The effect of concurrent androgen deprivation and 3D conformal radiotherapy on prostate volume and clinical organ doses during treatment for prostate cancer

C ONAL, MD, E TOPKAN, MD, E EFE, MS, M YAVUZ, MD, G ARSLAN, MS and A YAVUZ, MD

Department of Radiation Oncology, Baskent University Medical Faculty, Adana, Turkey

ABSTRACT. In this study, we investigated the shrinking effect of concurrent three-dimensional conformal radiotherapy (3D-CRT) and androgen deprivation (AD) on prostate volume, and its possible impact on the dose received by the rectum and bladder during the course of 3D-CRT. The difference between the prostatic volumes determined on pre-treatment planning CT (PL-CT) and post-treatment CT (PT-CT) following a 3D-CRT course was assessed in 52 patients with localised prostate carcinoma. The changes in mean prostate volume when compared with PL-CT and PT-CT-based measurements were assessed. The pre- and post-treatment mean prostate volumes for the whole study population were 49.7 cm³ and 41.0 cm³ ($p=0.02$), respectively. The study cohort was divided into two groups depending on the duration of neoadjuvant androgen deprivation (NAD): 23 patients (44.7%) were designated as "short NAD" (≤ 3 months; SNAD) and the remaining 29 (55.3%) as "long NAD" (> 3 months; LNAD). Patients on SNAD experienced a significantly greater reduction in prostate volume compared with those on LNAD (14.1% vs 5.1%; $p=0.03$). A significant increase in rectum V_{40-60} values in PT-CT compared with PL-CT was demonstrated. LNAD patients had significantly higher rectal V_{50-70} values at PT-CT compared with the SNAD group. There was a significant decline in V_{30-75} bladder values in PT-CT compared with PL-CT in the SNAD group. In conclusion, a higher prostate volume reduction during 3D-CRT was demonstrated when RT planning was performed within 3 months of NAD. However, this reduction and daily organ motion may lead to an unpredictable increase in rectal doses.

Received 9 November 2008
Revised 26 April 2009
Accepted 30 April 2009

DOI: 10.1259/bjr/65939531

© 2009 The British Institute of
Radiology

Prostate carcinoma is (in general) a hormone-sensitive disease that has been shown to significantly benefit from androgen deprivation (AD) when added to conventional radiation therapy (RT) doses of 65–70 Gy [1–7]. Results of large randomised clinical trials have demonstrated that AD significantly improves the outcome of patients with locally advanced prostatic carcinoma when treated with external beam RT with regard to local control, biochemical-free survival and freedom from distant metastases [1, 3, 5, 8–10]. Furthermore, in the studies of the European Organization for Research and Treatment of Cancer (EORTC 22961) [1, 3] and the Radiation Therapy Oncology Group (RTOG) protocol 85–31 [2], this improvement turned into a survival advantage.

Neoadjuvant androgen deprivation (NAD) before RT has been demonstrated to shrink the prostate volume effectively [11, 12], and thus has become a widely accepted and essential part of locally advanced prostate cancer management. On average, the prostate gland shrinks about 20–50% of its initial volume within 3 months of NAD [11–15] and, although the rate slows down, this shrinking effect continues beyond this period [16–19]. The cytoreduction in the prostate provided by NAD may

lower the complication rates observed at higher RT doses by reducing the target volumes, depending on the reduced doses received by normal tissues [15, 20].

A relatively long treatment interval (7–8 weeks) is usually mandated for three-dimensional conformal radiotherapy (3D-CRT) of prostate carcinoma, and the shrinkage of the prostate gland continues during this period. In this setting, it is reasonable to assume, theoretically, that there is a possibility of a larger than planned volume of surrounding critical organs that may shift into the intermediate or high-dose regions during the RT course, which may unpredictably increase the dose received by the rectum and bladder [11, 12, 21]. Based on the above assumption, we planned to evaluate prostate shrinkage during 3D-CRT in relation to NAD duration, and to investigate the possible impact of this volume reduction on the dose received by the rectum and bladder by comparing the pre- and post-treatment dose volume histograms (DVHs).

Methods and materials

Patient data

The clinical and dosimetric data from 52 patients with histologically proven T1c–3N0M0 (American Joint

Address correspondence to: Cem Onal, Baskent University Medical Faculty, Adana Research and Treatment Centre, Department of Radiation Oncology, 01120, Yuregir, Adana, Turkey. E-mail: hcemonal@hotmail.com

Committee on Cancer, 1997 staging system) prostate adenocarcinoma treated with 3D-CRT between January 2007 and October 2007 were utilised for this study. Informed consent was obtained from all patients before treatment. Baskent University's Institutional Review Board approved this study design.

Based on our departmental policy, all patients were first prescribed NAD containing goserelin and bicalutamide for 3 months before undergoing 3D-CRT. However, the duration of NAD differed between patients, largely because of patient preferences about the date of pre-treatment planning CT (PL-CT) and the referring urologist's preferences. As a result, 26 of 47 patients (55.3%) received NAD for at least 3 months before PL-CT and continued to do so until the end of the planned treatment. Patients were divided into two groups based on the median duration of NAD before PL-CT: there were 23 patients (44.3%) in the "short NAD" group (≤ 3 months; SNAD) and 29 patients (55.7%) in the "long NAD" group (> 3 months; LNAD).

Treatment planning

As part of the treatment planning, all patients underwent a PL-CT scan 4 days (range, 2–7 days) before initiation of 3D-CRT (with 2.5 mm sections in the treatment position). For this scan, patients were placed in the supine position and their feet fixed in a commercially available knee support device. Patients were asked to empty their rectum before treatment; no enema or laxatives were used before PL-CT and during treatment. CT scans were re-taken even if rectum volumes exceeded 100 cm³ during 3D-CRT. Patients were also instructed to refrain from micturating prior to the examination to ensure that their bladders were full, and 50 ml of dilute contrast medium was administered through a catheter before each CT scan [22]. We asked the patients to have a comfortably full bladder, *i.e.* the feeling of having a full bladder during treatment [23].

The clinical target volume (CTV) comprised the entire prostate and seminal vesicles. The planning target volume (PTV) was defined by adding an additional

1 cm margin around the CTV except at the posterior margin, where it was 0.8 cm at the prostate and rectum interface. The treatment volume included an additional 0.7 cm margin circumferentially for beam penumbra in all directions. The isocentre was set at the centre of the PTV and beams were shaped with multileaf collimators (MLCs) (Varian DHX 3323; Varian Medical Systems, Palo Alto, CA). On the final day of RT, a second CT (post-treatment CT (PT-CT)) was obtained by the same process as described above. The same planning procedures were performed for both the PT-CT and the PL-CT, and MLC profiles were transferred on PT-CT slices with the isocentre aligned to the PL-CT position according to skin markers and bony landmarks. For calculations, the dosimetric parameters (*e.g.* beam weights and International Commission on Radiation Units and Measurements (ICRU) point) utilised for PL-CT were also used for PT-CT.

Organs at risk — including the rectum, bladder and bilateral femurs — were contoured. Skin was contoured for defining the external contour of the body. The radiation dose was prescribed to at least a 95% isodose line covering the entire PTV. All treatments were planned using a treatment planning system (Eclipse®; Varian Medical Systems, Palo Alto, CA), and a total of 70 Gy (2 Gy per fraction; daily; Monday to Friday) was delivered using 18 MV photons. Invariably, all eligible patients were treated with the well-known 6-field technique, using the same fraction size and total dose. Any patients with deviations from either of the technique or dose constraints described recently [24] were excluded from the study. Portal images were obtained from the anterior set-up and two lateral fields on the first treatment day and then once weekly, or more frequently if necessary, and then compared with the digitally reconstructed radiographs by the treating physician to confirm field verifications throughout the RT period.

Determination of prostate volume

For the purpose of the current study, the CTV was contoured by a single observer on each data set, as appropriate. The observer was blind to the timing of CT (PL-CT *vs* PT-CT). Moreover, intra-observer variability was also assessed on 10 sample patients by a blind repetition of rectum and prostate contouring on randomly chosen CT scans. The average intra-observer variability was 0.7 mm and 0.9 mm for the cranial and caudal margins, respectively, with a maximum 1.2 mm intra-observer variation at the caudal limit of the rectum. Likewise, we also evaluated intra-observer variability for contouring of the prostate gland, and we found that the median absolute and percentage variations of the prostate gland were 2.9 cm³ and 6.4%, respectively.

Rectum and bladder DVH analysis

The observer was asked to draw outer contours of the rectum and bladder. The rectum, from the anal verge to the recto-sigmoid junction, and the whole bladder were contoured. For each patient, the rectum was required to be empty and the total length of the rectum was kept

Table 1. Patient characteristics

Variable	SNAD <i>n</i> (%)	LNAD <i>n</i> (%)
Age (years)		
Median (range)	71 (63–76)	69 (61–78)
Pre-treatment PSA (ng ml ⁻¹)		
Median (range)	10.5 (6–57.4)	14.2 (4.4–86)
T Stage		
T1c	4 (17)	3 (10)
T2a	11 (48)	12 (42)
T2b	5 (22)	5 (17)
T3a	1 (4)	3 (10)
T3b	2 (9)	6 (21)
Gleason score		
< 7	15 (63)	16 (55)
≥ 7	8 (37)	13 (45)

SNAD, short neoadjuvant androgen deprivation; LNAD, long neoadjuvant androgen deprivation; PSA, prostate-specific antigen.

constant for PL-CT and PT-CT. Pre- and post-treatment DVHs for the rectum and bladder were created and, for each organ, cumulative DVH calculations were analysed comparatively. DVHs of the rectum and bladder for PL-CT and PT-CT were also comparatively analysed for the whole patient population, and the same comparisons were performed separately for patients treated with LNAD and SNAD. Absolute differences in the percentage of rectum and bladder receiving 20–75 Gy in 10 Gy increments were calculated and the means reported.

Statistical analysis

The dosimetric variables considered were mean ICRU doses and volumes of bladder and rectum receiving 20–75 Gy (V_{20} – V_{75}). The percentage reduction in prostate volume was calculated for each patient by dividing the PT-CT prostate gland volume by the PL-CT prostate volume, and comparisons were made between SNAD and LNAD. The PL-CT and PT-CT cumulative DVH calculations for both the rectum and the bladder were analysed for each patient. Absolute differences in the percentage of rectum and bladder receiving 20–75 Gy were calculated and the means were compared between SNAD and LNAD groups. Means were compared by non-parametric rank tests; a value of $p < 0.05$ (two-sided) was considered significant.

Results

Patient characteristics are summarised in Table 1. The median duration of SNAD and LNAD was 2.7 months (range, 2.2–3.0 months) and 4.8 months (range, 3.3–10.7 months), respectively. For the overall study population, the mean prostate volumes determined by PL-CT and PT-CT were 49.7 cm³ (95% confidence interval (CI): 43.5–55.8 cm³) and 41.0 cm³ (95% CI: 35.9–46.1 cm³), respectively. The mean percentage prostate volume change in relation to the duration of NAD is depicted in Figure 1. For the whole study cohort, we also reported the exponential curve ($R^2=0.49$) that fits the results of patients receiving NAD. These curves confirm that the shrinking effect of AD on prostate volume is most prominent during the first 3 months and that the shrinking effect of NAD on prostate volume decreases with increasing duration of NAD before RT.

On average, patients receiving LNAD had a significantly smaller prostate gland volume on PL-CT compared with patients receiving SNAD (39.5 cm³ vs 60.3 cm³; $p=0.03$). Although a difference was observed at PT-CT for the two groups, it was not statistically significant ($p=0.1$). Patients undergoing SNAD showed a 14.1% reduction of the prostate gland at PT-CT compared with patients undergoing LNAD (5.1% reduction) ($p=0.03$).

Mean percentage variations in the bladder and rectum between PL-CT and PT-CT were quite similar. As shown in Table 2, the rectum and bladder volume changes did not significantly differ between PL-CT and PT-CT. In particular, we observed a ~5% increase in rectal volume and a 5–10% reduction of bladder volume at PT-CT compared with PL-CT.

Figure 1. Mean prostate gland percentage reduction by duration of neoadjuvant androgen deprivation (NAD).

The volumes of rectum and bladder receiving 20–75 Gy (V_{20} – V_{75}) for the whole patient group are summarised in Table 3. A significant increase in rectum doses was seen at intermediate dose levels (40–60 Gy) in PT-CT when compared with PL-CT. However, the differences at lower (20–30 Gy) and higher (70–75 Gy) dose regions did not reach significance. Regarding the comparative bladder doses, our results demonstrated a significant dose reduction between the pre- and post-treatment measures (30.1% vs 26.5%, respectively; $p=0.04$) at the V_{70} point; although similar reductions at lower and intermediate dose regions were observed, these did not reach a level of statistical significance.

As shown in Table 4, a significant increase in V_{50} – V_{70} rectum values were found for the LNAD cohort in PT-CT compared with PL-CT. The same was not true for patients receiving SNAD. Meanwhile, a significant decline in V_{30} – V_{75} bladder values was seen for the SNAD group in PT-CT compared with PL-CT, which was not significant in the LNAD group. The average absolute differences in rectum and bladder volumes on pre- and post-treatment DVH analysis according to the NAD interval are depicted in Table 5. A slight increase in the rectal volume receiving 20–75 Gy in the LNAD group and a significant decline in the bladder volume receiving 20–75 Gy was observed on PT-CT compared with PL-CT in the SNAD group.

The average increase in the mean rectal volume in PT-CT compared with PL-CT for SNAD and LNAD cohorts was $1.2 \pm 1.1\%$ to $6.6 \pm 3.8\%$ and $1.3 \pm 1.1\%$ to $7.6 \pm 4.2\%$, respectively (Figure 2). Among patients with SNAD and LNAD, the average difference in rectal DVH reached a maximum at 60 Gy (6.6% vs 7.6%). Differences among the groups were not significant. In contrast, a statistically significant decrease in PT-CT bladder dose was demonstrated in DVHs compared with PL-CT (Figure 3). The maximum average difference in bladder DVH occurred at 60 Gy (–9.1%) for the SNAD group and at 20 Gy (–4.1%) for the LNAD group. The decrease in mean bladder volume ranged from 5.0% to 9.1% in the SNAD

Table 2. Mean relative change (%) in rectum and bladder volumes between PL-CT and PT-CT

Group	Rectum		Bladder	
	% (95% CI)	p-value	% (95% CI)	p-value
LNAD	4.3 (−3.9–12.5)	0.3	−9.9 (−21.9–2.2)	0.1
SNAD	5.2 (−2.7–13.0)	0.2	−6.7 (−19.5–4.0)	0.4
Total	4.7 (−0.1–10.2)	0.1	−7.7 (−16.4–2.0)	0.2

SNAD, short neoadjuvant androgen deprivation; LNAD, long neoadjuvant androgen deprivation; CI, confidence interval; PL-CT, pre-treatment planning CT; PT-CT, post-treatment CT.

group compared with 0.4–4.1% in the LNAD group ($p=0.02$).

Discussion

In this current study, the effect of concurrent AD and 3D-CRT on prostate volume in patients with prostate carcinoma who were treated previously with NAD was assessed by comparing the pre- and post-treatment CT-based treatment plans. We demonstrated clearly that all patients experienced a significant volume reduction compared with their pre-treatment prostatic volumes at the completion of the RT course. This shrinking effect resulted in a further increase in the rectal dose and a reduction in the bladder dose. The increase in the dose received by the rectum was not influenced by the duration of NAD, whereas bladder doses were found to be significantly lower in the SNAD group compared with the LNAD group.

The shrinking effect of NAD on the prostate gland has been well demonstrated [12, 16, 21]. Available data suggest that even after 2–3 months of NAD, as occurs in concurrent administration with RT, a further reduction of the prostate gland can take place with use of AD. Lilleby et al [18] reported that the estimated accumulated reduction in prostate size was 33%, 35%, 45% and 46% at 3, 6, 9 and 12 months after the onset of NAD, respectively, in patients with T2–T3 tumours. Within a randomised trial comparing 3 months and 8 months of NAD before radical prostatectomy, the average prostate gland volume reduction was 37% and 45% after 3 months and 8 months, respectively ($p=0.01$) [16]. The interval between PL-CT and the end of a typical course of RT is longer, and is approximately 2 months. A relatively significant decrease in the prostate gland can

occur, even if RT is initiated within 3 months from the onset of NAD. Although the additional shrinkage of the prostate gland slows down during this period, it is significantly far from negligible. Sanguineti et al [25] found that patients starting AD within 3 months of PL-CT had a significantly larger reduction in prostate volume (14.2%) than patients with LNAD (1.1%). In the current study, the prostate volume change (49.7 cm³ vs 41.0 cm³; 18.5%) during the course of AD + 3D-CRT in all study cohorts appears to be slightly higher than the finding of Sanguineti et al [25], which may be related to its concurrent use in our study [25]. Additionally, considering the effect of NAD duration, the present finding of a larger reduction in prostate volume in SNAD patients during treatment compared with LNAD patients (14.1% vs 5.1%; $p=0.03$) correlates well with the findings of Sanguineti et al [25].

In the absence of NAD, changes in prostate volume on multiple CT scans during RT are usually minimal [26, 27]. In one study, the mean reduction in prostate volume between CT before RT and a second CT scan performed at the fourth to fifth week of RT was found to be 4.55 cm³ [28]. Although the size of the prostate gland was not used to select patients for NAD and its duration, it is not reasonable to neglect the differences in tumour load (T

Table 3. The volumes of rectum and bladder receiving 20–75 Gy (V_{20} – V_{75}) at PL-CT and PT-CT

Volume/ dose	Rectum (%)			Bladder (%)		
	PL-CT	PT-CT	p-value	PL-CT	PT-CT	p-value
V_{20}	85.2	86.7	0.08	72.5	68.6	0.06
V_{30}	78.9	79.2	0.3	63.0	59.2	0.1
V_{40}	70.7	73.6	0.04	55.8	51.5	0.06
V_{50}	60.1	63.7	0.02	49.5	45.5	0.07
V_{60}	42.4	51.1	0.001	42.4	38.5	0.06
V_{70}	27.9	32.2	0.09	30.1	26.5	0.04
V_{75}	4.6	5.2	0.07	7.1	5.8	0.2

PL-CT, pre-treatment planning CT; PT-CT, post-treatment CT.

Table 4. The volumes of rectum and bladder receiving 20–75 Gy (V_{20} – V_{75}) at PL-CT and PT-CT by duration of neoadjuvant deprivation

Volume/ dose	LNAD			SNAD		
	PL-CT	PT-CT	<i>p</i> -value	PL-CT	PT-CT	<i>p</i> -value
	Rectum (%)					
<i>V</i> ₂₀	83.9	85.5	0.2	86.9	88.1	0.2
<i>V</i> ₃₀	77.6	80.0	0.1	80.5	76.0	0.3
<i>V</i> ₄₀	69.2	72.7	0.07	72.6	74.7	0.4
<i>V</i> ₅₀	58.6	62.5	0.05	62.1	65.1	0.2
<i>V</i> ₆₀	45.2	49.8	0.02	47.8	52.7	0.08
<i>V</i> ₇₀	26.0	30.3	0.03	30.2	34.6	0.1
<i>V</i> ₇₅	7.1	7.7	0.7	14.7	11.8	0.3
	Bladder (%)					
<i>V</i> ₂₀	66.3	63.2	0.3	80.3	75.4	0.08
<i>V</i> ₃₀	55.9	53.7	0.5	72.0	66.7	0.07
<i>V</i> ₄₀	48.8	45.9	0.4	64.7	58.6	0.05
<i>V</i> ₅₀	42.6	40.5	0.5	58.1	51.8	0.04
<i>V</i> ₆₀	36.1	34.0	0.5	50.3	44.2	0.03
<i>V</i> ₇₀	25.2	22.9	0.4	36.4	31.0	0.04
<i>V</i> ₇₅	6.2	4.8	0.5	8.6	7.1	0.007

SNAD, short neoadjuvant androgen deprivation; LNAD, long neoadjuvant androgen deprivation; PL-CT, pre-treatment planning CT; PT-CT, post-treatment CT.

Table 5. Mean absolute change in the percentage of the rectal and bladder volumes (V) receiving different dose levels by hormonal treatment group

Volume/dose	Rectum (%) (95% CI)			Bladder (%) (95%CI)		
	SNAD	LNAD	p-value	SNAD	LNAD	p-value
V ₂₀	1.6 (−0.8–4.0)	2.0 (−1.2–5.3)	0.2	−5.0 (−12.2–2.1)	−4.1 (−12.5–4.2)	0.02
V ₃₀	2.6 (−1.7–7.0)	3.0 (−0.7–6.8)	0.3	−6.1 (−14.9–2.7)	−2.1 (−12.9–8.7)	<0.001
V ₄₀	4.0 (−2.5–10.5)	5.3 (−0.3–10.8)	0.1	−7.1 (−16.8–2.5)	−2.9 (−14.8–9.0)	<0.001
V ₅₀	5.2 (−1.5–14.9)	5.8 (0.8–12.9)	0.2	−8.3 (−18.5–1.9)	−1.4 (−13.8–9.1)	<0.001
V ₆₀	6.6 (−1.9–12.1)	7.6 (1.2–18.0)	0.09	−9.1 (−20.3–2.1)	−1.3 (−14.5–9.9)	<0.001
V ₇₀	4.7 (−2.5–15.9)	5.7 (0.7–17.9)	0.2	−7.4 (−23.9–9.0)	−0.4 (−16.8–5.9)	<0.001
V ₇₅	1.2 (−3.3–3.8)	1.3 (0.1–4.6)	0.7	−6.1 (−13.1–2.2)	−0.3 (−15.1–4.8)	<0.001

SNAD, short neoadjuvant androgen deprivation; LNAD, long neoadjuvant androgen deprivation; CI, confidence interval.

stage and prostate-specific antigen) and/or Gleason scores between the hormonally treated and untreated patients, which may have impacted the extent and the rate of prostate volume reduction during 3D-CRT [13, 18, 19]. Therefore, we believe that, as NAD cannot be

omitted from the current treatment of prostate carcinoma, a comparison of target shrinkage between patients treated with SNAD and LNAD might be more appropriate and clinically relevant. As all of our patients received NAD, based on the current recommendations but differing from the above study, we compared the

Figure 2. Mean rectal dose–volume histograms by hormonal treatment group: (a) short neoadjuvant hormone therapy (SNAD) and (b) long neoadjuvant hormone therapy (LNAD). PL-CT, pre-treatment planning CT; PT-CT, post-treatment CT.

Figure 3. Mean bladder dose–volume histograms by hormonal treatment group: (a) short neoadjuvant hormone therapy (SNAD) and (b) long neoadjuvant hormone therapy (LNAD). PL-CT, pre-treatment planning CT; PT-CT, post-treatment CT.

volumetric parameters of patients with SNAD and LNAD followed by 3D-CRT with concurrent AD.

Uncertainties in the delineation of the prostate gland and the surrounding tissues may cause changes in prostate volume. As CT has a limited accuracy in demonstrating prostate borders, intra-observer variability has been reported to be substantial [29, 30]. In order to minimise the uncertainties in contouring, one observer performed all of the contouring. In addition, we decided to blind the CT data, to eliminate obvious bias of knowing. We made a blind repetition of prostate contouring on randomly chosen CT scans in 10 sample patients, and found that median absolute and percentage variations in the prostate gland were 2.9 cm³ and 6.4%, respectively, which is close to findings reported in the literature [25, 30].

Whether the relative increase in the percentage of rectal volume receiving intermediate to high total doses carries a clinical value is not yet known. However, in a multi-institutional analysis, a strong correlation between rectal bleeding and rectal DVH parameters was demonstrated [31]. The correlation was stronger for intermediate (50–60 Gy) doses than for higher doses. Similarly, Jackson et al [32] reported that, although relatively small differences in the high-dose region (70–75 Gy) was evident, the largest difference in the DVH shape between bleeders and non-bleeders was in the 40–50 Gy region. In this current study, DVH changes were particularly prominent at the intermediate-dose region (V_{40} – V_{60}) rather than the high-dose region (V_{70}) for all groups. Although the relative change in rectal and bladder DVHs was constant for all dose levels, we found that patients receiving LNAD had a significant worsening of rectal DVH at intermediate- to high-dose levels (V_{50} – V_{70}) at PT-CT. However, the mean absolute changes in rectal volume receiving different dose levels (V_{20} – V_{75}) did not differ significantly between SNAD and LNAD groups (Table 5).

The position of the bladder and rectal wall relative to the prostate movement and prostate volume decrement will vary daily, depending on how well the patient follows preparation instructions. Van Herk et al [33] demonstrated that prostate motion is acceptable in all directions, except for anteroposterior translation (2.7 mm SD) and rotation around the left/right (L/R) axis (4.0°), in which plan matching was performed by using bony landmarks. In another study, Hoogeman et al [34] reported that the largest component of prostate motion was rotation around the L/R axis and that the average L/R axis rotation between the planning and repeat CT scans correlated significantly with the rectum volume in the PL-CT scan. In the current study, we treated patients with the same empty rectum and comfortably full bladder during each treatment in order to minimise the daily organ motion. In order to make two plans similar, we positioned the isocentre not only on skin markers but also according to bony landmarks at PT-CT planning. However, despite the rectal length being kept constant between PL-CT and PT-CT, *i.e.* from the anal verge to the rectosigmoid junction, rectal volume changes showed a variation around the mean because of differences in organ filling between CT sessions (Table 2). Rectal volume changes at PL-CT and PT-CT may have an effect on DVHs. Although there was a significant increase in

rectal dose at intermediate-dose levels for the whole study group and the LNAD group, we did not find a significant increase in rectal dose for the SNAD group. The rectal volume difference between PL-CT and PT-CT in the SNAD group was higher than that in the LNAD group (5.2% *vs* 4.1%), which may predict results of the DVH changes.

The prostate is closely located to the mid-rectum, whereas the seminal vesicles cover the anterior portion of the rectum. Because of this close anatomical relationship, rectal motion influences prostate motion, with rectal filling being known to directly affect prostate positioning [33, 35, 36]. Currently, most radiotherapy plans are based on a single PL-CT scan, and measures to ensure consistent rectal volume throughout treatment are not used. The recent development of cone-beam CT allows the on-treatment acquisition of 3D images with excellent bony and reasonable soft-tissue definition at acceptable radiation doses [37]. Information can therefore be acquired for treatment set-up verification, including organ positioning, such that the volume treated and the daily delivered dose may be calculated. Recently, Sripadam et al [36] demonstrated that CTV coverage was inadequate, at the prostate base only, in 38% of the fractions delivered to 4/7 patients with a large rectum at planning (>100 cm³) and in patients with a small rectum at planning (<50 cm³); up to 25% more rectal volume than predicted was included in the high-dose region. In this current study, in order to minimise geographic miss, we performed CT scans again if rectum volumes exceeded >100 cm³ before RT planning. Meanwhile, as mean rectal volume in the SNAD group was lower than in the LNAD group (60.1 cm³ *vs* 74.5 cm³), rectal doses were found to be higher in the SNAD group.

In the current study, a ~10–15% prostate volume reduction during 3D-CRT was demonstrated when RT planning was performed within 3 months of NAD. However, this reduction and daily organ motion may lead to an unpredictable increase in the percentage of rectal volume exposed to intermediate doses. We believe that, in the era of adaptive RT, at least a second treatment planning during the course of 3D-CRT may be beneficial for the prevention of unnecessary dose-limiting organ exposures; however, the exact timing of this needs to be addressed.

References

1. Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff RO, Storme G, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;337:295–300.
2. Pilepich MV, Caplan R, Byhardt RW, Lawton CA, Gallagher MJ, Mesic JB, et al. Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: report of Radiation Therapy Oncology Group Protocol 85-31. *J Clin Oncol* 1997;15:1013–21.
3. Bolla M, Collette L, Blank L, Warde P, Dubois JB, Mirimanoff RO, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet* 2002;360:103–6.

4. Roach M 3rd, DeSilvio M, Lawton C, Uhl V, Machtay M, Seider MJ, et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. *J Clin Oncol* 2003;21:1904–11.
5. Pilepich MV, Winter K, John MJ, Mesic JB, Sause W, Rubin P, et al. Phase III radiation therapy oncology group (RTOG) trial 86–10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2001;50:1243–52.
6. Akyol F, Selek U, Ozyigit G, Onal C, Akdogan B, Karabulut E, et al. Preliminary results of bicalutamide monotherapy on biochemical failure of localized prostate cancer. *J Natl Med Assoc* 2006;98:1058–61.
7. Ozyigit G, Akyol F, Onal C, Sari S, Gurdalli S, Yapici B. Combined hormonotherapy and definitive radiation therapy in localized prostate adenocarcinoma. *UHOD – International Journal of Haematology and Oncology* 2003;13:177–89.
8. Pilepich MV, Krall JM, al-Sarraf M, John MJ, Doggett RL, Sause WT, et al. Androgen deprivation with radiation therapy compared with radiation therapy alone for locally advanced prostatic carcinoma: a randomized comparative trial of the Radiation Therapy Oncology Group. *Urology* 1995;45:616–23.
9. Lawton CA, Winter K, Byhardt R, Sause WT, Hanks GE, Russell AH, et al. Androgen suppression plus radiation versus radiation alone for patients with D1 (pN+) adenocarcinoma of the prostate (results based on a national prospective randomized trial, RTOG 85–31). *Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys* 1997;38:931–9.
10. Lawton CA, Winter K, Murray K, Machtay M, Mesic JB, Hanks GE, et al. Updated results of the Phase III Radiation Therapy Oncology Group (RTOG) trial 85–31 evaluating the potential benefit of androgen suppression following standard radiation therapy for unfavorable prognosis carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2001;49:937–46.
11. Forman JD, Kumar R, Haas G, Montie J, Porter AT, Mesina CF. Neoadjuvant hormonal downsizing of localized carcinoma of the prostate: effects on the volume of normal tissue irradiation. *Cancer Invest* 1995;13:8–15.
12. Yang FE, Chen GT, Ray P, Vaida F, Chiru P, Hamilton RJ, et al. The potential for normal tissue dose reduction with neoadjuvant hormonal therapy in conformal treatment planning for stage C prostate cancer. *Int J Radiat Oncol Biol Phys* 1995;33:1009–17.
13. Padhani AR, MacVicar AD, Gapinski CJ, Dearnaley DP, Parker GJ, Suckling J, et al. Effects of androgen deprivation on prostatic morphology and vascular permeability evaluated with mr imaging. *Radiology* 2001;218:365–74.
14. Shearer RJ, Davies JH, Gelister JS, Dearnaley DP. Hormonal cytoreduction and radiotherapy for carcinoma of the prostate. *Br J Urol* 1992;69:521–4.
15. Zelefsky MJ, Leibel SA, Burman CM, Kutcher GJ, Harrison A, Happersett L, et al. Neoadjuvant hormonal therapy improves the therapeutic ratio in patients with bulky prostatic cancer treated with three-dimensional conformal radiation therapy. *Int J Radiat Oncol Biol Phys* 1994;29:755–61.
16. Gleave ME, Goldenberg SL, Chin JL, Warner J, Saad F, Klotz LH, et al. Randomized comparative study of 3 versus 8-month neoadjuvant hormonal therapy before radical prostatectomy: biochemical and pathological effects. *J Urol* 2001;166:500–6, discussion 506–7.
17. Kojima M, Ohe H, Watanabe H. Kinetic analysis of prostatic volume in patients with stage D prostatic cancer treated with LHRH analogues in relation to prognosis. *Br J Urol* 1995;75:492–7.
18. Lilleby W, Fossa SD, Knutsen BH, Abildgaard A, Skovlund E, Lien HH. Computed tomography/magnetic resonance based volume changes of the primary tumour in patients with prostate cancer with or without androgen deprivation. *Radiother Oncol* 2000;57:195–200.
19. Okihara K, Watanabe M, Saitoh M, Ohe H, Watanabe H. Kinetic analysis of focal hypoechoic lesion in the prostate treated by castration. *Prostate* 1994;24:252–6.
20. Greco C, Castiglioni S, Fodor A, Mazzetta C, De Cobelli O, Orecchia R. Androgen ablation therapy does not increase the risk of late morbidity following 3D-conformal radiotherapy of organ-confined prostate cancer: the experience of the European Institute of Oncology. *Tumori* 2004;90:567–72.
21. Zelefsky MJ, Harrison A. Neoadjuvant androgen ablation prior to radiotherapy for prostate cancer: reducing the potential morbidity of therapy. *Urology* 1997;49:38–45.
22. Mazonakis M, Damilakis J, Varveris H, Prassopoulos P, Gourtsoyannis N. Image segmentation in treatment planning for prostate cancer using the region growing technique. *Br J Radiol* 2001;74:243–8.
23. Pinkawa M, Asadpour B, Siluschek J, Gagel B, Piroth MD, Demirel C, et al. Bladder extension variability during pelvic external beam radiotherapy with a full or empty bladder. *Radiother Oncol* 2007;83:163–7.
24. Matzinger O, Poortmans P, Giraud JY, Maingon P, Budiharto T, van den Bergh AC, et al. Quality assurance in the 22991 EORTC ROG trial in localized prostate cancer: Dummy run and individual case review. *Radiother Oncol* 2009;90:285–90.
25. Sanguineti G, Marcenaro M, Franzone P, Foppiano F, Vitale V. Neoadjuvant androgen deprivation and prostate gland shrinkage during conformal radiotherapy. *Radiother Oncol* 2003;66:151–7.
26. Antolak JA, Rosen, II, Childress CH, Zagars GK, Pollack A. Prostate target volume variations during a course of radiotherapy. *Int J Radiat Oncol Biol Phys* 1998;42:661–72.
27. Roeske JC, Forman JD, Mesina CF, He T, Pelizzari CA, Fontenla E, et al. Evaluation of changes in the size and location of the prostate, seminal vesicles, bladder, and rectum during a course of external beam radiation therapy. *Int J Radiat Oncol Biol Phys* 1995;33:1321–9.
28. Zellars RC, Roberson PL, Strawderman M, Zhang D, Sandler HM, Ten Haken RK, et al. Prostate position late in the course of external beam therapy: patterns and predictors. *Int J Radiat Oncol Biol Phys* 2000;47:655–60.
29. Cazzaniga LF, Marinoni MA, Bossi A, Bianchi E, Cagna E, Cosentino D, et al. Interphysician variability in defining the planning target volume in the irradiation of prostate and seminal vesicles. *Radiother Oncol* 1998;47:293–6.
30. Fiorino C, Reni M, Bolognesi A, Cattaneo GM, Calandrino R. Intra- and inter-observer variability in contouring prostate and seminal vesicles: implications for conformal treatment planning. *Radiother Oncol* 1998;47:285–92.
31. Fiorino C, Dell'Oca I, Pierelli A, Broggi S, De Martin E, Di Muzio N, et al. Significant improvement in normal tissue sparing and target coverage for head and neck cancer by means of helical tomotherapy. *Radiother Oncol* 2006;78:276–82.
32. Jackson A, Skwarchuk MW, Zelefsky MJ, Cowen DM, Venkatraman ES, Levegrun S, et al. Late rectal bleeding after conformal radiotherapy of prostate cancer. II. Volume effects and dose-volume histograms. *Int J Radiat Oncol Biol Phys* 2001;49:685–98.
33. van Herk M, Bruce A, Kroes AP, Shouman T, Touw A, Lebesque JV. Quantification of organ motion during conformal radiotherapy of the prostate by three dimensional image registration. *Int J Radiat Oncol Biol Phys* 1995;33:1311–20.

34. Hoogeman MS, van Herk M, de Bois J, Lebesque JV. Strategies to reduce the systematic error due to tumor and rectum motion in radiotherapy of prostate cancer. *Radiother Oncol* 2005;74:177–85.
35. Mageras GS, Kutcher GJ, Leibel SA, Zelefsky MJ, Melian E, Mohan R, et al. A method of incorporating organ motion uncertainties into three-dimensional conformal treatment plans. *Int J Radiat Oncol Biol Phys* 1996;35:333–42.
36. Sripadam R, Stratford J, Henry AM, Jackson A, Moore CJ, Price P. Rectal motion can reduce CTV coverage and increase rectal dose during prostate radiotherapy: a daily cone-beam CT study. *Radiother Oncol* 2009;90:312–7.
37. McBain CA, Henry AM, Sykes J, Amer A, Marchant T, Moore CM, et al. X-ray volumetric imaging in image-guided radiotherapy: the new standard in on-treatment imaging. *Int J Radiat Oncol Biol Phys* 2006;64:625–34.