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American Brachytherapy Task Group Report: Adjuvant vaginal brachytherapy for early-stage endometrial cancer: A comprehensive review

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ABSTRACT This article aims to review the risk stratification of endometrial cancer, treatment rationale, outcomes, treatment planning, and treatment recommendations of vaginal brachytherapy (VBT) in the postoperative management of endometrial cancer patients. The authors performed a thorough review of the literature and reference pertinent articles pertaining to the aims of this review. Adjuvant VBT for early-stage endometrial cancer patients results in very low rates of vaginal recurrence (0–3.1%) with low rates of late toxicity which are primarily vaginal in nature. Post-Operative Radiation Therapy in Endometrial Cancer 2 (PORTEC-2) supports that VBT results in noninferior rates of vaginal recurrence compared to external beam radiotherapy for the treatment of high-intermediate risk patients. VBT as a boost after external beam radiotherapy, in combination with chemotherapy, and for high-risk histologies have shown excellent results as well though randomized data do not exist supporting VBT boost. There are many different applicators, dose-fractionation schedules, and treatment planning techniques which all result in favorable clinical outcomes and low rates of toxicity. Recommendations have been published by the American Brachytherapy Society and the American Society of Radiation Oncology to help guide practitioners in the use of VBT. Data support that patients and physicians prefer joint decision making regarding the use of VBT, and patients often desire additional treatment for a marginal benefit in risk of recurrence. Discussions regarding adjuvant therapy for endometrial cancer are best performed in a multidisciplinary setting, and patients should be counseled properly regarding the risks and benefits of adjuvant therapy.

Keywords: Endometrial cancer; Vaginal brachytherapy; Vaginal cuff brachytherapy; Vaginal cuff; Vaginal cylinder; Gynecologic brachytherapy

Introduction

In 2015, it is estimated 54,870 women were diagnosed with and 10,170 died of endometrial cancer (1). The primary management of endometrial cancer is total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO). The role of pelvic and para-aortic lymph node dissection is controversial in the surgical management of endometrial cancer (2–6). Adjuvant radiation therapy for endometrial cancer is also controversial but is routinely recommended based on presence of adverse risk factors such as higher stage, increased depth of myometrial invasion (MMI), higher grade, presence of lymphovascular

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space invasion (LVSI), increasing age, increasing tumor size, histology, and lymph node positivity (2,4,5,7–9). The role of vaginal brachytherapy (VBT) in the postoperative management of endometrial cancer continues to evolve. The purpose of this review is to thoroughly address the role of VBT in the postoperative management of endometrial cancer patients.

Risk grouping

The understanding of risk factors and risk grouping of early-stage endometrial cancer has evolved over the past several decades. The Gynecologic Oncology Group (GOG) 33 study demonstrated that increasing depth of MMI and higher grade led to increased risk for both pelvic and para-aortic lymph node metastases (3). In a randomized study of postoperative VBT ± pelvic external beam radiotherapy (EBRT), Aalders *et al.* showed that the addition of EBRT to VBT decreased vaginal and nodal failures, especially for patients with deeply invasive, Grade 3 tumors. Presence of LVSI was discovered to be an adverse risk factor for both disease recurrence and overall survival (2). The GOG 99 study and the first Post-Operative Radiation Therapy in Endometrial Cancer (PORTEC-1) study addressed the role of adjuvant EBRT for intermediate risk endometrial cancer patients. Each of these two studies identified a subgroup of patients at highest risk for recurrence, hence classified as the high-intermediate (H–I) risk group. Table 1 shows the criteria for H–I risk group classification. The risk factors regarded as having the greatest impact on locoregional recurrence are advancing age, higher tumor grade, deeper MMI, and LVSI (4, 5).

Local control and toxicity with EBRT

PORTEC-1 and GOG 99 are similar studies which randomized intermediate risk patients to observation or EBRT. They both showed no difference in overall survival with EBRT. EBRT decreased the recurrence rate from 12–15% to 3–6% for these intermediate risk patients.

Table 1
High-intermediate risk groups in FIGO stage I endometrial cancer as defined by PORTEC-1 and GOG 99

	PORTEC-1	GOG 99
Age	>60	See below
Grade	3	2–3
Myometrial invasion	>50% (outer 1/2)	>66.6% (outer 1/3)
Lymphovascular space invasion	N/A	Present
High-intermediate risk group	At least 2/3 of above	Any age, all 3 of above risk factors; age > 50, 2 of above risk factors; age > 70, 1 of above risk factors

FIGO = International Federation of Gynecology and Obstetrics; PORTEC = Post-Operative Radiation Therapy in Endometrial Cancer; GOG = Gynecologic Oncology Group.

Adjuvant EBRT decreased the risk of recurrence for patients with H–I risk disease from 18–26% to 5–6%. All other patients were classified as low-intermediate risk, and EBRT decreased recurrence rate from 5–6% to 2% (4, 5, 10, 11).

The improved rate of locoregional control with adjuvant EBRT comes at the increased risk of toxicity. PORTEC-1 demonstrated toxicity to be 26% (mostly Grade 1) with EBRT compared to 4% without ($p < 0.0001$) (12). GOG 99 showed a significant increase in hematologic, genitourinary (GU), gastrointestinal (GI), and cutaneous toxicities with adjuvant EBRT (5). PORTEC-1 also reported long-term quality-of-life (QOL) data revealing poorer urinary and bowel function as well as declined physical functioning with EBRT compared to observation (13). It should be noted, however, that these trials used relatively older radiation techniques. In fact, 30% of the patients treated on PORTEC-1 were treated with an AP/PA technique (12). The use of more modern techniques, including intensity-modulated radiation therapy, may lead to a significantly improved therapeutic ratio.

Salvage therapy for recurrent disease

PORTEC-1 and GOG 99 demonstrated decreased risk of locoregional recurrence with adjuvant EBRT for patients with early-stage endometrial cancer. Among patients who had disease recurrence, the vagina was the only site of recurrent disease in 37 of 51 patients (72.4%) in PORTEC-1 and in 15 of 21 patients (71.4%) in GOG 99; hence, the vagina was the most common location of failure (4, 5). In GOG 99, 12 of 13 patients with a vaginal only recurrence in the observation arm were treated with salvage radiation therapy (RT). Crude observation suggested that 5 of the 13 patients (38.5%) with vaginal recurrence died as a result of endometrial cancer (5). Salvage radiation therapy resulted in Grade 3–4 GI toxicity of 18% and Grade 3 or greater vaginal toxicity of 50% (14). Recurrent disease, even in the vagina, has a high rate of second recurrence even after definitive radiation, and the intensive therapy required to treat recurrent disease has significant associated toxicity. Therefore, the ability to prevent disease recurrence is highly beneficial for patients.

Vaginal brachytherapy

Adjuvant VBT as monotherapy

As previously mentioned, EBRT decreases the risk of locoregional failure but with increased toxicity compared to observation. Because the vagina is the most common location of recurrence, VBT rather than EBRT is a good option for many patients to decrease this risk of recurrence and the potential need for salvage therapy. In patients treated with VBT, vaginal failure ranges from 0% to 3.1% as shown in Table 2. Pelvic (nonvaginal) recurrences

Table 2
Outcomes with postoperative vaginal cuff brachytherapy alone

Authors/reference	Publication year	*N*	Treatment	Control/survival	Total pelvic recurrence (%)[a]	Vaginal recurrence alone (%)
Aalders *et al.* (2)	1980	277	60 Gy at surface (LDR)	5-y OS, 91%	6.9[b]	
Sorbe and Smeds (15)	1990	404	Ranging from 4.5 Gy × 6 to 9 Gy × 4 at 1.0 cm	5-y OS, 91.8%	3.0	0.7
Noyes *et al.* (16)	1995	63	16.2 Gy × 2 ovoids at surface	Median f/u 1.6-y OS, 98.5%	1.6	0
Kloetzer *et al.* (17)	1997	108	10 Gy × 4 to 0.5 cm or 1.0 cm	3-y OS, 96%	0	0–3.1
Eltabbakh *et al.* (18)	1997	332	30 Gy at 0.5 cm (LDR)	5-y DFS, 98.9%	0.6	0
MacLeod *et al.* (19)	1998	141	8.5 Gy × 4 at surface	5-y OS, 86–94%	0.7	1.4
Weiss *et al.* (20)	1998	122	7 Gy × 3 at surface	5-y RFS, 86.8%	4.1	1.6
hadha *et al.* (21)	1999	38	7 Gy × 3 at 0.5 cm	5-y OS, 93%	0	0
Petereit *et al.* (22)	1999	191	16.2 Gy × 2 at surface of ovoids	4-y OS, 95%	0.5	0
Anderson *et al.* (23)	2000	102	5 Gy × 3 at 0.5 cm	5-y OS, 84%	2.0	1.0
Horowitz *et al.* (24)	2002	164	7 Gy × 3 at 0.5 cm	5-y OS, 87%	1.2	1.2
Alektiar *et al.* (25)	2002	233	7 Gy × 3 at 0.5 cm	5-y OS, 90% ≥ 60 yr, 99% < 60 yr	1.7	1.3
Jolly *et al.* (26)	2005	50	5 Gy × 5 at 0.5 cm	4-y OS, 97%	2.0.	2.0
Alektiar *et al.* (27)	2005	382	7 Gy × 3 at 0.5 cm	5-y OS, 93%	3.1	0.8
Solhjem *et al.* (28)	2005	100	7 Gy × 3 at 0.5–0.7 cm	3-y OS, 97.9%	0	0
Atahan *et al.* (29)	2008	128	5.5 Gy × 5 at 0.5 cm	5-y OS, 96%	1.6	0
McCloskey *et al.* (30)	2010	87	7 Gy × 3 at 0.5 cm (HDR) or 30 Gy at 0.5 cm (LDR)		2.3	1.1
Nout *et al.* (PORTEC-2) (6)	2010	213	7 Gy × 3 at 0.5 cm (HDR) or 30 Gy at 0.5 cm (LDR)	5-y OS, 84.8%	3.8	1.8
Sorbe *et al.* (31)	2012	263	3 Gy × 6 or 5.9 Gy × 3 at 0.5 cm (HDR) or 20 Gy at 0.5 cm (LDR)	5-y OS, 90%	2.3	0.7
Diavolitsis *et al.* (32)	2012	169	7 Gy × 3 or 5.5 Gy × 4 at 0.5 cm (HDR) or 70 Gy at ovoid surface (LDR)	5-y OS, 95.5%	2.4	0.6
Eldredge-Hindy *et al.* (33)	2014	31	7 Gy × 3 at 0.5 cm or 6 Gy × 5 at surface, at least proximal 4 cm length of vagina	3-y OS, 83%, 3-y DFS, 79%	3.2	3.2
Paydar *et al.* (34)	2015	22 (Stage II)	42 Gy at 0.5 cm depth (HDR) or 65 Gy at surface (LDR)		4.5	4.5

Gy = Gray; LDR = low dose rate; y = year; OS = overall survival; DFS = disease-free survival; RFS = relapse-free survival; HDR = high dose rate; PORTEC = Post-Operative Radiation Therapy in Endometrial Cancer.

[a] Defined as pelvic alone and simultaneous pelvic plus vaginal; vaginal recurrences alone are not included.

[b] Vaginal and pelvic combined, results not separated.

occur in 0–4.1% of patients. Like with EBRT, VBT has not been shown to increase overall survival although no study has been properly powered for this end point (2,6,15–34). EBRT remains a reasonable option for patients with the aforementioned risk factors and felt to be at risk for a nonvaginal pelvic recurrence. Adjuvant VBT yields very low rates of vaginal recurrence with minimal toxicity.

The PORTEC-2 study aimed to compare these two adjuvant radiotherapy options in a Phase III, randomized, noninferiority trial. Patients had PORTEC-defined H–I risk endometrial cancer (Table 1) and were surgically managed with TAH-BSO without lymph node dissection. PORTEC-2 randomized patients to pelvic EBRT (46 Gy in 23 fractions) or VBT (high-dose-rate [HDR] 7 Gy × three fractions or low-dose-rate [LDR] 30 Gy specified to 0.5 cm depth). Five-year vaginal recurrence was 1.8% with VBT and 1.6% with EBRT ($p = 0.74$). Pelvic recurrence rates were higher in the group treated with VBT compared to EBRT (3.8% vs. 0.5%, $p = 0.02$). There was significantly less GI toxicity with VBT compared to EBRT. VBT results in similar rates of vaginal recurrence but with lower GI toxicity compared to pelvic EBRT for PORTEC-defined H–I risk endometrial cancer patients (6).

PORTEC-2 supports the role of VBT to decrease vaginal failure for H–I risk patients, but it does not address patients who are at lesser, but still potentially significant risk of a vaginal failure. As Table 2 shows, even patients who are at lesser risk of recurrence can benefit from VBT. Some of the authors previously published estimates and treatment recommendations based on the available literature to help guide discussions of the benefit of VBT with patients (35). It is important to estimate the risk of recurrence based on the patient's risk factors and discuss the risks, benefits, and side effects of both adjuvant therapy and salvage therapy along with potential toxicities.

Table 3
Outcomes with postoperative vaginal cuff brachytherapy combined with EBRT

Authors/reference	Publication year	*N*	Most common treatment	Control/survival	Pelvic recurrences (%)	Vaginal recurrences alone (%)
Aalders *et al.* (2)	1980	263	40 Gy EBRT + 60 Gy at surface (LDR)	5-y OS, 89%	2.0[a]	
Lybeert *et al.* (36)	1989	291	40 Gy EBRT + 5 Gy × 4 at 0.5 cm (HDR)	5-y RFS, 88% (Stage I), 68% (Stage II), 50% (Stage III/IV)	2.7	2.7
Nori *et al.* (37)	1994	300	40 Gy EBRT + 7 Gy × 3 at 0.5 cm (HDR)	20-y DFS, 96%	0.3	2.0
Cannon *et al.* (38)	2009	50	45–51 Gy EBRT + 5 Gy × 3 or 7.8 Gy × 2 at surface (HDR)	5-y OS, 82%	4.0	0
Sorbe *et al.* (31)	2012	264	46 Gy EBRT + 3 Gy × 6 or 5.9 Gy × 3 at 0.5 cm (HDR) or 20 Gy at 0.5 cm (LDR)	5-y OS, 89%	0	1.1
Paydar *et al.* (34)	2015	19 (Stage II)	50.4 Gy EBRT + 24 Gy at 0.5 cm (HDR)		5.3	5.3
Huddleston *et al.* (39)	2015	82 (Stage III)	45–50.4 Gy EBRT + 4–5 Gy × 3 at 0.5 cm or surface (HDR)		8.5	6.1

EBRT = external beam radiation therapy; Gy = Gray; LDR = low dose rate; y = year; OS = overall survival; RFS = relapse-free survival; DFS = disease-free survival; HDR = high dose rate.
[a] Vaginal and pelvic combined, results not separated.

Adjuvant VBT as a boost

There are several institutional series reporting on VBT boost after adjuvant EBRT, which are described in Table 3. As with reports of either EBRT or VBT alone, the combination of EBRT and VBT results in excellent locoregional control with vaginal recurrences of 0–2.7% and pelvic recurrences of 0.3–4.0% (2,31,34,36–39). There is no randomized data of EBRT ± VBT, although VBT boost is often performed for patients who are felt to benefit from EBRT with a higher risk of a vaginal failure, particularly when a modestly lower dose of pelvic radiation (45 Gy at 1.8 Gy/fraction) is delivered relative to doses used in randomized trials (46 Gy at 2 Gy per fraction or 50.4 Gy at 1.8 Gy per fraction).

There is randomized data supporting EBRT with VBT boost compared to VBT alone. Aalders *et al.* (2) showed that vaginal and pelvic recurrences were decreased from 6.9% to 1.9% with the addition of pelvic EBRT ($p < 0.01$). Sorbe *et al.* conducted a similar randomized trial comparing postoperative VBT with or without pelvic EBRT. They found overall pelvic relapse rate to be 0.4% with EBRT plus VBT boost and 5.3% with VBT alone ($p = 0.013$). There were no differences in vaginal recurrence or overall survival, and toxicity was decreased with VBT alone (31).

Radiation Therapy Oncology Group studies recommend 5–6 Gy specified to the vaginal surface for three fractions with 45 Gy EBRT and for two fractions with 50.4 Gy EBRT when a VBT boost is delivered (40, 41). Additional studies on patterns of recurrence after pelvic radiation with and without VBT will be helpful to clarify the role of VBT boost after EBRT.

VBT and chemotherapy

For patients at higher risk of treatment failure, especially distant failure, investigators have explored combination of VBT with chemotherapy (CT). Landrum *et al.* conducted a Phase II study of 23 GOG 99–defined H–I risk patients, which also included uterine serous carcinoma (USC) and clear cell carcinoma (CCC). They found 2-year progression-free survival to be 91%. Vaginal failure occurred in 1 patient (4.2%) which was concurrent with distant metastases (42).

Such promising results of VBT and CT lead to GOG 249, which was a Phase III trial of H–I risk and high risk patients randomized to either pelvic EBRT (control arm) or VBT and CT with three cycles of carboplatin and paclitaxel (study arm). Inclusion criteria were Stage I GOG 99–defined H–I risk (see Table 1 except outer ½ MMI rather than outer $^1/_3$ MMI was used as the depth of MMI risk factor), cervical stroma invasion (Stage II), or Stage I–II USC or CCC. At 2 years of followup, overall survival was 93% with pelvic EBRT and 92% with VBT and CT (p = NS) without statistical difference in vaginal recurrence rate. Patients receiving VBT and CT had higher rates of hematologic toxicity, neuropathy, and fatigue, whereas patients receiving EBRT had higher rates of Grade 2 diarrhea (43).

Both PORTEC-2 and GOG 249 included H–I risk patients, which creates challenges when generating adjuvant therapy recommendations. H–I risk patients fall along a spectrum of risk for microscopic disease in the lymph nodes. For instance, Patient A is aged 71 years with International Federation of Gynecology and Obstetrics (FIGO) IB (55% MMI), Grade 1, no LVSI with 0/20 positive nodes; she is at low risk for nodal metastases. Patient B is aged 71 years with FIGO IB (95% MMI), Grade 2, LVSI present with no lymph node dissection performed; she is at a moderate to high risk for nodal metastases. Patients A and B qualify for both PORTEC-2 and GOG 249 (6, 43). The authors would treat Patient A with VBT and Patient B with either EBRT or VBT + CT. This example highlights the heterogeneity within the H–I risk endometrial cancer group, and the necessity to individualize treatment recommendations based on the patient and her disease.

Table 4
Outcomes with postoperative vaginal cuff brachytherapy in high-risk histologies

Authors/ reference	Publication year	*N*	Treatment	Percentage of patients receiving chemotherapy	Control/survival	Total pelvic recurrence (%)	Vaginal recurrence alone (%)
Turner *et al.* (55)	1998	18 Stage I USC	7 Gy × 3, 7 Gy × 2, or 5 Gy × 3 at 0.5 cm	28	5-y OS, 94%	6.0	0
Low *et al.* (56)	2005	26 Stage I–IV USC	45–50.4 Gy EBRT + 5 Gy × 2 at 0.5 cm (Stages II–IV, $n = 22$), 5 Gy × 5 at 0.5 cm (Stage I, $n = 4$)	100	5-y OS, 72.9% (Stage I), 100% (Stage II), 58.9% (Stage III), 0% (Stage IV)	0 (Stages I–II, IV), 15.4 (Stage III)	
Kiess *et al.* (57)	2012	41 Stage I–II USC	6–7 Gy × 3 at 0.5 cm, proximal 2/3 vagina	100	5-y OS, 90%, 5-y DFS, 85%	9.0	0
Barney *et al.* (58)	2013	103 Stage I USC or CCC	7 Gy × 3 at 0.5 cm, entire length of vagina	34	5-y OS, 84%, 5-y DFS, 88%	4.0	2.0
Townamchai *et al.* (59)	2013	37 Stage I–II USC or CCC	4 Gy × 6 at surface, entire length of vagina minus 1 cm inferiorly	75	2-y OS, 100%, 2-y DFS, 89.3%	5.4	2.7
Eldredge-Hindy *et al.* (33)	2014	33 Stage I–II USC or CCC	7 Gy × 3 at 0.5 cm or 6 Gy × 5 at surface, at least proximal 4 cm length of vagina	91	3-y OS, 100%, 3-y DFS, 96%	3.0	0
Brown *et al.* (54)	2015	33 Stage I–II CS	7 Gy × 3 at 0.7 cm proximally tapering to surface distally or 4 Gy × 6 at surface, both to entire length of vagina minus 1 cm inferiorly	55	2-y OS 79%	18.0	
Guttmann *et al.* (53)	2016	42 Stage I–II CS	45 Gy EBRT + 6 Gy × 2 at 0.5 cm ($n = 20$), 7 Gy × 3 at 0.5 cm ($n = 22$)	64	2-y OS 85% (chemo + RT)	7.1	

USC = uterine serous carcinoma; CCC = clear cell carcinoma; EBRT = external beam radiation therapy; Gy = Gray; y = year; OS = overall survival; DFS = disease-free survival; CS = carcinosarcoma; RT = radiation therapy.

There are studies available that can help guide decision making for the heterogeneity of the H–I risk groups. GOG 33 can guide lymph node risk based on tumor grade and depth of MMI (3). In addition, nomograms can help guide practitioners to determine rates of locoregional recurrence, lymph node involvement, and survival to help guide treatment recommendations (44–50). As data matures for GOG 249, long-term outcomes and patterns of failure will help clarify the role of CT and VBT for this population.

VBT for high-risk histologies

Endometrial cancers of high-risk histology, such as USC, CCC, and carcinosarcoma (CS), are commonly treated more aggressively compared to endometrioid histology (51–54). These high-risk histologies were excluded from the major clinical trials for early-stage disease (PORTEC-1, GOG 99, and PORTEC-2) (4–6), but USC and CCC were included in GOG 249 though as a minority (20%) of the accrual (43). Creasman *et al.*

reported on Stage I high-risk histology outcomes and found that USC and CCC had similar survival to Grade 3 endometrioid-type adenocarcinoma. They found a small (6–8%) but nonsignificant survival benefit to adjuvant radiotherapy for high-risk histologies, but VBT and CT were not specifically analyzed (9). Table 4 describes the outcomes of VBT with or without CT for patients with high-risk histologies. Vaginal failure is generally low (range of 0–2.7%) although pelvic failure ranges from 0% to 9.0% for patients with Stage I–II disease (33,55–59).

Institutional reports on treatment of high-risk histologies with VBT and CT have been quite favorable. Turner *et al.* reported on patients with USC treated with VBT (LDR and HDR) and CT. They found 5-year survival of 94% for patients treated with HDR VBT plus CT compared to 65% with LDR plus whole pelvic or whole abdominal EBRT without CT (55). Low *et al.* described patients with USC (all stages) and reported results of adjuvant CT, EBRT, and VBT (noninvasive Stage I patients received CT and VBT without EBRT). They showed vaginal, pelvic (nonvaginal), and distant recurrence rates of 0%, 15%, and 38%, respectively (56). Kiess *et al.* reported on patients with USC treated with adjuvant VBT with six cycles of carboplatin and paclitaxel. They reported vaginal recurrence, pelvic (nonvaginal) recurrence, and distant metastasis rate to be 0%, 9%, and 10%, respectively. Five-year overall survival was 90% (57). Guttmann *et al.* reported on Stage I–II CS patients and found that CT combined with EBRT or VBT resulted in improved overall survival. Of those patients who did not undergo adjuvant therapy and failed, 44% of the failures were in the vagina. Vaginal failure rate was only 2% for patients who received adjuvant VBT. For patients with CS, the vagina is at risk for failure with low failure rates when treated with VBT. They conclude that adjuvant VBT is supported as a component of adjuvant therapy (53).

The role of VBT alone without CT has also been reported. There is controversy regarding the role of CT for such high-risk histologies. In a study of more advanced stage patients, there was no benefit to CT in patients with USC (52). Barney *et al.* (58) and Townamachi *et al.* (59) describe low rates of local, pelvic (nonvaginal), and distant failures with VBT alone. Barney *et al.* (58) did not show improvement in recurrence rates nor overall survival with the addition of CT. Studies have shown that disease-free and overall survival are lower for USC and CCC compared to endometrioid-type adenocarcinoma (60, 61). Brown *et al.* evaluated adjuvant VBT without EBRT for Stage I–II CS. They reported the 2-year vaginal failure rate and pelvic (nonvaginal) failure rate as 6% and 13%, respectively (54).

There is a paucity of data, especially randomized data, regarding these high-risk histologies to truly guide management. Because GOG 249 included about 20% high-risk histologies (USC and CCC), it is possible that more information will be elucidated from this study to guide the treatment of such malignancies.

Toxicity

Acute and chronic toxicity with VBT

VBT has increased viability in postoperative endometrial cancer patients not only due to decreased vaginal failures (which are similarly decreased with EBRT) but also due to the favorable toxicity profile. Surgery followed by adjuvant pelvic EBRT results in increased frequency and severity hematologic, GI (diarrhea or fecal incontinence), GU (cystitis or urinary incontinence) toxicities, as well as pelvic insufficiency fractures when compared to surgery alone (5, 13, 62).

VBT delivers a conformal dose to the vagina with less dose to surrounding normal tissues compared to EBRT. Hence, the rates of bladder, rectum, bowel, bone, and bone marrow toxicities are quite low. The primary risk of toxicity with VBT is to the proximal vagina resulting in vaginal atrophy, stenosis, and/or decreased vaginal length. Studies of VBT demonstrate low rates of high-grade vaginal complications, which can be significantly reduced with the use of lower dose per fraction regimens. Severe toxicity rates are 0–5.2%, which are primarily vaginal in nature, as shown in Table 5 (2,6,15–24, 26–29,31,32,36–38,63).

QOL analysis of EBRT in PORTEC-1 showed that about 20% of women experienced late GI and/or GU toxicities. These toxicities resulted in increased use of incontinence materials, need to remain close to a toilet, limitations in daily life, and lower sense of physical functioning and physical health. When these QOL factors were investigated in PORTEC-2, patients treated with VBT reported superior outcomes than those treated with EBRT, especially regarding diarrhea, fecal incontinence, and social functioning. VBT patients had no difference in sexual function compared to EBRT despite an increase in Grade 1–3 vaginal toxicity (36.6% vs. 17.7%; $p < 0.05$) (6, 64). Patients treated with VBT had decreased sexual QOL when compared to the norm population though (64). Bruner *et al.* (65) previously demonstrated that vaginal stenosis may result in decreased sexual frequency, sexual satisfaction, and dyspareunia. These toxicities are important in the discussion of VBT with patients, and although VBT is generally well tolerated, they should be reviewed in detail, so the patient can make an informed decision.

Secondary malignant neoplasm after VBT

Though rare, a potentially devastating side effect of VBT is development of a second malignant neoplasm (SMN). Any administration of radiotherapy can potentially result in an SMN as a function of dose, volume treated, and time. Population-based studies of endometrial cancer

Table 5
High-grade late toxicities for postoperative vaginal cuff brachytherapy

Authors/reference	Publication year	*N*	Vaginal length treated	Most common dose	Late toxicity
VBT alone					
Aalders *et al.* (2)	1980	277	Entire vaginal length	60 Gy at surface (LDR)	0.7%; 1 urethral stricture, 1 rectovaginal fistula
Sorbe and Smeds (15)	1990	404	Proximal 2/3 of vagina	Range from 4.5 Gy × 6 to 9 Gy × 4 at 1.0 cm	6.9% grade 2 or higher
Noyes *et al.*[a] (16)	1995	63	Vaginal cuff	16.2 Gy × 2 at surface of ovoids	None
Kloetzer *et al.* (17)	1997	108	Group A: entire length; Group B: upper vagina; Group C: upper vagina	10 Gy × 4 prescribed to: Group A: 1.0 cm apex and 0.5 cm lateral vagina; Group B: 1.0 cm apex and lateral vagina; Group C: 0.5 cm apex and lateral vagina	Bladder/rectal toxicity: Group A: 6.8%/12.6%; Group B: 6.2%/3.1%; Group C: 2.2%/0%
Eltabbakh *et al.* (18)	1997	332	Not reported	30 Gy at 0.5 cm (LDR)	2.1%; 1 rectovaginal fistula, 4 severe vaginal stenosis, 3 radiation cystitis, 1 radiation colitis
Macleod *et al.*[a] (19)	1998	141	Entire vaginal length	8.5 Gy × 4 at surface	None
Weiss *et al.*[a] (20)	1998	122	Proximal 2/3 of vagina	7 Gy × 3 at 0.5 cm	None
Chadha *et al.* (21)	1999	38	Proximal 1/2 to 2/3 of vagina	7 Gy × 3 at 0.5 cm	5.2%; 2 complete vaginal stenosis
Petereit *et al.* (22)	1999	191	Vaginal cuff	16.2 Gy × 2 at surface of ovoids	0.5%; 1 colovaginal fistula
Anderson *et al.* (23)	2000	102	Proximal 5 cm of vagina	5 Gy × 3 at 0.5 cm	None
Horowitz *et al.* (24)	2002	164	Proximal 5 cm of vagina	7 Gy × 3 at 0.5 cm	2.9%
Jolly *et al.* (26)	2005	50	Proximal 4 cm of vagina	5 Gy × 5 at 0.5 cm	None
Alektiar *et al.* (27)	2005	382	Proximal 1/2 to 2/3 of vagina	7 Gy × 3 at 0.5 cm	0.8%; 1 vaginal necrosis, 1 urethral stricture, 1 cystitis
Solhjem *et al.*[a] (28)	2005	100	Entire length of vagina	7 Gy × 3 at 0.5−0.7 cm	None
Atahan *et al.*[a] (29)	2008	128	Proximal 4 cm of vagina	5.5 Gy × 5 at 0.5 cm	None
Cannon *et al.* (38)	2009	20	Vaginal cuff	16.2 Gy × 2 or 12.2 Gy × 3 at surface	None
Nout *et al.* (PORTEC-2)[a,b] (6)	2010	213	Proximal 1/2 of vagina	7 Gy × 3 at 0.5 cm (HDR) or 30 Gy at 0.5 cm (LDR)	2.3%: 1 bowel obstruction, 4 vaginal atrophy
Sorbe *et al.*[a] (31)	2012	263	Proximal 2/3 of vagina	3 Gy × 6 or 5.9 Gy × 3 at 0.5 cm (HDR) or 20 Gy at 0.5 cm (LDR)	1.6%: 2 GU and 2 vaginal toxicities
Diavolitsis *et al.* (32)	2014	169	Proximal 3−5 cm	7 Gy × 3 or 5.5 Gy × 4 at 0.5 cm (HDR) or 70 Gy at surface of ovoids (LDR)	None
VBT + whole pelvis external beam therapy					
Aalders *et al.* (2)	1980	263	See above	40 Gy EBRT + 60 Gy at surface (LDR)	1.1%: 2 deaths related to RT complications, 1 bladder necrosis
Lybeert *et al.* (36)	1989	233	See above	40 Gy EBRT + 5 Gy × 4 at 0.5 cm (HDR)	0.9%: 1 ileus and 1 ureteral stenosis
Nori *et al.* (37)	1994	300	See above	40 Gy EBRT + 7 Gy × 3 at 0.5 cm (HDR)	None
Cannon *et al.* (38)	2009	50	Vaginal cuff	45−51 Gy EBRT + 5 Gy × 3 or 7.8 Gy × 2 at surface (HDR)	4.0%: 1 MSK, 1 GI
Sorbe *et al.*[a] (31)	2012	264	See above	45−51 Gy EBRT + 5 Gy × 3 or 7.8 Gy × 2 at surface (HDR)	3.7%: 5 GI, 5 GU

Gy = Gray; LDR = low dose rate; cm = centimeter; HDR = high dose rate; GU = genitourinary; GI = gastrointestinal; VBT = vaginal brachytherapy; EBRT = external beam radiation therapy; RT = radiation therapy; MSK = musculoskeletal; PORTEC = Post-Operative Radiation Therapy in Endometrial Cancer.

[a] All late toxicities reported (Grades 1−5).

[b] Randomized controlled trial comparison of EBRT vs. VBT.

patients treated with EBRT show an elevated risk of SMN elsewhere in the pelvis (66, 67). Recent data from the PORTEC and TME trials showed no significant increase in SMN in endometrial and rectal cancer patients, respectively, treated with pelvic RT (68). Brown *et al.* reported data from Surveillance, Epidemiology, and End Results (SEER) evaluating VBT and the risk of SMN. Their results demonstrated decreased risk of SMN with decreasing volumes of irradiated tissue among endometrial cancer patients. The observed:expected ratio of SMN (using standard incidence ratio of the general population) is 0.92 with observation, 0.97 with VBT alone, 1.10 with EBRT alone, 1.22 with EBRT and VBT, and 1.09 with radiotherapy of any modality. The 30-year risk of SMN of the bladder was increased with adjuvant VBT compared to observation, but there was no difference in any other pelvic anatomical site. They found that risk of bladder cancer increased from 1.25% with observation to 2.14% with VBT ($p = 0.006$) (69). As evidence shows, the risk of SMN as a result of VBT is very low and takes many years to demonstrate that small incremental risk. Surveillance of patients with screening colonoscopy and clinical emphasis on symptoms such as hematuria and hematochezia can help detect SMN so that early intervention may be initiated. It is important for patients, especially younger patients, to realize and understand that SMN is a potential effect of VBT.

VBT dose and treatment length

Toxicity associated with any brachytherapy application, including VBT, correlates with several factors. VBT total dose (both in combination with EBRT and as monotherapy), dose rate, fractionation, length of vagina treated, and depth of vagina treated all contribute to risk of potential toxicity. Sorbe and Smeds treated patients with HDR VBT to a dose of 9.0 Gy for four fractions, 6.0 Gy for five fractions, 5.0 Gy for six fractions, and 4.5 Gy for six fractions. All doses were prescribed to 1.0 cm depth from the vaginal surface. They showed that increasing dose per fraction yielded increased bladder, rectal, and late vaginal toxicities. They also found that patients treated to a longer length of the vagina experienced greater toxicity (15). Similar to the Sorbe and Smeds dose-fractionation with the lowest dose, Townamachi *et al.* reported on their regimen of 4.0 Gy for six fractions but specified to the vaginal surface rather than 1.0 cm depth. They had 0 cases of ≥ Grade 2 vaginal, GI, or GU toxicity among 157 patients (70). Additional studies show that increased dose per fraction and length of the vagina treated result in increased toxicity (37, 71). Park *et al.* (72) found that treating >60% of the vaginal length and total dose >14 Gy corresponded to increased ≥ Grade 1 vaginal stenosis.

Fayed *et al.* (63) compared HDR (2 Gy for six fractions to 0.5 cm depth) to LDR (60–70 Gy to the vaginal surface) VBT and showed no difference in Grade 3–4 toxicity. HDR VBT is being used by 96% of brachytherapists, which is a significant increase over the past decade. A wide range of doses in fractionation schemes are used based on the American Brachytherapy Society (ABS) pattern of practice survey of VBT, reporting 24 VBT dose-fractionation schedules are being used as monotherapy and 22 as a boost after EBRT (73).

PORTEC-4 was designed to identify the role and optimal dose of VBT. It randomized patients with postoperative H–I risk endometrial cancer to observation vs. VBT. Patients randomized to VBT underwent a secondary randomization of 7 Gy vs. 5 Gy each for three fractions at 0.5 cm depth. The study in its original design was closed due to poor accrual as a result of the observation arm being an unfavorable option for patients. It was estimated that only 1 of every 10–12 eligible patients enrolled in the study. It is expected to reopen in a modified design in 2016. Results for PORTEC-4 are not yet available but are eagerly awaited (74, 75). More data are required, preferably in randomized Phase III trials, to help elucidate optimal VBT dose, fractionation, and treatment length.

Vaginal toxicity prevention

The primary potential toxicities of VBT are vaginal atrophy and vaginal shortening which may result in decreased sexual QOL. As a measurement of vaginal length, Bruner *et al.* (76) showed that a simple vaginal sound can be used in the clinic as a documentation tool of vaginal length. In a separate study, Bruner *et al.* (65) showed that sexual frequency and satisfaction may decrease after surgery and VBT. In patients treated with simple hysterectomy and VBT, sexual dysfunction increases in patients who are postmenopausal, had a laparotomy, or did not use vaginal lubrication (77). When compared to patients treated with surgery alone, patients treated with adjuvant VBT had similar sexual QOL (78). Interventions that decrease toxicities and maintain sexual QOL may be beneficial for patients treated with VBT.

Interventions like usage of a vaginal dilator or resumption of sexual intercourse may be recommended to decrease the risk of vaginal toxicity. A study by Sorbe and Smeds showed that maintenance of vaginal intercourse after radiotherapy reduced the risk of vaginal shortening, but about 2/3 of patients reported some dyspareunia related to vaginal atrophy and shortening. They treated patients to the proximal vagina due to their hypothesis that dose to the distal 1/3 of the vagina contributed most to vaginal toxicity and sexual side effects (15). Bahng *et al.* (71) reported that patient use of a vaginal dilator significantly reduces incidence of vaginal atrophy. In a prospective study of vaginal dilator adherence, continued use of a vaginal dilator 6 months after pelvic radiotherapy decreased the rate of vaginal stenosis (79). Patients with higher mean vaginal doses may benefit the most from use of a vaginal dilator (80). A Cochrane review addressed vaginal dilation and concluded that there is insufficient reliable evidence to support routine vaginal

dilation during RT. The study admits that observational studies suggest that regular vaginal dilation may improve rates of patient-reported vaginal stenosis (81). Low rates of adherence to use of a vaginal dilator result in difficulty interpreting data on this topic, however (71, 79, 80). The use of a vaginal dilator after VBT may be a controversial topic, but many investigators including the authors recommend routine use for patients who are not sexually active.

Another controversial intervention for the treatment of vaginal atrophy is vaginal estrogen. Vaginal estrogen has been shown to decrease vaginal atrophy in postmenopausal patients in the general population (82). There is no high level evidence supporting vaginal estrogen in patients treated with pelvic radiotherapy, but small and dated studies suggest a potential decrease in vaginal atrophy (83, 84). Data suggest that vaginal estrogen topically does not increase serum levels of estrogen so systemic side effects are unlikely (85). The main side effects from topical estrogen are breast pain and perineal pain (86). Importantly, hormone replacement therapy does not increase the risk of endometrial cancer recurrence (87). The potential interventions to decrease vaginal atrophy are controversial, and the potential risk and interventions related to vaginal atrophy should be discussed with the patient.

VBT treatment delivery

Depth for dose specification

There is no consensus regarding the optimal dose-fractionation schedule, treatment length, or depth of dose specification for the delivery of VBT. The majority (95%) of vaginal lymphatics are located within 3 mm from the vaginal mucosa so ensuring adequate dose to this depth should be considered (88). The aforementioned studies specify dose at varying depths, routinely between the vaginal surface and 1 cm depth. Currently, dose is most commonly specified at either the vaginal surface or 0.5 cm depth as monotherapy with 7 Gy for three fractions to 0.5 cm depth as the most common regimen (73). Specifying VBT boost doses to the vaginal surface is supported by recent Radiation Therapy Oncology Group studies (40, 41). Despite the variety of dose-fractionation schedules and locations for dose specification, vaginal relapse rates are low with minimal late toxicity.

Length of proximal vagina for dose specification

Length of the vagina to be treated is also variable. Lengths treated in studies range from the proximal 1–10 cm (19, 89). Most commonly, dose is prescribed to the proximal 3–5 cm or the proximal 1/3–1/2 of the vagina, but there is no consensus. The ABS recommends treating the proximal 3–5 cm of the vagina (90). Treatment of the entire length of the vagina is decreasing due to the significant increased risk of stenosis and low rates of distal vaginal recurrence (73). Kloetzer *et al.* reported compared outcomes of patients treated to variable lengths of the proximal vagina: vaginal apex, proximal half of the vagina, and entire vagina. They report no difference in survival or vaginal recurrence by treating an increased length thus supporting treatment of the proximal vaginal canal only (14). There is no evidence that treatment of the entire vagina is ever indicated for adjuvant VBT. As previously described, treating increased length of the vagina results in increased vaginal toxicity although treating the upper 2/3 of the vagina in the setting of adverse histologies should be considered.

Dose rate

Before the introduction of HDR remote afterloaders, VBT was delivered with LDR (2). With increased availability of HDR remote afterloaders, VBT is now delivered with HDR by about 96% of brachytherapists, which is significantly increased from the 69% ($p < 0.001$) from the prior decade (73, 91). The potential advantages of HDR include dramatically decreased radiation exposure to health care providers and visitors, outpatient treatment delivery, and limited duration of patient immobilization which decreases risk of thromboembolism and improves patient comfort (63). HDR was additionally found to be less expensive than LDR for many of these reasons (92). Fayed *et al.* (63) compared outcomes of patients treated with HDR vs. LDR and found no difference in local control or overall survival. HDR has several advantages overall LDR without difference in outcomes which leads to its increasing use.

VBT applicators

The most commonly used applicator is the single channel vaginal cylinder (73). This applicator is the simplest to plan because it treats the vagina circumferentially and equally to the depth of dose specification. The single channel vaginal cylinder has decreased dose at depth superior to the vaginal apex as a result of anisotropy (93). Multichannel vaginal cylinders have the advantage of customizing dose to either deliver asymmetric doses or avoid adjacent normal structures (94, 95). The multichannel cylinder has been shown to decrease dose to the bladder and rectum but at the expense of increased vaginal mucosa dose (96). Patients with large lesions or those that are >5 mm thick may benefit from a multichannel cylinder, but they may still be difficult to adequately treat without delivering excess dose to the vaginal surface (97).

Vaginal colpostats have the theoretical advantage to allow dose to the vaginal apex while vaginal packing displaces the bladder and rectum. Vaginal packing may result in decreased dose to the at risk vagina as well though (93).

A ring applicator may be used similarly to the vaginal colpostats. An institutional series using a ring applicator to treat the vaginal cuff demonstrated a very low rate of vaginal relapse with similar rates of vaginal toxicity compared to other applicators (98). A vaginal mold applicator has been studied with the potential benefit of customization of the applicator to the patient's vaginal anatomy with decreased air pockets and potentially improved dosimetry (99). A vaginal balloon applicator has been used with favorable outcomes as well (100). There are many different applicators which can be used to deliver VBT, all of which have similar clinical outcomes despite some potential dosimetric differences.

Treatment planning

There are many different approaches to treatment planning of VBT. A comparison of 2D vs. 3D CT-based treatment planning demonstrated decreased dose to critical structures while maintaining similar dose to the clinical target volume (101). Most brachytherapists advocate using 3D treatment planning, most commonly at the first fraction or with each fraction (73). Multiple studies evaluated 3D treatment planning at the first fraction only or for each fraction. They show that 3D planning for each fraction does not decrease dose to the normal tissues but incurs greater expense than performing 3D planning for the first fraction only (102–104). CT-based treatment planning effectively allows assessment of air gaps between the applicator and the vaginal cuff before treatment delivery (105). For treatment planning, optimization points should be placed around both the apex and the lateral aspects of the applicator (90). Including optimization points around the apex and lateral aspects of the applicator decreases extreme hot and cold spots. Placing the optimization points at the surface of the applicator (surrogate for vaginal mucosa) provides greater uniformity of dose than optimizing at 0.5 cm depth (106).

Altering the internal anatomy has been investigated to determine its effects on target and normal tissue dose. In a prospective study, Stewart *et al.* found that bladder filling increased the maximum bladder dose and bladder volume receiving ≥70% of prescription dose. Bladder filling displaced the nearest bowel away from the vaginal cylinder though (107). Hung *et al.* (108) showed that bladder filling decreased small bowel dose without affecting dose to the bladder, rectum, or sigmoid colon. Effects of rectal filling were dosimetrically studied with larger rectal volumes resulting in higher rectal dose delivered (109). In addition, placement of a vaginal cylinder horizontal to the patient rather than in the "natural" angle of the vagina results in decreased dose to the rectum (110). Despite the many issues regarding VBT treatment planning, the translation of dose to vagina and normal tissues has an unclear correlation to clinical outcomes.

Treatment recommendations

American Brachytherapy Society

In 2000 and again in 2012, the ABS published recommendations for adjuvant VBT after surgical management of endometrial cancer (90, 111). The full details of these documents are beyond the scope of this review, but the authors encourage readers to reference them directly for full details. The ABS also conducted patterns of practice surveys in 2003 and 2014. There is increasing use of HDR vs. LDR brachytherapy, and HDR treatment dose-fractionation schedules are widely variable among brachytherapists (73, 91).

ASTRO executive summary

The American Society of Radiation Oncology (ASTRO) published their executive summary in 2014 addressing many controversial topics in the postoperative management of endometrial cancer patients. The executive summary assesses the level of data and provides panel recommendations for such topics (112). We would encourage readers to access the primary source for further details regarding the levels of evidence and panel recommendations regarding adjuvant radiotherapy, including VBT.

Patient evaluation and decision making

There are many, and potentially opposing, approaches to adjuvant radiotherapy for the postoperative early-stage endometrial cancer patient. Practitioners could use PORTEC-2 and other data from Table 2 to support VBT as a method of risk reduction, regardless of risk group. Vaginal cuff recurrences are potentially fatal, and salvage therapy can be quite traumatic and morbid. Therefore, prevention of local recurrences can be extremely beneficial, especially because the toxicity of VBT is quite modest. Such approaches would lead practitioners to support VBT for patients who had lesser risk disease than those included in PORTEC-2. Contrarily, because VBT and EBRT are equivalent in vaginal control and there is no survival benefit to EBRT compared to observation, it could be rationalized that any early-stage patient could forego adjuvant radiotherapy altogether (4–6).

It is the approach of the authors to estimate the risk of recurrence, especially vaginal cuff recurrence, with observation and with adjuvant VBT. We favor presenting these estimates to the patient. With a detailed discussion of side effects as well, the patient can make a decision based on the risks and benefits of adjuvant VBT. This approach is supported by a survey performed by Kunneman *et al.* from the Dutch Gynecologic Oncology Group. Their survey asked both patients and physicians to indicate the minimum acceptable benefit in local control to undergo VBT. They found that the median minimal improvement in local control with adjuvant VBT was 0% for patients and 8% and physicians ($p < 0.001$). Most patients (59%) would choose

adjuvant VBT even with no benefit in local control. The vast majority of both patients and physicians prefer joint decision making rather than the onus lying solely with either the patient or the physician (113). These data are supported by the patients choosing not to enroll to PORTEC-4 because there was an observation arm in the randomization (75).

Ultimately, we believe that a multidisciplinary approach, including a full discussion of radiotherapy and CT options, is the best way to manage postoperative endometrial cancer patients. We advocate an honest discussion with the patient so she can make an informed decision with the guidance of her surgeon and radiation oncologist.

Conclusion

Adjuvant radiotherapy for postoperative early-stage endometrial cancer has evolved over the last several decades. The low rates of vaginal failure and modest toxicity profile make VBT an integral modality for these patients. The use of VBT has also evolved over the years as PORTEC-2 supports VBT for many patients who would have previously received EBRT. Recommendations have been published by the ABS and ASTRO to guide practitioners at delivering brachytherapy appropriately. Data now exist that supports joint decision making between patient and physician which includes the notion that patients have a different threshold of integral benefit than physicians. Hence, the decision regarding adjuvant therapy should be the patient's with guidance and support from her physicians.

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