


Transabdominal Ultrasonography-Defined Optimal and Definitive Bladder-Filling Protocol With Time Trends During Pelvic Radiation for Cervical Cancer

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Abstract

Purpose: Advanced radiotherapy techniques have emphasized on the importance of accurate target volume localization and delineation. The aim of this study was to determine time taken to achieve moderate bladder volume under physiological conditions, using transabdominal ultrasound. **Materials and Methods:** Patients with cervical cancer undergoing radical radiation with or without concomitant chemotherapy underwent serial ultrasound to estimate bladder filling. With a strict bladder protocol of consuming 1000 mL of water orally over 30 minutes after emptying the bladder, ultrasound was done after 45 minutes from bladder emptying time and repeated at 15-minute interval till 300 (25) mL filling was achieved and repeated every week. **Results:** Forty-six patients with weekly ultrasound for bladder-filling documentation were evaluated. The mean (standard deviation) bladder volume measured at 45 minutes was 220 (93), 210 (95), 195 (91), 195 (96), and 190 (85) mL (average: 200; median: 195 mL) for the first to fifth week, respectively, and the mean (standard deviation) volume at 75 minutes was 300 (95), 310 (80), 290 (80), 295 (80), and 285 (70) mL (average: 295; median: 300 mL). The mean (standard deviation) time for bladder filling to 300 mL in the first, second, third, fourth, and fifth week was 57 (13.5), 67 (16.6), 66 (16.7), 66 (15.5), and 69 (17.1) minutes, respectively. **Conclusion:** Bladder filling to a definitive moderate volume at a reasonably fixed time period in each week of radiation is well tolerated, feasible, and measurable by weekly transabdominal ultrasound measurements.

Keywords

bladder-filling protocols, pelvic radiotherapy, ultrasonography, carcinoma cervix

Abbreviations

CT, computerized tomography; FIGO, Federation of International of Gynecologists and Obstetricians; HDR, high-dose rate; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; LWH, length, width, and height; MRI, magnetic resonance imaging; PTV, planning target volume; SD, standard deviation; US, ultrasound

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Introduction

In the era of high-precision radiotherapy, accurate localization and delineation of the target volume is imperative. In newer radiotherapy techniques such as intensity-modulated radiotherapy (IMRT), high-dose region conforms very precisely to the target volume, beyond which there is a rapid dose falloff. If the target volume is mobile, it can move out of high-dose region resulting in a geographical miss.¹ Hence, knowledge of the daily physiological variation in the position of target or

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adjacent organs guides in deriving appropriate internal margins.² Extrapolating these facts in IMRT for cervical cancers, variation in position of primary tumor and uterocervical complex due to bladder, and rectal filling poses a major concern.³ Thus, we need to formulate guidelines for both bladder and rectal filling during the simulation and treatment stages of pelvic radiotherapy.⁴ Chan et al and van De Bunt et al have studied the variation in uterine and cervical position during the course of radiotherapy.^{1,2} Studies assessing the relationship between bladder filling and uterine movement have shown that there is significant uterine motion in the cranial direction with minimal anteroposterior change in cervical position.^{5,6}

Reducing bladder-filling uncertainties would reduce to a large extent, extreme changes in the position of uterus and cervix. An empty bladder could lead to an excellent reproducibility but results in an increased integral dose, whereas a maximum filling results in a decrease in integral doses to bladder. The full bladder largely moves the small bowel out of the field⁷⁻⁹ and with increasing bladder filling, part of the bladder moves out of the treated volume.^{4,5,10} However, a maximum bladder filling cannot be maintained during the course of pelvic radiation due to varying grades of acute cystitis while treating patients with cervical cancer.⁵ Hence a moderate bladder filling with more or less constant volume would be desirable throughout the course of radiation. The aim of this study was to determine time taken to achieve moderate bladder volume under physiological conditions daily during the entire course of pelvic radiation which could be applicable in high-precision radiation practice. This was assessed using transabdominal ultrasound (US) at different time periods weekly after a planned bladder-filling protocol by consumption of water during the entire course of radiation therapy.

Materials and Methods

Patients

Forty-six consecutive patients with cervical cancer Federation of International of Gynecologists and Obstetricians (FIGO) II-IIIb treated with radical radiation therapy with or without concomitant weekly cisplatin chemotherapy in 2010 to 2011 were included in the study. After counseling and explaining the study details, an informed written consent was obtained. Maximum bladder capacity (cystometric) under physiological conditions is 500 to 650 mL, so a moderate filling of 300 (25) mL was chosen for this study. In order to achieve a uniform bladder-filling protocol, all patients were asked to consume 1000 mL of plain water orally over 20 to 30 minutes after emptying the bladder. Ultrasound was done after 45 minutes from bladder emptying time and repeated at 15-minute interval till 300 (25) mL, filling was achieved and repeated every week (Figure 1). A single planning computerized tomography (CT) scanning was performed after patients achieved 300 mL bladder filling with 3 to 5 mm slice thickness for external radiation planning. All these patients received pelvic radiation with 4-field box technique followed by high-dose rate (HDR)

brachytherapy as per institutional protocols.¹¹ Twenty-six (55%) patients received concomitant weekly cisplatin chemotherapy during external radiation while remaining 20 (45%) patients received radical radiation alone. These patients were deemed not suitable for concomitant cisplatin chemotherapy due to low-creatinine clearance, low-performance status, and so on. The chemotherapy schedule consisted of hydration pre- and post-cisplatin infusion (40 mg/m² infused over 2-3 hours) weekly for 4 to 5 fractions. Ultrasound measurements were avoided on the days of brachytherapy and cisplatin chemotherapy.

Ultrasound Protocol

Ultrasound was performed with a 3.5-MHz convex abdominal probe on Siemens SONOLINE Omnia (Siemens AG, Germany). Bladder volume was measured by radiologists (S.K./M.T.), and measurements (length [L], width [W], and height [H]) were obtained using the longest sagittal and the largest axial plane (for transverse and AP(Antero-posterior) dimensions). Bladder volume was calculated using the formula $\text{volume} = 0.5 \text{ LWH}$ using the prolate ellipsoid model that has the best accuracy among the volume determination by 2-dimensional methods.¹² Ultrasound was done after 45 minutes from bladder emptying to estimate the bladder volume and repeated at 15-minute intervals till the bladder volume reached 300 (25) mL. Ultrasound was repeated every week at 10 Gy intervals before scheduled daily treatment till completion of external radiation. All measurements and time taken for bladder filling to 300 (25) mL every week were noted, documented, and analyzed.

Statistical Methods

The data were analyzed using Statistical Package for the Social Sciences for Windows version 11.4. A correlation analysis was determined using Spearman rank coefficient, and a linear regression analysis was done so as to determine the coefficient of determination (r^2) and to find the "line of best fit."

Results

All patients tolerated the serial US and bladder-filling protocol. Five patients experienced some discomfort to the bladder filling at 60-minute US in the fourth to fifth week of treatment. Three patients completed planned external radiation within 4 weeks and hence did not undergo the fifth week US for bladder volume estimation. There was no correlation between FIGO stage with the bladder filling and discomfort during US measurements.

Bladder-Filling Rate

Table 1 shows the mean, median, and standard deviation (SD) for bladder volumes measured at 45, 60, and 75 minutes at weekly intervals after the planned bladder-filling protocol. The mean (SD) bladder volume measured at 45 minutes was 220 (93), 210 (95), 195 (91), 195 (96), and 190 (85) mL for the first

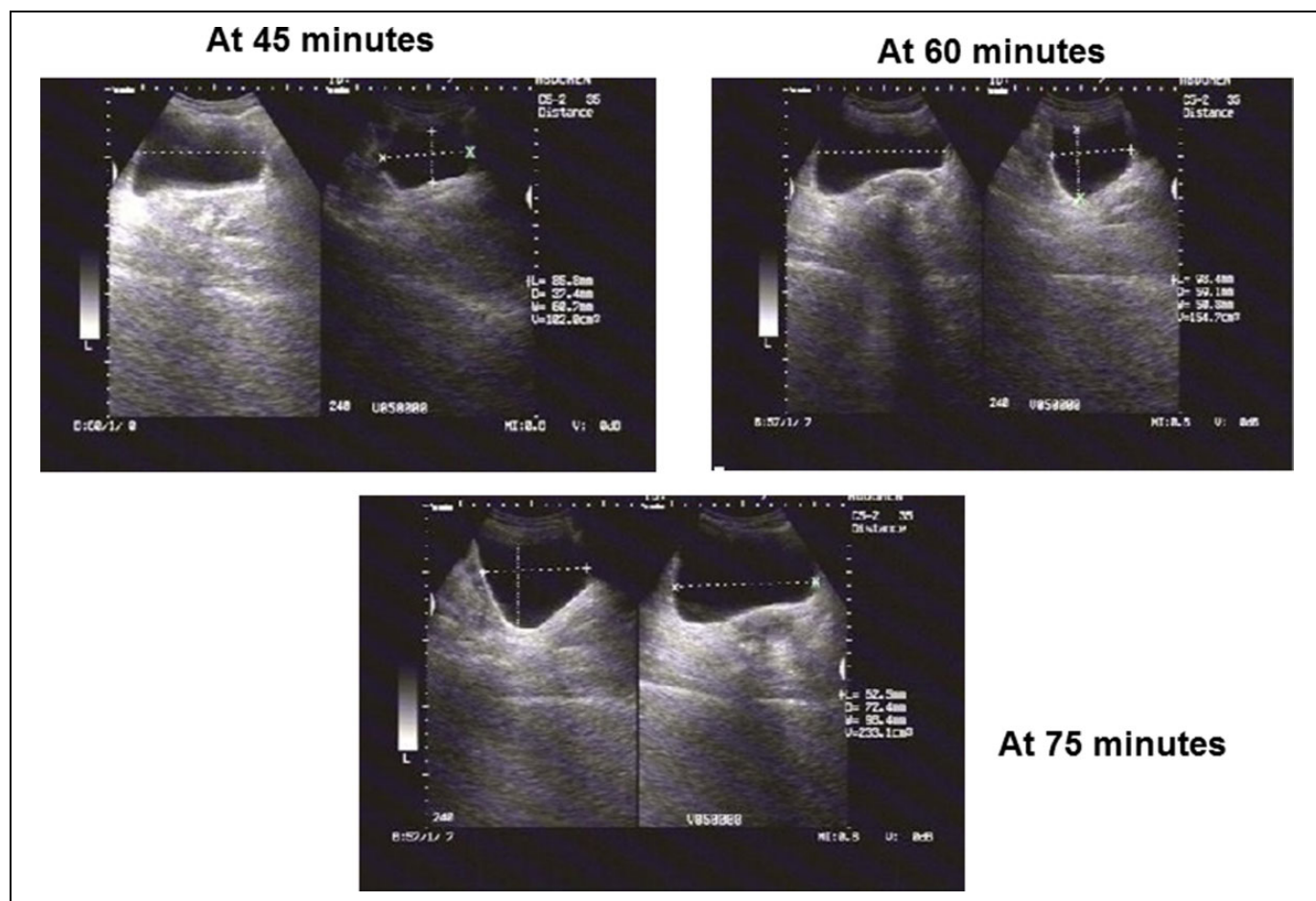


Figure 1. Ultrasonography (USG) images illustrating the bladder volume estimation at varying intervals to achieve 300 mL in a single patient.

Table 1. Showing Bladder Volumes (mL) Measured Weekly at Different Time Intervals Over 5 Weeks.

	Time in Minutes											
	45 Minutes			60 Minutes			75 Minutes					
	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD			
Week 1	220	235	90	220	220	95	300	320	95			
Week 2	210	200	95	220	220	80	310	320	80			
Week 3	195	185	90	240	245	80	290	270	80			
Week 4	195	175	95	200	210	80	295	310	80			
Week 5	190	180	85	190	190	70	285	300	70			
Overall	200	185	90	220	220	80	295	300	80			

Abbreviation: SD, standard deviation.

to fifth week, respectively, and the overall mean: 200 (90); median: 195 mL across all weeks (Figure 2). The mean bladder volume at 60 minutes was 220 (60), 220 (60), 240 (45), 200 (50), and 190 (45) mL for the first to fifth week, respectively, and the overall mean: 220 (80); median: 220 mL across all weeks. The mean bladder volume at 75 minutes was 300 (95), 310 (80), 290 (80), 295 (80), and 285 (70) mL for the first to fifth week, respectively, and the overall mean: 295 (80); median: 300 mL across all weeks (Figure 3).

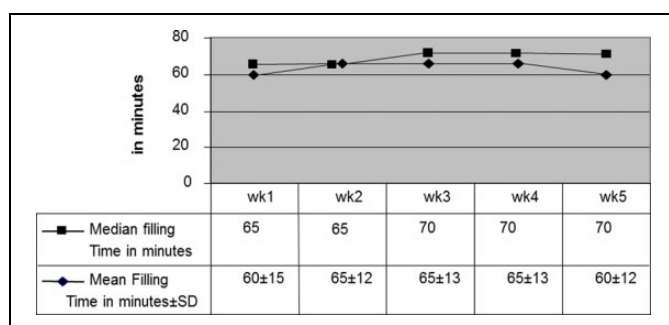


Figure 2. Illustration of mean and median bladder-filling time for every week.

Defined Bladder-Filling Time Trends

The mean (SD) and median time for bladder filling to 300 cm³ in the first, second, third, fourth, and fifth week were 60 (15) and 65, 65 (12) and 65, 65 (13) and 70, 65 (13) and 70, 70 (12) and 70 minutes, respectively (Figure 2). The time required to fill the bladder increased from the first to second week and later remains more or less constant subsequently (Figure 3). The Spearman rank coefficient of correlation of week 1 with respect to week 2, week 3, week 4, and week 5 was 0.139, 0.068, 0.138,

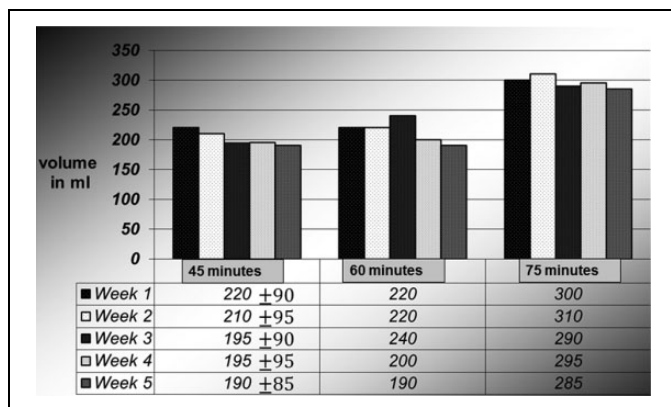


Figure 3. Bar charts showing the mean bladder-filling volumes with standard deviation (SD) measured at 45, 60, and 75 minutes at weekly intervals.

and 0.071, respectively. Although there is a minimal increase in the time taken for the definitive bladder volume filling in the first 2 weeks, but this is insignificant on regression analysis ($P = .964$). The coefficient of determination between the weeks and time required to fill the bladder ($r^2 = 0.04$) was affirmative for the constancy. Overall the mean time for physiological bladder filling up to 300 (25) mL after consumption of 1000 mL of water was 65 (15) minutes across all 5 weeks.

Discussion

The knowledge of the daily variation in the position of the target or adjacent organs is vital to determine appropriate internal margins for final clinical target volume to planning target volume (PTV) in high-precision radiation techniques. While treating cervical cancers with advanced radiation techniques, bladder-filling uncertainties and cranial and posterior movements of the uterus and cervix occurring during various phases of bladder filling have been reported.^{3,5}

We believe that reducing bladder-filling uncertainties would reduce to a large extent, extreme changes in the position of uterus and cervix. Although there have been few studies^{5,6} assessing the variation in uterocervical position and bladder filling during the course of radiotherapy, there are no systematic studies and consensus till date suggesting a fixed bladder-filling protocol for the entire course of radiation. Also, dose volume histogram and normal tissue complication probability would be representative and meaningful provided the bladder filling can be kept reasonably constant during treatment.¹³ Hence, with an aim to identify time required to achieve moderate bladder filling physiologically throughout the treatment, we undertook this prospective study.

The outcome of our study is 3-fold. First, we tried to achieve a definitive bladder-filling protocol physiologically during the whole course of radiation therapy for cervical cancer, which seems feasible and well tolerated for 300 mL (moderate volume) bladder filling. This assists to maintain reproducibility

and to keep the organ motion uncertainties to a minimum. This analogy can further add to the realm of IMRT of cancer cervix where serial CT scans could be done so as to check for the bladder volume variation during the course with a definitive bladder-filling protocol. An attempt was made earlier by Royal Marsden Group to identify time period required to achieve moderate bladder filling and constant volume in patients with prostate cancer. They reported that in their initial study group without a predefined bladder-filling protocol, patients were unable to maintain a constant bladder volume during planning and treatment, but consistent bladder volume was obtained in the patient group who followed a predefined bladder-filling protocol.¹⁴ Our study suggests that mean bladder-filling time required for 300 mL bladder filling was 65 (15) minutes with a systematic time-controlled bladder filling.

Second, we have prospectively measured bladder volumes at regular intervals after 45 minutes of bladder emptying and oral intake of 1000 mL of water at weekly interval till completion of pelvic radiation. The data suggest that a mean of 200 mL at 45 minutes, 215 mL at 60 minutes, and 295 mL at 75 minutes bladder filling can be achieved with the abovementioned protocol measured by serial abdominal US. These time periods and bladder filling achieved may be utilized to decide and choose an appropriate predefined bladder-filling protocol during pelvic radiation. Nevertheless, we decided to achieve a moderate and tolerable bladder filling of 300 mL for our patients, and further justification is explained later.

Third, the overall mean time to achieve bladder filling of at least 300 mL measured on weekly US during entire course of pelvic radiation was 65 (15) minutes from bladder emptying time across 5 weeks, which is a typical duration of external beam radiation therapy for gynecological malignancies. Studies have reported reduction in bladder-filling capacity during the course of pelvic radiotherapy.^{13,15,16} This makes pretreatment bladder volume verification all the more imperative. In our study, reduction in bladder-filling capacity was not evaluated and studied separately. There was a trend toward earlier bladder filling in the first week but was not statistically significant as compared to subsequent weeks. Most of our patients could tolerate retention of 300 mL urine till completion of treatment with minor discomfort seen in 10% (5 patients) patients in the fourth to fifth week of radiation. Various factors related to bladder filling such as repeated bladder catheterization during HDR brachytherapy, chemo-related hydration and concomitant cisplatin chemotherapy (55% of our patients received), treatment-related dehydration (poor intake and diarrhea), and varying degrees of acute cystitis may influence a predefined bladder-filling protocol of 300 mL throughout the course of radiation. These factors were avoided to a large extent or corrected during the US measurements, for example, US measurements were avoided on the day of cisplatin chemotherapy infusion because of anticipated bladder-filling variation due to parenteral hydration and mannitol infusion.

In our study, abdominal US was used for serial imaging because it is easily available and routinely used in clinical practice. Since its use is serial bladder volume estimation

objectively, it surmounts the disadvantage of operator-dependent subjectivity in our study. Although serial CT/magnetic resonance imaging (MRI) rather than US would have given a better insight, US scanner-determined bladder volume has been reasonably estimated and strongly correlated with CT scan bladder volume.¹⁷ Moreover, US being a noninvasive, no additional radiation exposure and portable would definitely be more cost-effective especially in developing countries. In resource constraint settings, a quick US bladder using portable US machine before radiation planning and treatment delivery in the treatment unit would be a big step toward improving quality care in the absence of commercially available expensive image-guided radiotherapy (IGRT) solutions. Also, newer and improved US software enable 3-dimensional and 4-dimensional reconstructed anatomy and coronal images, and it is possible to image and record dynamic events better now, which is an area of current research.¹⁸

Another issue was to determine the frequency of US measurements. Interfraction variation in bladder volume has been reported, with larger variation in bladder volume leading to an increase in interfraction motion of pelvic tumors and hence the uncertainties in PTV.^{13,19-22} There is no uniformity in the frequency of imaging protocols used. The imaging frequency ranges from daily,¹⁷ on 2 consecutive days,²³ once weekly,¹⁴ twice weekly,¹⁵ and alternate weekly protocols.¹³ Considering the logistics and patient convenience, we decided to do weekly US (at 10 Gy increments per week) that accounts for varying degrees of dehydration and acute radiation cystitis during the whole course of radiation. Each US examination was done after 45 minutes from bladder emptying at 15 minutes intervals to identify the time taken for moderate (300 [25] mL) bladder filling. Emptying the bladder before oral intake of planned quantity of water to a large extent minimizes the variation. The rate of physiological bladder filling reported varies between 0.9 and 9 mL/min.^{14,15,24} The maximum bladder capacity physiologically is 550 to 650 mL, and a moderate bladder filling of 300 (25) mL seems reasonable to achieve during pelvic radiation in patients with gynecological cancer which has also been suggested by Royal Marsden Group.^{14,25} However, the pattern and geometric expansion of bladder distension and its impact on the dose volume parameters need to be evaluated and is currently ongoing in our ongoing IGRT protocols. Nevertheless, there is still a whole assortment of dogmas correlating the exact nature of bladder filling, filling rates, and its correlation with bladder post-void volume. Natural bladder filling is slow, intermittent, and a variable process as the kidneys maintain internal homeostasis in response to a large number of internal and external factors, such as fluid consumption, environment, and variable levels of fluid loss via respiration and physical exertion. Hydronephrosis and impaired renal functions can reduce the rate of urine flow into urinary bladder. However, in our study, we did not find any significant difference in bladder volume and filling times of patients with impaired renal clearance. This mandates for further larger studies to establish the relationship between the bladder-filling time, the post-void bladder volume, and entire duration of radiation

course. It is also important to note that rectal filling could also influence the uterocervical positions and movements, which has not been evaluated and reported here. We routinely instruct our patients to empty their bowels daily before planning and treatment delivery. Although some of the recent studies have concluded that apart from bladder and rectal filling, other factors also have impact on internal target motion.^{1,2} Chan et al have advocated daily soft tissue imaging and correction for internal target motion, whereas van De Bunt et al have used weekly MRIs to derive inhomogenous PTV margins to account for internal target motion. These solutions may not be logistically feasible and cost-effective, especially in the context of developing countries that limits their wider applicability.

Conclusion

Bladder filling to a definitive moderate volume at a reasonably fixed time period in each week of radiation is well tolerated, feasible, and measurable by weekly transabdominal US measurements. Transabdominal US offers quick and reliable bladder volume measurements. However, it is difficult to recommend that US-based IGRT could decrease or replace the current standard IGRT practice.

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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References

1. Chan P, Dinniwell R, Haider MA, et al. Inter- and intrafractional tumor and organ movement in patients with cervical cancer undergoing radiotherapy: a cinematic-MRI point-of-interest study. *Int J Radiat Oncol Bio Phys*. 2008;70(5):1507-1515.
2. van de Bunt L, Jürgenliemk-Schulz IM, de Kort GA, Roesink JM, Tersteeg RJ, van der Heide UA. Motion and deformation of the target volumes during IMRT for cervical cancer: what margins do we need? *Radiother Oncol*. 2008;88(2):233-240.
3. Han Y, Shin EH, Huh SJ, Lee JE, Park W. Inter-fractional dose variation during intensity modulated radiation therapy for cervical cancer assessed by weekly CT evaluation. *Int J Radiat Oncol Bio Phys*. 2006;65(2):617-623.
4. Fokdal L, Honore H, Hoyer M, Meldgaard P, Fode K, von der Maase H. Impact of changes in bladder and rectal filling volume on organ motion and dose distribution of the bladder in radiotherapy for urinary bladder cancer. *Int J Radiat Oncol Biol Phys*. 2004;59(2):436-444.
5. Buchali A, Koswig S, Dinges S, et al. Impact of the filling status of the bladder and rectum on their integral dose distribution and the movement of the uterus in the treatment planning of gynecological cancer. *Radiother Oncol*. 1999;52(1):29-34.
6. Kaatee RS, Olofsen MJ, Verstraate MB, Quint S, Heijmen BJ. Detection of organ movement in cervix cancer patients

- using a fluoroscopic electronic portal imaging device and radiopaque markers. *Int J Radiat Oncol Biol Phys.* 2002; 54(2):576-583.
7. Kim TH, Chie EK, Kim DY, et al. Comparison of the belly board device method and the distended bladder method for reducing irradiated small bowel volumes in preoperative radiotherapy of rectal cancer patients. *Int J Radiat Oncol Biol Phys.* 2005;62(3): 769-775.
 8. Park W, Huh SJ, Lee JE, et al. Variation of small bowel sparing with small bowel displacement system according to the physiological status of the bladder during radiotherapy for cervical cancer. *Gynecol Oncol.* 2005;99(3):645-651.
 9. Brierley JD, Cummings BJ, Wong CS, McLean M, Cashell A, Manter S. The variation of small bowel volume within the pelvis before and during adjuvant radiation for rectal cancer. *Radiother Oncol.* 1994;31(2):110-116.
 10. Mundt AJ, Roeske JC, Lujan AE, et al. Initial clinical experience with intensity modulated whole-pelvis radiation therapy in women with gynecologic malignancies. *Gynecol Oncol.* 2001; 82(3):456-463.
 11. Tongaonkar HB. *Evidence Based Management Guidelines, Gynecological Cancers.* Vol. III. Tata Memorial Centre; Mumbai: Tata Memorial Hospital 2004:7-9. ISBN: 81-7525-583-8.
 12. Hvarness H, Skjoldbye B, Jakobsen H. Urinary bladder volume measurements: comparison of three ultrasound calculation methods. *Scand J Urol Nephrol.* 2002;36(3):177-181.
 13. Lebesque JV, Bruce AM, Kroes AP, Touw A, Shouman RT, van Herk M. Variation in volumes, dose-volume histograms, and estimated normal tissue complication probabilities of rectum and bladder during conformal radiotherapy of T3 prostate cancer. *Int J Radiat Oncol Biol Phys.* 1995; 33(5):1109-1119.
 14. O'Doherty UM, McNair HA, Norman AR, et al. Variability of bladder filling in patients receiving radical radiotherapy to the prostate. *Radiother Oncol.* 2006;79(3):335-340.
 15. Ahmad R, Hoogeman M, Quint S, Mens JW, de Pree I, Heijmen BJ. Inter-fraction bladder filling variations and time trends for cervical cancer patients assessed with a portable 3-dimensional ultrasound bladder scanner. *Radiother Oncol.* 2008;89(2): 172-179.
 16. Chang JS, Yoon HI, Cha HJ, et al. Bladder filling variations during concurrent chemotherapy and pelvic radiotherapy in rectal cancer patients: early experience of bladder volume assessment using ultrasound scanner. *Radiat Oncol J.* 2013; 31(1):41-47.
 17. Stam MR, van Lin EN, van der Vight LP, Kaanders JH, Visser AG. Bladder filling variation during the treatment of prostate cancer: can the use of bladder ultrasound scanner and biofeedback optimize bladder filling. *Int J Radiat Oncol Biol Phys.* 2006; 65(2):371-377.
 18. Yaman C, Fridrik M. Three-dimensional ultrasonography to assess the response to treatment in gynecological malignancies. *Gynecol Oncol.* 2005;97(2):665-668.
 19. Fiorino C, Foppiano F, Franzone P, et al. Rectal and bladder motion during conformal radiotherapy after radical prostatectomy. *Radiother Oncol.* 2005;74(2):187-195.
 20. Ten Haken RK, Forman JD, Heimburger DK, et al. Treatment planning issues related to prostate movement in response to differential filling of the rectum and bladder. *Int J Radiat Oncol Biol Phys.* 1991;20(6):1317-1324.
 21. Crook JM, Raymond Y, Salhani D, Yang H, Esche B. Prostate motion during standard radiotherapy as assessed by fiducial markers. *Radiother Oncol.* 1995;37(1):35-42.
 22. Langen KM, Jones DT. Organ motion and its management. *Int J Radiat Oncol Biol Phys.* 2001;50(1):265-278.
 23. Taylor A, Powell ME. An assessment of interfractional uterine and cervical motion: Implications for radiotherapy target volume definition in gynaecological cancers. *Radiother Oncol.* 2008; 88(2):250-257.
 24. Lotz HT, van Herk M, Betgen A, Pos F, Lebesque JV, Remeijer P. Reproducibility of the bladder shape and bladder shape changes during filling. *Med Phys.* 2005;32(8):2590-2597.
 25. Abdel Rahman M, Coulombe A, Devroede G, et al. Urorectodynamic evaluation of healthy volunteers. *Urology.* 1982;19(5): 559-564.