]. Thus, it is important to improve targeting accuracy and reduce the PTV expansions necessary to account for target-location uncertainties related to interfraction and intrafraction motion. Various prostate localization and stabilization strategies have been developed. Daily prostate motion can be determined for more precise localization, using techniques such as daily kilovoltage imaging of fiducial intraprostatic markers [7, 8] or 3-dimensional imaging, such as ultrasound and CT guidance [9]. Prostate stabilization has been achieved with immobilization devices including application of intrarectal saline or balloons [10]. Prior studies indicate that endorectal balloons decrease intrafraction motion, thereby reducing PTV margins and inner rectal wall volume exposed to radiation [11–13].

In this study, we discuss the relative value of fiducial markers to account for interfraction prostate motion in patients with low-risk prostatic adenocarcinoma receiving proton therapy (PT). Using pre- and post-treatment kV films, we also compared the effect of two immobilization devices (rectal saline vs. balloons) on prostatic intrafraction motion as well as resultant PTV expansion and range compensator smearing margins in this patient population.

With balloon and/or saline prostate stabilization, day-to-day interfraction prostate displacement was significant in magnitude, with maximum displacement values up to 12.8 mm. Daily imaging with intraprostatic markers permits localization of the actual prostate target, thereby accounting for interfraction displacement [14, 15] and eliminating the interfraction motion variable from the PTV margin calculation. For example, without fiducial markers, PTV margins in one study needed to be increased by 4.7 mm in the AP direction, 7.3 mm in the SI direction, and 3.6 mm in the LR direction to account for daily prostate

Table 4. PTV expansion margins in saline and balloon patients with and without fiducials to account for interfraction motion in millimeters.

Direction	Saline			Balloon		
	Anterior-posterior	Superior-inferior	Left-right	Anterior-posterior	Superior-inferior	Left-right
Interfraction	6.7	6.9	3.8	8.3	9.1	1.6
Intrafraction	3.4	3.1	1.2	2.1	2.3	0.6
Setup	1.2	1.2	1.6	0.9	1.3	0.9
With fiducials to eliminate interfraction component						
PTV	3.6	3.4	2.0	2.3	2.7	1.1
Without fiducial to account for interfraction component						
PTV	7.6	7.6	4.3	8.6	9.5	1.9

Abbreviation: PTV, planning target volume.

motion [16]. In the current study, without fiducial markers, additional PTV margins of up to 9.5 mm would be necessary to account for possible displacements from treatment planning position.

Although population means were not significantly different, interfraction motion variances trended toward an increase with balloons, especially in the SI direction. This variance difference may be due in part to the lack of consistent positioning of the endorectal balloons on a daily basis, leading to increased daily variation in prostate displacement compared with rectal saline administration. Wang et al also found larger interfractional displacement in the SI direction with endorectal balloons [17]. Additionally, these balloon deformations may contribute to rectal deformation, ultimately affecting the daily position of the prostate relative to bony anatomy.

These daily position variations could be important, particularly in proton therapy: even though beam realignment guided by fiducial markers eliminates targeting errors owing to interfraction motion, differences in target location relative to pelvic anatomy could impact the radiologic path length, which is affected by the proton stopping power of various tissues distributed along the path. In proton therapy, changes in the radiologic path length could impact the actual dose to the target. Vargas et al studied the impact of small beam-alignment changes to account for interfraction target displacements; with target displacement up to 10 mm in multiple directions, target coverage (V78) was improved with beam realignment without changes in any beam parameters (apertures, compensators, monitor units, etc). [3]. Although the maximum interfraction displacement was 12.8 mm, only 0.4% and 1% of displacements exceeded 10 mm in the AP and SI directions of the balloon population, respectively. Therefore, we feel that beam realignment based on daily imaging of fiducial markers provides an excellent strategy for assuring accurate daily targeting as well as dose delivery. Clinical outcome data showing 99% freedom from clinical and biochemical disease progression at 5 years in both low- and intermediate-risk prostate cancer patients treated during this era verifies the efficacy of this technique [18].

After removing interfraction prostate displacement as a source of targeting or delivery error, intrafraction motion becomes the most important remaining source of potential error and uncertainty in radiation targeting and delivery. Numerous techniques have been employed to detect and quantify intrafraction motion, including 2-dimensional imaging with orthogonal pairs of pre- and post-kV or MV x-rays to detect either changes in bony anatomy or fiducial markers within the target, 3-dimensional pre- and post-treatment imaging with cone-beam CT or MR, or real-time tracking with implanted electronic radiofrequency transponders. At the UFHPTI, we utilized radiologically detected fiducial markers with orthogonal kV imaging before and after each treatment fraction to determine prostate location and displacement. In line with prior literature, we demonstrated that the endorectal balloon is able to stabilize prostatic intrafraction displacement [19]. In a study by Mayyas et al, intrafraction prostate shifts between pre- and post-kV planar x-rays using fiducial marker guidance demonstrated increased systematic and random errors relative to our intrafraction motion values, yielding higher PTV margins of 6.6, 6.8, and 3.9 mm in the AP, SI, and LR directions, respectively [20]. Compared to the expansion values concluded by our study, these differences may be related to our use of rectal balloons for prostate stabilization and to the relatively shorter proton beam delivery time compared to IMRT delivery times, which may be substantially longer, potentially allowing time for greater prostate intrafraction motion.

Real-time intrafraction motion monitoring using cine-MR imaging and electromagnetic transponders has shown that intrafraction displacements are dependent on time [21], with a significant increase in motion occurring after 150 seconds [19]. Increased probability of prostatic motion with longer treatment times without prostate stabilization was also confirmed using post-treatment cone-beam CT where systematic errors of 1.7, 1.5, and 0.6 mm were observed in the AP, SI, and LR directions, respectively [22].

In addition to affecting PTV margins, interfraction and intrafraction motion also impact smearing margins. In proton therapy, tissue heterogeneity creates heterogeneous dose distributions, potentially leading to areas of under- or overdosing. Range compensators are utilized to shape the distal end of the proton beam. To account for setup errors and organ motion, smearing margins are applied to expand the range compensator to ensure adequate coverage with potential daily variations in composition, and thus length, of the beam path. Based on our interfraction and intrafraction motion data, we calculated a reduced smearing margin relative to the current value utilized at our institution. Although the dose distribution becomes more heterogeneous with smaller smearing margins, smaller smearing margins result in greater target conformity [23]. Consequently, doses to organs distal to the prostate in the beam path will be minimized.

Based on this study, we have validated the safety of our prior reduction of PTV margins from 8-mm and 5-mm margins to 6-mm and 4-mm margins in the craniocaudal and axial directions and established the safety of a further reduction to 4 mm and 3 mm in the craniocaudal and axial directions, respectively. In addition, we have validated the safety of a reduction in smearing margin from our current 19 mm to 11.

By accounting for interfraction motion with fiducial markers and minimizing prostate intrafraction motion with rectal balloons, PTV and smearing margins can be reduced, potentially reducing rectum and rectal wall DVH parameters as well as rectal toxicity. These strategies may thus impact the therapeutic ratio for radiation in prostate cancer in two ways: (1) by increasing accuracy in targeting and delivery, tumor control can be enhanced; (2) by reducing the PTV margin and smearing margin necessary, toxicity can be reduced.

Conclusions

Daily image guidance with fiducial markers is a valuable strategy for reducing the PTV expansion necessary to account for interfraction displacement. Rectal balloons are relatively more effective than instilled rectal saline for reducing intrafraction prostate motion and the PTV expansion necessary to account for it. In proton therapy, rectal balloons and fiducial markers also reduce the necessary smearing margin. We anticipate these strategies will positively impact the therapeutic ratio in prostate cancer by both enhancing disease control and reducing toxicity.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: Dr. Nancy P. Mendenhall is Editor-in-Chief of the *International Journal of Particle Therapy*. The other authors have no conflicts to disclose.

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