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Assessment of an ultrasound bladder scanner in prostate radiotherapy: a validation study and analysis of bladder filling variability.

Abstract:

Introduction: During prostate radiotherapy treatment it is important to ensure the position of the bladder and prostate is consistent between treatments. The aim of this study was to provide a quantitative basis for incorporating ultrasound bladder volume estimates into local practice for prostate radiotherapy.

Methods: Agreement between bladder volume estimates obtained using CT and ultrasound was assessed. Analysis of bladder volumes between planning and treatment scans was used to quantify expected variations in bladder volume over the course of radiotherapy. Dose-volume statistics were estimated and compared to planned dose constraints to propose a target bladder volume and tolerance.

Results: Bladder volume measurements were obtained from 19 radiotherapy patients using ultrasound and CT. Ultrasound underestimated bladder volume compared to CT with a mean bias of -28 ± 30 ml. Pre-treatment (planning) bladder volumes varied from 71 to 383 ml with a mean of 200 ml. Treatment bladder volumes reduced by more than half in 9% of patients during the course of their treatment, potentially leading to a 30% increase in mean bladder dose. Patients with pre-treatment bladder volumes < 200 ml were most likely to exhibit differences in bladder volume, resulting in ‘out of tolerance’ increases in dose.

Conclusions: A pragmatic individualised drinking protocol, aimed at achieving a minimum ultrasound bladder volume of 200 ml at planning CT, may be beneficial to reproducibility in radiotherapy treatment. Ultrasound measurements prior to treatment

should ideally confirm that bladder volume is at least half the volume measured at planning.

Introduction

The aim of radiotherapy is to accurately deliver a high dose of radiation to damage cancer cells whilst sparing surrounding healthy tissue and nearby organs at risk (OAR). External beam radiotherapy (EBRT) uses a machine called a linear accelerator to deliver a number of high energy x-ray beams aimed at the target area. Modern machines and techniques such as volumetric modulated arc therapy (VMAT) can deliver highly conformal treatments where the beam is shaped tightly around the target area, and dose drops off sharply to spare healthy tissue. In pelvic radiotherapy, the potential for increasing the amount of radiation, measured in grays (Gy), to cause more damage to the cancer cells is limited by the need to spare organs at risk (OAR) located close to the planning target volume (PTV). In prostate radiotherapy, the OAR are the bladder, rectum and small bowel. Planning CT scans are taken prior to treatment, and are used to plan and calculate target and organ doses to make sure they are within acceptable limits set out in clinical protocols. The CT scan therefore only provides a snapshot of the patient's anatomy prior to treatment and daily variations in organ positioning can occur. The total dose is delivered in small daily doses called fractions. If daily variations in the size and position of OAR are not accounted for, target volume coverage may be compromised and genitourinary (GU) and gastrointestinal (GI) toxicity could be increased [1]. This can lead to a reduction in local tumour control and an increase in GU and GI side effects such as dysuria, urinary urgency, incontinence, nausea and diarrhoea [2,3].

Difficulty in achieving a consistent bladder volume is a well-documented problem and many studies have shown that the bladder volume has a major impact on

urinary [4] and bowel toxicity [5]. Drinking protocols are often used to help control bladder filling during the treatment of pelvic cancers [6,7]. A comfortably full bladder is normally standard protocol; this achieves a balance between the bladder being empty (most comfortable for patient) and being full (which pushes the small bowel out of the high dose region) [8]. Despite these protocols, bladder filling variability is an on-going problem for many radiotherapy departments [1,5,6,7,8,9,10].

Daily cone-beam CT (CBCT) scans can be used to verify setup accuracy of the PTV and OAR positions. If the CBCT scan indicates that the bladder is grossly different to the planning CT, the patient is required to empty their bladder and repeat the bladder filling protocol, adapting the volume of water or waiting time according to any previous trends. A repeat CBCT is then required to set-up the patient for treatment again, which can cause unscheduled delays and represents an additional imaging dose. Additionally, multiple repeat CBCT scans require authorisation from the patient's consultant which can cause further delays. The use of an ultrasound bladder scanner prior to planning and treatment has potential to improve reproducibility in bladder volumes with the aim of reducing unnecessary repetition of CBCT scans and ensuring the dose to organs at risk is minimised. Many centres have carried out studies prior to introducing an ultrasound bladder scanner into their department. These are summarised in Table S1 (S = Supplementary Material).

The aim of this project was to firstly assess agreement between o a CUBEscan BioCon-700 (de Smit Medical Systems Ltd, UK) and CT, to enable CT tolerances to be translated to a target volume and tolerance for ultrasound measurements. The second aim was to assess intra-patient bladder filling variability between the planning CT and subsequent treatment scans and evaluate whether a clinically relevant tolerance can be

set for the difference between the patient's bladder volume at baseline CT compared to during daily treatment.

Materials and methods

Patients

Men due to start radiotherapy treatment for prostate cancer at our centre were eligible for the study if they were aged 18 or over. Written informed consent was received from eligible patients on the day of the CT planning scan.

Ultrasound equipment

Patients were scanned using a CUBEscan BioCon-700 [11,12] portable, battery-operated ultrasound bladder scanner. This provides an automatic, non-invasive measurement of bladder volume and is designed to be quick and easy to use, with little operator training. The scanner has three scanning modes; male, female and child. Within a measurement range of 0 – 999 ml the manufacturer's stated accuracy is ±15% or 15 ml, whichever is greater.

Repeatability and agreement of ultrasound measurements of bladder volume

Ultrasound bladder scan measurements

All operators attended a practice training session prior to obtaining measurements for this study. Patients were positioned supine on a CT or treatment couch and ultrasound gel was applied midline on the patient's abdomen approximately 3 cm above the pubic bone. The probe was angled towards the base of the spine following the manufacturer's instructions and the pre-scan image mode was used to visualise the bladder on screen. To optimise each measurement, the probe was moved until the image of the bladder was as large as possible and positioned centrally on the screen. The probe was then held still, and a volumetric scan of the bladder acquired. Over a period of ~ 4 seconds the

scanner automatically calculates the bladder volume which is displayed on the screen, as shown in Figure 1. [Insert Figure 1]

Measurements of bladder volume using the ultrasound scanner were obtained immediately prior to the planning CT scan to minimise the time elapsed between the ultrasound and CT, typically within 3 minutes. In addition, the first nine patients recruited to the study were scheduled to have an ultrasound scan immediately prior to their treatment verification CBCT scan, once a week, for the duration of treatment. To minimise intra-observer variability, for each measurement operators obtained three readings and an average value was calculated for further analysis.

CT and CBCT contouring

The bladder volume was delineated by a single investigator (LS) on all corresponding CT and CBCT scans using the Eclipse treatment planning software (Varian Medical Systems, Palo Alto, USA) for comparison with ultrasound measurements. A third of the datasets were validated by a member of the planning team (DH) who was blinded to the previous analysis.

Statistical methods

Reproducibility of the bladder scanner was assessed by comparing ultrasound (US) bladder volume (BV) estimates with the corresponding CT and CBCT volumes using the following method [13,14]:

(1) A plot of CT/CBCT BV vs. average ultrasound BV with a line of equality was performed as a first visual assessment of agreement and bias.
(2) Differences were confirmed to be normally distributed using visual inspection and through using a Shapiro-Wilk test (assumption required for limits of agreement to be valid).

(3) A Bland-Altman plot was performed to quantify 95% limits of agreement. This is a plot of differences (CT-US) against the mean of CT and US measurements. The mean difference between methods indicates the bias. The 95% limits of agreement are calculated using the standard deviation (SD) as mean ± 1.96 * SD. This plot also indicates whether the difference between methods depends on the magnitude of the bladder volume.

(4) A paired-samples t-test was used to compare means between methods adopting a conventional threshold for significance of $P < 0.05$.

All statistical analyses were performed using SPSS Version 24.0 (IBM Corporation, Armonk, NY, USA).

Target volume and tolerance

Bladder filling protocol

All patients were asked to follow our current departmental bladder filling protocol where patients are instructed to drink two cups of water (~200 – 300 ml) 30 minutes before their appointment.

Bladder filling variation

The bladder was manually contoured and its volume computed using Eclipse treatment planning software. The pre-treatment (planning) CT and alternate day CBCTs were analysed to assess variations in the patient's bladder filling throughout treatment.

Planning CT & CBCT dose analysis

Planning dose-volume constraints for the bladder were plotted against planning CT bladder volume to aid identification of a target bladder volume. To estimate the dose to the bladder throughout treatment, CBCTs were automatically rigidly registered to the planning CT scan in Eclipse and the bladder was outlined. It was not feasible to outline every single fraction; therefore randomisation of weekly CBCTs was performed in

Excel (Microsoft Corporation, Redmond, USA) to avoid bias. The bladder CBCT structures were transferred to the planning CT structure set and the dose distribution overlaid to obtain an estimate of the dose delivered for that fraction. For all patients, the bladder volume and mean dose were also recorded. Planning dose-volume constraints vary depending on the amount of dose and number of fractions for a given treatment. For example, for 74 Gy delivered in 37 fractions over 7.4 weeks (74 Gy/37 fractions), there are two acceptable constraints to meet for the bladder; no more than 65Gy to 50% of the volume (D50%<65Gy or V65Gy <50%) and no more than 70Gy to 35% of the volume (D35%<70Gy or V70Gy<35%). Therefore both the D50% and D35% were recorded for 74 Gy treatment, and for a 60 Gy treatment, the D50%, D25% and D5% were recorded. The full dose constraints are summarised in Table 1.

Table 1. Organ at risk constraints for prostate radiotherapy.

Fractionation	**Bladder constraints**
74 Gy/37 fractions*	*Acceptable:* V65Gy<50%, V70Gy<35%, *Optimal:* V50Gy<50%, V60Gy<25%, V70Gy<5%,
60 Gy/20 fractions**	V40.8Gy<50% V48.6Gy<25%, V60Gy<5%

*as defined in the PIVOTAL trial [21]
**as defined in the CHHiP trial protocol [22]

Dose and volume constraints were plotted against the absolute bladder volume to visually assess any trends with bladder volume. Additionally, all results were normalised to planned values to assess relative changes.

Results

Repeatability and agreement of ultrasound measurements of bladder volume

A total of 19 prostate radiotherapy patients were prospectively recruited between July 2017 and May 2018, using convenience sampling of eligible patients. All 19 patients invited to take part in the study consented. Of the 19 patients recruited to the study, 12/19 received treatment for prostate and nodes; 11/12 with the standard fractionation of 74 Gy in 37 fractions; 1/12 received 70 Gy in 35 fractions; 5/19 received prostate only radiotherapy with 60 Gy in 20 fractions; 1/19 received prostate bed treatment with 66 Gy in 33 fractions, and one patient was on a stereotactic trial and was treated with 36.25 Gy in five fractions.

Repeatability

Bladder volume readings were repeated three times. Pre-treatment baseline (planning) ultrasound and CT scans were obtained for 16/19 patients. In 2/19 patients there were difficulties with IV cannulation and for one patient there were time pressures on the CT scanner which meant that ultrasound and CT scans could not be obtained within a close enough time window. A total of 38 averaged measurements were taken prior to CBCT in subsequent follow-up treatments. There were difficulties in performing the ultrasound scan on five occasions, three of which occurred for the same patient where no bladder scanner measurements could be obtained prior to treatment. On reviewing this patient's CT and CBCT scans, it is thought the difficulty in measuring was due to small bladder in a very posterior position.

The reproducibility of repeated readings was assessed, and the results are summarised in Figure S1. Standard deviations ranged from 3 – 57 ml, with the mean standard deviation of repeated measurements being 14 ml. This is approximately the same as the manufacturers stated accuracy.

Agreement

CT and CBCT bladder volumes were plotted against mean ultrasound-measured bladder volumes, with a line of equality (dashed) and line of best fit (solid), shown in Figure S2 of the supplementary material. The bladder volume obtained from the CT scan was treated as the gold standard. A strong correlation is found, however, most of the ultrasound readings are below the line of equality suggesting that the bladder scanner tends to underestimate volume compared to contoured CT volumes. Figure 2 shows a Bland-Altman plot confirming the bias between ultrasound and CT of 28 ml. CT and CBCT measurements are indicated separately (CT=triangle, CBCT=circle). Differences are normally distributed, as assessed by a Shapiro-Wilk's test ($p>0.05$). The range of CT/CBCT contoured bladder volumes was 71 to 383 ml, with a mean of 183 ± 69 ml. One contour was excluded from analysis as not all of the bladder was captured on the CBCT. The range of ultrasound average bladder volumes was 46 to 368 ml, with a mean of 155 ± 83 ml. The mean difference was 28 ± 30 ml, with 95% limits of agreement between -31 ml and 88 ml. A paired-samples t-test found that the mean difference (CT-US) was statistically significant ($p<0.0005$). In developing a target and tolerance for ultrasound measurements it is important to account for this bias. [Insert Figure 2 here].

This Bland-Altman plot was reproduced indicating the operator who performed the scan. This is shown in Figure S3. The measurements are evenly spread, with no evidence of clusters or outliers. All individual operators' mean difference lie between 18 – 44 ml, with mean SD ranging from 7 to 28 ml. Considering the range of bladder volumes measured, reproducibility between operators appears acceptable. Repeated measurements are bound to exhibit some variability due to slight differences in probe positioning between measurements. All operators found the device easy to use, all

patients tolerated the measurements being taken, and it typically took less than 5 minutes to obtain readings.

Target volume and tolerance

Bladder filling variability

Bladder volumes were contoured from planning CT scans for 18/19 patients, and alternate treatment fraction CBCT scans, to assess bladder filling variability throughout treatment (n = 341). The patient receiving 36.25 Gy in five fractions was excluded from subsequent analysis to enable categorisation of fractionation regimes; of the remaining 18 patients, five received prostate only radiotherapy with a fractionation regime of 60 Gy/20 fractions, equivalent to 3 Gy per fraction. The remaining patients received 2 Gy per fraction regimes.

Figure 3 indicates the range of bladder volumes achieved for 18 patients throughout treatment measured from CT and CBCT scans. The black crosses indicate the bladder volume achieved at the planning CT. Data shown as green circles and blue triangles indicate 2 Gy per fraction and 3 Gy per fraction regimes, respectively; daily dose could impact the onset of side effects, which could influence ability to fill the bladder. Bladder volumes measuring from the planning CT ranged from 71 to 383 ml, with a mean of 200 ± 83 ml. Bladder volumes measured during treatment had a much larger range. For 2 Gy per fraction treatment, this was 61 to 668 ml with a mean of 185 ml. For 3 Gy per fraction treatment, this was 58 to 484 ml with a mean of 159 ml. The largest range for one individual was 195 ml to 663 ml (patient 14). Figure 3 shows that all patients had at least one treatment where the bladder was smaller than achieved at their planning CT scan. Mean bladder volume during treatment was found to be lower than in the pre-treatment planning CT scan in 11/18 patients. For two patients (8, 12), the bladder volume achieved at treatment was consistently lower than during planning.

Out of all treatment bladder volume measurements, 9% (31/341) were < 50% of the planned bladder volume. This occurred for 9/19 patients. Only 131/341 (38%) of volumes were found to be within 75% and 125% of the planning CT volume. [Insert Figure 3 here]

Planning CT & CBCT dose analysis

This part of the study looked at estimating dose-volume statistics compared to bladder volume measured at planning and for CBCT scans throughout treatment for 18 patients. The aim was to provide a quantitative indication of ideal target volumes. Table 1 lists the acceptable and optimal dose constraints for the radiotherapy treatment. Figures 4 and 5 show the dose-volume data against absolute bladder volume for 60 Gy and 74 Gy treatments respectively. The acceptable dose limits are shown as horizontal lines, and the mean bladder volume achieved at planning CT of 200 ml is also indicated.

Figure 4 shows that for volumes < 200 ml, the D25% and D5% are approaching or violating the accepted dose. The D50% approaches the constraint for volumes < 100 ml. Figure 5 shows that, although all required dose constraints (bold horizontal lines) were met for this cohort of patients, for volumes < 200 ml, the optimal constraint for D50% (dashed horizontal line) was only met 60% of the time, compared to 94% of the time for > 200 ml. [Insert Figure 4 here] [Insert Figure 5 here].

The effect of relative changes in bladder volume on mean bladder dose was estimated. In this study, bladder volumes < 50% of the planned volume were associated with an ~20% increase in the mean bladder dose for 60 Gy, shown on Figures S4 and S5. Lines of best fit are shown for each patient. Generally, a 50% reduction in volume leads to a ~10% increase in mean bladder dose. One patient's mean dose increased by

30% for a 50% reduction in bladder volume. This is likely due to the close proximity of the bladder to the high dose region.

Discussion

Previous studies have shown that the use of an ultrasound bladder scanner has potential to improve bladder volume reproducibility over the course of radiotherapy treatment by modification of individual drinking protocols [7,15,16,17,18], however, target bladder volumes and tolerances vary widely in the literature, as summarised in Table S2.

This study found ultrasound measurements of bladder volume were 28 ± 30 ml lower than CT measurements, with 95% limits of agreement between -31 ml and 88 ml. Given that previous studies suggest a range of bladder filling rates from 1.4 – 10.6 ml/min,. a short time-lag of only a few minutes between US measurement and CT acquisition could account for this bias [15]. Nonetheless, the observed bias is clinically acceptable. Agreement between methods is consistent with previous studies investigating the BioCon-700, (see Table S1 of the Supplementary Material).

The wide variability in intra-patient bladder filling observed in this study agrees with previous studies that have identified significant variations [1,5,6,8,9,20,21]. Mean bladder volume did not appear to be affected by treatment and did not vary significantly between fractionation regimes.

Our findings indicate that drinking protocols used at our centre do not lead to well-controlled bladder volumes. No repeat CBCT scans were performed for any patients in this study based on visual assessment of bladder size. Subsequently dose estimates were outside of accepted constraints for six scans. This highlights the potential of the bladder scanner to improve consistency. The importance of the drinking

protocol should also be emphasised to patients to try to improve patient compliance. However bladder filling is complex and is influenced by many other factors such as state of hydration, patient drinking habits, and time of day [7]. A simple reminder sheet with drinking volume and waiting time required to achieve an acceptable bladder size could be provided to the patient as a daily reminder to help improve compliance.

This study showed that patients with a baseline bladder volume < 200 ml at planning are more likely to violate the D25% and D5% bladder constraints for 60 Gy treatments, and optimal D50% constraint for 74 Gy treatments. The mean population bladder volume was 200 ± 83ml, therefore 200 ml appears to be an achievable target volume, and could be maintained over the course of treatment without too much discomfort to patients. A bladder volume of at least 200 ml, as indicated by the ultrasound scanner (~200 – 250 ml on CT considering established bias) would be an achievable target that would greatly improve conformity of dose. This is similar to other centres who have suggested target volumes in the literature, in the range of 150 – 400 ml, see Table S2.

In this study, 9% of patient bladder volumes measured just prior to treatment were less than 50% of the planned bladder volume, and dose analysis estimated that a 50% reduction in bladder volume can lead to a 30% increase in mean bladder dose. This agrees with Chen et al. [10] whose study found a 10% increase in bladder volume was associated with a 5.6% reduction in dose.

Locally, it would be impractical to intervene prior to treatment for >10% of prostate patients due to available linear accelerator machine time availability. Therefore, pragmatically, a 50% tolerance is the tightest that could be applied for busy departments such as ours. Therefore, if a patient's treatment bladder volume is <50% of the planned bladder volume, the patient's drinking protocol should be modified; either by extending

the time period between drinking and treating, or by emptying the bladder and increasing the volume of water based on the ultrasound reading. An individualised drinking protocol could then be recorded on the patient's treatment sheet and followed for subsequent fractions. Bladder volumes larger than achieved on planning are acceptable, since this study shows that the dose would decrease. This supports Nakamura *et al.*'s findings that bladder volumes > 200 ml didn't reduce the possibility of achieving an optimal plan [24]. A simplified proposed workflow for implementing ultrasound bladder scanning into a radiotherapy department is shown in Figures S6 and S7 of the supplementary material. This small research study is subject to several limitations. First, the generalisability of our results is limited by the small sample size, as the study was performed at a single centre using a specific drinking protocol and bladder scanner. The results may not be generalisable to other centres. Therefore, local validation of the protocol is recommended. Nonetheless, this study has added to the evidence for incorporating an ultrasound bladder scanner into local practice for prostate radiotherapy. A further limitation is that patients receiving a range of dose-fractionation regimes, in addition to patients receiving nodal irradiation, were included this study with the aim of increasing sample size. Whilst this benefits the repeatability, agreement and variability analysis, the study design could have been improved by focussing on a single site and single dose-fractionation for the dose-volume analysis. This may have enabled daily CBCTs to be analysed, rather than conclusions based on a weekly CBCT scans. The wide variation in fractionation regimes makes interpretation of the results difficult, since the importance of bladder volume and impact of out of tolerance constraints varies depending on the regime and site. Thirdly, the department's current protocol of drinking two cups of water was not altered for this study; this protocol therefore allowed a range of volumes to be consumed, contributing to the wide

variations observed. This should have been addressed prior to the start of the study, so that more solid conclusions could have been drawn from the bladder filling variation analysis. Lastly, the estimates of the effect of relative changes in bladder volume on mean bladder dose was based on a small amount of data. Therefore, to validate this preliminary study, taking into consideration these limitations, future work is necessary to analyse a larger patient cohort using the proposed workflow and stricter drinking protocol. In addition, a similar study should be carried out to validate the female mode of the scanner prior to using it for female pelvic radiotherapy patients. The current study was conducted solely in men.

Conclusion

Measurements of bladder volume using the CUBEscan BioCon-700 ultrasound bladder scanner were feasible in 18/19 of the patients we studied. There was a mean increase of 28 ± 30 ml between bladder volume estimates using the ultrasound scanner compared to CT based estimates obtained 3 minutes later, which is a clinically acceptable difference. Local bladder filling and image-guidance protocols were not found to be effective in achieving bladder filling consistency to protect organs at risk; 9% of treated volumes were < 50% of the planned volume and only 38% of treated bladder volumes were within ± 25% of the planned volume. We conclude that it is feasible to implement ultrasound bladder scanning for prostate cancer patients. Based on our findings we suggest a target bladder volume of at least 200 ml is achieved at the planning stage, and that prior to each treatment CBCT scan, the bladder volume measured using ultrasound should be at least 50% of the planned volume.

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Figure Legends

Figure 1. CUBEscan BioCon-700 display showing cross-sectional ultrasound images, and indicating measured bladder volume. This image was obtained on a member of the research study team.

Figure 2. Bland-Altman plot indicating a bias between CT and US of 28.4ml

Figure 3. Inter-patient bladder filling variability over the course of treatment for 2Gy per fraction (green circle) and 3Gy per fraction (blue triangle) fractionation schedules.

Figure 4. Bladder constraints for 60Gy in 20 fractions. Data from CT and CBCT scans. Below ~200ml, D25% and D5% is approaching or not meeting the acceptable constraint.

Figure 5. Bladder constraints for 74Gy in 37 fractions. Data from CT and CBCT scans. All acceptable constraints met (bold horizontal lines). Below 200ml, only 60% of doses meet the optimal D50% constraint (dashed horizontal line) and D5% less likely to be met.