What benefit could be derived from on-line adaptive prostate radiotherapy using rectal diameter as a predictor of motion?

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ABSTRACT

This study investigated a relationship between rectum diameter and prostate motion during treatment with a view to reducing planning target volume (PTV) margins for an adaptive protocol. One hundred and ninety-four cone-beam computed tomography (CBCT) images of 10 patients were used to relate rectum diameter on CBCT to prostate intrafraction displacement. A threshold rectum diameter was used to model the impact of an adaptive PTV margin on rectum and bladder dose. Potential dose escalation with a 6 mm uniform margin adaptive protocol was compared to a PTV margin of 10 mm expansion of the clinical target volume (CTV) except 6 mm posterior. Of 194 fractions, 104 had a maximum rectal diameter of ≤3.5 cm. The prostate displaced ≤4 mm in 102 of those fractions. Changing from a standard to an adaptive PTV margin reduced the volume of rectum receiving 25, 50, 60, and 70 Gy by around 12, 9, 10, and 16%, respectively and bladder by approximately 21, 27, 29, and 35%, respectively. An average dose escalation of 4.2 Gy may be possible with an adaptive prostate radiotherapy protocol. In conclusion, a relationship between the prostate motion and the diameter of the rectum on CBCT potentially could enable daily adaptive radiotherapy which can be implemented from the first fraction.

Key words: Cancer; image-guided; prostate; radiotherapy; rectum

Introduction

Increasing the dose delivered to the prostate improves treatment outcomes for prostate cancer radiotherapy.$^{[1]}$. To enable dose escalation to the prostate without increasing treatment toxicity requires reducing the planning target volume (PTV) margins which allow for prostate movement within the pelvis. A major cause of intrafraction prostate motion is due to changes in the rectal volume which lies adjacent to the prostate.$^{[2,3]}$. It has been demonstrated in cine-magnetic resonance imaging (Cine-MRI) studies that patients who present for treatment with a large rectum correlates with increased prostate motion during a treatment fraction.$^{[2]}$. Therefore, there is the potential to modify the PTV margin based on the rectum presentation at each daily treatment.

Many current PTV margins applied during prostate radiotherapy are based on historical practice or historical interfraction margin formula.$^{[4]}$. These data take into account random treatment errors for all treatment fractions, many of which will not be present at each fraction. This is supported by our previous work which demonstrated intrafraction motion of greater than 5 mm in only 4.7% of fractions.$^{[5]}$. That data showed that intrafraction motion was correlated with treatment fraction duration, although modifying margins based on fraction duration is difficult as it often varies from day-to-day.$^{[5]}$. Kupelian et al.$^{[6]}$ monitored prostate motion during radiotherapy using the Calypso implanted electromagnetic transponder system and reported that 59% of fractions display less than 3 mm of motion for more than...
a 30 s interval. However, the more conservative estimate by Langen et al.,[7] report 34% (188 of 550) of all fractions demonstrated less than 3 mm of prostate motion, and therefore a reduced margin could be potentially applied on these fractions. We hypothesize that patients who present with an empty rectum will be at much lower risk of intrafraction prostate motion compared to patients who present with a full rectum as supported by the cine-MRI data.[2,8] This relationship may form the basis of a daily adaptive treatment protocol where a smaller PTV margin is used when the prostate is at a lower risk of motion.

The primary aim for this study was to investigate a method for describing a relationship between prostate motion and rectum diameter by measuring the diameter of the rectum on cone-beam computed tomography (CBCT). The second aim was to model the dose to the organs at risk (OAR; rectum and bladder) for an adaptive margin compared to the dose received using standard technique. The third aim was to investigate the potential for dose escalation with adaptive margin reduction.

**Materials and Methods**

**Participant selection**

The study was approved by our institutional human research ethics committee. We used a pragmatic sample of 10 consecutive patient datasets from patients who had received radical prostate radiotherapy between 2nd February 2010 and 31st December 2010 and had CBCT imaging. The patients received three-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiotherapy (IMRT) to a dose of 78 Gy. Image guidance for patient positioning was done matching to fiducial markers with kV/kV imaging prior to treatment. A CBCT image was acquired post-treatment fractions 1–5 and every second fraction. All patients were contoured by a single observer to eliminate interobserver variation.

**Data acquisition**

Pretreatment kV/kV images and posttreatment CBCT datasets were available for 194 fractions in total. Intrafraction displacement was measured using the displacement of fiducial markers on the posttreatment CBCT relative to position of fiducials at the start of each fraction after online correction to gold fiducial markers. The fraction time was taken as the time stamp from the first kV image to the time stamp on the posttreatment CBCT.

The maximum true rectal diameter was measured on the coronal and sagittal sliced planes for the entire length of the prostate, and within 1.2 cm (4 × 3 mm slices) superior and inferior to the prostate on all CBCTs. The maximum true rectal diameter was determined to be the largest diameter measured on the coronal and sagittal planes with the diameter measured from the outer rectal walls perpendicular to the path of the rectum. Measuring in this way avoids overestimating the rectal diameter which is likely when it is measured only in the axial plane [Figure 1].

The maximum rectal diameter and prostate displacement were plotted for each CBCT acquired [Figure 2]. The authors used this data to select a rectal diameter which was associated with reduced intrafraction motion; this was subsequently used in planning for modeling an adaptive technique.

**Planning technique**

For study purposes the clinical target volume (CTV) was the prostate gland without seminal vesicles. The bladder was contoured as the external bladder wall to include the whole bladder. The rectum was contoured as the external rectal wall for the length of the PTV including an added length of 1.2 cm superior and 1.2 cm inferior to the PTV. The standard PTV margin was a 10 mm expansion of the CTV in all directions except 6 mm in the posterior direction. This is the standard margin used clinically in our department and a common margin which has been employed in large dose escalation trials.[9] The adaptive PTV margin was a 6 mm expansion in all directions, which allowed for 4 mm translocations of the prostate and a further 2 mm for prostate rotation/deformation. This margin has been demonstrated to safely allow for intrafraction rotations and deformations,[10] and has been demonstrated to have increased freedom from biochemical failure.[11]

Four plans per patient were created for the study: A standard margin 78 Gy plan (StanPlan78Gy), a 6 mm margin 78 Gy plan (6mmPlan78Gy), a total adaptive dose escalation plan (AdapPlanDoseEsc), and an adaptive margin 78 Gy plan (AdapPlan78Gy). All plans were 3DCRT plans with five fields comprised of two lateral fields, two anterior oblique fields, and an anterior field. Minimum planning
dose constraints were to be achieved for each plan. The PTV was to receive ≥ 74.1 Gy to 99% of the volume. The rectal dose volume histogram (DVH) constraints were V50, V60, and V70 Gv less than 50, 30, and 20%, respectively. The femoral head DVH constraints were V35, V45, and V60 Gv less than 100, 60, and 30%, respectively. Lastly, the bladder DVH constraint was V50 Gv < 50%.

The StanPlan78Gy was created to a dose of 78 Gy in 39 fractions using the study PTV (expansion of CTV which excluded seminal vesicles) and the standard planning contours. This plan was created to estimate the dose received by OAR using a standard margin alone. The 6mmPlan78Gy was also created using standard planning contours and a 6 mm CTV to PTV margin, which would simulate the dose to OAR if a 6 mm margin was used. These plans were used to calculate the volume of bladder and rectum receiving doses of 70, 60, 50, and 25 Gy. The dose data was used to calculate the reduction in dose to the rectum and bladder using a 6 mm PTV margin when compared to a standard margin.

The AdapPlanDoseEsc was created based on the proportion of fractions where an adaptive margin and standard margins could be used for dose escalated radiotherapy [Table 1]. The AdapPlanDoseEsc plan was dose escalated by 2 Gy fractions until the rectal V60 was nearest to the rectal V60 achieved in the StanPlan78Gy to estimate the dose escalation possible with an adaptive plan while maintaining the same toxicity profile. The contours used for AdapPlanDoseEsc were the planning rectum and bladder, and an adaptive 6 mm PTV and standard PTV expansion from the planning CTV.

To check the validity of dose reduction to the OAR, the first CBCT for each patient was selected for planning where the maximum rectal diameter was less than the threshold set by the authors. The CBCT was fused as per the pretreatment alignment to gold fiducial markers. The dosimetry was performed on the planning CT scan using CTV, 6 mm PTV, rectum and bladder contours from the posttreatment CBCT. The StanPlan78Gy was used as the starting point for the AdapPlan78Gy which generally required only modification of the port size and weightings. The AdapPlan78Gy was used to calculate the volume of bladder and rectum which would receive doses of 70, 60, 50, and 25 Gy during a treatment fraction, this was compared to the doses calculated from the StanPlan78Gy.

Descriptive statistics were used to report all data. The mean ± one standard deviation (SD) was used to report the fraction time, OAR dose volume reductions, and dose escalation.

Results

Of 194 fractions, 104 had a true maximum rectal diameter of 3.5 cm or less [Figure 2]. The prostate displaced 4 mm or less in 102 of those fractions. This indicates that potentially the rectum diameter may be a predictor of prostate displacement during a radiotherapy fraction and the authors therefore used a ≤ 3.5 cm rectum diameter threshold to determine adaptive fractions in the planning technique. The mean (±SD) fraction time was 11.1 (±3.9) min.

Estimated by the 6mmPlan78Gy; if a 6mm PTV margin was used when compared to the StanPlan78Gy, the reduction of the volume of rectum and bladder receiving 25, 50, 60, and 70 Gv are outlined in Table 1.

The AdapPlanDoseEsc figures [Table 2] indicate that an average dose escalation of 4.2 (±3.3) Gy would be possible for this patient group while maintaining the current rectal toxicity profile at the V60 dose constraint. The dose escalation achievable is largely dependent on the shape of the posterior edge of the CTV as illustrated in Figure 3. If the posterior CTV slopes superoposterior to inferoanterior then

Figure 2: Scatter plot of maximum rectal diameter versus intrafraction displacement for 194 fractions

Figure 3: Two patients representing differences in PTV margin expansion due to the posterior CTV angle with patient a demonstrating [a] greater reduction in posterior margin than patient [b]. The CTV is represented in blue, the 6 mm PTV expansion in green, standard PTV expansion in red, and rectum in brown
Table 1: The reduction in treated volume of organs at risk if 6 mm uniform PTV margin (6mmPlan78Gy) or adaptive margins (AdapPlan78Gy) were used when compared to a standard PTV margin of 10 mm expansion of the CTV except 6 mm posterior

| Plan             | OAR   | OAR volume reduction at dose level (% ±SD) |
|------------------|-------|------------------------------------------|
|                  | 25 Gy | 50 Gy | 60 Gy | 70 Gy |
| 6mmPlan78Gy      | Rectum| 12±3 | 9±5  | 10±5 | 16±7 |
|                  | Bladder| 28±5 | 32±5 | 36±6 | 43±8 |
| AdapPlan78Gy     | Rectum| 4±20 | 4±27 | 8±29 | 16±36|
|                  | Bladder| 43±19| 43±19| 45±20| 48±21|

PTV: Planning target volume, CTV: Clinical target volume, SD: Standard deviation, OAR: Organs at risk

Table 2: Estimated dose escalation achieved in 10 patients using an adaptive protocol, while maintaining equivalent rectal constraints

| Patient | Dose | Adap # | Standard # | RecV60DoseEsc | RecV60StanPlan |
|---------|------|--------|------------|---------------|----------------|
| 1       | 90   | 36     | 9          | 29            | 28.85          |
| 2       | 80   | 2      | 38         | 17.6          | 16.9           |
| 3       | 80   | 19     | 21         | 20.4          | 20.6           |
| 4       | 80   | 11     | 29         | 30.5          | 30.1           |
| 5       | 80   | 4      | 36         | 26.61         | 26.22          |
| 6       | 86   | 33     | 10         | 17.9          | 17.5           |
| 7       | 82   | 30     | 11         | 20.9          | 20.7           |
| 8       | 80   | 21     | 19         | 20.54         | 20.23          |
| 9       | 82   | 27     | 14         | 14.75         | 14.7           |
| 10      | 82   | 37     | 4          | 26.71         | 26.72          |
| Mean    | 82.2 | 22.1   | 19.0       | 22.5          | 22.3           |

Adap # and Standard # represent the number of fractions where an adaptive and a standard margin would be used for each patient

Discussion

This study has described a relationship between the maximum rectal diameter and the displacement of the prostate during a radiotherapy treatment fraction. We observed that a rectum diameter of 3.5 cm or less appears to result in prostate displacement of ±3 mm. The ability to predict prostate motion based on rectal diameter may allow for an adaptive margin to be applied for all treatment fractions where the pretreatment CBCT anatomy may predict that prostate motion will be small; however, a larger study is needed to confirm this. Our modeling indicates that there may be a reduction in the volume of OAR treated when an adaptive margin is used. Further, an adaptive margin may allow dose escalation while maintaining the current treatment toxicity profiles.

Previous studies have outlined offline, hybrid, and online protocols for adaptive prostate radiotherapy. A large number of reports have used the offline methods. Typically, these methods involve a series of repeat CTs or CBCTs being acquired early in the treatment course. An adapted plan is created based on the organ positions on the scans taken during the first four to six treatment fractions and used for the remaining fractions in the treatment course. The hybrid methods involve a combination of offline adaptive replanning with a grouping according to subpopulation of small, medium, or large prostate motion, or offline replanning with online image guidance. None of these methods offer an adaptive margin from the first fraction, which is a key point of difference from our approach.

Online methods involve aperture modification for CRT, segment modification for IMRT using multileaf collimator (MLC), or online inverse planning. The online methods described allow for modification of the dosimetry based on deformations and rotations of the prostate at the time of pretreatment imaging. These methods do not alter the treatment margin on a fraction to fraction basis, using a standard PTV margin to account for intrafraction motion. Our data highlights the importance of intrafraction prostate motion in setting PTV margins and the impact of rectal filling on the margin required. This is supported by cine-MRI data, which has shown that patients with a full rectum have a 10% probability of ≥3 mm of motion in 1 min. Additionally, data from 184 patients has shown that around 25% of fractions will have a displacement of ≥3 mm if the fraction time is >9 min, which is expected for online adaptive methods where reoptimization is used. This suggests that the 2 mm uniform PTV margin recommended by Ahunbay et al., for use in their adaptive methods may be inadequate. In contrast, the 5 mm margin used by Li et al., in their modeling study is more likely to be adequate. This is further supported by a study which demonstrated that margin reductions below
5 mm is associated with increased risk of biochemical failure in the image-guided radiotherapy setting. Our study used a 6 mm adaptive margin which accounted for 4 mm intrafraction displacement of the prostate and 2 mm to account for rotations and deformations. We used a 2 mm expansion for prostate rotation and deformation based on the data from Olsen et al., who demonstrated that expanding their 3 mm margin to 5 mm provided adequate prostate coverage for all sample patients when using Calypso with an online correction protocol of 3 mm. The 6 mm margin should safely account for posterior prostate motion which has been shown to be critical to increased risk of biochemical failure, particularly in the case of rectal distension at planning.

While this study suggests an average dose escalation of 4.2 Gy may occur while maintaining the existing toxicity profile, we would not aim to extend the fractionated treatment. Potential approaches for dose escalation would be hypofractionated treatment or dose adaptive treatments where an escalated dose per fraction would be treated at fractions where margin reduction was permitted.

The fraction time for online adaptive prostate radiotherapy would be similar to that required for online adaptive radiotherapy to the bladder where CBCT acquisition, decision making, plan scheduling, and treatment delivery is required. Online adaptive bladder radiotherapy required around 10.7 min for CBCT acquisition and decision making during a pilot study, which is similar to the fraction time of around 11 min seen in the present study. Subsequent to that pilot study, the fraction time for 50 online adaptive bladder patients was 13.9 min when beam delivery and a posttreatment CBCT quality assurance (QA) scan was included, indicating a learning curve in decision making time after the pilot. We estimate a fraction time of 15 min for the prostate adaptive method we have described when IMRT is used. Shorter times may be achieved for modulated arc therapy delivery and when newer record and verify processes for adaptive therapy become available.

A limitation of this study is that it relates posttreatment CBCT rectal diameter measurements to intrafraction displacement, which does not follow the workflow required for online adaptive prostate radiotherapy. The intrafraction displacement in this study is also only taken from two time points, which may not represent the full excursion of the prostate during treatment. The authors are currently investigating a larger sample of patients using pretreatment CBCT and more comprehensive intrafraction prostate motion data to confirm the relationship seen in this study. We will also investigate the effect of bowel gas on predicting prostate motion as gas has been shown to impact on prostate motion. Another possible limitation is that we purposely used 3DCRT for the planning study. While many centers would use IMRT, a 3DCRT solution provides more consistency between plans and eliminates the potential impact of the optimizer settings. Further studies will also be required to quantify the ability and consistency of radiation therapists measuring the maximum rectal diameter on CBCT.

Conclusions

Our study proposes a method of daily adaptive prostate radiotherapy by describing a relationship between the prostate motion and the diameter of the rectum on CBCT. This method can implement an adaptive margin from the first fraction. Our sample demonstrated a uniform PTV margin of around 6 mm would be required to account for intrafraction prostate motion in an adaptive protocol. Further study is required to confirm the relationship between maximum rectal diameter on pretreatment CBCT and prostate motion for use in an adaptive protocol.

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