American College of Radiology
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MANAGEMENT OF RECURRENT ENDOMETRIAL CANCER

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Summary of Literature Review

Introduction/Background

Endometrial cancer (EC) is the most common cancer of the female reproductive organs. More than 54,000 women in the United States are expected to be diagnosed with this disease in 2015 and over 10,000 women will die as a result [1]. The majority of women with EC will be cured after hysterectomy with or without adjuvant therapies. However, approximately 10%–15% of women with early-stage EC will experience tumor recurrence [2,3]. The chances of developing recurrence are greatest in those women with an advanced International Federation of Gynecology and Obstetrics (FIGO) stage tumor [4,5].

In women with EC, tumor recurrences tend to occur in the 2- to 3-year period following initial treatment (60% of relapses diagnosed within 2 years and 76% within 3 years) [6]. Despite this, recurrences can occur >15 years after completion of treatment [7,8].

Although the prognosis of women with recurrent EC is relatively good, a percentage of these patients will die from their recurrent disease. Known prognostic factors for recurrent EC include type of initial adjuvant management, site of recurrence (locoregional or distant), time to recurrence, and the histological type [6,9-15].

Management of disease recurrence in EC poses significant challenges. These patients represent a heterogeneous group where histological subtypes (endometrioid, serous, clear cell), the completeness of surgical staging, previous adjuvant management, interval since completion of adjuvant therapy, and size and site(s) of disease recurrence all have important implications on salvage therapies and prognosis. No randomized controlled trials have been published to determine optimal management in this group of patients.

At present, treatment of women with recurrent EC is mainly based on retrospective series of patients. Management of EC can be curative or palliative depending on the nature of the recurrence (local or systemic) and the aforementioned prognostic factors. In general, curative management of disease recurrence can include radiation therapy (RT), surgical resection, chemotherapy, and hormonal treatment or any combination of these modalities.

Workup for Recurrent Endometrial Cancer

When recurrence is suspected, a complete restaging workup should include at least computed tomography (CT) with contrast of the abdomen and pelvis. If a patient is unable to have CT with contrast, then magnetic resonance imaging (MRI), ideally with gadolinium, should be considered as an alternative. The role of fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET)/CT scan in EC remains controversial. In numerous retrospective series, PET/CT scan has been shown to be a highly accurate modality for detecting nodal recurrences [16-18]. A recent meta-analysis with over 500 patients showed a sensitivity of 95.8% and specificity of 92.5% with FDG-PET in detecting recurrent EC [18]. For detailed radiologic workup recommendations, please refer to the American College of Radiology (ACR) Appropriateness Criteria® "Pretreatment Evaluation and

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Follow-Up of Endometrial Cancer" [19]. Whenever feasible, pathologic diagnosis with biopsy should be done to confirm disease recurrence.

For the purpose of this article, we will divide the management of women with recurrent EC into 2 main categories: women who had previous adjuvant RT and those who had no adjuvant RT after hysterectomy. Furthermore, we will divide management of disease recurrence in women with EC who had adjuvant RT to those with recurrence in the irradiated field and those with recurrence outside the RT field. The main reason for this simple classification is the fact that previous RT will have some radiation dose limitation. Management of women with recurrent uterine sarcomas and carcinosarcomas will not be discussed in this article.

Recurrent Endometrial Cancer With No Previous Radiation Therapy

Generally, salvage RT is the recommendation of choice in radiation-naïve patients with local or locoregional recurrence. In certain circumstances, surgical resection of the recurrence and/or chemotherapy may also play a role, especially for patients with nonendometrioid histological types.

The prognosis of women with isolated vaginal recurrence is better compared to women with pelvic nodal recurrence [6]. The size (<2 cm) [10] and longer time to develop recurrent disease [11] were correlated with better tumor control. Histologic features of initial diagnosis (<50% myometrial involvement; grade 1–2) were significant predictors for overall survival (OS) after recurrence [9].

In the study by Wylie et al [9], 58 patients with recurrent disease received salvage RT, 3 received local surgical resection prior to RT, and 13 received hormonal treatments. It has been suggested as a result of this study that surgical cytoreduction or neoadjuvant chemotherapy followed by surgery and/or RT might be preferred in certain settings [14].

Isolated Vaginal Cuff Recurrence

The Postoperative Radiation Therapy for Endometrial Carcinoma-1 (PORTEC1) trial demonstrated in stage I patients that adjuvant pelvic radiation helped to reduce locoregional relapse. This did not translate into an OS benefit, likely due to the success of salvage therapy. In a retrospective analysis of the PORTEC1 study [7], 5-year OS after vaginal recurrence was 70% in the patients that did not receive adjuvant RT versus 38% in those that did. At 10 years, survival rates were 51% compared to 25%, respectively. Complete response to salvage therapy was reported in 89% of patients that were randomized to observation [6].

Patients that have not received adjuvant RT and develop an isolated vaginal cuff recurrence are generally managed with salvage RT (brachytherapy and/or pelvic external-beam RT [EBRT]). In this group, RT can achieve good local control and 5-year survival rates ranging from 55% to 85% for all-comers and >90% in patients with early-stage disease at the time of initial diagnosis [6,7,20-23]. In PORTEC1, 35 out of 39 patients with isolated vaginal recurrence received RT with curative intent, most often with pelvic external beam and brachytherapy. The combination of pelvic EBRT plus brachytherapy appears to provide the best outcomes [20,24-28] (see Variant 1).

To our knowledge, no randomized or otherwise controlled study has tried to address the question whether brachytherapy alone is a reasonable treatment for isolated superficial vaginal recurrences. Although some studies included women with recurrent EC who were successfully managed with vaginal brachytherapy alone as a small percentage of their cohorts [20,24], vaginal brachytherapy combined with pelvic EBRT showed improved OS over brachytherapy alone on univariate analysis in one study [24]. Although surgical resection of an isolated vaginal cuff recurrence is potentially acceptable, the number of patients treated with this approach is too small to recommend as a routine management option.

In the study reported by Lee et al [25], all of the RT-naïve patients were salvaged with combined treatment (pelvic EBRT + brachytherapy). In the Sorbe analysis [28], 86% of the patients treated with salvage brachytherapy alone achieved "complete vaginal remission," compared to 92% in the patients treated with combined treatment.

After EBRT and if the residual tumor measures ≥5 mm, interstitial brachytherapy has been successfully used in the salvage treatment of women with EC [26,27,29,30], with similar general conclusions that combining brachytherapy with EBRT yields more favorable results. If interstitial brachytherapy is indicated for large residual tumors after EBRT, laparoscopy, fluoroscopy, or real-time image guidance (ultrasound, CT, or MRI) should be considered to help avoid bowel perforation.

Isolated Pelvic Recurrence

Rates of pelvic-only recurrences vary from 4.9% (at 8 years for low-risk patients) [6] up to 26% (at 3 years in high-risk patients) [31]. Outcomes are substantially worse for patients with pelvic compared to vaginal-only recurrence. Poulsen et al [32] showed a 10-year actuarial survival of 50% and 24% in select patients with vaginal and pelvic recurrences, respectively. Numerous others have reported poor outcomes, including low salvage rates and high risk of metastatic failures, in patients with pelvic recurrences [33,34].

A number of retrospective studies include surgical intervention in patients that have not previously received RT. Surgical resection in this population, however, remains controversial. Considering the poor prognosis of women with pelvic recurrence is mainly due to a high risk of distant failures, combining salvage RT with systemic chemotherapy could potentially improve the therapeutic gain of salvage RT. Some prospective studies in women with advanced or recurrent EC have identified cisplatin, carboplatin, paclitaxel, and doxorubicin as active agents with response rates of 30%–35% [35,36]. However, the question whether the addition of chemotherapy to salvage RT provides a clinical benefit is currently unknown and requires a prospective randomized study (see Variant 2).

Currently, the Gynecologic Oncology Group (GOG) is conducting a randomized trial (GOG 238) in patients with a history of EC treated with hysterectomy and salpingo-oophorectomy who present with locoregional-only recurrence (pelvis and/or vagina). Previous pelvic RT is an exclusion criterion, but previous chemotherapy and/or hormones are allowed. Patients will be randomized to pelvic RT (EBRT and brachytherapy) alone or in combination with concurrent cisplatin chemotherapy.

Para-aortic Recurrence

Some investigators recommend treating para-aortic or common iliac nodal recurrence in RT-naïve patients with tumor-directed EBRT with or without chemotherapy [37]. In patients with resectable isolated para-aortic metastases, surgical resection can be considered with or without RT (see Variant 3).

In a study describing the use of intraoperative RT (IORT), 2 patients in the study cohort had isolated para-aortic recurrences [38]. Gross total resection was achieved in both patients and they were still alive at the last follow-up, corresponding to 54 and 71 months from the date of salvage surgical resection and administration of IORT.

Over the last few years, there has been a growing interest to boost grossly enlarged para-aortic lymph nodes with highly conformal RT using stereotactic body RT (SBRT). The majority of studies using SBRT are very small and likely included very selective groups of patients. One group in Korea [39] has published their experience of 7 patients using SBRT for isolated para-aortic cancer recurrences. Doses ranged from 36 to 51 Gy delivered in 3 total fractions. Survival rates were 100% and 71.4% at 1 and 3 years, respectively. Before widespread adoption of this technology in recurrent gynecologic malignancies, prospective studies are warranted.

Recurrent Endometrial Cancer With Previous Radiation Therapy

Recurrence Outside Irradiated Area

When a recurrence occurs in a patient who received adjuvant vaginal cuff brachytherapy, the recurrence sites tend to be pelvic or extrapelvic. Patients with isolated pelvic recurrence in the setting of previous vaginal cuff RT can be managed similarly to RT-naïve patients discussed above, with understanding of the previous brachytherapy dose distribution.

In the PORTEC-2 study, women with intermediate-risk EC were randomized to adjuvant pelvic EBRT versus vaginal brachytherapy. The rate of isolated pelvic recurrence in those receiving vaginal brachytherapy was only 1.5% (3 of 213) [40]. The majority of the vaginal brachytherapy patients that had pelvic failures also had distant metastatic recurrence.

Recurrence in Previously Irradiated Area

The management of patients with recurrent EC in previously irradiated sites remains not only controversial but also challenging. Management options include surgery with or without re-irradiation (eg, highly conformal RT, IORT), hormonal therapy, and/or chemotherapy.

Although curative re-irradiation is often difficult due to expected toxicity, one possible exception in highly selected cases may be isolated vaginal recurrence in the setting of previous pelvic EBRT and/or brachytherapy [25,29]. A recent study on the use of 3-D image-guided brachytherapy for vaginal recurrence of EC included 13 patients (of a total of 44) that had received prior RT, which included vaginal brachytherapy (n=6), pelvic RT

(n=4), and vaginal brachytherapy + pelvic RT (n=3). Modalities used for treatment of recurrence included brachytherapy alone (n=6) and EBRT + brachytherapy (n=7). The 2-year local failure rate was 39%; disease-specific survival, 26%; and OS, 55%. Not surprisingly, toxicity was higher in the group that received prior RT relative to those that were RT-naïve [25].

Surgery can range from laparoscopic cytoreduction to total pelvic exenteration. Survival outcomes are uniformly dependent on the extent of residual disease following surgery, with the best outcomes most readily achieved in patients with a single site of recurrence and smaller tumor burden prior to surgery [41-44]. Neither the likelihood of optimal cytoreduction nor survival outcomes were dependent on any other variable. Patients with gross residual disease seem to fare as well as those nonsurgically treated [41]. As a result, it is widely held that patients with carcinomatosis are poor cytoreductive candidates and, if discovered intraoperatively, carcinomatosis is considered a reason to abort surgery [42,45]. Laparoscopic approaches have been reported for use in recurrent EC although data are scarce [46-48]. Cytoreductive surgery remains controversial and careful selection of patients is critical; however, further clinical investigation appears warranted.

Pelvic exenteration has traditionally been considered the last possible procedure to obtain local control in central pelvic recurrences. Historically, pelvic exenteration was not considered in the treatment of women with recurrent EC [49,50]. However, with advances in surgical technique and postoperative care, pelvic exenteration can produce acceptable outcomes in carefully selected patients with recurrent EC for whom alternative treatments are limited [50,51]. One study reported long-term survival (>5 years) of 20% [52], and another showed a 5-year disease-free survival rate of 45% [50]. Despite improvements in surgical technique since its introduction in 1948, there remains significant morbidity ranging from 38% to 80% [50,51,53-55] (see Variant 4).

Recurrences in the pelvic sidewall, peritoneal cavity, and retroperitoneum have notoriously had poor outcomes. These recurrences tend to be poorly differentiated and not responsive to hormonal therapy. Multiagent chemotherapies can be associated with significant toxicity and result in response rates from 10%–45% and progression-free survival of approximately 6 months [56-61]. Three-year survival has been reported as <10% [6,34]. Several multimodality treatment strategies have been developed to address this patient population. They include surgery combined with IORT or hyperthermic intraperitoneal. The extent of salvage surgery in this setting (after any combination of previous surgery, RT, or chemotherapy) is often limited due to a delicate balance of achieving complete resection with the morbidity of achieving negative margins. As previously discussed, re-irradiation with EBRT is limited in the doses allowed due to cumulative tolerance of surrounding normal tissue. The main advantage of IORT is that it can maximize dose to the area of microscopic disease while minimizing the dose to the surrounding previously irradiated tissue. IORT can be delivered with electron beam or high- or low-dose-rate brachytherapy.

One of the first groups to publish on the use of IORT solely in EC recurrence was Dowdy et al [38]. In this cohort of 25 patients, only 56% had received adjuvant RT. Radical surgery was performed in all patients and included en bloc resection of the pelvic sidewall; 7 patients also required pelvic exenteration. All 25 patients received IORT. The overall 5-year survival was 47%, with a median survival of 57 months.

In the last several years, there have been a plethora of published studies describing applications for SBRT or stereotactic radiosurgery (SRS) in recurrent gynecological malignancies. Guckenberger et al [62] reported a series of 19 patients with locally recurrent cervical or EC treated with SBRT. Of these, 3 patients had prior RT. They were treated with SBRT 30 Gy in 3 fractions. No acute toxicity was reported, but follow-up was short.

Another series included 11 patients treated with SBRT for local and distant gynecological tumor recurrences. The 2-year local progression-free survival and metastasis-free survival were 81.8% and 54.5%, respectively [63]. Although emerging data suggest that SBRT/SRS may have a beneficial role in the treatment of recurrent EC in select patients, long-term follow-up is very important given the high dose per fraction that may be given to surrounding normal tissues and the concern of long-term toxicities (see Variant 5).

Distant Metastasis

EC can metastasize to the lung, bones, liver, brain, and other sites. Systemic treatment is generally indicated in these situations. Multiagent chemotherapy is the mainstay of treatment; however, single-agent therapy can also be used. Carboplatin and paclitaxel is often the preferred regimen based on the results of GOG 209 [36]. Studies looking at the potential role of targeted agents, such as bevacizumab, epidermal growth factor inhibitors, and mTOR inhibitors, have shown early potential [64,65].

Hormonal therapy can be considered in select patients with endometrioid histologies with receptor-positive tumors, especially if they are asymptomatic or have had a long recurrence-free interval. Generally, progestational agents are used [66,67]. Tamoxifen and aromatase inhibitors are alternatives that have also shown some benefit [66-69].

Surgery may prolong survival with minimal complications in well-selected patients with isolated or oligometastasis to the lung, liver, spleen, brain, and vulva [70,71]. Good performance status of the patient, long disease-free interval, absence of other systemic disease, and resectability, preferably with a clear margin, are favorable prognostic factors [71].

Palliative RT can also be used in symptomatic management of distant metastasis. Conventional RT has long been used to palliate bone pain, brain metastases, and vaginal bleeding. In recent years there has been a trend towards increased utilization of SBRT in the setting of oligometastatic disease. This paradigm shift resulted from an alternative theory of the natural history of cancer where a proposed intermediate state may exist between locoregionally limited disease and widespread metastasis, referred to as oligometastatic disease [72]. Advances in imaging, immobilization, and RT delivery technique have resulted in an ever-increasing body of evidence supporting the potential for improved outcomes in selected patients [72]. The use of SBRT or SRS allows for noninvasive, highly conformal RT that can provide a significant dose to the tumor while sparing surrounding normal tissues to a much greater extent than otherwise possible. SRS is well established for brain and spine metastases, and SBRT has been reported for metastatic gynecological cancers to the pelvic and para-aortic lymph nodes, lung, spine, mediastinum, liver, adrenals, and other sites with reasonable short-term outcomes [63,73,74]. Palliative radiation doses of 30 Gy in 10 fractions or similarly effective palliative dose fractions have been prescribed. Further recommendations in regards to management of spinal bone metastases have been described before; see the ACR Appropriateness Criteria® "Spinal Bone Metastases" [75] (see Variant 6).

Radiation Treatment Volumes, Doses, and Planning

In RT-naïve patients with vaginal cuff recurrence, the recommendation is for combination treatment with pelvic EBRT and vaginal brachytherapy using 45 Gy to the pelvis followed by high-dose-rate (HDR) brachytherapy (intracavitary or interstitial) based on the residual tumor after EBRT [76]. Cumulative doses >70 Gy in equivalent dose in 2-Gy fractions (EQD2) are recommended [25] for smaller residual tumors after EBRT, and higher doses (75–80 Gy) are recommended for bulky residual tumors [20,25,67]. In the re-irradiation setting, brachytherapy doses should be individualized accounting for prior RT doses and the size of disease at the time of salvage RT.

Similar to what has been described before, conformal RT techniques with an emphasis on sparing organs at risk should be considered, particularly if previous RT was received to the area of tumor recurrence to ensure less treatment-related morbidity (see the ACR Appropriateness Criteria® "Advanced Stage Endometrial Cancer" [77]).

Summary of Recommendations

- Women with recurrent endometrial carcinoma constitute a heterogeneous group of patients with varying prognoses.
- For women with locoregional recurrent disease (vaginal cuff and/or pelvic), pelvic RT followed by a boost to the grossly involved site is recommended. The role of concurrent chemotherapy with salvage RT in this setting is being investigated in the ongoing GOG study (GOG 238).
- Management of patients with tumor recurrence in previously irradiated area constitutes a major challenge. If re-irradiation is considered, careful attention should be paid in selecting RT modality and doses to significantly minimize treatment-related toxicities.
- Systemic chemotherapy should be considered for patients with distant metastases. Palliative RT can also be used in symptomatic management of metastatic sites.

Summary of Evidence

Of the 77 references cited in the *ACR Appropriateness Criteria® Management of Recurrent Endometrial Cancer* document, 74 are categorized as therapeutic references including 9 well designed studies, 39 good quality studies, and 6 quality studies that may have design limitations. Additionally, 2 references are categorized as diagnostic references including 1 good quality study and 1 quality study that may have design limitations. There are 20 references that may not be useful as primary evidence. There is 1 reference that is a meta-analysis study.

The 77 references cited in the *ACR Appropriateness Criteria® Management of Recurrent Endometrial Cancer* document were published from 1968-2015.

While there are references that report on studies with design limitations, 49 well designed or good quality studies provide good evidence.

Supporting Documents

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

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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: **Management of Recurrent Endometrial Cancer**

Variant 1: **66-year-old woman who had a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymph node dissection for uterine endometrioid cancer a year ago. The tumor was staged as 2009 FIGO IA grade 2 and she was managed with surveillance. Recently she started to complain of vaginal spotting, and pelvic examination showed a small lesion (about 2 cm in diameter) limited to the mucosa at the vaginal apex. Biopsy confirmed recurrent uterine endometrioid carcinoma. Restaging workup was negative for pelvic adenopathy or extrapelvic metastatic disease. She is otherwise a healthy woman.**

Treatment	Rating	Comments
Management		
Limited surgical resection alone	4	Limited data are available to justify routine surgery alone, but this option may be appropriate (eg, superficial lesion).
Limited surgical resection followed by RT	6	
Salvage RT alone	8	
Salvage RT with concurrent chemotherapy	5	
Hormonal treatment (megestrol acetate) only	2	
If RT Alone (no surgical resection)		
Pelvic EBRT alone	3	
Vaginal brachytherapy alone	3	
Pelvic EBRT with vaginal brachytherapy boost	8	
After 45 Gy Pelvic EBRT, the Recurrent Tumor now Measures <5 mm. The Recommended RT Modality for Tumor boost		
Intracavitary vaginal brachytherapy	8	
Interstitial brachytherapy	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
IMRT	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Management of Recurrent Endometrial Cancer**

Variant 2: **68-year-old woman underwent surgical staging with total abdominal hysterectomy, salpingo-oophorectomy, pelvic and para-aortic lymph node dissection (total of 54 lymph nodes removed), and peritoneal cytology 9 months ago. The tumor was staged as 2009 FIGO stage IB, grade 3 uterine endometrioid carcinoma with lymphovascular space involvement. She declined any adjuvant therapy. Recent CT of the abdomen and pelvis showed 2 pathologic right obturator lymph nodes measuring 1.8 and 2.4 cm in size as well as a 4-cm enhancing mass at the vaginal vault. PET/CT scan showed hypermetabolic activity in the right obturator nodes as well as the vaginal vault lesion. Biopsy was consistent with recurrent uterine endometrioid carcinoma.**

Treatment	Rating	Comments
Management		
Surgical resection alone for the vaginal lesion and the nodes	2	
Surgical resection followed by pelvic RT	3	
RT alone	7	
RT with concurrent chemotherapy	7	
Induction chemotherapy followed by RT	5	
RT +/- chemotherapy followed by adjuvant chemotherapy	7	
Chemotherapy only	3	
Hormonal treatment (megestrol acetate) only	2	
RT Volume (if used)		
Pelvic EBRT alone	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Pelvic EBRT with vaginal brachytherapy	8	
Pelvic EBRT, para-aortic RT, and vaginal brachytherapy	5	
Initial Pelvic RT Dose (without boost)		
45–50.4 Gy	8	
54–60 Gy	3	
Vaginal Cuff Total Dose in EQD2 with Brachytherapy (including boost)		
54–60 Gy	3	
60–66 Gy	4	
66–72 Gy	6	
72–78 Gy	7	
Vaginal Cuff Total Dose in EQD2 with IMRT (including boost)		
54–60 Gy	3	
60–66 Gy	5	
66–72 Gy	6	
72–78 Gy	5	This dose is appropriate if it can be safely delivered considering adjacent organs at risk.

The Recommended RT Modality to Boost the Vaginal Lesion after 45 Gy (assuming 2-cm residual disease) Intracavitary HDR brachytherapy with a single-channel vaginal cylinder	2	
Interstitial implant	8	
Boost using IMRT	5	This option is appropriate if interstitial is not available; patient refuses, or is medically unable.
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Management of Recurrent Endometrial Cancer**

Variant 3: **60-year-old woman who underwent complete surgical staging and was staged as 2009 FIGO IIIC1 uterine endometrioid carcinoma. She received 6 cycles of chemotherapy consisting of carboplatin and paclitaxel as a participant in a randomized trial. A recent CT scan of the abdomen 7 months after completion of chemotherapy showed bilateral pelvic and para-aortic adenopathy and a vaginal vault lesion. A biopsy of 1 of these lymph nodes confirmed the diagnosis of metastatic uterine carcinoma. She is healthy otherwise. She declined any further surgery.**

Treatment	Rating	Comments
Management		
Carboplatin and paclitaxel chemotherapy	3	
Different chemotherapy regimen	6	
Palliative RT to the pelvis and para-aortic area	4	This option is appropriate only if patient is symptomatic or to become symptomatic and is not a candidate for definitive therapy.
Salvage RT alone to the pelvis and para-aortic area	7	
Salvage RT to the pelvis/para-aortic area with concurrent chemotherapy	7	
Consider palliative care/hospice approach	3	
RT Consideration if Used		
Simulate the patient in supine position	8	
Simulate the patient in prone position with a belly board device	5	
Simulate with oral contrast	7	
Simulate with intravenous contrast	7	
Simulate with vaginal vault radiopaque marker	7	

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

Clinical Condition: **Management of Recurrent Endometrial Cancer**

Variant 4: **A healthy 55-year-old woman who had complete surgical staging for 2009 FIGO IIIC1 uterine endometrioid carcinoma. She received adjuvant pelvic RT to 45 Gy with concurrent cisplatin chemotherapy followed by 4 more cycles of chemotherapy (carboplatin and paclitaxel). One year later, she had a pelvic CT scan that showed an infiltrative left pelvic sidewall mass measuring 5.8 cm in size as well as an infiltrative rectovaginal mass 6.0 cm in size. Biopsy from the rectovaginal mass was consistent with recurrent uterine endometrioid carcinoma. Staging workup was negative.**

Treatment	Rating	Comments
Management		
Surgical exenterative procedure alone	3	
Surgical exenterative procedure + RT	4	
Surgical exenterative procedure + RT + systemic chemotherapy	3	
Surgical exenterative procedure + chemotherapy	4	
Re-irradiation to the pelvis alone	3	This option is focal only to the area causing symptoms, not the whole pelvis.
Re-irradiation to the pelvis + chemotherapy	3	
Chemotherapy alone	7	
Chemotherapy followed by RT	5	
Chemotherapy followed by surgical resection	4	
Chemotherapy followed by surgical resection and RT	5	
Consider palliative care/hospice approach	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
If Re-irradiation is Utilized with Surgery		
Preoperative conformal RT to the 2 areas	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Preoperative RT to the whole pelvis	3	
IORT	6	
Postoperative conformal RT	6	
If Re-irradiation is Utilized Alone, the Suggested RT Technique		
3-D technique	4	
IMRT	7	
SBRT	5	Due to limited data, this option can be used in a selected group of patients (eg, good response to chemotherapy with small residual disease).
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Management of Recurrent Endometrial Cancer**

Variant 5: **65-year-old woman who underwent complete surgical staging followed by adjuvant RT to the pelvis and para-aortic area up to L1 to 45 Gy with chemotherapy for her 2009 FIGO stage IIIC2 uterine endometrioid carcinoma. She was diagnosed with a biopsy-proven solitary nodal recurrent lesion at L2 (within the previous RT field) 9 months after completion of her adjuvant RT. The patient is healthy otherwise.**

Treatment	Rating	Comments
Management		
Surgical resection alone	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
Surgical resection followed by RT to tumor bed	6	
Surgical resection followed by chemotherapy	6	
Surgical resection after preoperative RT + chemotherapy	4	
Surgical resection followed by RT and chemotherapy	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.
RT alone	6	
RT with chemotherapy	5	
Chemotherapy alone	5	
Hormonal treatment (megestrol acetate) only	3	
Consider palliative care/hospice approach	3	
If Re-irradiation is Utilized Alone, the Suggested RT Technique		
3-D technique	3	
IMRT	7	
SBRT	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. Very limited data.
If Re-irradiation is Utilized Alone (with acceptable dose to surrounding normal tissues), the Suggested RT Dose would be		
Biological equivalent dose of 30 Gy	3	
Biological equivalent dose of 40 Gy	3	
Biological equivalent dose of 50 Gy	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. Dose would be determined by the surrounding organs at risk.
Biological equivalent dose of 60 Gy	6	This dose would be determined by the surrounding organs at risk.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Management of Recurrent Endometrial Cancer**

Variant 6: **75-year-old woman who was diagnosed with 2009 FIGO stage IIIC2 uterine serous carcinoma 9 months ago. She received adjuvant RT to the pelvic and para-aortic regions with concurrent cisplatin chemotherapy followed by 4 cycles of carboplatin and paclitaxel chemotherapy. Because she was complaining of back pains, follow-up CT and nuclear bone scans showed a new single metastatic disease in the thoracic spine (T6). Biopsy from T6 lesion confirmed metastatic uterine serous carcinoma.**

Treatment	Rating	Comments
Management		
Systemic chemotherapy only	4	
Localized RT to thoracic spine followed by chemotherapy	7	This option is appropriate depending on the patient's performance status.
Localized RT alone	7	
Consider palliative care/hospice approach	4	
If Localized RT to T6 is Utilized, the Suggested RT Dose and Fractionation Would Be		
30 Gy/10 fractions	7	
8 Gy/1 fraction	7	
SRS with 16–18 Gy/1 fraction	5	
SBRT with 30 Gy/5 fractions	5	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		