# American College of Radiology
# ACR Appropriateness Criteria®

## ADVANCED STAGE ENDOMETRIAL CANCER

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## 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-ophorectomy, 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

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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 ± 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

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**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 | |
| **Rating Scale:** **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 | |

**Rating Scale:** **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 | |
| IMRT | 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 | |

**Rating Scale:** **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** | | |