FULL PAPER

The impact of air pockets around the vaginal cylinder on vaginal vault brachytherapy

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Objective: To evaluate the incidence, size and predisposing factors for air pockets around the vaginal cylinder and their dosimetric effect on the vaginal mucosa.

Methods: We investigated 174 patients with endometrial carcinoma treated with external radiotherapy (RT) and brachytherapy (BRT) (101 patients, 58%) or BRT alone (73 patients, 42%). The quantity, volume and dosimetric impact of the air pockets surrounding the vaginal cylinder were quantified. The proportions of patients with or without air pockets during application were stratified according to menopausal status, treatment modality and interval between surgery and RT.

Results: Air pockets around the vaginal cylinder were seen in 75 patients (43%), while 99 patients (57%) had no air pockets. Only 11 patients (6.3%) received less than the prescribed dose (average 93.9% of prescribed dose; range, 79.0–99.2%). Air pockets were significantly fewer in pre-menopausal patients or in patients treated with the combination of external RT and BRT than in post-menopausal patients or patients treated with BRT alone. A significant correlation existed between the mucosal displacement of the air gap and the ratio of the measured dose at the surface of the air gap and prescribed dose (Pearson $r = -0.775$; $p < 0.001$).

Conclusion: Air pockets were still a frequent problem during vaginal vault BRT, especially in post-menopausal patients or in patients treated with BRT alone, which may potentially cause dose reductions at the vaginal mucosa.

Advances in knowledge: Air pockets around the vaginal cylinder remain a significant problem, which may potentially cause dose reduction in the target volume.

The primary treatment of choice in localized endometrial cancer is surgery. Adjuvant radiotherapy (RT) is recommended in intermediate- and high-risk patients in order to diminish disease recurrence. RT can be in the form of external RT (ERT) with vaginal vault brachytherapy (BRT) or BRT only, depending on the risk factors and stage of disease.

The purpose of vaginal vault BRT is to eradicate a microscopic tumour at the lymphatics located in the vaginal vault. It was demonstrated that >90% of lymphatics lie within 2–3 mm from the surface of stretched mucosa.[1] For this reason, in order to deliver adequate doses to the submucosal lymphatics, the vaginal cylinder must be in direct contact with the vaginal surface, as recommended by the American Brachytherapy Society (ABS).[2] The Group Europeén de Curiethérapie and the European Society for Radiotherapy & Oncology (GEC-ESTRO) guidance[3] is to prescribe vaginal BRT to 5 mm from the applicator surface with a 2-mm tolerance. The most commonly used applicator for vaginal vault high-dose-rate BRT is a segmented cylinder.[4] However, during application, air gaps may be observed, which may potentially cause underdosage of the vaginal mucosa.

Cameron et al[5] found that 18 of 25 patients (72%) had air gaps >2 mm in the cranial part of the vagina, with the median number of air pockets per patient being 1 (range, 0–5). Richardson et al[6] reported that 20 of 25 patients (80%) had at least 1 air pocket in the upper vagina. In another study, Humphrey et al[7] demonstrated >2 mm air gaps in 11/103 patients, while repositioning or use of a larger cylinder reduced air gaps in 7/103 patients. However, in all of these studies, applicators of different sizes were used with a limited number of patients and conflicting results have been reported.

In Baskent University Department of Radiation Oncology, Adana, Turkey, we prefer using cylinders with the largest diameter for reducing air gaps during vaginal vault BRT. The purpose of this study was to evaluate the incidence, size and dosimetric effects of these air pockets. In addition, the predisposing factors for the development of air gaps were analysed.

METHODS AND MATERIALS

Patients

The study population consisted of 174 consecutive patients with pathologically proven endometrial carcinoma treated with post-operative RT between January 2012 and May 2014. The BRT plans and patient data were retrospectively analysed. Protocol approval was obtained from the institutional review board for this study.

Before vaginal cylinder insertion, each patient had a detailed pelvic examination, and the vaginal vault size was determined upon examination and the vaginal cylinder with the largest diameter that each patient could tolerate was inserted. The range of cylinders in use varied in diameter between 3.0 and 3.5 cm. After insertion of the cylinder to the top of the vagina, the applicator was fixed with a universal applicator-clamping device (Varian®; Varian Medical Systems, Palo Alto, CA), which was underneath the patient. The length of the cylinder protruding outside the vagina was noted to ensure accurate repositioning for subsequent insertions. All subsequent treatments used the same diameter and length of the cylinder. Moreover, before each BRT session, the applicator was checked with fluoroscopy to confirm that the positioning was the same for each treatment.

A CT scan with 2.5-mm slice thickness through the pelvis was performed at the first BRT application in line with departmental policy. All CT slices were transferred, via a hospital network, to the treatment planning system (Brachyvision™ v. 8.1; Varian Medical Systems). The dose was prescribed to a 5-mm depth for the 3- to 5-cm cranial part of the vagina.[8] Patients were treated with an iridium-192 high-dose afterloader (Varisource®; Varian Medical Systems). The dose prescribed was 4 Gy for three fractions in patients treated with ERT and BRT, and 5 Gy for five fractions for patients treated with BRT only. 35 patients (20%) were treated with a 3.0-cm diameter cylinder, and 139 patients (80%) were treated with a 3.5-cm diameter cylinder.

Dosimetric analysis

The air pockets in the upper 3–5 cm of the vagina were contoured in the axial plane by a single investigator to minimize the risk of interobserver variation, and the volumes were calculated by the treatment planning system. The average number of air pockets, average air pocket volume and maximum displacement of the vaginal mucosa were recorded. The relative RT dose at the point of maximum air gap measured by the treatment planning system was recorded for all air gaps both at the surface and at 5 mm from the surface of the cylinder and vaginal mucosa by a single investigator (Figure 1). The ratio between the vaginal mucosa displaced by the air pocket and the prescribed dose was also recorded. The doses were calculated using the Task Group 43 formalism.[9]

Statistical analysis

Statistical analysis was performed using SPSS® v. 20.0 (SPSS Inc., Chicago, IL), software. Time to ERT and BRT was calculated as the time between surgery and initiation of ERT or BRT. The proportions of patients with or without air pockets during application were stratified by menopausal status, treatment modality and the interval between surgery and RT. A multiple linear regression model was used to identify independent predictors of air pockets around the vaginal cylinder. The χ^2 test or Fisher's exact test, where appropriate, was used to compare these proportions in different groups. The correlation between the dose ratio and mucosal height and their significance were calculated using the Pearson correlation test. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Patient characteristics

The median age of the patient cohort was 60 years (range, 27–81 years). Patient characteristics are summarized in Table 1. Most of the patients (86%) were post-menopausal, and the most commonly used vaginal cylinder (86%) was 3.5 cm in diameter. 101 patients (58%) were treated with ERT and BRT, while 73 patients (42%) were treated with BRT alone. Average times between surgery and the initiation of ERT and BRT were 35 days (range, 5–334 days) and 67 days (range, 12–370 days), respectively.

Figure 1. (a) Axial CT images of the vagina with a cylinder inserted demonstrating a small air pocket and (b) point dose calculation of the dose to the vaginal mucosa, where the prescribed dose was 4 Gy per fraction. The distance was measured from the surface of the cylinder to the point of maximum displacement by a single observer. The dose was then determined at that point and compared with the prescribed dose.
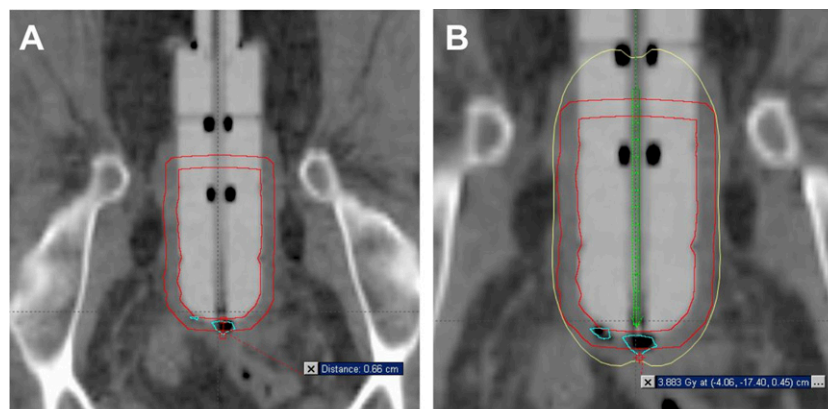
Table 1. Patient characteristics

Parameters	n	%
Stage		
IA	43	25
IB	52	30
II	26	15
IIIA	22	13
IIIB	3	2
IIIC	28	16
Menopausal status		
Pre-menopausal	25	14
Post-menopausal	149	86
Cylinder diameter		
3.0 cm	25	14
3.5 cm	149	86
Fraction dose		
4 Gy	84	48
5 Gy	90	52

Air pocket characteristics

Air pockets around the vaginal cylinder were seen in 75 patients (43%), while 99 patients (57%) had no air pockets.

36 patients (48%) had 1 air pocket, 27 patients (36%) and 12 patients (16%) had 2 and 3 air pockets, respectively. The air pockets were located in the apical part of the cylinder in 30 patients (40%) and in the lateral sides of the cylinder in 29 patients (39%), while 16 patients (21%) had air pockets located both at the apex and lateral sides of the cylinder.

The mean average distance of the mucosa displaced by air pockets was 3.6 mm (range, 1.8–8.8 mm), and the average volume of air pockets was 0.31 cm^3 (range, 0.04–2.93 cm^3). Out of 174 patients, 68 (39%) had air pockets that displaced the vaginal mucosa away from the surface of the cylinder by a distance of ≥2 mm. As demonstrated in Table 2, air pockets were significantly less in pre-menopausal patients or in patients treated with ERT and BRT than in post-menopausal patients or in patients treated with BRT alone. Menopausal status ($p = 0.006$ and $r = 0.191$) and treatment strategy ($p = 0.02$ and $r = 0.154$) were independent contributors to the incidence of air pockets. Age, the interval between surgery and ERT or BRT, and vaginal cylinder diameter had no significant impact on the incidence of air pockets.

Dosimetric effects of air pockets

The mean dose measured at the surface of the air gap was 6.13 Gy (range, 3.23–11.13 Gy). The dose ratio between the vaginal mucosa displaced by the air pocket and the dose prescribed was 1.41 (range, 0.79–2.25). Over the air gaps, the dose that the mucosa received at 0.5 cm was on average 90.4% (range, 81.7–99.3%) of that expected in the absence of air gaps. There was a significant correlation between the mucosal displacement

Table 2. Factors affecting the presence of air pockets around the vaginal cylinder

Factors	Air pockets around vaginal cylinder		
	Present, n (%)	Absent, n (%)	p-value
Age (years), median (range)	60 (39–81)	59 (37–80)	0.85
Menopausal status			
Pre-menopausal	5 (3)	20 (11)	0.02
Post-menopausal	70 (40)	79 (45)	
Treatment modality			
BRT alone	38 (22)	35 (20)	0.04
ERT + BRT	37 (21)	64 (37)	
Time between surgery and ERT			
<21 days	9 (9)	13 (13)	0.63
≥21 days	28 (28)	51 (50)	
Time between surgery and BRT			
<21 days	8 (5)	67 (39)	0.48
≥21 days	12 (7)	87 (50)	
Vaginal cylinder diameter			
3.0 cm	11 (6)	14 (8)	0.55
3.5 cm	64 (37)	85 (49)	

BRT, brachytherapy; ERT, external radiotherapy.

of the air gap and the ratio of the measured dose at the surface of the air gap and prescribed dose (Pearson $r = -0.775$; $p < 0.001$) (Figure 2). Only 11 patients (6.3%) with air gaps received less radiation, an average of 93.9% of the prescribed dose (range, 79.0–99.2%).

The height of the air gap was significantly less in patients with the 3.5-cm vaginal cylinder application than with the 3.0-cm application (3.23 ± 0.96 mm *vs* 3.88 ± 0.15 mm; $p = 0.03$). However, the mean dose measured at the surface of the air gaps (6.27 ± 1.10 Gy *vs* 6.12 ± 1.44 Gy; $p = 0.63$) and the ratio of the measured and prescribed doses (1.51 ± 0.23 *vs* 1.40 ± 0.29; $p = 0.23$) were not significantly different between the 3.0- and 3.5-cm vaginal cylinders.

DISCUSSION
In the present study, we investigated the incidence and predisposing factors for air pockets around the vaginal cylinder during vaginal vault BRT. In addition, we analysed the dosimetric effects of the air gaps. In this study, air pockets were seen in 75 of 174 patients (43%), and the average number of air pockets ranged from 1–3 per patient. However, only 11 patients (6.3%) received less than the prescribed doses, with an average of 93.9% (range, 79.0–99.2%). Furthermore, we demonstrated that air pockets were less frequent in pre-menopausal patients and in patients treated with post-operative ERT and BRT.

The results of randomized trials for patients with intermediate-risk endometrial carcinoma suggested that most (75%) locoregional recurrence was located in the vagina; thus, vaginal vault BRT may be most effective for patients with intermediate- and

high-risk features in order to obtain local control with fewer side effects compared with ERT and better quality of life.[10] Data from retrospective studies that used vaginal BRT alone for Stage I mainly low-risk endometrial carcinoma (EC) showed 5-year rates of vaginal relapse of 0–5%.[11,12] Final results of the post-operative radiation therapy for endometrial carcinoma (PORTEC)-2 trial showed vaginal BRT to be highly effective in preventing vaginal relapse. At median follow-up of 45 months, the estimated 5-year rates of vaginal recurrence were 1.8% for BRT and 1.6% for ERT ($p = 0.74$).[10] In view of the efficacy of vaginal BRT with fewer side effects and better quality of life, in many countries, BRT alone has become the standard of care for patients with endometrial cancer with intermediate- to high-risk features.

The results from the PORTEC trial found that the rate of vaginal relapse without RT is approximately 10%, with a vaginal vault relapse of 6.4%.[13] One possible cause of vaginal relapse is that the vaginal mucosa does not receive the prescribed dose because of the presence of air gaps. In a study by Cameron et al,[5] 18 of 25 (72%) patients had an average of 1 air gap, with a mean average area of the air gap of 0.20 cm^2 (range, 0.02–1.65 cm^2). This resulted in a mean average of 0.86% of the vaginal surface being displaced from the surface of the cylinder. Richardson et al[6] also reported that 20 of 25 patients (80%) had ≥ 1 air pocket present in the upper vagina in at least 1 of 6 treatment fractions. The average total pocket volume was 0.34 cm^3 (range, 0.01–1.32 cm^3), and the average distance that the mucosa was displaced was 3.7 mm (range, 1.3–8.0 mm) with 88.8% of the vaginal mucosa displaced away from the cylinder surface by ≥ 2 mm. Humphrey et al[7] found that 38 out of 103 patients (37%) had ≥ 1 air gap within the target volume, while air gaps

Figure 2. Regression plots of the mucosa elevated by the air gaps around the vaginal cylinder *vs* the ratio of the dose measured at the tip of the air gap to the prescribed dose [Pearson correlation coefficient (r) = -0.775; $p < 0.001$].
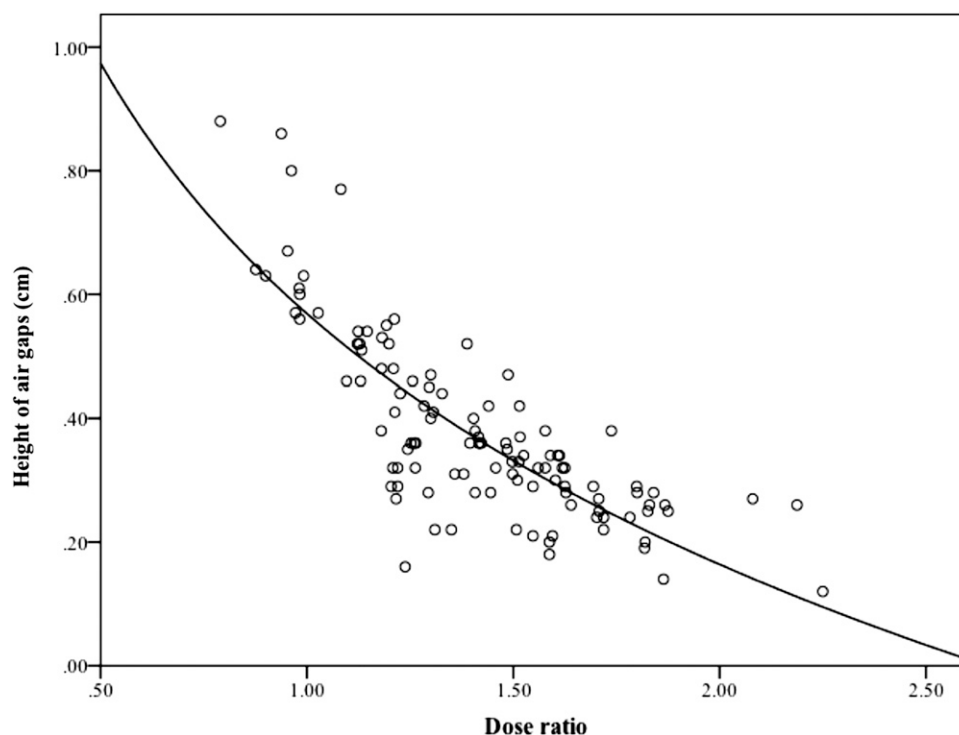
≥ 2 mm were seen in only 11 out of 103 patients. In this present study, we found that 75 patients (43%) had ≥ 1 air gap with a mean volume of 0.31 cm^3 (range, 0.04–2.93 cm^3) and an average distance of mucosa displacement of 3.6 mm (range, 1.8–8.8 mm) with 38.9% of the vaginal mucosa displaced away from the surface of the cylinder by ≥ 2 mm. The incidence of air gaps was lower and similar between our study and that of Humphrey et al,[7] because in these studies, the vaginal cylinder with the largest diameter (≥ 3.0 cm) was used more frequently than in other studies (Table 3). Another important finding was that the incidence of vaginal mucosa displaced away from the surface of the cylinder by ≥ 2 mm was the highest in patients for whom a smaller diameter cylinder was used compared with other studies. We also analysed the difference in the height of the air gap and found that the air gap height was significantly less in patients with the 3.5-cm vaginal cylinder application than with the 3.0-cm application. Therefore, we prefer using the cylinder with the largest diameter based on the patient and target geometry after detailed gynaecological examination before cylinder insertion, in order to ensure close mucosal apposition as recommended by the ABS.[2]

The dosimetric effect of air gaps around the vaginal cylinder has not been well described. Richardson et al[6] reported a 27% (range, 9–58%) dose reduction to the vaginal mucosa at the air pocket. However, the entire vaginal mucosal dose was not reported. Cameron et al[5] found that the dose at the mucosa over the air gaps received at 0.5 cm was on average 86.7% (range, 54.7–97.3%) of that which it would have received if there was no air gap. However, the dose at 0.5 cm of the whole vaginal mucosa within the target volume was 99.6% (range, 96–100%) of that prescribed. In the present study, although we found a significant correlation between the mucosal displacement of the air gap and the ratio of the measured dose at the surface of the air gap and prescribed dose, only 11 patients (6.3%) had less than the prescribed dose, which was still 93.9% (range, 79.0–99.2%).

ERT and/or vaginal BRT may cause shortening of the vagina and fibrosis as a late reaction, whereas vaginal mucositis and swelling might be seen acutely.[14,15] In patients treated with ERT, vaginal mucosal swelling and mucositis start during treatment because of dilatation of mucosal vessels causing oedema. Therefore, the vaginal cylinder could potentially cover the whole mucosal surface, with less air gaps observed, as seen in our study. Other factors including age and menopausal status were also found to be significant for developing vaginal mucositis in patients treated with ERT and vaginal BRT.[14,16] Thus, such factors may be important to consider because the vaginal mucosa of older, post-menopausal females becomes thin, is replaced by connective tissue and loses its vasculature, so the vaginal cylinder could not contact the whole vaginal mucosa, when compared with the vaginal mucosa of younger, pre-menopausal females, as observed in our study.

The present study has several limitations. The retrospective nature of our study is the first limitation. Secondly, we only performed a CT scan to investigate the air gaps present on the first fraction of BRT. Most patients received three to five fractions of BRT. The location of air gaps might have been different at each treatment, further diluting their overall effect.[6] Thirdly, the dose required to eradicate microscopic metastases is unknown. It is unclear whether an even lower dose would be equally effective for low- or intermediate-risk patients. Hence, even if there are air gaps, the dose to the raised vagina may still be sufficient to eradicate micrometastases. If this is true, and if the air gaps can be prevented, it may be possible that an even lower dose of RT will be effective. Finally, although air pockets were seen frequently, <1% of patients received less than the prescribed dose, which may have only a minor impact clinically. However, this study is important for demonstrating the incidence, predisposing factors and dosimetric effects of air gaps around vaginal cylinder vaginal vault BRT using a higher patient number than did previous studies.

CONCLUSION
To the best of our knowledge, this is the first study to evaluate the incidence, predisposing factors and dosimetric effects of air gaps during vaginal vault BRT. Although we used the largest cylinders that the patient could tolerate in this study, air pockets were still a frequent problem during vaginal vault BRT, especially in post-menopausal patients or in patients treated with BRT alone, which may potentially cause dose reductions at the vaginal mucosa. Since most centres prefer vaginal vault BRT alone in high- to intermediate-risk patients, dose reductions caused by air gaps may potentially allow local recurrence.

FUNDING

Table 3. The studies evaluating the incidence of air gaps according to cylinder diameter

Study	Patient number	Incidence of air gaps (%)	Cylinder diameter (%)			Mucosal elevation by ≥ 2 mm (%)
			<3.0 cm	3.0 cm	3.5 cm	
Cameron et al[5]	25	72	44	36	20	32
Richardson et al[6]	25	80	96	4	0	72
Humphrey et al[7]	103	37	17	54	30	11
Present study	174	43	0	14	86	39

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