Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 1, pp. 75–82, 2008

0360-3016/08/$–see front matter

doi:10.1016/j.ijrobp.2007.05.046

ASTRO Online CME

CLINICAL INVESTIGATION Prostate

ADAPTIVE RADIOTHERAPY FOR PROSTATE CANCER USING KILOVOLTAGE CONE-BEAM COMPUTED TOMOGRAPHY: FIRST CLINICAL RESULTS

JASPER NIJKAMP, M.SC., FLORIS J. POS, M.D., PH.D., TONNIS T. NUVER, PH.D., RIANNE DE JONG, R.T.T., PETER REMEIJER, PH.D., JAN-JAKOB SONKE, PH.D., AND JOOS V. LEBESQUE, M.D., PH.D.

Department of Radiation Oncology, The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

Purpose: To evaluate the first clinical results of an off-line adaptive radiotherapy (ART) protocol for prostate cancer using kilovoltage cone-beam computed tomography (CBCT) in combination with a diet and mild laxatives.
Methods and Materials: Twenty-three patients began treatment with a planning target volume (PTV) margin of 10 mm. The CBCT scans acquired during the first six fractions were used to generate an average prostate clinical target volume (AV-CTV), and average rectum (AV-Rect). Using these structures, a new treatment plan was generated with a 7-mm PTV margin. Weekly CBCT scans were used to monitor the CTV coverage. A diet and mild laxatives were introduced to improve image quality and reduce prostate motion.
Results: Twenty patients were treated with conform ART protocol. For these patients, 91% of the CBCT scans could be used to calculate the AV-CTV and AV-Rect. In 96% of the follow-up CBCT scans, the CTV was located within the average PTV. In the remaining 4%, the prostate extended the PTV by a maximum of 1 mm. Systematic and random errors for organ motion were reduced by a factor of two compared with historical data without diet and laxatives. An average PTV reduction of 29% was achieved. The volume of the AV-Rect that received >65 Gy was reduced by 19%. The mean dose to the anal wall was reduced on average by 4.8 Gy.
Conclusions: We safely reduced the high-dose region by 29%. The reduction in irradiated volume led to a significant reduction in the dose to the rectum. The diet and laxatives improved the image quality and tended to reduce prostate motion.

Adaptive radiotherapy, Prostate cancer, Cone-beam computed tomography, Bowel regimen, Organ motion.

INTRODUCTION

In the past decade, significant advances have been made in radiotherapy (RT) for patients with prostate cancer. Recent randomized phase III dose escalation studies (1–4) have shown a significant improvement in outcome, thus setting a new standard. Together with the improvement in outcome, acute and late rectal and bladder toxicity has also increased (2, 4); however, intensity-modulated RT (IMRT) (5, 6) and image-guided RT (7–10) can be used to reduce toxicity.

The prostate and seminal vesicles (referred to as the prostate henceforth) are located between the rectum and the bladder. The position of the prostate is affected by physiologic changes in the bladder and rectum volume. These variations in position and shape can be left unchanged and compensated for with margins, or reduced by image guidance resulting in smaller irradiated volumes. Smaller margins reduce the dose to the organs at risk; therefore, effort has been directed at reducing uncertainties with the use of image guidance.

Recently, many studies have been reported on image guidance strategies to correct for prostate motion with daily off-line or on-line position verification of the prostate. Most of these reports used implanted fiducial markers in the prostate (7, 8). Although fiducial marker-based correction strategies are already an important step forward, they have some shortcomings. The implantation of markers is an invasive procedure. Marker-based strategies correct for translations but tend to neglect rotations, which are known to be a large component of prostate motion (11). Also, marker-based correction strategies do not take into account changes in position of the seminal vesicles or the effect of a changed anatomy on planning, especially relevant for IMRT. Linear accelerators equipped with kilovoltage (kV) cone-beam computed

Note—An online CME test for this article can be taken at http://asro.astro.org under Continuing Education.

Reprint requests to: Floris J. Pos, M.D., Ph.D., Department of Radiation Oncology, The Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, Amsterdam 1066 CX, The Netherlands. Tel: (+31) 20-512-1715; Fax: (+31) 20-669-1101; E-mail: f.pos@nki.nl

Conflict of interest: none.

Received March 22, 2007, and in revised form May 31, 2007. Accepted for publication May 31, 2007.

tomography (CBCT) allow for soft-tissue registration immediately before treatment (12). With CBCT scan-based correction strategies, one should be able to overcome the limitations of marker-based strategies. Smitsmans *et al.* (13) developed an automatic, rigid, three-dimensional (3D) gray-value registration (3D-GR) method for fast prostate localization on CT scans. In a following study, they showed that the 3D-GR prostate localization also worked with CBCT scans and concluded that CBCT scans could be used for image-guided RT for prostate cancer (14).

The imaging information acquired with CBCT scans can be used for either off-line or on-line correction strategies to reduce systematic and/or random errors. As reported in previous studies, the reduction of systematic errors is more important than the reduction of random errors (9, 10). Adaptive RT (ART) for prostate cancer is an off-line correction strategy first introduced by Yan *et al.* (15) and Martinez *et al.* (16). ART uses imaging information from the first treatment fractions to reoptimize the treatment plan and thereby deal with systematic errors caused by setup errors and organ motion. The strategy they described was used to increase the dose to the prostate while maintaining a consistent dose to the organs at risk. However, variations in rectum shape were not taken into account. Recent phase II trial publications (17, 18) have shown that the use of their adaptive protocol allows for dose escalation. Nuver *et al.* (19) and Hoogeman *et al.* (11) described a similar protocol, tested retrospectively on repeat CT data, in which changes in rectal volume and shape were included. In this protocol, the first four scans were used in combination with the planning CT scan to create an average prostate position and rectal shape. In addition to a reduction from 10 to 7 mm for the planning target volume (PTV) margin, the systematic error for the rectal wall position was reduced by 43%, on average. With the improved estimate of the rectal shape, a better prediction of rectal dose could also be obtained.

We have introduced an adaptive protocol, which is a combination of the adaptive protocol described by Nuver *et al.* (19), the 3D-GR prostate localization on CBCT scans (14), and a diet and mild laxatives. Introduction of this adaptive protocol was not part of a study. In this report, we have evaluated the separately developed and analyzed steps as a whole protocol. We have described the protocol, assessed the feasibility of CBCT scans, evaluated whether the reduced PTV margin is sufficient, and estimated the expected reduction in the dose to the rectum. The evaluation of the diet and laxatives will be reported separately by Smitsmans *et al.*

METHODS AND MATERIALS

Patient group

We enrolled 23 consecutive patients with locally advanced prostate cancer in the ART protocol within 1 year.

General outline of ART procedure

In the ART protocol, patients began with an initial IMRT prostate treatment plan with a 10-mm PTV margin. During the first six fractions of each patient, a CBCT scan was acquired within 1 minute before treatment, referred to as the first six CBCT scans henceforth. After the acquisition of the CBCT scans, the six prostate images of each patient were localized using the 3D-GR method (14), and the rectum was delineated on all six scans. A radiation oncologist assessed all prostate registrations and rectum delineations. Using these registrations and delineations, the average prostate clinical target volume position (AV-CTV), and average rectal wall shape and position (AV-Rect) were calculated. Using these average structures, an adapted treatment plan was then produced with a reduced PTV margin (7 mm). The remainder of the treatment was delivered with the adapted plan. Weekly setup correction CBCT scans (20) were also used for soft-tissue treatment monitoring. A more detailed description of the different components of the ART protocol is given in the following subsections.

Initial prostate treatment plan

According to our standard protocol, the patients were treated up to 78 Gy delivered in 39 fractions with a five-field IMRT technique, including a simultaneous integrated boost (5). In brief, two target volumes were defined: the target volume irradiated to 70 Gy (PTV1) and the boost volume irradiated to 78 Gy (PTV2). The CTV to PTV1 margin was 10 mm, and the CTV to PTV2 margin was 5 mm in all directions, except for 0 mm toward the rectum. Three RT groups were defined, depending on the risk of seminal vesicle involvement: $\leq$10%, 10–25%, and >25%. For treatment group 1, the seminal vesicles were not treated; for treatment group 2, the seminal vesicles were included in PTV1; and for treatment group 3, the seminal vesicles were also included in PTV2. Patient treatment was planned with Pinnacle, version 7.4 (Philips Medical Systems, Best, The Netherlands). During treatment, an off-line shrinking action level protocol (20) was used for bony anatomy setup correction based on kV CBCT scans. These CBCT scans were not used to monitor whether the target volume stayed within the PTV, because the 10-mm margin was expected to be large enough.

All patients received written instructions to empty their bladder and rectum and then drink 250 mL of fluid 1 h before acquisition of the planning CT scan and before each treatment fraction. Patients with a rectal volume >100 cm^3 on the planning CT scan were considered for rescanning (21).

Bowel preparation

The success of the 3D-GR prostate localization method is sensitive to moving gas pockets in the rectum during scan acquisition (14). Furthermore, Ghilezan *et al.* (22) showed that intrafraction prostate motion is larger for patients with a full rectum. Therefore, we decided to include bowel preparations in this protocol. It consisted of dietary advice, with the aim to regulate meals and avoid foods known to cause bowel gas. This diet was prescribed in combination with a daily mild laxative (1,000 mg magnesium oxide) to reduce intestinal gas and obtain a reproducible bowel volume during CT acquisition and treatment sessions. To facilitate regular meals and a reproducible amount of bowel filling, patients received a treatment schedule with approximately regular treatment times. The treatment sessions were scheduled for after 10:00 am, because it was expected that most people would have defecated in the morning. A detailed report on bowel preparations and the effects on CBCT image quality and interfraction motion was beyond the scope of this study and will be presented as a separate report.

Automatic prostate localization

For localization of the prostate on the CBCT scans, the CTV delineation of the planning CT scan was expanded by 5 mm to create a shaped region of interest. The standard procedure was a gray-value registration with six degrees of freedom and three different starting positions (to avoid local minima in the optimization) (14). In cases in which the automatic match failed, the alternative was to perform a manual match. A radiation oncologist visually approved the registrations. The success rate of the automatic method, in addition to the number of manual matches, was used to assess the feasibility of using CBCT for ART.

Construction of average structures

For the calculation of the AV-CTV, the average of the translations and rotations of the rigid prostate in the registrations with respect to the original planning CT scan, plus the planning CT scan itself (translation and rotation, 0), were calculated and applied to the original rigid prostate structure (19). Before this procedure, at least four of the registrations had to have been approved. Six CBCT scans, instead of the required four (19), were used in the adaptive protocol to account for failures in prostate registration and rectum delineation.

The outer rectal wall was delineated on all CBCT scans with approved registrations, and the radiation oncologist visually approved these structures. The average outer rectal wall was constructed from the CBCT structures and the original planning CT structure. For each slice, 50 equidistant dot points were placed on all delineations. The dots were numbered clockwise, starting at the dorsal side of the rectum. The coordinates of corresponding points were averaged, yielding 50 dots per slice and altogether delineating the average outer rectal wall. In this procedure, the shortest delineated rectum determined the craniocaudal (CC) length of the average outer rectal wall. The inner rectal wall was constructed from the outer rectal wall using the model proposed by Meijer *et al.* (23). This model was based on the assumption that the amount of wall tissue is constant for each orthogonal cross section throughout the entire rectum. Thus, the wall thickness on each slice is dependent on the circumference of the delineated outer wall. The total volume between the inner and outer rectal wall was called the AV-Rect.

Construction of adapted treatment plan

For each patient, a new five-field IMRT plan was produced using the original planning CT scan and the constructed AV-CTV and AV-Rect. The difference between the adapted plan and the initial plan was that, for the PTV1, a 7-mm margin was used instead of the 10-mm margin. The margin could be reduced because the systematic error in prostate position was reduced. The margin was kept at 7 mm to account for residual systematic setup errors, prostate position errors, and random errors (19).

CBCT soft-tissue treatment monitoring

The weekly CBCT scans acquired for off-line bony anatomy setup correction protocol were also used for CBCT soft-tissue treatment monitoring. These CBCT scans are referred to as follow-up CBCT scans henceforth. The AV-PTV structure was projected onto the nonregistered CBCT scans (*i.e.,* the scanned prostate position, including setup error and organ motion). A visual assessment could then be made as to whether the CTV was located inside the AV-PTV. If the CTV was positioned outside the AV-PTV more than once, the treating oncologist was required to decide whether to revert back to the original treatment plan with the 10-mm margin or continue with the adapted treatment plan.

ART procedure analysis

The ART procedure was analyzed in terms of the gray-value registration success rate. The benefit of the adapted treatment plan was also assessed in terms of late toxicity probability. Furthermore, the effect of the diet on the rectal volume during the treatment course was evaluated. The prostate motion and residual systematic prostate position errors were summarized. Finally, the reduced margin of 7 mm was investigated by evaluating the CTV position within the follow-up CBCT scans.

Late toxicity reduction

The aim of our adaptive protocol was treatment volume reduction and, as a consequence, a reduction in late toxicity. Peeters *et al.* (24) found a strong correlation between the rectal volume that received >65 Gy (V_{65}) and late rectal bleeding and between the mean dose (D_{mean}) to the anus (the lowest 3 cm of the rectum) and fecal incontinence. The V_{65} to the rectum and D_{mean} to the anus were compared within both treatment plans.

Rectal volumes

Several studies (21, 25) have shown a negative time trend in rectal volume during treatment of prostate cancer patients. For each patient, the average volume of the rectum plus filling during treatment was calculated. For every scan, the relative rectal volume was calculated by dividing the rectal volume on the scan by the patient-specific average volume. The relative rectal volumes were plotted against the treatment day. We also compared, for the complete patient group, the mean of the relative rectal volumes during the first six scans with the mean of the relative rectal volumes in the follow-up scans.

Prostate motion

The prostates in the follow-up CBCT scans were also localized with the 3D-GR method. The translation and rotations retrieved from the gray-value registrations are represented by the group mean (μ), systematic (Σ), and random (σ) errors of prostate position with respect to the bony anatomy for the set of the first six CBCT scans and the set of follow-up CBCT scans. These data were compared to evaluate whether the first six scans were representative of the remainder of the treatment. For the follow-up CBCT scans, μ, Σ, and σ were also calculated with respect to the average prostate position (*i.e.*, residual errors after application of the adaptive procedure).

Residual systematic prostate position errors

The aim of the ART procedure was to reduce the systematic errors to enable margin reduction. Because a finite number of measurements were used to determine the average prostate position, it was impossible to eliminate all systematic errors. On the basis of the random errors (σ), the number of scans used to calculate the average prostate position (f), and the total number of scans per patient (n), the expected residual systematic error for the remainder of the treatment (9, 26) could be estimated as follows:

$$\sum_{RESIDUAL} = \sqrt{\left(\frac{\sigma}{\sqrt{f}}\right)^2 + \left(\frac{\sigma}{\sqrt{n-f}}\right)^2} \qquad (1)$$

Statistical analysis

For statistical analysis of late toxicity reduction and rectal volume time trends, a one-tailed z test was used to determine the p values.

RESULTS

Patient group

Of the 23 patients included in the study, 20 were treated according to the ART protocol. For 2 patients, the ART

Table 1. Patient characteristics

Characteristic	Value
Age (y)	
Range	56–79
Mean	68
T stage (*n*)	
T1	1
T2	6
T3	12
T4	1
N stage (*n*)	
N0	17
N1	1
Nx	2
Gleason score (*n*)	
2–4	1
5–7	14
8–10	5
PSA (ng/mL)	
Range	3.4–20.0
Mean	10.0

Abbreviation: PSA = prostate-specific antigen.

procedure was aborted because of poor CBCT image quality caused by moving gas. A third patient received a urinary catheter during the course of treatment. The catheter caused a significant shift in prostate position, which could only be accounted for with a new planning CT and treatment planning. Of the 20 patients, 5 were classified in treatment group 1, 14 in group 2, and 1 in group 3. The relevant details of these patients are given in Table 1.

Gray-value registration success rate

For the 20 ART patients, 116 CBCT scans were available for 3D-GR to create the adapted plan. Four scans were missing because of technical problems. For every scan, the 3D-GR procedure was first applied. If the procedure failed, manual registration was used.

Of the 116 CBCT scans, 103 were successfully registered using the automatic procedure and 3 scans were registered with the manual procedure. In total, 91% of the registrations could be used for the calculation of an average prostate position.

During treatment with the adapted plan, 143 follow-up CBCT scans were made, 128 of these scans were registered successfully using the 3D-GR procedure (90%). In Fig. 1, a good quality and a bad quality, due to moving gas, CBCT scan are shown.

CBCT soft-tissue treatment monitoring

In 137 (96%) of the 143 follow-up CBCT scans, the CTV was visually assessed as within the AV-PTV. For the 6 remaining CBCT scans, marginal misses occurred with a maximal estimated distance between CTV border and AV-PTV border of 1 mm. These maximal distances occurred in the scans of 5 different patients. The misses could be divided into two groups. Three misses were mainly caused by bony anatomy setup in which the setup error distance was greater than the 7-mm PTV margin. The remaining three misses were caused by organ motion. Two misses occurred in 1 patient, in whom a lymphocele was present in the surrounding tissue of the prostate and disappeared during the treatment course. The third organ motion miss was located at one of the seminal vesicles and was caused by large rectal filling.

Estimated late toxicity reduction

As expected, for all patients, the V_{65} was reduced. On average, the reduction was 19% (range, 4–37%; $p < 0.001$). For all but 1 patient, the D_{mean} to the anal wall was reduced. On average, the reduction was 4.8 Gy (range, −2.0 to 9.7; $p < 0.001$).

Workload

Compared with non-ART treatment within our hospital, the ART procedure took an additional 7 h (SD, 0.5) approximately per patient. Major contributors were delineation of the rectum (2 h) and repeat planning and paper work (4 h). The gray-value registration and follow-up both took approximately 30 min.

Bowel preparation and rectal volumes during treatment course

None of the patients underwent repeat scanning for the initial treatment planning. We evaluated the rectal volume during treatment (Fig. 2). No significant time trend was found

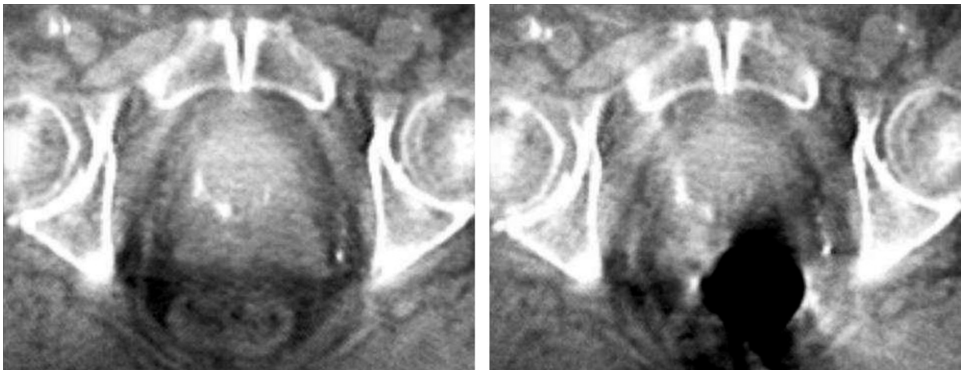

Fig. 1. (Left) Cone-beam computed tomography scan registered using automatic procedure. (Right) Cone-beam computed tomography scan that could not be used for adaptive radiotherapy procedure because of moving gas.

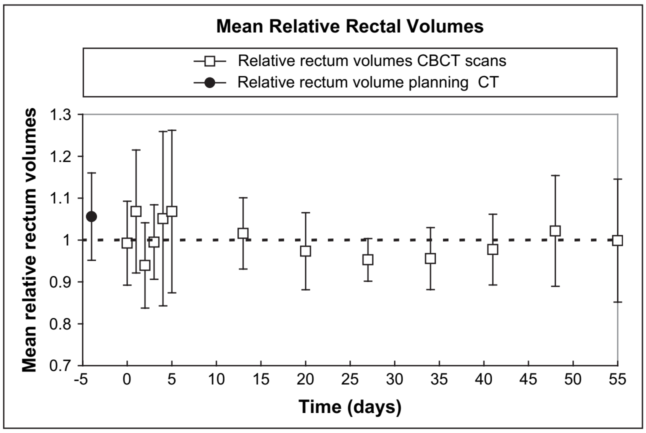

Fig. 2. Relative rectal volume as function of treatment day. Rectal volumes (wall including filling) were normalized to average rectal volume of patient during treatment. Error bars denote 95% confidence interval of relative rectal volume. Dot represents mean relative rectal volume of initial planning computed tomography scans. Squares indicate mean relative rectal volume of cone-beam computed tomography scans. First 6 days shown in separate squares; for follow-up scans, relative rectal volumes were averaged weekly.

during the treatment course. To compare the rectal volumes that were used to create the adapted plan with the rectal volumes during treatment with the adapted plan, we calculated the relative volume for both sets of delineations per patient. The mean relative rectal volume of the planning CT plus the first six CBCT scans was, on average, 4.8% larger than the mean relative rectal volume in the follow-up CBCT scans, but was not a significant difference ($p = 0.09$).

Prostate motion

Table 2 provides the statistical results of the prostate motion for the first six and the follow-up CBCT scans. The definition of the directions is shown in Table 3. Systematic errors, especially in rotations around the left–right (LR) axis, were small compared with the historical data (11). No large differences were found between the results of the first six CBCT scans and the follow-up scans. For the statistical analysis, we excluded the patient with a lymphocele, because the lymphocele was drained during the treatment course and the organ motion of this patient was atypical for our patient group. For the follow-up CBCT scans, we also performed statistical analysis for the residual errors of the organ motion after the correction (Table 4). Although systematic errors were reduced for all rotations and translations, they were still large for rotations around the LR axis and translations in the CC and anteroposterior (AP) directions.

In Table 5, the expected residual systematic errors are given. For the calculation (Eq. 1) we used f = 5.3, the mean number of scans to create the average, n = 11.7, the mean total number of scans per patient, and the random errors of all CBCT scans (a combination of the first six and follow-up data of Table 2).

Table 2. Prostate position results relative to bony anatomy

	First six CBCT scans			Follow-up CBCT scans		
	LR	CC	AP	LR	CC	AP
Rotation (°)						
μ	−1.1	−0.2	−0.2	−1.6	−0.1	−0.2
Σ	2.7	1.2	0.7	2.9	1.0	0.9
σ	2.6	1.0	0.8	3.0	1.1	1.0
Translation (mm)						
μ	−0.3	−0.6	−0.3	−0.4	−0.3	0.7
Σ	0.6	1.3	1.3	0.5	1.7	1.8
σ	0.9	1.4	1.8	0.5	1.5	1.9

Abbreviations: CBCT = cone-beam computed tomography; LR = left–right; CC = craniocaudal; AP = anteroposterior; μ = group mean error; σ = random error (1 standard deviation); Σ = systematic error (1 standard deviation).

Rotations determined with center of prostate mass as rotation point.

Table 3. Translation and rotation direction definitions

Rotation (R)	R_{LR} (from right)	R_{CC} (from cranial)	R_{AP} (from posterior)
Translation (T)	T_{LR} (to left)	T_{CC} (to cranial)	T_{AP} (to anterior)

For rotation, we listed from which direction along the rotational axis a positive rotation corresponded to clockwise rotation. A negative LR axis rotation, for example, means that the top of the prostate rotated to the posterior during treatment. For the translations, we listed the direction of a positive translation. A negative AP translation, for example, means that the prostate moved to the posterior during treatment.

DISCUSSION

In this report, we have described the first results of an offline ART protocol for prostate cancer using kV CBCT scans. Of the 23 patients, 20 (87%) were successfully treated according to the protocol. For 1 patient, treatment with the adapted plan had to be aborted. The introduction of a urinary catheter half way during treatment caused a systematic shift in prostate position. It is important to stress that with the initial treatment plan, using a margin of 1 cm, the treatment would also have been inadequate for this patient. For the other 2 patients, the CBCT image quality was poor because of moving gas, despite the bowel preparation measures. Hopefully, technical developments can further increase CBCT image quality to eliminate this problem. These 3 excluded patients were not

Table 4. Residual prostate position results of follow-up scans relative to average prostate position after six CBCT scans

	LR	CC	AP
Rotation (°)			
μ	−0.6	0.2	0.0
Σ	2.4	0.7	0.7
σ	3.2	1.2	1.1
Translation (mm)			
μ	−0.1	0.3	0.9
Σ	0.5	1.5	1.5
σ	0.5	1.5	1.9

Abbreviations as in Table 2.

Rotations determined with center of prostate mass as rotation point.

Table 5. Expected residual systematic errors

	LR	CC	AP
Rotation (°)			
Σ-expected	1.7	0.6	0.5
Difference with measured	1.7	0.3	0.4
Translation (mm)			
Σ-expected	0.4	0.9	1.2
Difference with measured	0.1	1.2	0.9

Abbreviations: Σ-expected = expected systematic error (1 standard deviation) in prostate position after correction according to first six CBCT scans; other abbreviations as in Table 2.

For the difference, quadratic difference between measured (see Table 4) and expected residual systematic errors were calculated.

analyzed, because they were not treated with an adapted treatment plan. Excluding these patients could have introduced a bias for the measured prostate motion; however, our aim was to describe and analyze the data from the patients with an adapted treatment plan. Nevertheless, we have shown that with the currently available CBCT scans, the image quality is adequate for the routine use of off-line soft-tissue image guidance for the great majority of patients.

Utility of CBCT scans

The utility of CBCT scans depends on image quality. The image quality is important for 3D-GR of the prostate and delineation of the rectum. All hardware and software we used to gather and reconstruct the CBCT scans is commercially available and can be reproduced by other centers.

Gray-value registration

The total success rate of 89% for the 3D-GR is slightly better than the results (83%) published by Smitsmans *et al.* (14). Although this seems reasonable, still approximately 10% of scans were ignored because no registration was possible. Poor image quality, caused by moving gas pockets or large rectal filling, was the main reason for the failure in registration. It is reasonable to assume that these were the scans that encompassed a large difference in prostate position with respect to the planning CT scan. Ignoring these poor image quality CBCT scans could lead to an underestimation of the prostate motion. For three scans, manual registration was used to localize the prostate. We have no data on the accuracy or reproducibility of this manual procedure, but the radiation oncologist also had to visually approve these matches.

Delineation of rectum

The potential advantages of CBCT image guidance (or other methods of soft-tissue image guidance) over marker-based correction strategies have been summarized in the ''Introduction.'' An additional major advantage would be the effect of a changed anatomy on IMRT planning. The present study is, to the best of our knowledge, the first to incorporate changes in rectal shape and position in image-guided RT for prostate cancer. We have demonstrated the feasibility of soft-tissue image guidance with CBCT; however, it has not been shown that it is superior to techniques with fiducial markers. On average, it took 2 h to delineate the rectum on the six CBCT scans. Nuver *et al.* (19) investigated several options that could be less time consuming, such as translating and rotating the rectum according to the average translation and rotation of the prostate, to evaluate whether it was possible to omit the delineation step. They concluded that, although it is time consuming, it is better to use an average rectal structure to optimize the adapted treatment plan when using a 3D conformal plan. To evaluate whether this conclusion is valid for this patient group in combination with IMRT, it would be necessary to perform a dedicated planning study. Such a study would investigate the influence of different rectal structures on the optimization of IMRT plans.

Initial plan vs. adapted plan

In the evaluation of the initial treatment plan and the adapted plan, the doses to the respective AV-PTV and the AV-Rect structure were compared. The dose to the average structures was compared because the average structures provide the best available estimate of the prostate position and the best available representation of the rectum shape and position during treatment.

Prostate (AV-PTV). The AV-PTV was 29% smaller than the initial PTV. In the comparison of the D_{mean} to the AV-PTV within the initial plan and the adapted plan, no significant difference was found, indicating that the 10-mm PTV margin in the initial plan was adequate.

Rectum (AV-Rect). A reduction of 19% for the V_{65} was found. Using the V_{65}, the probability of late rectal bleeding can be estimated using the model proposed by Peeters *et al.* (24). On average, the probability of late rectal bleeding was reduced by 19% (range, 3–45%; $p < 0.001$).

The D_{mean} to the anal wall decreased by 4.8 Gy. For 1 patient, the D_{mean} increased because the AV-CTV was located 4 mm caudal of the CTV on the planning CT. Using the D_{mean}, the probability for fecal incontinence was, on average, reduced by 16% (range, −8% to 31%; $p < 0.001$).

Note, that Peeters *et al.* based their models on the dose to the rectum on the planning CT. Although this might influence the estimation of the probability of late rectal toxicity, the reduction in the dose to the rectum and anus will always cause a reduction in toxicity.

Evaluation of ART protocol

For the development of the current ART protocol, Hoogeman *et al.* (11, 21) and Nuver *et al.* (19) used a data set of 19 patients with an average of 11 repeat CT scans per patient. On the basis of this data set, the adaptive treatment protocol was designed to use at least four scans and a CTV-to-PTV margin, after correction, of 7 mm. During the treatment of these patients, no bowel preparation was used.

Relative rectal volumes

Several studies have shown a negative time trend in rectal volume during RT, leading to a systematic error in prostate position (21, 24, 29). No time trends were found within our

Table 6. Errors in prostate position

Error	Hoogeman *et al.* (9)	Present study
Systematic		
T_{LR}	0.3	0.5
T_{CC}	2.1	1.4
T_{AP}	2.7	1.4
R_{LR}	5.1	2.6
R_{CC}	2.2	1.0
R_{AP}	1.3	0.7
Random		
T_{LR}	0.4	0.7
T_{CC}	2.1	1.5
T_{AP}	2.4	2.0
R_{LR}	3.6	2.9
R_{CC}	2.0	1.1
R_{AP}	1.6	0.9

Abbreviations as in Tables 2 and 3.

Systematic and random errors for repeat computed tomography study of Hoogeman *et al.* (9) shown next to errors of present study.

patient group (Fig. 2). It can be assumed that the introduction of the diet combined with the mild laxative helped to eliminate the time trend. Future research is needed to investigate this further.

Prostate motion

Several studies have shown a correlation between displacements of the rectal wall and displacements in prostate position (21, 27, 28). Because of the effect of the diet and laxatives on rectal volume, prostate movement was also influenced. Comparing the systematic and random prostate motion errors of Hoogeman *et al.* (11) and in our study, the errors were up to two times smaller in the present study (Table 6). Hoogeman *et al.* (11) used contour-based registration to determine organ motion. Smitsmans *et al.* (13) compared contour-based registration and 3D-GR. Compared with contour-based registration, they found a gray-value registration accuracy of 2.4°, 1.6°, and 1.3° (1 SD) for rotation and 0.7, 1.3, and 1.2 mm for translation in the LR, CC, and AP directions, respectively. Although the registration accuracy needs to be taken into account, these results still suggest that the diet combined with a mild laxative reduced organ motion.

The differences between the expected and measured systematic errors (Table 5) were within 0.5° and 0.5 mm for the rotations around the CC and AP axes and the translation in the LR direction, respectively. For the other directions, the first six CBCT scans were not representative of the entire treatment course. Although no significant time trend was found for the rectal volume within our patient group, the small trend was close to significance and could still have influenced the difference in the expected and measured systematic error. Hoogeman *et al.* (11) also presented their results for the expected and measured residual systematic errors. In their data set, the difference between the measured and expected systematic errors in rotation around the LR, CC, and AP axes was 1.9°, 0.7°, and 1.1° and for translation in the LR, CC, and AP direction was 0.4, 0.9, and 1.0 mm, respectively. These results are comparable to ours. For calculation of the residual systematic errors with Eq. 1, these differences should be taken into account.

ART treatment margin

This study has shown that the systematic and random prostate position errors were considerably smaller with respect to the repeat CT data (Table 6). The prostate motion might have been slightly underestimated, because approximately 10% of the CBCT scans were ignored. Nevertheless, the ART procedure as described was safe according to the imaging data. For the vast majority of follow-up scans, the CTV coverage was 100%, and only a few marginal misses occurred. We found a marginal miss in only 6 (4%) of 143 follow-up scans, and the maximal distance for the CTV border outside the AV-PTV was about 1 mm. Note, because of penumbra effects and nonperfect conformality, a considerable dose was still given outside the PTV. This suggests that the margin of 7 mm that was used after the off-line correction was probably still large and could be reduced even further. Nevertheless, before we can reduce the margins further, the success rate of 3D-GR for CBCT scans must be increased. One method to achieve this could be to combine 3D-GR on CBCT scans with the insertion of a small fiducial marker to use for registration of the 10% that cannot be registered with 3D-GR alone. Combined with technical improvements of the CBCT scanners, an almost 100% success rate should be achievable.

Future steps

With the use of an on-line adaptive protocol, the PTV margin might be reduced further to 5 mm. Instead of reducing the margin further, it might also be possible to change to a less time-consuming protocol. Delineation of the rectum and the planning and paperwork of the adapted plan were the major contributors to the 7 h of required extra time. Using imaging information to adapt an original treatment plan, with a 7-mm margin, by shifting the isocenter and changing the collimator angles could shorten the planning time. Additional investigation is currently underway to explore these possibilities.

CONCLUSIONS

With the introduction of our ART protocol, we were able to reduce the irradiated treatment volumes by 29%. In our patient group, the 7-mm PTV margin used in the adapted plan was considered more than adequate, as determined by the imaging data. With the reduction in irradiated volume, the probability for late rectal bleeding and fecal incontinence was significantly reduced by 19% and 16%, respectively. The absence of a time trend in rectal volume and the reduction of systematic and random errors on prostate position indicate that the combination of a diet, mild laxatives, and a fixed treatment time is a relative simple measure to improve prostate treatment. This is also valid for institutions that lack the ability of in-room imaging systems such as CBCT. To our knowledge, this clinical protocol is the first to use kV CBCT soft-tissue information to improve RT for prostate cancer.

REFERENCES

1. Zelefsky MJ, Leibel SA, Gaudin PB, *et al*. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. *Int J Radiat Oncol Biol Phys* 1998; 41:491–500.
2. Pollack A, Zagars GK, Starkschall G, *et al*. Prostate cancer radiation dose response: Results from the M.D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;53: 1097–1105.
3. Peeters STH, Heemsbergen WD, Koper PCM, *et al*. Dose-response in radiotherapy for localized prostate cancer: Results of the Dutch multicenter randomized phase III trial comparing 68 Gy with 78 Gy. *J Clin Oncol* 2006;24:1990–1996.
4. Peeters STH, Heemsbergen WD, van Putten WLJ, *et al*. Acute and late complications after radiotherapy for prostate cancer: Results of a multicenter randomized trial comparing 68 Gy to 78 Gy. *Int J Radiat Oncol Biol Phys* 2005;61:1019–1034.
5. Bos LJ, Damen EM, de Boer RW, *et al*. Reduction of rectal dose by integration of the boost in the large-field treatment plan for prostate irradiation. *Int J Radiat Oncol Biol Phys* 2002;52: 254–265.
6. Zelefsky MH, Fuks Z, Hunt M, *et al*. High-dose intensity modulated radiation therapy for prostate cancer: Early toxicity and biochemical outcome in 772 patients. *Int J Radiat Oncol Biol Phys* 2002;53:1111–1116.
7. van den Heuvel F, Fugazzi J, Seppi E, *et al*. Clinical application of a repositioning scheme, using gold markers and electronic portal imaging. *Radiother Oncol* 2006;79:94–100.
8. Litzenberg DW, Balter JM, Hadley SW, *et al*. Influence of intrafraction motion on margins for prostate radiotherapy. *Int J Radiat Oncol Biol Phys* 2006;65:548–553.
9. Litzenberg DW, Balter JM, Lam KL, *et al*. Retrospective analysis of prostate cancer patients with implanted gold markers using off-line and adaptive therapy protocols. *Int J Radiat Oncol Biol Phys* 2005;63:123–133.
10. Ghilezan M, Yan D, Liang J, *et al*. Online image-guided intensity-modulated radiotherapy for prostate cancer: How much improvement can we expect? *Int J Radiat Oncol Biol Phys* 2004;60:1602–1610.
11. Hoogeman MS, van Herk M, de Bois J, *et al*. Strategies to reduce the systematic error due to tumor and rectum motion in radiotherapy of prostate cancer. *Radiother Oncol* 2005;74: 177–185.
12. Jaffray DA, Siewerdsen JH. Cone-beam computed tomography with flat-panel imager: Initial performance characterization. *Med Phys* 2000;27:1311–1323.
13. Smitsmans MHP, Wolthaus JWH, Artignan X, *et al*. Automatic localization of the prostate for on-line or off-line image-guided radiotherapy. *Int J Radiat Oncol Biol Phys* 2004;60:623–635.
14. Smitsmans MHP, De Bois J, Sonke JJ, *et al*. Automatic prostate localization on cone-beam CT scans for high precision image-guided radiotherapy. *Int J Radiat Oncol Biol Phys* 2005;63: 975–984.
15. Yan D, Lockman D, Brabbins D, *et al*. An off-line strategy for constructing a patient-specific planning target volume in adaptive treatment process for prostate cancer. *Int J Radiat Oncol Biol Phys* 2000;48:289–302.
16. Martinez AA, Yan D, Lockman D, *et al*. Improvement in dose escalation using the process of adaptive radiotherapy combined with three-dimensional conformal or intensity-modulated beams for prostate cancer. *Int J Radiat Oncol Biol Phys* 2001; 50:1226–1234.
17. Brabbins D, Martinez A, Yan D, *et al*. A dose-escalation trial with the adaptive radiotherapy process as a delivery system in localized prostate cancer: analysis of chronic toxicity. *Int J Radiat Oncol Biol Phys* 2005;61:400–408.
18. Vargas C, Yan D, Kerstin L, *et al*. Phase II dose escalation study of image-guided adaptive radiotherapy for prostate cancer: Use of dose-volume constraints to achieve rectal isotoxicity. *Int J Radiat Oncol Biol Phys* 2005;63:141–149.
19. Nuver TT, Hoogeman MS, Remeijer P, *et al*. An adaptive off-line procedure for radiotherapy of prostate cancer. *Int J Radiat Oncol Biol Phys* 2007;67:1559–1567.
20. Bel A, van Herk M, Bartelink H, *et al*. A verification procedure to improve patient set-up using an off-line correction protocol based on a shrinking action level. *Radiother Oncol* 1993;29: 253–260.
21. Hoogeman MS, van Herk M, de Bois J, *et al*. Quantification of local rectal wall displacements by virtual rectum unfolding. *Radiother Oncol* 2004;70:21–30.
22. Ghilezan M, Jaffray D, Siewerdsen J, *et al*. Prostate gland motion assessed with cine-magnetic resonance imaging (cine-MRI). *Int J Radiat Oncol Biol Phys* 2005;62:406–417.
23. Meijer GJ, van den Brink M, Hoogeman MS, *et al*. Dosewall histograms and normalized dose-surface histograms for the rectum: A new method to analyze the dose distribution over the rectum in conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 1999;45:1073–1080.
24. Peeters STH, Lebesque JV, Heemsbergen WD, *et al*. Localized volume effects for late rectal and anal toxicity after radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2006;64: 1151–1161.
25. Lebesque JV, Bruce AM, Kroes AP, *et al*. Variation in volumes, dose–volume histograms, and estimated normal tissue complication probabilities of rectum and bladder during conformal radiotherapy of T3 cancer. *Int J Radiat Oncol Biol Phys* 1995;33: 1109–1119.
26. Bortfeld T, van Herk M, Jiang SB. When should systematic patient positioning errors in radiotherapy be corrected. *Phys Med Biol* 2002;47:N297–N302.
27. Padhani AR, Khoo VS, Suckling J, *et al*. Evaluating the effect of rectal distension and rectal movement on prostate gland position using cine MRI. *Int J Radiat Oncol Biol Phys* 1999;44: 525–533.
28. van Herk M, Bruce A, Kroes AP, *et al*. Quantification of organ motion during conformal radiotherapy of the prostate by three dimensional image registration. *Int J Radiat Oncol Biol Phys* 1995;33:1311–1320.
29. Pinkawa M, Siluschek J, Gagel B, *et al*. Influence of the initial rectal distension on posterior margins in primary and postoperative radiotherapy for prostate cancer. *Radiother Oncol* 2006; 81:284–290.