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IS A 3-MM INTRA-FRACTIONAL MARGIN SUFFICIENT FOR DAILY IMAGE-GUIDED INTENSITY-MODULATED RADIATION THERAPY OF PROSTATE CANCER?

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Abstract

Purpose—To determine whether a 3-mm isotropic target margin adequately covers the prostate and seminal vesicles (SVs) during administration of an intensity-modulated radiation therapy (IMRT) treatment fraction, assuming that daily image-guided setup is performed just before each fraction.

Methods and Materials—In-room computed tomographic (CT) scans were acquired immediately before and after a daily treatment fraction in 46 patients with prostate cancer. An eight-field IMRT plan was designed using the pre-fraction CT with a 3-mm margin and subsequently recalculated on the post-fraction CT. For convenience of comparison, dose plans were scaled to full course of treatment (75.6 Gy). Dose coverage was assessed on the post-treatment CT image set.

Results—During one treatment fraction (21.4 ± 5.5 minutes), there were reductions in the volumes of the prostate and SVs receiving the prescribed dose (median reduction 0.1% and 1.0% respectively, $p < 0.001$) and in the minimum dose to 0.1 cm³ of their volumes (median reduction 0.5 Gy and 1.5 Gy, $p < 0.001$). Of the 46 patients, three patients' prostates and eight patients' SVs did not maintain dose coverage above 70 Gy. Rectal filling correlated with decreased percentage-volume of SV receiving 75.6, 70, and 60 Gy ($p < 0.02$).

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CONFLICTS OF INTEREST NOTIFICATION

None of the authors have any actual or potential conflicts of interest.

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Conclusion—The 3-mm intrafractional margin was adequate for prostate dose coverage. However, a significant subset of patients lost SV dose coverage. The rectal volume change significantly affected SV dose coverage. For advanced-stage prostate cancers, we recommend to use larger margins or improve organ immobilization (such as with a rectal balloon) to ensure SV coverage.

Keywords

Organ motion; Intrafractional variation; Setup error; treatment margin; IMRT

INTRODUCTION

Recent advances in conformal radiotherapy have necessitated an increase in both the accuracy and precision of treatment delivery (1–6). The development of in-room image-guided target localization (5–15) and novel patient immobilization devices (7–10) has the potential to reduce interfractional treatment uncertainties. Tools have also been developed for monitoring intrafractional target motion during treatment by using ultrasound (11–13), implanted gold fiducial markers (14–18), and, more recently, electromagnetic beacon transponders (19–21). Most of these studies addressed geometric variations of prostate during treatment delivery. However, none of those studies investigated the dosimetric effect of intrafractional motion in an intensity-modulated radiation therapy (IMRT) setting using three-dimensional volumetric data. Although intrafractional motion of the pelvic anatomy has been shown to have relatively less effect on total treatment uncertainty than other sources have, its management can be more costly and challenging (22,23). The intrafractional margin for a prostate treatment if daily image guidance is used just before each treatment is still uncertain. Therefore, it is important to quantify the dosimetric consequences of intrafractional anatomy variations.

Several institutions have reported intrafractional variations of the prostate position during a treatment fraction using ultrasound, implanted fiducial markers, and cine magnetic resonance imaging (14,22,24–27). Using this information, clinicians could incorporate internal target volume margins to account for these motions and estimate their potential dosimetric effect. However, full computed tomographic (CT) analysis of the patient's anatomy would provide a better estimate of the dosimetric effect by allowing a full recalculation of the spatial dose distribution.

The choice of treatment margin is a question that needs to be properly addressed for the particular image-guided setup procedure. The size of the margin should be large enough to compensate for setup uncertainties, which include the measurement error of the imaging procedure, execution error when applying corrective shifts, and intrafractional target motion and deformation etc. In this study, we concentrate on the dosimetric impact of soft tissue target motion and deformation. We hypothesized that a 3-mm isotropic target margin adequately covers the prostate and seminal vesicles (SVs) targets during administration of an IMRT fraction, assuming that daily image-guided setup is perfectly performed before each fraction. The choice of a 3-mm target margin to account for intrafractional anatomic variation is based on the experience of previous investigators(28,29) and results from a recent analysis of anatomic variations.(30) In this study, we acquired two CT scans, one immediately before and the other immediately after an IMRT fraction in 46 patients. We found that the standard deviation of target displacement was less than 3 mm for all directions except anterior SV motion (4 mm). In this simulation study, we extended the previous study (30) and investigated the dosimetric consequences resulting from these anatomic variations by using a 3-mm intrafractional margin.

METHODS AND MATERIALS

Protocol and patients

Two study protocols, which were previously approved by our institutional review board, involved in-room CT imaging of each prostate cancer patient using the “CT-on-Rails” (EXaCT; Varian Oncology Systems, Palo Alto, CA) (31). The system allows for daily precise tumor localization without removing the patient from the treatment couch. Forty-six patients with pre-fraction and post-fraction CT images were included in this study.

Patient setup and daily image acquisition

Before daily imaging, the patients were immobilized with a Vac-Lok bag (Med-Tec, Inc., Orange City, IA) extending from the thigh to the feet, and their position was aligned using in-room lasers and skin markers. Patients were instructed to drink water and maintain a full bladder for subsequent ultrasound alignment (BATTM, North American Scientific, Chatsworth, CA), which is our in-house standard practice for setting up prostate patients. The first (pre-fraction) CT scan was acquired after the patient was immobilized. Immediately after the pre-fraction CT scan, the patient was aligned using ultrasound, and the IMRT was delivered. For the purpose of this study, one additional CT scan was acquired for each patient immediately after the IMRT fraction was delivered. The pre- and post-fraction CT image sets (one pair for each patient) were used as population samples to assess the dosimetric impact of intrafractional anatomic change. Ultrasound alignment is part of the patient daily treatment regimen and has no impact on our study other than increasing the time between our two CT image acquisitions. Any pelvic anatomic variation induced by the procedure itself is unlikely to be permanent. All CT scans were performed during the first two weeks of treatment and none of the scans was performed for the very first treatment fraction. The mean duration between two CT scans was 21.4 ± 5.5 minutes which included one complete CT scan procedure, one BAT alignment, and an 8-field IMRT treatment delivery.

Anatomy contouring

The CT image sets were contoured by one physician using the Pinnacle³ (Philips Medical Systems, Andover, MA) treatment planning system. The rectum was contoured from the recto-sigmoid flexure to the anus on the CT image set acquired before administration of the daily fraction. The pre-fraction rectal length was maintained when contouring the rectum on the post-fraction CT image set to minimize anatomic variation due to contouring differences between our image sets. Improper evaluation of rectal volume could compromise any subsequent dose-volume analysis.

Treatment plan design and image registration

To assess the dosimetric consequences of intrafractional anatomic variation, a new eight-field IMRT plan was created for each patient using the CT image set obtained before the daily treatment fraction. For the convenience of comparison, each plan was normalized to deliver a total of 75.6 Gy to a planning target volume enclosing both the prostate and entire SVs with an isotropic 3-mm margin while minimizing the dose to the bladder and rectum. Registration of the pre- and post-fraction CT image sets was accomplished with previously described in-house image registration software (32). Bony registration was necessary to ensure that soft tissue organ motion was the only factor causing the dosimetric changes by correcting patient's interfractional set-up errors. Then the treatment plan was copied to the post-fraction CT and recomputed for dosimetric analysis.

Dosimetric analysis

Analysis of the dosimetric change included measurement of the volume of the prostate and SVs receiving 75.6, 70, and 60 Gy as well as the minimum dose to 0.1 cm³ of the prostate and SVs. The choice of 0.1 cm³ for calculation of minimum dose was based on an internal survey that considered both the random statistical fluctuation of calculated dose in a small volume and the size of the cold-spot that could potentially have a clinical effect. Multivariate linear regression was used to search for correlations between rectal and bladder filling and target organ dosimetric changes. The dependent variables in our regression analysis were the percentage volume changes of the target organs receiving 75.6 Gy and the minimum dose change to 0.1 cm³ of the target organs. The independent variables in the regression analysis were the absolute volume changes of the rectum and bladder, the percentage volume changes of the rectum and bladder, and the radial changes of the rectum and bladder. Analysis of variance was used to generate an *F* test statistic and the significance of the model, denoted as p_{model} in the Results section. We report the significance value of each independent variable as well as the correlation coefficient of the entire model.

Deformable image registration

For patients who had particularly large dosimetric variation during the administration of the treatment fraction, we used deformable image registration to map dose calculated using the post-fraction CT images back to the pre-fraction anatomy (33,34). Deformable (non-rigid) image registration provided an additional method for understanding and interpreting the spatial change in dose distribution in the same reference coordinates as in the original (pre-fraction) plan.

RESULTS

Prostate coverage

Figure 1a displays the percent volume differences in the prostate coverage at 75.6, 70, and 60 Gy for each patient. The median percent changes were fairly small, at -0.5%, 0%, and 0% at the 75.6 Gy (100% of prescribed dose), 70 Gy (93% of prescribed dose), and 60 Gy (79% of prescribed dose) dose levels, respectively. However, the maxima were much larger: 23.8% and 7.0% for the 75.6 Gy and 70 Gy dose levels, respectively. Although the loss of dose to the prostate was not clinically significant for most of our patients, in three patients, complete prostate coverage was not maintained at 70 Gy during the daily treatment fraction.

Figure 2a displays the difference in the minimal dose delivered to 0.1 cm³ of the prostate. The group median minimal prostate dose before the fraction was 76.4 Gy. Based on the post-treatment CT, the minimal dose delivered to the prostate was reduced by ≥ 2 Gy for 12 patients (26% of total patients), by ≥ 4 Gy for eight patients (17%), and by ≥ 14 Gy for three (6.5%) patients. On the basis of these findings, clinicians using the minimal target dose as the criterion for target coverage would likely reject the use of the 3-mm planning margin used in this simulation study.

Seminal vesicle coverage

Figure 1b displays the percentage volume difference in the SV coverage before and after the daily fraction at the 75.6 Gy, 70 Gy, and 60 Gy dose levels along with range of the change. The median decrease in percentage volume coverage of the SVs ranged from -1.0% at 75.6 Gy to 0% at 60 Gy. Compared with the loss of prostate target coverage (i.e., Fig. 1a), the loss of SV coverage was much worse. Because the SVs are small structures with a greater range of motion and shape deformation than the prostate has, the potential dosimetric effect of anatomic variation is far greater for the SVs.

Figure 2b displays the minimal dose differences to the SVs before and after a treatment fraction. The median minimal dose decreased by 1.5 Gy, approximately three times the magnitude of the minimal dose change in the prostate. On the post-fraction CT image set, the SV minimum dose was reduced by 5–10 Gy for four patients (9% of all patients) and by > 10 Gy for another six patients (13%). The differences in minimum dose to the SVs were larger than changes in minimum dose to the prostate. The minimal dose to two patients was < 19 Gy (25% of the prescribed dose). A cold spot of this magnitude would have a significant clinical impact if it occurred repeatedly in the same position throughout the course of radiotherapy.

Multivariate correlation of target organ dosimetric change with rectal and bladder volume

The most prominent result from our multivariate linear regression analysis was the significance of the bladder volume variation in most models (Table 1). It particularly correlated with the prostate dosimetric changes. Although the increase in bladder volume was large and consistent, the dosimetric change to the prostate was typically small and infrequent. Based on the regression coefficient (not indicated in Table 1), a large increase in bladder volume (200 cm³) results in a dosimetric change of < 1% of the total prostate volume at the prescribed dose level. The rectum, however, correlated highly with all SV dose metrics and had regression coefficients that were nearly an order of magnitude greater than those for the changes in bladder volume. The results from Figs. 1 and 2 along with the models in Table 1 suggest that the large and infrequent intrafractional dosimetric variations of the SVs are a direct result of large and infrequent increases in the rectal volume due to filling.

Outlier analysis using deformable image registration

Factors other than rectal and bladder filling contribute to dosimetric variation, including changes in patient musculature and the migration of gas within the large intestine. Using deformable registration to map the dose calculated on the post-fraction anatomy back to the pre-fraction anatomy will provide an intuitive interpretation for some of these factors and their dosimetric effect.

In one example of outlier analysis, the patient had the largest increase in bladder volume (330 cm³) of all of our patients, but with little rectal volume variation. However, rather than displacing the prostate, that increase in bladder volume resulted in an anteroposterior displacement of the SVs (Fig. 3a). The original plan is shown in Figure 3b and applied to the post-fraction anatomy in Figure 3c. Deforming the dose onto the pretreatment anatomy indicated the reduction of dose coverage of the distal SVs (Fig. 3d).

Our second example is of a patient who had a large initial amount of gas that did not change in volume but rather changed position during administration of the treatment fraction. As Fig. 4a shows, the migration of gas was visually striking. The original plan is shown in Figure 4b. As a result, the patient's prostate and SVs were displaced by > 1 cm, which moved the SVs to outside the prescribed isodose line. Not shown in Figs. 4c or 4d are the large portions of each of the SVs that were outside both the 75.6 Gy and 60 Gy isodose levels.

Our last example is of a patient whose unique anatomic variation and dosimetric changes appeared to be the result of bladder filling (227 cm³) and possibly clenching of the pelvic and gluteal musculature. The original plan is shown in Figure 5b. Notice the systematic anterior shift of the tissue, particularly of the posterior of the target and rectum, as indicated in Fig. 5a. Figures 5c and 5d illustrate the reduction of coverage of the SVs. Although muscular tension has not been considered in previous literature to be one of the primary sources of intrafractional motion, it may explain why target organ uncertainty cannot be completely explained by just the filling of the rectum and bladder.

DISCUSSION

Few studies have addressed variations in dose distribution during administration of a radiation treatment fraction. In this study, we simulated the effect of anatomic variation on the dosimetric variance during a fraction using two CT image sets, obtained before and after the treatment fraction. Instead of using our clinical planning target volume margins of 5–8 mm, we chose a 3-mm isotropic margin to isolate the effects of intrafractional anatomy variation. We designed a new IMRT plan on each pre-treatment CT, which simulates an ideal correction for inter-fractional anatomic variations just before the treatment and allows us to evaluate the adequacy of a 3-mm intra-fractional margin with the CT image immediately acquired after the treatment fraction.

The choice of the 3-mm isotropic margin was based on the results from an earlier companion anatomic-variation study of the same group of patients.(30) In the earlier study, we found that the anterior and superior displacements of the prostate and SV correlated highly with the variations in rectal volume, and infrequent large anatomic displacements during 10–15% of treatment fractions were usually caused by large increases in the rectal volume due to gas buildup. The previous study agreed well with another intrafractional prostate motion study by Kupelian *et al.* (19). Those investigators used implanted electromagnetic transponders to continuously monitor prostate motion during administration of daily treatment fractions, and they reported observing displacements of > 3 mm and > 5 mm for cumulative durations of at least 30 seconds in 41% and 15% of sessions, respectively. The results from our current dosimetric study using a 3-mm isotropic margin for intrafractional variations mirror the results of the previous anatomic studies. The median differences of doses to the prostate were small overall. However, we found substantial target misses to the SVs in six of the 46 patients and moderate misses in an additional four of the patients. We also found that the rectum and bladder volumes did not correlate with dosimetric changes of the prostate, which implies that the 3-mm margin is adequate for the prostate target. The dosimetric change to the SVs, however, particularly that caused by changes in gas volume, correlated well with all metrics of rectal volume change.

Analysis of three of the dosimetric outliers in our study indicated that dosimetric variations of the pelvic anatomy during administration of a treatment fraction is the result of multiple factors, including rectal filling, bladder filling, and possibly muscular tension. None of our outlier patients exhibited all of these factors simultaneously.

Previous dosimetric studies

Although previous authors have measured interfractional dose variations with daily CT image sets (6), to the best of our knowledge, there are no published reports of estimating the dosimetric effect of intrafractional dose variation to the prostate using multiple CT sets acquired during administration of a single radiation fraction. The dosimetric effect of general intrafractional anatomic variations has been approximated by several authors by assuming rigid anatomy (*i.e.*, spatial invariance) and using a Gaussian model for random organ motion to recalculate the dose with a static dose field (*i.e.*, dose invariance), as discussed in the review by Bortfeld et al (35). However, anatomic and dose invariance can only be approximations, and direct recalculation is preferable if the data are available for such analysis. In this study, we used full CT scanning of the patient before and after delivery of one treatment fraction to recalculate the dose delivered. Thus, our results provide a more realistic assessment of the effect of intrafractional motion based on a comparison of the measurements of a patient's three-dimensional anatomy before and after the treatment. Moreover, we designed a special IMRT plan to test our hypothesis that a 3-mm margin would be enough if the pretreatment image-guided procedure can correct the interfractional setup error.

Study limitations

This study design did have some limitations, the largest of which was the approximation of the patients' anatomy over the duration of a treatment fraction using only two distinct time points. Real-time data, along with a method of accurately calculating the dose as it delivered, would provide a more accurate approximation. Unfortunately, such three-dimensional (*e.g.*, CT or magnetic resonance imaging) time-series data are not yet technologically achievable. Our pre-and post-CT data are perhaps the best available data sets at this time.

Another limitation was our measurement of only one fraction for each patient. The effect of this limited data collection depends on whether these variations are completely random across all patients or occur consistently in the same patient. In the former case, the reduced target coverage for a few radiotherapy fractions may not have a significant clinical effect on the patient's total treatment, whereas in the latter case, the clinical effect might be more significant. From the results of our repeat serial CT study of the same group of patients (in which we acquired three pre-treatment CT scans per week during the entire course of treatment), it appears that some patients may have a consistent problem with rectal gas buildup over the entire course of treatment, although this requires further investigation.

The cold spot (minimal dose) usually occurs in the peripheral of the prostate, most of the time in the superior border. The cold spot may occur in different places for some patients, however, for each individual patient, it is most likely that the cold spot will occur in the approximately the same place for a given treatment plan. For seminal vesicles, this variation can be quite different. Unfortunately, we don't have data to support this argument. The cold spot in the dose distribution mapped to the pre-fraction image will remain in the same anatomical location. The deformable image registration tracks the same portion of the anatomy.

Bony image registration may introduce additional uncertainties. However, our bone registration software was quite robust and accurate for pelvic bone.(36) Each registration was determined automatically and reviewed carefully. Because the entire bony reference structure was used for alignment, the overall accuracy was less than 1 mm in all cases.

Addition uncertainties are from the inter- and intra-observer variations in contouring. Our previous study analyzed this issue in detail.(30) Because we had a single physician who contoured both the pre- and post-fraction CT images, this study was not affected by the inter-observer variation. Intra-user contouring uncertainty may have an impact to our study; however, the uncertainty was measured to be small (sub-millimeter) except along the SI axis (1.4 mm), primarily due to the relatively large slice thickness (3mm). Compared to the shifts of the prostate in this study, they are unlikely to be the main factor for our results. Due to the large inter-observer variations in contouring, as reported by many other studies,(37–41) the overall treatment margin with daily image-guided setup should be evaluated carefully by each individual institution.

Our patient treatment practice may introduce study bias that may not be present at other institutions. All our patients went on an ultrasound alignment protocol, which required them to drink 20 oz. of water before each treatment. Therefore all patients demonstrated significant bladder filling. Fortunately, our data suggested that the impact of bladder variations was secondary to the rectum variations. On the other hand, our current practice did little to proactively address intra-fractional rectal filling.

Additional analysis revealed that intra-fractional rectal volume change was statistically correlated with the pre-fraction volume of the rectum ($p=0.034$, Spearman's Correlation). This implies that the larger, initial rectal volume before treatment may result in a higher chance of intra-fractional variations in the prostate and SV positions. This also suggests that an empty

rectum before treatment is a preferred strategy. A study by Stasi et al. demonstrated that emptying the rectum before treatment delivery limited the variations of rectal dose-volume parameters as well.(42) Alternatively, proactive internal target immobilization methods (e.g. rectal balloon) or real-time *in vivo* target-monitoring methods may achieve similar results.

CONCLUSION

Radiation coverage of the prostate while using a 3-mm planning target margin to account for intrafractional motion appeared to be sufficient for most patients. The dosimetric variance for the prostate over the course of a treatment fraction was moderate. However, coverage of the SVs was compromised in at least 6 patients, and those dosimetric changes could have significant clinical implications, such as local recurrence of cancer after treatment. Bladder filling and, to a greater extent, rectal filling correlated with dosimetric variance, especially in the SVs. For patients with advanced-stage prostate cancers, the use of a 3-mm margin may therefore place the patient at unnecessary risk of loss of adequate dose coverage in significant portions of the SVs unless additional procedures are performed, such as rectal purging, proactive internal target immobilization methods (e.g. rectal balloon), or real-time *in vivo* target-monitoring methods.

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Fig. 1.

The percentage volume dosimetric difference in (a) the prostate and (b) the seminal vesicles before and after a daily radiation treatment fraction at three distinct dose levels ($V_{75.6}$, V_{70} , and V_{60} .) Each short horizontal bar represents one patient case and the vertical bar represents the range of differences at each dose level.

Fig. 2. Histograms of the minimal dose differences to 0.1 cm³ of (a) the prostate and (b) the seminal vesicles (SV) before and after administration of a daily radiation treatment fraction.

Fig. 3.

(a) The displacement vector field of a patient with extreme bladder filling during a radiation treatment fraction. The anatomy shown in (a) is before the treatment fraction. The red arrows indicate the direction that the anatomy will shift during the treatment fraction. The dose distributions are calculated in (b) before and (c) immediately after treatment for the same patient. (d) shows the dose distribution of (c) mapped to the anatomy of (b) by the deformable image registration. The structure in orange is the seminal vesicle with a blue PTV of 5mm expansion. The isodose lines are: yellow 45 Gy; orange 60 Gy; red: 75.6 Gy.

Fig. 4.

(a) The displacement vector field of a patient with rectal gas migration during a treatment fraction. The dose distributions are calculated in (b) before and (c) immediately after treatment for the same patient. (d) shows the dose distribution of (c) mapped to the anatomy of (b) by the deformable image registration.

Fig. 5.

(a) The displacement vector field of a patient with possible pelvic and gluteal muscular tension during a treatment fraction. The red arrows indicate the difference in thickness of the clenched pelvic muscles between the "before" and "after" images and the resulting shift of the target organs and bladder relative to the mid pubic symphysis. (b) The planned treatment fraction as calculated before treatment for that patient. (c) The planned treatment fraction calculated directly after treatment for this patient (d) The dose distribution after treatment was mapped to the before fraction anatomy by the deformable image registration method.

Table 1
Statistical significance and correlation coefficients for each multivariate regression model

Target Organ	Dose Metric	Rec/Bla Metric	P _{model}	P _{rectum}	P _{bladder}	R	F-value
Prostate	75.6Gy Percent Volume	Volume	0.019	0.942	0.006	0.406	4.353
		Percent Volume	0.020	0.716	0.006	0.405	4.310
		Radius	0.013	0.862	0.004	0.422	4.779
	Minimum Dose	Volume	0.005	0.705	0.001	0.460	5.918
		Percent Volume	0.002	0.820	0.000	0.498	7.246
Seminal Vesicles	75.6Gy PercentVolume	Radius	0.002	0.720	0.000	0.503	7.455
		Volume	0.000	0.001	0.169	0.548	9.448
		Percent Volume	0.000	0.000	0.058	0.563	10.210
		Radius	0.000	0.000	0.068	0.570	10.610
		Volume	0.002	0.010	0.058	0.493	7.080
	Minimum Dose	Percent Volume	0.001	0.003	0.029	0.520	8.135
		Radius	0.001	0.004	0.027	0.524	8.333

Abbreviations: Rec/Bla = rectum/bladder; pmodel = significance of the entire model; Prectum = significance of the rectum variable; pbladder = significance of the bladder variable; R = Correlation Coefficient.