

American College of Radiology ACR Appropriateness Criteria®

ADVANCED STAGE ENDOMETRIAL CANCER

Expert Panel on Radiation Oncology–Gynecology: Mohamed A. Elshaikh, MD¹; Catheryn M. Yashar, MD²; Aaron H. Wolfson, MD³; Higinia Rosa Cardenas, MD, PhD⁴; Beth Erickson, MD⁵; Anuja Jhingran, MD⁶; Shruti Jolly, MD⁷; Elizabeth Kidd, MD⁸; Larissa J. Lee, MD⁹; Nina A. Mayr, MD¹⁰; David Moore, MD¹¹; Gautam G. Rao, MD¹²; William Small Jr, MD¹³; Mahesh A. Varia, MD¹⁴; Andrew O. Wahl, MD¹⁵; William Yuh, MD¹⁶; David K. Gaffney, MD, PhD¹⁷

Summary of Literature Review

Introduction

Endometrial cancer is the most common gynecological malignancy in the United States and ranks second in gynecologic cancer mortality following only ovarian cancer [1]. More than 84% of patients present with International Federation of Gynecology and Obstetrics (FIGO) stage I–II disease [2]. By definition, patients with advanced stage uterine carcinoma (FIGO stages III–IV) are those with extrauterine disease and are at significant risk of dying from uterine cancer. They constitute a very heterogeneous group of patients with varying risk factors yielding highly variable clinical outcomes. Within the same FIGO stage, patients with disease involving multiple extrauterine sites fare worse compared with patients with involvement of a single site [3-5]. In a series of patients with FIGO stage IIIC, Mariani et al [5] reported a 5-year relapse-free survival of 68% for patients with only lymph node metastases compared to 25% for patients with lymph node metastases plus peritoneal cytologic, vaginal, uterine serosal or adnexal involvement, or a combination of these.

Additionally, data suggest that the survival outcome in patients with para-aortic lymphadenopathy is worse compared to those with pelvic only lymphadenopathy [6]. The revised FIGO staging system [7] acknowledged this difference in outcome and split stage IIIC into stage IIIC1 and IIIC2 to reflect a worse survival rate in women with para-aortic lymphadenopathy. On the other hand, uterine serous and clear cell carcinomas are biologically more aggressive than the endometrioid type with tendency for intra-abdominal spread. Although they comprise less than 15% of all endometrial carcinomas, they account for approximately 40% of the deaths caused by uterine carcinomas [8].

Abdominal exploration (either as open or minimally invasive procedure) with hysterectomy, bilateral salpingo-oophorectomy, and surgical staging is the cornerstone of surgical management in patients with uterine carcinoma. Several studies reported a potential survival advantage of cytoreductive surgery in advanced stage endometrial carcinoma [9,10]. Postoperatively, patients with advanced stage disease may require adjuvant therapy(s) to reduce the chance of tumor recurrence with the potential to improve survival. However, the optimal adjuvant therapy is yet to be established. At present, adjuvant therapeutic options could be chemotherapy alone, radiation therapy (RT) alone or a combined modality therapy (CMT). (See [Variant 1](#).)

Rationale for Adjuvant Chemotherapy Alone

The role of systemic chemotherapy in the adjuvant setting in patients with advanced stage endometrial carcinoma has been established in the last few years based on data from several important studies. In a prospectively randomized phase III study conducted by Gynecologic Oncology Group (GOG), Randall et al [11] reported the outcome of stage III–IVA patients who were treated with adjuvant chemotherapy (cisplatin and doxorubicin [CA]) or whole abdominal radiation treatment (WART). The study showed that 5-year overall stage-adjusted

¹Principal Author, Henry Ford Health System, Detroit, Michigan. ²Co-author University of California San Diego, San Diego, California. ³Co-author University of Miami, Miami, Florida. ⁴Panel Vice-chair, Indiana University Medical Center, Indianapolis, Indiana. ⁵Medical College of Wisconsin, Milwaukee, Wisconsin. ⁶University of Texas, MD Anderson Cancer Center, Houston, Texas. ⁷University of Michigan Health System, Ann Arbor, Michigan. ⁸Stanford Cancer Center, Stanford, California. ⁹Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, Massachusetts. ¹⁰UW Medicine, University of Washington, Seattle, Washington. ¹¹Indiana University School of Medicine, Indianapolis, Indiana, American College of Obstetricians and Gynecologists. ¹²University of Maryland School of Medicine, Baltimore, Maryland, American Society of Clinical Oncology. ¹³Stritch School of Medicine Loyola University Chicago, Maywood, Illinois. ¹⁴University of North Carolina School of Medicine, Chapel Hill, North Carolina. ¹⁵University of Nebraska Medical Center, Omaha, Nebraska. ¹⁶Fred Hutchinson Cancer Center, University of Washington, Seattle, Washington. ¹⁷Panel Chair, University of Utah Medical Center, Salt Lake City, Utah.

The American College of Radiology seeks and encourages collaboration with other organizations on the development of the ACR Appropriateness Criteria through society representation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply individual or society endorsement of the final document.

Reprint requests to: Department of Quality & Safety, American College of Radiology, 1891 Preston White Drive, Reston, VA 20191-4397.

survival was 50% for women who received chemotherapy compared to 38% for those who received adjuvant WART, although the pelvic control rate was better in women who were assigned to WART.

To explore more effective chemotherapy regimens, The GOG conducted 2 prospective studies in patients with advanced or recurrent endometrial carcinoma. In GOG 0177, patients were randomized to receive cisplatin plus doxorubicin chemotherapy, with or without paclitaxel, for a maximum of 7 cycles. Patients receiving the 3-drug combination also received filgrastim. The authors reported that the addition of paclitaxel improves response rates as well as progression-free survival (PFS) and overall survival (OS) [12]. However, when used as adjuvant treatment following surgery and volume-directed RT, the addition of paclitaxel to cisplatin and doxorubicin (CAP) did not improve survival outcome. The percentage of patients alive and recurrence-free at 3 years was 62% for women who received cisplatin and doxorubicin versus 64% for women who received the 3-drug combination with $P=.21$ [13].

The preliminary results of another GOG study were recently presented (GOG 209). The study randomized patients to adjuvant chemotherapy consisting of CAP versus a less toxic regimen consisting of paclitaxel and carboplatin for 7 cycles. In this study adjuvant radiation treatment was also allowed before chemotherapy. The authors reported that paclitaxel and carboplatin were not inferior to CAP in terms of PFS and OS based on interim analysis. The toxicity profile favors the paclitaxel and carboplatin regimen [14].

Rationale for Radiation Treatment Alone

Traditionally, RT has been used in patients with advanced stage endometrial carcinoma to improve locoregional control after hysterectomy. Its role has been established in patients with early-stage intermediate and high-risk endometrial cancer [15-17]. Pelvic irradiation with or without para-aortic RT is commonly used in patients with advanced uterine carcinoma with the expectation of reducing the risk of nodal recurrence; there have been no randomized studies to demonstrate survival advantage. Several retrospective studies have reported the impact of adjuvant RT in this setting, but most of these studies are small and include highly variable groups of patients [18-22]. In general, these studies suggest some benefits from adjuvant RT after complete surgical staging. However, the mode of relapse in these patients was mainly systemic, reflecting the fact that single-treatment modality is not adequate to prevent disease recurrences.

When RT is used alone, optimal treatment volume, however, is less defined. Various radiation treatment volumes include external beam radiation therapy (EBRT) to the pelvis with or without para-aortic irradiation, combination of EBRT and vaginal cuff brachytherapy, and WART, incorporating pelvic boost with or without vaginal cuff brachytherapy. (See [Variant 2](#).)

Rationale for Combined Modality Therapy (Chemotherapy and Radiation Treatment)

The randomized phase III study (GOG 122) showed improved survival outcomes with CA chemotherapy compared to WART in women with advanced stage endometrial carcinoma. However, chemotherapy alone has been reported to have locoregional relapse rates of 18%–46% [11,23,24]. For patients randomized to chemotherapy in the GOG study 0122, only 50% were predicted to be alive and disease free at 5 years, highlighting the necessity for improving the therapeutic gain of adjuvant treatment of patients with advanced stage endometrial carcinoma.

In another prospectively randomized study reported by Maggi et al [25], patients with high-risk endometrial carcinoma (65% were FIGO stage III) were randomized to 5 cycles of adjuvant chemotherapy (CAP) versus adjuvant EBRT to the pelvis \pm para-aortic area. The 5-year PFS and OS was 63% and 66%, respectively, for patients who were treated with chemotherapy compared to 63% and 69% for those who were treated with RT. The authors reported no statistical differences between the 2 treatment groups in terms of PFS and OS. In this study, although RT delayed local relapse, chemotherapy delayed systemic relapse. In a pooled analysis of 2 randomized trials [26], the addition of chemotherapy to adjuvant RT improved PFS but not OS in stage I-III patients.

In a multicenter retrospective study for patients with FIGO stage III endometrial carcinoma, 3-year relapse-free survival was 86.5% for patients who received CMT compared to only 65.8% and 44.1% for patients treated with chemotherapy alone or RT alone, respectively [27].

A strategy combining chemotherapy and RT would potentially yield better results in this patient population by controlling both systemic and local recurrences. Several studies have reported that adjuvant therapy with both chemotherapy and RT for women with advanced stage endometrial cancer is well-tolerated [28-30]. Several authors have reported that the prognosis of patients who received adjuvant CMT are superior compared to those

treated with either RT alone, or chemotherapy alone [24,27,31,32]. The currently open GOG study 0258 is randomizing patients to chemotherapy alone (6 cycles of carboplatin and paclitaxel) versus tumor-directed RT with concurrent cisplatin chemotherapy followed by 4 cycles of carboplatin and paclitaxel. It should shed light on this important question of whether or not the combination of chemotherapy and radiation treatment is superior to chemotherapy alone [33].

The phase II trial run by the RTOG (protocol 9708) demonstrated feasibility and high efficacy of a combined chemotherapy and radiation treatment approach in endometrial cancer patients at high risk of recurrence. The regimen studied here involved cisplatin given together with pelvic radiation (45 Gy) followed by 4 cycles of cisplatin and paclitaxel. At 4 years, the cumulative proportions of patients with pelvic, regional, and distant recurrence are 2%, 2%, and 19%, respectively. The percentage of patients alive or alive and disease-free at 4 years was 85% and 81%, respectively. For stage III patients, 4-year OS and disease-free survival was 77% and 72%, respectively [34].

The recently reported results of GOG 184 suggest that a combined volume-directed RT followed by systemic chemotherapy yields 3-year recurrence-free survival (RFS) of 62%–64%. In this study, after surgical staging and volume-directed RT to the pelvis/para-aortic lymph nodes, women with stage III and IVA endometrial carcinoma were randomized to 6 cycles of CA with or without paclitaxel (CAP). There was no statistically significant difference in RFS with the addition of paclitaxel to the CA regimen. The OS data is not yet reported [13].

The appropriate sequence of administering chemotherapy and volume-directed radiation treatment, as well as the most appropriate chemotherapy agents to use, remains controversial. Some investigators reported satisfactory experiences for patients with advanced stage endometrial carcinoma using adjuvant chemotherapy upfront followed by RT and followed by more chemotherapy “sandwich” [24,35-40]. Other reported sequences of chemotherapy and RT included RT concurrently with cisplatin followed by more chemotherapy [34,40], RT upfront followed by chemotherapy [13], or chemotherapy followed by RT [41]. However, there is no prospective study to date comparing these available sequences for chemotherapy and RT. (See [Variant 3](#).)

Salvage Management of Recurrence

Although no established standard exists, the majority of the panel supports individualized care, which accounts for factors such as site and size of recurrence, patient’s performance status, prior adjuvant therapy, etc. (See [Variant 4](#).)

Radiation Treatment Volume and Planning

There appears to be little role for WART in patients with stage III–IV endometrial carcinoma. The toxicity profile from WART suggests a better role for a more conformal or volume-directed RT with 3-D (3DRT) or intensity-modulated radiation therapy (IMRT). Different radiation techniques are available (eg, 4-field box technique) to encompass the whole pelvis using bony landmarks to ensure adequate coverage of tumor bed and nodal areas at risk. Although no phase III trial has been designed to compare 3DRT and IMRT, IMRT may further improve treatment of areas at risk for tumor recurrence while sparing adjacent normal tissues [42].

Several studies of IMRT for gynecologic malignancies showed that, compared with external beam pelvic RT, IMRT improved target coverage and reduced the volume of normal tissues receiving the prescription dose [43-45]. Treatment studies of IMRT for gynecologic malignancies showed also that this reduction in dose resulted in a reduction in both acute [46] and chronic gastrointestinal [47] side effects compared with historic controls.

At the time of simulation, and based on the site of treatment, the use of oral and/or IV contrast would help in accurately delineating the surrounding normal tissues as well as the target volume. Techniques to displace small bowel out of the pelvis to diminish treatment-related morbidity are discussed in other publications and are not the focus of this report (eg, using prone position, treatment with a belly board, etc). See the ACR Appropriateness Criteria[®] “[Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer](#).”

According to a recently published RTOG protocol 0418 [42], it is highly encouraged to insert radio-opaque marker seeds into the vaginal apex before simulation to help identify the vaginal apex on the computed tomography (CT) scan. Markers or devices that distend or otherwise alter the vaginal anatomy are strongly discouraged. A minimum of 3 cm of the proximal vagina need to be contoured. It is very important to account for vaginal wall motion during planning and treatment [48]. In addition, a nodal clinical target volume (CTV) is defined that includes the regional nodes (common iliac, internal and external iliac, and obturator ± para-aortic

lymph nodes) and paravaginal tissues. An online atlas detailing the nodal CTV and the vaginal CTV was posted on the RTOG website to help standardize delineation of these target volumes [49].

For the purpose of this current American College of Radiology panel deliberation, the CTV dose is 45–50 Gy at 1.8–2.0 Gy per fraction. Vaginal cuff brachytherapy may be added to external beam as a boost (eg, in case of cervical stromal involvement). It is recommended that the vaginal treatment volume include the proximal 3–5 cm of the vaginal length [50].

Follow-up after Treatment

Although no established standard exists, the majority of the panel supports a general examination, including a complete history and a pelvic-rectal examination, conducted every 3 months for the first 2 years and semiannually thereafter as suggested by the Society of Gynecologic Oncology [51]. Since the majority of patients with recurrence are usually symptomatic and virtually all recurred within 5 years, it seems reasonable that patients return to annual population-based general physical and pelvic examination after 5 years of recurrence-free follow-up. (See [Variant 5](#).) It is recommended that all patients undergo a targeted investigation to rule out recurrence if symptomatic, since patients with local recurrence are potentially curable with further therapy.

There is insufficient evidence to recommend the routine use of Pap smear, abdominal/pelvic CT scan, positron emission tomography (PET) or CA 125 testing to detect asymptomatic recurrences. However, imaging studies are strongly recommended if clinically indicated (eg, suspicion of disease recurrence or to evaluate response to treatment).

It is also strongly recommended patients be counseled on the potential adverse effects of treatment and their quality of life aspects, especially sexual quality of life, with each follow-up visit. Patients should be instructed to use a vaginal dilator at least weekly for the first 12 months after vaginal brachytherapy. Additionally, patients should be instructed to follow the screening guidelines for mammography and colonoscopy.

Summary

- Patients with advanced stage endometrial carcinoma constitute a very heterogeneous group of patients with varying prognostic factors yielding highly variable clinical outcomes.
- Surgical staging is the cornerstone of curative management of these patients. Adjuvant multimodality therapy is highly recommended to reduce the chance of tumor recurrence with the potential to improve survival. A combination of systemic chemotherapy and radiation treatment is usually appropriate adjuvant treatment option.
- Randomized studies are underway to monitor our progress in the treatment of advanced endometrial carcinoma.
- For adjuvant radiation treatment, IMRT and 3-D radiation treatment are the most appropriate treatment techniques.

Supporting Documents

- [ACR Appropriateness Criteria® Overview](#)
- [Evidence Table](#)

References

1. American Cancer Society. *Cancer Facts & Figures 2012*: Atlanta: American Cancer Society; 2012.
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. *Int J Gynaecol Obstet*. 2006;95 Suppl 1:S105-143.
3. Connell PP, Rotmensch J, Waggoner S, Mundt AJ. The significance of adnexal involvement in endometrial carcinoma. *Gynecol Oncol*. 1999;74(1):74-79.
4. Greven KM, Corn B, Lanciano RM, Case D, Randall ME. Pathologic stage III endometrial carcinoma: Significance of extrauterine sites. *Radiation Oncology Investigations*. 1996;4(3):122-128.
5. Mariani A, Webb MJ, Keeney GL, Haddock MG, Aletti G, Podratz KC. Stage IIIC endometrioid corpus cancer includes distinct subgroups. *Gynecol Oncol*. 2002;87(1):112-117.
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. *Obstet Gynecol*. 2010;116(5):1141-1149.
7. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet*. 2009;105(2):103-104.

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. *Br J Cancer*. 2006;94(5):642-646.
9. Lambrou NC, Gomez-Marin O, Mirhashemi R, et al. Optimal surgical cytoreduction in patients with Stage III and Stage IV endometrial carcinoma: a study of morbidity and survival. *Gynecol Oncol*. 2004;93(3):653-658.
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. *Gynecol Oncol*. 2007;107(2):190-193.
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. *J Clin Oncol*. 2006;24(1):36-44.
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. *J Clin Oncol*. 2004;22(11):2159-2166.
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. *Gynecol Oncol*. 2009;112(3):543-552.
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. *Gynecol Oncol*. 2012;125(3):771.
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. *Lancet*. 2000;355(9213):1404-1411.
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. *Gynecol Oncol*. 2004;92(3):744-751.
17. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet*. 2010;375(9717):816-823.
18. 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. *Gynecol Oncol*. 2009;115(1):6-11.
19. Mundt AJ, Murphy KT, Rotmensch J, Waggoner SE, Yamada SD, Connell PP. Surgery and postoperative radiation therapy in FIGO Stage IIIC endometrial carcinoma. *Int J Radiat Oncol Biol Phys*. 2001;50(5):1154-1160.
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. *Gynecol Oncol*. 1999;75(2):211-214.
21. Slomovitz BM, Burke TW, Eifel PJ, et al. Uterine papillary serous carcinoma (UPSC): a single institution review of 129 cases. *Gynecol Oncol*. 2003;91(3):463-469.
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. *Gynecol Oncol*. 1995;56:135-136.
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. *Int J Radiat Oncol Biol Phys*. 2001;50(5):1145-1153.
24. Secord AA, Geller MA, Broadwater G, et al. A multicenter evaluation of adjuvant therapy in women with optimally resected stage IIIC endometrial cancer. *Gynecol Oncol*. 2013;128(1):65-70.
25. 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.
26. 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.
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. *Oncology*. 2011;81(2):104-112.
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. *Gynecol Oncol*. 2009;112(1):134-141.
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. *Gynecol Oncol*. 1996;63(3):299-303.
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. *Gynecol Oncol*. 2011;122(1):59-62.

31. Schwandt A, Chen WC, Martra F, Zola P, Debernardo R, Kunos CA. Chemotherapy plus radiation in advanced-stage endometrial cancer. *Int J Gynecol Cancer*. 2011;21(9):1622-1627.
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. *Gynecol Oncol*. 2009;114(3):442-447.
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.
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. *Gynecol Oncol*. 2006;103(1):155-159.
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). *Gynecol Oncol*. 2008;108(1):201-206.
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. *Gynecol Oncol*. 2009;112(3):553-557.
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. *Gynecol Oncol*. 2010;118(1):19-23.
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. *Gynecol Oncol*. 2011;121(1):112-117.
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. *Int J Radiat Oncol Biol Phys*. 2007;67(1):110-116.
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. *Gynecol Oncol*. 2013;130(3):436-440.
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. *Gynecol Oncol*. 2004;93(2):345-352.
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. *Int J Radiat Oncol Biol Phys*. 2012;84(1):e23-28.
43. Bouchard M, Nadeau S, Gingras L, et al. Clinical outcome of adjuvant treatment of endometrial cancer using aperture-based intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys*. 2008;71(5):1343-1350.
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. *Int J Radiat Oncol Biol Phys*. 2005;62(4):1117-1124.
45. 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.
46. Mundt AJ, Lujan AE, Rotmensch J, et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. *Int J Radiat Oncol Biol Phys*. 2002;52(5):1330-1337.
47. Mundt AJ, Mell LK, Roeske JC. Preliminary analysis of chronic gastrointestinal toxicity in gynecology patients treated with intensity-modulated whole pelvic radiation therapy. *Int J Radiat Oncol Biol Phys*. 2003;56(5):1354-1360.
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. *Int J Radiat Oncol Biol Phys*. 2012;82(1):256-262.
49. Small W, Jr., Mundt AJ. Consensus Guidelines for the Deliniation of the CTV in the Postoperative Pelvic Radiotherapy of Endometrial and Cervical Cancer. 2013; Available at: <http://www.rtog.org/CoreLab/ContouringAtlases/GYN.aspx>. Accessed March 14, 2013.
50. 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.
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. *Am J Obstet Gynecol*. 2011;204(6):466-478.

The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Clinical Condition: **Advanced Stage Endometrial Cancer**

Variant 1: **A 66-year-old woman with vaginal bleeding undergoes total abdominal hysterectomy, salpingo-oophorectomy and pelvic/para-aortic lymphadenectomy, peritoneal cytology. Pathology review of the specimens reveals uterine endometrioid carcinoma FIGO grade 3, invading 19 mm out of 20 mm myometrial thickness, with involvement of cervical stroma, right ovary, and negative peritoneal cytology. There was no lymphovascular space involvement. All 32 examined lymph nodes were negative for metastatic involvement. (Stage IIIA).**

Treatment	Rating	Comments
Chemotherapy Alone		
Cisplatin and doxorubicin for 7 cycles	4	
Carboplatin/paclitaxel for 6–7 cycles	6	
Carboplatin/paclitaxel for 3 cycles	3	
Radiation Treatment Alone		
Pelvic external beam	6	
Vaginal cuff brachytherapy alone	3	
Pelvic external beam with vaginal cuff brachytherapy	7	
Whole abdominal radiation treatment	3	
Combined Chemotherapy and Radiation Treatment		
Chemotherapy followed by radiation treatment	6	
Radiation treatment followed by chemotherapy	6	
Chemotherapy × 3 cycles followed by radiation treatment, then 3 more chemotherapy cycles “sandwich”	5	
Radiation treatment with concurrent cisplatin followed by more chemotherapy after completion of radiation treatment	7	
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Advanced Stage Endometrial Cancer**

Variant 2: **A 65-year-old woman undergoes modified radical hysterectomy and salpingo-oophorectomy. Pelvic and para-aortic sampling was not performed. Preoperative imaging did not show pathologic adenopathy. Pathology review of the pathologic specimens reveals uterine clear cell carcinoma involving >50% of myometrial thickness and involving cervical stroma and serosa of the uterus. Lymphovascular space involvement was present. Peritoneal cytology was negative.**

Treatment	Rating	Comments
Surgical restaging with lymph node dissection	5	
Adjuvant Management (If Surgical Restaging Is not Feasible)		
Chemotherapy alone	3	
Radiation treatment alone	4	Consider this procedure if the patient cannot tolerate chemotherapy.
Combined chemotherapy and radiation treatment	7	
Radiation Treatment Volume (If RT Alone)		
Vaginal cuff brachytherapy alone	2	
Pelvic external beam alone	5	
Pelvic and para-aortic external beam	4	
Pelvic external beam with vaginal cuff brachytherapy	7	
Pelvic, para-aortic external beam with vaginal cuff brachytherapy	5	
Radiation Treatment Volume (If Used With Chemotherapy)		
Vaginal cuff brachytherapy alone	3	
Pelvic external beam alone	5	
Pelvic and para-aortic external beam	3	
Pelvic external beam with vaginal cuff brachytherapy	7	
Pelvic and para-aortic external beam with vaginal cuff brachytherapy	3	
If Vaginal Cuff Brachytherapy Is Used, Active Vaginal Length You Would Treat		
Upper one-third–one-half	8	
Entire vaginal length	4	
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Advanced Stage Endometrial Cancer**

Variant 3: **A 69-year-old woman undergoes complete surgical staging including omentectomy. Preoperative staging CT was negative for metastatic disease. Pathology review of the specimens reveals uterine serous carcinoma, invading > 50% of myometrial thickness, without involvement of cervical stroma or adnexa. Two out of 29 lymph nodes were involved with metastatic disease (one right obturator and one para-aortic node). Peritoneal cytology and omental specimen were negative of malignant cells. There was no lymphovascular space involvement. Patient agreed to receive multimodality treatment (chemotherapy and radiation therapy).**

Treatment	Rating	Comments
Radiation Treatment Consideration		
Repeat CT scan of the chest, abdomen and pelvis before RT if chemotherapy is delivered first	6	
Simulate the patient in supine position	7	
Simulate the patient in prone position with a belly board device	5	
Simulate with oral contrast	8	
Simulate with intravenous contrast	7	
Simulate with vaginal cuff radio opaque marker	7	
Radiation Treatment Volume		
Pelvic	3	
Pelvic and para-aortic external beam	8	
Pelvic, para-aortic external beam and vaginal cuff brachytherapy	5	
Vaginal cuff brachytherapy	3	
Pelvic external beam with vaginal cuff brachytherapy	3	
Radiation Therapy Technique		
2-D	2	
3-D conformal treatment	7	
<u>IMRT</u>	8	
Radiation Therapy Dose to the Pelvis and/or Para-aortic Area		
45 Gy	8	
50.4 Gy	7	
45–50.4 Gy with vaginal cuff boost using brachytherapy	7	
<u>Rating Scale:</u> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: Advanced Stage Endometrial Cancer

Variant 4: A 67-year-old woman undergoes complete surgical staging. Pathology revealed 2009 FIGO stage IIIC2 endometrioid carcinoma grade 3. Radiologic restaging after 3 cycles of carboplatin and Taxol chemotherapy alone and before starting adjuvant radiation treatment showed interval disease progression with pelvic and para-aortic lymphadenopathy. The patient is healthy otherwise.

Treatment	Rating	Comments
Management		
Continue same chemotherapy alone regimen with 3–6 more cycles	2	
Start different chemotherapy alone regimen	5	
Surgical debulking prior to further adjuvant therapy	3	
Radiation treatment alone to the pelvis and para-aortic area	6	
Radiation therapy with chemotherapy	7	
Consider palliative care/hospice approach	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 5: A 51-year-old woman undergoes complete surgical staging. Pathology showed uterine endometrioid carcinoma FIGO grade 2, >50% of myometrial thickness, with involvement of cervical stroma and left fallopian tube. Two pelvic lymph nodes out of 30 pelvic/para-aortic lymph nodes were positive for metastatic involvement. Assume adjuvant chemotherapy and radiation treatment (pelvic and vaginal cuff) have been completed.

Treatment	Rating	Comments
Routine Follow-up Recommendations		
Follow-up visits every 3–6 months with pelvic examination with/without Pap smears for at least 5 years	8	
Discuss the use of vaginal dilator at least weekly for the first 12 months after treatment	8	
Follow-up with imaging studies at least yearly in the first 5 years or sooner if clinically indicated	5	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		