Bladder filling variation during conformal radiotherapy for rectal cancer

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Abstract Conformal radiotherapy for rectal cancer is associated with small bowel toxicity mainly diarrhea. Treating patients with a full bladder is one of the practical solutions to reduce small bowel toxicity. Previous studies on prostate and cervix cancer patients revealed that maintaining consistent bladder volume throughout radiotherapy treatment is challenging. The aim of this study was to measure bladder volume variation throughout radiotherapy treatment. This study also measured the association between bladder volume changes and diarrhea. Twenty two rectal cancer patients were recruited prospectively. Patients were planned for treatment with full bladder following departmental bladder filling protocol and the planning bladder volume was measured during CT-simulation. During radiotherapy, the bladder volume was measured weekly using cone-beam computed tomography (CBCT) and compared to planning bladder volume. Incidence and severity of diarrhea were recorded during the weekly patient review. There was a negative time trend for bladder volume throughout five weeks treatment. The mean bladder volume decreased 18 % from 123 mL (SD 54 mL) during CT-simulation to 101 mL (SD 71 mL) on the 5th week of radiotherapy, but the decrease is not statistically significant. However, there was a large variation of bladder volume within each patient during treatment. This study showed an association between changes of bladder volume and diarrhea (P = 0.045). In conclusion bladder volume reduced throughout radiotherapy treatment for conformal radiotherapy for rectal cancer and there was a large variation of bladder volume within patients.

1. Introduction

Radiotherapy combined with chemotherapy or chemo-radiotherapy (CRT) is established as a standard treatment for locally advanced rectal cancer and improves local control [1]. A significant number of patients treated with radiotherapy for rectal cancer experience gastrointestinal acute and late toxicity. Acute and late gastrointestinal toxicity such as pain, bloating, nausea, fecal urgency, diarrhea, and rectal bleeding have a significant impact on patient's quality of life. In a study by Gérard et al. [2], 8-40% of patients were reported to have acute toxicity (grade ≥ 3) and 24 % late toxicity. The volume of irradiated small bowel and the radiation dose were reported as major factors affecting small bowel toxicity [3].

Therefore, non-invasive, effective and clinically practical approaches were needed to reduce the amount of small bowel in an irradiated field. Kavanagh et al. [4] and Fiorino et al. [5] described several methods to minimise the amount of small bowel in the treatment volume using surgical and non-surgical methods. Surgical techniques are procedures such as clip placement in high-risk areas, pelvic reconstruction, re-peritonealisation of the pelvic floor, and placement of an omental sling,

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retroversion of the uterus and by placing a synthetic prosthesis under the small bowel (a removable pelvic spacer). The irradiated small bowel volume can also be minimalized by radiotherapy techniques such as 3D conformal radiotherapy; intensity modulated radiotherapy (IMRT), adaptive radiotherapy, customised shielding, a shrinking field technique, bladder distension and optimal irradiation position such as supine, prone or by using a belly board.

Many institutions combined bladder distension with radiotherapy technique such as using belly board as a method to reduce the amount of small bowel in the irradiated field because it is more practical. Kim et al. [6] reported that bladder distension is more effective in reducing the irradiated small bowel compared to using belly board. A distended bladder pushes the small bowel superiorly and away from radiotherapy treatment field [7, 8, and 9]. However, maintaining consistent bladder volume throughout radiotherapy treatment is challenging.

Previous studies have shown that consistent bladder volume throughout radiotherapy treatment is difficult to reproduce. Most studies showed a reduction in the bladder volume towards the end of treatment particularly in prostate and cervical cancer [10], [11], [12] and [13]. Reduction or variation in bladder volume leads to the inconsistent amount of small bowel being irradiated. There are limited studies on efforts to maintain bladder volume for rectal cancer treatment. Therefore, the implementation of an effective bladder filling protocol is required for rectal cancer patients. Effective bladder filling protocol will also result in greater treatment accuracy, particularly with the advancement in IMRT in future and reduced incidence of diarrhea, which will eventually improve patient's quality of life during and after radiotherapy.

This is a preliminary study to assess the effectiveness of existing bladder filling protocol in maintaining bladder volume consistency in our radiotherapy department. This study assesses the bladder volume variation, trend of bladder volume changes throughout radiotherapy treatment and the association of bladder volume changes and incidence of diarrhea in rectal patients treated with conformal radiotherapy in Radiotherapy and Oncology Department, Hospital Kuala Lumpur.

2. Materials and method

2.1. Patient population

This study enrolled 22 rectal cancer patients who were scheduled for radical pre- and post-operative pelvic radiotherapy based on stratified random sampling. Informed consent was obtained from all the patients. Patients receiving palliative radiotherapy, radical short course pre-operative radiotherapy, had a functional disorder in their bladder, had cystectomy were excluded from this study. Those patients, who showed a strong aversion to retaining urine, had previous lower gastrointestinal radiotherapy and patients with the Eastern Cooperative Oncology Group (ECOG) performance status of 2 and lower were also excluded. This study was conducted with Malaysian Medical Research and Ethics Committee approval NMRR-15-807-24333(IIR) from October 2015 until May 2016. The clinical profiles of patients are shown in Table 1.

Table 1. Clinical profiles of patients.

Criteria	No (%)
Age , average (range)	55 (27 – 71)
Male	16 (72)
Female	6 (27)
Pre-operative	11 (50)
Post-operative	11 (50)
Concurrent chemo radiotherapy	15 (68)
Radiotherapy dose (Gy) , average	45
Radiotherapy fractions	25

2.2. CT-simulation
According to departmental bladder filling protocol, patients were required to empty the bladder, drink 200ml of water and wait for 30 minutes before CT-simulation. CT-simulation was carried out using Brilliant Big Bore Philips CT-simulator. A radio-opaque marker was placed on the anal verge. Patients were positioned supine with both hands resting on chest. CT scan was performed from the level of third lumbar vertebrae until the middle of the femur with 5 mm slice thickness.

2.3. Radiotherapy treatment
Patients are treated using 10-MV Varian Medical System- Silhouette Edition linear accelerator and Varian Clinac RapidArc linear accelerator. Dosage and fractionation for rectal cancer radiotherapy was 45 Gy in 25 daily fractions over five weeks. The superior border: 1.5 cm superior to sacral promontory, which correlates to L5-SI inner space. The lateral borders: 2 cm lateral to pelvic brim and inlet to include iliac lymph nodes. The inferior border: includes the entire obturator foramina, although this may vary depending on the location of the tumor. The recommended inferior margin is 3 to 5 cm from the gross tumor pre-operatively or below the most distal extent of dissection post-operatively. The posterior field border: 1.5 to 2 cm behind the anterior bony sacral margin. Anterior field border: the anterior edge of the femoral heads to ensure coverage of internal iliac nodes. Organs at risk are small bowel, femoral head and neck, bladder, and rectum.

2.4. Bladder volume measurement
During planning, bladder volume was measured from CT planning images. Planning bladder volume was used as the reference to measure the variation of bladder volume during treatment. Treatment bladder volume was derived every week from offline treatment Cone Beam CT (CBCT) images. In this study the both the CT-simulation and treatment bladder volume were measured using calculation based on ellipsoid formula. This is because bladder volume could not be measured directly from CBCT images. The accuracy of ellipsoid formula were validated by comparing with bladder volume derived from bladder contour by physician on CT-simulation images. Bladder width, height, and depth were used to calculate bladder volume using ellipsoid formula. Two senior radiation therapists measure the bladder dimension independently, and the average measurement was taken. Each patient has 5 CBCT images.

2.5. Assessment on diarrhea
The incidence and severity of diarrhea were assessed weekly during patient’s weekly review by attending medical officer or oncologist. A standardised form derived from National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE version 3.0) Events: Diarrhea was used to scoring diarrhea.

2.6. Statistical test
The accuracy of bladder volume measurement using ellipsoid formula and bladder contour in CT-simulation images was determined using Pearson correlation coefficient. Variation of mean bladder volume during CT-simulation and fifth week of radiotherapy was compared using paired t-test. Spearman’s rank test was used to determine the association between changes in bladder volume with incidence and severity of diarrhea. All the statistical test was carried out using SPSS version 23.0 (IBM, Armouk, NY, USA).

3. Results and discussion

3.1. Validation of ellipsoid formula
The mean difference between the bladder volume measurement using ellipsoid formula and bladder volume measurement from bladder contour on CT-simulation images is 1.45 mL ± 10.74 mL. There is a strong correlation between bladder volume measurement using ellipsoid formula and bladder volume

measurement from bladder contour on CT-simulation images, r = 0.98, P < 0.01 (Figure 1). The accuracy of ellipsoid formula for measuring bladder volume was earlier validated by Miralbell et al. [13] ($r^2 = 0.9859$) and Dicuio et al. [14].

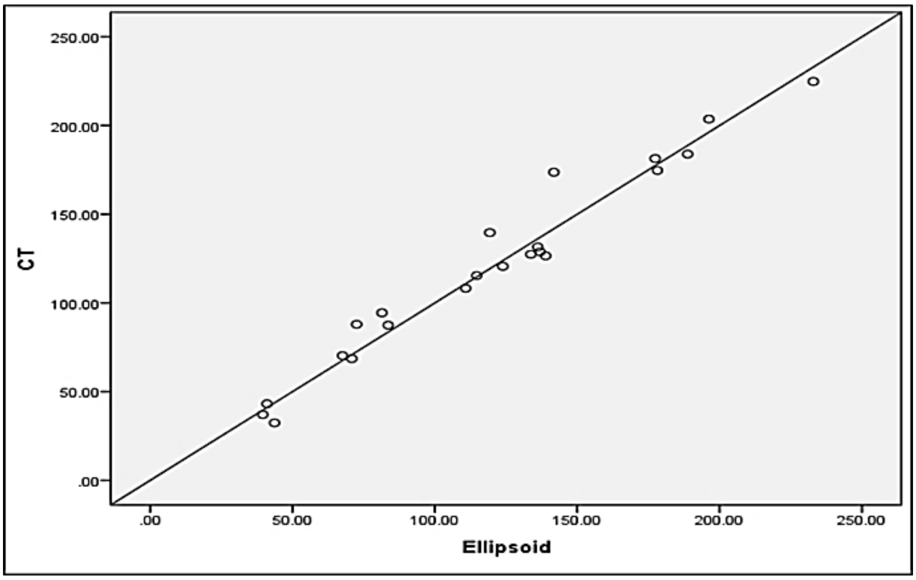

Figure 1. Correlation between bladder volume (mL) measurement using ellipsoid formula and bladder volume (mL) measurement from bladder contour on CT-simulation images.

3.2. Bladder volume variation

The population mean bladder volume variation for 22 patients throughout the five weeks radiotherapy treatment was compared with the bladder volume during CT-simulation as shown in figure 2. A total of 110 images were used in this study. Mean bladder volume during CT-simulation was 123 ± 54 mL During week four and week five, treatment bladder volume reduced 10% to 111 ± 85 mL and 18% to 101 ± 71 mL respectively from CT-simulation bladder volume. However, the population mean bladder volume reduction is not statistically significant (P = 0.104). The reduction of bladder volume during the last two weeks of radiotherapy treatment could be due to patients becoming less attentive in the following bladder filling instructions towards the end of radiotherapy treatment or due to increased frequency of diarrhea which makes it difficult for patients to control micturition.

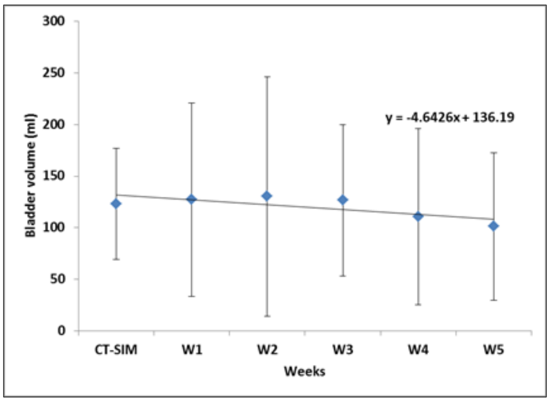

Figure 2. The change and variation in bladder volume during treatment compared to bladder volume during planning (CT-sim).

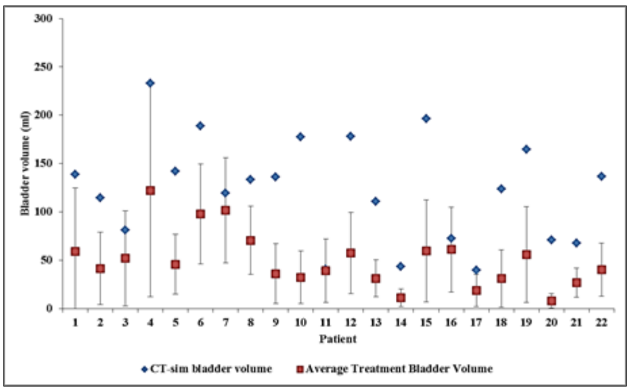

Figure 3. Variation of bladder volume within patient. Diamond: Bladder volume during CT simulation. Square: Mean Bladder volume for each patient during treatment.

Similar studies on bladder volume variation for prostate and cervix cancer patients reported a significant reduction in bladder volume [10], [11], [12] and [13]. Patients enrolled in all the above studies had larger mean bladder volume at CT-simulation compared to this study, ranging from 219 mL – 378 mL It has been reported that maintaining consistency of large bladder volume throughout radiotherapy treatment is more difficult than smaller bladder volume.

However, in this study bladder volume variation within each patient was large (Figure 3). During the first week of radiotherapy treatment, 50% of patients were having more than 50% change in bladder volume and on the fifth week of treatment 64 % of patients are having more than 50% change in bladder volume compared to planning bladder volume (Table 2). Such large variation of bladder volume within patients during radiotherapy treatment could lead to significant change in the volume of small bowel in the irradiated field. Joost J Nuyttens et al. [15] studied the implication of variation of small bowel in rectal cancer radiotherapy and had found that variation in bladder volume cause shift the clinical target volume (CTV) by 7 mm cranially and 2.5 cm caudally. Therefore, large variation in bladder volume could affect the accuracy of treatment and dose volume histogram of organ at risk particularly of the small bowel. Small bowel toxicity was shown to be primarily dependent on the volume of small bowel receiving over 15 Gy, therefore reducing the volume of the small bowel may have an impact on the tolerance to therapy.

Table 2. Number and percentage (%) of patients having bladder volume changes of more than 50% and 100% throughout five weeks radiotherapy treatment.

Percentage of bladder volume change	Week 1	Week 2	Week 3	Week 4	Week 5
>50%	11/22 (50.0%)	10/22 (45.6)	4/22 (25.0%)	9/22 (41.0%)	14/22 (64.0%)
>100%	2/22 (9.1%)	4/22 (18.2%)	2/22 (9.1%)	2/22 (9.1%)	1/22 (4.5%)

There was a correlation between bladder volume changes and incidence and severity of diarrhea (Spearman's rank correlation r_s = -0.432, P = 0.045). The highest score for diarrhea is 2 which indicates an increase of 4–6 stools/day over baseline; moderate increase in ostomy output compared with baseline. During the third week of radiotherapy 10/22 (45%) of patients were reported having score 2 for diarrhea and was later controlled with medication and diet modification. Future research is required to reduce the variation of bladder volume within patients throughout radiotherapy treatment to improve treatment accuracy and minimise acute and chronic small bowel toxicity.

The standardized protocol in this study was not successful in ensuring a consistent bladder volume within patient. This could be because patients were given instruction on the importance for having full bladder only on the first day of treatment and there were no written information given to patients. There were no tools used to measure patient's bladder volume daily prior to treatment. Written bladder filling instructions and measurement of bladder volume using ultrasound was reported to reduce bladder volume variation within patients [11]. Therefore, future study need to include written bladder filling instruction and measurement of bladder volume using ultrasound prior to treatment in bladder filling protocol in order to reduce bladder volume variation within patients.

4. Conclusion

There was 18% reduction of population mean bladder volume from CT-simulation to the fifth week of radiotherapy (123 ± 54 mL to 101 mL ± 71 mL) (p = 0.104), however within patient bladder volume variation was large. Further study using a more effective protocol is required to reduce variation of bladder volume within patient. The reduction in bladder volume was correlated with incidence and severity of acute diarrhea.

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