American College of Radiology
ACR Appropriateness Criteria®
ADJUVANT MANAGEMENT OF EARLY STAGE ENDOMETRIAL CANCER

Expert Panel on Radiation Oncology – Gynecology: Andrew O. Wahl, MD[1]; David K. Gaffney, MD, PhD[2]; Anuja Jhingran, MD[3]; Catheryn M. Yashar, MD[4]; Matthew Biagioli, MD[5]; Mohamed A. Elshaikh, MD[6]; Shruti Jolly, MD[7]; Elizabeth Kidd, MD[8]; Larissa J. Lee, MD[9]; Linna Li, MD[10]; David H. Moore, MD[11]; Gautam G. Rao, MD[12]; Ned L. Williams, DO[13]; William Small Jr, MD.[14]

Summary of Literature Review

Introduction/Background

Endometrial cancer is the most common gynecologic malignancy diagnosed in the United States and is second to ovarian cancer in annual mortality for gynecologic cancers, with 10,170 deaths [1]. With the decline in hormone replacement therapy utilization, there was a corresponding decline in the incidence of endometrial cancer. However, more recently this trend has reversed as obesity rates have increased [2]. The majority of new endometrial cancers will be International Federation of Gynecology and Obstetrics (FIGO) stage I-II disease, at approximately 85% of new cases [3]. Recurrence rates of early endometrial cancers vary within a specific stage and thus treatment options differ across the early endometrial cancers [4,5]. Endometrial cancer is less likely to lead to death than other medical comorbidities [6-8]. A Surveillance, Epidemiology, and End Results (SEER) study of early-stage, low-grade endometrial carcinoma showed that 7% of patients diagnosed died of malignancy, whereas 42% died of cardiovascular disease [9].

The most common presenting symptom of uterine carcinoma is vaginal bleeding, typically after menopause. Workup of a suspected endometrial cancer includes history and physical examination with an endometrial biopsy. A false-negative result can occur in 10% of cases, so a negative biopsy is typically followed by dilation and curettage [10]. Once a histopathologic diagnosis is established and uterine-confined disease is suspected, blood counts, routine biochemistry, and chest radiographs are recommended to complete workup [11]. Surgery consists of total hysterectomy and bilateral salpingo-oophorectomy with or without lymph node dissection. Visual inspection of the peritoneal, serosal, and diaphragmatic surfaces with biopsy of suspicious lesions is required to evaluate for extrauterine disease. FIGO recommends obtaining peritoneal washings even though a positive finding was removed from the most recent staging system.

Vaginal Brachytherapy

The recommendations for adjuvant radiation therapy in early-stage endometrial cancer depend on the presence or absence of several risk factors, such as older age, deep myometrial invasion, high grade, large tumor size, and lymphovascular space invasion (LVSI) [12-14]. Classification into low-risk, intermediate-risk, and high-risk early-stage uterine cancer is based on a combination of these risk factors, but investigators and studies often differ in their definitions. In early-stage endometrial cancer, the most common site of recurrence in the absence of adjuvant radiation therapy is the vaginal cuff. Vaginal brachytherapy reduces the risk of a vaginal recurrence and has a low side-effect profile.

Sorbe et al [15] published a randomized trial comparing adjuvant vaginal brachytherapy to observation in grade 1 or 2, stage IA endometrioid carcinoma in 645 patients. After a median follow-up of 68 months, there was no difference in vaginal recurrence rates (1.2% in the brachytherapy group versus 3.1% in the observation group (P=0.114). The impact of adjuvant brachytherapy appears to be limited in low-risk patients. The toxicity of vaginal brachytherapy is mild and limited to urinary (2.8% brachytherapy group versus 0.6% observation group (P=0.063), and vaginal side effects (8.8% brachytherapy group versus 1.5% observation group, P<0.01) [15].

[1]Principal Author, University of Nebraska Medical Center, Omaha, Nebraska. [2]Co-author and Panel Vice-chair, University of Utah Medical Center, Salt Lake City, Utah. [3]Co-author, University of Texas MD Anderson Cancer Center, Houston, Texas. [4]Co-author, University of California San Diego, San Diego, California. [5]H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida. [6]Henry Ford Health System, Detroit, Michigan. [7]University of Michigan Health System, Ann Arbor, Michigan. [8]Stanford Cancer Center, Stanford, California. [9]Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, Massachusetts. [10]Bryn Mawr Hospital, Bryn Mawr, Pennsylvania. [11]Indiana University School of Medicine, Indianapolis, Indiana, American College of Obstetricians and Gynecologists. [12]University of Maryland School of Medicine, Baltimore, Maryland, American Society of Clinical Oncology. [13]Huntsman Cancer Institute University of Utah, Salt Lake City, Utah. [14]Panel Chair, Stritch School of Medicine Loyola University Chicago, Maywood, Illinois.

Reprint requests to: publications@acr.org

Fluoroscopic or computed tomography (CT)–based treatment planning for vaginal brachytherapy is generally used. Confirmation of appropriate placement of the cylinder at the top of the vagina is generally accomplished utilizing fiducials placed at the top of the vagina or review of CT images. The dose fractionation regimens for high-dose-rate (HDR) vaginal brachytherapy have generally been developed to approximate 60 Gy low-dose-rate (LDR) equivalent to the surface of the vagina. Lower-dose HDR regimens may provide an equivalent outcome with lower toxicity rates. A prospective, randomized trial of 2 dose fractionation regimens, 2.5 Gy × 6 fractions versus 5.0 Gy × 6 fractions, was carried out in 230 patients. The dose was prescribed to 5 mm in both groups. There was no difference in local control between the 2 doses but vaginal foreshortening was more pronounced in the 5.0 Gy fraction group [16]. Other investigators have reported other dose fractionation regimens with good outcomes, 7.0 Gy × 3 fractions prescribed to 5 mm [17], 4 Gy × 6 fractions prescribed to the surface [18], 6 Gy × 5 fractions prescribed to the surface [16,19] and 5.5 Gy × 4 fractions prescribed to 0.5 cm [20].

Clearly, multiple dose fractionation regimens exist and future trials, such as Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC)–4, may help establish care. Ninety-five percent of the vaginal lymphatics lie within 3 mm of the vaginal surface, so ensuring adequate dose to at least this depth may be important [21]. In a recent survey of U.S. radiation oncologists, 61.1% prescribe to 5 mm and 22.5% prescribe to the vaginal surface. The 3 most common doses utilized were 7 Gy × 3 to 0.5 cm, 6 Gy × 5 to the vaginal surface (16%) and 5.5 Gy × 4 to 0.5 cm (9%) [22].

There is also variation in the appropriate length of vagina to treat with vaginal brachytherapy. It is important to establish the length of the vagina on physical exam prior to treatment in order to prescribe the dose to the correct length. The upper one-half of the vagina was treated in PORTEC-2 and the upper two-thirds of the vagina was treated in Sorbe et al [15-17]. The most common prescription length in the United States was either the upper one-half or upper 4 cm of the vagina [22], and the American Brachytherapy Society recommended treatment of the upper 3–5 cm of the vagina [19] (see Variant 1).

Pelvic Radiation Therapy

Patients with intermediate-risk endometrial cancer have higher risks of recurrence than low-risk patients and are thus more likely to benefit from adjuvant radiation therapy. There are differing definitions of intermediate-risk and high-intermediate–risk disease, which makes comparisons of randomized trials challenging. Typically, intermediate-risk disease consists of early-stage patients with risk factors such as high grade, deep myometrial invasion, LVSI, and/or older age. Numerous retrospective studies of vaginal brachytherapy alone for intermediate-risk endometrial cancer have been published with good outcomes [23-26].

PORTEC-2 was a randomized trial of vaginal brachytherapy versus whole-pelvic radiation therapy (WPRT) in high-intermediate–risk uterine cancer. Inclusion criteria were age >60 years, >50% myometrial invasion, and grade 1/2; age >60 years, <50% myometrial invasion, and grade 3; or cervical glandular involvement at any age. Staging lymphadenectomy could not be performed. There was no difference in vaginal recurrence rate between vaginal brachytherapy and WPRT (1.8% versus 1.6%, P=0.74). WPRT resulted in a lower risk of pelvic recurrence (3.8% compared to 0.5%, P<0.02). After randomization, a central pathology review was conducted and the most frequent tumor grade change was from grade 2 to 1, resulting in 79% of the patients having grade 1 disease. Fourteen percent of enrolled patients would have ultimately been ineligible and considered as low-intermediate–risk disease [17].

Two randomized trials of vaginal brachytherapy versus vaginal brachytherapy plus WPRT have been conducted. The most recent study included intermediate-risk patients defined as nuclear grade 1 or 2, stage I endometrioid carcinoma with 1 of the following: deep myometrial invasion, DNA aneuploidy, or FIGO grade 3. Locoregional relapse rates were higher in the vaginal brachytherapy–alone arm (5.0% versus 1.5%, (P=0.013) with no corresponding difference in overall survival between arms [27]. An earlier randomized trial from Norway included 537 stage I endometrial cancer patients. Vaginal brachytherapy was compared to vaginal brachytherapy plus WPRT. WPRT resulted in a lower local recurrence rate (2% versus 7%, P<0.01) [28]. Although the results of these 2 trials were similar, the lack of well-defined risk groups in the Norwegian trial makes a comparison to modern trials challenging.

The Medical Research Council ASTEC trial was a randomized trial of standard surgery of hysterectomy, bilateral salpingo-oophorectomy, washings, and palpation of suspicious lymph nodes with or without lymphadenectomy. In women with intermediate-risk or high-intermediate–risk disease, there was a second randomization of pelvic radiation therapy versus observation. Vaginal brachytherapy could be given in a nonrandomized fashion on study

and 52% of participants in the observation arm received vaginal brachytherapy [29]. Pelvic recurrence rate was 3.2% in the pelvic radiation therapy group versus 6.1% in the observation arm, with no difference in overall survival. There was no difference in effectiveness of pelvic radiation therapy between surgical arms.

Only 2 randomized trials, Gynecologic Oncology Group (GOG)–99 and PORTEC-1, compared adjuvant pelvic radiation therapy to no adjuvant radiation therapy in early-stage, intermediate-risk endometrial carcinoma. GOG-99 defined intermediate-risk as stage I or occult stage II patients, and all patients had pelvic and para-aortic lymphadenectomy. External-beam radiation therapy (EBRT) reduced the recurrence rate (12% in observation group and 3% in radiation therapy group). As a result of lower-than-expected local failure rate, the investigators identified a high-intermediate–risk subgroup on post hoc analysis with the risk factors of grade 2-3, outer one-third invasion, or LVSI. If a patient's age was >70, 1 risk factor was necessary; if age was >50, 2 risk factors were necessary; and if age was <50, 3 risk factors were necessary. The recurrence rate in the high-intermediate–risk group was 27% with observation and 13% with EBRT. At 4 years, the incidence of death was 12% and 26% in the EBRT group and observation group, respectively [4].

In PORTEC-1, patients had grade 1 disease with more than one-half myometrial invasion, grade 2 disease with any invasion, or grade 3 disease with less than one-half myometrial invasion. Surgical staging was not performed. A statistically significant reduction in local failures was noted with the addition of adjuvant pelvic radiation therapy (12% versus 4%, $P<0.001$) [30]. Based on the recurrence rates seen in PORTEC-1 and -2, a nomogram was developed to estimate recurrence rates [31]. No improvement in overall survival was noted with the addition of adjuvant WPRT in either GOG-99 or PORTEC-1. Creutzberg et al [32] reported a 58% overall survival and a 14% locoregional relapse rate in patients with grade 3, outer one-half myometrial invasion, and treated with pelvic radiation therapy. A SEER study of 21,249 patients demonstrated an improved overall survival with the addition of pelvic radiation therapy in patients with invasion of the outer one-half of the myometrium [33] (see Variant 2).

Pelvic Radiation Therapy Technique

Pelvic radiation therapy is generally associated with more side effects than vaginal brachytherapy. A long-term quality-of-life analysis of PORTEC-2 patients was carried out with a median follow-up of 65 months. The pelvic radiation therapy group reported worse social functioning ($P=0.005$) and higher symptom scores for diarrhea, fecal leakage, and need to stay near a toilet ($P<0.001$) compared to vaginal brachytherapy [34]. In the acute phase of side effects, 50%–80% of pelvic radiation therapy patients experienced grade 2 or greater diarrhea [35].

Two-field or 4-field treatment techniques have traditionally been used to deliver pelvic EBRT using field borders based on bony anatomy. However, using bony landmarks as the sole method of defining treatment fields can lead to a geographic miss, particularly the lateral external iliac lymph node region [36,37]. If CT imaging is obtained, contouring the at-risk nodal groups, vaginal cuff, and organs at risk permits customization of field borders. In cases where a lymphadenectomy was not performed, cross-sectional imaging can be obtained prior to radiation therapy if risk of pelvic lymph node involvement is sufficient. Intensity-modulated radiation therapy (IMRT) has been shown to reduce dose to critical structures in dosimetric studies, and retrospective reviews of IMRT for early-stage endometrial cancer have shown excellent local control rates with low gastrointestinal toxicity rates [38-41]. It is critical to accurately define clinical target volumes using expert consensus guidelines for gynecologic IMRT. Movement of the vaginal cuff is dependent on bladder and rectal filling. Generation of an internal target volume using full and empty bladder scans can account for this movement since nodal volumes move independently with bony landmarks. Image-guidance radiation therapy may account for some degree of independent movement of the vaginal cuff and nodal volumes but is unlikely to help in moderate to extreme cases of bladder or rectal filling where the vaginal clinical target volume is displaced. The ongoing Radiation Therapy Oncology Group® (RTOG) TIME-C trial compares the impact of IMRT to 3D conformal radiation therapy on patient-reported gastrointestinal toxicity.

Vaginal Cuff Brachytherapy Boost

Vaginal cuff brachytherapy combined with WPRT is associated with a low risk of vaginal and pelvic recurrences [27,42,43]. Because WPRT alone results in low recurrence rates in early-stage endometrial cancer, the addition of vaginal cuff brachytherapy to WPRT may be of marginal benefit. Two retrospective reviews revealed no improvement in local control with a vaginal cuff brachytherapy boost [44,45]. Common fractionation regimens from RTOG trials are 6 Gy × 3 fractions prescribed to the surface after 45 Gy EBRT or 6 Gy × 2 fractions prescribed to the surface after 50.4 Gy EBRT [46,47]. Although high-level evidence is lacking, vaginal cuff

brachytherapy boost can be administered in grade 3 disease, presence of lymphovascular invasion, or when cervical stromal invasion is present [48,49].

Adjuvant Chemotherapy

Adjuvant chemotherapy is not routinely used in early endometrial cancer as distant recurrence rates are low; however, high-risk endometrioid cancer with grade 3 tumors, deeply invasive tumors, or stage II disease may preferentially benefit. The largest series of patients with cervical stromal invasion who did not receive chemotherapy had a 5-year relapse-free survival rate of 77% and disease-specific survival rate of 91%, which is similar to some stage I patients [50]. Most randomized trials comparing EBRT to sequential EBRT and chemotherapy exclude early-stage disease. The combined analysis of the NSGO/EORTC and MaNGO ILIADE-III trials consisted of FIGO stage I-III endometrial cancer patients who were randomized to EBRT or sequential EBRT and chemotherapy. The addition of chemotherapy resulted in improved cancer-specific survival (hazard ratio [HR], 0.55; P=0.01) and a trend to improved overall survival (HR, 0.69; P=0.07). Seventy-one percent of patients had endometrioid histology and 79% were FIGO stage I and II [51].

A Japanese trial compared pelvic radiation therapy to cyclophosphamide, doxorubicin, and cisplatin in FIGO I-IIIC endometrial cancer patients with deep myometrial invasion. Nearly 78% of patients were stage I or II. There was no difference in recurrence patterns, disease-free survival, or overall survival [52]. A similar study from Milan comparing adjuvant pelvic or extended-field radiation therapy to chemotherapy demonstrated no difference in progression-free or overall survival [53].

GOG-249 randomized 601 patients with high-intermediate–risk stage I (see GOG-99, except greater than one-half invasion was used), stage II, or stage I-II uterine papillary serous carcinoma or clear cell carcinoma. Patients received either WPRT or vaginal cuff brachytherapy with 3 cycles of carboplatin/paclitaxel. At 2 years, overall survival and relapse-free survival was 93% and 82% in the pelvic radiation therapy arm and 92% and 84% in the vaginal brachytherapy/chemotherapy arm. Acute toxicity was more common in the vaginal brachytherapy/chemotherapy group [54] (see Variant 3).

Salvage Radiation Therapy

When determining whether adjuvant radiation therapy may be of benefit, one must identify who is at appropriate level risk of recurrence, determine if the adjuvant radiation therapy will reduce the risk of recurrence, and estimate associated toxicity of radiation therapy. It is also critical to determine the probability of a successful salvage treatment in case of a recurrence and determine the toxicity associated with salvage treatment. Pelvic recurrences with or without prior radiation therapy have a low rate of salvage, with a 3-year survival rate of 8% in the PORTEC-1 series [55]. There are emerging data on the use of dose-escalated IMRT for isolated nonvaginal pelvic or para-aortic nodal recurrences in patients who have not previously received radiation therapy. Two-year survival rates were 71%, with a late grade 3-4 gastrointestinal toxicity rate of 8% [56]. Isolated vaginal recurrences in absence of previous radiation therapy can be successfully salvaged with EBRT plus brachytherapy or surgery with or without further radiation therapy. Isolated vaginal cuff recurrences treated with EBRT plus brachytherapy have local control rates of 50%–80% and survival rates of 40%–65% [55,57-59]. The grade 4 toxicity rate of this approach is 9% [57].

EBRT doses range from 45–50 Gy, followed by a brachytherapy boost to at least 70- to 80 Gy LDR equivalent [19,57]. Using the linear quadratic model, HDR brachytherapy doses can be converted to LDR doses for tumor and normal tissues [60]. After EBRT, the use of interstitial or intracavitary brachytherapy is dependent on the size and location of the tumor. If the thickness of the residual tumor is ≥5 mm or tumor involves the lower vagina, interstitial brachytherapy under laparoscopic, CT, or MR guidance is recommended. 3D planning is commonly used with CT or MRI. In the unusual situation where a patient is not medically able to undergo interstitial brachytherapy, an external-beam boost can be considered. The ongoing GOG-238 trial is randomizing patients with an isolated vaginal cuff recurrence to definitive radiation therapy with or without weekly cisplatin. In this protocol, the EBRT dose is 45 Gy. If the residual tumor is <5 mm, then intracavitary HDR brachytherapy is recommended using 7 Gy × 3 fractions prescribed to 5 mm.

Summary of Recommendations

- Early-stage endometrial cancer patients are a heterogeneous group of patients with different recurrence rates and treatment approaches.

- Consider observation in patients with low-grade, early-stage endometrial adenocarcinoma without risk factors.
- Vaginal brachytherapy or WPRT can be considered in early-stage patients with risk factors such as high grade, deep myometrial invasion, or LVSI.
- 3D conformal radiation therapy and IMRT are reasonable treatment techniques for adjuvant radiation therapy.

Summary of Evidence

Of the 60 references cited in the *ACR Appropriateness Criteria® Adjuvant Management of Early Stage Endometrial Cancer* document, 57 are categorized as therapeutic references including 14 well designed studies, 28 good quality studies, and 6 quality studies that may have design limitations. Additionally, 3 references are categorized as diagnostic references including 3 quality studies that may have design limitations. There are 9 references that may not be useful as primary evidence.

The 60 references cited in the *ACR Appropriateness Criteria® Adjuvant Management of Early Stage Endometrial Cancer* document were published from 1965-2016.

While there are references that report on studies with design limitations, 42 well designed or good quality studies provide good evidence.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin.* 2015;65(1):5-29.
2. McCullough ML, Patel AV, Patel R, et al. Body mass and endometrial cancer risk by hormone replacement therapy and cancer subtype. *Cancer Epidemiol Biomarkers Prev.* 2008;17(1):73-79.
3. Beller U, Quinn MA, Benedet JL, et al. Carcinoma of the vulva. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet.* 2006;95 Suppl 1:S7-27.
4. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol.* 2004;92(3):744-751.
5. Price JJ, Hahn GA, Rominger CJ. Vaginal Involvement in Endometrial Carcinoma. *Am J Obstet Gynecol.* 1965;91:1060-1065.
6. Nicholas Z, Hu N, Ying J, Soisson P, Dodson M, Gaffney DK. Impact of comorbid conditions on survival in endometrial cancer. *Am J Clin Oncol.* 2014;37(2):131-134.
7. Ruterbusch JJ, Ali-Fehmi R, Olson SH, et al. The influence of comorbid conditions on racial disparities in endometrial cancer survival. *Am J Obstet Gynecol.* 2014;211(6):627 e621-629.
8. Truong PT, Kader HA, Lacy B, et al. The effects of age and comorbidity on treatment and outcomes in women with endometrial cancer. *Am J Clin Oncol.* 2005;28(2):157-164.
9. Ward KK, Shah NR, Saenz CC, McHale MT, Alvarez EA, Plaxe SC. Cardiovascular disease is the leading cause of death among endometrial cancer patients. *Gynecol Oncol.* 2012;126(2):176-179.
10. Leitao MM, Jr., Kehoe S, Barakat RR, et al. Comparison of D&C and office endometrial biopsy accuracy in patients with FIGO grade 1 endometrial adenocarcinoma. *Gynecol Oncol.* 2009;113(1):105-108.
11. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet.* 2009;105(2):103-104.
12. AlHilli MM, Podratz KC, Dowdy SC, et al. Risk-scoring system for the individualized prediction of lymphatic dissemination in patients with endometrioid endometrial cancer. *Gynecol Oncol.* 2013;131(1):103-108.
13. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. *Cancer.* 1987;60(8 Suppl):2035-2041.
14. Zaino RJ, Kurman RJ, Diana KL, Morrow CP. Pathologic models to predict outcome for women with endometrial adenocarcinoma: the importance of the distinction between surgical stage and clinical stage--a Gynecologic Oncology Group study. *Cancer.* 1996;77(6):1115-1121.
15. Sorbe B, Nordstrom B, Maenpaa J, et al. Intravaginal brachytherapy in FIGO stage I low-risk endometrial cancer: a controlled randomized study. *Int J Gynecol Cancer.* 2009;19(5):873-878.

16. Sorbe B, Straumits A, Karlsson L. Intravaginal high-dose-rate brachytherapy for stage I endometrial cancer: a randomized study of two dose-per-fraction levels. *Int J Radiat Oncol Biol Phys.* 2005;62(5):1385-1389.
17. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet.* 2010;375(9717):816-823.
18. Townamchai K, Lee L, Viswanathan AN. A novel low dose fractionation regimen for adjuvant vaginal brachytherapy in early stage endometrioid endometrial cancer. *Gynecol Oncol.* 2012;127(2):351-355.
19. Small W, Jr., Beriwal S, Demanes DJ, et al. American Brachytherapy Society consensus guidelines for adjuvant vaginal cuff brachytherapy after hysterectomy. *Brachytherapy.* 2012;11(1):58-67.
20. Diavolitsis V, Rademaker A, Lurain J, Hoekstra A, Strauss J, Small W, Jr. Clinical outcomes in international federation of gynecology and obstetrics stage IA endometrial cancer with myometrial invasion treated with or without postoperative vaginal brachytherapy. *Int J Radiat Oncol Biol Phys.* 2012;84(2):415-419.
21. Choo JJ, Scudiere J, Bitterman P, Dickler A, Gown AM, Zusag TW. Vaginal lymphatic channel location and its implication for intracavitary brachytherapy radiation treatment. *Brachytherapy.* 2005;4(3):236-240.
22. Harkenrider MM, Grover S, Erickson BA, et al. Vaginal brachytherapy for postoperative endometrial cancer: 2014 Survey of the American Brachytherapy Society. *Brachytherapy.* 2016;15(1):23-29.
23. Anderson JM, Stea B, Hallum AV, Rogoff E, Childers J. High-dose-rate postoperative vaginal cuff irradiation alone for stage IB and IC endometrial cancer. *Int J Radiat Oncol Biol Phys.* 2000;46(2):417-425.
24. Chong I, Hoskin PJ. Vaginal vault brachytherapy as sole postoperative treatment for low-risk endometrial cancer. *Brachytherapy.* 2008;7(2):195-199.
25. Fanning J. Long-term survival of intermediate risk endometrial cancer (stage IG3, IC, II) treated with full lymphadenectomy and brachytherapy without teletherapy. *Gynecol Oncol.* 2001;82(2):371-374.
26. McCloskey SA, Tchabo NE, Malhotra HK, et al. Adjuvant vaginal brachytherapy alone for high risk localized endometrial cancer as defined by the three major randomized trials of adjuvant pelvic radiation. *Gynecol Oncol.* 2010;116(3):404-407.
27. Sorbe B, Horvath G, Andersson H, Boman K, Lundgren C, Pettersson B. External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma--a prospective randomized study. *Int J Radiat Oncol Biol Phys.* 2012;82(3):1249-1255.
28. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. *Obstet Gynecol.* 1980;56(4):419-427.
29. Blake P, Swart AM, Orton J, et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. *Lancet.* 2009;373(9658):137-146.
30. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet.* 2000;355(9213):1404-1411.
31. Creutzberg CL, van Stiphout RG, Nout RA, et al. Nomograms for prediction of outcome with or without adjuvant radiation therapy for patients with endometrial cancer: a pooled analysis of PORTEC-1 and PORTEC-2 trials. *Int J Radiat Oncol Biol Phys.* 2015;91(3):530-539.
32. Creutzberg CL, van Putten WL, Warlam-Rodenhuis CC, et al. Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the Postoperative Radiation Therapy in Endometrial Carcinoma Trial. *J Clin Oncol.* 2004;22(7):1234-1241.
33. Lee CM, Szabo A, Shrieve DC, Macdonald OK, Gaffney DK. Frequency and effect of adjuvant radiation therapy among women with stage I endometrial adenocarcinoma. *JAMA.* 2006;295(4):389-397.
34. Nout RA, Putter H, Jurgenliemk-Schulz IM, et al. Five-year quality of life of endometrial cancer patients treated in the randomised Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial and comparison with norm data. *Eur J Cancer.* 2012;48(11):1638-1648.
35. Mundt AJ, Roeske JC, Lujan AE, et al. Initial clinical experience with intensity-modulated whole-pelvis radiation therapy in women with gynecologic malignancies. *Gynecol Oncol.* 2001;82(3):456-463.
36. Kim RY, McGinnis LS, Spencer SA, Meredith RF, Jennelle RL, Salter MM. Conventional four-field pelvic radiotherapy technique without computed tomography-treatment planning in cancer of the cervix: potential geographic miss and its impact on pelvic control. *Int J Radiat Oncol Biol Phys.* 1995;31(1):109-112.

37. Bonin SR, Lanciano RM, Corn BW, Hogan WM, Hartz WH, Hanks GE. Bony landmarks are not an adequate substitute for lymphangiography in defining pelvic lymph node location for the treatment of cervical cancer with radiotherapy. *Int J Radiat Oncol Biol Phys.* 1996;34(1):167-172.
38. Beriwal S, Jain SK, Heron DE, et al. Clinical outcome with adjuvant treatment of endometrial carcinoma using intensity-modulated radiation therapy. *Gynecol Oncol.* 2006;102(2):195-199.
39. Heron DE, Gerszten K, Selvaraj RN, et al. Conventional 3D conformal versus intensity-modulated radiotherapy for the adjuvant treatment of gynecologic malignancies: a comparative dosimetric study of dose-volume histograms. *Gynecol Oncol.* 2003;91(1):39-45.
40. Knab BR, Roeske JC, Mehta N, Sutton H, Mundt AJ. Outcome of endometrial cancer patients treated with adjuvant intensity modulated pelvic radiation therapy. *International Journal of Radiation Oncology*Biology*Physics.* 2004;60(1):S303-S304.
41. Roeske JC, Lujan A, Rotmensch J, Waggoner SE, Yamada D, Mundt AJ. Intensity-modulated whole pelvic radiation therapy in patients with gynecologic malignancies. *Int J Radiat Oncol Biol Phys.* 2000;48(5):1613-1621.
42. Fayed A, Mutch DG, Rader JS, et al. Comparison of high-dose-rate and low-dose-rate brachytherapy in the treatment of endometrial carcinoma. *Int J Radiat Oncol Biol Phys.* 2007;67(2):480-484.
43. Nori D, Merimsky O, Batata M, Caputo T. Postoperative high dose-rate intravaginal brachytherapy combined with external irradiation for early stage endometrial cancer: a long-term follow-up. *Int J Radiat Oncol Biol Phys.* 1994;30(4):831-837.
44. Greven KM, D'Agostino RB, Jr., Lanciano RM, Corn BW. Is there a role for a brachytherapy vaginal cuff boost in the adjuvant management of patients with uterine-confined endometrial cancer? *Int J Radiat Oncol Biol Phys.* 1998;42(1):101-104.
45. Randall ME, Wilder J, Greven K, Raben M. Role of intracavitary cuff boost after adjuvant external irradiation in early endometrial carcinoma. *Int J Radiat Oncol Biol Phys.* 1990;19(1):49-54.
46. Jhingran A, Winter K, Portelance L, et al. A phase II study of intensity modulated radiation therapy to the pelvis for postoperative patients with endometrial carcinoma: radiation therapy oncology group trial 0418. *Int J Radiat Oncol Biol Phys.* 2012;84(1):e23-28.
47. Viswanathan AN, Moughan J, Miller BE, et al. NRG Oncology/RTOG 0921: A phase 2 study of postoperative intensity-modulated radiotherapy with concurrent cisplatin and bevacizumab followed by carboplatin and paclitaxel for patients with endometrial cancer. *Cancer.* 2015:[E-pub ahead of print].
48. Harkenrider MM, Block AM, Siddiqui ZA, Small W, Jr. The role of vaginal cuff brachytherapy in endometrial cancer. *Gynecol Oncol.* 2015;136(2):365-372.
49. Klopp A, Smith BD, Alektiar K, et al. The role of postoperative radiation therapy for endometrial cancer: Executive summary of an American Society for Radiation Oncology evidence-based guideline. *Pract Radiat Oncol.* 2014;4(3):137-144.
50. Elshaikh MA, Al-Wahab Z, Mahdi H, et al. Recurrence patterns and survival endpoints in women with stage II uterine endometrioid carcinoma: a multi-institution study. *Gynecol Oncol.* 2015;136(2):235-239.
51. Hogberg T, Signorelli M, de Oliveira CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. *Eur J Cancer.* 2010;46(13):2422-2431.
52. Susumu N, Sagae S, Udagawa Y, et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. *Gynecol Oncol.* 2008;108(1):226-233.
53. Maggi R, Lissoni A, Spina F, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. *Br J Cancer.* 2006;95(3):266-271.
54. McMeekin DS, Filiaci VL, Aghajanian C, et al. 1A randomized phase III trial of pelvic radiation therapy (PXRT) versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy (VCB/C) in patients with high risk (HR), early stage endometrial cancer (EC): A Gynecologic Oncology Group trial. *Gynecol Oncol.* 2014;134(2):438.
55. Creutzberg CL, van Putten WL, Koper PC, et al. Survival after relapse in patients with endometrial cancer: results from a randomized trial. *Gynecol Oncol.* 2003;89(2):201-209.
56. Ho JC, Allen PK, Jhingran A, et al. Management of nodal recurrences of endometrial cancer with IMRT. *Gynecol Oncol.* 2015;139(1):40-46.
57. Jhingran A, Burke TW, Eifel PJ. Definitive radiotherapy for patients with isolated vaginal recurrence of endometrial carcinoma after hysterectomy. *Int J Radiat Oncol Biol Phys.* 2003;56(5):1366-1372.

58. Lin LL, Grigsby PW, Powell MA, Mutch DG. Definitive radiotherapy in the management of isolated vaginal recurrences of endometrial cancer. *Int J Radiat Oncol Biol Phys.* 2005;63(2):500-504.
59. Wylie J, Irwin C, Pintilie M, et al. Results of radical radiotherapy for recurrent endometrial cancer. *Gynecol Oncol.* 2000;77(1):66-72.
60. Nag S, Gupta N. A simple method of obtaining equivalent doses for use in HDR brachytherapy. *Int J Radiat Oncol Biol Phys.* 2000;46(2):507-513.

Clinical Condition: **Adjuvant Management of Early Stage Endometrial Cancer**

Variant 1: **56-year-old woman undergoes a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and para-aortic/pelvic lymph node dissection for a grade 2 endometrial adenocarcinoma, endometrioid type, invading 12 mm of a 22-mm myometrial wall. No LVSI present. Tumor size was 4.0 cm. Para-aortic and pelvic lymph nodes were negative.**

Treatment	Rating	Comments
Adjuvant Management		
Observation	6	
Vaginal cuff brachytherapy	7	
WPRT	3	
Vaginal Brachytherapy Dose		
7 Gy × 3 prescribed to 5 mm	8	
5.5 Gy × 4 prescribed to 5 mm	7	
6 Gy × 5 to surface	7	
4 Gy × 3 prescribed to 5 mm	3	
4 Gy × 6 to surface	6	
Vaginal Length Treated if Using Vaginal Brachytherapy		
Upper 1/3	8	
Upper 1/2	7	
Upper 2/3	3	
Upper 3 cm	8	
Upper 4 cm	7	
Upper 5 cm	5	
Entire vagina	2	
Brachytherapy Planning		
2D planning with fiducial placement	7	Practice varies by institution, but treatment plans are rarely changed based on CT imaging. CT can provide more information regarding implant quality.
3D planning with CT simulation prior to each insertion	7	
3D planning with CT simulation before first insertion	7	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Adjuvant Management of Early Stage Endometrial Cancer**

Variant 2: **70-year-old woman undergoes a total abdominal hysterectomy and bilateral salpingo-oophorectomy without a pelvic lymph node dissection for a grade 2 endometrial adenocarcinoma, endometrioid type, invading 8 mm of a 15-mm myometrial wall. LVSI was present. Patient is healthy otherwise.**

Treatment	Rating	Comments
Nodal Evaluation Prior to Radiotherapy		
No lymphadenectomy	5	
No lymphadenectomy after CT or PET/CT obtained	7	
Pelvic node dissection	5	
Pelvic and para-aortic node dissection	5	
Adjuvant Management		
Observation	3	
Vaginal cuff brachytherapy	6	
WPRT	7	
WPRT with vaginal cuff brachytherapy boost	5	
Upper Field Border if Using WPRT		
Bony landmark L5-S1	7	
Bony landmark L4-L5	7	
Aortic bifurcation	7	
Common iliac bifurcation	6	
WPRT Technique if Using WPRT		
2D radiotherapy	3	
3D conformal radiotherapy	7	
IMRT	7	
Daily image guidance if using IMRT	7	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Adjuvant Management of Early Stage Endometrial Cancer**

Variant 3: **66-year-old woman undergoes a total abdominal hysterectomy and bilateral salpingo-oophorectomy with a para-aortic and pelvic lymph node dissection for a grade 3 endometrial adenocarcinoma, endometrioid type, with deep myometrial invasion (19/21 mm). No LVSI was present. Deeply invasive cervical stromal invasion was present. Margins were negative. Five left pelvic, 6 right pelvic, and 4 para-aortic lymph nodes were negative.**

Treatment	Rating	Comments
Adjuvant Management		
Observation	2	
Vaginal cuff brachytherapy	4	
WPRT alone	6	
WPRT with vaginal cuff brachytherapy boost	7	
Vaginal cuff brachytherapy with paclitaxel and carboplatin for 3 cycles	4	
Upper Field Border if Using WPRT		
Bony landmark L5-S1 or common iliac bifurcation	7	
Bony landmark L4-L5 or aortic bifurcation	7	
Vaginal Length Treated if Using Vaginal Brachytherapy		
Upper 1/3	7	
Upper 1/2	7	
Upper 2/3	4	
Entire vagina	3	
Brachytherapy Dose if Using Vaginal Cuff Boost after 50.4 Gy WPRT		
6 Gy × 2 fractions to surface	7	
6 Gy × 3 fractions to surface	6	
5.5 Gy × 2 fractions to 5 mm	5	
5.9 Gy × 3 fractions to 5 mm	3	
Simulation for WPRT		
Empty bladder	4	
Full bladder	7	
Full bladder and empty bladder fusion for ITV generation	8	
Adjuvant Chemotherapy		
Yes	5	
No	7	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		