Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 3, pp. 892–897, 2006

0360-3016/06/$–see front matter

doi:10.1016/j.ijrobp.2006.07.013

**PHYSICS CONTRIBUTION**

# ONLINE ADAPTIVE RADIOTHERAPY OF THE BLADDER: SMALL BOWEL IRRADIATED-VOLUME REDUCTION

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**Purpose: To assess the potential reduction of small bowel volume receiving high-dose radiation by using kilovoltage X-ray cone beam computed tomography (CBCT) and quantized margin selection for adaptive bladder cancer treatment.**
**Methods and Materials: Twenty bladder patients were planned conformally using a four-field, 15-mm uniform margin technique. Two additional planning target volumes (PTVs) were created using margins quantized to 5 and 10 mm in the superior direction only. CBCTs (~8 scans/patient) were acquired during treatment. CBCT volumes were registered with CT planning scans to determine setup errors and to select the appropriate PTV of the day. Margin reduction in other directions was considered. Outlining of small bowel in every fraction is required to properly quantify the volume of small bowel spared from high doses. In the case of CBCT this is not always possible owing to artifacts created by small bowel movement and the presence of gas. A simpler method was adopted by considering the volume difference between PTVs created using uniform and adapted margins, which corresponds to the potential volume of small bowel sparing.**
**Results: The average small bowel volume that can be spared by this form of adaptive radiotherapy is 31 ± 23 cm$^3$ (±1 SD). The bladder for 1 patient was systematically smaller than the planning scan and hence demonstrated the largest average reduction of 76 cm$^3$. The clinical target volume to PTV margins in other directions can be safely reduced to 10 mm except in the anterior direction where, like the superior direction, the bladder showed significant variation.**
**Conclusions: Online CBCT-assisted plan selection based on quantized margins can significantly reduce the volume of small bowel receiving high doses for some bladder patients. CBCT allows the 15-mm margins used in some directions to be safely reduced to 10 mm.** © 2006 Elsevier Inc.

**Bladder cancer, Adaptive radiotherapy, Image-guided radiotherapy, Cone beam CT.**

## INTRODUCTION

In conformal radiotherapy, accurate delineation, localization and delivery are vital to improve tumor control and reduce normal tissue toxicity. The tumor and the microscopic spread of the disease constitute the clinical target volume (CTV). A margin is applied to the CTV to account for setup variability and organ motion producing the planning target volume (PTV) (1). When treating the whole bladder, margins of 15 to 20 mm are common (2–5) although a recent study has found this margin to be inadequate in 65% of cases when using concomitant boost radiotherapy (6).

In the case of the bladder, large internal organ motion is expected as it is a mobile organ that distends, i.e., changes shape and dimension depending on filling. It is therefore common for centers to employ a voiding strategy to try to minimize day-to-day variation. This will usually involve the patient voiding before treatment to try to achieve a consistent bladder volume. Alternatively, the patient can have a full bladder if a boost treatment is used to try to minimize the volume of healthy bladder tissue treated in the boost volume (6). Despite these strategies, large, interfraction bladder volume changes are seen, which appear to be unpredictable (7, 8).

Nevertheless, considering shape rather than volume, a recent study has quantitatively shown that bladder motion in the cranial direction is generally more pronounced than in other directions (2). In addition to the inherent variability of the bladder position, size, and shape, the variation in rectal volume is known to contribute to bladder position (6, 7).

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Received Jan 6, 2006, and in revised form June 29, 2006. Accepted for publication July 2, 2006.

The rectum and surrounding small bowel are organs at risk in the treatment of bladder cancer so the dose that they receive must be minimized to reduce adverse side effects. This leads to additional planning considerations in determining the margins to be used in bladder treatments.

Adaptive radiotherapy is a technique whereby the radiotherapy treatment is reoptimized during the course of the treatment on an individual patient basis. This is beneficial to the treatment, because computed tomography (CT)-based treatment planning utilizes a simple "snap-shot" of the patient, which may not be an accurate representation of anatomic shape and position at each stage of a prolonged treatment. These uncertainties are incorporated into the margin added to the CTV in the International Commission on Radiation Units and Measurements (1) approach to conformal radiotherapy. However, a modern approach adapts the treatment based on measurements from the verification images by adjusting margins and setup position after the treatment has commenced. Off-line adaptation has been reported by Yan *et al.* for radiotherapy of the prostate where the plan is modified on the basis of daily portal imaging measurements of organ motion and patient setup errors performed in the early stages of treatment (9). There are few studies involving the bladder, where an adaptive radiotherapy approach has the potential to offer improved accuracy in delivery as a result of the large internal motion associated with the bladder (6).

The integration of a kilovoltage X-ray source and a flat panel in the Elekta Synergy treatment machine (Elekta, Crawley, UK) has enabled the cone beam CT (CBCT) imaging of soft tissues in the treatment position on a daily basis. This allows direct visualization of the position of the actual CTV in relation to planned PTV at the time of treatment delivery. We therefore performed a planning study in which several different PTVs were overlaid on the CBCT acquired at treatment delivery to assess the PTV margins required at each bladder wall to ensure CTV coverage, determine where margin reduction may be possible, and quantify volume of small bowel spared. The priority was to determine a simple strategy for coping with unpredictable bladder volume changes by the prior creation of multiple PTVs from a small range of quantized margins, shown to encompass the range of most likely changes in projected bladder shape. PTV selection at each treatment fraction would then be informed by the details seen in cone beam scans.

## METHODS AND MATERIALS

The proposed online adaptive technique for bladder cancer treatment utilizes CBCT images acquired before treatment delivery to: (*1*) correct patient setup errors determined from automatic registration of the CBCT with the planning CT; (*2*) select the most appropriate PTV, from several PTVs created with a variable cranial margin, that covers the bladder shape on that day.

Twenty patients were included in this planning study. These patients were part of a study that had Local Research and Ethics Committee approval (North Manchester Local Research Ethics Committee approval number 03/NM/126). Informed written consent was obtained from all patients. CBCTs were acquired for each patient after setup into the treatment position on the first 5 days of treatment and then on a weekly basis until the end of treatment. The time between pretreatment void and the acquisition of CBCT ranged from 10 to 20 min. Up to eight scans were acquired for each patient in the study. A brief description of patient and tumor characteristics is given in the study by Henry *et al.* (10).

### *Treatment planning*

Each patient had been planned on the Pinnacle$^3$ treatment planning system (Philips Medical Systems, Andover, MA) with a prescription dose of 52.5 Gy delivered in 20 fractions. A four-field conformal brick technique is used at the Christie Hospital for the treatment of bladder cancer. For treatment planning, a contrast-enhanced CT scan is acquired, with the patient in the supine treatment position, on which the whole bladder is outlined manually by the clinical oncologist to produce the CTV. A generic 15-mm uniform margin is then added to the CTV to form the PTV to account for the setup error and internal organ motion for the patient population. Patients are asked to void before treatment with no drinking protocol.

In addition to the standard 15-mm uniform margin PTV, two further PTVs were created from the original CTV. The CTV was expanded in the superior direction with margins reduced in 5-mm steps to 10 mm then 5 mm while leaving margins in the inferior, left, right, anterior, and posterior directions unchanged.

### *CBCT registration and setup correction*

Cone beam CTs were registered to the primary planning CT scan using the Syntegra automatic registration software operating within Pinnacle$^3$. A local correlation algorithm was used for the registration, which is primarily influenced by bony anatomy and other edge detail (11). To quantify the magnitude of benefit from the adaptive technique, daily setup correction was analyzed, with the systematic and random setup errors determined for each patient and for the whole group.

The process of registering images and correcting for setup errors reduces the uncertainty resulting from setup error and potentially allows for margin reduction. Each margin was considered in turn using transverse, coronal, and sagittal views through the CBCT to determine the margin sizes that would provide the best all-round PTV. Margin size was again considered in 5-mm increments to sensibly constrain the selection process with the impact of motion on CBCT imaging resolution in mind. The 95% confidence level for the population was then used to determine whether these margins could be safely reduced.

### *"PTV of the day" selection*

For each registered CBCT scan, all three PTVs were assessed. The PTV that covered the bladder with a clearance of 2 mm between the visible extent of the bladder and the PTV boundary was selected as the PTV of choice for that day of treatment. The tolerance margin allowed for any additional movement of the patient or bladder that might have occurred after the initial setup, i.e., intrafraction motion. If the image was of insufficient quality to make an accurate decision, for example because of streaking caused by gas in the rectum or small bowel, the plan for the standard cranial margin of 15 mm was selected. The volume of small bowel that could be spared by using this adaptive technique was estimated by subtracting the volume of the PTV chosen for

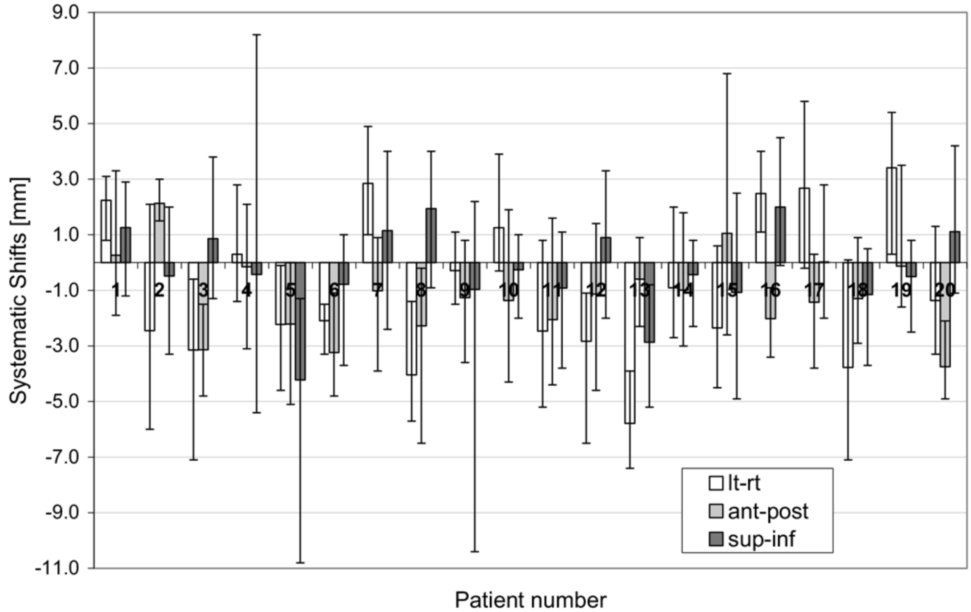


Fig. 1. Mean shifts (right-left, anterior-posterior, and superior-inferior) required to move the patient to the intended treatment position determined after registration with the planning computed tomographic scan. The mean shift in each direction is represented by the solid bars; the error bars represent the range. Ant-post = anterior-posterior; lt-rt = left-right; sup-inf = superior-inferior.

each fraction from the standard PTV volume. This assumes that all tissue in the larger PTV but not in the smaller PTV is small bowel. However, we believe this measure is a good indicator of the potential benefits of the technique.

The use of an adaptive technique requires consistent judgment when selecting the appropriate PTV. Therefore the inter- and intraobserver variability of "PTV of the day selection" was investigated using 5 patients randomly selected from within the study (Patients 3, 4, 8, 9, and 15). The PTV selection for each patient was repeated by one observer (N.A.B.) three times to assess the intrasubject variability. A physicist (A.A.) and a research radiographer (J.S.) were asked to make PTV selections for the same 5 patients to assess the interobserver variability. A protocol was developed for the PTV selection process to introduce a standardized and repeatable PTV selection process that would be practical in a clinical environment.

## RESULTS

Registration of the daily CBCTs with the planning CT scan identifies any shifts in the patient position from its intended position. Figure 1 shows the mean shifts (systematic errors) in the three orthogonal directions for each patient. The error bars represent the maximum and minimum shifts required and, therefore, the ranges involved. This demonstrates that both systematic and random errors occur at setup which can be corrected for with the acquisition of daily CBCTs. The maximum setup error was found to be 11 mm for Patient 5. Based on the formulae recommended in the BIR publication (12), the systematic ($\sum_{setup}$) and random ($\sigma_{setup}$) setup errors for the population were calculated. These are summarized in Table 1. The largest random error is in the cranio-caudal direction, whereas the largest systematic error was in the lateral direction.

After CBCT-to-CT registration using the Philips Syntegra software, the appropriate plan of the day was selected. A stacked histogram of the number of selected PTVs for each patient is shown in Fig. 2. This demonstrates that for the majority of patients an online adaptive technique would be beneficial as the PTV required for adequate bladder coverage varies on a daily basis.

For Patient 1, the bladder was systematically smaller on all CBCTs compared with the planning CT scan. For Patient 18, however, the superior edge of the bladder fell outside the largest PTV on several days. This may necessitate asking the patient to try harder to empty their bladder before beam delivery and performing a repeat CBCT before making a final decision. In this particular case, the patient went into urinary retention, he was given medication, and subsequent bladder volumes were smaller. Another patient whose bladder was outside the 15-mm margin complained of obstructive urinary symptoms, whereas no clinical explanation

Table 1. Systematic and random set-up errors for the three orthogonal directions calculated from recommendations in the BIR publication (Geometric Uncertainties in Radiotherapy [12]).

| | Systematic error ($\sum_{set-up}$) (mm) | Random error ($\sigma_{set-up}$) (mm) |
|---|---|---|
| Lateral | 2.7 | 1.5 |
| AP | 1.4 | 1.5 |
| SI | 1.5 | 2.1 |

*Abbreviations:* AP = anteroposterior; SI = superior-inferior.

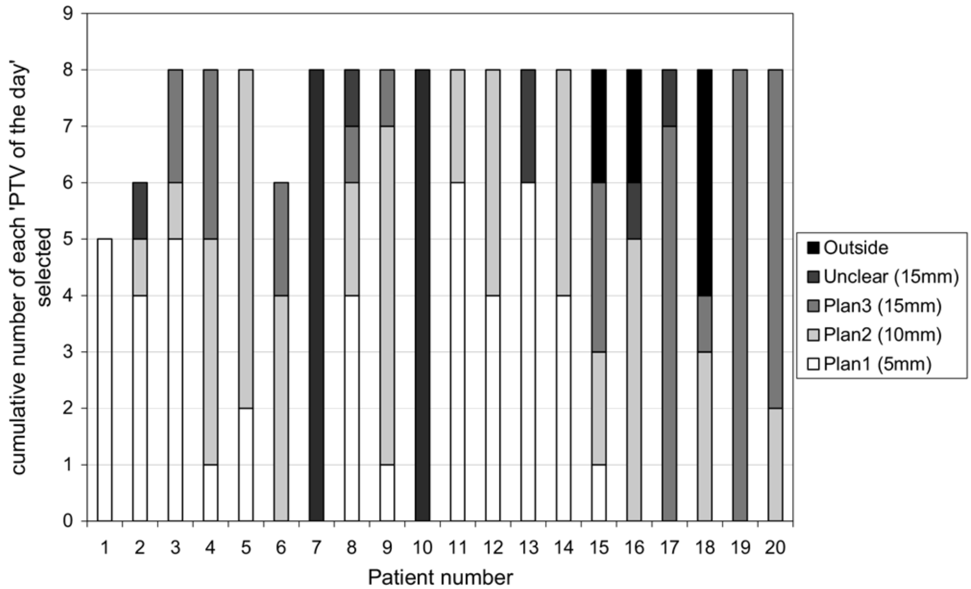


Fig. 2. Number of planning target volume (PTV) selections based on bladder coverage with a 2-mm margin. The dotted region represents the selection of the standard 15-mm margin planning target volume where the bladder was not clear in the X-ray volume image.

was found for the other two. One possible explanation for this is noncompliance with the voiding protocol. The CBCTs for 2 of the 20 patients (Patients 7 and 10) were of reduced quality, which made decisions concerning bladder coverage difficult. In these cases the standard 15-mm uniform margin PTV was selected.

Figure 3 shows coronal slices of registered CBCTs for the bladder of Patient 15 acquired on three fractions with the PTV options overlaid. As can be seen, the bladder shape clearly varies from one day to another. As a result, the use of a single PTV and plan based on 15-mm uniform margins may result in a significant volume of normal tissue being in the high-dose region on some days (Fig. 3a), whereas on other days part of the bladder may be located outside the PTV (Fig. 3c), thus highlighting the need for an adaptive technique.

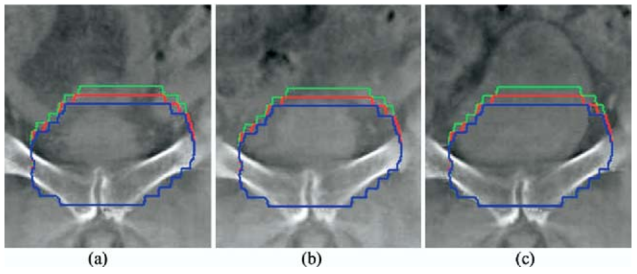


Fig. 3. Registered X-ray volumetric images of a bladder cancer patient acquired on three fractions showing bladder volume variation. The three planning target volumes created for the study are overlaid to select the appropriate planning target volume of the day based on the imaged bladder position and shape. The three planning target volumes were created with 5-mm, 10-mm, and 15-mm margins between the clinical target volume and planning target volume in the superior direction and 15 mm elsewhere.

In practice, the decision to select from only three PTVs for "the PTV of the day" was found to be adequate for 15 of the 20 patients included in this study. The other patients had systematically smaller or larger bladders, suggesting replanning was required, or they had a maximum of 2 fractions in which the bladder fell outside the PTV, which suggests that the patients had not fully voided and could have been asked to void again before beam delivery.

Small bowel sparing was characterized by the volume difference between the original PTV (15-mm uniform margins) and "the PTV of the day", selected after registration of the X-ray volume image with the planning CT scan. The results are shown in Fig. 4. The average volume of small bowel that can be spared from high doses for all patients is 31 $\pm$ 23 $cm^3$ ($\pm$1 SD). The maximum average small bowel sparing was 76 $cm^3$ for Patient 1 whose bladder was found to be consistently smaller at the time of treatment compared with that of the radiotherapy treatment planning (RTP) scan.

When deciding on the PTV of the day, there are five options: 5-mm superior margin, 10-mm superior margin, 15-mm superior margin, "PTV too small", or "image too poor". One observer (N.A.B.) made PTV choices three times for 5 randomly selected patients. The PTV choices between each repetition were compared as a measure of the intrasubject variability. Seventy-three percent of the time the choice of "PTV of the day" was the same. There were no PTV choices that differed by more than 5 mm. A similar result was seen for the intersubject variability for which 70% of the choices were the same. The extra 2-mm margin for intrafraction motion was often a differentiating factor. In these cases both PTV choices would almost certainly ensure adequate bladder coverage.

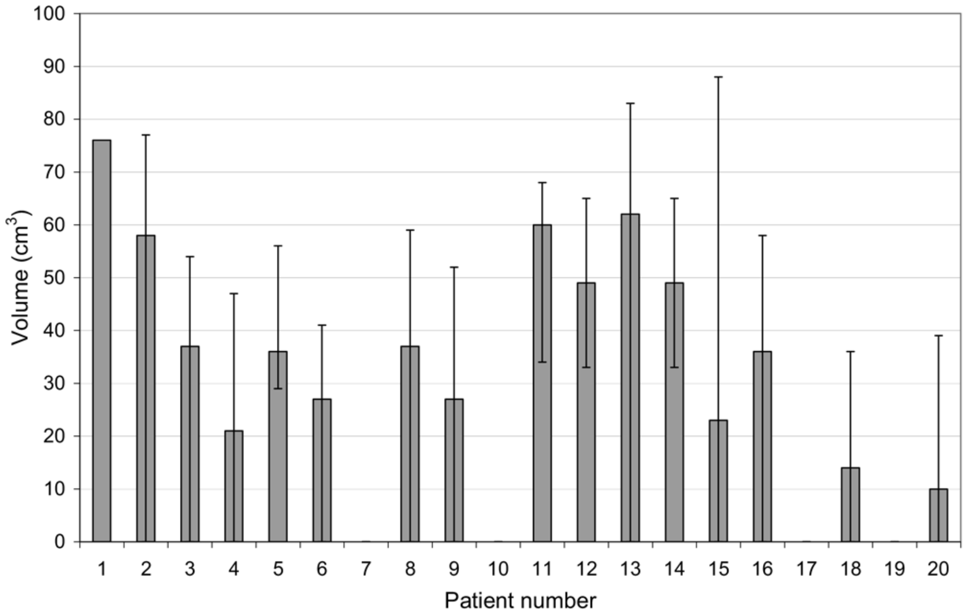


Fig. 4. Volume of small bowel that could be spared from the high-dose region by adapting the treatment on a daily basis. The solid bars represent the mean volume that could be spared over the eight fractions where X-ray volume images were acquired. The error bars represent the range of values.

Figure 5 shows the frequency of the margins required for adequate coverage in each direction. Appropriate margins were determined by the 95% confidence level for the population ($n$ = 115). Based on these levels, there is potential to reduce margins in the posterior, inferior, right, and left directions to 10 mm. A 15-mm margin is still required in the anterior direction. If the potential margin reduction in the superior direction was being considered, then 15 mm would still be required based on these results. However, this direction has been chosen to be adapted. The results therefore reinforce this choice as this direction showed the greatest variation. Even after correction for setup errors, the margins required for adequate coverage are still relatively large.

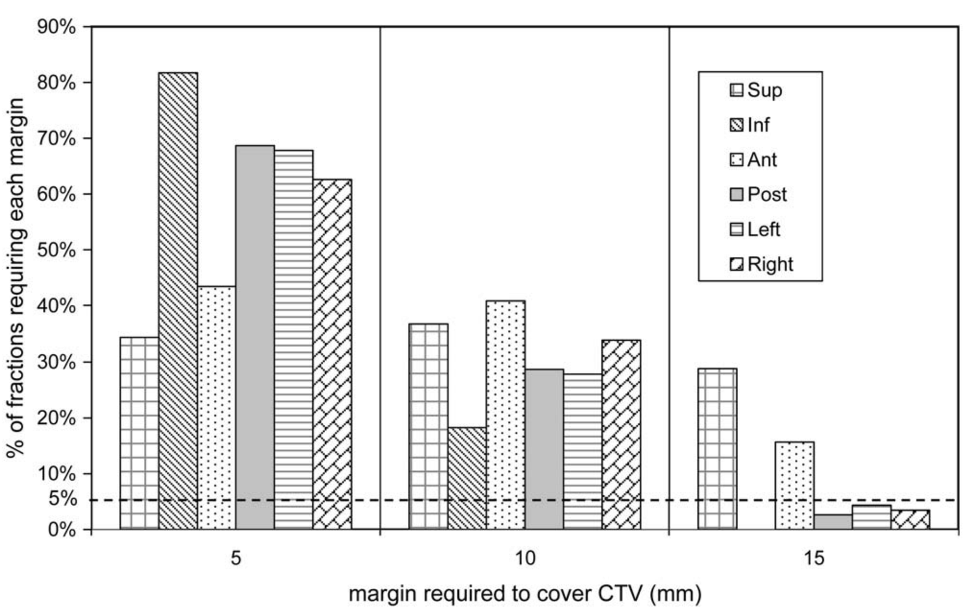


Fig. 5. Percentage of each margin required in each direction for adequate bladder coverage after correction for setup errors based on automatic online registration. The dashed line shows the 95% confidence level and demonstrates that the posterior, inferior, left, and right margins can potentially be reduced to 5 mm. It also demonstrates that the superior margin varies the most. Note that no patient needed a margin greater than 10 mm in the inferior direction. CTV = clinical target volume.

## DISCUSSION

Many groups have investigated the movement of the bladder during a course of radiotherapy to gain some insight into the margins that should be applied to the CTV (2, 3, 6, 7). Indeed, the consensus is that movement is most pronounced in the cranial and anterior directions, as also observed in this study, which suggests the need for nonuniform margins.

The large variation in bladder motion primarily in the cranial direction lends itself to a simple, quantized image-guided adaptive technique. This would ensure adequate bladder coverage as well as offering the possibility of a reduction to the dose to normal tissues, in particular small bowel, which is a dose-limiting factor for bladder radiotherapy.

Ideally, for "PTV of the day" selection, numerous PTVs would be created that offer variability in all directions. The most appropriate PTV would then be selected depending on the position, size, and shape of the bladder seen using CBCT on the particular day of treatment. In a busy, routine clinical environment, this is impractical. In our study, the margin choices are quantized in recognition of the need for online adaptive image-guided techniques to be uncomplicated and, therefore, both safe and efficient. Evidence-based margin quantization offers the flexibility to adapt to the large variations in bladder motion. This work has shown that daily correction of setup errors allows noncranial margins to be reduced from 15 to 10 mm in all directions, except in the anterior direction, where the bladder varies significantly.

The observations made using CBCT at the time of treatment in this study are in broad agreement with other studies of the range and direction of bladder motion (3, 7). Using CBCT, it becomes clear that the volume of small bowel in the high-dose region can indeed be reduced. However, different parts of the small bowel could be spared at each fraction, depending on which loop extends down to the level of the bladder on a particular day. Clearly, this makes detailed analysis of the dose changes within the small bowel difficult.

The potential benefit of online adaptive radiotherapy of the bladder for the majority of patients (75%) has been demonstrated. Patients with systematically smaller or larger bladders may need replanning (25%). These individuals can be identified from CBCT acquired during the initial few days of treatment.

The additional time required for adaptive image-guided radiotherapy is a cause for concern. However, simple PTV selection from a pool of just three precalculated plans may well be justified by a reduction in toxicity, potentially allowing safe dose escalation. This approach also removes the need for precise organ delineation using high-quality CBCT images, which in turn reduces the pressure to increase CBCT imaging dose. For the low-dose CBCT technique in use at the Christie Hospital, image guidance adds 10 mGy (weighted dose) per scan. For 20–40 treatment fractions this would amount to an acceptable 0.2–0.4 Gy, permitting genuine adaptation throughout treatment.

In conclusion, a practical, quantized adaptive radiotherapy technique with online CBCT assisted plan selection can significantly reduce the volume of small bowel receiving high doses. Using CBCT to adapt treatment could also allow the 15-mm margins currently used to be safely reduced to 10 mm in some directions. Whether or not this will translate into reduced acute and late bowel toxicity with similar or improved local control rates will require further clinical study.

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