Adjuvant Management of Early Stage Endometrial Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin.* 2015;65(1):5-29.	Review/Other-Tx	N/A	To provide the expected numbers of new cancer cases and deaths in 2015 nationally and for each state, as well as a comprehensive overview of cancer incidence, mortality, and survival rates and trends using the most current population-based data. The article also estimates the total number of deaths averted nationally during the past 2 decades and by state in 2011 as a result of the continual decline in cancer death rates and present actual number of deaths reported in 2011 by age for the 10 leading causes of death and for the 5 leading causes of cancer death.	Cancer death rates have been continuously declining for the past 2 decades. Overall, the risk of dying from cancer decreased by 22% between 1991 and 2011. Regionally, progress has been most rapid for residents of the Northeast, among whom death rates have declined by 25% to 30%, and slowest in the South, where rates declined by about 15%. Further reductions in cancer death rates can be accelerated by applying existing cancer control knowledge across all segments of the population, with an emphasis on those in the lowest socioeconomic bracket and other disadvantaged populations.	4
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.	Observational-Tx	318 cases	To prospectively examine the association between BMI and incident endometrial cancer in postmenopausal women from the United States, focusing on patterns of risk associated with never postmenopausal hormone therapy use and ever estrogen plus progestin use, location of weight deposition, and type I and type II cancers.	As expected, adult BMI was a strong predictor of risk [rate ratios, 4.70; 95% CI, 3.12–7.07 for BMI 35+ vs 22.5–25.0, *P* trend <0.0001]. Use of estrogen plus progestin postmenopausal hormone therapy modified the association. Among never-users, risk was significantly linear across the entire range of BMI examined (rate ratios, 0.51; 95% CI, 0.29–0.92 for <22.5 vs 22.5–25.0; rate ratios, 4.41; 95% CI, 2.70–7.20 for ≥35 vs 22.5–25.0, *P* trend <0.0001), but among ever estrogen plus progestin users, the association was not significant (*P* trend =1.0; *P* interaction <0.0001). We observed no difference in risk according to tendency for central vs peripheral fat deposition. Greater BMI (≥30 vs <25.0) increased risk of both "type I" (classic estrogen pathway, rate ratios, 4.22; 95% CI, 3.07–5.81) and "type II" (serous, clear cell, and all other high grade) cancers (rate ratios, 2.87; 95% CI, 1.59–5.16).	2
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.	Review/Other-Tx	N/A	To review carcinoma of the vulva.	No results reported in abstract.	4

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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.	Experimental-Tx	392 patients	To determine if adjunctive EBRT lowers the risk of recurrence and death in women with endometrial cancer International Federation of Gynecology and Obstetrics (FIGO) stages IB, IC, and II (occult disease).	392 women met all eligibility requirements (202 no additional therapy, 190 RT). Median follow-up was 69 months. In the entire study population, there were 44 recurrences and 66 deaths (32 disease or treatment-related deaths), and the estimated 2-year cumulative incidence of recurrence was 12% in the no additional therapy arm and 3% in the RT arm (relative hazard: 0.42; *P*=0.007). The treatment difference was particularly evident among the high intermediate risk subgroup (2-year cumulative incidence of recurrence in no additional therapy vs RT: 26% vs 6%; relative hazard = 0.42). Overall, radiation had a substantial impact on pelvic and vaginal recurrences (18 in no additional therapy and 3 in RT). The estimated 4-year survival was 86% in the no additional therapy arm and 92% for the RT arm, not significantly different (relative hazard: 0.86; *P*=0.557).	1
5. Price JJ, Hahn GA, Rominger CJ. Vaginal Involvement in Endometrial Carcinoma. *Am J Obstet Gynecol.* 1965;91:1060-1065.	Review/Other-Dx	N/A	To evaluate the incidence of vaginal recurrence in endometrial carcinoma, its curability, the methods of management, and prevention.	No abstract available.	4
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.	Observational-Tx	490 patients	To evaluate the contribution of multiple medical comorbidities on the OS of endometrial cancer patients.	In this study, 47% of patients had hypertension, 26% had diabetes mellitus, 11% were smokers, 64% were stage I, 39% were grade 1, and 36% received RT. The presence of diabetes mellitus and hypertension on univariate analysis resulted in decreased survival with [HR 1.70; 95% CI, 1.18–2.46] and (HR 1.66; 95% CI, 1.17–2.36), respectively. On multivariate analysis after correction for stage, age, and grade, diabetes mellitus and hypertension continued to show a reduced survival rate (HR 1.58; 95% CI, 1.07–2.33 and HR 1.51; 95% CI, 1.06–2.15, respectively). BMI, smoking, parity, age at menarche, and years of estrogen exposure did not affect survival before or after correction for stage, age, and grade.	3

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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.	Observational-Tx	271 black women and 356 white women	To evaluate the role of comorbid conditions as modifiers of endometrial cancer survival by race.	Black women experienced a higher hazard of death from any cause (HR 1.51; 95% CI, 1.22–1.87) and from endometrial cancer (HR, 2.42; 95% CI, 1.63–3.60). After adjustment for known clinical prognostic factors and comorbid conditions, the hazard of death for black women was elevated but no longer statistically significant for OS (HR, 1.22; 95% CI, 0.94–1.57), and the hazard of death from endometrial cancer remained significantly increased (HR, 2.27; 95% CI, 1.39–3.68). Both black and white women with a history of hypertension experienced a lower hazard of death from endometrial cancer (HR, 0.47; 95% CI, 0.23–0.98; and HR, 0.35; 95% CI, 0.19–0.67, respectively).	2
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.	Observational-Tx	401 patients	To evaluate the effect of age and comorbidity on endometrial cancer treatment and outcome.	Median follow-up time was 7.8 years. In this cohort, 148 (37%), 152 (38%), and 101 (25%) were aged <65, 65–74, and ≥75 years, respectively. Charlson comorbidity scores ≥2 were found in 18% of patients. Distributions of disease stage, tumor characteristics, and surgical therapy were similar across age and comorbidity subgroups. Standard surgery in this cohort comprised hysterectomy without routine lymphadenectomy. In stage Ic disease, the use of postoperative RT declined with advanced age (96%, 97%, and 74% in patients aged <65, 65–74, and ≥75 years, respectively, P=0.05) and with increased comorbidities (91% and 79% in patients with Charlson score 0–1 and ≥2, respectively, P=0.07). Among stage Ic patients aged ≥75 years, pelvic/vaginal relapse occurred in 2 of 6 patients treated with hysterectomy alone compared with 0 of 20 patients treated with postoperative RT (P=0.006). On multivariable Cox modeling, age at diagnosis, performance status, stage, grade, lymphovascular invasion, surgery, and RT use, but not Charlson comorbidity score, were significant predictors for OS.	2

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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.	Observational-Tx	33,232 women	To evaluate the causes of death among women with endometrial cancer.	33,232 women with incident cases of endometrial cancer had died at the time of last follow-up. Overall, women were most likely to die from cardiovascular disease (35.9%, 95% CI, 35.3%–36.3%), followed by other causes, other malignancies, and endometrial cancer. Women with low grade localized cancer were most likely to die of cardiovascular disease, while women with high grade advanced cancer were least likely to die of cardiovascular disease and most likely to die of endometrial cancer. For the entire population, risk of death from cardiovascular causes surpasses the risk of death from endometrial cancer 5 years after diagnosis.	2
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.	Observational-Dx	490 cases	To compare the accuracy of D&C vs office endometrial biopsy in predicting final post-hysterectomy FIGO grade in patients diagnosed with a preoperative FIGO grade 1 endometrial adenocarcinoma.	We identified 490 cases with a preoperative FIGO grade 1 endometrial adenocarcinoma. In 482 cases, FIGO grade was determined to be greater in 71 (14.7%) cases; in the final hysterectomy specimen, 66 (13.7%) were found to be grade 2 and 5 (1%) were found to be grades 2-3/3. Serous or clear cell histology was diagnosed in 6 (1.2%) additional cases. D&C was performed in 187 (38.6%) cases and office endometrial sampling in 298 (61.4%); in 5 cases the method used was not discernible. The final post-hysterectomy FIGO grade was higher in 16/187 (8.7%) cases diagnosed by D&C compared to 52/298 (17.4%) diagnosed by office endometrial sampling (P=0.007).	3
11. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet.* 2009;105(2):103-104.	Review/Other-Tx	N/A	A consensus document on revised FIGO staging for carcinoma of the vulva, cervix, and endometrium.	No results stated in abstract.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	883 patients	To develop a risk-scoring system for the prediction of lymphatic dissemination after hysterectomy in endometrioid endometrial carcinoma.	Overall, 883 patients were assessed of which 521 (59.0%) underwent pelvic and/or para-aortic lymphadenectomy and 57 (10.9%) had positive lymph nodes. Of patients who did not undergo pelvic and/or para-aortic lymphadenectomy (N=362) or had negative nodes (N=464), 10 (1.2%) patients had pelvic and/or para-aortic lymph node recurrence. Myometrial invasion, tumor diameter, FIGO grade, cervical stromal invasion and lymphovascular space invasion were significant on univariable analysis. All preceding variables were included in a multivariable logistic model. A parsimonious model and an alternative full model not including tumor diameter were considered. The full model with tumor diameter (illustrated in nomogram) had the highest predictive ability (concordance index 0.88).	2
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.	Observational-Tx	621 patients	To report the surgical pathologic findings and their correlation in a group-wide prospective study.	All patients were treated with primary surgery consisting of total abdominal hysterectomy, bilateral salpingo-oophorectomy, selective pelvic and para-aortic lymphadenectomy and peritoneal cytology. An appreciable number of patients (144%–22%) with stage I cancers have disease outside of the uterus (lymph node metastasis, adnexal disease, intraperitoneal spread and/or malignant cells in peritoneal washings). Multiple prognostic factors particularly grade and depth of invasion are related to extrauterine disease.	2
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.	Observational-Tx	819 patients	To examine a variety of pathologically defined risk factors by univariate analysis.	We confirmed the importance of age, depth of myometrial invasion, and to a lesser degree, histologic grade, and cell type, as independent prognostic variables.	2

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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.	Experimental-Tx	645 patients	To compare postoperative vaginal irradiation with surgery alone in low-risk FIGO stage IA-IB endometrial carcinoma.	A total of 319 patients were treated with surgery plus vaginal irradiation (treatment group), and 326 patients with surgery alone (control group).26 recurrences (4.0%) were recorded in the complete series. The locoregional recurrence rate was 2.6%, whereas distant metastases occurred in 1.4%. The rate of vaginal recurrences was 1.2% in the treatment group vs 3.1% in the control group. The difference was not statistically significant (P=0.114). Side effects were few and mild (grade 1-2). Dysuria, frequency, and incontinence were slightly more common after vaginal irradiation (2.8% vs 0.6%, respectively). Late intestinal problems were few and similar in the 2 groups.	1
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.	Experimental-Tx	290 patients	To compare 2 different fractionation schedules for postoperative vaginal HDR irradiation in endometrial carcinomas.	The overall locoregional recurrence rate of the complete series was 1.4% and the rate of vaginal recurrences 0.7%. There was no difference between the 2 randomized groups. The vaginal shortening measured by colpometry was not significant (P=0.159) in the 2.5-Gy group (mean, 0.3 cm) but was highly significant (P<0.000001) in the 5.0-Gy group (mean 2.1 cm) after 5 years. Mucosal atrophy and bleedings were significantly more frequent in the 5.0-Gy group. Symptoms noted in the 2.5-Gy group were not different from what could be expected in a normal group of postmenopausal women.	1

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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.	Experimental-Tx	427 patients	To compare outcomes and adverse effects after VBT and EBRT, and to establish optimum adjuvant treatment for patients with endometrial carcinoma of high-intermediate risk.	At median follow-up of 45 months (range 18–78), 3 vaginal recurrences had been diagnosed after VBT and 4 after EBRT. Estimated 5-year rates of vaginal recurrence were 1.8% (95% CI, 0.6–5.9) for VBT and 1.6% (0.5–4.9) for EBRT (stage HR 0.78, 95% CI, 0.17–3.49; *P*=0.74). 5-year rates of locoregional relapse (vaginal or pelvic recurrence, or both) were 5.1% (2.8–9.6) for VBT and 2.1% (0.8–5.8) for EBRT (HR 2.08, 0.71–6.09; *P*=0.17). 1.5% (0.5–4.5) vs 0.5% (0.1–3.4) of patients presented with isolated pelvic recurrence (HR 3.10, 0.32–29.9; *P*=0.30), and rates of distant metastases were similar (8.3% [5.1–13.4] vs 5.7% [3.3–9.9]; HR 1.32, 0.63–2.74; *P*=0.46). We recorded no differences in OS (84.8% [95% CI, 79.3–90.3] vs 79.6% [71.2–88.0]; HR 1.17, 0.69–1.98; *P*=0.57) or DFS (82.7% [76.9–88.6] vs 78.1% [69.7–86.5]; HR 1.09, 0.66–1.78; *P*=0.74). Rates of acute grade 1-2 gastrointestinal toxicity were significantly lower in the VBT group than in the EBRT group at completion of RT (12.6% [27/215] vs 53.8% [112/208]).	1
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.	Observational-Tx	157 patients	To evaluate LC, survival and toxicity in patients with early-stage endometrioid adenocarcinoma of the uterus treated with adjuvant HDR VBT alone using a novel low dose regimen.	All 157 patients completed the prescribed course of VBT. Median follow-up time was 22.8 months (range, 1.5–76.5). 2 patients developed vaginal recurrence, 1 in the periurethral region below the field and 1 in the fornix after treatment with a 2.5-cm cylinder. 3 patients developed regional recurrence in the para-aortic region. 2 patients developed distant metastasis (lung and carcinomatosis). The 2-year rate of vaginal control was 98.6%, locoregional control was 97.9% and DFS was 96.8%. The 2-year OS rate was 98.7%. No Grade 2 or higher vaginal, gastrointestinal, genitourinary or skin long-term toxicity was reported for any patient.	3

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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.	Review/Other-Tx	N/A	To develop recommendations for the use of adjuvant vaginal cuff brachytherapy after hysterectomy and update previous American Brachytherapy Society (ABS) guidelines.	The ABS endorses the National Comprehensive Cancer Network guidelines for indications for RT for patients with endometrial cancer and cervical cancer and the guidelines on quality assurance of the American Association on Physicists in Medicine. The ABS made specific recommendations for applicator selection, insertion techniques, target volume definition, dose fractionation, and specifications for postoperative adjuvant vaginal cuff therapy. The ABS recommends that applicator selection should be based on patient anatomy, target volume geometry, and physician judgment. The dose prescription point should be clearly specified. Suggested doses were tabulated for treatment with brachytherapy alone, and in combination with EBRT, when applicable. A properly fitted brachytherapy applicator should be selected that conforms to the vaginal apex and achieves mucosal contact with optimal tumor and normal tissue dosimetry. Dose prescription points may be individually selected but doses should be reported at the vaginal surface and at 0.5-cm depth.	4

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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.	Observational-Tx	252 patients	To assess the clinical outcomes of patients with Stage IA endometrial cancer with myometrial invasion treated with postoperative VBT with those who received no adjuvant therapy.	Of 252 patients with Stage IA endometrial cancer with superficial (<50%) myometrial invasion who met the inclusion criteria, 169 underwent VBT and 83 received no adjuvant therapy. The median follow-up in the VBT and no adjuvant therapy groups was 103 and 61 months, respectively. In the VBT group, 56.8% had Grade 1, 37.9% had Grade 2, and 5.3% had Grade 3 tumors. In the no adjuvant therapy group, 75.9%, 20.5%, and 3.6% had Grade 1, 2, and 3 tumors, respectively. Lymphatic or vascular space invasion was noted in 12.4% of the VBT patients and 5.6% of the no adjuvant therapy patients. The 5-year overall survival rate was 95.5%. The 5-year recurrence-free survival rate was 92.4% for all patients, 94.4% for the VBT group, and 87.4% for the no adjuvant therapy group (*P*=NS). Of the 169 VBT patients and 83 no adjuvant therapy patients, 8 (4.7%) and 6 (7.2%) developed recurrent disease. One vaginal recurrence occurred in the VBT group (0.6%) and 3 in the no adjuvant therapy group (3.8%). Recurrences developed 2–102 months after surgical treatment. 2 of the 4 vaginal recurrences were salvaged. No Grade 3 or higher acute or late radiation toxicity was noted.	2
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.	Observational-Tx	45 slides: 31 patients, 2 autopsy specimens	To examine the depth distribution of lymphatics lying beneath the mucosal surface of the vagina.	For the nonstretched samples, the percentages of lymphatics located within 1, 1–2, 2–3, and 3–4 mm were 50.5%, 30.7%, 11.9%, and 6.9%, respectively. For the stretched samples, the percentages of lymphatics located within 1, 1–2, 2–3, and 3–4 mm were 44.0%, 33.8%, 18.8%, and 3.4%, respectively. The differences of lymphatic percentages within and superficial to 1 mm (*P*=0.60), 1–2 mm (*P*=0.85), 2–3 mm (*P*=0.89), and 3–4 mm (*P*=0.99) were not statistically significant between the stretched and nonstretched states.	2

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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.	Observational-Tx	331 respondents	To report current practice patterns for postoperative endometrial cancer emphasizing VBT.	A total of 331 respondents initiated the VBT survey, of whom 289 (87.3%) administered VBT in the prior 12 months. Lymph node dissection and number of nodes removed influenced treatment decisions for 90.5% and 69.8%, respectively. High-dose-rate was used by 96.2%. The most common vaginal length treated was 4 cm (31.0%). 3D planning was used by 83.2% with 73.4% of those for the first fraction only. Doses to normal tissues were reported by 79.8%. About half optimized to the location of dose specification and/or normal tissues. As monotherapy, the most common prescriptions were 7 Gy for 3 fractions to 0.5-cm depth and 6 Gy for 5 fractions to the surface. As a boost, the most common prescriptions were 5 Gy for 3 fractions to 0.5-cm depth and 6 Gy for 3 fractions to the vaginal surface. Optimization points were placed at the apex and lateral vagina by 73.1%. Secondary quality assurance checks were performed by 98.9%.	3
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.	Observational-Tx	102 patients	To evaluate the effectiveness of postoperative HDR vaginal cuff irradiation alone (1500 cGy in 3 fractions) in patients with stage Ib and Ic endometrial cancer.	The 5-year actuarial OS is 84% and the 5-year DFS is 93%. Locoregional disease control (pelvic control) was excellent with 97% of the patients free of pelvic disease at 5 years. Of the 3 pelvic failures only 1 was in the vaginal cuff. Lymphovascular invasion, lower uterine segment involvement, Grade 3 and/or outer third myometrial involvement were identified in 41 patients. 31 of these patients underwent a lymphadenectomy and there were 2 regional failures within this increased-risk group.	2

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24. Chong I, Hoskin PJ. Vaginal vault brachytherapy as sole postoperative treatment for low-risk endometrial cancer. *Brachytherapy.* 2008;7(2):195-199.	Observational-Tx	173 patients	To evaluate the efficacy and side effect profile of adjuvant vaginal vault brachytherapy alone after hysterectomy in stage I endometrial carcinoma.	There were 19 deaths in this series, 6 (3.5%) from disseminated endometrial cancer and 13 (7.5%) from unrelated causes. High-risk features of stage 1C, Grade G3, or clear cell histology were present in all 6 patients who developed metastatic disease. One patient developed a local recurrence alone, which was salvaged with EBRT. The low-risk group defined by stage 1B and G1 or G2 did not develop distant relapse in this series. Late morbidity was rare except for vaginal stenosis seen in 13%.	2
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.	Observational-Tx	66 patients	To determine long-term survival and late complications of intermediate risk endometrial cancer (stage IG3, IC, and II) treated with full lymphadenectomy and brachytherapy without teletherapy.	At a mean follow-up of 4.4 years, Kaplan-Meier estimated 5-year PFS is 97%. 2 patients (3%) developed distant recurrence (abdomen, lungs) with no vaginal or pelvic recurrence. Major complications occurred in 6% of patients.	2
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.	Observational-Tx	87 patients	To review our outcomes among high risk patients defined according to the PORTEC, GOG 99, and/or Aalders randomized trials of pelvic radiation vs observation to determine if acceptable rates of locoregional control could be achieved with VBT alone in this highest risk patient population.	Among 87 high risk patients treated with VBT alone, 36, 77, and 14 were high risk per PORTEC, GOG 99, and Aalders respectively. 40 (46%) underwent pelvic lymph node dissection. With a median follow-up of 52 months, 3 (3.4%) pelvic recurrences were observed including 1 vaginal recurrence, 1 pelvic recurrence, and 1 local recurrence involving both the vagina and pelvis. All 3 local recurrences were successfully salvaged with pelvic RT+/-surgery.	2

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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.	Experimental-Tx	527 patients	To evaluate the value of adjuvant EBRT as adjunct to VBT in medium-risk endometrial carcinoma, with regard to locoregional tumor control, recurrences, survival, and toxicity.	5-year locoregional relapse rates were 1.5% after EBRT plus VBT and 5% after vaginal RT alone (P=0.013), and 5-year OS rates were 89% and 90%, respectively (P=0.548). Endometrial cancer-related death rates were 3.8% after EBRT plus VBT and 6.8% after VBT (P=0.118). Pelvic recurrences (exclusively vaginal recurrence) were reduced by 93% by the addition of EBRT to VBT. Deep myometrial infiltration was a significant prognostic factor in this medium-risk group of endometrioid carcinomas but not FIGO grade or DNA ploidy. Combined RT was well tolerated, with serious (Grade 3) late side effects of < 2%. However, there was a significant difference in favor of VBT alone.	1
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.	Experimental-Tx	540 patients	To evaluate the effect of postoperative external pelvic irradiation.	During the follow-up period of 3 to 10 years a significant reduction in vaginal and pelvic recurrences was found in group B as compared with group A (1.9 vs 6.9%, P<.01). On the other hand, more patients in group B developed distant metastases than those in group A (9.9 vs 5.4%). Thus, the 5-year survival rate was not improved by external irradiation. A more detailed analysis of the series led to the conclusion that only patients with poorly differentiated tumors (grade 3), which infiltrate more than half the myometrial thickness, might benefit from additional external RT. In almost 20% of 151 consecutive patients, tumor cells were found in endothelial lined spaces. Significantly more deaths and recurrences were found among these patients compared to those without vessel invasion (26.7 vs 9.1%, P<.01).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Meta-analysis	ASTEC/EN. 5-905 GOG-392 PORTEC-714	To report the findings from the ASTEC and EN.5 trials, which investigated adjuvant EBRT in women with early-stage disease and pathological features suggestive of intermediate or high risk of recurrence and death from endometrial cancer.	After a median follow-up of 58 months, 135 women (68 observation, 67 EBRT) had died. There was no evidence that OS with EBRT was better than observation, HR 1.05 (95% CI 0.75-1.48; *P*=0.77). 5-year OS was 84% in both groups. Combining data from ASTEC and EN.5 in a meta-analysis of trials confirmed that there was no benefit in terms of OS (HR 1.04; 95% CI 0.84–1.29) and can reliably exclude an absolute benefit of EBRT at 5 years of more than 3%. With brachytherapy used in 53% of women in ASTEC/EN.5, the local recurrence rate in the observation group at 5 years was 6.1%.	M
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.	Experimental-Tx	714 patients	A multicenter prospective randomized trial to find whether postoperative pelvic RT improves locoregional control and survival for patients with stage 1 endometrial carcinoma.	The median duration of follow-up was 52 months. 5-year actuarial locoregional recurrence rates were 4% in the RT group and 14% in the control group (*P*<0.001). Actuarial 5-year OS rates were similar in the 2 groups: 81% (RT) and 85% (controls), *P*=0.31. Endometrial-cancer-related death rates were 9% in the RT group and 6% in the control group (*P*=0.37). Treatment-related complications occurred in 25% of RT patients, and in 6% of the controls (*P*<0.0001). Two-thirds of the complications were grade 1. Grade 3-4 complications were seen in 8 patients, of which 7 were in the RT group (2%). 2-year survival after vaginal recurrence was 79%, in contrast to 21% after pelvic recurrence or distant metastases. Survival after relapse was significantly (*P*=0.02) better for patients in the control group. Multivariate analysis showed that for locoregional recurrence, RT and age below 60 years were significant favorable prognostic factors.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	1,240 patients for training set; 244 and 291 patients in the validation sets	To develop treatment decision support nomograms, including outcomes with and without adjuvant treatment.	Accuracy of the developed models was good, with training accuracies between 0.71 and 0.78. The nomograms validated well for distant relapse (0.73), DFS (0.69), and OS (0.70), but validation was only fair for locoregional relapse (0.59). Ranking of variables as to their predictive power showed that age, tumor grade, and lymph-vascular invasion were highly predictive for all outcomes, and given treatment for locoregional relapse and DFS. The nomograms were able to significantly distinguish low- from high-probability patients for these outcomes.	2
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.	Experimental-Tx	444 patients	To determine the rates of relapse and survival for the registered patients with stage IC, grade 3 disease and focuses on the comparison of their outcome with that of the patients randomly assigned to treatment in the PORTEC trial.	The actuarial 5-year rates of locoregional relapse were 1% to 3% for PORTEC patients who received RT, compared with 14% for stage IC, grade 3 patients. 5-year distant metastases rates were 3% to 8% for grade 1 and 2 tumors; 20% for stage IB, grade 3 tumors; and 31% for stage IC, grade 3 tumors. OS rates were 83% to 85% for grades 1 and 2; 74% for stage IB, grade 3; and 58% for stage IC, grade 3 patients (P<.001). In multivariate analysis grade 3 was the most important adverse prognostic factor for relapse and death as a result of endometrial cancer (HRs, 5.4 and 5.5; P<.0001).	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	21,249 patients	To evaluate the frequency and effect of adjuvant RT on OS and relative survival within a large U.S. population database.	Of 21,249 women, 4,080 received adjuvant RT (19.2%) and 17,169 did not receive adjuvant RT (80.8%). The mean age at diagnosis was 63.2 years (range, 14–99 years). Adjuvant RT significantly improved OS for patients with stage IC/grade 1 (P<.001) and stage IC/grades 3 and 4 (P<.001). Cox proportional hazards regression analysis revealed a statistically detectable association of adjuvant RT with improved relative survival in patients with stage IC/grade 1 and stage IC/grades 3 and 4 (HR, 0.44; 95% CI, 0.31–0.63; P<.001; and HR, 0.72; 95% CI, 0.57–0.92; P=.009; respectively). A separate analysis of those patients with a surgical lymph node examination at the time of total abdominal hysterectomy and bilateral salpingo-oophorectomy revealed similar estimates (HR, 0.59; 95% CI, 0.39–0.90; P=.01; and HR, 0.73; 95% CI, 0.55–0.96; P=.02; respectively).	2
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.	Experimental-Tx	348 responders	To evaluate long-term health related quality of life), and compare health related quality of life of patients to an age-matched norm population.	Median follow-up was 65 months; 348 (81%) patients were evaluable for health related quality of life (EBRT n=166, VBT n=182). At baseline, patient functioning was at lowest level, increasing during and after RT to reach a plateau after 12 months, within range of scores of the norm population. VBT patients reported better social functioning (P=0.005) and lower symptom scores for diarrhea, fecal leakage, need to stay close to a toilet and limitation in daily activities due to bowel symptoms (P=0.001), compared to EBRT. There were no differences in sexual functioning or symptoms between the treatment groups; however, sexual functioning was lower and sexual symptoms more frequent in both treatment groups compared to the norm population.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	15 women with cervical (9) or endometrial (6) cancer received IM-WPRT; 25 patients treated with conventional WPRT	To describe initial experience with IM-WPRT in gynecologic malignancies.	IM-WPRT plans provided excellent coverage of the target structures in all patients and were highly conformal, providing considerable sparing of the bladder, rectum, and small bowel. Treatment was well tolerated, with grade 0-1 gastrointestinal and genitourinary toxicity in 46% and 93% of patients, respectively. IM-WPRT patients had a lower rate of grade 2 gastrointestinal toxicity (53.4% vs 96%, P=0.001) than those treated with conventional WPRT. Moreover, the percentage of women requiring no or only infrequent antidiarrheal medications was lower in the IM-WPRT group (73.3% vs 20%, P=0.001).While grade 2 genitourinary toxicity was also lower in the IM-WPRT patients (6.7% vs 16%), this difference did not reach statistical significance (P=0.38).	2
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.	Observational-Tx	34 patients	To evaluate the impact of inadequate margins on pelvic control using the conventional four-field pelvic portals without CT-treatment planning.	All 34 patients had adequate margins for anterio-posterior/posterio-anterior portals. However, 19 patients had an inadequate margin at the posterior border (S2-S3 interspace) and/or custom-shaped rectal block for lateral pelvic portals. 2 patients had inadequate margins at the anterior border (level of symphysis pubis) due to an enlarged uterus. With a median follow-up of 36 months, pelvic control for adequate margins and inadequate margins was 100% and 71% for stage IB disease and 88% and 50% for stage IIB disease, respectively. However, pelvic control for stage IIIB disease was 50% for both groups. There was no difference in total dose to point A or point B between the 2 groups.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Dx	22 patients	To determine if bony landmarks could accurately substitute for lymphangiography as a means of determining lymph node position for the purpose of pelvic RT treatment planning.	On A/P simulation films, the distance of visualized lymph nodes had mean values of -1.6 +/- 1.7 cm (range -4.1 to -0.4 cm), -1.3 +/- 1.5 cm (range -3.4 to 0.0 cm), and 1.2 +/- 1.8 cm (range -1.0 to 2.6 cm) from the sacro-iliac joint at the superior, middle, and inferior points, respectively. The mean distance of the nodes from the pelvic rim at points 1 and 2 cm above the acetabulum was 0.3 +/- 1.2 cm (range -0.6 to 1.8 cm) and 0.2 +/- 1.8 cm (range -1.6 to 2.1 cm), respectively. On LAT simulation films, the distance of lymph nodes from points 0, 4, and 8 cm from the previously described reference line had mean values of 2.0 +/- 1.0 cm (range 1.3 to 3.0 cm), 0.9 +/- 3.9 cm (range -1.9 to 5.1 cm), and 1.8 +/- 2.1 cm (range -0.8 to 3.5 cm), respectively. 10 of 22 (45%) patients would have had inadequate nodal irradiation if their fields had been designed according to standard GOG parameters. In all cases, these incompletely irradiated lymph nodes were from the lowest of the lateral external iliac group.	3
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.	Experimental-Tx	47 patients	To assess LC and chronic toxicity with IMRT for adjuvant treatment of endometrial carcinoma.	IMRT dosimetry showed excellent coverage of the PTV with mean PTV 95, PTV 110 and PTV 120 of 97.8%, 8.2% and 0.9% respectively. At a median follow-up of 20 months, 4 patients have recurred at extra pelvic sites. No patient had pelvic recurrence. The treatment was well tolerated with late toxicities as follows: small bowel grade 1: 25%, rectal grade 1: 2% and bladder grade 1: 13%. One patient had grade 3 small bowel toxicity. The 3-year actuarial rate of grade 2 or greater toxicity, DFS and OS rate were 3.3%, 84% and 90%, respectively.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	10 patients	To evaluate the feasibility of pelvic IMRT in the adjuvant treatment of gynecologic malignancies and to compare the dose-volume histograms and determine the potential impact on acute and long-term toxicity based on the dose to target and nontarget tissues for both planning techniques.	The volume of each organ of interest (small bowel, bladder, and rectum) receiving doses in excess of 30 Gy was compared in the 3D and IMRT treatment plans. The mean volume of small bowel receiving doses in excess of 30 Gy was reduced by 52% with IMRT compared with 3D. A similar advantage was noted for the rectum (66% reduction) and the bladder (36% reduction). The nodal regions at risk and the upper vagina all received the prescribed dose of 45.0 Gy.	3
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.	Experimental-Tx	31 patients	To present a preliminary analysis of our experience using adjuvant IMRT in endometrial cancer patients assessing tumor control.	All IMRT plans were highly conformal, with excellent PTV coverage and considerable sparing of the small bowel, bladder and rectum. At a median follow-up of 24 months (range, 5.4–44.6 months), 5 patients (16.1%) have recurred, for a 3-year actuarial DFS of 80.6%. The most significant factor correlated with relapse was histology. Patients with unfavorable histologies had a worse 3-year DFS (P=0.04) than those with adenocarcinomas. All 5 patients who recurred failed in extra-pelvic sites. No patient recurred in the pelvis/vagina. Treatment was well tolerated with no patient developing grade 2 or greater chronic sequelae. 6 patients (19%) developed grade 1 toxicity, predominantly mild diarrhea with select foods. One patient with a history of multiple abdominal surgeries developed an upper abdominal small bowel obstruction outside the irradiated field requiring surgery.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	10 patients	To evaluate the ability of IMRT to reduce the volume of small bowel irradiated in women with gynecologic malignancies receiving WPRT.	The IM-WPRT plan reduced the volume of small bowel irradiated in all 10 patients at doses above 30 Gy. At the prescription dose, the average volume of small bowel irradiated was reduced by a factor of 2 (17.4 vs 33.8%, P=0.0005). In addition, the average volume of rectum and bladder irradiated at the prescription dose was reduced by 23% in both cases (P=0.0002 and P=0.0005, respectively). The average PTV doses delivered by the conventional and IM-WPRT plans were 47.8 Gy and 47.4 Gy, respectively. Corresponding maximum doses were 50.0 Gy and 54.8 Gy, respectively. However, on average, only 3.2% of the PTV received greater than 50.0 Gy in the IM-WPRT plans.	2
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.	Observational-Tx	1,179 patients	To compare the outcomes for endometrial carcinoma patients treated with either HDR or LDR brachytherapy.	For all stages combined, the OS, DFS, and LC at 5 years in the LDR group were 70%, 69%, and 81%, respectively. For all stages combined, the OS, DFS, and LC at 5 years in the HDR group were 68%, 62%, and 78%, respectively. There were no significant differences in early or late Grade 3 and 4 complications in the HDR or LDR groups.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	295 patients	To evaluate the long-term control of disease and cure rate, complications, second malignancy, and survival of early-stage endometrial cancer patients treated with surgery, HDR brachytherapy, and EBRT.	The patients were followed for 5–24 years (median 12). The actuarial PFS rate was 96.6%. Post-treatment grade 1-2 actuarial complication rate was 9.5%, including cystitis (4.5%), vaginal stenosis (2.5%), proctitis (1.5%), vaginal necrosis (0.5%), and partial bowel obstruction (0.5%). Neither grade 3-4 complications nor additional late complications were observed in any of our patients. Relapse rate was only 3.7%, of which 45.5% were local, 45.5% were distant, and 9% were mixed. All the patients with relapse were postmenopausal, age range of 58–77 years, with tumor grade 2-3 in 64%. Second primary cancer rate was 12.8% (mostly breast and colon). Factors that were associated with improved prognosis were young age, premenopausal, low grade, no extrauterine disease, and a histology of adenocarcinoma (adenocarcinoma with squamous metaplasia).	2
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.	Observational-Tx	270 patients	To review the role of brachytherapy VCB in patients who have uterine-confined endometrial cancer with prognostic factors predictive of recurrence and treated with adjuvant pelvic radiation.	Chi-square analysis revealed that the only difference between the 2 groups was the presence of more stage II patients in group B (38% vs 14%). No difference was detected for 5 year pelvic control and DFS rates between groups A and B.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	154 patients	To assess the effects on LC and complication rates of an intracavitary VCB given after EBRT.	102 Group I and 52 Group II patients were evaluable for analysis. Median follow-up was 78.0 months for Group I and 60.0 months for Group II. Despite a preponderance of poor prognostic factors in Group II, no significant difference in local failure was seen. A component of local failure was seen in 6 Group I patients (6.0%) and 4 Group II patients (7.7%), *P*=0.74. Distant failure, reflecting more advanced disease, was higher in Group II (19.2%) than in Group I (9.0%). Late complications included rectal bleeding/proctitis in 18.6% of Group I patients and 3.8% of Group II patients (*P*=0.01). Overall, grade 2 complications occurred in 27.5% and 15.4% of Group I and II patients, respectively (*P*=0.09). No difference in frequency of grade 3 complications was evident.	2
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.	Observational-Tx	43 patients	To determine the feasibility of pelvic IMRT for patients with endometrial cancer in a multi-institutional setting and to determine whether this treatment is associated with fewer short-term bowel adverse events than standard RT.	58 patients were accrued by 25 institutions; 43 were eligible for analysis. 42 patients (98%) had an acceptable IMRT plan; 1 had an unacceptable variation from the prescribed dose to the nodal PTV. The proportions of cases in which doses to critical normal structures exceeded protocol criteria were as follows: bladder, 67%; rectum, 76%; bowel, 17%; and femoral heads, 33%. 12 patients (28%) developed grade ≥2 short-term bowel adverse events.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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].	Experimental-Tx	30 patients	To assess acute and late adverse events, OS, pelvic failure, regional failure, distant failure, and DFS in a prospective phase 2 clinical trial of bevacizumab and pelvic IMRT with chemotherapy in patients with high-risk endometrial cancer.	A total of 34 patients were accrued from November 2009 through December 2011, 30 of whom were eligible and received study treatment. 7 of 30 patients (23.3%; 1-sided 95% CI, 10.6%–36.0%) developed grade ≥3 treatment-related nonhematologic toxicities within 90 days; an additional 6 patients experienced grade ≥3 toxicities between 90 and 365 days after treatment. The 2-year OS rate was 96.7% and the DFS rate was 79.1%. No patient developed a within-field pelvic failure and no patients with FIGO stage I to IIIA disease developed disease recurrence after a median follow-up of 26 months.	2
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.	Review/Other-Tx	N/A	To review the data, rationale, and recommendations of VBT in the post-operative treatment of endometrial cancer patients.	VBT for the adjuvant treatment of early stage endometrial cancer patients results in a low rate of recurrence (0%–3.1%) with very low rates of toxicity. PORTEC-2 supports the use of adjuvant VBT vs EBRT specifically for high-intermediate risk endometrial cancer patients. VBT has low rates of acute and chronic gastrointestinal and genitourinary toxicity and very low rates of second primary malignancy. The primary toxicity of VBT is vaginal atrophy and stenosis with controversy regarding the use of vaginal dilators for prevention. Data support that patients prefer to be involved in the decision making process for their adjuvant therapy, and patients have a lower minimal desired benefit of adjuvant VBT than do physicians. Guidelines exist from the ABS and American Society of Radiation Oncology with support from the Society for Gynecologic Oncologists regarding the use of adjuvant VBT.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	N/A	To present evidence-based guidelines for adjuvant radiation in the treatment of endometrial cancer.	Patients with grade 1 or 2 cancers with either no invasion or <50% myometrial invasion, especially when no other high risk features are present, can be safely observed after hysterectomy. Vaginal cuff brachytherapy is as effective as pelvic RT at preventing vaginal recurrence for patients with grade 1 or 2 cancers with ≥50% myometrial invasion or grade 3 tumors with <50% myometrial invasion. Patients with grade 3 cancer with ≥50% myometrial invasion or cervical stroma invasion may benefit from pelvic radiation to reduce the risk of pelvic recurrence. There is limited evidence for a benefit to vaginal cuff brachytherapy following pelvic radiation. Multimodality treatment is recommended for patients with positive nodes or involved uterine serosa, ovaries or fallopian tubes, vagina, bladder, or rectum.	4
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.	Observational-Tx	130 patients	To investigate prognostic factors, recurrence patterns and survival endpoints in this group of patients.	Median follow-up was 44 months. 120 patients (92%) underwent simple hysterectomy, 78% had lymph node dissection and 95% had peritoneal cytology examination. 99 patients (76%) received adjuvant RT. 5-year recurrence-free survival, disease-specific survival, and OS rates were 77%, 90%, and 72%, respectively. On multivariate analysis of recurrence-free survival, adjuvant RT, the presence of lymphovascular space invasion and high tumor grades were significant predictors. For disease-specific survival, lymphovascular space invasion and high tumor grades were significant predictors while older age and high tumor grade were the only predictors of OS.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	534 patients	Two randomized clinical trials (NSGO-EC-9501/EORTC-55991 and MaNGO ILIADE-III) were undertaken to clarify if sequential combination of chemotherapy and RT improves PFS in high-risk endometrial cancer.	In the NSGO/EORTC study, the combined modality treatment was associated with 36% reduction in the risk for relapse or death (HR 0.64, 95% CI, 0.41–0.99; *P*=0.04); two-sided tests were used. The result from the Gynaecologic Oncology group at the Mario Negri Institute (MaNGO)-study pointed in the same direction (HR 0.61), but was not significant. In the combined analysis, the estimate of risk for relapse or death was similar but with narrower confidence limits (HR 0.63, CI 0.44–0.89; *P*=0.009). Neither study showed significant differences in the OS. In the combined analysis, OS approached statistical significance (HR 0.69, CI 0.46–1.03; *P*=0.07) and cancer-specific survival was significant (HR 0.55, CI 0.35–0.88; *P*=0.01).	4
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.	Experimental-Tx	385 patients	To establish an optimal adjuvant therapy for intermediate- and high-risk endometrial cancer patients, we conducted a multi-center randomized phase III trial of adjuvant pelvic RT vs cyclophosphamide-doxorubicin-cisplatin chemotherapy in women with endometrioid adenocarcinoma with deeper than 50% myometrial invasion.	No statistically significant differences in PFS and OS were observed. The 5-year PFS rates in the pelvic RT and cyclophosphamide-doxorubicin-cisplatin groups were 83.5% and 81.8% respectively, while the 5-year OS rates were 85.3% and 86.7% respectively. These rates were also not significantly different in a low- to intermediate-risk group defined as stage IC patients under 70 years old with G1/2 endometrioid adenocarcinoma. However, among 120 patients in a high- to intermediate-risk group defined as (1) stage IC in patients over 70 years old or with G3 endometrioid adenocarcinoma or (2) stage II or IIIA (positive cytology), the cyclophosphamide-doxorubicin-cisplatin group had a significantly higher PFS rate (83.8% vs 66.2%, log-rank test *P*=0.024, HR 0.44) and higher OS rate (89.7% vs 73.6%, log-rank test *P*=0.006, HR 0.24). Adverse effects were not significantly increased in the cyclophosphamide-doxorubicin-cisplatin group vs the pelvic RT group.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	345 patients	To assess whether adjuvant chemotherapy confers an advantage for OS and PFS and on the incidence of local and distant relapses over standard pelvic RT, in high-risk patients without residual tumor.	Patients with high-risk endometrial carcinoma were randomly assigned to adjuvant chemotherapy (cisplatin (50 mg m(-2)), doxorubicin (45 mg m(-2)), cyclophosphamide (600 mg m(-2)) every 28 days for 5 cycles, or EBRT (45-50 Gy on a 5 days week(-1) schedule). The primary end points were OS and PFS. After a median follow-up of 95.5 months women in the chemotherapy group as compared with the RT group, had a no significant stage (HR) for death of 0.95 (95% CI, 0.66–.36; *P*=0.77) and a nonsignificant HR for event of 0.88 (95% CI, 0.63–1.23; *P*=0.45). The 3, 5 and 7-year OSs were 78%, 69% and 62% in the RT group and 76%, 66% and 62% in the chemotherapy group. The 3, 5 and 7-year PFSs were, respectively, 69%, 63% and 56% and 68%, 63% and 60%.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	601 patients	To determine if VCB/C could increase recurrence-free survival compared to pelvic RT. The secondary objectives included comparisons in survival (OS), frequency/severity of adverse events, and recurrence sites between the treatment arms.	A total of 601 patients were accrued; pelvic RT was assigned to 301 (18 did not receive study treatment) and VCB/C to 300 (9 did not receive study treatment). The median age was 63 years, 74% had stage I disease, and 89% underwent lymphadenectomy. Histology included 71% with endometrioid type, 15% S, and 5% CC. Nearly all patients completed the prescribed therapy (91% pelvic RT, 87% VCB/C). Acute toxicity was more common with VCB/C. Recurrence sites totaled to 5 vs 3 vaginal, 2 vs 19 pelvic, and 32 vs 24 distant failures with pelvic RT vs VCB/C. With a median follow-up of 24 months, the 24-month recurrence-free survival was 82% vs 84% for pelvic RT and VCB/C and treatment HR was 0.97 (95% CI, 0.635–1.43) (VCB/C relative to pelvic RT). The 24-month survival was 93% vs 92% for pelvic RT and VCB/C and treatment HR was 1.28 (95% CI, 0.689–2.36) (VCB/C relative to pelvic RT). There was no statistically significant treatment effect heterogeneity with respect to recurrence-free survival among clinical-pathologic variables evaluated.	1

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Experimental-Tx	714 patients	To determine the rates of LC and survival after relapse in patients with stage I endometrial cancer treated in the multicenter randomized PORTEC trial.	The analysis was done by intention-to-treat. A total of 714 patients were evaluated. At a median follow-up of 73 months, 8-year actuarial locoregional recurrence rates were 4% in the RT group and 15% in the control group (P<0.0001). The 8-year actuarial OS rates were 71 (RT group) and 77% (control group, P=0.18). 8-year rates of distant metastases were 10% and 6% (P=0.20). The majority of the locoregional relapses were located in the vagina, mainly in the vaginal vault. Of the 39 patients with isolated vaginal relapse, 35 (87%) were treated with curative intent, usually with external RT and brachytherapy, and surgery in some. A complete remission was obtained in 31 of the 35 patients (89%), and 24 patients (77%) were still in complete remission after further follow-up. 5 patients subsequently developed distant metastases, and 2 had a second vaginal recurrence. The 3-year survival after first relapse was 51% for patients in the control group and 19% in the RT group (P=0.004). The 3-year survival after vaginal relapse was 73%, in contrast to 8% and 14% after pelvic and distant relapse (P<0.001). At 5 years, the survival after vaginal relapse was 65% in the control group compared to 43% in the RT group.	1
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.	Observational-Tx	38 patients	To investigate outcomes after definitive management of nodal relapses of endometrial cancer with IMRT.	The median OS from date of recurrence was 46.1 months and the 2-year survival was 71%. Patients who received concurrent chemotherapy had a significantly longer median survival (61.9 months vs 28.7 months, P=0.034). In-field failures were more frequent in patients who received chemotherapy prior to RT, had a shorter recurrence-free interval, received a lower radiation dose, and had higher tumor grade. 3 patients (8%) experienced grade 3-4 late gastrointestinal toxicity.	2

Adjuvant Management of Early Stage Endometrial Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Observational-Tx	91 patients	To determine the outcome of patients after radical RT for isolated vaginal recurrence of endometrial carcinoma and to determine the clinical and pathologic predictors of outcome.	The 2- and 5-year LC rate and OS rate was 82% and 75% and 69% and 43%, respectively. The median time from initial diagnosis of endometrial cancer to death from disease was 38 months. On univariate analysis, a dose to the relapse site of ≥80 Gy and EBRT plus brachytherapy vs single-modality therapy were significant predictors of improved LC. On multivariate analysis, only the type of treatment correlated significantly with LC (P=0.03). On univariate analysis, Grade 1 or 2 vs Grade 3 tumor and EBRT plus brachytherapy vs single-modality therapy were significant predictors of improved OS.	2
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.	Observational-Tx	50 patients	To assess prognostic factors and OS after salvage RT for patients who had endometrial carcinoma and who experienced an isolated vaginal recurrence.	The 5-year and 10-year DFS and OS were 68% and 55%, and 53% and 40%, respectively. On multivariate analysis, age (P=0.0242), Grade 1 or 2 vs Grade 3 tumor (P=0.002), and size of recurrence (P<0.001) were significant predictors of OS. All patients who had Grade 3 disease were dead by 3.6 years from the time of recurrence. 5 patients experienced a Grade 3 or 4 complication.	3
59. Wylie J, Irwin C, Pintilie M, et al. Results of radical radiotherapy for recurrent endometrial cancer. *Gynecol Oncol.* 2000;77(1):66-72.	Observational-Tx	58 patients	To determine the OS and LC achieved in patients developing a locoregional recurrence of endometrial carcinoma and to define those prognostic factors that predict for improved LC and OS.	The median time to relapse from original diagnosis was 1.3 years (range 0.2–13.4 years). The actuarial 5- and 10-year OS was 53% and 41%, respectively. The respective results for LC were 65% and 62%. All end-points were measured from the time of relapse. The median total dose received was 81.5 Gy. Univariate analysis showed that favorable histological features at original diagnosis (<50% myometrial involvement, grade 1-2, P=0.007) and Perez modified staging (P=0.02) were significant predictors for OS. The Perez staging (P=0.02) and size of recurrence (<2 cm vs ≥2 cm, P=0.04) were predictors for LC.	2

Adjuvant Management of Early Stage Endometrial Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
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.	Review/Other-Tx	N/A	To develop a simple program that can be easily used by clinicians to calculate the tumor and late tissue equivalent doses (as if given in 2 Gy/day fractions) for different HDR brachytherapy regimens. The program should take into account the normal tissue sparing effect of brachytherapy.	The spreadsheet program created requires the clinician to enter only the external beam total dose and dose/fraction, HDR dose, and the number of HDR fractions. It automatically calculates the equivalent doses for tumor and normal tissue effects, respectively. Generally, the dose modifying factor applied is <1 since the doses to normal tissues are less than the doses to the tumor. However, in certain circumstances, a dose modifying factor of > 1 may need to be applied if the dose to critical normal tissues is higher than the dose to tumor. Additionally, the alpha/beta ratios for tumor and normal tissues can be changed from their default values of 10 Gy and 3 Gy, respectively. This program has been used to determine HDR doses needed for treatment of cancers of the cervix, prostate, and other organs. It can also been used to predict the late normal tissue effects, alerting the clinician to the possibility of undue morbidity of a new HDR regimen.	4

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
  a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
  b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
  c) the study is an expert opinion or consensus document.
- M = Meta-analysis

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

BMI = Body mass index

CI = Confidence interval

DFS = Disease-free survival

EBRT = External beam radiation therapy

HDR = High-dose-rate

HR = Hazard ratio

IM-WPRT = Intensity-modulated whole-pelvic radiation therapy

IMRT = Intensity-modulated radiotherapy

LC = Local control

LDR = Low-dose-rate

OS = Overall survival

PFS = Progression-free survival

PTV = Planning target volume

RT = Radiation therapy

VBT = Vaginal brachytherapy

VCB = Vaginal cuff boost