

Effects of bladder distension on dose distribution of vaginal vault brachytherapy in patients with endometrial cancer

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Abstract

Purpose: To investigate dosimetric effects of bladder distention on organs at risk (OARs) during treatment of endometrial cancer using 3D image-based planning of postoperative vaginal vault brachytherapy (BRT).

Material and methods: Fifteen patients with early-stage endometrial cancer were studied, each undergoing adjuvant BRT of vaginal vault via 3.5 cm diameter cylinder. As treatment, 25 Gy in 5 fractions were delivered to 5 mm depth of the vaginal mucosa. Dose-volume histograms of OARs were generated individually with bladder empty and with bladder inflated by sterile saline (180 ml), to compare doses received.

Results: Bladder distention appreciably impacted dosimetry of bladder, sigmoid colon, and small bowel, but dosimetry of rectum was unaffected. With bladder inflated, mean cylinder-to-bowel distance increased significantly (1.69 cm vs. 1.20 cm; $p = 0.006$). Mean minimum dose to most exposed 2 cc (D_{2cc}) volume also rose significantly at bladder (5.40 Gy vs. 4.55 Gy [18.7%]; $p < 0.001$), as opposed to near-significant reductions in D_{2cc} at sigmoid colon (15.1%; $p = 0.11$) and at small bowel (10.5%; $p = 0.14$). A full bladder had no effect on dose to 50% volume ($D_{50\%}$) of bladder or rectum, and declines seen in mean $D_{50\%}$ values of sigmoid colon (22.7%; $p = 0.12$) and small bowel (19.0%; $p = 0.13$) again fell short of statistical significance.

Conclusions: The combination of a full bladder and an empty rectum may cause significant unwanted increases in BRT dosing of bladder, without significantly impacting sigmoid colon and small bowel exposures. These findings should be validated through further clinical studies.

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Key words: bladder distention, brachytherapy, dosimetry, endometrial cancer, vaginal vault.

Purpose

Endometrial cancer is the most common gynecologic malignancy and is largely diagnosed in early stages [1,2]. The primary means of treating localized disease is total abdominal hysterectomy and bilateral salpingo-oophorectomy. For all but low-risk tumors, adjuvant radiotherapy (RT) is thought to reduce chances of loco-regional relapse [3], which develops in 10-15% of patients with early-stage disease (chiefly as vaginal vault recurrence). Adjuvant treatment generally consists of either external beam RT (ERBT) or internal brachytherapy (BRT) [3]. In recent studies, especially in early stage endometrial carcinoma, EBRT has shown no advantage over BRT, and EBRT carries a greater risk of complications [4]. The PORTEC-II (Postoperative Radiation Therapy for Endometrial Carcinoma) study, a randomized trial of adjuvant RT for endometrial cancer, confirmed that vaginal BRT is effective and does not decrease quality of life as much as EBRT, leading to an upsurge in the use of high dose rate (HDR)

vaginal vault BRT [3-5]. In the PORTEC-II trial compared with EBRT, reports of toxicity due to vaginal vault BRT are fewer, although currently does indicate a 12.6% rate of Grade 1 and 2 gastrointestinal side effects with some Grade 3 events (< 1%) emerging as late complications [5].

Most of the data published lately on vaginal vault BRT stem from 2D plain film-derived conventional plans. The chief drawback of this approach is that doses to adjacent organs, mainly rectum and bladder, may be inadequately assessed. With the advent of computed tomography (CT)-based conformal plans, prescribed doses to target volumes and collateral exposure to bladder and rectum are clearly identified [6,7]. However, the International Commission on Radiation Units and Measurements (ICRU) defines only bladder and rectal reference points in 2D plans, which may not represent actual 3D dose distributions. Even more worrisome is the fact that doses to small bowel are simply ignored in conventional BRT plans, despite the close proximity of vaginal cylinder.

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Many studies have evaluated the use of CT-based conformal plans in patients with cervical and endometrial cancers [6-9], although dosimetric parameters of 2D and 3D BRT plans were being compared. The GEC-ESTRO Brachytherapy Working Group has recommended contouring guidelines, concepts, and terms in three-dimensional magnetic resonance image-based treatment planning in cervical cancer BRT, with reports confirming the safety, feasibility, definite advantages, clinical outcome, and late toxicities [10,11]. The impact of bladder filling on dose distribution has likewise been amply studied in the context of cervical cancer and endometrium cancer, with conflicting results [9,12-15]. Still, Hung *et al.* [16] have made a formal claim that bladder distention reduces BRT dose to small bowel in patients with endometrial cancer. Kobzda *et al.* [15] found that the dose to the empty bladder was lower than when the bladder was full, and the doses to the bowels increased proportionally in the empty state of the bladder comparing to the full organ. Despite the abundance of data on bladder distention during BRT with the uterus intact, BRT delivery via vaginal cylinder is seldom a focus of 3D image-based dosimetric studies.

The purpose of this study was to investigate the dosimetric effects of bladder distention on organs at risk (OARs) during treatment of endometrial cancer (i.e., bladder, rectum, sigmoid colon, and small bowel) using 3D image-based planning of postoperative HDR vaginal vault BRT.

Material and methods

Patients

Between November 2013 and January 2014, a total of 15 consecutive patients with early-stage endometrial cancer were recruited for study, each of whom submitted to postoperative adjuvant BRT of vaginal vault. All had undergone total abdominal hysterectomy, and none had received EBRT prior to BRT. Approval was obtained from the institutional review board for this outcome analysis.

Before delivery of BRT, a detailed gynecologic examination was performed to evaluate vaginal vault and to determine applicator diameter. A laxative or enema purge of intestinal contents was also required in advance. Intracavitary BRT was achieved by using plastic, CT-compatible applicators to position standard 3.5 cm diameter cylinders. After insertion of cylinder to the top of the vagina, the applicator was fixed with a universal applicator clamping device (Varian Medical Systems, Inc., Palo Alto, CA, USA), which was underneath the patient. The length of the cylinder protruding outside the vagina was noted to ensure accurate repositioning for subsequent insertions. The same applicators were utilized throughout the course of treatment. Additionally, before each BRT sessions, the applicator was checked with fluoroscopy whether it was at the same position as the first application. A CT scan with 2.5 mm slice thickness through the pelvis was carried out at the first BRT application in line with departmental policy.

Treatment planning

Prior to BRT, a Foley catheter was inserted, with 7 ml of contrast material filling the balloon. Two CT scans were then performed following BRT, leaving in place the secured vaginal cylinder applicator. The initial CT scan was done with an empty bladder, thereafter infusing sterile saline (180 ml) via catheter. A metal clamp was placed to prevent voiding, and second CT scan was done with the bladder full. The pelvis was scanned from lumbosacral junction to ischial tuberosity at 2.5 cm slice thickness. All CT slices were ultimately transferred to the 3D treatment planning system (BrachyVision™ Eclipse; Varian Medical Systems, Palo Alto, CA, USA).

The dose was prescribed to 5 mm depth for the cranial 3 to 5 cm of the vagina, and the dose delivered during the treatment was 25 Gy in 5 fractions. Vaginal length was measured on CT images, and two-thirds of the vaginal cylinder was routinely activated, in accordance with our institutional protocol.

Organs at risk

Bladder, rectum, sigmoid colon, and small bowel constituted OARs. In each axial CT slice, external pelvic contours of bladder (empty or full), rectum, sigmoid colon, and small bowel were delineated by the treatment planning system, using sagittal and coronal views to supplement. Oral or intravenous contrast was not used during planning CT. Rectum was defined as the colonic segment between rectosigmoid junction and anal verge [17]. The length of bowel extending proximal to rectum and delimited by a transition to vertical orientation was considered sigmoid colon. Small bowel encompassed the remaining individual intestinal loops, up to the level of the inferior sacroiliac joints (excluding rectum and sigmoid colon), as was previously defined [12]. To ensure structural consistency of patient scan sets (with bladder empty and full), contours of rectum, sigmoid colon, and small bowel were examined in corresponding CT slices to verify that bony landmarks and axial sections of organs closely matched.

For assessment of the distance between the cylinder applicator and bowel, the cylinder-to-bowel distance was defined as the shortest distance from the cylinder apex to the contoured sigmoid or small bowel. Distances were measured by use of the sagittal slice through the mid-plane of the cylinder, by a single investigator to minimize the risk of interobserver variation.

Statistical analysis

Statistical analysis relied on standard software (SPSS v20.0; SPSS Inc., Chicago, IL, USA). Volumes of all OARs specified were determined, and dose-volume histograms generated in each bladder state were compared. Volume dose values were expressed as minimum doses to most exposed 0.1-, 0.2-, 0.5-, 1.0-, and 2.0-cc volumes ($D_{0.1cc}$ to D_{2cc}) and dose received by 50% of OAR volume ($D_{50\%}$). In addition, OAR dosing minimum (D_{min}), maximum (D_{max}), mean (D_{mean}), and median (D_{median}) values were calculated for both plans. The Wilcoxon matched-pairs test was applied to

identify statistical differences in volumes and doses of empty and full bladder states. The Mann-Whitney *U* test was also engaged to compare volumes or dose values in independent patient groups. All *p* values were two-sided, with statistical significance set at $p < 0.05$.

Results

Median age of the 15 patients analyzed was 58 years (range, 38-81 years). Eight patients (53%) had stage IA endometrial cancer, and seven patients (47%) had stage IB disease. As demonstrated in Table 1, all target and OAR volumes (except bladder) were similar. Typically, small bowel was displaced anteriorly and superiorly from the vaginal cylinder applicator (shown in Fig. 1), significantly

Table 1. Target volume and organ-at-risk volumes in full and empty bladder plans

Volume	Empty bladder (cc ± SD)	Full bladder (cc ± SD)	<i>p</i>
CTV	99.4 ± 21.5	100.4 ± 22.3	0.27
Rectum	81.3 ± 31.7	83.9 ± 39.1	0.31
Bladder	55.0 ± 14.4	255.1 ± 32.3	< 0.001
Sigmoid	59.9 ± 29.7	63.5 ± 30.2	0.76
Intestine	348.5 ± 107.6	337.9 ± 104.6	0.27

CTV – clinical target volume

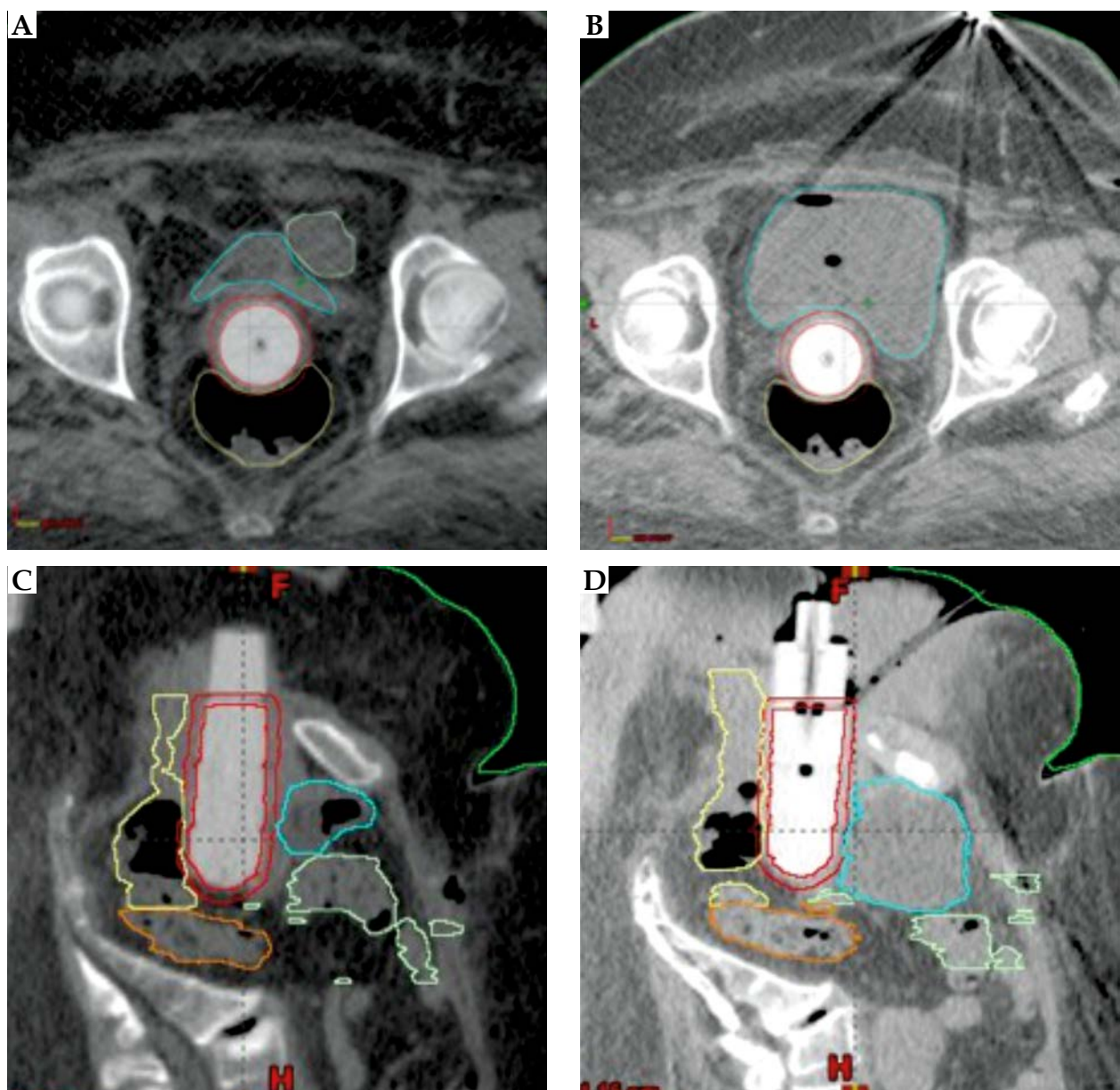


Fig. 1. Organs at risk (OARs) in axial plane with bladder empty (A) and full (B) (small bowel displaced by vaginal cylinder applicator); Vaginal cylinder (relative to OARs) in sagittal plane with bladder empty (C) and full (D) (small bowel displaced anteriorly and superiorly but stable posteriorly)

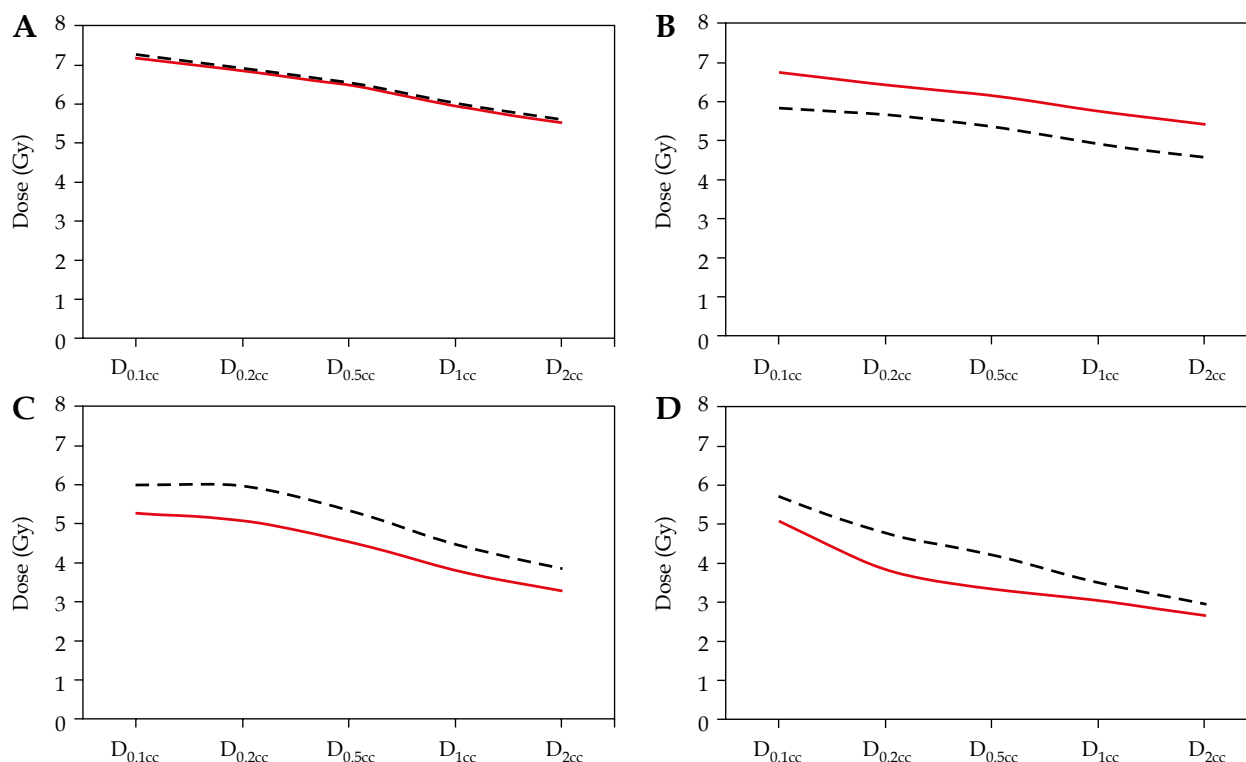


Fig. 2. Dose-volume histograms with bladder empty (dashed line) and full (red line): (A) rectum, (B) bladder, (C) sigmoid colon, and (D) small bowel

increasing mean cylinder-to bowel distance (1.69 cm vs. 1.20 cm; $p = 0.006$).

Bladder distention had no impact on dosimetry of rectum (Fig. 2A). However, the effects on bladder (Fig. 2B), sigmoid colon (Fig. 2C), and small bowel (Fig. 2D) dosimetry were appreciable. With a full bladder, mean D_{2cc} of bladder significantly increased from 4.55 Gy to 5.40 Gy (18.7% gain; $p < 0.001$), and reductions in mean D_{2cc} values of sigmoid colon (15.1%) and small bowel (10.5%) neared statistical significance (Table 2).

$D_{50\%}$ values of rectum and bladder were unaffected by bladder distention (Table 3), and declines seen in mean $D_{50\%}$ values of sigmoid colon (22.7%, $p = 0.12$) and small bowel (19.0%, $p = 0.13$) again fell short of statistical significance.

Discussion

In this study, we determined that the combination of a distended bladder and an empty rectum prior to BRT significantly increases bladder doses, with decreases in sigmoid colon and small bowel exposures that neared statistical significance and no impact on rectal dosimetry.

Based on PORTEC-II study outcomes, adjuvant vaginal vault BRT has been accepted as standard therapy in early-stage endometrial cancer. Unfortunately, earlier methods of BRT planning involved orthogonal films, restricting doses to a 5 mm distance from cylinder. In addition, doses to rectum and bladder were perhaps inaccurately gauged by ICRU reference points. Although the chief toxicities for vaginal cuff BRT are appropriate to be intestinal, due to close proximity of the vaginal cylinder,

conventional plans provide no reference points for defining doses to small bowel. Hence, determining OAR exposures through CT-based planning is of particular interest.

CT-based plans have been routinely used in cervical cancer BRT, where target volumes are managed with comparatively greater sophistication. A US survey indicates that most centers do not routinely document OAR doses during adjuvant vaginal cuff BRT after hysterectomy [3]. Holloway *et al.* [18] investigated the need for CT-based treatment planning on each insertion of vaginal vault BRT, and found that doses to adjacent organs did not vary significantly between fractions. Nevertheless, an awareness of collateral exposures is needed to ensure that side effects of such therapy, given as prophylactic treatment, are not excessive.

In order to reduce OAR doses, the impact of bladder distention has been investigated. Results of this strategy in patients with cervical cancer have conflicted, most reporting marginal differences in dosing decrements [12-14]. Few researchers have examined the impact of bladder distention on dose to OARs in patients treated post-hysterectomy with HDR vaginal cuff BRT [15,16,19,20]. Hoskin and Vidler [19] found that 100 ml bladder infusions reduced exposure of small bowel within the high-dose treatment region (as measured on CT slices through cranial-most dwell positions) by 57.5%, compared with a voided bladder. At the same time, mean maximal bladder dose did not change significantly. Of note, values were based on 2D measurements of bladder height; thus, volumetric parameters of bladder were not assessed, and doses to sigmoid colon and small bowel were not evaluated. Kobzda *et al.* [15] found the dose to

Table 2. Mean D_{2cc} of organs at risk in empty and full bladder plans

Organs	Empty bladder (Gy \pm SD)	Full bladder (Gy \pm SD)	% Change	<i>p</i>
Rectum	5.51 \pm 1.01	5.59 \pm 1.01	+0.5	0.61
Bladder	4.55 \pm 0.72	5.40 \pm 1.22	+18.7	< 0.001
Sigmoid	3.83 \pm 2.00	3.25 \pm 1.27	-15.1	0.11
Bowel	2.94 \pm 1.72	2.63 \pm 1.88	-10.5	0.14

Table 3. Mean $D_{50\%}$ of organs at risk in empty and full bladder plans

Organs	Empty bladder (Gy \pm SD)	Full bladder (Gy \pm SD)	% Change	<i>p</i>
Rectum	3.51 \pm 1.61	3.34 \pm 1.85	-4.8	0.33
Bladder	2.92 \pm 1.23	3.05 \pm 2.28	+4.5	0.69
Sigmoid	1.98 \pm 1.53	1.53 \pm 0.98	-22.7	0.12
Bowel	1.53 \pm 0.64	1.24 \pm 0.50	-19.0	0.13

the empty bladder is lower than when the bladder is full (4.6 Gy (range: 3.1-5.6 Gy) vs. 4.9 Gy (range: 3.9-5.9 Gy); $p < 0.05$), and the doses to the bowels increase proportionally in the empty state of the bladder comparing to the full organ (4.6 Gy (range: 2.5-7.3 Gy) vs. 4.1 Gy (range: 1.3-5.7 Gy); $p < 0.05$).

When Stewart *et al.* [20] examined the effects of bladder distention on BRT doses to bladder, rectum, and urethra using 3D image-based treatment planning, they found a correlation between midline maximal bladder point dose and maximal rectal point dose. Their conclusion was that maximal bladder point and maximal rectal point were acceptable surrogates of D_{2cc} volumetric assessment. Similar to our findings, Stewart *et al.* [20] reported that bladder distention increased the D_{2cc} of bladder, with no appreciable change in D_{2cc} of rectum. Dosimetry of sigmoid colon and small bowel, were not evaluated, but they too documented a significant increase in cylinder-to-bowel distance (0.57 cm to 1.16 cm; $p = 0.002$) with filling of the bladder. In our study, cylinder-to-bowel distance increased from 1.20 cm to 1.69 cm ($p = 0.006$).

Hung *et al.* [16] also evaluated OAR doses to rectum, bladder, sigmoid colon, and small bowel. As reported, a full bladder resulted in a significant reduction in mean D_{2cc} of small bowel (677 to 408 cGy; -39.7%) and $D_{50\%}$ of small bowel (168 to 132 cGy; -21.4%). Corresponding D_{2cc} and $D_{50\%}$ doses to rectum and to sigmoid colon were unaffected by bladder distention. Our detailed dosimetric assessment was at odds with these findings, showing instead that bladder distention significantly increases doses to bladder, whereas sigmoid colon and small bowel exposures declined to near significant levels.

Above differences may be attributed to the inherent uncertainties in measuring exceedingly small distances of select regions in mid-sagittal imaging plane. Variance in full bladder volumes between studies also may have contributed to disparities. In the study conducted by Stewart *et al.* [20], a full bladder was defined as the volume achieved by a 32 oz intake of water 1 hour prior to cylinder insertion. Similarly, Kobzda *et al.* [15] provided

a sufficient bladder filling by asking to consume 400 ml of water 40 minutes before the CT scans were taken. On the other hand, Hung *et al.* [16] defined a full bladder as a 180 ml infusion of sterile water.

We performed two CT scans, one with the bladder emptied by Foley catheter, and one following retrograde infusion of saline (180 ml) via Foley catheter. Mean full bladder volumes of 32 US fl oz (946 ml) for Stewart *et al.* [20], 235.0 ml for Hung *et al.* [16], 229.7 ml for Kobzda *et al.* [15], and 255.1 ml in the current study were subsequently recorded. Another reason of having larger bladder volume in Stewart *et al.* and our study is, in both studies urinary catheter was used to inflate bladder, compared to other studies. A larger bladder expanse may displace small bowel to a greater extent, thus explaining the increases in cylinder-to-bowel distance registered by Stewart *et al.* [20] and in our work.

Our dosimetric study has some limitations, primarily, the limited number of patients recruited, both of which curtail any generalization of results. Furthermore, without standardization of bladder filling it is difficult to issue recommendations for filling of the bladder during vaginal vault BRT. However, our study does underscore that bladder distention may cause unwanted increases in bladder doses, while decreasing doses to sigmoid colon and small bowel. Finally, our investigation was a dosimetric study by design, devoid of clinical outcomes. Further clinical investigation with extended follow-up is needed to determine its practical merit.

Conclusions

This dosimetric study illustrates that the combination of a distended bladder and an empty rectum prior to BRT of vaginal vault may cause significant increases in bladder doses, while possibly lowering doses to sigmoid colon and small bowel. Because the impact of bladder distention on gastrointestinal and genitourinary toxicities has yet to be demonstrated, a suitable bowel prep before each therapeutic session may suffice (especially in

high-volume patient clinics), with no need to inflate the bladder. The core concept here is tentative, requiring further dosimetric and clinical corroboration.

Disclosure

Authors report no conflict of interest.

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