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Review

Pros and cons of vaginal brachytherapy after external beam radiation therapy in endometrial cancer

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HIGHLIGHTS

- Stage I endometrial cancer outcomes may not be improved by vaginal brachytherapy after beam (EB + VB).
- EB + VB may improve local-regional recurrence in high-risk endometrial cancer (*e.g.* stage II-III).
- A randomized prospective clinical trial is needed to determine the role for EB + VB

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ABSTRACT

A large number of studies have looked at the role of radiation therapy in the treatment of endometrial cancer. One particular radiation strategy in common practice is the use of adjuvant external beam (EB) radiotherapy followed by vaginal brachytherapy (VB). While the addition of VB to EB provides a theoretical benefit of a localized boost with higher focused dose to an area of potentially high recurrence risk, a randomized clinical trial to compare outcomes and toxicities of EB + VB *vs.* EB alone is lacking. The goal of this review is to present the current data for and against the use of this combined radiation modality and to provide some preliminary evidence regarding which patient populations may be most likely to benefit.

Contents

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1. Introduction

Endometrial cancer is the most commonly diagnosed gynecologic cancer in the United States with approximately 52,000 new cases in 2014 [1]. Low-risk disease is typically cured with surgery alone but much investigation has focused on the appropriate treatment for more advanced disease. It is well established that radiation therapy decreases loco-regional recurrence (LRR) rates but whether there is a benefit to adding vaginal brachytherapy (VB) after external beam (EB) radiotherapy, in certain subgroups, remains an open question. The recently published ASTRO endometrial cancer guidelines concluded that there was low-quality evidence to support EB + VB and as a result gave this combined approach a weak recommendation, indicating the controversial nature of this topic [2].

Over several decades, many centers have adopted EB + VB as a part of routine practice in endometrial cancer treatment. A Surveillance, Epidemiology and End Results (SEER) analysis of practice patterns of radiation oncologists from 1988–2002 found that this is a treatment modality in active use. The most common application is in the treatment of stage II disease, with 27% of patients with this diagnosis receiving EB + VB. The second most common use of EB + VB is in stage I disease with >50% myometrial invasion (MI) [3]. Per the ASTRO endometrial cancer guidelines, given the lack of prospective data to validate the use of EB + VB, this approach "is not generally warranted, unless risk factors for vaginal recurrence are present" [2]. As noted in the guidelines, cervical involvement is often cited as a predictor of vaginal recurrence. In that context, patients with Stage II or III disease are frequently considered for EB + VB, though there is no clear cohort of patients for whom EB + VB has been established as the standard of care. The gold-standard study to support the use of EB + VB would be a prospective, randomized clinical trial comparing the outcomes and toxicities of EB + VB *vs.* EB alone in endometrial cancer patients at high risk of recurrence. Unfortunately no such study exists. However, several prospective studies include cohorts of patients who received EB + VB and had this regimen compared to various other treatment modalities. In addition, multiple retrospective studies have included patients receiving EB + VB. Together these studies can provide some information about the efficacy, and to a lesser degree, the toxicity, that might be expected.

The goal of this review is to explore the existing evidence for and against adding VB after EB in the post-operative setting and to investigate whether there are particular patient populations that are most likely to benefit. To simplify risk assessment, only studies with predominantly endometrioid histology were included. In addition, while there are studies using EB + VB as far back as the 1970s, it is difficult to interpret the treatment effects prior to the introduction of the International Federation for Gynecologic Oncology (FIGO) 1988 surgical/histopathologic staging system. Further complicating the discussion is the evolution of the FIGO system, particularly with regard to stage II disease, which was initially sub-divided into IIA (endocervical glandular involvement only) and IIB (cervical stromal invasion) but after the 2009 revision was altered such that previously IIA disease was no longer included in the stage II categorization, which now requires disease in the cervical stroma [4]. In an attempt to describe a consistent group of patients across time, for studies prior to 2009, the categorization of "stage II" will be used to refer to patients with FIGO 1988 stage IIB disease. In addition, while multiple studies treating stage III-IV disease with EB + VB have been published, these studies typically involve the use of chemotherapy, which complicates the interpretation of radiation effect and as a result will not be emphasized here. In summary, the criteria for our literature search were studies that: (1) were published after 1988, (2) that included endometrial-cancer patients with predominantly endometrioid histology, and (3) had either an explicitly noted cohort that received EB + VB or a significant number of total patients studied who received this treatment. Prospective studies where patients received chemotherapy were included though retrospective studies where patients received chemotherapy were not, for the reasons discussed above.

1.1. Pro: the combination of EB + VB is of benefit to patients

1.1.1. VB alone may not be sufficient therapy in patients without lymphadenectomy

VB alone has been established as an excellent treatment option for endometrial cancer patients with intermediate-risk disease [5]. This is particularly true of patients who receive lymph node dissections where practice patterns tend to favor VB over EB [6]. The rationale for this can be seen in the long-term follow-up data from PORTEC-1 where most LRR after hysterectomy alone in women with intermediate risk disease was vaginal. Specifically, the 15-year risk of any vaginal recurrence without radiation was 11%, whereas the risk of any non-vaginal pelvic recurrence was 4.5% [7]. While VB is able to help prevent vaginal recurrence, it does not prevent recurrent pelvic disease. This was seen in PORTEC-2 where the risk of any pelvic recurrence after VB was 3.8% [5]. Of note, after central pathology review, 79% of those patients were found to have grade 1 histology, which suggests that more advanced disease may be associated with an even higher rate of pelvic recurrence after VB. For example, in the Gynecologic Oncology Group (GOG) study GOG-33, there was a >10% risk of lymph node involvement with grade 3 disease or deep MI. Such regional disease would not be targeted by VB alone [8].

The explicit benefit of EB + VB compared to VB alone for patients who did not have lymphadenectomy was first seen 35 years ago in a randomized prospective study by Aalders et al. (Table 1) [9]. That study included 540 patients with stage I disease who received 60 Gy low-dose-rate (LDR) VB after surgery. Patients were then randomized to no further treatment or to 40 Gy EB. After 3–10 years of follow-up, LRR rates were significantly lower in patients receiving combined VB and EB than in those treated with VB alone (1.9% *vs.* 6.9%, $p < 0.01$) [9]. The study did not present separate vaginal and pelvic recurrence rates. Of note, unlike most other studies discussed in this review, these patients received EB after VB rather than *vice versa* and all VB was administered using LDR and not HDR as is currently more commonly used. Despite these changes over time, however, this was the first study to suggest that VB may be insufficient in patients who do not have lymph node dissections.

1.1.2. Pelvic recurrence can occur in patients receiving VB alone, even after lymphadenectomy

Three decades after Aalders et al., the question of whether adding EB to VB would improve outcomes in "medium-risk" endometrial cancer was addressed in another prospective, randomized clinical trial by Sorbe et al. (Table 1) [13]. That study treated 527 patients with stage I endometrial cancer, endometrioid histology and one risk factor for medium-risk disease (grade 3 histology, ≥50% MI or DNA aneuploidy) with surgery and VB with our without EB. VB was administered to a target volume of the proximal 2/3 of the vagina with dose prescribed to a depth of 5 mm. The most common regimen used was 18 Gy in 6 fractions but individual centers also used 17.7 Gy in 3 fractions or 20 Gy LDR. EB was administered to a target volume that included the previous site of the uterus and adnexa, the parametria, proximal 2/3 of the vagina and lymphatic draining regions along the iliac vessels up to the superior border of the L5-S1 disk. The total dose delivered was 46 Gy in 1.8 or 2.0 Gy fractions [10].

In that study, the 5-year actuarial LRR rate for EB + VB was 1.5%, which was significantly less than the 5.0% LRR rate for VB alone. As might be expected, this effect was largely due to EB + VB preventing pelvic recurrences, with 0.4% of patients who received EB + VB having a pelvic recurrence without vaginal involvement compared to 5.3% of patients treated with VB alone. Vaginal recurrence was seen in 1.9% of patients who received EB + VB and 2.7% of patients treated with VB alone. The overall recurrence rates (including distant metastases)