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Prostate Radiotherapy: Evaluating the Effect of Bladder and Rectal Changes on Prostate Movement-A CT Study

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Abstract: Prostate motion during radiotherapy is influenced mainly by both bladder and rectal filling. This study assesses the impact of bladder and rectal changes on prostate movement and determines whether there are any predictive factors for prostate motion from the initial radiotherapy planning scan. Twenty six patients undergoing conformal radiotherapy for prostate cancer had two CT scans approximately 35 min apart whilst remaining in the same radiotherapy planning position. Prostate, bladder and rectal contours were outlined on both CTs and prostate movement with respect to the bony pelvis was calculated after fusion of CT data sets. This method for determining prostate movement was validated by fiducial markers placed in 6 patients. Cross sectional and volumetric bladder and rectal data were analysed from each scan and correlated with prostate movement. Considerable intra-patient variations in bladder and rectal volumes occurred over a 35 min interval. There were no predictive bladder, or rectal parameters on initial CT to predict for prostate motion, with poor correlations observed between A-P prostate movement and the initial rectal volume ($r = -0.19$), cross sectional area ($r = 0.17$) and A-P diameter ($r = -0.21$), and only weak positive correlations between S-I prostate movement and both initial rectal volume ($r = 0.43$, $p = 0.03$) and A-P diameter ($r = 0.44$, $p = 0.02$). However the changes between the initial and final rectal cross sectional area ($r = 0.82$, $p<0.001$) and AP diameter ($r = 0.81$, $p<0.001$) were more closely related to A-P prostate movement. These findings confirm the principal that as the rectum expands it moves the prostate anteriorly, whilst changes in bladder volume seems to contribute less to inferior prostate motion. Strategies to manage these movements include adapting the posterior margin to the degree of rectal filling, or using methods to empty the rectum prior to treatment.

Key words: Prostate motion, radiotherapy, bladder, rectal changes

Introduction

The anatomical position of the prostate and seminal vesicles are affected by physiological movements of surrounding pelvic organs; mainly the rectum and bladder (Ten-Haken *et al*., 1991; Zelefsky *et al*., 1999). Such movement can contribute to the dosimetric uncertainties when treating prostate cancer with conformal radiotherapy. Using these techniques, the treatment margins may be

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closely tailored to the prostate and inadequate allowance for prostate movement during radiotherapy may result in a geographical miss resulting in decreased control rates. However if as a result larger radiotherapy fields were applied to take this movement into account, then there is a risk of increasing the chance of normal tissue toxicity and this will have implications for dose escalation regimes.

Both inter and intra-fractional prostate movements during radiotherapy have been reported. Inter-fractional motion has been studied using repeated serial CT examinations, (Ten-Haken *et al*., 1991; Schild *et al*., 1993; Beard *et al*., 1996; Melian *et al*., 1997; van Herk *et al*., 1995; Roach *et al*., 1997; Roeske *et al*., 1995), often aided by fiducial markers (Vigneault *et al*., 1997; Balter *et al*., 1995; Crook *et al*., 1995; Dehnad *et al*., 2003; Herman *et al*., 2003; Litzenberg *et al*., 2002), the use of daily ultrasound (Mohan *et al*., 2000; Langen *et al*., 2003; Artigan *et al*., 2004), or the use of rectal and bladder contrast (Tinger *et al*., 1998; Antolak *et al*., 1998) whilst intra-fractional movement has been investigated using cine MRI (Padhani *et al*., 1999).

The Royal Marsden Hospital has recently assessed a commercial ultrasound system (BAT® SXi, Nomos Corp./North American Scientific, Chatsworth CA.) for positioning prostate cancer patients for external beam radiotherapy. As part of a study evaluating the accuracy of this system, prostate movement was assessed by co-registration of two localization CT scans. These were performed over a thirty-five minute interval, with the patient remaining in the same radiotherapy delivery position. This provided an opportunity to investigate the relationship between bladder and rectal volumes in relation to prostate movement by using the interval CT scan with the patient remaining in the same position. In particular we wanted to see whether any bladder or rectal parameters could be identified on the initial CT scan that might be used in a predictive way to account for prostate movement. This would be important especially for those institutions who don't have access to some form of localization system for monitoring movements during radiotherapy. Also we wanted to evaluate our department's specific drinking protocol on the impact of bladder volume and prostate movement.

Materials and Methods

Twenty six patients receiving radical radiotherapy to the prostate and to either the base of the seminal vesicles or the whole seminal vesicles, gave consent to participate in this study, conducted at The Royal Marsden Hospital during 2004. All patients had received 8-10 weeks of neo-adjuvant androgen deprivation. The Royal Marsden NHS Foundation Trust Research Ethics Committee gave approval for this study.

Patients were scanned in a supine position with a GE HiSpeed QX/I® multi-slice CT scanner (General Electric Medical Systems). In the hour before the first scan patients were asked to void their bladders and then drink 350 mL of water providing a partially filled, comfortably full bladder. Ankle stocks and knee supports were used for patient immobilization. Skin markers were placed anteriorly and laterally and a helical scan was acquired using 2.5 mm slice thickness reconstruction. The scans were sent to the Pinnacle^3 ® treatment planning system (ADAC Laboratories, Milpitas, CA/Philips Electronics N.V.) and the prostate, rectum and bladder contours were manually outlined by a clinician (SM or JC). The scans were then exported back to the BAT® system where they were co-registered with the ultrasound images and used to evaluate the BAT as a daily positioning system. To evaluate and compensate for any prostate movement during the interval between the acquisition of the first CT (CT1) and the ultrasound scan, a second CT scan (CT2) was acquired immediately after the ultrasound.

Prostate movement was determined by co-registration of the two CT scans taken whilst the patient remained in the same position. To correct for any patient movement between the two CT scans, the scans were fused manually with reference to bony structures. To determine prostate movement the co-ordinates of centre of the prostate for each scan was determined by the ADAC software. The co-ordinates from CT 1 were subtracted from the co-ordinates of the second scan -CT2 to determine independent prostate shift. This method of determining prostate movement was validated in six patients who also had localization seeds inserted into the prostate

The prostate, bladder and rectum were manually outlined on CT2 by the same clinician who had outlined these structures on CT1. To ensure the structures were outlined consistently CT2 was outlined with the scans adjacent to CT1 on the Pinnacle termiual and the number of prostate slices outlined in each of the scans compared. For each patient the entire bladder was outlined. The rectum was outlined from two slices caudal to the most inferior CT image on which the prostate was identified to two slices cephalad to the most superior CT image containing seminal vesicle. The volume of both structures was recorded. The cross-sectional area and maximum A-P diameter of the rectum was taken at 1.5 cm below the root of the semiual vesicles, so that this corresponded to the central part of the prostate gland. This process did not precisely mimic the rectal outlining protocol we use in clinical practice, but ensured the relevant part of the rectum was available for analysis (inferior anal margin-rectosigmoid). To take into account both changes in rectal diameter and proximity of the rectum to the posterior margin of the prostate, the extent of rectal distension by air and/or faecal material was also assessed subjectively using an impact assessment scale as used by Padhani *et al*. (1999).

Results

All 26 patients completed both CT scans and adhered to the drinking protocol advised. The demographics of the subjects and staging information are shown in Table 1. The results for evaluating the BAT system for prostate localization are not discussed here, but initial reports have been presented (Coffey *et al*., 2004) and final results are awaiting publication.

Table 2 results represent the median movement in either direction (unsigned) and show movement predominantly in the Anterior-Posterior (AP) and Superior-Inferior (SI) directions. The methodology of determining prostate motion using interval CT Scans were correlated with prostate motion observed using gold seed displacements in six patients. The strongest correlations were observed for A-P (0.95) SI (0.84) movements (Table 2).

Table 1: Patient demographics

n = 26	
Age-median-68 year (range 55-78)	
Initial PSA-mean 13 (median 11.85, range 5.5-26)	
Gleason score-	6- 5
	7- 18
	8- 3
Clinical stage-all N0, M0 (includes radiological)	
T1C - 6	
T2A - 4	
T2B - 5	
T3A - 10	
T3B - 1†	

†- This pt received 6 months neoadjuvant hormones prior to radiotherapy. All others received upto 3 months neoadjuvant hormones

Table 2: Prostate movement. (after fusion and co-registration of CT 2 and CT 1)

	A-P (Post-ve)	L-R (Rt-ve)	S-I (sup-ve)
Median prostate movement (mm)- unsigned	1.2	0.6	1.2
Inter-quartile range (mm)	0.6-3.1	0.4-1.2	0.5-2.0
Range (mm)	0.3-5.9	0-2.5	0.1-7.4
Correlation with gold grains	0.95	0.78	0.84

Table 3: The mean and standard deviation of bladder and rectal parameters

n = 26, calculated from bladder outline on CT scans (thirty five minute interval)	
mean initial bladder volume	229 mL
SD (range)	133 (46-485) mL
mean increase in bladder volume	125 mL
SD (range)	70 (30-279) mL
mean bladder fill rate	3.7 mL min^{-1}
SD (range)	2.3 (0.9-9.0) mL min^{-1}
mean Initial rectal volume	52 cm^3
range	17-139 cm^3

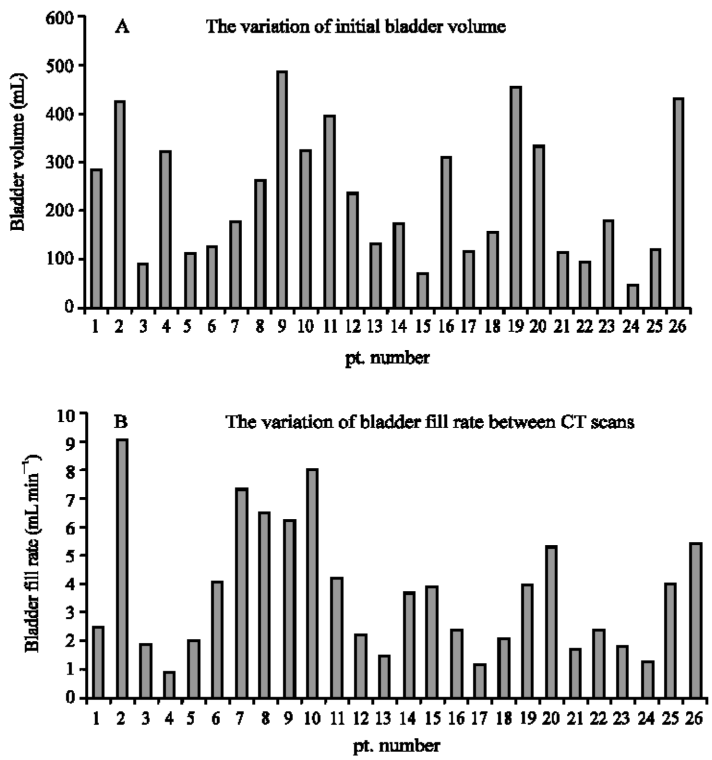

Fig. 1: The variation of (a) initial bladder volume, (b) bladder fill rate and © the correlation between the two parameters

The results for various bladder and rectal parameters are shown in Table 3. Despite adherence to the drinking protocol there were considerable variations in initial bladder volume (46-485 mL) (Fig. 1A) and also the rate of bladder fill (0.9-12.4 mL min^{-1}) (Fig. 1B). The correlation between bladder fill rate and initial bladder volume was 0.55. There was also a wide variation in rectal volumes seen both on the initial and subsequent CT scan.

Table 4: The correlation between various rectal and bladder parameters with respect to prostate movement

	Prostate movement					
	A-P	S-I	L-R			
Variable	Coefficient	p-value	Coefficient	p-value	Coefficient	p-value
Initial rectal vol.†	-0.20	0.33	0.43	0.03	0.00	0.99
Initial A-P diameter	-0.21	0.31	0.44	0.02	0.24	0.23
Initial cross-sectional area	-0.17	0.39	0.36	0.08	0.26	0.20
Initial bladder vol.	0.09	0.65	-0.17	0.41	-0.06	0.77
Change in rectal volume	0.57	0.002	-0.38	0.06	0.07	0.73
Change A-P diameter	0.82	<0.001	-0.23	0.25	0.01	0.94
Change cross-sectional area	0.81	<0.001	-0.15	0.46	0.05	0.83
Change bladder volume	-0.22	0.28	0.42	0.03	-0.09	0.65
Subjective Classification (*)	-0.01	0.95	0.13	0.54	-0.13	0.52

†rectal volume calculated from 5 mm above and below the seminal vesicle. (*) Analysis using Spearman's Rank correlation

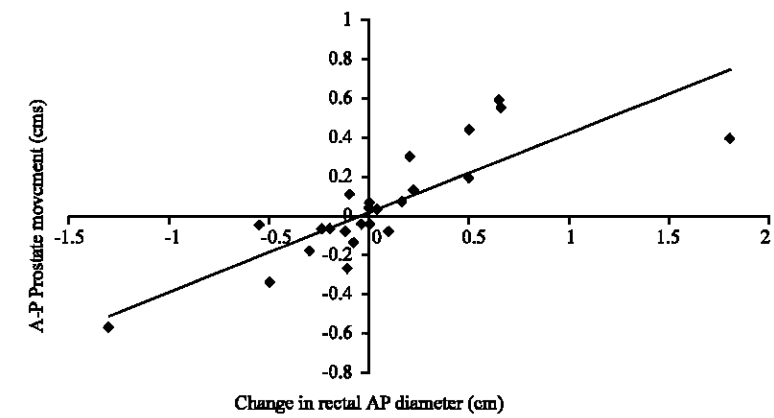

Fig. 2: The correlation between A-P prostate movement and changes in rectal diameter observed over a thirty five minute interval

Table 4 shows the Pearson correlation co-efficient for each rectal and bladder parameters with regards to their effects on prostate movement. Little association was seen between the initial rectal and bladder parameters identified from CT 1 (initial rectal volume, cross sectional area, AP diameter, initial bladder volume and change in bladder volume) on A-P movement. However, a weakly positive correlation between S-I prostate movement and both initial rectal volume ($r = 0.43$, $p = 0.03$) and initial A-P diameter ($r = 0.44$, $p = 0.02$) were observed. The subjective assessment of initial rectal distension was assessed using Spearman's Rank correlation and showed a weak association with prostate movement.

The changes in cross sectional area and A-P diameter at the level of the mid prostate however, were strongly correlated with A-P movement. The correlation between change in rectal A-P diameter and prostate movement is depicted in Fig. 2. This demonstrates that as the rectum fills it moves the prostate anteriorly. The association between changes in bladder volume and S-I prostate movement was less strong ($r = 0.42$, $p = 0.03$).

Table 5: Demonstrating the feasibility of using anisotropic prostate margins. Evaluating the margins required to cover the prostate in order to compensate for prostate movement

	% pts who have adequate coverage of prostate						
	Prostate margin (mm)						
	0	1	2	3	4	5	6
Large rectum							
Anterior margin	66.7	66.7	100	100	100	100	100
Posterior margin	33.3	33.3	67	67	67	67	100
Moderate rectum							
Anterior margin	37.5	50	50	50	62.5	75	100
Posterior margin	62.5	100	100	100	100	100	100
Small/ minimal rectum							
Anterior margin	53	80	93	100	100	100	100
Posterior margin	47	73	86	93	100	100	100

Table 5 uses the data obtained from this study on prostate movement to demonstrate the anisotropic margins that would be required around the prostate to prevent a geographical miss. (Note the size of these margins would only account for prostate movement and not set up error) the results show that for those with initially large rectal distensions a posterior margin of 6 mm would be required to compensate for the observed prostate motion compared to 3 mm for those that had smaller rectal distensions initially.

Discussion

This study has allowed us to assess the magnitude of prostate motion that occurs in relation to physiological changes in bladder and rectal filling over a thirty five minute interval. The findings confirm the principal that as the rectum expands it moves the prostate anteriorly, whilst changes in bladder volume seems to contribute less to inferior prostate motion. Although no predictive bladder or rectal parameters were seen on initial CT to predict for such motion, the data highlights some general strategies that could be employed to deal with prostate motion based on information from the planning scan.

Prostate motion has been extensively reported on and as a result a variety of localization methods have been evaluated. It is thought that the physiological movements of both the rectum and bladder contribute to this motion, the magnitude of which may be similar to daily positioning uncertainties (Verhey, 1995; Rudat *et al*., 1996; Tinger *et al*., 1996; Hanley *et al*., 1997). Allowing for both of these errors is essential in determining the size of the PTV (van Herk, 2004). The use of image registration of sequential CT scans over the course of radiotherapy has been used to evaluate methods of daily prostate localization such as the use of ultrasound (Mohan *et al*., 2000; Langen *et al*., 2003; Artigan *et al*., 2004; Lattanzi *et al*., 1999) and fiducial markers, the latter of which now forms benchmark for assessing prostate motion (Vigneault *et al*., 1997; Balter *et al*., 1995; Crook *et al*., 1995; Dehnad *et al*., 2003; Herman *et al*., 2003; Litzenberg *et al*., 2002). More recently advances in image gnidance have seen the introduction of 3-D megavoltage CT (Langen *et al*., 2005) to allow verification of the target volume and adjustment of the treatment plan to account for set up error and organ motion. However, these techniques are still under evaluation and although appear promising are yet to reach mainstream clinical practice.

The method of co-registering CT scans using bony landmarks with the patient remaining in the treatment position is a very crude way of estimating prostate motion, this method will not account for any rotational movements or deformations of the prostate. In addition we did not compare rectal cross sectional areas at different levels of the prostate. However, for the purposes of this study we were not concerned with actual prostate motion but rather the trends and correlations observed between rectal and bladder parameters thus we accepted such associated systematic error. Errors in target delineation were minimized by the use of a single outliner for both scans for each patient, though repeated outlines were not performed by different outliners for comparison.

Nevertheless our method was validated by monitoring the vector changes of fiducial markers which were placed in 6 patients and the results obtained for prostate motion are in keeping with published data suggesting that the greatest magnitude of motion is in the A-P and S-I directions (Verhey *et al*., 1995; Rudat *et al*., 1996; Tinger *et al*., 1996; Hanley *et al*., 1997).

Our results show a strong correlation between changes in rectal parameters (A-P diameter and cross-sectional area (measured at the level of mid prostate) and A-P movement of the prostate. An increase in either of these parameters causes anterior movement of the prostate. Although the time interval (35 min) was too long to long to characterise precisely the variation of intrafractional prostate motion, the magnitude of changes observed over this period suggest that prostate movement at this level is likely to be important and may have overestimated any intrafractional changes. Ten Haken *et al*. (1991) were one of the first groups to report prostate movement as a response to the state of rectal and bladder filling. Observed motion in the A-P direction was as much as 2 cm, which was determined by the use of rectal or bladder contrast at the time of simulation. These findings are in accordance with other studies (Beard *et al*., 1996; Melian *et al*., 1997; van Herk *et al*., 1995; Balter *et al*., 1995) and confirm the notion that as the rectum fills it displaces the prostate anteriorly. Present study did not demonstrate a strong relationship between S-I movement of the prostate and any rectal parameters.

In those that had large initial rectal cross sectional areas (>10 cm^2), although you would expect a physiological reflex to empty the filled rectum, there was little change in the cross sectional area and overall volume over the time interval in 40% of patients. This suggests that larger rectal distension may be related to chronic constipation that can result in bowel hypotonia and thus subsequently impair rectal activity and movements. Rectal peristalsis and passage of flatus must also contribute as some (40%) patients had a decrease, whilst others (10%) had an actual increase in cross sectional area at the same level on the second scan.

In this study, as with our own practice, no specific instructions were given to the patients about evacuating their bowels prior to their CT scan. It is interesting to note that in cases (5 patients) where the rectal wall was not abutting the posterior margin of the prostate (scoring minimal on the subjective assessment score) 80% were associated with A-P movements of < 1 mm. This suggests that the proximity of the rectum to the posterior border of the prostate is also important to consider as well as changes in rectal diameter. Although the subjective assessment impact scale as used by Padhani *et al*. (1999) takes both of these factors into account, the overall correlation with A-P prostate movement is weak, supporting the idea that other factors such as the passage of flatus and rectal peristalsis must play an integral part in causing rectal changes this observation suggests that maintaining an empty rectum may be important in reducing the degree of prostate motion

We did not find a strong association with regards to bladder volume and S-I prostate movement. Although the small positive correlation noted (0.42, $p = 0.03$) may suggest that as the bladder fills, this is displacing the prostate inferiorly, it is more likely that as the bladder fills the predominant movement is superiorly with probably little change at the bladder neck. Although our own previous studies (McNair *et al*., 2005) found that the use of a bladder drinking protocol resulted in a more constant bladder volume during a course of radiotherapy, this study using the same protocol showed still wide individual variation in bladder volume and more importantly the rate of bladder fill.

The reason for treating with a relatively full bladder is to reduce the bladder volume in the high dose zone and to displace small bowel loops from the treatment field. South *et al.* (2005) found that the DVH'S for bladder constraints were met when the bladder volume was greater than 250 mL when using conformal radiotherapy techniques for treating the prostate. Another possible reason for S-I prostate movement apart from changes in bladder volume is the intermittent clenching of pelvic floor muscles as patients try to maintain continence of their full bladder or rectum. This is yet to be formally tested. The bladder fill rate may be dependent on pre-hydration status and the time of day in which the patient was scanned. Not all of our patients were scanned in the morning. It may be important to devise such protocols to take both of these factors into account.

Similar results have been reported by Beard *et al.* (1996), where although a good correlation between rectal parameters and prostate movement. little effect from bladder distension was noted. Patients in this study were however, treated with an empty bladder.

Although no predictive parameters from the initial CT scan were demonstrated. The strong correlation observed between changes in rectal A-P diameter and prostate motion support the concept that by minimizing rectal change prostate motion can be reduced. A variety of strategies have been investigated.

The use of laxative suppositories to empty the rectum before treatment may minimise rectal changes, but efficacy and acceptability have not been widely studied (Stroom *et al.*, 1999). A more reliable albeit more cumbersome method of making sure that the rectum is empty and the prostate is at its most dorsal position is the use of a rectal enema given prior to radiotherapy treatment (Pickett *et al.*, 1995). The use of a rectal balloon (Patel *et al.*, 2003) may provide a degree of constancy by reducing the displacement of the prostate gland as a result of rectal changes as well as facilitating localisation on port films (Patel *et al.*, 2003; McGary *et al.*, 2001). However, a recent study has still shown prostate movement of a similar magnitude to that measured in men treated with a rectal balloon. Build up of flatus and stool beside the balloon was suggested as the likely explanation (van Lin *et al.*, 2005).

Treating the prostate with patients having an empty rectum may be advantageous in terms of being able to reduce the posterior margin needed around the prostate and thus reduce toxicity. Present data shows the principal that for those with larger initial rectal distensions a larger posterior margin would be required. To prove that this principal actually reduces toxicity, rectal dosimetry and dose-volume data will need to be evaluated with respect to differing posterior margins of the PTV This strategy however is in agreement with other published series (Pickett *et al.*, 1995) and our current hypo-fractionation studies, we routinely allow for a larger posterior PTV margin (10 mm compared to 5 mm) in those with large/ moderate rectal distension on initial planning CT (NCRN Trial ID-1281).

Conclusions

Rectal changes influence prostate movement to a much greater extent than changes in bladder volume. Although no rectal parameters were identified on the planning CT scan to predict for prostate motion, strategies to either minimize rectal change or adapting the posterior margin of the target volume to the degree of initial rectal distension may help to address this important issue.

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