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Image-Guided Radiotherapy for Localized Prostate Cancer: Treating a Moving Target

Patrick A. Kupelian, MD, Katja M. Langen, PhD, Twyla R. Willoughby, MS, Omar A. Zeidan, PhD, and Sanford L. Meeks, PhD

Prostate motion during external-beam radiotherapy can affect outcomes in patients with localized prostate cancer. Prostate motion and deformation are currently being characterized with different techniques. There is significant individual variation among patients with respect to the observed motion and its dosimetric consequences. There is also significant difference in the accuracy of different localization methods currently used to adjust for prostate motion. The motion of the prostate gland can itself affect the accuracy of different localization methods. The dosimetric impact on target areas and organs at risk should be studied for different localization techniques, treatment plan margins, and treatment schedules. Such assessments will be increasingly important with smaller treatment margins, smaller fraction numbers, and higher radiation doses. Understanding and managing the consequences of anatomic variations within the lower pelvis should be a priority in designing and implementing future clinical trials.
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The need for high radiation doses for effective control of localized prostate cancer has resulted in the use of gradually smaller radiation field sizes. This, in turn, has necessitated a better understanding of the location and shape of the target areas (in this case, principally the prostate gland but also the surrounding normal tissues). During the past 10 years, imaging and localization techniques prior and during radiation delivery flourished and significantly contributed to this knowledge. The aim of the present review is 3-fold: (1) present our current understanding of these issues, (2) clarify how different current targeting methods attempt to address these issues, and (3) review the limited available clinical outcome data (tumor control and toxicity) resulting from the use of such targeting techniques.

Historically, the term "organ motion" has been applied to describe mostly positional variations of target areas from one fraction to the other, often documented with "snapshots" (ie, static images obtained with different technologies before treatment delivery on each treatment day). However, anatomic changes within an individual patient are more complex in nature. The 2 main phenomena potentially affecting small-field radiation therapy are motion and deformation. These happen in 2 different timeframes generally described as interfraction (from day to day) and intrafraction (during a treatment session). The phenomenon least studied is intrafraction deformation. Only recent studies have indirectly addressed this issue by analyzing interfraction deformation.[1,2] Currently, intrafraction deformation is difficult to assess and react to. The dosimetric impact of intrafraction deformation of the prostate gland is probably minimal. It is possible that this could be shown to be an important phenomenon to affect radiation delivery but is currently largely ignored. Therefore, 3 principal phenomena are relevant: interfraction motion, intrafraction motion, and interfraction deformation. The focus of this communication is the analysis of interfraction and intrafraction motion.

Imaging and localization techniques are crucial in the acquisition and use of the knowledge that we currently use in the treatment of localized prostate cancers. Therefore, it is important to understand how different imaging and localization techniques handle the three problems of interfraction motion, intrafraction motion, and interfraction deformation. It is also important to understand how these techniques affect the integrity or documentation of delivered doses. Ultimately, localization is performed for accurate radiation delivered to areas intended to receive specified doses, not for an independent determination of the location (and/or shape) of the targeted areas at different points in time. This dosimetric aspect is, unfortunately, frequently ignored when localiza-

Department of Radiation Oncology, M.D. Anderson Cancer Center, Orlando, FL.

Address reprint requests to Patrick A. Kupelian, MD, Department of Radiation Oncology, M.D. Anderson Cancer Center Orlando, 1400 South Orange Avenue, Orlando, FL 32806. E-mail: patrick.kupelian@orhs.org

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tion methods are analyzed. Typically, localization data are used for the determination of treatment planning margins.

Finally, there are no current techniques that comprehensively address the issues of interfraction motion, intrafraction motion, and interfraction deformation. These techniques are still largely works in progress. Therefore, it will be difficult in the near future to accurately and comprehensively assess the potential dosimetric impact, and even less the clinical impact, of such techniques on cure rates and toxicity rates.

Interfraction Motion

Although the term interfraction motion will be continued to be used in this communication, "motion" is a misnomer in this context. The true description should probably be interfraction position variation. Historically, relatively generous fields were typically used for the treatment of localized prostate cancers. The first attempts to repeatedly localize the prostate gland during radiation came from repeated computed tomography (CT) scans or repeated x-rays with implanted metallic markers.[3] Prostate location variations were studied relative to either external skin marks and/or to the adjacent bony anatomy. It is now obvious that the actual prostate location is poorly correlated to external skin marks or bony anatomy.[4] Analyzing serial CT or magnetic resonance imaging of the pelvis, the observed positional variations are caused by a variety of factors but largely caused by the different degrees of rectal filling.[5] Currently, there is reasonable consensus that the positional variations of the prostate gland can be significant. Interfraction positional variations have been documented through a multitude of techniques. Each method has inherent uncertainties in determining prostate location. For all these methods, the primary approach is to determine the position of the prostate by analyzing pelvic images obtained through either ultrasound, radiograph, or CT scan and, subsequently (ie, after the image analysis), adjust the target area position by adjusting the treatment couch and then proceeding with radiation delivery. Therefore, these techniques provide a static image of the prostate position before the actual radiation delivery. Depending on the technique, the process of acquiring images, determining and applying the offsets required to correct for misalignments, and starting radiation delivery, can take less than 1 minute to up to 20 to 25 minutes. This assumes that the prostate location did not vary significantly during that period of time.

Daily image guidance with daily positional adjustments, a strategy often termed "online," is 1 method of using localization information during a course of fractionated radiotherapy. The alternative is following a certain imaging schedule and applying determined offsets during fractions when imaging is not performed, typically termed "offline" strategies. Such strategies have the only advantage of decreasing the imaging frequency, thereby potentially increasing patient throughput. Different offline strategies can be applied (eg, imaging daily for the first 5 days and then applying the mean shift on subsequent days). This type of approach can also be used to determine treatment margins on the basis of the motion observed over a patient population using formulas such as van Herk et al's.[6] It is important to realize that this particular formula was designed to ensure a minimum dose to the clinical target volume of 95% for 90% of the patients by prescribing a target margin of at least 2.5 times systematic standard error plus 0.7 times random standard setup error. Therefore, by definition, significant dose discrepancies will happen in 10% of the time when applying the van Herk formula.

Alternatively, if soft-tissue imaging is performed repeatedly in the early part of the treatment course, treatment plans can be modified to account for the observed motion in the first few days of therapy, a process described as "offline adaptive."[7-10] On subsequent treatment days, fewer images are acquired for motion assessment. Although attractive as an approach in that a dosimetric evaluation is also included in addition to simple motion analysis, it does assume that normal and target tissue anatomies remain relatively stable during subsequent fractions. Indeed, as shown by Litzenberg et al,[11] motion analysis on subsequent days showed that an offline approach would not adequately account for random target position variations on subsequent days.

To study the influence of motion, 8 different potential nondaily imaging strategies were tested in a cohort of 74 patients treated at our center who actually underwent daily imaging with implanted metallic fiducials. Daily positional adjustment data were available for a total of 2,252 fractions (average 30 per patient). Given the daily positional adjustments, a variety of protocols differing in imaging frequency and methodology were retrospectively studied. The 8 protocols were (1) no imaging; (2) initial fraction only; (3) mean of initial 3 fractions; (4) mean of initial 5 fractions; (5) weekly imaging, 3 mm threshold; (6) mean of initial 7 fractions; (7) first 5 fractions + weekly imaging, patient specific threshold; and (8) imaging every other fraction, running mean. The imaging frequency ranged from 0% to 49% for the 8 different protocols studied. On days that imaging would not have been performed, residual location errors were retrospectively determined for each protocol. As expected, systematic errors were effectively reduced with increasing imaging frequency. However, the random errors were unaffected and contributed to significant residual errors on days imaging was not performed, regardless of the protocol used. For the 8 different imaging protocols, the increasing imaging frequencies of 0%, 3%, 10%, 16%, 21%, 23%, 32%, and 49% resulted in residual errors exceeding 5 mm, respectively, in 73%, 70%, 52%, 44%, 50%, 39%, 39%, and 24% of fractions. The same imaging frequencies resulted in residual errors exceeding 1 cm in 20%, 23%, 10%, 8%, 12%, 6%, 7%, and 4% of fractions. Given the systematic and random errors observed with each protocol, the treatment margins (as determined by van Herk's formula[6]) were calculated for each protocol in each dimension for the fractions when image guidance would not be performed. This assumes that a tight margin plan would be used for days when image guidance is performed, and a separate larger margin plan would be used on days when image guidance is not performed. Table 1 shows the treatment margins in each direction that would be associated with each imaging protocol for days when imaging is not performed. Margins were reduced with increasing imaging fre-

Table 1 Treatment margins needed on days imaging is not performed according to individual imaging scenario, as determined by the van Herk formula[6]

Scenarios	Image Guidance Frequency (%)	Margins (mm) Anterior/Posterior	Lateral	Superior/Inferior
1. No imaging	0	12	10	10
2. Initial fraction only	3	14	14	7
3. Mean of initial 3 fractions	10	10	9	5
4. Mean of initial 5 fractions	16	9	8	5
5. Mean of initial 7 fractions	23	8	7	5
6. Weekly imaging, 3-mm threshold	21	8	8	6
7. First 5 fractions + weekly imaging, patient-specific threshold	32	7	8	5
8. Imaging every other fraction, running mean	49	7	7	4

quency, after the reduction in the systematic component of the alignment errors. However, even with every other day imaging, treatment margins would have to still remain around 7 mm. With varying imaging frequencies, residual errors in prostate location are significant even with every other day imaging, mostly because of a significant residual random component. Decreasing imaging frequencies result in substantial increases in the size of treatment margins.

However, it is not clear if an offline adaptive approach would compromise delivered doses, even if online adjustments are not made. Such dosimetric evaluations would require daily soft-tissue imaging with daily dose recalculations for all relevant structures, and subsequent assessment if an offline approach would have impacted delivered doses. One such analysis of daily delivered dose evaluation was performed in a series of 10 patients who had megavoltage CT images and daily dose recomputations.[12] The treatment was planned with 4-mm margins posteriorly and 6 mm in all other directions. Daily targeting was performed with alignment on implanted metallic fiducials. Retrospective dose recomputations were performed with definition of the target (the prostate gland) and normal tissues (bladder and rectum). With these treatment margins and daily online targeting, the target areas did receive the intended dose in the overwhelming majority of fractions. However, because of large variations in rectal and bladder anatomy on a daily basis, the rectal and bladder doses varied significantly. Figure 1 shows 2 instances in which significant anatomic changes were observed between simulation and treatment. Figure 2 shows the individual variations in the rectal volume receiving the full fractional dose of 2 Gy. It is clear that deviations from the initial plan are extremely variable. In this case, daily positional adjustments of the prostate were made with daily alignment on intraprostatic metallic fiducials. However, it would be interesting to determine what the dosimetric impact would be on target areas and organs at risk if any strategy was used other than daily imaging.

Intrafraction Motion

Intrafraction motion is also described as "real-time" motion of the prostate. This is motion that occurs after an initial targeting, alignment, and during the process of radiation delivery. True intrafraction motion should be considered as motion occurring only during the radiation delivery itself. For example, if the alignment process (including image analysis, offset determination, and application of those offsets to a treatment couch) takes several minutes, motion will cause the prostate to be a different location at the time of the delivery per se. It is important to understand the nature of real-time motion not necessarily as a phenomenon occurring within the bony anatomy of the patient but rather as an overall cause of misalignment of the prostate gland with respect to the external-beam radiation therapy source. Therefore, patient pelvic musculature changes, breathing patterns, and rectal peristalsis could be causes of real-time prostate motion.

Real-time motion has been evaluated through different methods. A comprehensive review of these methods and observed motions has been published by Ghilezan et al.[5] It is obvious that the methods used to observe "real" motion of the prostate are typically imaging methods that provide repeated static images of the anatomy at different time intervals ranging from a few seconds to several minutes. In addition, most observations have been made on a small number of patients and with only a few observations per patient. Ideally, observations about real-time motion need to be performed with a near continuously monitoring method in a large number of patients and repeated over a time period equivalent to a fractionated radiation therapy course. Real-time motion observed with cine magnetic resonance imaging (cineMRI) is probably the most convincing, particularly if soft-tissue deformation is also to be evaluated. In general, studies performed with cineMRI have reported relatively small mean motion extents but relatively large standard deviations of observed motion. Mah et al[13] reported a mean (± standard deviation) motion in the craniocaudad dimension of 0.02 (±3.36) cm. Padhani et al[14] reported 29% of patients exhibiting anterior-posterior displacements exceeding 5 mm.

Electromagnetic transponders implanted within the prostate are a recent technical development that allow near real-time observation of prostate motion while the patient is in a treatment position. The actual technical characteristics of the system have been detailed elsewhere.[15-17] The system works with the location of the center of mass of the implanted transponders being recorded at a frequency of 10 Hz. The system can be left in place during irirradiation. A recent analysis of

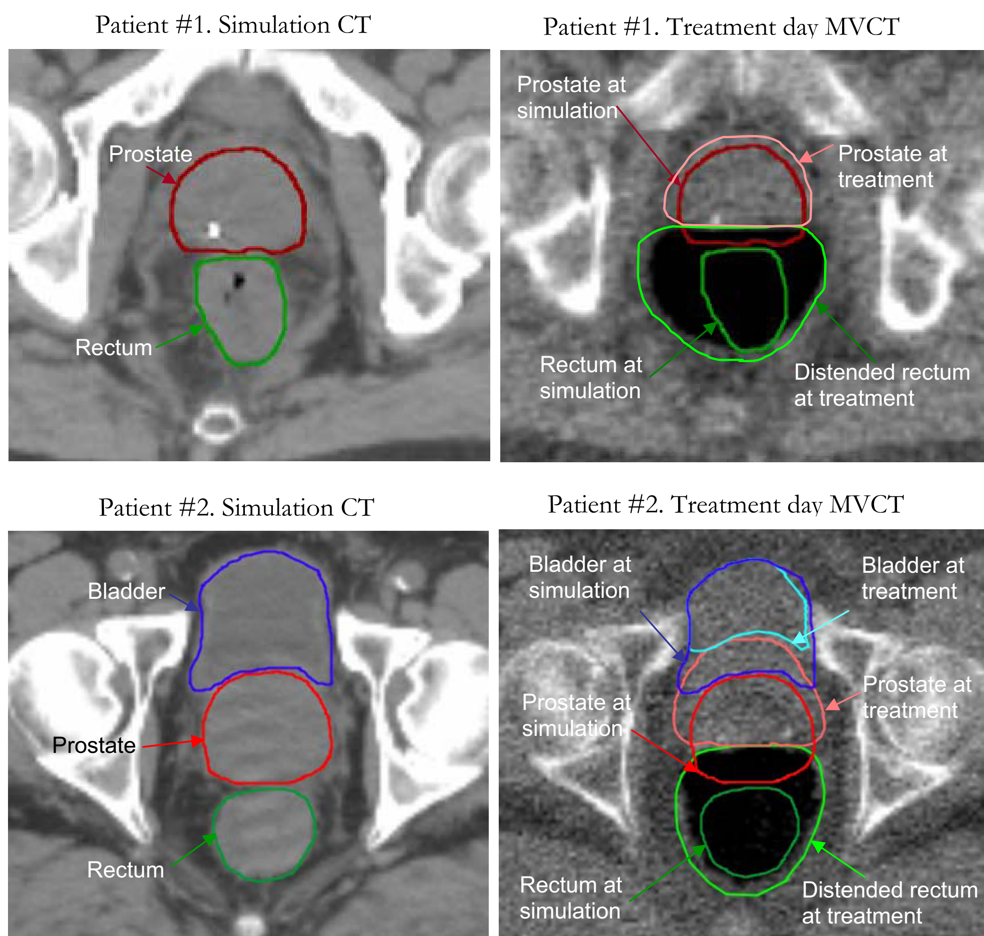

Figure 1 Comparison of pelvic anatomy in 2 separate patients between the simulation day (kilovoltage CT) and the treatment day. MVCT, megavoltage CT. These CT scans show the deformation of the prostate, rectum, and bladder that would result in variations in delivered doses.[12] (Color version of figure is available online.)

real-time prostate motion during 1,157 sessions lasting on average around 10 minutes in 35 separate patients was reported.[18] The analysis revealed that by weighting the location by the time duration, a 3-dimensional offset exceeding 3 mm was observed in 41% of fractions, and a 3-dimensional offset exceeding 5 mm was observed in 15% of fractions. However, there was significant variation within individual patients; the ranges of the percentage of fractions with ≥3-mm displacements were 3% to 86% and with ≥5 mm displacements 0% to 56%. In a subset of the 35 patients, data from 17 patients and 550 fractions were placed into time interval bins. Table 2 shows the results of that analysis showing the percentage of the total time during which the prostate is beyond a 3-dimensional distance (eg, the average time the prostate was beyond 3 mm for all 17 patients [550 fractions] was 14%). However, in individual patients, that percentage ranged from 0.4% to 36%. Probably, the most relevant use of the knowledge of real-time prostate position is determining at least the probability that a static image acquired at a certain point represent the "true" prostate position during the radiation delivery itself. This would be to determine the probability that a static image (as typically obtained nowadays for image guidance with radiograph, ultrasound, or CT-based techniques) would represent the prostate position within a certain distance. From the observations made on the 17 patients described previously, the probability that a static image would represent the "baseline" prostate position within 3 mm was determined to be 86%, and 97% at the 5-mm level. Therefore, the probability of introducing a systematic error before delivery

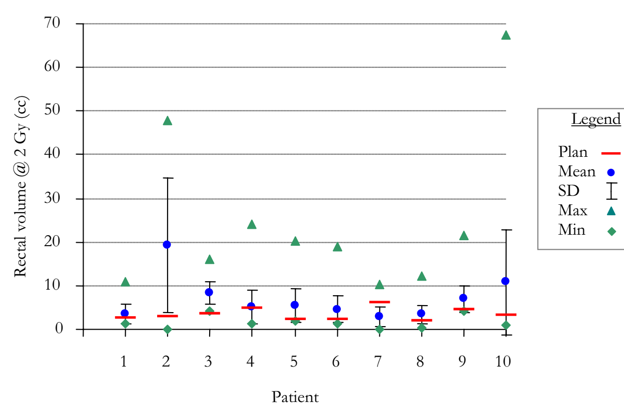

Figure 2 Rectal volume receiving the fraction dose of 2 Gy. Planned rectal volume at 2 Gy versus average (± standard deviation) and range of rectal volume at 2 Gy in the individual 10 patients.[12] (Color version of figure is available online.)

Table 2 Percentages of the total electromagnetic tracking time during which the prostate was beyond a 3-dimensional distance. Data are from 17 patients and 550 fractions. Average tracking time was around 10 minutes during each fraction

Patient	3-D > 10 mm	3-D > 7 mm	3-D > 5 mm	3-D > 3 mm
1	0.0	0.3	2.3	13.8
2	0.0	1.2	8.5	34.4
3	0.9	1.8	4.6	10.5
4	0.1	1.4	7.2	18.9
5	0.1	0.4	2.0	15.3
6	0.0	0.0	0.0	0.4
7	0.1	0.3	1.6	7.8
8	0.6	2.0	3.0	6.9
9	0.3	3.1	10.9	33.2
10	0.3	1.7	6.9	36.2
11	0.0	0.2	0.7	14.0
12	0.0	0.1	0.6	10.6
13	1.3	2.6	5.7	9.0
14	0.1	0.4	1.0	4.3
15	0.1	0.1	0.2	4.0
16	0.0	0.0	0.1	1.9
17	0.0	0.0	1.1	9.6
Average	0.2	0.9	3.3	13.6
1 SD	0.4	1.0	3.4	11.1
Median	0.1	0.4	2.0	10.5
Min	0.0	0.0	0.0	0.4
Max	1.3	3.1	10.9	36.2

because of the impact of real-time motion on static image determination was 14% at the 3-mm level and 3% at the 5 mm level. However, for an individual patient, the introduction of a systematic error at the 5-mm level was observed at as high as 36%.

Similar to the impact of interfraction on delivered radiation doses, the impact of intrafraction motion on delivered doses should also be evaluated. To date, such evaluation has been relatively limited. A clear distinction should be made between geographic misses and dosimetric misses. All types of factors will contribute to dosimetric variations. Motion is an important factor contributing to dosimetric variations. However, dosimetric endpoints should be considered more important than geographic ones. Dosimetric evaluations have to be performed carefully because of the complexity of factors contributing to such evaluations. The time and treatment dynamics should be played realistically to reflect the true treatment deliveries. The interactions of motion and treatment from individual fields should be simulated realistically, that is, the following factors should be incorporated as (1) taking into account intervals of time typical for image registration and subsequent potential drift of target position until delivery time, (2) the prostate motion and treatment dynamics (eg, leaf patterns for individual fields), and (3) intervals of time between fields. In contrast to static field delivery, 1 treatment delivery system that is intrinsically tied to time is helical tomotherapy. Therefore, it is possible to obtain cumulative dose information for a moving target when target motion data are fed into a 4-dimensional dose calculation engine. For 13 patients from our center who had serial real-time localization performed, treatment plans were generated with margins of 6 mm, except 4 mm posteriorly. Individual fractional doses were calculated by moving individual patient anatomy through the calculation engine. The doses were finally cumulated to represent the potential dosimetric effect for an entire treatment course. With the planning target volume or the clinical target volume, the D95 values were <1.2% for all fractions and all patients. However, in individual fractions, the variations in doses ranged from −21% to 6%. It is crucial to understand that these observations will be valid for the previously described treatment margins, for standard fraction sizes and conventional treatment schedules (>30 fractions), and with treatment delivery starting immediately after alignment.

Interfraction Deformation

Interfraction deformation occurs mostly secondary to rectal filling. Even with accurate position adjustment on clear points such as implanted metallic markers, deformation can be observed at the level of the base and particularly at the seminal vesicles.[2,5] To quantify deformation is difficult. The most reasonable method to study the impact of interfraction deformation is dosimetric. If soft-tissue images of the prostate are obtained, dosimetric impacts of deformation can be evaluated. In 10 patients treated at our center to 78 Gy with treatment plans using 6-mm margins (except 4 mm posteriorly), daily prostate alignment was performed on implanted markers.[12] Bladder, rectum, and prostate contours were adjusted on the daily images. Dose reconstruction was performed for each fraction. Even with interfraction deformation, the prostate dosimetry was largely unaffected, but rectal and bladder dosimetry varied greatly among individual patients. Again, this observation can be made only for the treatment margins and setups described earlier.

Techniques

External Markers

External markers are what historically have been used by using skin marks and setup lasers determined from an initial simulation CT scan. Because of a variety of factors, skin marks are not adequate surrogates for prostate position. From several imaging studies, the treatment margins required in the treatment of prostate cancers to accommodate for motion would be as large 1.5 to 2 cm.[19] These are large margins that are incompatible with the delivery of the high radiation doses above 70 Gy that are currently used in routine practice.

Skeletal Anatomy

Initial assessments with either implanted markers or CT scans showed a poor correlation of prostate position and bony anatomy.[3] Differences in the order of 5 to 10 mm were frequent. More recently, Schallenkamp et al[4] described these differences extensively.

Internal Markers

Endorectal balloons. The use of endorectal balloon can serve 3 general purposes: internal immobilization of the prostate gland, surrogate for targeting (defining the posterior portion of the bladder), and improving rectal dosimetry. The most recent report on the impact of endorectal balloons on localization and immobilization shows minimal benefit from the balloon.[20] In patients with intraprostatic implanted markers, the use of an endorectal balloon did not decrease the systematic and random errors associated with day-to-day prostate positions. However, some reports have shown the benefit of an endorectal balloon in decreasing the rectal radiation doses.[21-23] The most comprehensive study of the dosimetric impact of endorectal balloons on the rectum was published recently by van Lin.[24] The rectal wall doses on the initial treatment plan were correlated with rectal mucosal changes on sigmoidoscopy and subsequent rectal bleeding rates. There was a clear benefit with the use of endorectal balloons, indicating that endorectal balloons render the rectal dosimetry more predictable by making the rectal anatomy more reproducible from day to day. The improved rectal bleeding rates with the use of the rectal balloon suggest that a distended rectum is a more favorable anatomic configuration with respect to rectal toxicity. With daily image guidance, the impact of rectal distention is of minimal or no consequence with respect to introducing positional errors during therapy.

Implanted Fiducials (Detected by X-Rays)

The use of implanted markers and in-room radiograph based methods is increasingly being used for targeting. Markers are detected with either planar or volumetric imaging. Interuser variability of the registration process is improved with the use of implanted markers even with volumetric imaging.[25] Marker stability within the prostate has been well documented.[26-29] The accuracy of the markers as surrogates of position of the entire prostate gland has been questioned, mostly because of possible deformation and/or rotation of the prostate at the time of treatment delivery.[2] The most critical anatomic area to correctly align is the posterior prostate and anterior rectum. Therefore, placing the markers in the posterior part of the prostate will ensure that even with deformation of the prostate, the surrogates remain an adequate part of the relevant anatomy of the targeted areas. Rotations are typically limited to pitch with the superior part of the prostate either falling posterior because of a deflated upper rectum or moving anterior because of an inflated upper rectum. The limited interuser variability and the marker stability make markers an ideal surrogate for the prostate position and rotation. However, deformation might not be represented overall by implanted fiducials, although relevant anatomic landmarks (such as the prostate/rectal interface) can be identified and targeted/avoided adequately.

Implanted Transponders for Electromagnetic Tracking

The implantation process of transponders is similar to metallic markers. The stability of the transponders has been shown.[16] The position of the transponders can be verified with in-room imaging because images are not associated with electromagnetic tracking. Electromagnetic tracking is performed continuously throughout the time the patient is on the treatment couch. Position coordinates are generated and displayed nearly real time (at 10 Hz). Position determination is objective, independent from user interpretation, and continuous. Similar to markers, volumetric information is absent, and deformations cannot be adequately assessed. Unlike static images, initial position determination and alignment is reliant on multiple position samples of the prostate, thus avoiding the possibility of motion introducing a systematic error before the actual delivery.

Transabdominal Ultrasound

Transabdominal ultrasound is an efficient tool that enabled daily targeting. However, it has been associated with significant interuser variability, with reports of acceptable images and acceptable alignments ranging from 68% to 97%.[30-32] In addition, when compared with prostate positioning on CT scans or implanted markers, the accuracy of transabdominal ultrasound has been questioned.[33-35]

It is difficult to assess if the discrepancies are because of interuser variability, differences between ultrasound volumes and CT contours, or other factors. To assess the in vivo accuracy of transabdominal ultrasound in localizing the prostate gland, comparisons to alignments on CT scans or implanted markers have been reported.[33,34,36] Lattanzi et al[36] compared CT and ultrasound alignments and showed that the means (± standard deviation) of the differences between the 2 modalities were 3.0 (±1.8), 2.4 (±1.8), and 4.6 (±2.8) mm in the vertical, lateral, and longitudinal dimensions. In addition, the maximum differences were 5.9, 7.9, and 9.0 mm in the vertical, lateral, and longitudinal dimensions. In a more contemporary comparison of CT scan and ultrasound, Dong et al[33] reported somewhat better correlation with the differences being 0.7 (±4.5), 0.5 (±3.6), and 0.4 (±3.9) mm in the vertical, lateral, and longitudinal dimensions. Comparing ultrasound versus implanted fiducials, Langen et al[34] reported differences of 0.7 (±5.2), 1.8 (±3.9), and 2.7 (±4.5) mm in the vertical, lateral, and longitudinal dimensions. Finally, comparing implanted markers to ultrasound, Scarbrough et al[35] reported discrepancies exceeding 1 cm in 26% of patients.

To determine the dosimetric consequences of alignments with different methods, O'Daniel et al[37] analyzed minimum target doses in a cohort of 10 patients who had repeat CT scans throughout treatment. Alignments on skin and bone provided acceptable prostate coverage for only 70% of patients. Alignment on transabdominal ultrasound provided acceptable prostate coverage in 90% of patients and CT alignment for 100%. For the seminal vesicles, the dosimetric coverage varied dramatically from patient to patient, with ultrasound alignment providing full-dose coverage in 70% of cases and CT alignments in 80%. This study clearly shows that ultrasound alignment will have suboptimal target coverage compared with CT alignments.

Although the accuracy of transabdominal ultrasound is questionable, the clinical efficiency of such a system in per-

forming daily image guidance for prostate localization ensured a rapid spread in radiotherapy departments.

In-Room CT

Several in-room CT solutions exist today. Helical kilovoltage on-rail CT, kilovoltage or megavoltage cone-beam CT, and helical megavoltage CT scans are methods of in-room volumetric imaging. The image characteristics of these technologies are different, and each has advantages and disadvantages. Overall, these technologies enable the use of bony anatomy, implanted fiducials, or the prostate gland identified on the soft-tissue images for targeting. In addition, soft-tissue images enable the evaluation of the anatomic variations of other structures such as the rectum and the bladder. Because the prostate can be visualized on CT scans, alignment could be potentially performed directly on the prostate gland itself. However, similar to the interpretation of ultrasound images, determining the exact location of the prostate gland can be challenging. Studies comparing implanted fiducial marker alignments and CT-image alignment have been performed. Different techniques can be applied for alignment such as using the entire grayscale anatomy to using the contours from the initial simulation CT to align on the prostate. The interpretation of the prostate location on CT images is associated with interuser variability. Therefore, even with the use of CT scans, the use of intraprostatic fiducials might still be required. The comparison with marker positions is probably the best method to test the accuracy and reproducibility of CT images in localizing the prostate. Langen et al[38] reported on using two separate registration methods with in-room megavoltage CT images. Radiation therapists and 1 physician were asked to localize the prostate using either the entire grayscale anatomy or only the contours from the initial simulation CT. The alignments were then compared with the location of markers as the "true" reference position of the prostate. The frequencies of misalignment within 5 mm were small when the entire anatomy was used. However, with the registration performed by therapists with a 3-mm threshold, misalignments were observed in 24% and 33% along the vertical and longitudinal dimensions. For a 3-mm threshold, the misalignments with physician localizations were 7% and 13% along the vertical and longitudinal dimensions, indicating the localization could be improved with training. At the 5-mm level, misalignments occurred in less than 5% of the time when the entire anatomy was used rather than just the contours. In addition, when using only the contours, therapists' localizations were off by 5 mm or more in a quarter of the patients in the vertical and longitudinal dimensions. This clearly indicates that using the contours from simulation is not adequate for performing localization on in-room CT images (in this instance megavoltage CT images). Conversely, using the entire anatomy ensured that the prostate could be accurately localized within 5 mm if megavoltage CT images are used without markers. Precision within 3 mm will require intraprostatic fiducials. Similar work reported by Moseley et al[25] also show that with the use of the cone-beam CT images, the interuser variability increases, and the discrepancies between alignments on CT and markers increase. Obviously, misalignments will impact treatment only as much as they affect the delivered doses. With the uses of soft-tissue images for alignment, as long as minimum treatment margins of 5 to 7 mm are used, it is unlikely that the delivered doses will be affected because of misalignments caused by CT-image interpretation.

Ultimately, the main advantage of using CT-based methods is the ability to evaluate soft-tissue changes such as prostate deformation but, more importantly, rectal distention, bladder filling, and other anatomic daily variations that could have an impact on outcomes. Correlating rectal doses as the rectum changes daily with ultimate rectal toxicity would be only possible if CT images of the pelvis are obtained throughout the course of treatment, preferably on a daily basis. Such correlations, taking into account daily anatomic changes and ensuing dosimetric changes, require robust deformable registration algorithms. Such algorithms are currently in development and need validation specifically for pelvic structures such as the rectum before any reasonable correlations with outcomes can be made that are associated with daily anatomic variations. In the interim, daily dose-volume histogram evaluations can be performed provided daily CT images are available and daily contouring is performed. As previously mentioned, in 10 patients aligned every day on implanted markers, the anatomy was recontoured every day and daily dose-volume histograms of the prostate, bladder, and rectum were evaluated.[12] In 1 of the 10 cases, the average rectal volume receiving the full fraction dose of 2 Gy throughout 39 fractions was more than 4 times larger than planned. Such evaluations would not be possible if daily CT images were not obtained, although the target alignment per se was still done on implanted markers. A larger series of patients imaged daily with CT scans, with daily target and normal tissue dosimetric evaluations, should be used to correlate these dosimetric variables with ultimate outcomes. Not only is the prostate a moving target, but organs at risk such as the rectum are also structures that are moving.

Clinical Outcomes

The relevance of imaging and targeting the prostate gland should be judged by the ultimate clinical outcomes in patients rather than geometric or dosimetric outcomes. Because targeting (particularly daily targeting) has been performed starting only recently, long-term outcomes in prostate cancer patients are not available. No randomized studies are available and are unlikely to be performed in the future. Even historic controls are difficult to evaluate because more modern series of patients treated with image guidance have been associated with higher radiation doses.

However, the impact of missing the target has been shown in a series of patients treated before the image guidance era by de Courvoisier et al.[39] The biochemical relapse-free survival rates were compared in patients who had rectal distention at the time of initial simulation versus patients who did not, with half the patients having a distended rectum by their definition of a cross-sectional area of the rectum exceeding 11.2 cm^2. The difference in the biochemical relapse-free sur-

vival rates was 29% between patients who had a distended rectum versus a deflated rectum. Rectal distention was shown to be an independent predictor of failure. This observation was confirmed by Heemsbergen et al[40] in patients treated without image guidance from a Dutch dose randomization protocol. These series clearly show that anatomic variations in individual patients introduce significant errors in the delivery of radiation therapy that, in turn, impact tumor control. In this case, rectal distention at the time of simulation resulted in the placement of external alignment marks that were not adequate surrogates of the prostate position during therapy. This could be described as a systematic error; however, it is more a reflection of anatomic variations during an entire treatment course that are not necessarily predictable. In the series of patients reported on by de Courvoisier et al,[39] there was also a suggestion that rectal distention at the time of simulation resulted in a lower incidence of subsequent late rectal toxicity with decreased bleeding. Again, this is because of the placement of the radiation fields on skin marks that were placed more anterior than what happened during therapy. In a patient cohort treated with a similar radiation delivery technique, it is reasonable to assume that rectal toxicity rates would be higher if image guidance was used daily because a larger volume of the rectum would be potentially irradiated. Anatomic variations affected both tumor control and toxicity rates. If repeated imaging of the prostate was performed, such errors would be minimized. In a recent analysis, the biochemical relapse-free survival rates were studied in 488 prostate cancer patients treated with an aggressive hypofractionated radiotherapy schedule (70 Gy in 28 fractions) and daily image guidance with transabdominal ultrasound. Rectal distention at the time of simulation was not a factor predicting biochemical relapse-free survival in this group of patients because daily image guidance had been performed, thereby decreasing the impact of anatomic variations on the introduction of targeting errors. These observations on clinical outcomes underline the importance of proper delivery of radiation therapy. Proper delivery of radiation therapy should not be based on multiple untested assumptions about the stability of the anatomy during the delivery itself. The large differences in outcomes in patients with a simple factor such as rectal distention at the time of simulation, as reported by de Courvoisier et al, cast a serious shadow on the adequacy of historical radiation therapy series in representing the outcomes in more modern patients treated with image guidance. This renders historical comparisons particularly difficult.

The Future

Modern external-beam radiation therapy for the treatment of localized prostate cancers should be considered still largely a work in progress, particularly because of the anatomic challenges the lower pelvis presents. High radiation doses needed for adequate tumor control require smaller treatment margins that might be inadequate for a moving target. The impact of such motion is dependent on the actual delivery technique, and the interplay of motion, treatment margins, delivery techniques, and treatment schedules should be properly studied. Prostate motion and anatomic variations of the lower pelvis (particularly of organs such as the rectum) vary from patient to patient, rendering class solutions and population based predictions difficult to apply for individual patients. Even within an individual patient, anatomic variations can lead to significant errors resulting in demonstrable decreases in tumor control rates and also toxicity rates.

Ultimately, full documentation of treatment delivery should include imaging showing the anatomic variation and motion evaluation because all these factors impact delivered doses. These are quality assurance issues that need to be solved for individual patients. What needs to be primarily determined is if the planned treatment was delivered correctly in each patient. The smaller the fields, the higher the radiation doses, and the fewer the fractions, the more important full dose documentation will be. However, such documentation is also relevant with more standard doses, techniques, and fractionations. Even with large fields delivering low radiation of conventional size fractions, anatomic variation could potentially have an impact on outcomes. Currently, not all parameters potentially affecting delivered doses can be evaluated with a single system. However, many of the known parameters needed to be documented in the process of radiation delivery are currently being collected with different techniques and can be used to improve radiation therapy as a local treatment modality.

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