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Modeling positioning uncertainties of prostate cancer external beam radiation therapy using pre-treatment data

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Abstract

Purpose—To investigate the influence of treatment plan data and image guidance (IG) on positioning uncertainty during prostate cancer (PCa) radiotherapy (RT).

Methods—Body mass index (BMI), planning target volume (PTV), bladder volume (BV), and rectal cross section area (RCS) were collected for 267 consecutive PCa patients undergoing daily IGRT. Radiographic isocenter corrections to intra-prostatic fiducials for 12,490 treatment fractions were used to derive random (RE) and systematic (SE) inter-fraction uncertainties for the cardinal axes. These data were used to simulate RE and SE for weekly IG and Action Level (AL)-IG treatment protocols.

Results—SE and RE were 2–5 and 3–4 mm in the cardinal axes, respectively, during simulation of no IG. Without IG, positive correlations ($p < 0.01$) were noted for (1) anterior-posterior RE vs. RCS and BV and (2) cranio-caudal RE vs. RCS, BV and BMI. The RE increase was 3 mm for the highest quartile of RCS, BV and BMI. Daily IGRT eliminated this relationship. 3D IG corrections of 1 cm or more occurred in 27% of treatment fractions and in 97% of patients.

Conclusion—PCa patients with elevated pre-treatment BV, RCS and BMI have increased inter-fractionation positioning uncertainty and appear the primary candidates for daily IGRT.

Keywords

Image guided radiotherapy; IGRT; Prostate cancer; Interfraction motion

Advances in external beam radiotherapy (RT) have allowed safe dose-escalation for localized prostate cancer (PCa). The maximum tolerable dose (MTD) for 2D-RT techniques

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was 70 Gy in RTOG 77–06 [1]. The advent of 3D conformal RT (3D-CRT) enabled prospective trials to demonstrate benefit in biochemical progression free survival (bPFS) across all risk categories of patients with doses $\geq$ 70 Gy [2]. Contemporary studies such as a large prospective, non-randomized dose-escalation trial at the Memorial Sloan-Kettering Cancer Center (MSKCC), which included doses up to 86.4 Gy, continue to suggest dose-dependent bPFS and distant metastasis rate benefit [3].

The increasing dependence on highly conformal RT techniques to achieve such dose-escalation has highlighted the impact of treatment protocol and pre-treatment anatomy on treatment accuracy and outcomes. Changes in bladder volume (BV) and rectum volume have been correlated with prostate displacement during treatment [4]. Moreover, increased rectal cross section (RCS) area at CT simulation has been correlated with inferior bPFS [5,6]. Similarly, body mass index (BMI) has been correlated with random positioning uncertainty [7]. BMI was a predictor of decreased bPFS in one study [8], but data were conflicting in another [9].

Various image-guidance (IG) RT protocols to address such issues have led to a reduction in inter-fraction systematic and random uncertainties over skin-mark based positioning protocols [10,11]. This includes Action Level (AL)-based protocols, where imaging based corrections during the initial fractions of treatment schedule are used to calculate an average correction for the rest of treatments [12–14], and daily IGRT protocols. In one AL protocol, the correlation of RCS with bPFS was no longer observed [15]. At MSKCC, initial introduction of daily IGRT with an unchanged planning treatment volume (PTV) margin resulted in an improved bPFS for high risk patients and reduced late urinary toxicity in all patients [16]. However, in another setting, the introduction of daily IGRT coupled with a reduced PTV margin was correlated with inferior bPFS, stressing the importance of validating this technology [17].

The interplay of dose, patient setup protocols, and treatment argue for the inclusion of dosimetric analysis of treatment delivery uncertainties in future external beam RT studies. In contrast to older series of EBRT, contemporary use of IGRT has made available data characterizing individual patient setup. As noted, investigations into potential factors affecting setup uncertainty have been pursued in the pre-IGRT era and in select AL and IGRT protocols. However, there are limited data on the influence of pre-treatment information such as BV, RCA, PTV and BMI on the positioning uncertainty of prostate cancer in large data sets of contemporary, fiducial-guided IGRT with modern dose-escalated therapy.

Therefore, in this study, we aimed to characterize the effects of such variables on systematic and random positioning uncertainty for 267 PCa patients consecutively treated with fiducial-based daily IGRT. Specifically, given prior data describing the impact of RCA on bPFS, we hypothesized that high RCA is associated with increased positioning uncertainty.

Methods and materials

Patient data and treatment protocol

A retrospective review was conducted of patients consecutively treated for localized PCa with definitive intent using pre-treatment, fiducial-based image guidance and IMRT at our institution from February, 2007–July, 2010. Patients with American Joint Committee on Cancer 7th edition clinical T4 and M1 disease were excluded. A total of 267 patients remained eligible for analysis. The planning and treatment procedure has been described in more detail previously [16]. Briefly, radio-opaque gold-markers were inserted into the prostate gland at least 5 days prior to CT-simulation. At CT-simulation, the reference position was tattooed into the patient's skin. Intentional full-bladder protocol was used only in patients with abnormal location of small bowel within anticipated high-dose areas of the pelvis. Normal structure delineation included the BV, bladder wall, small and large bowel, outer rectum volume, rectum wall, and left and right femurs. Clinical target volume (CTV) was defined as the prostate and seminal vesicles. Planning target volume (PTV) was defined as a 10 mm expansion of the CTV, except a reduced 6 mm expansion posteriorly. A standard dose of 8640 cGy in 180 cGy fractions was prescribed to the PTV except for patients with prior history of transurethral resection of the prostate, who were treated to 8100 cGy. In patients treated to the pelvic lymph nodes, a PTV encompassing the bilateral lymphatic drainage was prescribed to receive 4500–5040 cGy. IMRT plans were constructed using five to seven 15 MV photon beams. At treatment, the patients were first carefully setup to tattoos using in-room lasers. The On-Board Imaging (OBI) system (Varian Medical Systems, Palo Alto) was subsequently used to take X-rays before each daily treatment fraction. The X-rays were compared to Digitally Reconstructed Radiographs (DRR) from CT-simulation data. The IG protocol was based on Left–Right (LR), Cranio–Caudal (CC) and Anterior–Posterior (AP) translations performed daily. Treatment couch translation was derived from the center of mass of three gold markers visualized using a pair of orthogonal orthovoltage X-ray radiographs and registered onto the DRRs, and image registration metrics were recorded. Individual and the combination of rotations and deformations of the three marker positions compared to the DRRs were not considered or recorded. Treatment couch shifts were performed if deviations of the actual position were larger than 2 mm in one or more of the cardinal axes. If a shift was performed, a second pair of orthogonal X-ray images was collected to verify positioning stability.

Pre-treatment anatomic variables

BMI data were derived from a combination of measured and patient-reported height and weight at initial consultation. RCS was calculated as the volume of the delineated rectum divided by its length. The remainder of anatomic measurements was collected as originally delineated normal structures during treatment planning, as described above.

Calculating positioning uncertainty during daily IGRT and other simulated IG protocols

Pre-treatment positioning correction data based on the radiographic matches with DRRs for the patients were extracted from the log-files. We confirmed that the radiographic matching was in accordance with the actual couch shifts performed. However, no couch shift was performed if the radiographic deviation was less than 2 mm. Radiographic matching data

were used to derive uncertainties as random and systematic components (RE and SE, respectively) in each cardinal direction following Kutcher et al. [18] under the assumption that positioning was performed using only skin marks, as schematically depicted (Supplemental Fig. 1). The calculated uncertainties thus included a combination of inter-fraction prostate motion and patient setup. The average and the distribution of SE and RE for all the patients were studied in AP, LR and CC directions. The Shapiro-Wilk test was used to test if SE and the natural logarithm of RE were following a normal distribution. The averages of all patients' systematic deviations in each separate axis were calculated and were referred to as the population systematic deviations. A further analysis estimated the fraction of treatment fractions that would be inside a dorsal PTV margin from 0 to 15 mm to provide a practical measure of the effect of these uncertainties.

The procedure of generating and analyzing RE and SE was repeated for simulations of treatment protocols employing a weekly IGRT and an 'Action Level' approach. The 'weekly IGRT protocol' (indexed WKLY) stipulated correction by the deviation found with IG on the first fraction of every week, guiding non-IGRT treatments for the rest of each week. Using the 'Action Level protocol' (indexed AL), we assumed that imaging was employed during the first 5 fractions of the treatment course, for which the residual errors were assumed to be zero. The average correction of those 5 fractions was then used to derive a correction for subsequent fractions where no IG was used.

Modeling factors affecting positioning uncertainty

The data for positioning uncertainty during daily IGRT and simulations of other or no IGRT protocols were evaluated against pre-treatment anatomic data. Scatter plots revealed weak univariate relationships that visually appeared best described by linear regression models. Thus, those pre-treatment anatomic data that significantly correlated with RE or SE on multivariate analysis were used to form our model (Eq. (1)):

$$\text{RE or SE} = a \cdot \text{BV} + b \cdot \text{RCS} + c \cdot \text{PTV} + d \cdot \text{BMI} \quad (1)$$

Here, a – d are fitting coefficients that were allowed to be optimized such that the combined model had the maximum predictive power. In the model, coefficients a – d were eliminated if the contribution was insignificant, i.e. coefficients were kept if non-zero with a p -value of 0.05 or less. The correlation of RE and the absolute of SE were pair-wise tested in each cardinal direction and within the group of RE and SE (Pearson). Finally, the relationship of the absolute SE in the CC and AP axes vs. BV and RCS, respectively, was tested.

Results

Patient characteristics and positioning uncertainty

The patient characteristics are presented in Table 1. A wide range of clinical characteristics, BMI, PTV, BV and RCS were observed. BMI frequencies by NIH group were normal (25.8%), overweight (35.4%), obese (15.1%) or very obese (8.1%) with a single underweight (0.4%) patient. BMI data were not available for 15.1% of patients.

A total of 12,490 fractions were available for analysis. Loss of data occurred in less than 0.5% of the fractions. No time-trends were observed in the data in terms of patients treated earlier or later in the cohort or within a treatment course. The population average error was less than 0.1 cm in all directions (i.e. the average of all systematic deviation). Estimated Random and Systematic uncertainties (RE and SE) are presented in Table 2 for no, AL-IG, weekly and daily IG. Interestingly, the weekly IGRT protocol showed a low SE but increased RE as compared to no IG. The AL protocol reduces the SE, as demonstrated before [12]. The residual RE for daily IG was estimated to be 2 mm (2 SD), which is the tolerance for IG correction at our institution. We note that inclusion of uncertainties arising from potential sources of error other than daily positioning variation such as target delineation uncertainty, organ deformation, intra-fraction motion, marker migration, isocentricity of the IG system and image registration are not included in Table 2. The probability of a treatment fraction being inside the 6 mm dorsal margin together with a representative treatment plan is shown in Fig. 1. Three-dimensional corrections larger than 1 cm occurred in 27% of the fractions, and 97% of patients had at least one such correction.

After the removal of one outlier of SE in the CC direction, the population of SE data were distributed in a normal pattern (Shapiro–Wilk’s test). The distributions of RE were approximately log-normal. RE in all directions were internally correlated, as were RE with the absolute of the SE in the corresponding direction (p -values <0.01).

Multivariate modeling of factors affecting positioning uncertainty

The multivariate analysis provided evidence of correlation of BMI, RCS and BV with the RE in the AP and CC directions (significant coefficients a , b , c and d are presented in Table 3) for simulations of no IGRT, weekly IGRT, and AL. Correlations were strongest between RE in the AP and CC directions with RCS and BV. No association with PTV size and RE or SE was found ($c = 0$ for RE and SE). Further, SE was not associated with BV, BMI, PTV or RCS (i.e. $a = b = c = d = 0$ for SE).

The correlation coefficients of individual significant parameters were weak with 1–2 mm increased RE in both the AP and CC directions for the highest values in each group (Supplemental Fig. 2) However, using the multivariate model, patients with combined higher BMI, RCS and BV had substantially higher average RE, ranging from approximately 2–6 mm in the CC and AP directions (1 SD). This association was maintained even if a simulated weekly or AL-IG protocol was employed. A margin expansion based on the formalism presented by van Herk et al. was derived based on the multivariate correlation parameters (see Supplemental Fig. 3). In contrast, there was little evidence in this work of a relationship of SE with the pre-treatment parameters. Only a weak correlation of the SE in the AP direction with RCS was found ($p = 0.04$), but the correlation disappeared by using any of the IG protocols.

Discussion

The positioning uncertainties found in this study were numerically approximately the same as found in previous work, though these previous studies were typically based on a much smaller treatment population with some notable exceptions [13]. The large size of the data

cohort here allowed a more in-depth analysis of positioning uncertainty and its interaction with metrics previously correlated with clinical outcome, such as BMI and RCS. Consistent with these findings, we observe that patients with an elevated BMI, RCS and BV at CT-simulation were at higher risk for having a larger inter-fraction treatment positioning uncertainty unless daily IG is employed. Interestingly, however, Stillie et al. found no association with RCS and positioning uncertainty [19]. It is beyond the scope of this work to clarify to what extent dosimetry and clinical outcome can be impacted by the increased RE found for patients with elevated RCS, BV and BMI.

By simulating alternative IG approaches, we showed that a weekly IG or action-level based positioning protocol reduces systematic uncertainty, but the correlation of BMI, RCS and BV with increased random positioning uncertainty remains. Thus, the patients in the upper range of the observed BMI, BV and RCS appear to be the most relevant candidates for a more intensive IGRT protocol, such as daily guidance as in our cohort. This was also supported by our finding that RE in all axes of motion were correlated with each other. The strong correlation between the RE and SE in the AP and CC directions could imply that rotation about the LR axis is important [20].

With these findings, we can hypothesize that the optimal choice of prescription dose, PTV margin and IGRT technique are inter-dependent and varying between patients. For instance, if the IGRT protocol is altered, the PTV margin and/or prescription dose would in turn benefit from being re-optimized. In our institution, improved bPFS for high NCCN risk group patients and reduced toxicity in all groups of patients was observed after the introduction of daily image guidance while keeping the radiation dose constant and PTV margins constant [16]. The current study appears to provide mechanistic evidence of the presumed rationale for this clinical benefit by noting that >1 cm 3D couch corrections occurred in 27% of fractions and at least in one fraction for 97% of patients. These would surpass the standard 1 cm PTV employed in the prior study. Further, the positioning uncertainties found suggest that a 0.6 cm dorsal margin could be insufficient to avoid decreased dose coverage in the peripheral zone where the majority of prostate cancer is believed to arise (Fig. 1). In contrast, with daily image guidance, a strong majority of fractions were likely to be on target within the unchanged margins. We do note a limitation of our model in not accounting for the potential contribution of prostate gland deformation or rotation, as well as the emerging question of intra-fraction motion [21] in this regard. A further limitation is that we limited the analysis to a single AL-IG protocol, as studying other protocols were beyond the scope of the current study.

In the supplemental data section we illustrate that how treatment margins could vary if adjusted based on BV, RCS and BMI for no IG, weekly and AL-based IG. A BV, RCS and BMI smaller than or greater than the average would thus warrant a reduced or increased margin, respectively. Using daily IG the inter-fraction positioning uncertainty is most likely unaffected by BMI, BV and RCS, and a margin adjustment is not warranted based on this study. The patients on a full-bladder protocol are likely to have increased BV and the use of daily IG could be especially beneficial for this subgroup.

Finally, the correlation of pre-treatment BMI, RCS, and BV with positioning uncertainty and the correlation of the RE in separate directions together suggest that there are subgroups of patients with an elevated risk of geometrical targeting misses. As a consequence, the prescription radiation dose might be an inadequate solitary descriptor of the intensity of radiation treatment of prostate cancer without IG, particularly in these patients. In conclusion, prostate cancer patients with elevated BMI, BV and RCS pre-treatment should be the primary candidates for daily IG in favor of other positioning protocols when access to daily IG technology is limited.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.radonc.2013.12.010>.

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Fig. 1.

Left: Dose distribution in color scale of a representative patient case, with delineated rectum (orange) and planning treatment volume (PTV, yellow). *Right:* The probability of a delivered treatment fraction falling within the dorsal PTV is shown as a function of dorsal PTV margin for treatment setup using IGRT and for treatment setup using skin marks for patients with or without larger rectal cross sectional area (RCS, $>6.1\text{cm}^2$) and bladder volume (BV, $>204\text{cm}^3$). The MSKCC dorsal PTV margin is indicated at 0.6cm. These plots demonstrate increased risk of treatment delivery outside of the dorsal PTV margin if no IGRT were used at the margin used at our institution. Further reduction of dorsal PTV margin to compromise coverage to spare rectum appears to increase this risk, as the curves further separate at low PTV margins.

Table 1

Characteristics of the 267 patients included in the study.

Parameter	Median	Range	
Age	71	46–85 years	
BMI	27	18–48 kg/m ²	
PTV	175	51–467 cm ³	
BV	204	14–1069 cm ³	
RCS	6.1	1.8–19.6 cm ³	
	Group	N	%
Radiation dose (cGy)	8100	58	21.7
	8640	206	77.2
	Other *	3	1.1
Pelvic radiation	No	217	81.3
	Yes	50	18.7
Hormone therapy	No	134	50.2
	Yes	133	49.8
Year of radiation therapy (start)	2007	65	24.3
	2008	114	42.7
	2009	63	23.6
	2010	25	9.4
Clinical T stage	T1c	165	61.8
	T2a	35	13.1
	T2b	27	10.1
	T2c	19	7.1
	T3a	14	5.2
	T3b	7	2.6
Gleason score	6	60	22.5
	7	156	58.4
	8	34	12.7
	9	13	4.9
	10	2	0.7
	Missing	2	0.7
Pretreatment PSA	<10	196	73.4
	10–20	47	17.6
	20	23	8.6
	Missing	1	0.4
NCCN risk group	Low	44	16.5
	Intermediate	150	56.2
	High	73	27.3

Abbreviations: BMI = body mass index; BV = bladder volume; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; PTV = planning target volume; RCS = rectal cross section.

* Three of the patients missed one or two of their intended 48 fractions.

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Table 2

Systematic (SE) and random (RE) positioning uncertainty, in the anterior–posterior (AP), left–right (LR), and cranio–caudal (CC) directions expressed in cm and at the level of 1 standard deviation (SD). Values in bold are significantly different from the reference no IGRT (skin marks) using an *F*-test ($p < .05$).

IGRT strategy	SE_CC	RE_CC	SE_LR	RE_LR	SE_AP	RE_AP
Skin marks (reference)	0.50	0.44	0.23	0.29	0.28	0.31
Daily IGRT	N/A	0.10	N/A	0.10	N/A	0.10
1st fr. IGRT (AL)	0.26	0.42	0.15	0.28	0.21	0.29
Weekly IGRT (WKLY)	0.12	0.52	0.08	0.35	0.09	0.37

Abbreviations: IGRT = image-guided radiotherapy; N/A = not available.

Table 3

Correlation of random (RE) positioning uncertainty in the anterior–posterior (AP) and cranio–caudal (CC) directions with bladder volume (BV), rectal cross section (RCS), and body mass index (BMI) for skin marks (no IGRT), weekly IGRT (WKLY), and action level IGRT (AL). No correlation with planning target volume was found, and systematic positioning uncertainty was uncorrelated with BV, BMI, PTV, and RCS. Coefficients $a-d$ (Eq. (1)) are given only if significantly contributing to the model (i.e., a non-zero coefficient with $p < .05$) and are otherwise not available (N/A).

Parameter	IGRT protocol	RE AP (cm)		RE CC (cm)	
		<i>p</i> Value	Coefficient	<i>p</i> Value	Coefficient
BV	Skin marks	<.001	.0002	.009	.0002
RCS	Skin marks	.001	.0066	<.001	.0136
BMI	Skin marks	.316	N/A	.001	.0062
BV	WKLY IGRT	<.001	.0002	.078	N/A
RCS	WKLY IGRT	.008	.0065	.001	.0117
BMI	WKLY IGRT	.056	N/A	.002	.0066
BV	AL-IGRT	<.001	.0002	.008	.0002
RCS	AL-IGRT	.002	.0060	.001	.0136
BMI	AL-IGRT	.233	N/A	.002	.0058

Abbreviation: IGRT = image-guided radiotherapy.