Strahlentherapie
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Original Article

Variability in Bladder Volumes of Full Bladders in Definitive Radiotherapy for Cases of Localized Prostate Cancer

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Background and Purpose: To evaluate variation in bladder volume of full bladders in definitive radiotherapy for localized prostate cancer and to investigate potential predictors of increased bladder volume variations.
Patients and Methods: In 40 patients, the bladder volume was measured with megavoltage computed tomography (MVCT) imaging performed just before irradiation during the administration of the 1st fraction (#1), the 10th fraction (#10), the 20th fraction (#20), and the 30th fraction (#30). Patients were instructed to avoid urinating for 60–90 minutes before the planning CT (pln-CT) scan and before daily irradiation. Patients were also encouraged to drink an unspecified volume of liquid that would result in a clear but tolerable urge to urinate.
Results: The population-mean bladder volume (±1SD) was 219 ml (±83 ml) at the planning CT scan (pln-CT), 186 ml (±96 ml) at #1, 149 ml (±73 ml) at #10, 137 ml (±59 ml) at #20, and 136 ml (±60 ml) at #30. The mean intrapatient variation in bladder volume (1 SD relative to the mean bladder volume of each patient) was 38% (range: 10–84%). The bladder volume at the pln-CT was correlated with the intrapatient variance in bladder volume with a correlation coefficient of 0.54 and $p<0.001$.
Conclusion: We observed a significant decline in bladder volumes during the course of radiotherapy. The bladder volume at the pln-CT was a significant predictor of increased bladder volume variations.

Key Words: Radiotherapy · Prostate cancer · IMRT · Bladder volume · Full bladder · MVCT

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Schwankungen des Volumens gefüllter Blasen in der definitiven Radiotherapie bei lokalisiertem Prostatakarzinom

Hintergrund und Zweck: Die Evaluierung der Schwankungen des Blasenvolumens gefüllter Blasen in der definitiven Radiotherapie bei lokalisiertem Prostatakrebs sowie die Untersuchung potenzieller Prädiktoren für erhöhte Schwankungen des Blasenvolumens.
Patienten und Methoden: Das Blasenvolumen von vierzig Patienten wurde mittels Megavoltage-Computertomographie (MVCT) bestimmt, die bei der Verabreichung der 1. Fraktion (#1), der 10. Fraktion (#10), der 20. Fraktion (#20) und der 30. Fraktion (#30) kurz vor der Bestrahlung durchgeführt wurde. Die Patienten wurden angewiesen, 60–90 Minuten vor dem Planungs-CT (pln-CT)-Scan und vor der täglichen Bestrahlung nicht zu urinieren. Die Patienten wurden zudem ermuntert, eine nicht näher bestimmte Menge an Flüssigkeit zu sich zu nehmen, um einen deutlichen aber tolerierbaren Harndrang herbeizuführen.
Ergebnisse: Der Mittelwert der Grundgesamtheit des Blasenvolumens (±1SA) lag beim Planungs-CT-Scan (pln-CT) bei 219 ml (±83 ml), 186 ml (±96 ml) bei #1, 149 ml (±73 ml) bei #10, 137 ml (±59 ml) bei #20 und 136 ml (±60 ml) bei #30. Der Mittelwert der Schwankung des Blasenvolumens innerhalb eines Patienten (1SA bezogen auf den Mittelwert des Blasenvolumens des einzelnen Patienten) lag bei 38 % (Spannweite: 10–84 %). Das Blasenvolumen zum Zeitpunkt des pln-CT wurde mit der Streuung des Blasenvolumens innerhalb eines Patienten korreliert, woraus sich ein Korrelationskoeffizient von 0,54 mit $p<0,001$ ergab.
Fazit: Im Laufe der Radiotherapie konnte eine deutliche Verringerung der Blasenvolumen festgestellt werden. Das Blasenvolumen zum Zeitpunkt des pln-CT-Scans erwies sich als signifikanter Prädiktor erhöhter Schwankungen im Blasenvolumen.

Schlüsselwörter: Radiotherapie · Prostatakarzinom · IMRT · Blasenvolumen · Gefüllte Harnblase · MVCT

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Introduction

The bladder is filled to various volumes during fractionated radiotherapy. Changes in the bladder volumes affect both bladder dose volume and the position of adjacent organs (the prostate, seminal vesicles, small intestine, sigmoid colon, and rectum). Furthermore, significant variations in bladder volume can confound the planned dose distributions for three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) [8, 9, 14, 20, 23]. Therefore, bladder volume must be kept consistent throughout planning and treatment to reduce positional uncertainties related to the prostate and the risk of increased toxicity in the normal surrounding tissue.

There is no current consensus regarding optimal bladder volumes. One possible advantage of maintaining a full bladder is that part of the bladder is moved away from the target volume, thus, reducing bladder toxicity [6, 11, 12]. Moreover, a full bladder moves the small intestine and the sigmoid colon out of the irradiation field, also reducing toxicity in these organs [3, 5, 10, 13]. For these reasons, we ask patients scheduled to undergo irradiation for prostate cancer to maintain a full bladder during irradiation. However, in patients with full bladders, large variations in bladder volume vs. time trends have been observed during the course of radiotherapy course [11, 16, 18].

The aim of this study was to quantify the variations and trends in full bladder volume during the course of radiotherapy in patients being treated for prostate cancer. The second aim was to investigate the potential predictors of increased bladder volume variations.

Methods and Materials

Patient Characteristics

Between December 2007 and March 2008, 40 patients with localized prostate cancer (cT1-3N0M0) were enrolled into this study (Table 1).

Table 1. Patient characteristics. cT: stage clinical tumor stage; PSA: prostate-specific antigen; IPSS: International Prostate Symptom Score.

Tabelle 1. Patientenmerkmale. cT-Stadium: klinisches Tumorstadium; PSA: prostataspezifisches Antigen; IPSS: International Prostate Symptom Score (Internationaler Prostata-Symptomscore).

	No. (%)
cT stage (TNM 6th ed.)	
1–2a	19 (48)
2b	4 (10)
2c–3	17 (43)
Gleason score	
2–6	15 (38)
7	9 (23)
8–10	16 (40)
Initial PSA	
0–10	25 (63)
10–20	10 (25)
>20	5 (13)
D'Amico's risk group	
Low	10 (25)
Intermediate	8 (20)
High	22 (55)
IPSS	
0–8	22 (55)
9-1-9	13 (33)
20–30	5 (13)
Neoadjuvant hormone therapy	
Yes	21 (53)
No	19 (48)
Age mean (range)	71 (53–83)

Radiotherapy

All patients received definitive radiotherapy with helical tomotherapy using the Hi-Art System (TomoTherapy, Inc., Madison, WI, USA) at Edogawa Hospital (Tokyo, Japan). Patients were classified according to D'Amico's risk-group definition [4]. The clinical target volume (CTV) was defined as prostate only for low-risk patients, and prostate with a 5 mm margin and a 2 cm wide section of the proximal seminal vesicle for the intermediate-risk and high-risk patients. The planning target volume (PTV) was defined as the CTV plus a 5 mm margin. The prescribed dose, which was defined as 95% of the PTV receiving 100% of the prescribed dose (D95), was 72 Gy in 36 fractions for the low-risk patients and 76 Gy in 38 fractions for the intermediate-risk and high-risk patients. Treatment planning optimization was performed to satisfy the dose constraints defined by the in-house protocols for both the PTV and the organs at risk (OAR). The dose constraints for the PTV are a mean dose <79.8 Gy (105% of the prescribed dose) and a maximum dose <83.6 Gy (110% of the prescribed dose). The dose constrains for OAR are (1) the rectum wall defined as 0.5 cm above and below the PTV of no more than 10% of the volume to receive a dose >78 Gy, no more than 25% of the volume to receive a dose >70 Gy, no more than 35% of the volume to receive a dose >60 Gy, and no more than 65% of the volume to receive a dose >40 Gy; (2) the bladder wall of no more than 35% of the volume to receive a dose >70 Gy, and no more than 65% of the volume to receive a dose >40 Gy; (3) the sigmoid colon of no more than 0.5 ml to receive a dose >65 Gy; and (4) the small bowel of no more than 0.5 ml to receive a dose >60 Gy. A total of 21 patients (53%) underwent hormone therapy sequentially and/or concurrently. The patients were irradiated in a supine position with a knee support. A megavoltage computed tomography (MVCT) scan was performed just before the daily irradiation. In addition, soft tissue-based 3D–3D matching of the MVCT images with the planning CT (pln-CT) images was performed with the couch shifted to the optimal position.

Patient preparations

The patients were instructed to refrain from urinating for 60–90 minutes before the planning CT scan (pln-CT) and before daily irradiation. The patients were also encouraged to drink an unspecified volume of liquids to ensure a clear but tolerable urge to urinate. The patients were instructed to take laxatives before the pln-CT, although no specific instructions regarding bowel movements before daily irradiation were issued.

Bladder volume measurement

Bladder volume at the pln-CT was measured by kilovoltage CT (kVCT) imaging with a thickness of 2.5 mm. Bladder volume was also measured by MVCT imaging with a thickness of 4 mm four times during the course of radiotherapy: at the 1st fraction (#1), at the 10th fraction (#10), at the 20th fraction (#20), and at the 30th fraction (#30). All bladder volumes were measured by the same radiation oncologist (N.N.) by delineating whole bladder outlines in Focal (CMS Inc., St. Louis, MO, USA) (Figure 1).

We assessed the variability in population bladder volumes throughout pln-CT and radiotherapy by calculating mean population bladder volumes and standard deviations (SD). The mean of five measurements for each patient is shown as V_{mean}. As a measure of variation in intrapatient bladder volumes, the SD of V_{mean} (denoted as σ_{bl}) is used, whereas, $\sigma_{bl\text{-}rel}$ was defined asσ_{bl} relative to V_{mean}.

Potential predictors

We also assessed the correlations between intrapatient bladder volume variations ($\sigma_{bl\text{-}rel}$) and potential univariate predictors. The following potential predictors were evaluated: age (continuous), T stage (T1–T2a, T2b, T2c–T3), Gleason score (2–6, 7, 8–10), pretreatment prostate-specific antigen (PSA) (continuous), risk group (low, intermediate, high), international prostate symptom score (IPSS) [2] (continuous), hormone therapy (with or without), bladder volume at the pln-CT (continuous), prostate volume (continuous), PTV volume (continuous), and acute cystitis (grade 0–1, grade 2, grade 3–5) .

Statistical analysis

We used Prism version 5 (GraphPad Software Inc., La Jolla, CA, USA) for statistical analysis. Differences were considered significant if the relevant two-tailed p values were less than 0.05. The incidence of acute cystitis was described according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Results

All patients completed radiotherapy free of unscheduled interruptions exceeding 2 days. We successfully acquired all planned bladder volume measurements. The mean prostate volume was 27 ml (range: 9–77 ml), the mean PTV volume was 108 ml (range: 49–240 ml). The incidence of acute cystitis during radiotherapy was grade 2 in 7 patients (18%). No cases of grade 3–5 acute cystitis were observed.

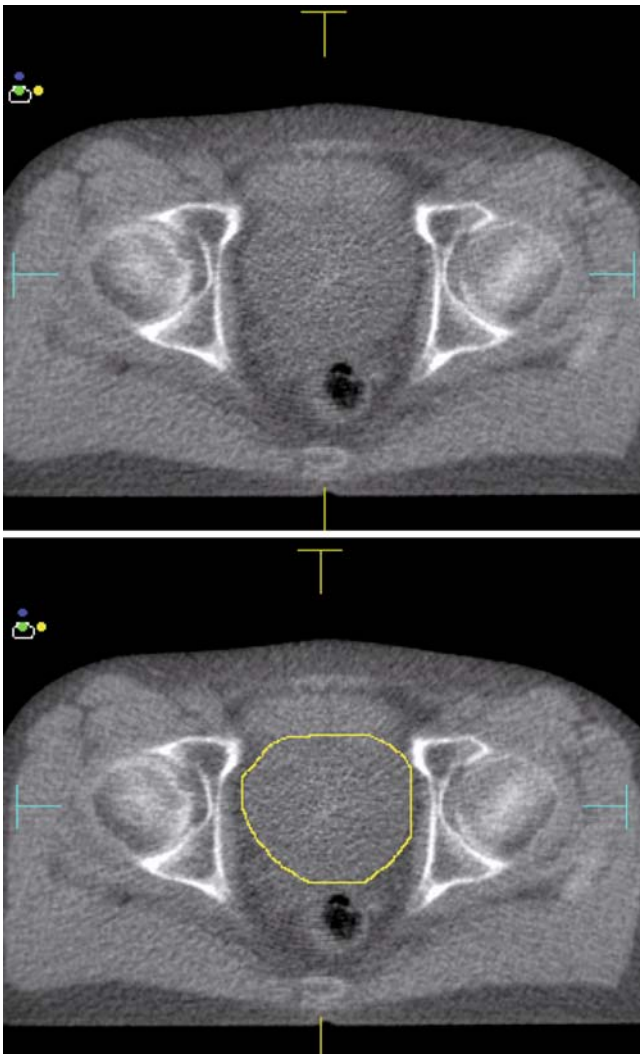

Figure 1. An example of mega voltage computed tomography (MVCT) imaging.

Abbildung 1. Beispiel einer Megavoltage-Computertomographie (MVCT).

Bladder volume trends

The mean population bladder volume (±1 SD) was 219 ml (±83 ml) at the pln-CT, 186 ml (±96 ml) at #1, 149 ml (±73 ml) at #10, 137 ml (±59 ml) at #20, and 136 ml (±60 ml) at #30 (Figure 2). A mean population bladder volume reduction of 38% was observed from the pln-CT to #30 ($p<0.001$ by Wilcoxon's matched pairs test). A significant mean population bladder volume reduction was also found from #1 to #30 ($p<0.001$ by Wilcoxon's matched pairs test). The meanσ_{bl} was 62 ml (range: 11–141ml), while the mean$\sigma_{bl\text{-}rel}$ was 38%

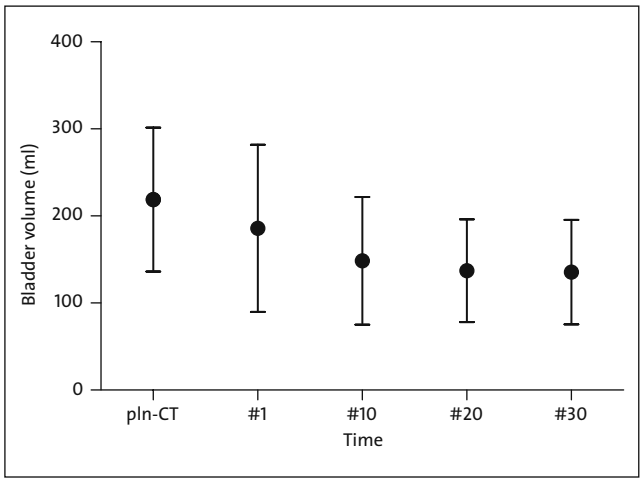

Figure 2. Population-mean bladder volume measured at the planning computed tomography scan (pln-CT) and during the course of radiotherapy. Error bars indicate one standard deviation. *#1, #10, #20, #30* = at the 1st fraction, at the 10th fraction, at the 20th fraction, and at the 30th fraction of radiotherapy, respectively.

Abbildung 2. Mittelwert der Grundgesamtheit des Blasenvolumens, der zum Zeitpunkt des Planungs-Computertomographie-Scans (pln-CT) und während des Verlaufs der Radiotherapie gemessen wurde. Die Fehlerbalken weisen auf eine Standardabweichung hin. *#1, #10, #20, #30* = bei der Verabreichung der 1. Fraktion, der 10. Fraktion, der 20. Fraktion bzw. der 30. Fraktion der Radiotherapie.

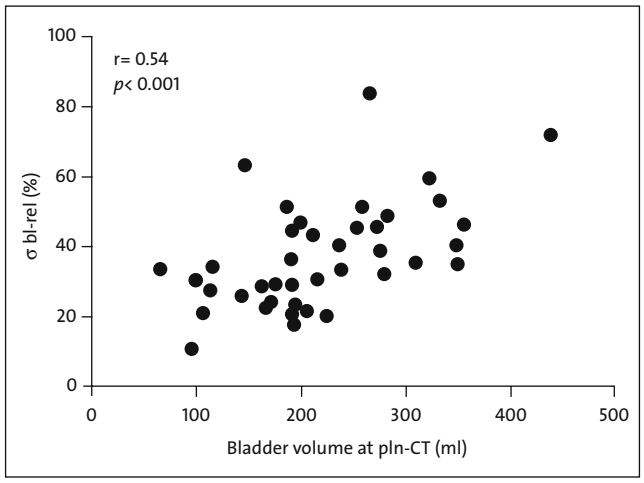

Figure 3. Correlation graph showing bladder volumes at the planning computed tomography scan (pln-CT) vs. intrapatient bladder volume variations ($\sigma_{bl\text{-}rel}$). $\sigma_{bl\text{-}rel}$ σ_{bl} relative to V_{mean}, σ_{bl} standard deviation of V_{mean}, V_{mean} the mean of five measurements of a patient.

Abbildung 3. Auf diesem Korrelationsdiagramm ist die Beziehung zwischen den Blasenvolumen zum Zeitpunkt des Planungs-Computertomographie-Scans (pln-CT) und den Schwankungen des Blasenvolumens innerhalb eines Patienten abgebildet ($\sigma_{bl\text{-}rel}$). $\sigma_{bl\text{-}rel}$ σ_{bl} relativ zu V_{mean}, σ_{bl} Standardabweichung von V_{mean}, V_{mean} der Mittelwert von fünf an einem Patienten vorgenommenen Messungen.

(range: 10–84%). We observed a statistically significant correlation between intrapatient variation in bladder volume ($\sigma_{bl\text{-}rel}$) and bladder volume at the pln-CT (Pearson r=0.54, $p<0.001$) (Figure 3). The intrapatient variation in bladder volume ($\sigma_{bl\text{-}rel}$) was not significantly associated with age ($p=0.68$), T stage ($p=0.88$), Gleason score ($p=0.78$), pretreatment PSA ($p=0.12$), risk group ($p=0.67$), IPSS ($p=0.66$), hormone therapy ($p=0.34$), prostate volume ($p=0.80$), PTV volume ($p=0.74$), or acute cystitis ($p=0.11$).

Discussion

In order to improve bladder volume consistency when the goal is to maintain a full bladder, many institutions specify the volume of liquids to be consumed and the times at which such liquids should be consumed (e.g., drink 500 ml of fluid an hour before the planning CT scan and treatment) [1, 5, 15, 19, 22]. However, large variations in bladder volume have been reported with such protocols [1]. O'Doherty et al. [16] report that a fixed drinking protocol did not eliminate all variations in the bladder volume, in part due to significant individual variations in velocity of bladder filling. They [16] also reported that patients are able to accurately judge their bladder filling state and suggested that subjective patient assessments should be taken into account during efforts to control bladder volume. Stam et al. [18] found a weak but significant correlation between subjective scores for urge to urinate and bladder volume. For these reasons, our institution applied a protocol that did not specify liquid volumes. Instead, the patients were told to adjust the amount of liquid ingested based on their urge to urinate. Nonetheless, our study showed large variations in bladder volume. In an alternative approach, Stam et al. [18] measured daily bladder volumes during daily treatment using a bladder ultrasound scanner and provided patients with feedback to achieve reproducible bladder volumes. The feedback consisted of informing the patients of their daily bladder volume coupled with drinking advice. However, the daily variations in bladder volume did not differ significantly between the control group and the feedback group ($p=0.20$). Table 2 summarizes the findings of previous reports on variations in intrapatient bladder volume, suggesting that no protocol can ensure consistent bladder volumes when the goal is to maintain a full bladder.

Our study showed a decline in bladder volumes during the treatment course. Several previous reports [11, 16, 18] on bladder volume variance in definitive radiotherapy for prostate cancer have found the same trend. This trend was also reported in postoperative radiotherapy for prostate cancer [7] and in radiotherapy for uterine cervical cancer [1]. Although various protocols intended to achieve reproducible bladder volumes were used in these studies, a decreasing trend in bladder volume was a common finding. The reason for the decline in bladder volume remains unclear and may be multifactorial. Although Pinkawa et al. [17] hypothesized that cystitis might lead to a decline in bladder volume, our study showed no sig-

Table 2. Previous reports on bladder volume variation.

*intrapatient one standard deviation (one standard deviation relative to mean bladder volume).

Tabelle 2. Frühere Berichte zur Variation des Blasenvolumens.

*eine Standardabweichung innerhalb eines Patienten (eine Standardabweichung gegenüber dem Mittelwert des Blasenvolumens).

Author	Diagnosis	Volume drunk	No. of patients	No. of measurements	Initial bladder volume	Bladder volume reduction	Bladder volume variation*
Lebesque et al. [9]	Prostate cancer	not fixed	11	3	255 ml	28%	89 ml (33%)
Stam et al. [14]	Prostate cancer	not fixed (control group)	18	Daily	348 ml	31%	149 ml (47%)
		gave patients drinking advice according to their daily bladder volume (feedback group)	16	Daily	367 ml	19%	156 ml (40%)
Ahmad et al. [19]	Uterine cervical	500 ml (1 hour before)	24	Twice weekly	378 ml	71%	168 ml
This study	Prostate cancer	not fixed	40	4	219 ml	38%	62 ml (38%)

* intrapatient one standard deviation (one standard deviation relative to mean bladder volume).

nificant correlation between intrapatient variations in bladder volume and the incidence of acute cystitis, and the mechanism underlying the decline in bladder volume can not be explained by cystitis alone, since our study and previous reports [1, 11, 16, 18] showed that reductions in bladder volume occurred immediately after treatment had been initiated. Bladder volume reductions during a treatment course may result in inadequate bladder dose–volume histograms (DVH) and may move the small intestine and sigmoid colon into the high dose irradiated field, increasing the potential toxicity for these organs. Based on the clear trend toward a decline in bladder volume during the course of radiotherapy, a more effective approach may be to perform planning CT scans in the middle of the fractionated radiotherapy course and perform replanning when large bladder volume variations are found.

In our study, larger bladder volumes at planning CT scans correlated with larger bladder volume variations, and previous studies reported similar findings [11, 16, 18, 21]. On the other hand, excessively small bladder volumes make it difficult to satisfy the planning dose constraints for adjacent organs (the bladder, small intestine, and sigmoid colon). For these reasons, several institutions target a half-full bladder or a comfortably full bladder [16, 18]. A half-full bladder appears to represent a reasonable target, offering the potential to improve bladder volume consistency in order to satisfy the dose constraints of the adjacent organs.

We used two different modalities to measure bladder volume: kVCT and MVCT. While the difference between these two modalities may have affected our results, the finding of bladder volume reductions during the treatment course was clear and definite. We also found significant population-mean bladder volume reductions from #1 to #30, which were both measured by MVCT imaging.

Conclusions

A significant decline in bladder volumes during the course of radiotherapy was observed. The bladder volume at the pln-CT was a significant predictor of increased bladder volume variations. It may be possible to harness this trend to reduce bladder volume variance in order to avoid over-full bladders.

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