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Dynamic Changes in Bladder Morphology Over Time in Cervical Cancer Patients

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Abstract

Objectives: Continuous surveillance of bladder volume (BV) is beneficial during the treatment of various urogenital diseases because the bladder is always changing its position, size and even shape at different filling phases. For this purpose, we quantified the motion of the urinary bladder.

Methods: Daily ultrasound measurements and weekly cone-beam computed tomography scans were obtained from 89 patients in the supine position. BV, bladder centroid positions, and triaxial lengths in the left-right (LR), anterior-posterior (AP), and superior-inferior (SI) directions were compared across different time points.

Results: BV linearly increased over time, and the mean urinary filling rate (v_{tot}) was correlated with the patients' age and water consumption. The greatest bladder centroid motion occurred longitudinally, with less movement observed laterally. The maximum bladder centroid movement was 18.8 $\pm$ 2.2 mm inferiorly and 1.8 $\pm$ 0.9 mm posteriorly for every 10% decrease in BV. The rates of changes in triaxial lengths differed across the 4 filling phases. The rate was the largest at a BV range of 10-80 mL, especially in the LR direction, with values of 5.9 $\pm$ 1.0, 3.6 $\pm$ 1.0, and 3.9 $\pm$ 1.0 mm per every 10-mL BV increase for LR, AP, and SI, respectively. With bladder filling (<80 mL), the maximum increase in triaxial length was observed in the SI direction and the rates of all changes considerably decreased, especially at BV > 600 mL.

Conclusion: The v_{tot} could be used to evaluate the temporal changes in the bladder. The spatial changes should be assessed according to different filling phases based on the centroid position and triaxial lengths.

Keywords
bladder, morphology, filling phase, supine position, cervical cancer

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Introduction

The pelvic organs are naturally prone to changes in both position and volume over time, such as during bladder filling. During surgical procedures, these changes can influence the motion of other adjacent organs, with a risk of causing long-term bladder damage.[1] In external-beam radiotherapy (RT), these motions can have a major impact on the precise delivery of the RT dose, often leading to a missed target or large safety margins around the target volume, and/or severe gastrointestinal and genitourinary toxicities.[2,3] In brachytherapy, such changes can also occur after the implantation of the applicator and before and during the treatment, thereby affecting the final plan optimization and dose distribution.[4]

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A bladder diary is used to record information-rich parameters, such as the minimum and total voided volumes. The association between urogenital symptoms and these parameters is assessed to help decision-making,[5] whereas the parameters are usually related to the urinary filling rate and bladder capacity. Likewise, many clinical applications of modern RT also concern changes in bladder volume (BV) and bladder shape.[6-8] Both empty and full bladder protocols are adopted, although a full bladder is usually preferred because it allows greater sparing of healthy tissues, such as the small bowel and the healthy part of the bladder. However, studies have demonstrated that despite strict drinking protocols, patients experience difficulties in maintaining a constant BV.[9] In addition, the BV has been shown to decrease during RT, probably owing to reduced bladder capacity and radiation cystitis.[10]

Recently, we have investigated strategies for maintaining a consistent BV.[10,11] A "comfortably full bladder" approach was adopted using measurements with a portable ultrasound (US) scanner. Consistent BV was mostly achieved after multiple measurements within 2 h after water intake, and target margins were reduced in the superior-inferior (SI) direction.[10] To decrease patient discomfort caused by holding on to urine and to reduce technician labor, a parameterized model for the mean urinary filling rate was proposed, and the optimal US scanning number and RT time were determined using this model. The accuracy of the model was successfully assessed in patients with good compliance (79.2% of all patients), and the proportion of RT fractions with zero wait time (one US scan) increased from 6.5% to 41.2%.[11]

However, these findings of previous studies covered a wide BV range, and it is unknown whether the variations in bladder shape and position were similar across the entire range, which was directly correlated with the RT dose coverage. Hence, the aims of this study were to further investigate the patterns of bladder motion, and to characterize the temporal and spatial changes of the bladder as a function of the BV (10-800 mL). We believe that such information will be helpful in designing an adaptive treatment strategy, owing to the correlation between the clinical target volume (CTV) coverage and bladder injury and bladder filling.[12,13] Moreover, we considered that a bladder diary that records supplementary information serves as a noninvasive tool for evaluating bladder sensation.

Methods and Materials

Patients

A total of 89 patients with stage II-IIIB cervical cancer were included. Ethical approval for this study was obtained from the Medical Ethics Committee of Chongqing University Cancer Hospital with the following reference number CZLS2014048-A. All patients provided written informed consent, and all methods were performed in accordance with the relevant guidelines and regulations. The median patient age was 52.5 years (range, 40-75 years). The patients were asked to empty their bladders and rectum, and underwent controlled water intake to achieve a comfortably full bladder before the planning computed tomography (CT) scan. The median water uptake before the measurements was 300 mL (60-600 mL). The amount of water intake before each treatment fraction depended on the patient's initial BV during the planning CT scan.[10] All patients received a total dose of 50 Gy in 25 daily fractions of 2 Gy.

Planning CT Scan

On the basis of our previous results, a clinical target volume-to-planning target volume (PTV) margin of 6.4 mm was generated in the SI direction for cervical cancer.[10] A planning CT scan was performed with a 5-mm slice thickness on a Brilliance-16 system system (Philips Medical Systems, Inc., Cleveland, OH) because the CT slice thickness influences the accuracy of margin growth and the volume of a region of interest.[14,15] The uterus, cervix, vagina, bladder and rectum were contoured by radiation oncologists specializing in gynecological cancer.

Bladder Scan Protocol

Two radiation therapists measured the BV using a portable 3-dimensional US bladder scanner (BVI9400, Verathon Medical B.V., Netherlands). The scanning mode was set for scanning a female patient who had not undergone a hysterectomy. For each patient before each RT fraction, the first US measurement was performed 1 h after drinking the required amount of water, and multiple measurements were performed at regular 10-min intervals until the BV was consistent with that of the planning CT BV. On the basis of our previous reports, the recommended default tolerance of BV is $\pm 15\%$ to maintain a constant BV throughout each RT fraction. In addition, multiple scans were also performed for each US measurement in a single moment. The mean values of BV were chosen, and the standard deviations were considered uncertainties. After the US measurements, cone-beam CT (CBCT) (Varian Medical Systems, Inc., Palo Alto, CA) was performed weekly before RT. The patients voided their bladder immediately after the completion of treatment, and the postvoid residual urine was evaluated using BVI9400.

Data Analysis

The bladder was contoured on all CBCT scans, and bony matching to the planning CT was performed. The triaxial lengths were measured in the axial, coronal, and sagittal planes using the maximum values. The influences of contouring differences among oncologists, and registration differences due to the region-of-interest selection were investigated. The mean values of BV, centroid coordinates, and triaxial lengths for different contourings and registrations were chosen, and the standard deviations were considered uncertainties (error bars in the figures). For each patient, the shift of the center of the bladder and changes in triaxial lengths on CBCT scans as a function of BV compared with those of planning CT were

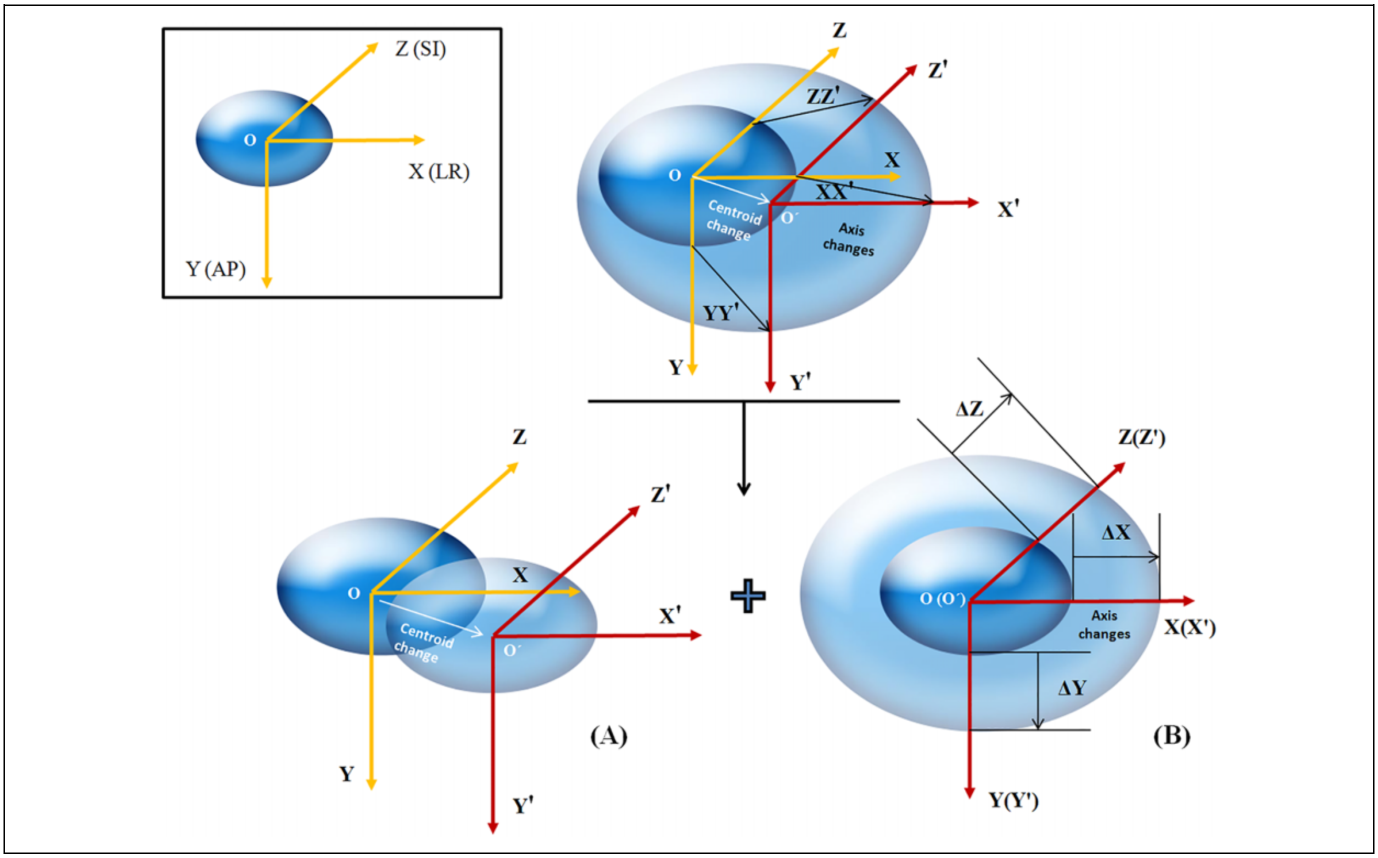

Figure 1. The upper-left image: definition of bladder coordinate system. The upper-right image: the schematic of bladder motion, OO′: centroid shift, XX′, YY′, and ZZ′: the vertex shift of bladder wall. The bottom figure: (A) centroid shift only without triaxial changes; (B) triaxial changes only without centroid shift.

calculated in the left-right (LR), SI, and anterior-posterior (AP) directions. Positive values for LR, SI and AP indicated motion in the right, cranial and posterior directions, respectively. As shown in Figure 1, the bladder motion (the upper-right image) was divided into two separate motions (bottom images A and B, centroid and triaxial–length) to simplify the calculations.

Statistical analyses were performed using the Statistical Package for the Social Sciences program (IBM SPSS Statistics version 22, SPSS22), with the threshold for statistical significance set at $P < 0.05$. The correlation between the mean urinary filling rate (v_{tot}) and age (P_{age}) or water consumption (P_{wat}) was described using Pearson's correlation coefficient, and the relationships among these variables were tested using multivariable linear regression. The slopes of the centroid position and triaxial length with the increasing BV were calculated using the method of least squares.

Results

Bladder Filling Over Time

The relative BV ($\Delta V(t)$) was defined as $V(t) - V_0$, where t is the time of the US scans. V_0 is the BV of the first US measurement, and V(t) is the measured BV at 10-min intervals. $\Delta V(t)$ showed a linear behavior over time. The mean urinary filling rate, v_{tot}, was defined as $\Delta V(t) / t$. The v_{tot} largely varied among patients, ranging from 0.19 ± 0.08 to 6.19 ± 4.32 (mL/min). It was correlated with age (P_{age}, $R = -0.28$, $P = 0.04$) and water consumption (P_{wat}, $R = -0.65$, $P = 0.00$). The relationship between v_{tot} and P_{age} and P_{wat} can be expressed as follows:

$$v_{tot} = 3.22(\pm 0.80) - 0.04(\pm 0.01)P_{age} + 0.01(\pm 0.00)P_{wat}(P < 0.001) \quad (1)$$

Bladder Shape

Owing to CBCT error or poor patient compliance, only 437 planning CT and CBCT scans in this study were performed in this study (Figure 2). Figure 2 shows the product of the 3-axis lengths $L_xL_yL_z$ as a function of BV together with a linear fit for all patients. The fitting parameter was 0.47 ($prob = 1$), and the difference between this value and $6 / \pi$, the standard coefficient of the volume formula of an ellipsoid, was only 0.05. The BV could be calculated as approximately $0.47L_xL_yL_z$ in this study.

Centroid Position With Increasing BV

The relative BV ($\delta V(f)$) was defined as $(V(f) - V(1)) / V(1)$, where f is the RT fraction. V(1) is the BV at the planning CT

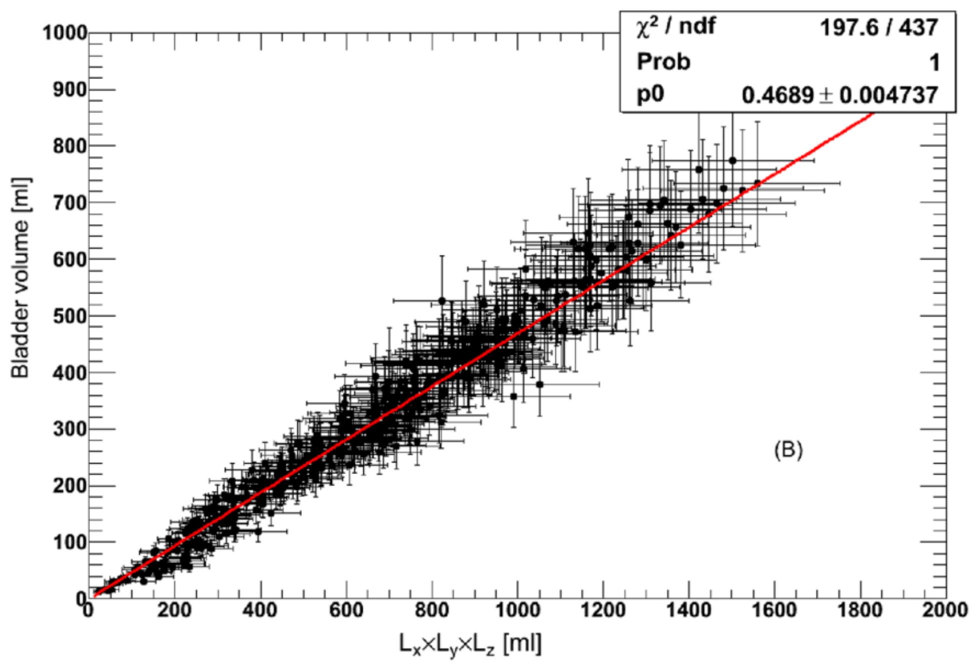

Figure 2. The product of 3-axes lengths as a function of BV together with a linear fit. The error bars indicated the US and CBCT measurement uncertainties.

scan, and V(f) is the measured BV at the subsequent CBCT scan. In this study, δV(f) ranged from −0.92 to 1.09. When δV(f) changed from −0.3 to 0.3, the greatest centroid motion occurred longitudinally, with less movement observed laterally, and the bladder centroid shifted toward the superior and anterior directions with an approximately constant rate. The maximum bladder centroid movement was 18.8 ± 2.2 mm inferiorly and 1.8 ± 0.9 mm posteriorly for every 10% decrease in BV. When δV(f) was > 0.3, the rate decreased by 62.7% in the SI direction, but the centroid continued to shift toward anterior direction at the same rate. However, when δV(f) was < −0.3, the movement became irregular (Figure 3).

Triaxial Lengths With Increasing BV

After multiple-slope (Sp) fitting using the method of least squares, we observed that the divisions of BV subranges (i.e., 10-80, 80-320, 320-600, and 600-800 mL) had the highest sum of possibilities, compared with the other divisions of BV subranges (Figure 4A-C). For example, all possibilities of fitting to the 4 subranges in Figure 4C were 1. For a small BV (10-80 mL), L_x, L_y, and L_z rapidly increased with bladder filling, especially in the LR direction. The slope in the LR direction (Sp_{LR}) of 0.06 cm^{-2} was 1.52-1.66 times as large as the slopes in the SI and AP directions (Sp_{SI}, Sp_{AP}). Sp_{LR}, Sp_{AP}, and Sp_{SI} all decreased with increasing BV subranges, although Sp_{AP} showed little change in the BV range of 320-800 mL. When BV was > 80 mL, Sp_{SI} became the largest, followed by Sp_{AP} and Sp_{LR}.

Eccentricity With Increasing BV

Different changing rates of triaxial length will inevitably lead to constant changes in bladder shape. We used variable eccentricity to describe this change (Figure 4D). In the coronal plane, the eccentricity increased first and reached the maximum value, then decreased with increasing BV. In the transverse plane, the eccentricity always decreased. The length axes of these ellipsoids were both oriented in the LR direction in the above two planes. In the sagittal plane, the eccentricity also decreased when the BV was < 540 mL in this study. When BV was > 540 mL, the eccentricity began to steadily increase.

Discussion

To design the optimal treatment for urogenital diseases (especially cancer), detailed information about the bladder is often recorded in a bladder diary, including 24-h voiding frequency, minimum and maximum voided volumes, and total voided volume. These parameters are usually related to the urinary filling rate and bladder capacity. A previous study reported large variations in the urinary filling rate among different patients.[11] In this study, the mean urinary filling rate also largely varied among patients. Fortunately, the approximate value can be calculated using a water-drinking- and age-based linear formula, and the result was also consistent with the previous findings.[11] Coincidentally, many age-based formulae for the bladder capacity benchmark are available.[16] These formulae can also be used to evaluate the movement of the bladder during treatment.

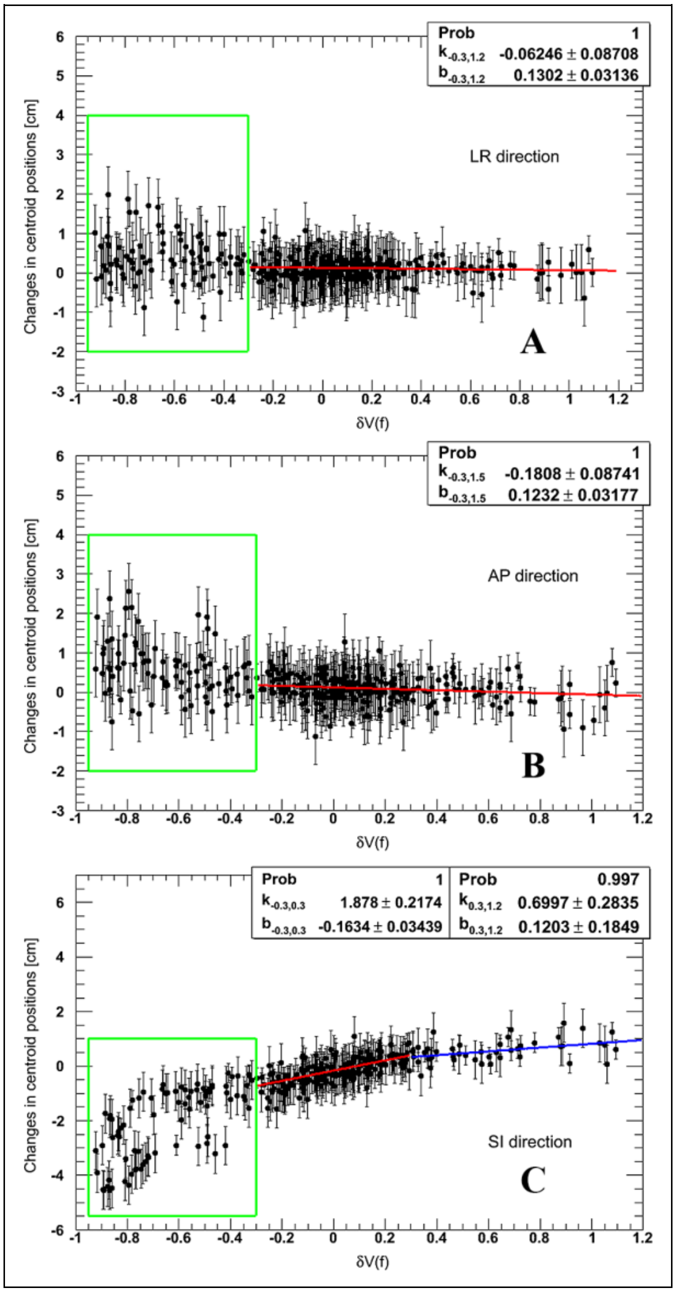

Figure 3. Changes in centroid position as a function of the relative BV (δV(f)) together with a linear fit in the LR (A), AP (B), and SI (C) directions.

Given the movement of the bladder, a comfortably full bladder is preferred in the treatment of cervical and related cancers based on the organ at risk criteria. Not only during the highly conformal external-beam RT but also during 3-dimensional magnetic resonance/CT-based brachytherapy, bladder motion is a contributory factor to the variations in the target and organs at risk. Early in 2008, Chan et al observed that the uterine fundus moved 18 mm inferiorly and the cervical os moved 3 mm anteriorly for every 10 mL decrease in BV.[17] Pinkawa et al also demonstrated that bladder filling can cause the maximal bladder wall displacements of 15 and 21 mm in the anterior and superior directions, within a BV ranging from −100 to 200 mL relative to the planning BV (217 mL, i.e. $-0.4 < \delta V(f) < 0.9$).[18]

In this study, we did not use the point-of-interest analysis or investigated bladder wall movements at 6 isolated borders, as did previous studies. Instead, we analyzed the entire region of the bladder and investigated its changes and interactions on the three axes. We found that the BV changes were similar among all participants. The bladder centroid maximally moved by 18.8 ± 2.2 mm inferiorly and 1.8 ± 0.9 mm posteriorly for every 10% decrease in BV. The centroid motion in the LR direction was negligible. The maximum rates of changes in triaxial lengths were observed in the BV range of 10-80 mL, and the displacements were almost constant for every 10 mL increase in BV: 5.9 ± 1.0, 3.6 ± 1.0, and 3.9 ± 1.0 mm for LR, AP, and SI respectively. The dominant source of short-term bladder motion was bladder filling.

In the study by Chan et al, the mean BV was approximately 90 mL. If calculated according to our findings, the bladder centroid moved by approximately 18.8 ± 2.2 and 1.8 ± 0.9 mm, and the triaxial lengths decreased by 1.8 and 0.8 mm in the SI and AP directions for every 10 mL decrease in BV. The magnitudes of bladder movements were completely comparable to those reported by Chan et al with respect to movements of the uterine fundus and cervical os. These data again confirmed that uterine motion is predominantly influenced by bladder filling.[19] Meanwhile, the median BV in Chan et al's study was only 28 mL (3.3-652 mL).[17] The BV in this study ranged from 10 to 800 mL, and the average and median values were 312 and 295 mL respectively. Because these data were more closer to the bladder filling protocol, our conclusion is more adaptable in clinical RT practice.

In addition, the bladder was considered to be a semi-ellipsoid to simplify the calculation. Information on asymmetry and symmetry in the human pelvic cavity is shown in Figures 3 and 4. Lateral and posterior movements are strongly limited by the pelvic bones and sacral bone, respectively, although the soft tissues and bowel loops in the anterior and superior directions can be easily shifted. However, the bladder is not a perfect symmetric spheroid. The foci of the ellipsoid in the right and posterior directions are further away from the centroid. In the SI direction, the inferior focal length is large for $-0.3 < \delta V(f) < 0.3$; for $\delta V(f)$ of > 0.3, the superior focal length becomes larger than the inferior value. This phenomenon can be verified in Figure 3, owing to non-zero changes in the centroid position when $\delta V(f) = 0$. Conversely, the bladder seems to be a plate-shaped organ when it is fully emptied; the lengths were 5.48 ± 0.48 and 4.24 ± 0.48 cm in the LR and AP directions, and the bladder wall thickness was 0.77 ± 0.51 cm when the residual urine was neglected. This is consistent with the wall thickness obtained using the ellipsoid and automated methods.[20] This value will also help in delineating the inner bladder surfaces via the outer bladder for an accurate RT dose reconstruction.[21]

It is known that bladder motion can lead to a change in the dose delivered to the bladder itself and adjacent structures.[22]

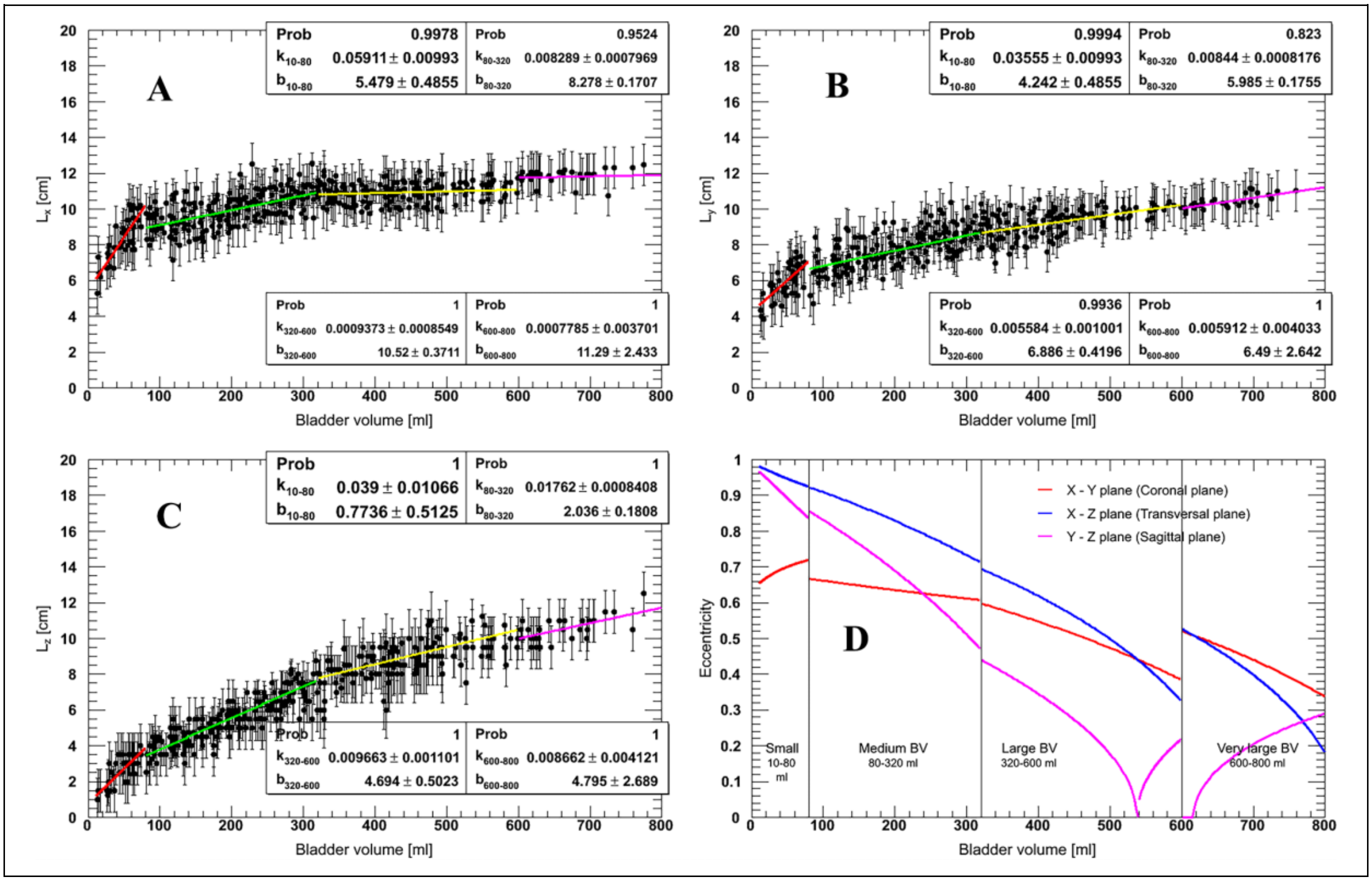

Figure 4. Changes in triaxial lengths as a function of the bladder volume together with a linear fit in the LR (A), AP (B), and SI (C) directions. (D) The eccentricity changes as a function of the bladder volume.

These variations might result in alterations in clinical outcomes, such as increased toxicity. A univariate analysis showed that bladder filling was the only factor related to grade ≥ 2 acute genitourinary toxicity, and was also the factor with the greatest influence on acute gastrointestinal toxicity on multivariate analysis.[23] Although our study did not investigate the impact of bladder motion on RT dose variations, we evaluated temporal and spatial changes of the bladder as a function of the BV using a imaging-guided RT technique. We found that the position and size of the bladder should be assessed according to 4 filling phases: 10-80, 80-320, 320-600, and 600-800 mL. A previous analysis also showed patients could easily achieve a comfortably full bladder in the following range of initial BV: approximately 300 mL without BVI9400 measurement and approximately 160-450 mL with BVI9400 measurement.[10] Therefore, a BV of 320-450 mL measured using BVI9400 is recommended in the future clinical practice because the change rates of triaxial lengths will dramatically decrease. The triaxial lengths decreased from 8.3, 8.4, and 17.6 mm to 0.9, 5.6, and 9.6 mm in the LR, AP, and SI directions, respectively, for every 100 mL decrease in BV.

One limitation of this study is that we did not investigate the impacts of different body positions and gender on bladder motion. In addition, we did not consider the issues of target margin generation and variations in target dose, and the possible relationship to bladder filling variations. This is due to the limited resolution of CBCT, and it is difficult to contour CTV. Another unresolved issue with impact on bladder injury is how bladder filling contributes to the positioning of the bladder neck, the trigone, and the orifices of the ureters, because these parts are crucial for acute and late toxicity.[24,25] Further investigations are planned to clarify these matters.

Conclusion

The bladder is always changing its position, size and even shape. In order to design the optimal treatment for urogenital diseases, we should quantify the motion of the urinary bladder. The temporal changes in the bladder could be evaluated by the v_{tot}, and it was correlated with the patients' age and water consumption. The spatial changes in the bladder could be assessed according to different filling phases (i.e., 10-80, 80-320, 320-600, and 600-800 mL) based on the centroid position and triaxial lengths; the greatest bladder centroid motion occurred longitudinally, with less movement observed laterally, and the rates of changes in triaxial lengths differed across the 4 filling phases.

Abbreviations

BV, bladder volume; US, ultrasound; CBCT, cone-beam computed tomography; L_x, L_y, L_z, 3-axes lengths; LR, left–right; AP, anterior–posterior; SI, superior–inferior; Sp, slope; RT, radiotherapy; GI, gastrointestinal; GU, genitourinary; CTV, clinical target volume; PTV, planning target volume.

Authors' Note

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request. Ethics approval for this study was obtained from the Medical Ethics Committee of Chongqing University Cancer Hospital with the following reference number CZLS2014048-A. All patients gave written informed consent, and all methods were performed in accordance with the relevant guidelines and regulations. The abstract of this paper was presented at the ASTRO as a poster presentation with interim findings. The poster's abstract was published in "Poster Abstracts" in *Int J Radiat Oncol Biol Phys.* (2019 Volume 105, Issue 1, Supplement, Pages E742-E743): Hyperlink with DOI https://doi.org/10.1016/j.ijrobp.2019.06.849.

Author Contributions

Fu Jin and Qiang Liu contributed equally to this work. Fu Jin and Huanli Luo participated in the design of the study and performed the statistical analysis. Qiang Liu, Rui Zhu, Yanhong Mou, and Huanli Luo participated in the data collection. Yongzhong Wu and Ying Wang conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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