Biomedical Sciences and Clinical Medicine 2023;62(2):39-45.
doi: 10.12982/BSCM.2023.08
https://www.med.cmu.ac.th/bscm/

BSCM
Biomedical Sciences and Clinical Medicine

Original Article **Open Access**

Planning Target Volume Margin Determination for Volumetric Modulated Arc Therapy Planning in Cervix Cancers Using an Empty Bladder Protocol

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Received: January 10, 2023;
Revised: April 26, 2023;
Accepted: June 15, 2023

ABSTRACT

OBJECTIVE To evaluate the planning target volume (PTV) margin and bladder volume variation of volumetric modulated arc therapy (VMAT) in cervical cancer using an empty bladder protocol.

METHODS Ten patients with cervical cancer who had indications to receive whole pelvic radiotherapy and who had been identified to receive whole pelvic irradiation with a dose of 46-55.2 Gy in 23 fractions planned by VMAT were included. International Commission on Radiation Units and Measurements (ICRU) Report 83 was used to report plan parameters. The empty bladder protocol is designed for use with all patients before simulation and irradiation. From June 2020 to February 2021, 215 fractions from the 10 patients were evaluated. The 'all fraction' set-up errors were recorded using cone-beam computed tomography (CBCT) and were interpreted as error margins using the Van Herk Formula.

RESULTS The calculated PTV margins were 0.75, 0.84, and 0.98 cm on the X, Y, and Z-axes, respectively. The median volume of the bladder before irradiation was 40.6 cc, with an interquartile range of 31.9 to 59.2 cc. The average change in bladder volume from the planning volume was 23.56%.

CONCLUSIONS Using the empty bladder protocol, the clinical target volume (CTV) to PTV margin was 1 cm following the Van Herk formula. No patients experienced side effects of grade 3 or greater. The empty bladder protocol is a method which can reduce target placement error and reduce patient discomfort without causing serious side effects.

KEYWORDS PTV margin, VMAT, IGRT, cervix cancer, empty bladder

INTRODUCTION

Cervical is one of the most common female cancers (1). Treatments for cervical cancer include surgery, radiotherapy, and systemic therapy. Radiotherapy plays the role of adjuvant treatment after surgery and of radical treatment for patients with locally advanced diseases. Whole pelvic radiotherapy (WPRT) is an essential part of the treatment of the target (uterus or vaginal cuff) as well as the pelvic lymph nodes. Conventionally, whole pelvic radiotherapy with two or four fields and a dose of 45-50.4 Gy has been used for a long time (2).

Volume-based planning of intensity-modulated radiation therapy (IMRT) allows for better conformity to the target while sparing normal

tissues (3). With these techniques, treatment quality has improved, especially in IMRT. A published study of IMRT versus 3D-conformal radiotherapy (3D-CRT) found that IMRT improved dosimetry, toxicity, and the quality of life of cervical cancer patients (4,5). This irradiation technique has since been further developed into a more effective method with a shorter irradiation time, known as volumetric modulated arc therapy (VMAT). VMAT uses an image-guided system of cone-beam computed tomography (CBCT) for patient position verification.

Although whole pelvic intensity-modulated radiotherapy (WP-IMRT) has yielded many benefits, it requires many additional procedures to maintain treatment quality. First, immobilization of the patient is strongly recommended. Second, patient preparation (an empty rectum and a tolerably full bladder) is necessary to keep the target's same position each time irradiation is applied. For the patient preparation process, an empty rectum (achieved by laxative or enema) is strongly recommended and is generally accepted by the patient without argument. For bladder preparation, a tolerably full bladder (drink 500-1,000 mL of water and wait 30-60 minutes before scanning) is recommended (6,7). However, some patients, especially elderly patients, cannot tolerate this volume of liquid. An empty bladder can also reduce volume variation throughout the course of treatment (8). An empty bladder may be an option with WPRT in cases of gynecologic cancer.

The concept of an empty bladder in pelvic cancer treatment started with prostate cancer irradiation as described in a publication by Chetiyawardana et al. (9) in the UK which reported non-inferiority results with an empty bladder compared to the full bladder protocol based on biochemical progression-free survival rate and at least grade 2 genitourinary toxicity.

Planning target volume (PTV) is the extended margin of clinical target volume (CTV) covering variations in size, shape, volume, and location of the target caused by motion of the target organ and volume variation of adjacent organs. PTV also covers patient positioning set-up errors and the mechanical stability of the measuring equipment. Calculating appropriate margins is necessary because the marginal expansion value is calculated to include errors in systems and equipment to help ensure that the irradiation field does not miss the target and that the organs at risk (OARs) do not receive unnecessary radiation. Building on these promising advances in prostate cancer treatment, this study was conducted to evaluate the safety margin of whole-pelvic volumetric-modulated arc therapy (WP-VMAT) for cervical cancer patients who were prepared with an empty bladder prior to irradiation and whose bladder volume variation during the entire course of treatment was monitored.

METHODS

This prospective study evaluated the PTV margin of cervical cancer treatment using WP-VMAT with an empty bladder during irradiation. Ten patients with cervical cancer who had indications to receive WP-VMAT at adjuvant or radical settings were enrolled in this study. CT simulation was performed with a 3-mm slice thickness from L3 to the lesser trochanter. Before the CT simulation, patients were instructed to void their bladder and then to lie in a supine position with a foot lock for immobilization. After voiding, a CT simulation was performed within 10 minutes. After the CT simulation, the CT dataset was transferred to a contouring workstation (Oncentra Masterplan version 4.3, Elekta, Stockholm, Sweden). The CTV, PTV, and OARs, consisting of the bladder, rectum, bowel, and heads of the femurs were contoured by a radiation oncologist (RO). After the contouring process, the CT dataset with contours was transferred to a VMAT planning workstation (Monaco treatment planning system version 5.11.01, Elekta, Stockholm, Sweden). The planning aim was 46 Gy in 23 fractions to D50 of PTV according to ICRU Report 83 (10). The simultaneous integrated boost (SIB) of 55.2 Gy in 23 fractions to D50 of PTV macroscopic lymph nodes (PTV-LN) followed the same plan. For the OARs (bladder, rectum, small bowels, and heads of the femurs), dose constraints from Radiotherapy Oncology Group (RTOG) 1203 were followed in the evaluation (11). The VMAT plans with 6-MV X-rays consisted of two full arcs with the same isocenter moving in both clockwise and counterclockwise directions. The

finished plan was approved by the RO. During the treatment period, the 10 patients were instructed to empty their bladder within 10 minutes prior to setup as in the CT simulation. After voiding, patients were set up on the treatment couch. Kilovoltage cone-beam CT (kV-CBCT) scans were performed daily using an Elekta Synergy XVI system (Elekta, Stockholm, Sweden) to register with the planned CT dataset, starting with bony auto-matching by radiotherapy technologists (RTT), then soft tissue manual-matching by the RO to verify the appropriate position for treatment. This verification process was used to adjust the target (uterus or vaginal cuff) to be as close to the planned CTV as possible. The data on table shifting were recorded for each fraction in the lateral (X), longitudinal (Y), and vertical (Z) directions as patient set-up errors. A flowchart of the study procedure is shown in Figure 1. The details of shifting were recorded and evaluated by the Van Herk Formula (12) using the following equation:

$$\text{PTV margin} = 2.5\Sigma + 0.7\sigma$$

where Σ is total standard deviation (SD) of preparation (systematic) errors and σ is the total root mean square (RMS) of execution (random) errors. The patient characteristics and dosimetric data were collected and evaluated by descriptive analysis. The mean, median, and standard deviation were recorded in Microsoft Excel and analyzed using the Statistical Package for Social Sciences (SPSS) version 22.0. (IBM).

RESULTS

Ten patients with a total of 215 fractions were enrolled. The mean age was 62 years (range 41-92 years). Nine patients were treated with radical treatment, while one was treated with adjuvant treatment. Patients' characteristics are shown in Table 1.

The mean bladder volume from the planning CT was 45.5 cc (range 22.6-129.3 cc). The mean CTV volume was 604.61 cc (range 352.38 - 909.96 cc). The D2% of bladder, rectum, and bowels was 46 Gy. The mean±SD of all parameters are shown in Table 2. The random error data is shown in Figure 2. The CTV to PTV margin in the lateral (X), longitudinal (Y), and vertical (Z) directions were 0.75 cm, 0.84 cm,

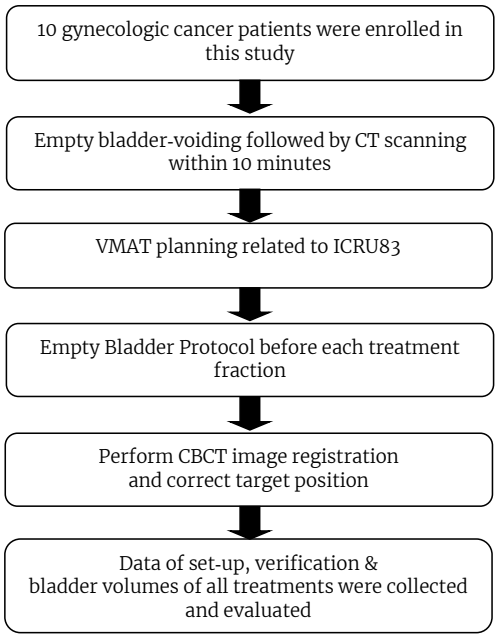

Figure 1. Study procedure

Table 1. Patient characteristics

Patient	Age	Stage	Histology	Setting	SIB	NACT	CCRT
1	92	IIB	SCCA	Radical	No	No	No
2	79	IVB	SCCA	Radical	No	No	No
3	68	IIIC2	SCCA	Radical	Yes	Yes	Yes
4	46	recur	SCCA	Radical	No	Yes	Yes
5	42	IIIC1	NET	Adjuvant	No	Yes	Yes
6	67	IIIB	Adenocarcinoma	Radical	No	No	Yes
7	54	IIIC1	SCCA	Radical	No	Yes	Yes
8	65	IIB	SCCA	Radical	No	Yes	Yes
9	70	IIIC2	SCCA	Radical	Yes	No	No
10	41	IVA	SCCA	Radical	No	Yes	Yes

CCRT, concurrent chemoradiotherapy; NACT, neoadjuvant chemotherapy;
NET, neuroendocrine tumor; SIB, simultaneous integrated boost;
SCCA, squamous cell carcinoma

Table 2. Planning parameters

Parameters	Mean ± SD
PTV	
· D50 (Gy)	47.98±3.98
· D98 (Gy)	45.91±4.45
· D2 (Gy)	49.33±3.90
Bladder	
· D2 (Gy)	46.19±0.75
· V45 Gy (%)	33.64±26.79
Rectum	
· D2 (Gy)	46.57±0.63
· V40 Gy (%)	80.01±13.09
Small bowel	
· D2 (Gy)	46.30±0.73
· V40 Gy (%)	27.20±13.64
· V45 Gy (cc)	124.70±46.23
Head of femur Right	
· D10 (Gy)	27.71±5.00
Head of left femur	
· D10 (Gy)	28.65±4.18

D, dose at volume (%) or dose at radiation dose;
V, volume at radiation dose; PTV, planning target volume

and 0.98 cm, respectively. Calculations are shown in Table 3. Evaluation of the fractions in the set-up error dimension with a 1 cm cut-off margin found the error percentages in the X, Y, and Z-axis were 2.8%, 2.3%, and 2.3%, respectively (Table 4). The bladder volume from CBCT during irradiation is summarized in Table 5 and the overall mean percentage of bladder variation (defined as the ratio of CBCT bladder volume to planned bladder volume) was 23.56%. The median volume of the bladder was 40.6 cc, with an interquartile range (IQR) from 31.9 to 59.2 cc.

DISCUSSION

The use of IMRT in the treatment of gynecological cancer is currently increasing in response to positive results of randomized controlled trials by RTOG1203 and Postoperative Adjuvant Radiation in Cervical Cancer (PARCER) studies that have reported on the benefits of IMRT in adjuvant whole pelvic radiotherapy in reducing acute toxicity and improving quality of life (11, 13,5). For IMRT, the issue of the target position is of primary importance, and the full bladder protocol is widely used in routine practice. However, using of a full bladder protocol in our practice has resulted in pain points that can affect reproducibility and patient tolerance per treatment. The non-inferiority results of an empty bladder in prostate cancer treatment has sparked interest in the use of an empty bladder

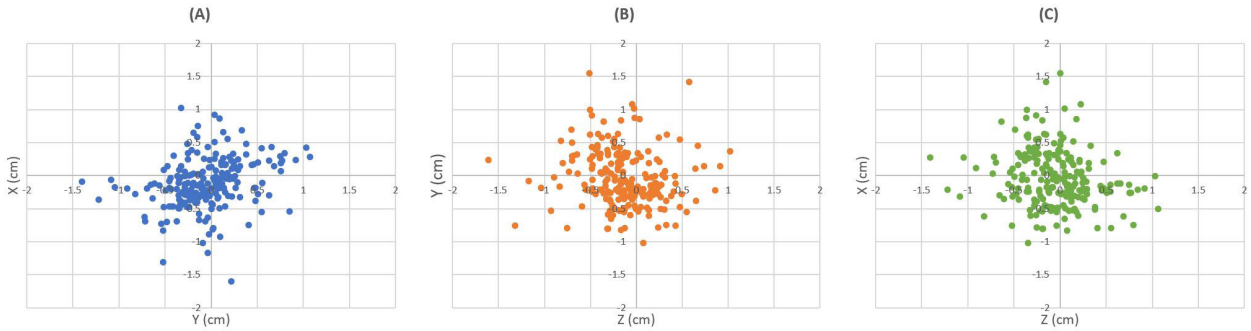

Figure 2. Comparison of variations in patient set-up errors in the (A) X-Y, (B) Y-Z, and (C) X-Z axes

Table 3. PTV margin calculation using Van Herk formula

Parameters	X-axis (cm)	Y-axis (cm)	Z-axis (cm)
M_{pop}	-0.039	-0.114	-0.047
$(m_i - Mpop)^2$	0.386	0.583	0.815
$(m_i - Mpop)^2/(n-1)$	0.043	0.065	0.091
Σ_{pop} (system error)	0.207	0.255	0.301
$2.5\Sigma_{pop}$	0.517	0.636	0.752
SD^2	1.066	0.890	1.012
σ_{pop} (random error)	0.327	0.298	0.318
$0.7\ \sigma_{pop}$	0.229	0.209	0.223
PTV margin	0.746	0.845	0.975

M_{pop}, Population mean error; m_i, Individual mean error; SD, standard deviation of individual error; PTV, planning target volume

Table 4. Percent of fractions over the cut-off margin

Over the cut-off fractions in each axis	Cut-off margin				
	> 1.5 cm	> 1.2 cm	> 1.0 cm	> 0.8 cm	> 0.5 cm
X-axis	0 (0.00%)	2 (0.93%)	6 (2.79%)	10 (4.65%)	36 (16.74%)
Y-axis	1 (0.47%)	1 (0.47%)	5 (2.33%)	12 (5.58%)	34 (15.81%)
Z-axis	1 (0.47%)	2 (0.93%)	5 (2.33%)	16 (7.44%)	52 (24.19%)

Table 5. Bladder volume variation in each patient

Patient	Bladder volume parameter					
	Planning Vol. (cc)	CBCT				Mean variation from plan (%)
		Min	Max	Mean	SD	
1	129.35	45.73	193.55	101.06	33.28	-21.87
2	25.80	13.04	48.49	26.60	8.45	+3.12
3	44.16	25.68	46.52	37.57	4.41	-14.93
4	53.96	42.31	92.78	60.15	12.29	+11.47
5	43.71	18.07	72.70	33.20	10.51	-24.04
6	26.71	22.71	51.50	37.38	7.37	+39.94
7	22.65	21.96	103.70	58.38	21.28	+157.73
8	29.63	18.41	81.23	34.73	12.76	+17.21
9	29.11	30.61	50.36	39.51	6.09	+35.72
10	49.87	33.64	117.04	65.48	23.92	+31.29
Overall	45.50	13.04	193.55	49.41	14.04	+23.56

CBCT, cone-beam computed tomography

in gynecologic cancer in our practice (9).

In the present study, the CTV to PTV margins in the lateral, longitudinal, and vertical directions were 0.75 cm, 0.84 cm, and 0.98 cm, respectively. The reported set-up errors in 67 patients in a study by Mahanshetty et al. (7) showed systematic and random errors of 2-7 mm in anisotropic margins in various directions, e.g., 10 mm in the vertical and lateral directions and 12-20 mm in the longitudinal direction (CTV-ITV for uterine fundus). Set-up errors in our study are no higher than those in studies with a comfortably full bladder. During irradiation the median volume of the bladder was 40.6 cc, with an IQR from 31.9 to 59.2cc. The bladder volumes in our study were smaller than those in a full bladder study by Mahanshetty et al. (7) which reported a mean bladder volume during radiotherapy of 284 cc (range of 60-650 cc). In that study, each patient had a mean bladder volume of about 60-200 cc over the course of their treatment. Additionally, the change in bladder volume from the planning volume of our study was 23.56% compared to the full bladder study of Ahmad et al. (14) and that of Chen et al. (8) which were 39.24% and 31.86%, respectively. This supports that an empty bladder protocol has lower variation than full bladder protocol. However, as shown in Table 5, the change in bladder volume from the planning volume in patient no. 7 was 157.73%. Although the percentage change was high, the variation of bladder volume in this patient was low (from 21 cc to 103 cc). This may result from urinary retention that may occur due to tumor extension at diagnosis or to inflammation of the bladder and urethra during radiotherapy.

For the small bowels, although the radiation dose received by the empty bladder protocol was higher than with the full bladder protocol, none of the plans in this study exceeded the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) guidelines (V45 Gy < 195 cc) (15). Regarding acute gastrointestinal (GI) and genitourinary (GU) toxicity during treatment, no grade 3-4 toxicity was observed in our study. A clinical study of the empty bladder protocol was first reported by Chetiyawardana et al. in prostate carcinoma treated by 60 Gy in a 20 fractions regimen. That study showed promising results following the empty bladder protocol with no difference in toxicity profiles between comfortably full and empty bladder procedures (9). Although the treatment field

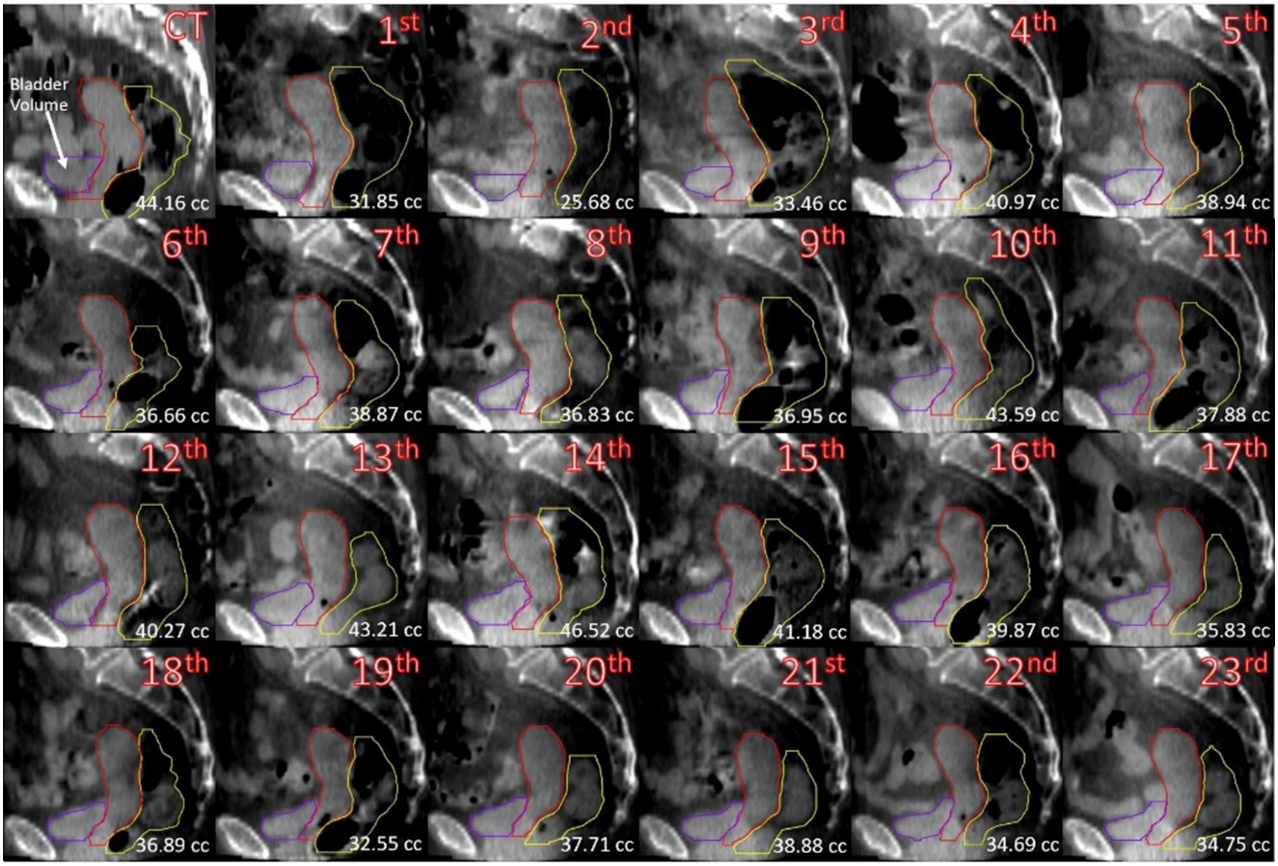

Figure 3. Example of a cervical cancer patient (Stage IIB) showing the variation of bladder volume during treatment

in gynecologic cancer is more extensive than in prostate cancer, the dose of 46 Gy is lower than that in prostate treatment.

The percentage set-up error over the cut-off margin fraction (Table 4) shows that using a 1 cm PTV margin will have a target volume error in each direction of the treatment field of less than 3% without image registration. Also, the empty bladder protocol is easily reproducible. Figure 3 shows an example of cervical carcinoma treated by radical radiotherapy. From the 1st to 23rd fractions, bladder volume ranged from 25.7 to 46.5 cc with an average value of 37.6 cc. This supports that an empty bladder is easier for the RTT to manage and more comfortable for the patient than a full bladder protocol.

There are some limitations in this study. First, only a small number of patients were enrolled in the study. Second, total fractions could not be collected due to technical difficulties with the imaging device. However, the study did demonstrate the reproducibility of the empty bladder protocol in treating cervical cancer. Further investigation is needed to evaluate the clinical results in terms of toxicity and aspects quality of life.

CONCLUSION

Our study suggests that the appropriate PTV margin in an empty bladder-cervical cancer patient is 1.0 cm. The frequency of the error exceeding the margin is less than 3 percent on all axes. The empty bladder protocol method can reduce target placement error without causing serious side effects to the patient's excretory system and can also be used with people who have urinary incontinence problems.

ACKNOWLEDGEMENTS

The authors would like to thank all the patients who participated in this study. We would also like to thank the staff of the Division of Therapeutic Radiology and Oncology, Faculty of Medicine, Chiang Mai University for supporting this study.

FUNDING

No funding.

CONFLICTS OF INTEREST

No conflicts of interest.

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