

**Advanced Stage Endometrial Cancer
EVIDENCE TABLE**

| Reference | Study Type | Patients/ Events | Study Objective (Purpose of Study) | Study Results | Study Quality |
|---|------------------|---------------------|--|---|------------------|
| 1. American Cancer Society. <i>Cancer Facts & Figures 2012</i> : Atlanta: American Cancer Society; 2012. | Review/Other-Tx | N/A | To provide the estimated numbers of new cancer cases and deaths in 2012 along with cancer incidence, mortality, and survival statistics and information on cancer symptoms, risk factors, early detection, and treatment | No results stated in abstract. | 4 |
| 2. Creasman WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. <i>Int J Gynaecol Obstet.</i> 2006; 95 Suppl 1:S105-143. | Review/Other-Tx | N/A | To review the carcinoma of the corpus uteri including treatment options. | No results stated in abstract. | 4 |
| 3. Connell PP, Rotmensch J, Waggoner S, Mundt AJ. The significance of adnexal involvement in endometrial carcinoma. <i>Gynecol Oncol.</i> 1999; 74(1):74-79. | Observational-Tx | 382 patients | To evaluate the prognostic significance of and predictive factors for adnexal involvement in patients with endometrial carcinoma. | Of the 382 cases reviewed, 40 (10.5%) had adnexal involvement. Patients with adnexal involvement had a worse 5-year DFS (73.1 vs 37.1%, $P<0.0001$) than patients without adnexal involvement. However, patients with adnexal involvement had multiple adverse features, including high grade disease, lymphovascular invasion, and additional sites of extrauterine disease. After controlling for these factors on multivariate analysis, adnexal involvement lost its prognostic significance ($P=0.56$). The 12 adnexal involvement patients without other extrauterine disease had a favorable outcome (5-year DFS of 70.9%). Factors predictive of adnexal involvement on logistic regression were metastatic disease, positive peritoneal washings, cervical involvement, and unfavorable histology | 2 |

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| 4. Greven KM, Corn B, Lanciano RM, Case D, Randall ME. Pathologic stage III endometrial carcinoma: Significance of extrauterine sites. <i>Radiation Oncology Investigations</i> . 1996; 4(3):122-128. | Observational-Tx | 105 patients | To review patients with pathologic stage III disease (1988 FIGO system) who were treated between 1970 and 1990. | Following hysterectomy, all patients received postoperative EBRT to the pelvis alone (88 patients) or to the pelvis and para-aortic regions (17 patients) for pathologically positive para-aortic nodes. Actuarial techniques were used to analyze survival and recurrences. Range of follow-up was 7–251 months (median 83 months). 5-year DFS for all patients was 64%. Multivariate analysis revealed clear cell/papillary serous histology and histologic grade to be significant predictors of DFS. Based on our analysis, four prognostic groups are described for the purpose of predicting outcome and patterns of disease recurrence. Patients who have a single extrauterine site of involvement and histologic grade 1 tumors have an excellent prognosis. Patients with a single extrauterine site of involvement and grade 2 or 3 tumors have a lower DFS rate, as do patients with two or more sites of extrauterine involvement. | 2 |
| 5. Mariani A, Webb MJ, Keeney GL, Haddock MG, Aletti G, Podratz KC. Stage IIIC endometrioid corpus cancer includes distinct subgroups. <i>Gynecol Oncol</i> . 2002; 87(1):112-117. | Observational-Tx | 46 patients | To assess the outcomes of patients with stage IIIC disease according to the extent of extrauterine disease. | Patients with stage IIIC(0) cancer had a 5-year cause-specific survival of 72% and a 5-year RFS of 68%, and those with stage IIIC(ab) had a cause-specific survival of 33% and an RFS of 25% ($P < 0.01$). Of the 22 patients with stage IIIC(0) endometrioid cancer, 21 had adjuvant RT (1 also received chemotherapy) and 1 was not treated. Relapse occurred in 7 (32%) patients, with only 1 having an initial failure component outside the node-bearing areas (lung). Of the 24 patients with stage IIIC(ab) cancer, 16 received adjuvant RT (1 had concomitant chemotherapy), 2 had chemotherapy, 4 had hormonal therapy, and 2 were not treated. We observed 16 recurrences (67%). Of the 14 patients with known initial sites of failure, 9 had an extranodal failure component. | 2 |

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| 6. Lewin SN, Herzog TJ, Barrena Medel NI, et al. Comparative performance of the 2009 international Federation of gynecology and obstetrics' staging system for uterine corpus cancer. <i>Obstet Gynecol.</i> 2010;116(5):1141-1149. | Observational-Tx | 81,902 women | To perform a population-based analysis, comparing the performance of the 1988 and 2009 International Federation of Gynecology and Obstetrics (FIGO) staging systems. | A total of 81,902 women were identified. Based on the 1988 staging system, survival for stage IA was 90.7% (95% CI, 90%-91%) compared with 88.9% (95% CI, 88%-89%) for IB tumors. In the 2009 system, survival was 89.6% (95% CI, 89%-90%) for stage IA and 77.6% (95% CI, 76%-79%) for stage IB. The survival for FIGO 1988 stage IIA was superior to stage IC, whereas in the 2009 system, survival for stage II was inferior to all stage I patients. The newly defined stage IIIC substages are prognostically different. Survival for stage IIIC1 was 57.0% (95% CI, 54%-60%) compared with 49.4% (95% CI, 46%-53%) for stage IIIC2. | 1 |
| 7. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. <i>Int J Gynaecol Obstet.</i> 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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| 8. Hamilton CA, Cheung MK, Osann K, et al. Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers. <i>Br J Cancer</i> . 2006;94(5):642-646. | Observational-Tx | 4,180 women | To compare the survival of women with UPSC and clear cell carcinoma (CC) to those with grade 3 endometrioid uterine carcinoma. | Of 4,180 women, 1,473 had UPSC, 391 had clear cell carcinoma, and 2,316 had grade 3 endometrioid uterine carcinoma cancers. UPSC and clear cell carcinoma patients were older (median age: 70 years and 68 vs 66 years, respectively; $P<0.0001$) and more likely to be black compared to grade 3 endometrioid uterine carcinoma (15% and 12% vs 7%; $P<0.0001$). A higher proportion of UPSC and clear cell carcinoma patients had stage III-IV disease compared to grade 3 endometrioid uterine carcinoma patients (52% and 36% vs 29%; $P<0.0001$). UPSC, clear cell carcinoma and grade 3 endometrioid uterine carcinoma patients represent 10%, 3%, and 15% of endometrial cancers but account for 39%, 8%, and 27% of cancer deaths, respectively. The 5-year disease-specific survivals for women with UPSC, clear cell carcinoma and grade 3 endometrioid uterine carcinoma were 55%, 68%, and 77%, respectively ($P<0.0001$). The survival differences between UPSC, clear cell carcinoma and grade 3 endometrioid uterine carcinoma persist after controlling for stage I-II (74%, 82%, and 86%; $P<0.0001$) and stage III-IV disease (33%, 40%, and 54%; $P<0.0001$). | 2 |

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| 9. Lambrou NC, Gomez-Marín O, Mirhashemi R, et al. Optimal surgical cytoreduction in patients with Stage III and Stage IV endometrial carcinoma: a study of morbidity and survival. <i>Gynecol Oncol.</i> 2004; 93(3):653-658. | Observational-Tx | 85 patients | To evaluate the survival impact of residual disease at the time of primary surgery for patients with stage III and IV endometrial carcinoma; to assess morbidity associated with surgical cytoreduction. | 85 patients were identified: 66 stage III and 19 stage IV. Only stage IIIC and stage IV were included in survival analysis: 72% (33 stage IIIC, 9 stage IV) had optimal cytoreduction and 28% (6 stage IIIC, 10 stage IV) had suboptimal cytoreduction. The median survival for stage IIIC and IV disease was 6.7 months for patients with suboptimal cytoreduction and 17.8 months for patients with optimal cytoreduction ($P=0.001$). The proportion of patients with major postoperative complications (37.50% vs 7.25%, $P=0.005$), unplanned postoperative surgical intensive care unit admissions (31.25% vs 7.25%, $P=0.018$), and length of hospital stay exceeding 15 days (31.25% vs 4.35%, $P=0.005$) was greater in patients with suboptimal cytoreductive surgery. | 2 |
| 10. Thomas MB, Mariani A, Cliby WA, Keeney GL, Podratz KC, Dowdy SC. Role of cytoreduction in stage III and IV uterine papillary serous carcinoma. <i>Gynecol Oncol.</i> 2007; 107(2):190-193. | Observational-Tx | 125 patients | To assess the role of cytoreduction in stage IIIC-IV UPSC. | Of the 125 UPSC patients, analysis of stage IIIC-IV patients ($n=70$; stage IIIC 12, stage IV 58) was performed. Optimal cytoreduction was achieved in 42/70 (60%) patients, and optimal cytoreduction with no visible residual disease in 26/70 (37%) patients. Patients with no visible residual disease after cytoreduction had a better median survival (51 months) compared to optimally cytoreduced albeit with residual disease (14 months), and suboptimally cytoreduced patients (12 months) ($P=0.002$). Of the 45 patients who received chemotherapy, the median survival of patients with no residual disease vs patients with residual disease was 52 months vs 16 months ($P<0.001$) respectively. No reduction in survival was noted when radical procedures were necessary to completely remove all residual disease. Regression analysis identified absence of visible residual disease (stage (HR)=0.30, $P<0.001$) and chemotherapy (HR=0.56, $P=0.07$) as independent predictors of OS. | 2 |

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| 11. Randall ME, Filiaci VL, Muss H, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. <i>J Clin Oncol</i> . 2006; 24(1):36-44. | Experimental-Tx | 396 patients | To compare WAI and doxorubicin-cisplatin chemotherapy in women with stage III or IV endometrial carcinoma having a maximum of 2 cm of postoperative residual disease. | Most patient and tumor characteristics were well balanced. The median patient age was 63 years; 50% had endometrioid tumors. Median follow-up time was 74 months. The stage for progression adjusted for stage was 0.71 favoring doxorubicin-cisplatin (95% CI, 0.55 to 0.91; P<.01). At 60 months, 50% of patients receiving doxorubicin-cisplatin were predicted to be alive and disease free when adjusting for stage compared with 38% of patients receiving WAI. The stage-adjusted death stage was 0.68 (95% CI, 0.52 to 0.89; P<.01) favoring doxorubicin-cisplatin. Moreover, at 60 months and adjusting for stage, 55% of doxorubicin-cisplatin patients were predicted to be alive compared with 42% of WAI patients. Greater acute toxicity was seen with doxorubicin-cisplatin. Treatment probably contributed to the deaths of 8 patients (4%) on the doxorubicin-cisplatin arm and 5 patients (2%) on the WAI arm. | 1 |
| 12. Fleming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. <i>J Clin Oncol</i> . 2004; 22(11):2159-2166. | Experimental-Tx | 273 patients | To determine whether the addition of paclitaxel to doxorubicin plus cisplatin improves OS in women with advanced or recurrent endometrial carcinoma. Secondary comparisons included PFS, response rate, and toxicities. | 273 women (10 ineligible) were registered. Objective response (57% vs 34%; P<.01), PFS (median, 8.3 vs 5.3 months; P<.01), and OS (median, 15.3 vs 12.3 months; P=.037) were improved with TAP. Treatment was hematologically well tolerated, with only 2% of patients receiving doxorubicin-cisplatin, and 3% of patients receiving TAP experiencing neutropenic fever. Neurologic toxicity was worse for those receiving TAP, with 12% grade 3, and 27% grade 2 peripheral neuropathy, compared with 1% and 4%, respectively, in those receiving doxorubicin-cisplatin. Patient-reported neurotoxicity was significantly higher in the TAP arm following 2 cycles of therapy. | 1 |

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| 13. Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A Gynecologic Oncology Group study. <i>Gynecol Oncol</i> . 2009; 112(3):543-552. | Experimental-Tx | 552 patients | Treatment was randomized to compare RFS and toxicity between two chemotherapy regimens for the treatment of women with advanced stage endometrial carcinoma. | Of 659 patients enrolled following surgery, 552 eligible patients were randomized to chemotherapy after irradiation. Accrual closed to stage IV patients in June, 2003. Approximately 80% completed 6 cycles of chemotherapy. Three deaths resulted from bowel complications and one death was due to renal failure. Hematologic adverse events, sensory neuropathy and myalgia, were more frequent and severe in the paclitaxel arm ($P<0.01$) which was confirmed by Quality of Life assessments. Percentage of patients alive and recurrence-free at 36 months was 62% for cisplatin and doxorubicin vs 64% for cisplatin and doxorubicin with paclitaxel. The hazard of recurrence or death relative to the cisplatin and doxorubicin arm stratified by stage is 0.90 (95% CI, 0.69 to 1.17, $P=0.21$, one-tail). However, in subgroup analysis, cisplatin and doxorubicin with paclitaxel was associated with a 50% reduction in the risk of recurrence or death among patients with gross residual disease (95% CI, 0.26 to 0.92). Stage, residual disease, histology/grade, positive para-aortic node and cytology, pelvic metastases and age were significantly associated with RFS. | 1 |

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| 14. Miller D, Filiaci V, Fleming G, et al. Late-Breaking Abstract 1: Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. <i>Gynecol Oncol</i> . 2012; 125(3):771. | Experimental-Tx | 1,381 patients | To determine if the combination of carboplatin and paclitaxel chemotherapy is clinically inferior to the combination of TAP chemotherapy with regard to survival and to assess differences in toxicity profile, specifically neurotoxicity and infection between TAP and carboplatin and paclitaxel. | Treatment was hematologically well tolerated, with only 7% of patients receiving TAP and 6% on carboplatin and paclitaxel experiencing neutropenic fever. Neurologic toxicity for those receiving TAP was 26% grade N1 sensory neuropathy compared with 19% in those receiving carboplatin and paclitaxel (pb.01). Common grade N2 toxicities more often (pb.01) reported with TAP included: Thrombocytopenia (23% vs 12%), other hematologic (30% vs 22%), vomiting (7% vs 4%), diarrhea (6% vs 2%), and metabolic (14% vs 8%); whereas neutropenia (52% vs 79%) was more often reported with carboplatin and paclitaxel. Study treatment was discontinued due to toxicity in 18% on TAP and 12% on carboplatin and paclitaxel. The 7 planned cycles were completed in 62% of those on TAP and 69% on carboplatin and paclitaxel (P=.01). The interim analysis adjusted 90% upper confidence limit for the death stage (HR) of carboplatin and paclitaxel relative to TAP was 1.16 and excludes the inferiority region bounded at 1.2. PFS (median carboplatin and paclitaxel vs TAP, 14 vs 14 months; HR = 1.03) and OS (median carboplatin and paclitaxel vs TAP, 32 vs 38 months; HR = 1.01) results for carboplatin and paclitaxel were not inferior to TAP. A homogeneity test suggests consistent treatment effects across strata defined by measurable/recurrent vs primary disease and pelvic irradiation history (pN.1). | 1 |

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| 15. 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. <i>Lancet</i> . 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 two 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 |
| 16. 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. <i>Gynecol Oncol</i> . 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 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 |

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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. <i>Lancet</i> . 2010; 375(9717):816-823. | Experimental-Tx | 427 patients | To compare outcomes and adverse effects after vaginal brachytherapy 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 vaginal brachytherapy and 4 after EBRT. Estimated 5-year rates of vaginal recurrence were 1.8% (95% CI, 0.6-5.9) for vaginal brachytherapy 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 vaginal brachytherapy 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 vaginal brachytherapy group than in the EBRT group at completion of RT (12.6% [27/215] vs 53.8% [112/208]). | 1 |

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| 18. Klopp AH, Jhingran A, Ramondetta L, Lu K, Gershenson DM, Eifel PJ. Node-positive adenocarcinoma of the endometrium: outcome and patterns of recurrence with and without external beam irradiation. <i>Gynecol Oncol.</i> 2009; 115(1):6-11. | Observational-Tx | 71 patients | To evaluate treatment outcomes and patterns of recurrence in patients with node-positive FIGO stage IIIC adenocarcinoma of the uterus without serous or clear cell differentiation. | 39% (28/71) of patients had involved para-aortic lymph nodes, while 61% (43/71) had only pelvic lymph nodes. 5- and 10-year disease-specific survival rates were 63% and 54%, respectively; corresponding OS rates were 60% and 47%. Grade was strongly associated with disease-specific survival (76% vs 46% at 5 years for low-grade vs high-grade tumors, $P=0.004$). Cervical or adnexal involvement was associated with decreased disease-specific survival, but lymph-vascular space invasion, age, race, body mass index, and number and location of positive nodes were not. 5-year pelvic-relapse-free survival (98% vs 61%, $P=0.001$), disease-specific survival (78% vs 39%, $P=0.01$), and OS (73% vs 40%, $P=0.03$) were significantly better for the regional RT group than the systemic therapy group. In patients treated without regional RT, the most common site of relapse was the pelvis. Disease-specific survival was not significantly correlated with number of nodes removed in the regional RT group but was in patients treated without regional RT ($P=0.001$). | 2 |

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| 19. Mundt AJ, Murphy KT, Rotmensch J, Waggoner SE, Yamada SD, Connell PP. Surgery and postoperative radiation therapy in FIGO Stage IIIC endometrial carcinoma. <i>Int J Radiat Oncol Biol Phys</i> . 2001; 50(5):1154-1160. | Observational-Tx | 30 patients | To determine the outcome, pattern(s) of failure, and optimal treatment volume in stage IIIC endometrial carcinoma patients treated with surgery and postoperative RT. | At a median follow-up of 32 months, the actuarial 5-year DFS and cause-specific survivals of the entire group were 33.9% and 55.8%, respectively. Overall, 16 women (53%) relapsed. Sites of failure included the pelvis (23%), abdomen (13%), para-aortic lymph nodes (13%), and distant (40%). Of the 7 pelvic failures, 4 were vaginal (3 vaginal only). Patients treated with vaginal brachytherapy had a trend to a lower vaginal recurrence rate (0/10 vs 4/20, P=0.12) than those not receiving vaginal brachytherapy. All 4 para-aortic lymph nodes failures were in women treated with WPRT (2 negative, 1 unsampled, and 1 positive para-aortic lymph nodes). None of the 10 EFRT patients (2 negative, 8 positive para-aortic lymph nodes) recurred in the para-aortic lymph nodes. No patient developed an isolated abdominal recurrence. 2 patients developed significant RT sequelae: chronic diarrhea in 1 patient treated with WPRT and vaginal brachytherapy, and small bowel obstruction in 1 patient treated with EFRT. | 2 |
| 20. Nelson G, Randall M, Sutton G, Moore D, Hurteau J, Look K. FIGO stage IIIC endometrial carcinoma with metastases confined to pelvic lymph nodes: analysis of treatment outcomes, prognostic variables, and failure patterns following adjuvant radiation therapy. <i>Gynecol Oncol</i> . 1999; 75(2):211-214. | Observational-Tx | 782 patients | To evaluate the prognostic significance of isolated positive pelvic lymph nodes on survival and to analyze other prognostic variables, OS, and failure patterns in surgically staged endometrial carcinoma patients with positive pelvic lymph nodes and negative para-aortic lymph nodes following RT. | With a median follow-up of 51 months the actuarial 5-year DFS was 81% and the actuarial 2-year and 5-year OS rates were 81% and 72%, respectively. Univariate analysis revealed that positive peritoneal cytology in conjunction with positive pelvic lymph nodes imparts a greater risk of recurrence and decreased OS. There were no pelvic and/or upper abdominal failures, but there were recurrences in the para-aortic lymph nodes (2 patients) and distantly (2 patients). | 2 |

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| 21. Slomovitz BM, Burke TW, Eifel PJ, et al. Uterine papillary serous carcinoma (UPSC): a single institution review of 129 cases. <i>Gynecol Oncol.</i> 2003; 91(3):463-469. | Observational-Tx | 129 patients | To identify clinical and pathologic characteristics of patients with UPSC who were all surgically managed at a single institution. The identified characteristics were then correlated with OS. | There were 52 patients with stage I disease, 5 with stage II, 41 with stage III, and 31 with stage IV. The median age at the time of diagnosis was 68 years (range, 44-93 years). A personal history of breast cancer was reported by 12.4% of the patients, and a family history of breast cancer was reported by 16%. The 5-year OS among all patients was 45.9%. Among the stage I patients (IA, n=19; IB, n=26; and IC, n=7), the 5-year OS was 62.9% (IA, 81.5%; IB, 58.6%; and IC, 34.3%). The 5-year OS for patients with stage III and IV disease was 37.3% and 19.9%, respectively. Pathologic features predictive of OS included lymph node status ($P \leq 0.01$), lymph vascular invasion ($P \leq 0.05$), and depth of uterine invasion ($P \leq 0.05$). Among patients with no uterine invasion (n=32), surgical staging revealed that 37% had stage III or IV disease. Among stage III patients, those who received chemotherapy had a longer OS than those who did not receive chemotherapy ($P=0.03$). | 3 |

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| 22. Axelrod J, Bundy B, Roy T, King M, Sutton G, Rosenshein N. Advanced Endometrial Carcinoma (EC) Treated with Whole Abdomen Irradiation (WAI): A Gynecologic Oncology Group (GOG) Study. <i>Gynecol Oncol.</i> 1995;56:135-136. | Observational-Tx | 165 patients | To evaluate toxicity, survival, and progression-free interval or advanced surgically staged III and IV, endometrial carcinoma maximally debulked <2cm. | Typical adenocarcinoma patients were significantly younger than papillary-serous and clear cell carcinoma patients. Typical adenocarcinoma patients had significantly less poorly differentiated tumors. Trends observed in the distribution of race and pelvic nodes : Ratio typical adenocarcinoma to papillary-serous and clear cell carcinoma patients, 1:1 for whites, 1:3 for blacks; 60% for typical adenocarcinoma patients had + pelvic nodes vs 46% of papillary-serous and clear cell carcinoma patients. Similar distribution was observed for performance status, para-aortic nodes status, site and extent of disease, and FIGO stage. The frequency for severe/life-threatening adverse effects for surgery (n = 165) was 0.6% hematology, 0.6% gastrointestinal, and 6% postoperative cardiovascular. 6 patients did not receive any RT. 20 patients had a major (20%) deviation from protocol. The frequency for severe/life-threatening adverse effects for RT (N = 159) was 12.5% bone marrow depression, 11% acute gastrointestinal, and 6.7% chronic gastrointestinal (including 7 small bowel obstruction, 2 malnutrition, 1 fistula, and 1 gastrointestinal bleeding), and 1.8% hepatic. For all patients (n = 165), progression-free interval at 3 years was 35% for typical adenocarcinoma and 31% for papillary-serous and clear cell carcinoma patients; survival at 3 years was 31% for TA and 33% for papillary-serous and clear cell carcinoma patients. | 2 |

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| 23. Mundt AJ, McBride R, Rotmensch J, Waggoner SE, Yamada SD, Connell PP. Significant pelvic recurrence in high-risk pathologic stage I--IV endometrial carcinoma patients after adjuvant chemotherapy alone: implications for adjuvant radiation therapy. <i>Int J Radiat Oncol Biol Phys.</i> 2001; 50(5):1145-1153. | Observational-Tx | 43 patients | To evaluate the risk of pelvic recurrence in high-risk pathologic stage I--IV endometrial carcinoma patients after adjuvant chemotherapy alone. | 29 women (67.4%) relapsed. 17 (39.5%) recurred in the pelvis and 23 (55.5%) in extrapelvic sites. The 3-year actuarial pelvic recurrence rate was 46.5%. The most significant factors correlated with pelvic recurrence were cervical involvement (P=0.01) and adnexal (P=0.05) involvement. Of the 17 women who developed a pelvic recurrence, 8 relapsed in the vagina, 3 in the nonvaginal pelvis, and 6 in both. The 3-year vaginal and nonvaginal pelvic recurrence rates were 37.8% and 26%, respectively. The most significant factor correlated with vaginal pelvic recurrence was cervical involvement (P=0.0007). Deep myometrial invasion (P=0.02) and lymph nodal involvement (P=0.03) were both correlated with nonvaginal pelvic recurrence. 9/29 relapsed patients (31%) developed pelvic recurrence as their only (6) or first site (3) of recurrence. Factors associated with a higher rate of pelvic recurrence (as the first or only site) were cervical involvement and stage I--II disease. | 2 |

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| 24. Secord AA, Geller MA, Broadwater G, et al. A multicenter evaluation of adjuvant therapy in women with optimally resected stage IIIC endometrial cancer. <i>Gynecol Oncol.</i> 2013; 128(1):65-70. | Observational-Tx | 265 patients | To determine if there is an advantage to combination chemotherapy and radiation for optimally resected stage IIIC endometrial cancer. | 265 patients with optimally resected stage IIIC endometrial cancer were identified. Postoperative therapies included RT in 17% (n=45), chemotherapy in 17% (n=46), and both chemotherapy and RT in 61% (n=161). 3-year RFS was 56% for chemotherapy alone, compared to 73% for RT alone, and 73% for combination therapy (P=0.12). Those receiving chemotherapy alone had the worst 3-year OS (78%) compared to either RT alone (95%) or combination therapy (90%) (p=0.005). After adjustment for stage and grade those treated with chemotherapy alone were at a 2.2 fold increased risk of recurrence (95% CI, 1.2 to 4.2; P=0.02) and 4.0 fold increased risk of death (95% CI, 1.6 to 10.0; P=0.004) compared to those treated with chemotherapy and RT. In contrast there was no significant difference in RFS [HR=1.0 (95% CI, 0.5 to 2.0; P=0.92)] or OS [HR=1.1 (95% CI, 0.3 to 3.6; P=0.91)] for those treated with RT alone compared to those treated with chemotherapy and RT. | 2 |
| 25. Maggi R, Lissoni A, Spina F, et al. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. <i>Br J Cancer.</i> 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, 0.66-1.36; 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 |

**Advanced Stage Endometrial Cancer
EVIDENCE TABLE**

| Reference | Study Type | Patients/ Events | Study Objective (Purpose of Study) | Study Results | Study Quality |
|--|------------------|---------------------|---|--|------------------|
| 26. Hogberg T, Signorelli M, de Oliveira CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. <i>Eur J Cancer</i> . 2010;46(13):2422-2431. | Review/Other-Tx | 534 patients | Two randomized clinical trials (NSGO-EC-9501/EORTC-55991 and MaNGO ILIAD-III) were undertaken to clarify if sequential combination of chemotherapy and radiotherapy 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 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 |
| 27. Marchetti C, Pisano C, Mangili G, et al. Use of adjuvant therapy in patients with FIGO stage III endometrial carcinoma: a multicenter retrospective study. <i>Oncology</i> . 2011; 81(2):104-112. | Observational-Tx | 82 patients | To describe the outcome in a cohort of patients with stage III endometrial cancer treated with chemotherapy and/or RT. | 78 (95%) patients received an adjuvant treatment: chemotherapy (41; 50%), RT (18; 22%), or combined chemo-RT (19; 23%). 4 patients were excluded from analysis because they were not treated with any adjuvant therapy. At univariate analysis, tumor grade (G3 vs G1-G2; P=0.003) was associated with risk of recurrence; similarly, patients treated with RT alone (P=0.031, stage 0.19, 95% CI 0.04-0.86) or chemotherapy alone (P=0.053, stage 0.54, 95% CI 0.29-1.01) had a significantly higher risk for relapse, compared to those treated with the multimodality approach. Relapse-free survival at 3 years was 86.5%, 65.8% and 44.1%, with the multimodality approach, chemotherapy and RT, respectively. At multivariable analysis, age and grading were independently associated with RFS. HR for relapse-free survival was 0.14 (95% CI, 0.02-1.04) and 0.20 (95% CI, 0.04-1.11) for multimodality treatment compared to chemotherapy alone and RT alone, respectively. | 2 |

**Advanced Stage Endometrial Cancer
EVIDENCE TABLE**

| Reference | Study Type | Patients/ Events | Study Objective (Purpose of Study) | Study Results | Study Quality |
|--|------------------|---------------------|--|--|------------------|
| 28. McMeekin DS, Walker JL, Hartenbach EM, Bookman MA, Koh WJ. Phase I trial of the treatment of high-risk endometrial cancer with concurrent weekly paclitaxel and cisplatin and whole abdominal radiation therapy: a Gynecologic Oncology Group study. <i>Gynecol Oncol.</i> 2009; 112(1):134-141. | Observational-Tx | 35 patients | To determine the maximum tolerated dose and feasibility of weekly cisplatin and paclitaxel chemotherapy administered concurrently with WAI in women with high-risk endometrial cancer. | 35 patients were enrolled in the study, including 21 in the dose finding portion, and 14 in the feasibility portion of the trial. The initial dose level tested was paclitaxel 10 mg/m(2) and cisplatin 20 mg/m(2). The maximum tolerated dose identified was at dose level-3 using paclitaxel 20 mg/m(2) and cisplatin 25 mg/m(2). The most common acute dose-limiting toxicities were gastrointestinal and hematologic. The prescribed RT was successfully delivered to 32/35 patients. 20 patients (6 phase I, 14 feasibility) were assessed at the maximum tolerated dose. No acute grade 4 toxicities, and two grade 3-4 chronic toxicities were observed in these patients. Treatment contributed to the deaths of 2 patients. | 2 |
| 29. Reisinger SA, Asbury R, Liao SY, Homesley HD. A phase I study of weekly cisplatin and whole abdominal radiation for the treatment of stage III and IV endometrial carcinoma: a Gynecologic Oncology Group pilot study. <i>Gynecol Oncol.</i> 1996; 63(3):299-303. | Review/Other-Tx | 8 patients | To determine the side effects of concurrent cisplatin and WAI associated with this treatment. | This regimen was well tolerated accurately. The two chronic adverse effects seen were chylous ascites and a bowel obstruction which have been reported with WAI alone. | 4 |
| 30. Wrenn DC, Saigal K, Lucci JA, 3rd, et al. A Phase I Study using low-dose fractionated whole abdominal radiotherapy as a chemopotentiator to full-dose cisplatin for optimally debulked stage III/IV carcinoma of the endometrium. <i>Gynecol Oncol.</i> 2011; 122(1):59-62. | Observational-Tx | 12 patients | To evaluate the feasibility of combining low-dose fractionated WAI with weekly full-dose cisplatin for patients with stage III/IV endometrial carcinoma | 12 patients were enrolled from January 2005 to June 2009 with median follow-up of 13.5 months (range: 5-27 months). 75% of enrolled patients had uterine papillary serous histology. 11 patients at least partially completed therapy (range: 2-6 cycles of weekly full-dose cisplatin/low-dose fractionated WAI) with one additional patient opting out at the higher dose level. Combination therapy overall was well tolerated. 3 patients in each cohort experienced grade 3 acute hematologic events with one recorded grade 4 toxicity in the second cohort. Of patients receiving any of the experimental treatment, 5 have experienced recurrences. 3 of these patients were in cohort one and received 0.5 Gy/fx low-dose fractionated WAI. | 2 |

**Advanced Stage Endometrial Cancer
EVIDENCE TABLE**

| Reference | Study Type | Patients/ Events | Study Objective (Purpose of Study) | Study Results | Study Quality |
|---|------------------|---------------------|---|--|------------------|
| 31. Schwandt A, Chen WC, Martra F, Zola P, Debernardo R, Kunos CA. Chemotherapy plus radiation in advanced-stage endometrial cancer. <i>Int J Gynecol Cancer</i> . 2011; 21(9):1622-1627. | Observational-Tx | 125 patients | To investigate the clinical benefit of chemotherapy with radiation or the clinical benefit of chemotherapy alone among patients with stage III or IVA endometrial cancer treated in 2 international cancer centers. | The addition of radiation to chemotherapy improved the rate of clinical benefit from 55% to 77%. Differences in clinical benefit were attributed to a reduction in the number of pelvic relapses after chemoradiation. There were no substantial differences in the rate of extrapelvic relapse events seen between the chemotherapy alone and chemoradiation groups. Patients receiving radiation had prolonged median PFS (36 vs 17 months in chemotherapy alone) and median OS (70 vs 64 months in chemotherapy alone). | 2 |

**Advanced Stage Endometrial Cancer
EVIDENCE TABLE**

| Reference | Study Type | Patients/ Events | Study Objective (Purpose of Study) | Study Results | Study Quality |
|---|------------------|---------------------|---|--|------------------|
| 32. Secord AA, Havrilesky LJ, O'Malley DM, et al. A multicenter evaluation of sequential multimodality therapy and clinical outcome for the treatment of advanced endometrial cancer. <i>Gynecol Oncol.</i> 2009; 114(3):442-447. | Observational-Tx | 109 patients | To evaluate the outcome and adverse effects in patients with advanced stage endometrial cancer treated with postoperative chemotherapy and radiation to determine whether there was an advantage to a particular sequencing modality. | 109 patients with advanced stage endometrial cancer were identified who received postoperative adjuvant therapies; 41% (n=45) chemotherapy followed by radiation and then further chemotherapy, 17% (n=18) radiation followed by chemotherapy, and 42% (n=46) chemotherapy followed by radiation. The median age was 62 years (range: 35-83); 48% had endometrioid tumors; and 90% underwent optimal cytoreduction. There was no difference in the frequency of adverse effects due to either chemotherapy (P=0.35) or RT (P=0.14); dose modifications (P=0.055); or delays (P=0.80) between the various sequencing modalities. There was a significant difference between adjuvant treatment groups for both OS (log rank P=0.011) and PFS (log rank P=0.025), with those receiving chemotherapy followed by radiation and then further chemotherapy having a superior 3-year OS (88%) and PFS (69%) compared to radiation followed by chemotherapy (54% and 47%) or chemotherapy followed by radiation (57% and 52%). After adjusting for stage, age, grade, race, histology and cytoreduction status the OS HR for therapy was 5.74 (95% CI, 1.96 to 16.77) for radiation followed by chemotherapy and 2.60 (95% CI, 1.01 to 6.71) for chemotherapy followed by radiation, compared to chemotherapy followed by radiation and then further chemotherapy, P=0.003. When the analysis was restricted to optimally cytoreduced patients, those who were treated with radiation followed by chemotherapy were at higher risk for disease progression [HR=3.53 (95% CI, 1.29 to 9.71)], P=0.024, and death [HR=7.24 (95% CI, 2.25 to 23.37)], P=0.001, than patients who received sequential chemotherapy followed by radiation and then further chemotherapy. | 2 |

**Advanced Stage Endometrial Cancer
EVIDENCE TABLE**

| Reference | Study Type | Patients/ Events | Study Objective (Purpose of Study) | Study Results | Study Quality |
|--|------------------|---------------------|---|---|------------------|
| 33. Gynecologic Oncology Group. Carboplatin and Paclitaxel With or Without Cisplatin and Radiation Therapy in Treating Patients With Stage I, Stage II, Stage III, or Stage IVA Endometrial Cancer. In: ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). 2013 January 5. Available from: http://www.clinicaltrials.gov/ct2/show/NCT00942357?id=0258&rank=10 . NLM Identifier: NCT00942357. | Review/Other-Tx | Ongoing | A randomized phase III trial to study carboplatin and paclitaxel to see how well they work when given with or without cisplatin and RT in treating patients with stage I, stage II, stage III, or stage IVA endometrial cancer. | This trial is still recruiting study subjects and results are not available yet. | 4 |
| 34. Greven K, Winter K, Underhill K, Fontenesi J, Cooper J, Burke T. Final analysis of RTOG 9708: adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer. <i>Gynecol Oncol</i> . 2006; 103(1):155-159. | Observational-Tx | 46 patients | To assess the feasibility, safety, toxicity, and patterns of recurrence and survival when chemotherapy was combined with adjuvant radiation for patients with high-risk endometrial cancer. | 46 patients were entered between 10/97 and 4/99. Follow-up times range from 6.8 to 72 months with a median of 4.3 years. Maximum late toxicity was grade 1 in 16%, grade 2 in 41%, grade 3 in 16%, and grade 4 in 5%. At 4 years pelvic, regional and distant recurrence rates are 2%, 2%, and 19%, respectively. OS and DFS rates at 4 years are 85% and 81%, respectively. 4-year rates for survival and DFS for stage III patients are 77% and 72%, respectively. There have been no recurrences for patients with stage IC, IIA, or IIB. | 1 |
| 35. Fields AL, Einstein MH, Novetsky AP, Gebb J, Goldberg GL. Pilot phase II trial of radiation "sandwiched" between combination paclitaxel/platinum chemotherapy in patients with uterine papillary serous carcinoma (UPSC). <i>Gynecol Oncol</i> . 2008; 108(1):201-206. | Experimental-Tx | 30 women | To evaluate DFS and OS in patients treated with pelvic radiation "sandwiched" between 6 cycles of paclitaxel/platinum chemotherapy with optimally reduced UPSC. | 30 women were enrolled between 1999 and 2004. Median age was 69 years (45-82 years). 60% (18/30) of patients had disease confined to the uterus (stage I/II) and 40% (12/30) had extra-uterine disease (stage III/IV). 29 patients completed protocol treatment. One patient was discontinued due to non-compliance and recurred at 7 months. All 30 patients are included in survival analysis. 3-year DFS and OS with stage I/II disease was 69% and 75% and stage III/IV disease was 54% and 52%, respectively. Of 177 chemotherapy cycles administered, grade 3 or 4 neutropenia, thrombocytopenia or anemia occurred in 42%, 1% and 3% of cycles, respectively. 6 cycles were delayed 1 week for neutropenia. 43% of all neutropenic episodes occurred after RT. | 1 |

**Advanced Stage Endometrial Cancer
EVIDENCE TABLE**

| Reference | Study Type | Patients/ Events | Study Objective (Purpose of Study) | Study Results | Study Quality |
|---|------------------|---------------------|--|--|------------------|
| 36. Fowler JM, Brady WE, Grigsby PW, Cohn DE, Mannel RS, Rader JS. Sequential chemotherapy and irradiation in advanced stage endometrial cancer: A Gynecologic Oncology Group phase I trial of doxorubicin-cisplatin followed by whole abdomen irradiation. <i>Gynecol Oncol.</i> 2009; 112(3):553-557. | Experimental-Tx | 31 patients | To evaluate the feasibility and toxicity of delivering sequential doxorubicin-cisplatin followed by WAI. | 31 patients were entered onto the study. 29 were evaluable for feasibility of the regimen, and 22 patients were evaluable for chronic radiation toxicity with a median follow-up of 21 months. 3 patients (14%) experienced severe chronic toxicity including 1 treatment-related death. The 5-year PFS and OS was 52.5% and 60.1% respectively. | 2 |
| 37. Geller MA, Ivy J, Dusenbery KE, Ghebre R, Isaksson Vogel R, Argenta PA. A single institution experience using sequential multi-modality adjuvant chemotherapy and radiation in the "sandwich" method for high risk endometrial carcinoma. <i>Gynecol Oncol.</i> 2010; 118(1):19-23. | Observational-Tx | 23 patients | To evaluate the outcomes and feasibility associated with delivering sequential chemotherapy and radiation in advanced stage endometrial cancer. | 23 patients met entry criteria and were included in the analysis. The median age was 57 years (range 28-78). The majority of patients were stage III (78%) and the most common histologic type was serous (52%). The combination of a taxane and carboplatin was administered in 100% of cases. All planned cycles of chemotherapy were completed (100%) with the majority being prescribed 6 cycles (82%). Of the 23 patients, 5 progressed of which 3 died during the follow-up period. The Kaplan-Meier estimate of 1, 3, and 5 year PFS is 100%, 80%, and 74%, respectively. The Kaplan-Meier estimate for 1, 3, and 5 year OS is 100%, 88% and 79%, respectively. | 2 |
| 38. Geller MA, Ivy JJ, Ghebre R, et al. A phase II trial of carboplatin and docetaxel followed by radiotherapy given in a "Sandwich" method for stage III, IV, and recurrent endometrial cancer. <i>Gynecol Oncol.</i> 2011; 121(1):112-117. | Observational-Tx | 41 patients | To determine feasibility and efficacy of administering docetaxel and carboplatin chemotherapy followed by pelvic RT and then consolidation chemotherapy in patients with advanced or recurrent endometrial cancer. | 42 patients enrolled, 7 did not complete therapy. 95% (39/41) had primary disease. Median age = 58 years (range: 21-81 years). 78% (32/41) = endometrioid histology. Stages = 10 IIIA, 21 IIIC, 1 IVA, 7 IVB, (recurrent = 1 IC, 1 IIA). There were 23 non-hematologic and 14 grade 3 and 16 grade 4 hematologic toxicities. 7 patients died following treatment with a median follow-up of 28 months (range: 7-70 months). Kaplan-Meier estimates and 95% CIs for OS at 1 year were 95% (82%-99%), at 3 years 90% (75%-96%), and at 5 years 71% (45%-86%). Of the 39 with primary disease, 11 progressed or died within 5 years of study enrollment. Kaplan-Meier estimates and 95% CIs for PFS at 1 year were 87% (72%-94%), at 3 years 71% (51%-83%), and at 5 years 64% (42%-80%). | 1 |

**Advanced Stage Endometrial Cancer
EVIDENCE TABLE**

| Reference | Study Type | Patients/ Events | Study Objective (Purpose of Study) | Study Results | Study Quality |
|--|------------------|---------------------|--|--|------------------|
| 39. Lupe K, Kwon J, D'Souza D, et al. Adjuvant paclitaxel and carboplatin chemotherapy with involved field radiation in advanced endometrial cancer: a sequential approach. <i>Int J Radiat Oncol Biol Phys.</i> 2007; 67(1):110-116. | Observational-Tx | 33 patients | To determine the feasibility of adjuvant paclitaxel and carboplatin chemotherapy interposed with involved field RT for women with advanced endometrial cancer. | 33 patients (median age, 63 years) received treatment between April 2002 and June 2005. Median follow-up was 21 months. Stage distribution was as follows: IIIA (21%), IIIC (70%), IVB (9%). Combination chemotherapy was successfully administered to 30 patients (91%) and 25 patients (76%), before and after RT respectively. 9 patients (27%) experienced acute Grade 3 or 4 chemotherapy toxicities. All patients completed pelvic RT; 19 (58%) received standard 4-field RT and 14 (42%) received IMRT. 10 (30%) received EFRT radiation. 4 patients (12%) experienced acute Grade 3 or 4 RT toxicities. 6 (18%) patients developed chronic RT toxicity. There were no treatment-related deaths. 2-year DFS and OS rates were both 55%. There was only one pelvic relapse (3%). | 1 |
| 40. Milgrom SA, Kollmeier MA, Abu-Rustum NR, et al. Postoperative external beam radiation therapy and concurrent cisplatin followed by carboplatin/paclitaxel for stage III (FIGO 2009) endometrial cancer. <i>Gynecol Oncol.</i> 2013;130(3):436-440. | Observational-Tx | 40 patients | To report an institutional experience using this approach in stage III (FIGO 2009) endometrial cancer. | Of the 40 eligible patients, 7 (18%) were stage IIIA and 33 (82%) IIIC. 19 patients (48%) were ≥60 years of age. T23 (58%) had ≥50% myometrial invasion, 30 (75%) lymphovascular invasion, 11 (28%) cervical stromal invasion, and 5 (12%) positive peritoneal cytology. Histology was endometrioid in 32 (80%), serous in 6 (15%), and clear cell in 2 (5%). At a median follow-up of 49 months, the 5-year freedom from relapse was 79% and OS 85%. The 5-year rate of vaginal recurrence was 3%, non-vaginal pelvic recurrence 3%, para-aortic recurrence 11%, peritoneal recurrence 5%, and other distant recurrence 11%. 31 patients (78%) were able to complete the planned RT/cisplatin and 4 cycles of carboplatin/paclitaxel. Acute grade 3 toxicity occurred in 10 patients (4 neutropenia, 2 anemia, 1 fatigue, 2 diarrhea). No late toxicity was grade ≥3. | 2 |

**Advanced Stage Endometrial Cancer
EVIDENCE TABLE**

| Reference | Study Type | Patients/ Events | Study Objective (Purpose of Study) | Study Results | Study Quality |
|--|------------------|---------------------|--|---|------------------|
| 41. Bruzzone M, Miglietta L, Franzone P, Gadducci A, Boccardo F. Combined treatment with chemotherapy and radiotherapy in high-risk FIGO stage III-IV endometrial cancer patients. <i>Gynecol Oncol</i> . 2004; 93(2):345-352. | Observational-Tx | 45 patients | To assess the efficacy and toxicity of a platinum- and doxorubicin-containing chemotherapy followed by conventional RT. | Chemotherapy was well tolerated: WHO grade 4 neutropenia, without fever or other symptoms, has been recorded in 6 patients (8.8%) at nadir, but no patient required hospitalization or colony-stimulating factors support during chemotherapy. RT timing was not delayed by systemic treatment. Toxicities observed during radiation treatment are superimposable to those referred for not pretreated patients. At a median follow-up time of 63 months (range 4-112), 18 patients progressed and 16 patients have died: actuarial 9 years PFS and survival are 30% and 53%, respectively. | 2 |
| 42. 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. <i>Int J Radiat Oncol Biol Phys</i> . 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 planning target volume. 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 |

**Advanced Stage Endometrial Cancer
EVIDENCE TABLE**

| Reference | Study Type | Patients/ Events | Study Objective (Purpose of Study) | Study Results | Study Quality |
|--|------------------|---------------------|---|---|------------------|
| 43. Bouchard M, Nadeau S, Gingras L, et al. Clinical outcome of adjuvant treatment of endometrial cancer using aperture-based intensity-modulated radiotherapy. <i>Int J Radiat Oncol Biol Phys</i> . 2008;71(5):1343-1350. | Observational-Tx | 15 patients | To assess disease control and acute and chronic toxicity with aperture-based IMRT for postoperative pelvic irradiation of endometrial cancer. | At a median follow-up of 27 months (range, 23-30), no relapse was noted among the aperture-based IMRT group compared with 5 relapses in the control group (P=0.1). The characteristics of each group were similar, except for the mean body mass index, timing of brachytherapy, and applicator type used. Patients treated with aperture-based IMRT experienced more frequent Grade 2 or greater gastrointestinal acute toxicity (87% vs 53%, P=0.02). No statistically significant difference was noted between the 2 groups regarding the incidence or severity of chronic toxicities. Aperture-based IMRT plans significantly improved target coverage (93% vs 76% of planning target volume receiving 45 Gy for aperture-based IMRT vs conventional 4-field technique, respectively). The sparing of organs at risk was similar to that of beamlet-based-IMRT. | 1 |
| 44. Ahamad A, D'Souza W, Salehpour M, et al. Intensity-modulated radiation therapy after hysterectomy: comparison with conventional treatment and sensitivity of the normal-tissue-sparing effect to margin size. <i>Int J Radiat Oncol Biol Phys</i> . 2005; 62(4):1117-1124. | Observational-Tx | 10 patients | To determine the influence of target-volume expansion on the reduction in small-bowel dose achieved with use of IMRT vs standard conformal treatment of the pelvis after hysterectomy, and to investigate the influence of patient body habitus on the normal-tissue sparing achieved with use of IMRT. | Significantly less small bowel was irradiated by IMRT than by 2 conformal fields (P<0.0001) or 4 conformal fields (P<0.0001) for doses >25 Gy. Significantly less rectum was irradiated by IMRT than by 2 conformal fields (P<0.0001) or 4 conformal fields (P<0.0001). Significantly less bladder was irradiated by IMRT than by 2 conformal fields (P<0.0001). However, the magnitude of the sparing achieved by use of IMRT decreased as margins increased. In particular, the volume of small bowel spared by IMRT vs 2 conformal fields or 4 conformal fields decreased as margin size increased (P=0.0002 and P=0.008 for 2 conformal fields and 4 conformal fields, respectively). The amount of normal-tissue sparing achieved by use of IMRT vs 4 conformal fields was inversely correlated with patient body mass index. | 2 |

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EVIDENCE TABLE**

| Reference | Study Type | Patients/ Events | Study Objective (Purpose of Study) | Study Results | Study Quality |
|---|------------------|------------------------|---|---|------------------|
| 45. Roeske JC, Lujan A, Rotmensch J, Waggoner SE, Yamada D, Mundt AJ. Intensity-modulated whole pelvic radiation therapy in patients with gynecologic malignancies. <i>Int J Radiat Oncol Biol Phys.</i> 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 two (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 planning target volume 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 planning target volume received greater than 50.0 Gy in the IM-WPRT plans. | 2 |
| 46. Mundt AJ, Lujan AE, Rotmensch J, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. <i>Int J Radiat Oncol Biol Phys.</i> 2002; 52(5):1330-1337. | Observational-Tx | 40 gynecology patients | To describe our initial clinical experience with IM-WPRT in women with gynecologic malignancies. | IM-WPRT plans provided excellent planning target volume coverage, with considerable sparing of the surrounding normal tissues. On average, 98.1% of the planning target volume received the prescription dose. The average percentage of the planning target volume receiving 110% and 115% of the prescription dose was 9.8% and 0.2%, respectively. IM-WPRT was well tolerated, with no patient developing Grade 3 toxicity. Grade 2 acute gastrointestinal toxicity was less common in the IM-WPRT group (60% vs 91%, $P=0.002$) than in the conventional WPRT group. Moreover, the percentage of IM-WPRT and WPRT patients requiring no or only infrequent antidiarrheal medications was 75% and 34%, respectively ($P=0.001$). Although less Grade 2 genitourinary toxicity was seen in the IM-WPRT group (10% vs 20%), this difference was not statistically significant ($P=0.22$). | 2 |

**Advanced Stage Endometrial Cancer
EVIDENCE TABLE**

| Reference | Study Type | Patients/ Events | Study Objective (Purpose of Study) | Study Results | Study Quality |
|---|------------------|------------------------|---|---|------------------|
| 47. Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. <i>Int J Radiat Oncol Biol Phys.</i> 2003; 56(5):1354-1360. | Observational-Tx | 36 gynecology patients | To provide a preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with IM-WPRT. | The IM-WPRT and WPRT groups were well balanced in terms of most patient and treatment factors, including age, site, stage, chemotherapy, WPRT dose, and brachytherapy, except for a higher frequency of surgery (75% vs 54%, P=0.02) in the IM-WPRT group. Overall, IM-WPRT patients had a lower rate of chronic gastrointestinal toxicity (11.1 vs 50.0%, P=0.001) than WPRT patients. The percentage of IM-WPRT patients with Grade 1, 2, and 3 toxicity were 8.3%, 2.8%, and 0%, respectively. Corresponding percentages in the WPRT group were 30.0%, 16.7%, and 3.3%, respectively. The only other factor correlated with chronic gastrointestinal toxicity was age (P=0.02). On multivariate (logistic regression) analysis controlling for age and other clinical factors, IM-WPRT retained its statistical significance (P=0.01; odds ratio 0.16; 95% CI 0.04, 0.67). | 1 |
| 48. Jhingran A, Salehpour M, Sam M, Levy L, Eifel PJ. Vaginal motion and bladder and rectal volumes during pelvic intensity-modulated radiation therapy after hysterectomy. <i>Int J Radiat Oncol Biol Phys.</i> 2012;82(1):256-262. | Observational-Tx | 24 patients | To evaluate variations in bladder and rectal volume and the position of the vaginal vault during a 5-week course of pelvic IMRT after hysterectomy. | The mean full and empty bladder volumes at simulation were 480 cc (range, 122-1,052) and 155 cc (range, 49-371), respectively. Bladder volumes varied widely during IMRT: the median difference between the maximum and minimum volumes was 247 cc (range, 96-585). Variations in rectal volume during IMRT were less pronounced. For the 16 patients with vaginal fiducial markers in place throughout IMRT, the median maximum movement of the markers during IMRT was 0.59 cm in the right-left direction (range, 0-0.9), 1.46 cm in the anterior-posterior direction (range, 0.8-2.79), and 1.2 cm in the superior-inferior direction (range, 0.6-2.1). Large variations in rectal or bladder volume frequently correlated with significant displacement of the vaginal apex. | 2 |

**Advanced Stage Endometrial Cancer
EVIDENCE TABLE**

| Reference | Study Type | Patients/ Events | Study Objective (Purpose of Study) | Study Results | Study Quality |
|--|-----------------|---------------------|---|--|------------------|
| 49. Small W, Jr., Mundt AJ. Consensus Guidelines for the Delination of the CTV in the Postoperative Pelvic Radiotherapy of Endometrial and Cervical Cancer. Available at: http://www.rtog.org/CoreLab/ContouringAtlases/GYN.aspx . Accessed 14 March 2013 | Review/Other-Tx | N/A | To illustrate consensus guidelines with respect to the clinical target volume for post-operative therapy of endometrial and cervical tumors. | No results stated in abstract. | 4 |
| 50. Small W, Jr., Beriwal S, Demanes DJ, et al. American Brachytherapy Society consensus guidelines for adjuvant vaginal cuff brachytherapy after hysterectomy. <i>Brachytherapy</i> . 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 external beam RT, 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 |

**Advanced Stage Endometrial Cancer
EVIDENCE TABLE**

| Reference | Study Type | Patients/ Events | Study Objective (Purpose of Study) | Study Results | Study Quality |
|--|-----------------|---------------------|---|--|------------------|
| 51. Salani R, Backes FJ, Fung MF, et al. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. <i>Am J Obstet Gynecol.</i> 2011;204(6):466-478. | Review/Other-Tx | N/A | To review the most recent data on surveillance for gynecologic cancer recurrence in women who have had a complete response to primary cancer therapy. | Although gynecologic cancers account for only 10% of all new cancer cases in women, these cancers account for 20% of all female cancer survivors. Improvements in cancer care have resulted in almost 10 million cancer survivors, and this number is expected to grow. Therefore, determining the most cost-effective clinical surveillance for detection of recurrence is critical. Unfortunately, there has been a paucity of research in what are the most cost-effective strategies for surveillance once patients have achieved a complete response. Currently, most recommendations are based on retrospective studies and expert opinion. Taking a thorough history, performing a thorough examination, and educating cancer survivors about concerning symptoms is the most effective method for the detection of most gynecologic cancer recurrences. There is very little evidence that routine cytologic procedures or imaging improves the ability to detect gynecologic cancer recurrence at a stage that will impact cure or response rates to salvage therapy. | 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.

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

- CI = Confidence interval
- DFS = Disease-free survival
- EBRT = External-beam radiation therapy
- EFRT = Extended-field radiation therapy
- HR = Hazard ratio
- IM-WPRT = Intensity-modulated whole pelvic radiotherapy
- IMRT = Intensity-modulated radiation therapy
- OS = Overall survival
- PFS = Progression-free survival
- RFS = Recurrence-free survival
- RT = Radiation therapy
- TAP = Doxorubicin, cisplatin, and paclitaxel
- UPSC = Uterine papillary serous carcinoma
- WAI = Whole-abdominal irradiation
- WPRT = Whole-pelvic radiation therapy