

Original paper

Effects of vaginal cylinder position on dose distribution in patients with endometrial carcinoma in treatment of vaginal cuff brachytherapy

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Abstract

Purpose: To investigate the impact of different cylinder positions on dosimetry of critical structures in patients with endometrial carcinoma undergoing three-dimensional image-based vaginal cuff brachytherapy (VCB).

Material and methods: We delivered VCB at a dose of 4 Gy to a depth of 5 mm in the vaginal cuff of 15 patients using three different cylinder positions (neutral [N], parallel [P], and angled [A]) according to the longitudinal axis of the patient. We analyzed the dose-volume distribution and volumetric variability of the rectum and bladder. We converted the total doses to equivalent doses in 2 Gy (EQD₂) using a linear-quadratic model (a/b = 3 Gy).

Results: The mean rectum volume for the N, P, and A positions was 68.2 ± 22.7 cc, 79.3 ± 33.7 cc, and 74.2 ± 29.6 cc, respectively. The mean rectum volume for the P position was significantly larger than that for the N position ($p = 0.03$). Relative to the N position, the A position resulted in a lower total EQD₂ in the highest irradiated 2 cc (D_{2cc}; $p = 0.001$), 1 cc (D_{1cc}; $p = 0.004$), and 0.1 cc (D_{0.1cc}; $p = 0.047$) of the rectum. Similarly, the P position resulted in a lower EQD₂ in the D_{2cc} ($p = 0.018$) and D_{1cc} ($p = 0.024$) of the rectum relative to the N position. In the bladder, the P position resulted in a higher EQD₂ in the D_{2cc} relative to the N position ($p = 0.02$). There was no dosimetric difference between the P and A positions in either the rectum or the bladder.

Conclusions: Vaginal cuff brachytherapy in the P and A positions is significantly superior to that in the N position in terms of rectum dosimetry. The bladder dose in the N position is considerably lower than that in the other positions.

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Key words: brachytherapy, cylinder positions, endometrial cancer, EQD₂.

Purpose

Endometrial carcinoma (EC) is the most common gynecological malignancy in developed countries, with the highest incidence occurring in the sixth and seventh decades of life [1]. Surgery is the first step of treatment, followed by external beam radiotherapy (EBRT) with vaginal cuff brachytherapy (VCB) in selected cases [2,3]. After surgery, VCB may be used either as the sole adjuvant modality in patients with intermediate-risk EC or as a complementary component with EBRT in high-risk patients [4]. Vaginal cuff brachytherapy has a steep dose fall-off, which restricts critical organ doses while applying a high and localized radiation dose to the vaginal cuff.

The most common site of recurrence in patients with EC is the vaginal cuff [5,6]. That recurrence pattern may be one of the major reasons to use VCB as a localized adjuvant treatment directed to the vaginal cuff in patients with EC. In the PORTEC-2 trial, patients with stage I or IIA disease, including high-intermediate risk factors, were randomized and treated with either EBRT or VCB.

In that study, there was no significant difference in local recurrence between the two treatments; however, the patients treated with VCB had less gastrointestinal toxicity and better quality of life [7,8]. During VCB application, the anterior rectal wall, bladder, and sigmoid are located near the area that is exposed to high-dose radiation. The high radiation dose to those organs may cause certain toxicities following the treatment. Therefore, it is important to consider all factors related to the dosimetry of critical organs and the target volume. Although numerous studies have investigated the effects of indication [4,9], treatment time [10], size [4,11], and style [12] of the cylinder, filling of the bladder and rectum [4,13,14], dose fractionation, and prescription [4,15], the impact of the cylinder position has received little study.

The purpose of this study was to analyze whether changes in the cylinder position impact the radiation dose delivered to critical structures in patients undergoing three-dimensional (3D) image-based high-dose-rate brachytherapy.

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Material and methods

Patients

In our study, we enrolled 15 patients with endometrial adenocarcinoma, undergoing post-surgery VCB and EBRT. External beam radiotherapy was delivered to pelvic lymphatics and the primary tumor bed at a prescribed dose of 45 Gy in 25 fractions using 3D conformal radiotherapy. This study was approved by the Baskent University Institutional Review Board (Project no: KA16/362), and supported by the Baskent University Research Fund.

The treatment protocol used in our department was described elsewhere [13]. Briefly, all patients had a thorough gynecologic examination to assess wound healing and to evaluate vaginal size before the placement of the VCB cylinder. The largest computed tomography (CT) - compatible vaginal cylinder was chosen for each patient to achieve the best contact between the vaginal mucosa and the surface of the cylinder. Lubricated condoms were used to facilitate the application and cleaning. In our routine practice, CT planning in the parallel (P) position is performed for the first fraction of application, and the same plan is used for the subsequent fractions of VCB. Catheterization of the bladder and rectal enema are not routinely used. The length of the cylinder protruding outside the vagina is noted to provide uniformity for subsequent insertions.

Treatment planning

Three consecutive CT images were obtained for each patient by setting the cylinder in neutral (N), parallel (P), and angled (A) positions according to the cranial-caudal axis of the patient (Figure 1). In the N position, the cylinder was inserted into the vagina in a manner consistent with the patient's anatomy, and no effort was made to correct the natural insertion angle of the cylinder. In the P position, the cylinder was tilted downwards, so that it was as parallel as possible to the cranial-caudal axis of the patient. In the A position, the tip of the cylinder was moved upwards from the patient's axial plane, keeping the caudal end of the cylinder stationary. After each ma-

neuver, the cylinder was immobilized with a universal applicator clamping device (Varian Medical Systems, Inc., Palo Alto, CA, USA), which was located underneath the patient. A CT scan with 2.5 mm slice thickness through the pelvis was used for treatment planning. Every patient was prompted to empty the bladder before the initial CT process.

All CT slices were transferred to a 3D treatment planning system (BrachyVision™ Eclipse; Varian Medical Systems, Palo Alto, CA, USA). A dose of 12 Gy in three fractions was applied to a depth of 5 mm from the cylinder surface to treat the entire vaginal cuff. The vaginal length was measured on CT images, and the apical two-thirds of the vaginal cylinder were activated, except in patients with a short vaginal length, in accordance with our institutional practice. As a result, a total of 45 CT scans, including three cylinder positions for each patient, were analyzed.

Organs at risk

In order to minimize inter-observer variability, a single physician contoured the clinical target volume (CTV), bladder, and rectum of each patient. The contour of the CTV was determined by expanding the upper two segments of the cylinder by 5 mm in all directions from the cylinder surface. The outer wall of the rectum and the entire bladder were delineated as critical organs. To accommodate the volumetric rectal variations relative to the position of the cylinder, the rectum was contoured in a manner suggested in a previous study [16]. Thus, the rectum was delineated from 1 cm above the cylinder apex to 1.5 cm below the last activated cylinder segment. We also recorded the volumes of the rectum and bladder to assess the volumetric variations due to the different cylinder positions. For the critical organs, we calculated the minimum dose to the highest irradiated 2 cc (D_{2cc}), 1 cc (D_{1cc}), and 0.1 cc ($D_{0.1cc}$) of the rectum, and to the D_{2cc} and $D_{0.1cc}$ of the bladder in each application. The dose statistics for the rectum are shown in Table 1. We converted the physical dose distributions in Table 1, in terms of the VCB (for one fraction) and the previous EBRT (for 25 fractions), to biologically equivalent

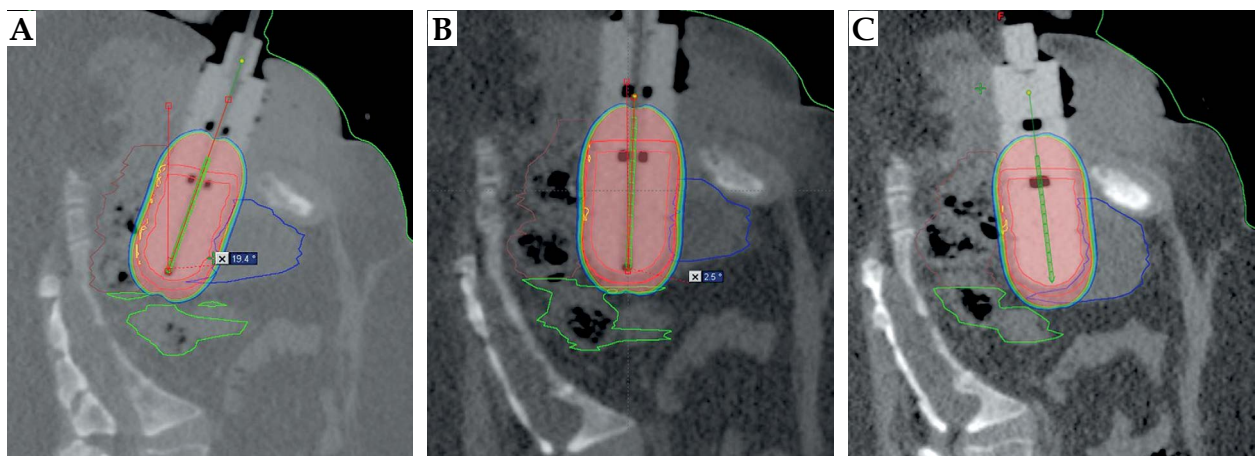


Fig. 1. The 4 Gy isodose area (red) according to the vaginal cylinder in the (A) neutral, (B) parallel, and (C) angled positions in a representative patient

Table 1. Dose levels to the rectum according to the cylinder positions in vaginal cuff brachytherapy (VCB) and equivalent dose calculated in 2 Gy (EQD₂) of external beam radiotherapy

Cases	EQD ₂ EBRT (1.8 Gy × 25 fx)	VCB (fx)	D _{2cc} (fx/Gy)			D _{0.1cc} (fx/Gy)			D _{1cc} (fx/Gy)		
			N	P	A	N	P	A	N	P	A
1	43.2	3	4.9	4.5	4.5	6.4	6.3	5.6	5.2	4.8	5.1
2	43.2	3	5.2	4.5	4.5	6.5	6.2	5.4	5.5	4.8	4.9
3	43.2	3	5.3	4.8	3.7	6.2	5.9	4.6	5.8	5.1	4.0
4	43.2	3	5.6	3.2	4.4	7.2	3.9	5.5	6.2	3.5	4.7
5	43.2	3	4.9	4.8	5.6	6.3	5.7	8.3	5.2	5.1	6.0
6	43.2	3	5.4	4.9	4.2	6.4	6.3	5.1	5.4	5.5	4.4
7	43.2	3	5.2	5.2	4.7	5.3	5.6	5.6	5.4	5.4	4.9
8	43.2	3	5.1	4.7	4.1	6.6	5.4	4.9	5.4	4.9	4.4
9	43.2	3	4.0	3.6	3.8	4.9	4.1	4.5	4.3	3.8	4.0
10	43.2	3	6.0	5.1	5.0	8.4	6.1	5.5	7.2	5.5	5.3
11	43.2	3	5.3	4.7	4.9	6.3	5.9	5.9	5.6	4.9	5.2
12	43.2	3	5.0	4.4	4.2	6.3	5.1	5.1	5.2	4.6	4.5
13	43.2	3	3.8	5.2	3.8	5.1	8.1	5.1	4.2	5.8	4.2
14	43.2	3	6.4	4.7	4.6	9.2	8.8	5.6	7.5	5.7	5.1
15	43.2	3	4.1	4.1	4.1	4.9	4.6	5.1	4.3	3.6	4.4

EQD₂ – equivalent dose calculated in 2 Gy, Gy – gray, fx – fractions, D_{2cc, 0.1cc, 1cc} – the minimum dose to the most irradiated of 2 cc, 0.1 cc, and 1 cc of organ, VCB – vaginal cuff brachytherapy, N, P, A – neutral, parallel, and angled cylinder positions, respectively

doses {BED; BED = n.d. [1 + d/(a/b)]} to account for the dose per fraction as given in fractions of 2 Gy [EQD₂; EQD₂ = BED/[1 + 2/(a/b)]] using a linear quadratic model with a/b = 3 Gy [17]. Additionally, we estimated an approximate EQD₂ VCB value for the three fractions of VCB, based on the doses shown in Table 1.

Statistical analysis

We analyzed the data using SPSS version 20 (SPSS, Chicago, IL, USA). We determined the volumes of all specified organs at risk and compared the dose-volume histograms for each of the cylinder positions. We used the Wilcoxon matched-pairs test to determine significant differences in volumes and doses between the cylinder positions. We considered differences statistically significant at $p < 0.05$.

Results

We analyzed a total of 45 CT scans from 15 patients with cylinders in the N, P, and A positions. The cylinder diameter was 3.5 cm for all of the patients. The mean rectal volume for the P, A, and N positions was 79.3 ± 33.7 cc, 74.2 ± 29.6 cc, and 68.2 ± 22.7 cc, respectively. The mean rectum volume for the P position was significantly larger than that for the N position ($p = 0.03$). There was no significant difference in bladder volume among the three cylinder positions.

The D_{2cc}, D_{0.1cc}, and D_{1cc} of the rectum in the three positions are shown in Table 2. The BED_{EBRT} and EQD₂ EBRT were 72 Gy and 43.2 Gy, respectively. The sum of the two modalities (EQD₂ EBRT and EQD₂ VCB) in the rectal D_{2cc}, D_{0.1cc}, and D_{1cc} is listed for three fractions of VCB in Table 3. The total EQD₂ in the D_{2cc} ($p = 0.001$), D_{0.1cc}

Table 2. Mean rectum dose statistics according to the vaginal cylinder positions for one fraction of brachytherapy

Rectal dose statistics	Cylinder position			p		
	N (Gy ± SD)	P (Gy ± SD)	A (Gy ± SD)	N vs. P	N vs. A	P vs. A
D _{2cc}	5.1 ± 0.7	4.5 ± 0.6	4.4 ± 0.5	0.013	0.001	0.6
D _{0.1cc}	6.4 ± 1.2	5.9 ± 1.3	5.5 ± 0.9	0.15	0.001	0.3
D _{1cc}	5.5 ± 0.9	4.9 ± 0.7	4.7 ± 0.6	0.03	0.005	0.5

N – neutral, P – parallel, A – angled, D_{2cc, 0.1cc, 1cc} – the minimum dose to the most irradiated of 2 cc, 0.1 cc, and 1 cc of organ, Gy – gray

Table 3. Total* rectal doses according to cylinder position

Dose-volume parameters	Cylinder position			<i>p</i>		
	N (Gy ± SD)	P (Gy ± SD)	A (Gy ± SD)	N vs. P	N vs. A	P vs. A
D _{2cc}	67.3 ± 5.5	63.4 ± 4.8	62.1 ± 3.8	0.028	0.002	0.34
D _{0.1cc}	79.3 ± 12	73.1 ± 12.3	70.5 ± 8.4	0.08	0.028	0.49
D _{1cc}	70.9 ± 8.4	66.1 ± 5.6	64.5 ± 4.3	0.043	0.007	0.35

*Total dose is provided in equivalent dose calculated in 2 Gy (EQD₂) and EQD₂ is calculated as EQD₂EBRT + EQD₂VCB. The EQD₂VCB was calculated based on the D_{2cc, 0.1cc, 1cc} values presented in Table 1. The EQD₂EBRT was calculated for the total EBRT fractions
EBRT – external beam radiotherapy, VCB – vaginal cuff brachytherapy, Gy – gray, N – neutral, P – parallel, A – angled, D_{2cc, 0.1cc, 1cc} – the minimum dose to the most irradiated of 2 cc, 0.1 cc, and 1 cc of organ

($p = 0.047$), and D_{1cc} ($p = 0.004$) of the rectum for the A position was significantly lower than the corresponding values for the N position. Similarly, the EQD₂ in the D_{2cc} ($p = 0.018$) and D_{1cc} ($p = 0.024$) of the rectum for the P position was significantly lower than the corresponding values for the N position. The differences in the dose statistics maintained their significance when we estimated the EQD₂ for three fractions of VCB (Table 3). Despite the significant differences between the N and P positions and between the N and A positions, there was no difference in terms of rectal doses between the P and A positions (Figure 2).

Regarding the bladder, the EQD₂ in the D_{2cc} for the P position was significantly higher than that for the N position (2.2 ± 0.5 vs. 2.0 ± 0.4 ; $p = 0.02$).

Discussion

Although some brachytherapy studies have focused on the association between the angles or positions of the vaginal cylinder and rectal doses in patients with EC, there is little data showing the impact of the vaginal cylinder position on the critical organ doses in the context of EQD₂. Our analysis demonstrated that the N position was associated with unfavorable EQD₂ values compared with the P and A positions in terms of the rectal D_{2cc}, D_{0.1cc}, and D_{1cc}. Additionally, manipulating the cylinder

in a more angular manner, moving the cylinder from the P position to the A position, did not make any difference in the rectal doses. Conversely, despite the disadvantages of the N position in terms of the rectal doses, the bladder doses for the N position were lower than those for the P and A positions. However, the bladder was not the main topic in our study.

The relationship between the dose and the effect in radiotherapy is linear-quadratic rather than linear. Therefore, the cumulative effect of different treatment methods cannot be identified by adding the doses linearly [18]. The various fractions of VCB and EBRT used in clinical practice can be considered together by converting the different units into a single unit, a concept known as EQD₂, which allows clinicians to compare different dose rates and dose fractions.

Regarding the rectal dose statistics, the D_{2cc} (EQD₂) is the most established parameter as a predictor of rectal toxicity in studies of intracavitary brachytherapy (ICB) and interstitial brachytherapy (IB) [19,20,21,22]. In a previous study, Georg *et al.* assessed the D_{2cc} in patients with cervical carcinoma who were treated with EBRT and ICB in terms of Grade 1-4 rectal toxicities on the Late Effects on Normal Tissues-Subjective, Objective, Management, and Analytic (LENT-SOMA) scale and found that 72 Gy was more relevant than 63 Gy [21]. Chopra *et al.* [20] suggested that limiting the D_{2cc} exposure to < 55 Gy was as-

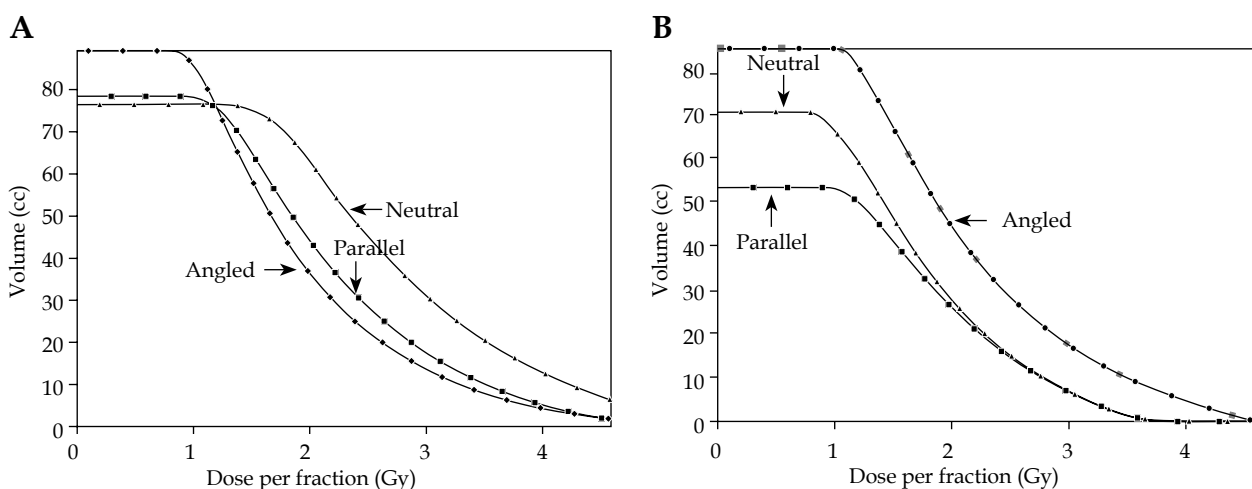


Fig. 2. Comparative dose-volume histogram of the (A) rectum and (B) bladder according to the vaginal cylinder in the neutral (triangle), parallel (square), and angled (sphere) positions

sociated with less Grade 2 rectal toxicity in patients with recurrent cervical carcinoma. In addition, Sakata *et al.* [23] found that patients with maximal rectal EQD₂ > 60 Gy experienced more rectal toxicity. Supporting the results of Sakata *et al.*, another report showed that a cumulative dose of > 65 Gy (EQD₂) was associated with more Grade 2 LENT-SOMA rectal morbidities [24].

Our study demonstrates only a dosimetric pattern and lacks toxicity data; however, the rectal dose statistics, shown in Table 3, may offer some foresight into possible rectal toxicities in the period following treatment. For the total EQD_{2_VCB}, we used the initial rectal dose statistics in the first fraction of VCB for two subsequent imaginary fractions. Significant variation in rectal dose should not be expected among the three fractions of VCB when differences in cylinder position or angle are excluded, considering the common clinical practice of performing the fractions of VCB based on the initial planning CT [25].

According to our results, the mean values of the dose statistics (D_{2ccr}, D_{0.1ccr} and D_{1cc}) in terms of EQD₂ were all significantly higher for the N position than for the P and A positions (Table 3). Despite the lack of a symptomatic assessment of rectal toxicity in our study, the mean EQD₂ for the D_{2cc} (67.3 ± 5.5), D_{0.1cc} (79.3 ± 12), and D_{1cc} (70.9 ± 8.4) of the rectum in our study appeared to be safer than those observed by Georg *et al.* (72 ± 6, 88 ± 10, and 76 ± 7, respectively) [21].

There have been some reports of the advantages of 3D VCB compared with two-dimensional (2D) VCB [26,27]. In contrast to the dose specification process of 2D planning, which is based on the pelvic bone, 3D VCB uses volumetric treatment planning, and hence has more precise target coverage, which is critical for certain patients. For instance, while patients who undergo VCB without EBRT are expected to experience limited rectum and bladder toxicities, the VCB-related dose may become important in patients who receive an EBRT dose of 45-50.4 Gy prior to VCB. Additionally, further techniques have been utilized to minimize the critical organ doses, including modifications of the bladder [13,28] or rectal filling [29], the position of the patient on the couch [30], or the geometry of the vaginal cylinder [31].

In a previous study, Hoskin *et al.* moved the vaginal cylinder from the N position to the P position in 30 patients with EC who were treated with VCB and reported an average rectal dose reduction of 1.3 Gy for a prescribed dose of 5.5 Gy [31]. Our results differ from those of Hoskin *et al.* in some instances. First, we performed a dosimetric analysis of three different positions of the vaginal cylinder according to the cranial-caudal plane of the patient. Second, we used CT images, which are more reliable to assess the variability of doses and critical-organ delineations, among different set-up positions compared with the radiographs used by Hoskin *et al.* Third, our report is more comparable to other reports in terms of cumulative doses and possible side effects because of our use of EQD₂ in our analyses. However, our results agree with those of Hoskin *et al.* in that the rectal doses in our patients diminished as the tip of the cylinder was moved upward from the axial plane of the patient ($p < 0.05$ for

D_{1cc} and D_{2cc} in the A position) at the cost of increasing the mean bladder dose.

Another previous dosimetric study lends indirect support to our results. Lati *et al.* [30] investigated the influence of two different patient positions without correcting the cylinder angle in the vagina. The rectal dose in patients positioned with a leg extended was lower than that in patients in the lithotomy position (D_{2ccr} 4.24 Gy vs. 5.14 Gy; $p = 0.003$). The lithotomy position may be considered as the opposite of our A position, because the vaginal cuff in the lithotomy position is moved posteriorly, approaching the rectum, and consequently, the rectum is exposed to higher radiation doses because of its proximity to the vaginal cylinder in the cuff.

Our volumetric analyses showed that the rectal volume for the P position was significantly larger than that for the N position (79.3 ± 33.7 cc vs. 68.2 ± 22.7 cc; $p = 0.03$). The movement of rectal contents and gas through the hollow rectum during the application in different cylinder positions may be the major reason for the volumetric variation. Additionally, CT may have limited sensitivity to delineate the rectal wall, especially for the distal part of the organ.

Our study has several limitations. First, our patient cohort was small, and all of the patients were treated at a single institution. Second, the angled application of the cylinder was performed arbitrarily without a fixed angle, which might cause some angular variability. Third, although the P and A positions had advantages relative to the N position in terms of the rectal radiation dose, we did not attempt to determine the optimal cylinder angles.

Conclusions

We examined the dosimetric influence of three different cylinder positions for the application of VCB in terms of EQD₂ in patients with EC. Our results demonstrate that VCB in the P and A positions results in significantly lower rectal radiation doses compared with that in the N position, at the expense of higher bladder doses. Despite the similar rectal dosimetry of the P and A positions, the bladder dose may increase when the cylinder is moved upward from the patient's axial plane. Further studies, including toxicity analysis in larger cohorts, may be more demonstrative of the optimal cylinder position for the treatment of the vaginal cuff.

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Disclosure

Authors report no conflict of interest.

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