

# Vaginal cuff brachytherapy in endometrial cancer – a technically easy treatment?

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**Abstract:** Endometrial cancer (EC) is one of the most common gynecological cancers among women in the developed countries. Vaginal cuff is the main location of relapses after a curative surgical procedure and postoperative radiation therapy have proven to diminish it. Nevertheless, these results have not translated into better survival results. The preeminent place of vaginal cuff brachytherapy (VCB) in the postoperative treatment of high- to intermediate-risk EC was given by the PORTEC-2 trial, which demonstrated a similar reduction in relapses with VCB than with external beam radiotherapy (EBRT), but VCB induced less late toxicity. As a result of this trial, the use of VCB has increased in clinical practice at the expense of EBRT. A majority of the clinical reviews of VCB usually address the risk categories and patient selection but pay little attention to technical aspects of the VCB procedure. Our review aimed to address both aspects. First of all, we described the risk groups, which guide patient selection for VCB in clinical practice. Then, we depicted several technical aspects that might influence dose deposition and toxicity. Bladder distension and rectal distension as well as applicator position or patient position are some of those variables that we reviewed.

**Keywords:** endometrial cancer, vaginal cuff brachytherapy, rectum, bladder, technique

## Introduction

Endometrial cancer (EC) is a leading cause of female cancer in developed countries. It is the fifth most common cancer worldwide in women. Approximately 40% of EC is diagnosed in Europe, representing the fourth neoplasm among women and the third gynecological cancer after breast and ovarian cancers.<sup>1</sup> The annual incidence in developed countries varies from 12.9 to 15.6 per 100000 women in the European countries and up to 19.1 per 100000 women in the US, while these figures drop to <5 per 100000 women in Africa and 2.7 in South-Central Asia.<sup>2</sup>

Most EC is diagnosed in its early stages due to the promptness of symptoms, mainly postmenopausal vaginal bleeding. The cornerstone of treatment, after metastases are ruled out, is surgery, which aside from its curative nature is the main staging procedure, and postoperative irradiation is added for patients at risk of relapse.<sup>3</sup> The majority of EC patients have low-to-intermediate-risk (55%) or high-to-intermediate-risk (30%) tumors; only 15% of patients have high-risk tumors.<sup>3</sup> Patient selection for adjuvant treatment depends on the clinicopathological factors of risk and the type of surgery undertaken.<sup>3</sup> Brachytherapy has, since 1903, been a well-established radiotherapy technique to treat cancer in several locations, such as the prostate, penile, skin and head-and-neck tumors, in addition to gynecological tumors.<sup>4-7</sup>

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While the current standard surgical management for early EC clearly involves a total hysterectomy with bilateral salpingo-oophorectomy, the role of lymphadenectomy is controversial at the moment and its practice varies worldwide. Pelvic lymphadenectomy or multiple site sampling remains the standard procedure in many departments except for patients at high risk of surgical morbidity. Para-aortic lymphadenectomy is more controversial besides its use on high-risk patients with high-grade or stage II tumors. Despite single-center and retrospective reports having reported lymphadenectomy benefits,<sup>8,9</sup> randomized trials have failed to demonstrate an overall or a progression-free survival advantage.<sup>10,11</sup> In addition, low-risk disease patients have not benefited from this procedure,<sup>12</sup> which is associated with 8%–50% of lymphedema. In any case, lymphadenectomy has shown benefits as a staging procedure. Laparoscopic surgery improves patient recovery compared with the laparotomic approach.<sup>13</sup> The LAP2 study<sup>14</sup> demonstrated a significant reduction in moderate-to-severe postoperative adverse complications of the laparoscopy compared to the laparotomy (14% vs 21%) despite the longer operation time (mean, 204 vs 130 minutes). In all, 25.8% of the patients assigned to laparotomy required conversion to laparotomy. Significantly, pelvic and para-aortic nodes were not removed in 8% of laparoscopic patients compared to 4% of laparotomy patients. A step forward in reducing surgical morbidity further has been the removal of selective sentinel lymph nodes. The FIRES trial<sup>15</sup> successfully mapped at least one sentinel lymph node in 86% of patients. No lymph node metastases were identified in 3% of patients with node-positive disease. Sensitivity and negative predictive values were of 97.2% and 99.6%, respectively.

Recurrence following initial treatment appears in 10–13% of patients; >70% of failures appear in the vagina but an extrapelvic failure can be detected in >75% of the relapsed patients.<sup>16</sup> Hematogenous metastases have been reported in 6–10% of patients,<sup>17</sup> the lungs being the most common site (2–8% of EC patients). A review carried out in Poland of 1610 patients found 134 hematogenous metastases in 110 patients with stages I and II. Sites of metastases were the lungs (69 metastases), liver (32 metastases), bones (23 metastases) and brain (10 metastases).<sup>18</sup> These figures can increase up to 24% in patients with unfavorable histologies, such as clear-cell (CC) carcinoma.<sup>19</sup> A total of 10% of patients who died from their EC had disease in the pelvis, 37% had in the abdomen (liver metastases accounted for 35% of these) and 53% had at distant places (lungs hosted metastases in 78% of these patients).<sup>20</sup> Prospective studies have demonstrated

a decrease in local relapses with postoperative radiotherapy, either external beam radiotherapy (EBRT) or vaginal cuff brachytherapy (VCB), but results have not translated to a survival advantage. Nevertheless, these randomized studies have not been powerful enough to detect it. Analyses of the large National Cancer Database (NCDB), which collects data from >1500 facilities in the US, showed a survival benefit among patients at high-to-intermediate-risk and high-risk patients treated with postoperative radiotherapy.<sup>21</sup> The analyses of >132000 patients showed up to a 22% decrease in mortality risk in these patient groups, and postoperative irradiation was an independent factor for overall survival in a multivariate analysis. Data from the Surveillance, Epidemiology, and End Results (SEER) database have shown an improvement in survival with EBRT or VCB among intermediate- patients and high-risk patients without lymph node dissection,<sup>22,23</sup> but a further analysis of 58,172 patients included in the SEER database failed to demonstrate an improvement in cancer-specific mortality.<sup>24</sup> Additionally, smaller population-based reports, like the Danish population-based study, also failed to demonstrate improvement in survival.<sup>25</sup> These doubts about survival have raised the need for evaluating the costs of VCB. Postoperative VCB cost for intermediate-risk EC patients was USD 38764/life saved,<sup>26</sup> which is less than the value generally considered the acceptable cutoff for intervention (USD 50000/life saved).

Owing to the increasing trend for using VCB, reported from the SEER data,<sup>27</sup> it is a good idea to describe patient selection and technical issues related with VCB in EC, some of which are not usually addressed. The manuscript is focused on high-dose rate (HDR) because nowadays only 3.8% of the US radiation oncologists use low-dose rate (LDR). VCB reviews usually summarize patient selection and group description because VCB is regarded as a simple and easy technique that is generally well tolerated.<sup>28</sup> Instead, we dealt in-depth with patient and technical issues, not usually covered in other critical reviews, such as body mass index, patient position, applicator position or rectum and bladder filling, among others.<sup>29–33</sup> Several of these issues have not been covered in the recent American Brachytherapy Task Group Report.<sup>34</sup>

## Patient selection and risk groups

Clinicopathological findings define the risk for disease relapse and guide indications for postoperative treatments. Indications include age, International Federation of Gynecology and Obstetrics (FIGO) stage, histological type, depth of myometrial invasion, pathological grade and lymphovascular space

invasion (LVSI), and some guidelines add tumor size to this list when recommending adjuvant radiation. Several risk groups have been proposed that do not match completely (Table 1). American Society for Radiation Oncology (ASTRO)/American Society of Clinical Oncology (ASCO) guidelines provide the simpler definition of a high-to-intermediate-risk group.<sup>35</sup> In a randomized trial of low-risk patients, only 4% of the overall group relapsed, suggesting that they would not benefit from adjuvant irradiation.<sup>36</sup> Intermediate-risk patients, however, can benefit from postoperative radiotherapy. Three large randomized trials<sup>10,37,38</sup> have demonstrated a reduction in pelvic and local relapses, 70% of which appear in the vaginal vault, and failed to improve survival (Table 2). A Cochrane meta-analysis determined that EBRT produced an absolute risk reduction of locoregional recurrences of 6%, meaning that one locoregional relapse is prevented in every 16.7 treated patients.<sup>39</sup> Sorbe et al<sup>40</sup> also have demonstrated that VCB provides similar tumor control than EBRT at lower

toxicity and, thus, a better quality of life. The VCB arm was associated with significantly less diarrhea, fecal leakage, need of the toilet and less limitation in daily activities. Table 3 shows the National Comprehensive Cancer Network (NCCN) guidelines for postoperative radiotherapy. Irradiation in stage III/IV has been less studied; a retrospective SEER analysis of 1577 patients demonstrated higher 5-year overall survival with the addition of EBRT or EBRT + VCB (surgery 40%, EBRT 56%, EBRT + VCB 65%).<sup>41</sup> Results from the NCDB have shown that VCB improves survival among women with stage IA.<sup>42</sup> Results from the same database show that the addition of VCB to EBRT improves survival in stage III patients with cervical involvement (hazard ratio 0.86).<sup>43</sup> Results from the SEER database show that among stage I patients graded into PORTEC-risk groups, there is a significant improvement in survival in high-to-intermediate- and high-risk patients irrespective of the irradiation technique.<sup>21</sup> Analysis of this database also shows an improvement in survival with

**Table 1** Risk group descriptions in the different definitions

Study	Risk group			
	Low	Intermediate	High-to-intermediate	High
PORTEC-1 <sup>37</sup>	G1–2, <50% MI, EC	Stage I, EC <ul style="list-style-type: none"> <li>• G1 and ≥50% MI</li> <li>• G2</li> <li>• G3 and &lt;50% MI</li> </ul>	EC with at least 2/3 factors <ul style="list-style-type: none"> <li>• &gt;60 years</li> <li>• G3</li> <li>• ≥50% MI</li> </ul>	Stages III–IV <ul style="list-style-type: none"> <li>• Uterine serous or CC carcinoma, any stage</li> </ul>
PORTEC-2 <sup>44</sup>			<ul style="list-style-type: none"> <li>• &gt;60 years</li> <li>• Stage IC + G1–2</li> <li>• Stage IB + G3</li> </ul> Stage IIA (excluded >50% MI + G3)	
GOG-99 <sup>38</sup>	Stage IA, G1–2, endometrioid	≤50 years and ≤2 PRF* 50–69 years and ≤1 PRF* ≥70 years and no PRF*	Any age and 3 PRF* 50–69 years and ≥2 PRF* ≥70 years and ≥1 PRF*	Stages III–IV, any histology or grade <ul style="list-style-type: none"> <li>• Uterine serous or CC carcinoma, any stage</li> <li>• Stage IB, G3, endometrioid</li> <li>• Non-endometrioid, all stages</li> </ul>
ESMO 2013 <sup>58</sup>	Stages IA–IB endometrioid No LVSI	Stage IA, G3, endometrioid Stage IB, G1–2, endometrioid		Stage I endometrioid Stage I endometrioid Stage I endometrioid Stage I endometrioid Stage II Stage III endometrioid, no residual disease Non-endometrioid Papillary serous and CC subtypes All other subtypes <ul style="list-style-type: none"> <li>• IC, G3</li> <li>• IIA, G3</li> <li>• IIB</li> </ul>
ESMO 2016 <sup>114</sup>	Stage I endometrioid <ul style="list-style-type: none"> <li>• G1–2</li> <li>• &lt;50% MI</li> <li>• No LVSI</li> </ul>	Stage I endometrioid <ul style="list-style-type: none"> <li>• G1–2</li> <li>• ≥50% MI</li> <li>• No LVSI</li> </ul>	Stage I endometrioid <ul style="list-style-type: none"> <li>• G3</li> <li>• &lt;50% MI</li> <li>• Regardless of LVSI status</li> </ul>	
MRC ASTEC <sup>10</sup>		No papillary serous and CC <ul style="list-style-type: none"> <li>• Stages IA–IB, G3</li> <li>• Stages IC–IIA, G1–2</li> </ul>		
ASTRO/ASCO <sup>35</sup>			G3 ≥50% MI	

**Notes:** \*PRF (pathological risk factors): grade 2 or 3, positive LVSI, myometrial invasion to outer third. Not all of the trials provided information for each risk group.

**Abbreviations:** G, grade; MI, myometrial invasion; EC, endometrial carcinoma; CC, clear cell; PRF, pathological risk factors; LVSI, lymphovascular space invasion; ASTRO, American Society for Radiation Oncology; ASCO, American Society of Clinical Oncology.

**Table 2** Randomized trials of adjuvant radiation and clinical results

Reference	Arm	Locoregional relapse	Overall survival
Aalders et al <sup>52</sup>	VCB (n = 277)	7% 5 years	89% 5 years
	EBRT + VCB (n = 263)	2% 5 years	91% 5 years
PORTEC-1 <sup>37</sup>	Observation (n = 360)	14% 5 years	85% 5 years
	EBRT (n = 354)	4% 5 years	81% 5 years
GOG-99 <sup>38</sup>	Observation (n = 202)	12% 2 years	86% 4 years
	EBRT (n = 190)	3% 2 years	92% 4 years
ASTEC/EN.5 <sup>10</sup>	Observation (n = 453)	7% 5 years	83.9% 5 years
	EBRT (n = 452)	4% 5 years	83.5% 5 years
PORTEC-2 <sup>44</sup>	EBRT (n = 214)	2% 5 years	80% 5 years
	VCB (n = 213)	2% 5 years	85% 5 years
Sorbe et al <sup>40</sup>	EBRT + VCB (n = 264)	1.5% 5 years	89% 5 years
	VCB (n = 263)	5% 5 years	90% 5 years

**Abbreviations:** VCB, vaginal cuff brachytherapy; EBRT, external beam radiotherapy.

**Table 3** Adjuvant treatment according to the NCCN guidelines (v.1.2017)

Stage	Postoperative findings	Tumor grade		
		G1	G2	G3
I	<50% MI, risk factors (-)	Observe	Observe VCB	Observe VCB
	<50%, risk factors (+)	Observe VCB	Observe VCB ± EBRT	Observe VCB ± EBRT
	≥50% MI, risk factors (-)	Observe VCB	Observe VCB	VCB ± EBRT EBRT Observe
	≥50% MI, risk factors (+)	Observe VCB ± EBRT EBRT	Observe VCB ± EBRT EBRT	EBRT ± VCB ± systemic therapy VCB ± systemic therapy
II		VCB ± EBRT EBRT	VCB ± EBRT EBRT	EBRT ± VCB ± systemic therapy

**Note:** Risk factors: age, positive lymphovascular invasion, tumor size, depth of invasion and lower uterine involvement.

**Abbreviations:** NCCN, National Comprehensive Cancer Network; G, grade; MI, myometrial invasion; VCB, vaginal cuff brachytherapy; EBRT, external beam radiotherapy.

postoperative irradiation among intermediate- and high-risk patients.<sup>22</sup> Discrepancies between randomized and database studies are due to including low-risk patients who die from EC and due to a lack of power in the randomized trials. It has been calculated that 2115 patients in each arm are necessary to carry out a powered enough assay.<sup>21</sup>

### VCB as a boost

No randomized trial has evaluated the value of VCB boost after EBRT, but two studies have evaluated the effect of EBRT added to VCB.<sup>40,45</sup> While the older study<sup>45</sup> did not find any statistically significant difference by adding EBRT, after a median of 20.5 years of follow-up, Sorbe et al<sup>40</sup> observed a significant improvement in the locoregional

relapses (Table 2), although no differences in survival were achieved. A SEER database analysis demonstrated a significant survival advantage among 1333 early stage uterine papillary serous (UPSC) and CC carcinoma patients who had undergone adjuvant radiotherapy (106 vs. 151 months for observation and radiotherapy, respectively [*p* = 0.006]).<sup>46</sup> Nevertheless, a later analysis of 1653 patients who had high-risk stages I–II, high-grade endometrioid carcinoma and non-endometrioid histologies was unable to find any improvement in cancer survival by adding VCB after EBRT.<sup>47</sup> Similar results were found after an analysis of 3395 high-risk stages I and II EC patients retrieved from the same database.<sup>48</sup> Lack of patient selection and control of confounding variables, such as pathological factors or chemotherapy among patients at a high risk of distant relapses, might explain it because the SEER database does not record specific pathological information, site of relapse or chemotherapy administration. Bingham et al<sup>43</sup> who analyzed stage III EC reported an improvement in survival only with the addition of VCB to EBRT among the subgroup with cervical involvement. In a multivariate Cox analysis, chemotherapy has been shown to reduce the crude percentage of initial extra-abdominal failure from 19% to 10%<sup>49</sup> compared with whole-abdominal irradiation and improve survival significantly.<sup>43</sup> An increase in late toxicity linked to the use of VCB as a boost has been described. Despite these facts, 28% of the respondents of a recent survey stated to use this approach only in a high-risk disease, and 6.3% of the respondents always use it.<sup>50</sup>

### High-risk and unfavorable histology tumors

This group of patients include those with high-risk endometrioid carcinomas (grade 3 and locally advanced tumors) and

high-risk histologies (UPSC and CC tumors). Stages III–IV of UPSC and CC tumors have a more aggressive natural history and lower overall survival than grade 3 endometrioid carcinomas (55%, 68% and 77%, respectively).<sup>51</sup> Patients at stage IC G3 recruited in the Norwegian trial<sup>52</sup> had lower survival rates than lower risk patients. A retrospective analysis of 125 patients treated for stage IA unfavorable histology endometrial carcinoma indicated an improved 5-year locoregional control and overall survival with postoperative irradiation compared with no irradiation (97.8% vs 80.1%,  $p = 0.018$ , and 84.9% vs 68.1%,  $p = 0.0062$ , respectively).<sup>53</sup> The GOG-122 trial demonstrated, in spite of the reduction in local relapses, a detrimental effect in 5-year survival with postoperative radiotherapy (abdominal irradiation [30 Gy] followed by an external pelvic boost up to 45 Gy) compared with the group treated with chemotherapy (38% vs 50%, respectively).<sup>49</sup> Two other trials<sup>54,55</sup> included 385 and 345 patients, respectively, and were unable to demonstrate differences between the radiotherapy arm and chemotherapy arm.

A retrospective analysis of 37 patients treated with postoperative VCB without EBRT for early-stage UPSC and CC was carried out at the Dana-Farber Cancer Institute. Only four patients relapsed; the 2-year vaginal control rate and 2-year disease-free and overall survival were 96.8%, 89.3% and 100%, respectively.<sup>56</sup> A retrospective analysis of 84 women with stage I UPSC or CC compared postoperative EBRT + VCB with VCB alone. No significant differences were observed in disease-free survival or in overall survival (88% vs 84%,  $p = 0.6$ , and 100% vs 94%,  $p = 0.6$ , respectively).<sup>57</sup> A SEER database analysis found a median survival improvement with the use of postoperative irradiation (106 vs 151 months,  $p = 0.006$ ).<sup>46</sup> The analysis of 1653 patients with UPSC, CC and high-grade endometrioid carcinoma, from the same database, found no statistically significant cause-specific survival differences between patients treated with postoperative EBRT and EBRT + VCB (85.3% vs 86.5%,  $p = 0.72$ ).<sup>47</sup> No comparisons with a large number of patients treated with VCB alone have been reported.

## Dose fractionation

The widespread use of HDR brachytherapy has allowed for a greater flexibility in the irradiation delivery. The 2014 American Brachytherapy Society (ABS) update survey<sup>34</sup> reports that 7 Gy for three fractions is the most common schedule for postoperative VCB alone and 5 Gy for three fractions is the most common schedule for VCB as a boost after EBRT, both delivered to a depth of 0.5 cm. Nevertheless, a wide variation in the dose schedules was noted; 24 regimens

for monotherapy and 22 as a boost were recorded. Because comparative studies of dose fractionation are scarce,<sup>59,60</sup> the schedule used depends on the doctors' experience, preference or workload. No clear optimal dose for VCB has been established; the reported doses for VCB alone range from 35 to 48 Gy EQD2 and 57 to 69 Gy EQD2 after EBRT.<sup>39</sup> Sorbe et al<sup>59</sup> randomized 290 low-risk EC patients to six fractions of 2.5 Gy (total dose of 15.0 Gy) or 5.0 Gy (total dose of 30.0 Gy). No differences on locoregional control were observed, but mucosal atrophy, bleeding and vaginal shortening were significantly more frequent in the 5.0-Gy group. Rovirosa et al<sup>60</sup> compared two VCB schedules in 319 patients (three fractions after EBRT and six fractions in the exclusive VCB at a dose of 4–6 Gy/fraction, three to four fractions per week vs two fractions after EBRT and four fractions in the exclusive VCB at a dose per fraction of 5–6 Gy daily). No differences in relapses or toxicity were observed. Large doses per fraction have been related to vaginal shortening;<sup>59</sup> 2.5 Gy per fraction did not produce a statistically significant vaginal shortening (0.3 cm, 3%) compared with the pre-VCB measure, while 5 Gy per fraction produced a significant mean vaginal shortening (2.1 cm, 25%). The percentage of late vagina complications can vary widely depending on the treatment schedule, the length of treated vagina and the score system used for their recording. Owing to the low toxicity associated with the procedure, assays have been carried out to minimize the number of fractions or to reduce the total length of its administration.<sup>60–62</sup> No significant differences in late toxicity or VC relapses were observed with the accelerated schedules.

## Applicator type and position, patient position and volume to treat

The majority of the treatments are carried out with a single-channel cylinder (83.2%) due to its simplicity and resources compared to the use of colpostats or vaginal molds.<sup>63</sup> However, this technique is not without its drawbacks. In spite of using the largest cylinder that can comfortably fit into the vagina, there can still be air gaps on the vaginal surface.<sup>64</sup> This can increase when the vaginal introitus is smaller than the apex. Avoiding the smaller cylinder diameters reduces toxicity. A multichannel cylinder allows a better conformal dosimetry and reduces bladder and rectum doses.<sup>65</sup> Compared to cylinders, vaginal colpostats can reduce percentage depth doses in the anterior/posterior and lateral directions as well as the dose falloff along the longitudinal axis.<sup>66</sup> The main drawback is the possibility of producing cold spots due to the vaginal packing. Ring applicators have also been used,

with similar clinical results to cylinders.<sup>67</sup> The 5-year overall survival of 100 patients was 84%, and 6% of the patients showed failure (one isolate in the vaginal vault and two in the vaginal vault and pelvis simultaneously; three other patients relapsed out of the field or distant). “Dog-ear” vaginal vaults can be underdosed with standard cylinders and are best irradiated with vaginal molds<sup>68</sup> or ovoids.<sup>69</sup> Molds do not need vaginal packaging compared with ovoids and provide a good solution in irregular vaults where a good contact between cylinders and mucosa may not be achievable. The classic technique is to create it from a vaginal impression, which can optimize catheter configuration with the aid of computed tomography (CT) imaging.<sup>70</sup> The growing use of the three-dimensional (3D) printing technologies in the brachytherapy field<sup>71</sup> improves mold design and creates highly personalized applicators. These 3D printing applicators made from 3D images might improve dose deposition by conforming to the patient’s anatomy and optimizing the range of catheter sources to the individual anatomy.<sup>72</sup> Intravaginal balloons have also been used for postoperative VCB.<sup>73</sup>

Humphrey et al<sup>74</sup> assessed 103 CT scans, and air gaps were visible in 38 patients accounting for a total of 67 air gaps. However, air gaps of >2 mm that lead to repositioning or use of large cylinders were only reported in 11 out of 103 patients. After correction, only 7% of the patients had air gaps of >2 mm. Two other reports have reported 32% and 72% of air gaps of >2 mm, respectively,<sup>64,75</sup> but the majority are not clinically significant<sup>64</sup> and only represent 0.86% of the vaginal surface. The ratio of patients to air pockets has been as high as 58% (29/50) of the patients or 33% (45/135) of the VCB plans.<sup>76</sup> Their volume can reach up to 2.1 cm<sup>3</sup>, and the displacement of the vaginal mucosa from the cylinder surface can be up to 1.09 cm. The relationship between the cylinder applicator diameter and air gaps forces the selection of the largest applicator diameter that will comfortably fit into the vagina. Similarly, Onal et al<sup>77</sup> described air pockets in 43% of patients treated with cylinders, but only 6.3% of the total patients received less than the prescribed dose (average 93.9% of the prescribed dose, range 79%–99.2%). Monte Carlo calculations show a maximum dose deviation due to air pockets of 2.4% compared with the TG-43 formalism.<sup>78</sup> This study observed that the most common radial size was between 2 and 3 mm, and the average dose reduction was 14.8%.

Only one study has analyzed the influence of patient position on dose to organs at risk.<sup>30</sup> Planning with legs extended produced significantly lower rectum  $D_{1cc}$  and  $D_{2cc}$  values compared with planning in the gynecology position (4.69

vs 5.66 Gy and 4.24 vs 5.14 Gy, respectively). The angle of the applicator influences the location of dose deposition. The “natural” angle position of the cylinder,<sup>31</sup> which tips the cylinder points posteriorly, has been linked to an increase in the rectal dose, while cylinders placed horizontally reduced rectal doses and increased the bladder values.<sup>32</sup> Nevertheless, one study failed to demonstrate a correlation between the cylinder angle and the bladder dose although a posterior angle increased rectal  $D_{2cc}$ .<sup>79</sup>

The majority of the patients have irradiation of the upper 2.5–3 cm or the upper third of the vagina. Nevertheless, an interesting study limiting the vaginal coverage to the upper 1 cm length has been reported, but only in the abstract form.<sup>80</sup> Increasing the length of the vagina irradiation has been linked to an increase in toxicity,<sup>81</sup> but no relationship has been described between the length of the vagina irradiation and vaginal relapses or survival.<sup>82</sup>

## Rectum volume

Nonsignificant rectal  $D_{2cc}$  differences among planned and delivered brachytherapy fractions (14.25 vs 13.95 Gy,  $p = 0.155$ ) were observed in a recent study.<sup>79</sup> In that study, a nonsignificant decrease in rectal volumes on the delivered CTs was observed compared to the planning CT. A positive correlation has been demonstrated between rectal volume and  $D_{max}$ ,  $D_{0.1cc}$ ,  $D_{1cc}$  and  $D_{2cc}$ , which remained significant in multiple linear regression models.<sup>32</sup> Rectal contrast, traditionally, has been used to improve rectal visualization in orthogonal radiographs, although it must be avoided because a CT-based study demonstrated a statistically significant increase of up to 10.4% in some rectal dose parameters.<sup>83</sup> This was linked to an increase in the rectal volume of up to  $27.6 \pm 41.6$  cm<sup>3</sup>. The presence of gas pockets in the rectum during VCB has also been associated with higher rectal doses.<sup>84</sup> Removal of these pockets significantly decreased the mean rectum volume by 29% and  $D_{2cc}$  by 11% as well as the rectum dose area under the curve by 33%. In light of these data, a prospective trial was carried out to analyze the effect of rectal enemas on rectal dosimetric parameters.<sup>85,86</sup> The enema protocol involved two Fleet enemas, the first administered the night before the procedure and the second before hospital admittance for the procedure. No significant dose parameter differences were observed between fractions with or without Fleet enemas.

## Bladder volume

Patel et al<sup>79</sup> observed lower bladder volumes on planning CT compared with the treatment CT acquired before each brachytherapy fraction. At the same time, the delivered bladder

$D_{2cc}$  was significantly higher than the planned  $D_{2cc}$  (18.83 vs 13.2 Gy,  $p = 0.0053$ ). Studies comparing full and empty bladders have been reported. A total of 15 patients underwent a CT scan before the first fraction with an empty bladder followed by a second CT scan done with the bladder full.<sup>87</sup> This maneuver increased significantly the cylinder-to-bowel distance (1.68 vs 1.2 cm,  $p = 0.006$ ). The full bladder produced a significant 18.7% bladder  $D_{2cc}$  increase and a nonsignificant rectum  $D_{2cc}$  increase of 0.5%. A nonsignificant reduction in sigmoid (-15.1%) and bowel (-10.5%)  $D_{2cc}$  was observed. Another study reported a reduction of 0.5 Gy on average in bladder doses in 35 out of 45 women with an empty bladder, but 10 out of 45 patients' bladder doses increased to 0.2 Gy on average.<sup>88</sup>  $D_{2cc}$  significantly decreased the bladder empty (4.9 vs 4.6 Gy), while  $V_{50}$  increased significantly (10.1% vs 17.7%). It was associated with a significant  $D_{2cc}$  bowel dose reduction (4.1 vs 4.6 Gy). Hoskin and Vidler<sup>89</sup> carried out a comparative paired analysis with an empty bladder and three full bladder volumes (35, 70 and 100 mL). Mean maximum bladder dose was lower with the empty bladder than with any of the full ones. Stewart et al<sup>90</sup> compared CT-planning dose parameters on fractions with an empty bladder and fractions with a full bladder with images acquired 1 hour after consumption of 32 oz of water.  $D_{2cc}$  and  $V_{50}$  were significantly greater in the full bladder state (4.56 vs 4.06 Gy and 18.47 vs 10.52 cm<sup>3</sup>, respectively). The median distance to the nearest point of bowel nearly doubled with the filling of the bladder (11.6 vs 5.75 mm,  $p = 0.002$ ). The instillation of 180 mL to an empty bladder produced significant  $D_{50\%}$  bladder and bowel dose reduction of 36.7% and 21.4%, respectively.<sup>33</sup> A significant 39.7%  $D_{2cc}$  reduction in the bowel values was also seen.

## Dose prescription

Until recently, two-dimensional (2D) dosimetry calculated from orthogonal RX films was the standard. The spread of CT images raised the need to evaluate the impact of 3D images on dosimetry. Studies have demonstrated the variation of doses to organs depending on the calculation method. Comparisons of International Commission of Radiation Units and Measurements (ICRU) doses on 2D images and maximum and  $D_{2cc}$  doses on 3D images were carried out.<sup>91</sup> Maximum bladder and rectal doses were 178% and 135% of ICRU doses, respectively. No significant bladder dose differences between  $D_{2cc}$  and ICRU doses were observed, but a significant rectal difference was found, with a ratio of  $D_{2cc}$  to ICRU equal to 0.87. Bladder and rectal  $D_{2cc}$  values were 59% and 64% of maximum doses, respectively. Kim et al<sup>92</sup> described significant lower  $D_{2cc}$  rectum (82.6% vs 78.2%) and bladder

(80.6% vs 77%) doses with 3D planning compared with 2D planning. Hung et al<sup>33</sup> reported small but significant lower  $D_{2cc}$  doses than the respective ICRU values.

Usually, dose is prescribed to the applicator surface or at 0.5 cm depth. The rationale is the vaginal wall thickness and the depth placement of the lymphatic vessels. In all, 50% of the lymphatic channels are located at 1 mm beneath the mucosa and 7% lie within 3–4 mm.<sup>93</sup> A total of 95% of vaginal lymphatic channels are located within the first 3 mm from the vaginal surface. The need to individualize the prescription depth according to the vaginal thickness has been suggested in order to reduce toxicity. Surface dose prescription produces a more uniform dose to the mucosa and at every depth, an acceptable target coverage and almost the same dose falloff compared with 0.5 cm depth dose prescription.<sup>94</sup> Dose surface ranged from 81% to 172% for the 0.5-cm depth prescription compared with 90% to 106% for the surface prescription, and large dose variations at the surface appeared with the 2-cm cylinder. A formula was derived to transform 0.5-cm depth dose prescription to surface prescription by magnifying the prescription dose by an  $M$  factor that takes into account the cylinder size ( $S$ ) and activated length ( $L$ ):  $M \approx 1.00 + 0.64 \text{ (cm)}/L + 1.23 \text{ (cm)}/S$ . That study also reported extreme cold and hot spots when no optimization points were used at the cylinder tip.

## Custom or standard radiotherapy planning

Nowadays, the majority of VCB treatments are 3D planned (83.2%) according to the 2014 ABS survey, but the majority of the respondents (73.4%) only planned the first fraction.<sup>63</sup> ABS guidelines do not demand that each fraction of VCB is planned because there is an assumed fixed geometry of the implant. Image at each fraction of three increments costs 35% compared with a single simulation but did not produce any dosimetric advantage.<sup>95</sup> Similar results with single-channel or multichannel cylinders were observed; imaging at each fraction was 19% and 22% more expensive, respectively.<sup>96</sup> Sabater et al<sup>97</sup> compared three approaches for dose summation, a single plan approach that used a crude dose summation of a single plan that was replicated to every fraction and dose summation of customized plans for every fraction using both rigid and deformable registration. No significant rectal dose differences were observed, but some limited differences in bladder dose metrics were found, something which does not justify the higher costs linked to the customized approach. Multichannel cylinders have also been evaluated in this setting,<sup>98</sup> and results show an excess of maximum bladder or rectum doses in 41% of cases when a single plan approach was used.

## Image-guided brachytherapy

Nowadays, simulation for postoperative EC relies on CT volumetric images, which have proven to detect air pockets around the cylinders<sup>74,76,77</sup> or inside the rectum<sup>84</sup> or evaluate bladder volume<sup>79</sup> and improve dose deposition. Magnetic resonance imaging (MRI) is considered the optimal imaging method to delineate volumes in cervical cancer,<sup>99</sup> but its value in EC is less clear and availability is limited, so strategies to integrate clinical images into the radiotherapy workflow have been studied.<sup>100</sup> Average absolute percentage dose differences for the bladder, rectum and prescription points on CT and MRI were 2.2%, 2.3% and 2.2%, respectively, and the mean central source deviation was 0.6 mm, which was associated with longer acquisition times in MRI.<sup>101</sup> Chapman et al<sup>102</sup> carried out sequential MRI and CT scans. They observed using MRI that 69% of the patients had at least 1 cm<sup>3</sup> of VC receiving <75% of the prescription dose. The reasons were that areas of undistended vagina now seen in CT and suture material prevented full cylinder insertion. These results question the minimum doses necessary to avoid relapses. Owing to the steep dose gradient, small changes in the structures close to the sources produce large dose–volume histogram changes. Applicator displacement between fractions has a similar effect, so reproducibility is crucial. Although the ABS guidelines recommend a customized plan with each fraction, they state that this may not be necessary, assuming a fixed geometry of the implant for every insertion based on the first fraction.<sup>103</sup>

## Comparison of brachytherapy with advanced EBRT techniques (intensity-modulated radiotherapy–stereotactic body radiotherapy)

Brachytherapy has intrinsic advantages compared to modern EBRT techniques, mainly intensity-modulated radiotherapy (IMRT) and stereotactic body radiotherapy (SBRT), due to the close contact between radioactive sources and volume to treat. IMRT has generally been used to irradiate the pelvis but with less toxicity.<sup>104</sup> The main drawback to the use of EBRT techniques is that the vagina moves, so there is a risk of geographical “miss of target”, which leads to increased margins and higher integral doses to small bowel.<sup>105</sup> Average VC movement for 11 patients was  $16.2 \pm 8.3$  mm during an EBRT course, with a maximum movement of 34.5 mm.<sup>106</sup> Large variations in bladder and rectum volumes correlate with significant displacement of the VC.<sup>107</sup> Aydogan et

al<sup>108</sup> concluded that IMRT could be an alternative to HDR brachytherapy and provided a suitable immobilization system. Both techniques, brachytherapy and IMRT, covered the target volume well, but brachytherapy produced higher doses. In order to control vaginal movements an applicator-guided IMRT technique has been proposed.<sup>109</sup> It was used to compare 3D conformal radiotherapy (3D-CRT), IMRT and volumetric-modulated arc therapy (VMAT) in irradiating the VC.<sup>110</sup> Dose coverage was similar across the three techniques. VMAT showed the highest level of conformity and produced a significant reduction in rectal and bladder volumes compared with 3D-CRT. VMAT needed 28% less monitor units compared with IMRT, and treatment duration reduced from 11 to <3 minutes for a dose of 6 Gy. Pedicini et al<sup>111,112</sup> compared VMAT, IMRT and 3D-CRT using a vaginal cylinder for vaginal immobilization to 3D brachytherapy. The cylinder was able to reduce the movement in the VMAT course and reduced planning target volume margin to 2 mm. EBRT techniques always delivered higher integral doses but reduced rectal doses compared with brachytherapy. VMAT produced a uniform dose distribution, while VCB doses were much higher than the prescription. No direct cost comparisons between these modalities have been published, but three fractions of VCB course with one image study has been calculated to cost between US\$1235 and \$1293,<sup>95</sup> while four to five fractions of SBRT for lung cancer cost \$10616.<sup>113</sup>

In summary, we believe that despite the widespread use of the VCB and the simplicity of its performance, several technical subjects have to be considered by the radiation oncologists aside from the usual groups of risk involved in patient selection. The technical subjects reported so far have been reviewed here, although additional research is merited, such as the impact of VCB on survival, dose–fractionation direct comparisons or the use of short schedules.

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## Disclosure

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