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CLINICAL INVESTIGATION **Prostate**

INTRAFRACTION PROSTATE MOTION DURING IMRT FOR PROSTATE CANCER

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Purpose: Although the interfraction motion of the prostate has been previously studied through the use of fiducial markers, CT scans, and ultrasound-based systems, intrafraction motion is not well documented. In this report, the B-mode, Acquisition, and Targeting (BAT) ultrasound system was used to measure intrafraction prostate motion during 200 intensity-modulated radiotherapy (IMRT) sessions for prostate cancer.

Methods and Materials: Twenty men receiving treatment with IMRT for clinically localized prostate cancer were selected for the study. Pre- and posttreatment BAT ultrasound alignment images were collected immediately before and after IMRT on 10 treatment days for a total of 400 BAT alignment procedures. Any ultrasound shifts of the prostate borders in relation to the planning CT scan were recorded in 3 dimensions: right–left (RL), anteroposterior (AP), and superior-inferior (SI). Every ultrasound procedure was evaluated for image quality and alignment according to a 3-point grading scale.

Results: All the BAT images were judged to be of acceptable quality and alignment. The dominant directions of intrafraction prostate motion were anteriorly and superiorly. The mean magnitude of shifts (±SD) was 0.01 ± 0.4 mm, 0.2 ± 1.3 mm, and 0.1 ± 1.0 mm in the left, anterior, and superior directions, respectively. The maximal range of motion occurred in the AP dimension, from 6.8 mm anteriorly to 4.6 mm posteriorly. The percentage of treatments during which prostate motion was judged to be ≤5 mm was 100%, 99%, and 99.5% in the RL, AP, and SI directions, respectively. Three of the measurements were >5 mm. The extent of intrafraction motion was much smaller than that of interfraction motion. Linear regression analysis showed very little correlation between the two types of motion ($r = 0.014$, 0.029, and 0.191, respectively) in the RL, AP, and SI directions.

Conclusion: Using an ultrasound-based system, intrafraction prostate motion occurred predominantly in the anterior and superior directions, but was clinically insignificant. Intrafraction motion was much smaller than interfraction motion, and the two types of movement did not correlate. © **2002 Elsevier Science Inc.**

Prostate motion, IMRT, Ultrasonography, Prostate cancer.

INTRODUCTION

The development of three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) has enabled the delivery of escalated doses to the tumor target while simultaneously sparing the surrounding structures. The translation of these advances into therapeutic gain is dependent on the adequacy of the margins to account for setup error and internal target motion. The margins must also facilitate conformal avoidance of the normal tissues. The uncertainty of prostate position limits the optimization of conformal radiotherapy, because it requires the radiation oncologist to expand the planning target volume (PTV).

Organ movement may be divided into two general categories: interfraction and intrafraction (1). Interfraction prostate motion affects day-to-day prostate position changes, as does error in patient setup. This motion has been extensively studied through the use of fiducial markers (2–6), multiple CT scans (7–14), and ultrasound-based systems (15, 16). Studies have reported movement mainly in the anteroposterior (AP) and superior-inferior (SI) dimensions (1, 6, 11, 12), with the maximal shifts ranging between 14 and 20 mm (10, 17). These interfraction motion measurements highlight the importance of precise prostate localization before delivering each radiation fraction.

Intrafraction motion refers to the internal organ motion occurring during the actual radiation treatment. Understanding the extent of this motion has important implications in conformal treatment planning and the design of PTV margins. Intrafraction prostate motion, however, is not well documented. The purpose of this report was to describe the intrafraction motion of the prostate during IMRT using an ultrasound-based localization system.

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Table 1. Grading criteria for evaluating image quality and alignment quality

Grade	Quality	Alignment (mm)
1	Near perfect	Misalignment ≤2
2	Fair	Misalignment >2–5
3	Unacceptable	Misalignment >5

METHODS AND MATERIALS

Patient characteristics

Between March and May 2001, 20 men receiving treatment with IMRT for clinically localized prostate cancer who had good pretreatment ultrasound images were selected for this study. Before beginning radiotherapy (RT), the patients underwent CT scanning in the supine position. The images were transferred to a CT simulation workstation (Voxel-Q, Marconi Medical Systems, Cleveland, OH) in which the prostate, bladder, rectum, seminal vesicles, and femoral heads were outlined by the radiation oncologist. The CT images along with the outlined anatomic structures were then sent to an IMRT planning workstation (Corvus, Nomos, Sewickley, PA) in which the PTV margins were defined as 5 mm posteriorly and usually 8 mm in the other directions. Eighteen of the patients received 75.6 Gy delivered in 42 fractions, and 2 patients received 72 Gy in 30 fractions. The length of each IMRT fraction was 15–20 min.

Ultrasound prostate localization

Stereotactic prostate localization was performed using the B-mode, Acquisition, and Targeting (BAT) ultrasound system (Nomos, Sewickley, PA). On 10 treatment days during RT, each of the patients underwent pre- and posttreatment BAT localization, yielding a total of 400 BAT alignment procedures. Experienced radiotherapists performed all BAT alignment procedures without physician supervision. The alignment sequence involved first setting the patient up to the isocenter skin marks, which were checked weekly for alignment with the bony anatomy using port films per routine. Immediately before each fraction, suprapubic transverse and sagittal ultrasound images were captured localizing the prostate, seminal vesicles, bladder, and rectum. The positions of these organs were compared with the contour information from the IMRT treatment plan. Misalignments of the ultrasound-based prostate borders in relation to the pretreatment CT scan prostate borders were recorded in 3 dimensions: right-left (RL), anteroposterior (AP), and superior-inferior (SI). The couch was then shifted accordingly to align the IMRT treatment plan and the real-time ultrasound images. Immediately after each fraction, posttreatment ultrasound images were captured by the same method, and any shifts in prostate location were recorded. Experienced radiotherapists performed the entire process of positioning, localization, and alignment without physician guidance. The daily BAT images were saved, and one person (E.H.) reviewed every image for image quality and alignment quality according to a grading scale from 1 to 3 (Table 1). Image quality that was rated 1–2 was believed to be acceptable for making alignments.

Statistical analysis

Linear regression analysis was performed to obtain the correlation between interfraction motion and intrafraction motion of the prostate.

RESULTS

All the images were judged to be of acceptable quality and alignment (Table 2). Grade 2 misalignments of >2–5 mm (Table 1) by the therapists were observed in 84 (21%) of the 400 total BAT procedures. Of the 200 IMRT treatments, Grade 2 misalignments were seen on 58 treatment days. On 23 of these days, the misalignments were Grade 2 in both the pre- and posttreatment, were in the same direction, and were similar in extent. On the other 35 treatment days, a Grade 2 misalignment was paired with a Grade 1 alignment. In these cases, a slight underestimation of the intrafraction shift would occur.

Tables 3 and 4 describe the measured interfraction and intrafraction prostate motion and classify every alignment into quartiles according to the magnitude of shift. The mean magnitude of interfraction shifts (±SD) was 0.4 ± 2.2 mm, 0.4 ± 4.0 mm, and 1.5 ± 3.3 mm in the right, anterior, and inferior directions, respectively. Interfraction shifts were observed in 77.5%, 85.5%, and 88.0% of the treatments in the RL, AP, and SI directions, respectively. The percentages of treatments with shifts >5 mm were 6.0%, 20.5%, and 15.5% in the RL, AP, and SI directions, respectively.

The dominant directions of intrafraction prostate motion were anteriorly and superiorly. The mean magnitude of intrafraction shifts (±SD) was 0.01 ± 0.4 mm, 0.2 ± 1.3 mm, and 0.1 ± 1.0 mm in the left, anterior, and superior directions, respectively. The maximal range of motion occurred in the AP dimension (6.8 mm anteriorly to 4.6 mm posteriorly) and the SI dimension (3.5 mm superiorly to 6.8 mm inferiorly).

Table 2. Image quality and alignment quality results for 400 ultrasound procedures

Grade	Image quality (%)	Image alignment (%)	Direction of misalignment (%)					
			Superior	Inferior	Anterior	Posterior	Right	Left
1	63	79	91	96	95	97	97	98
2	37	21	9	4	5	3	3	2

Table 3. Summary of interfraction motion: Results of 200 pretreatment ultrasound procedures

Direction	Mean ± SD (mm)	No shift (%)	Shift ≤2.5 mm (%)	Shift >2.5 to 5 mm (%)	Shift >5 mm (%)
RL	0.4 ± 2.2 (10.1 to −6.1)	22.5	56.0	15.5	6.0
AP	0.4 ± 4.0 (11.8 to −13.4)	14.5	44.5	20.5	20.5
SI	−1.5 ± 3.3 (7.6 to −10.6)	12.0	46.0	26.5	15.5

Minus sign denotes motion to the left, posteriorly, or inferiorly.
Abbreviations: RL = right–left; AP = anteroposterior; SI = superoinferior.
Numbers in parentheses are the range.

The percentages of treatments with no perceptible intrafraction shift were 80.5%, 72.0%, and 72.5% in the RL, AP, and SI directions, respectively. A total of 20 shifts (10% of treatments) were >2.5 mm in 10 different patients; 6 patients had 1 such shift, 1 patient had 2 such shifts, and 4 patients had 3 such shifts. Of these, 3 shifts (1.5% of treatments) were >5 mm in 3 separate patients: 5.7 mm anteriorly, 6.8 mm anteriorly, and 6.8 mm inferiorly.

Figure 1 illustrates the distributions of every posttreatment shift according to the magnitude in the 3 dimensions. The distributions appear gaussian. The vast majority (142 of 200) of these posttreatment BAT procedures did not show a shift in prostate position in any dimension, as perceived by the treating radiotherapist. When evaluated by the reviewing physician, however, 23% of these 142 "no shift" BAT procedures were judged to be Grade 2 with respect to the quality of alignment (Table 1).

Figure 2 shows the mean and SD of intrafraction motion for each of the 20 patients in the 3 dimensions. The per-patient mean shifts were within ±1 mm in the RL dimension and ±2 mm in the AP and SI dimensions. Mean posttreatment BAT shifts >1 mm were seen in 2 patients in the AP dimension and 1 in the SI dimension.

The extent of intrafraction motion was found to be much smaller than that of the interfraction motion. Linear regression analysis showed very little correlation between the two types of motion in the RL ($r = 0.014$, $p = 0.840$), AP ($r = 0.029$, $p = 0.688$), and SI ($r = 0.191$, $p = 0.007$) dimensions (Fig. 3).

DISCUSSION

BAT system

The reference standard for localizing the prostate is CT. Although this procedure is very accurate, error is associated with CT measurements related to slice thickness. Moreover, daily CT adds to the normal tissue radiation dose, and CT requires considerable technical and personnel resources, which thus far have precluded its daily use for the duration of treatment. As an alternative to daily CT, the BAT ultrasound system is portable, easy to use, much less costly, and does not involve radiation. The entire process of patient positioning, imaging, and alignment is completed in approximately 5–10 min, enabling daily verification of organ location while the patient is in the treatment position. More importantly, this ultrasound system has been shown to be accurate and functionally equivalent compared with CT with high correlation between shifts ($r \geq 0.87$) and a small difference between the magnitudes of shifts (mean ≤0.16 ± 2.8 mm) (16).

A limiting factor in this study was that the BAT system provides only one snapshot image of the prostate after each treatment. Thus, every prostate shift during treatment would not be measured nor would the duration of such movements.

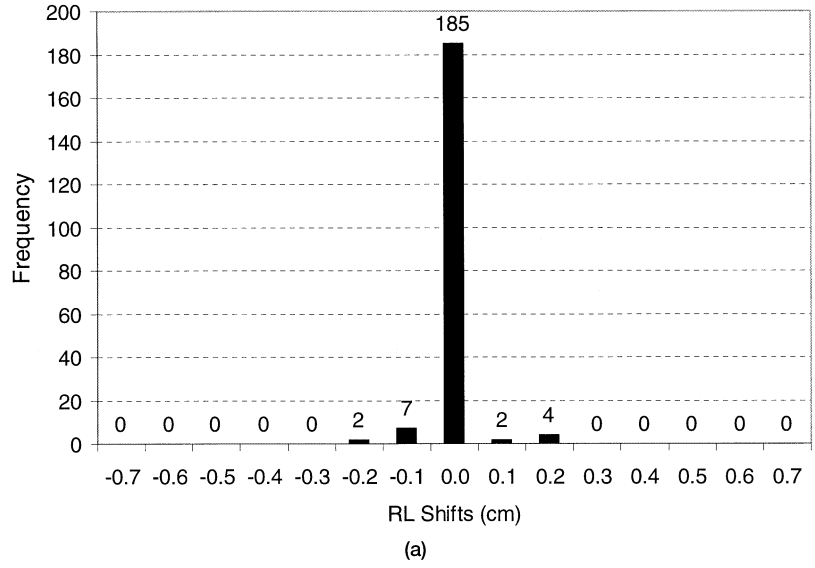
Intrafraction prostate motion

Only a few studies in the literature have examined intrafraction prostate motion. Vigneault *et al.* (6) first investigated intrafraction motion in 2 patients using radiopaque fiducial markers; however, no motion was detected. Padhani *et al.* (18) used an interesting technique using cine MRI in 55 patients. By imaging the prostate every 10 s during 7 min, they observed movement in 29% of the patients, with 16% having movements >5 mm. Similar to our results, they reported that the predominant direction of shift occurred anteriorly. The mean duration of prostate movement was approximately 5% of the time, or 20 of 420 s. Shimizu *et al.* (5) used gold fiducial markers and posttreatment fluoroscopic images to observe intrafraction motion. They also reported that the motion occurred predominantly in the AP axis. Similar to our results,

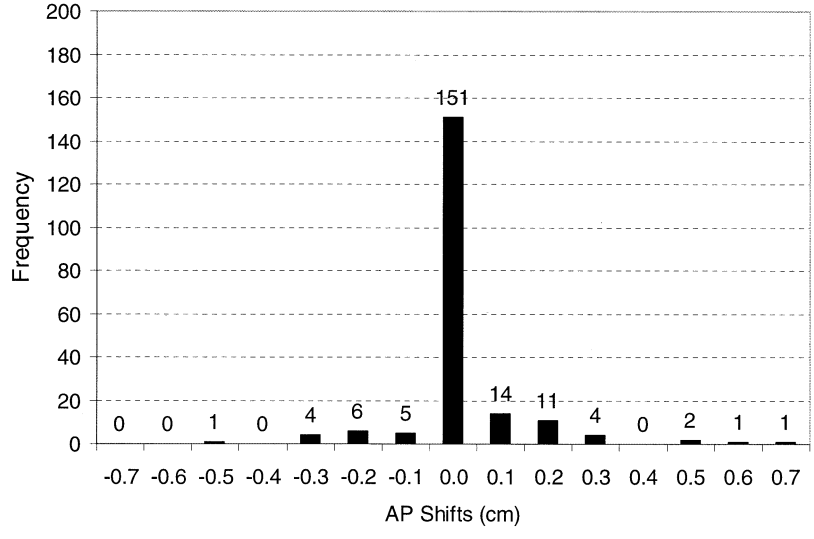
Table 4. Summary of intrafraction motion: Results of 200 posttreatment ultrasound procedures

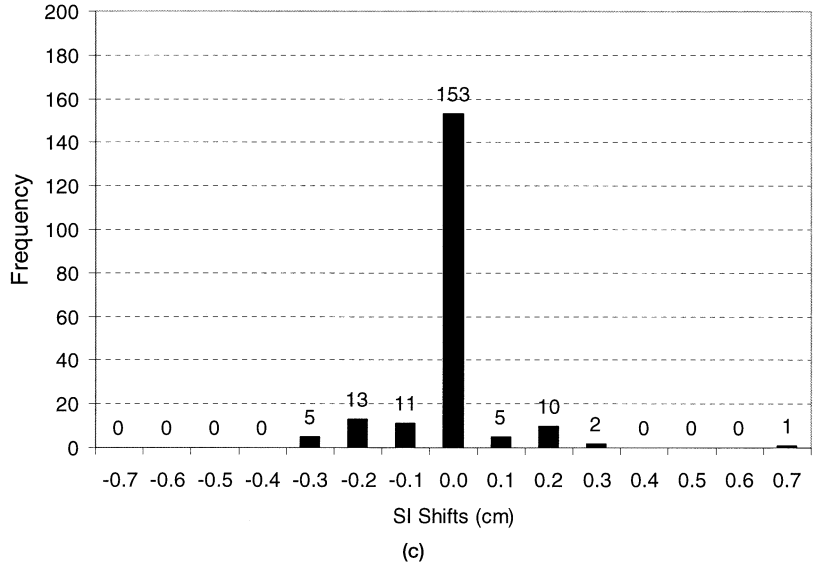
Direction	Mean ± SD (mm)	No shift (%)	Shift ≤2.5 mm (%)	Shift >2.5 to 5 mm (%)	Shift >5 mm (%)
RL	−0.01 ± 0.4 (2.5 to −2.4)	80.5	19.5	0	0
AP	0.2 ± 1.3 (6.8 to −4.6)	72.0	21.5	5.5	1.0
SI	0.1 ± 1.0 (3.5 to −6.8)	72.5	23.5	3.5	0.5

Minus sign denotes motion to the left, posteriorly, or inferiorly.
Abbreviations as in Table 3.
Numbers in parentheses are the range.



(a)





(c)

Fig. 1. Distributions of intrafraction motion according to magnitude in the (a) RL dimension, (b) AP dimension, and (c) SI dimension. "−" refers to motion toward the right, posterior, or superior direction.

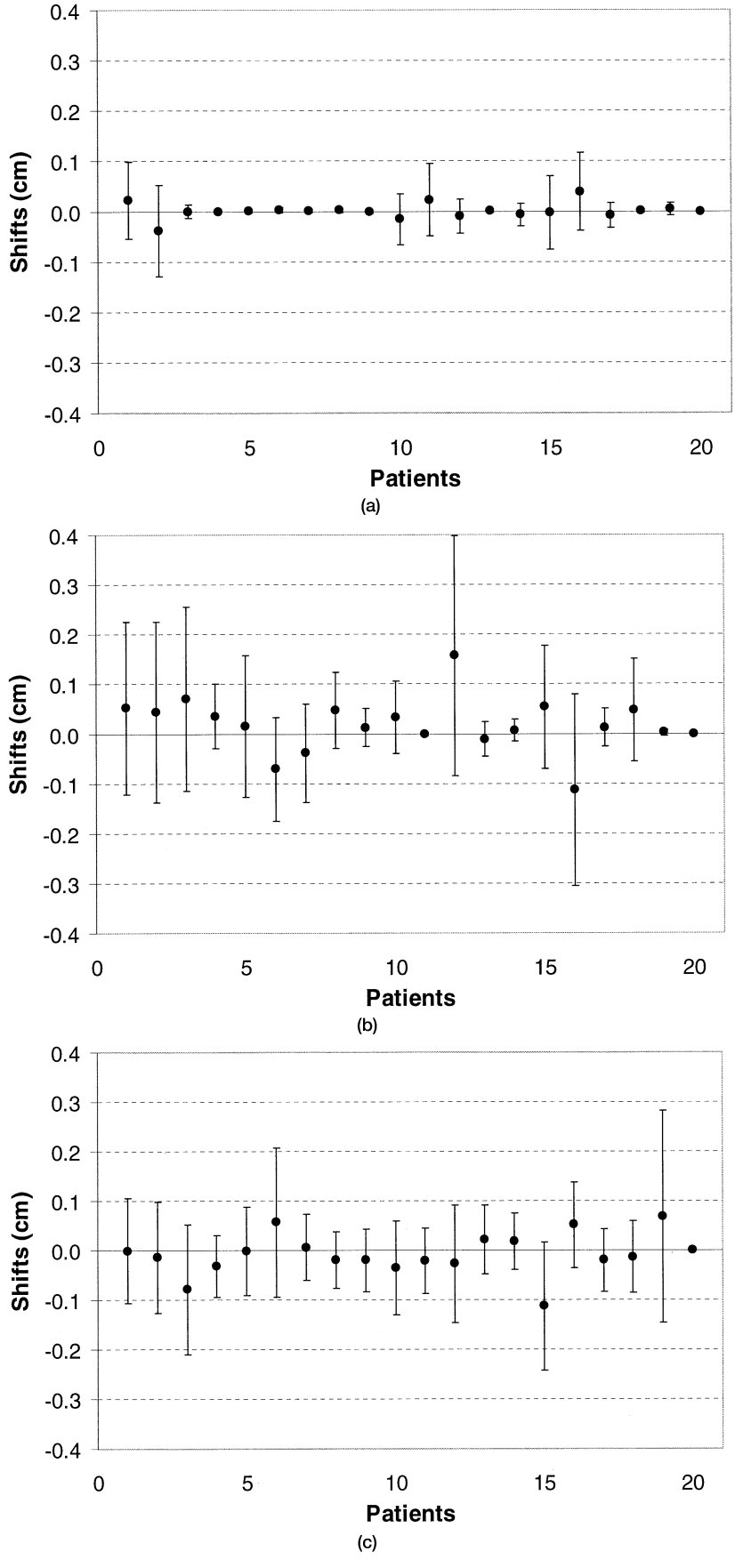


Fig. 2. Per-patient mean ± SD (error bars) of intrafraction motion displayed in the (a) RL dimension, (b) AP dimension, and (c) SI dimension. "−" refers to motion toward the right, posterior, or superior direction.

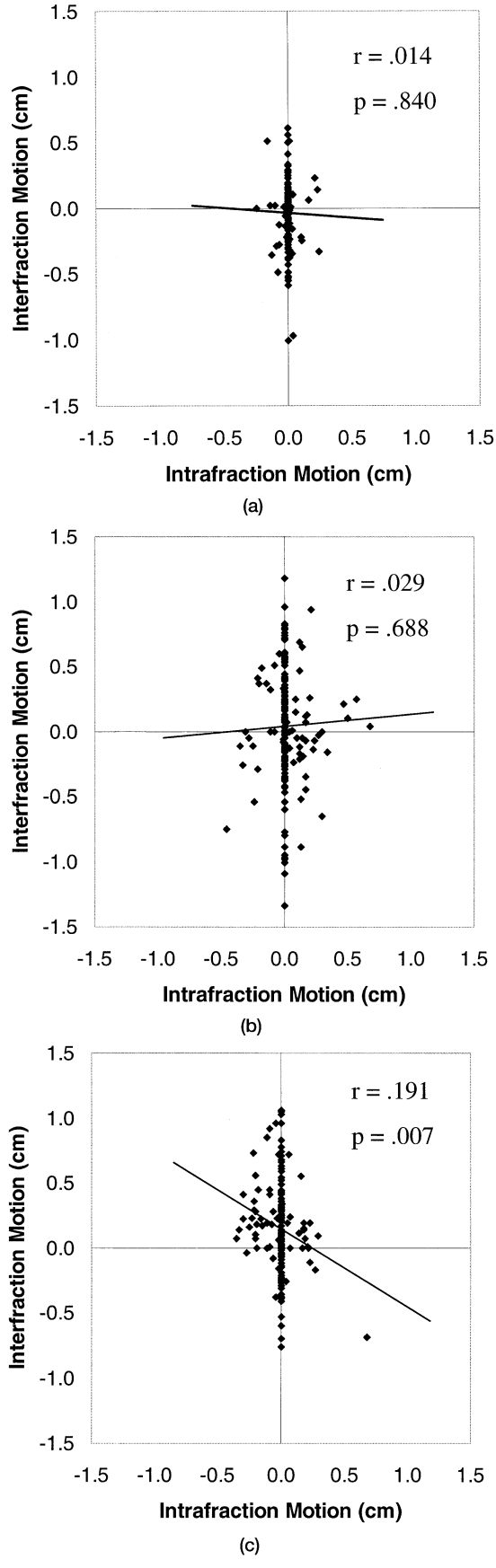


Fig. 3. Linear regression analysis of interfraction vs. intrafraction prostate motion in the (a) RL dimension, (b) AP dimension, and (c) SI dimension. "−" refers to motion toward the right, posterior, or superior direction.

they observed that 81% of the treatments had movement of <3 mm, and 98% were <5 mm.

Sources of intrafraction motion

Rectal volume changes, bladder volume changes, and patient respiration have been found to contribute to intrafraction prostate movement. Several studies have shown a significant correlation between rectal volume changes and prostate motion in the AP dimension (7–9, 14, 18–20), and the degree of prostate shifts has correlated well with the magnitude of rectal movement (18). As we described (Table 4, Fig. 1B), other investigators have reported that when the patient is in the supine position, the predominant direction of motion was anteriorly rather than posteriorly (2, 8, 17–19). Because of the close anatomic location between the two structures, direct mechanical forces produced by rectal filling, such as gas or stool, readily explain this phenomenon. Large prostate shifts >5 mm correlated with rectal gas pockets >2 cm in diameter (20) and with the introduction of 50 mL of contrast into the rectum (17). Zelefsky *et al.* (12) reported that the only independent predictor of prostate shifts >3 mm was the combination of rectal volume >60 cm^3 and bladder volume >40 cm^3.

Although the AP movement of the prostate correlates more with changes in rectal volume than with bladder volume (7, 12), large bladder volumes can shift the prostate posteriorly. This is more often observed with patients in the prone position, because the bladder cannot stretch much anteriorly, resulting in a more posterior displacement of itself and the prostate.

Prostate motion due to patient respiration has been studied by Dawson *et al.* (21) using fiducial markers under fluoroscopy for periods of 10–30 s. They observed that when the patient was placed in the supine position, prostate motion was negligible (<1 mm in all directions). With deep breathing, however, prostate motion became noticeable in the SI dimension, with shifts ranging from 2 to 7 mm. Malone *et al.* (22) also reported that respiratory-induced prostate motion >20 s decreased significantly when the patients were positioned supine without the use of thermoplastic shells. Although providing valuable data concerning ventilatory movement, these motion studies did not assess prostate movement within a period comparable to an IMRT fraction. Because of this limitation, the results may not account for other sources of intrafraction motion such as rectal and bladder volume changes during the 10–20-min period required to deliver an IMRT fraction.

As described by Padhani *et al.* (18), contraction of the pelvic floor muscles when patients try to maintain full continence of the bladder may also contribute to intrafraction prostate movement. Prostate cancer patients are often told to maintain large bladder volumes during RT as a method of displacing small bowel away from the treatment field. For the purposes of our study, large bladder volumes were desirable because they improved the quality of the BAT ultrasound images, facilitating accurate prostate localization. Although this hypothesis has not been formally assessed, it is possible that the intermittent clenching of the pelvic muscles may cause periodic intrafraction motion that would not be captured by the posttreatment BAT image.

CONCLUSION

Using the BAT ultrasound system, we found that intrafraction prostate motion occurred predominantly in the anterior and superior directions. In 98.5% of the prostate alignments, the posttreatment shifts were ≤5 mm and safely within the defined PTV; 2 of the 3 intrafraction shifts >5 mm were in the AP dimension and had the potential to violate the PTV (the margins in the other dimensions were larger). However, one must consider that the error of BAT ultrasound measurements is on the order of 2–3 mm and that perhaps violation of the PTV might occur in some additional cases. Another possible contributing factor in underestimating the extent of the shifts was that in 35 pre- and posttreatment BAT alignments, one of the alignments was judged to be of Grade 2 quality and the other of Grade 1 quality. Such measurement differences were thought to be relatively minor overall, considering that the shifts in only 1 patient with paired Grade 1 alignments (n = 142) in the pre- and posttreatment ultrasound procedures were >5 mm. Overall, intrafraction motion was considerably smaller than, and independent of, interfraction motion in which >20% of the treatments had shifts >5 mm. The significant degree of interfraction prostate positional error, combined with clinically insignificant intrafraction movement, highlights the importance of localizing the prostate before each fraction and correcting for interfraction motion errors.

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