Evidence-based review of the utility of radiation therapy in the treatment of endometrial cancer

SB Dewdney† & DG Mutch

Endometrial cancer is the most common cancer of the female genital tract in the USA and usually presents at an early stage. Most women are cured with surgery, however, some patients may require adjuvant therapy including radiation and/or chemotherapy. Risk factors determine the need for adjuvant treatment and, based on these risk factors, patients are categorized as being at low, intermediate or high risk for recurrence. In this article we will review the best level of evidence available for the use of radiation therapy within each risk stratum. The most controversy and debate is associated with patients stratified to the intermediate-risk group.

Learning objectives

Upon completion of this activity, participants should be able to:

• Describe risk factors for and the typical presentation of endometrial cancer
• Describe treatment options – including prognosis – for low-, intermediate-, and high-risk endometrial cancer

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In the USA, endometrial cancer is the most common malignancy of the female genital tract. It is estimated that 42,160 women were diagnosed with this disease in 2009, resulting in 7780 deaths [1]. Fortunately, the majority of endometrial cancer cases are diagnosed at an early stage and present with abnormal uterine bleeding and most of these women are cured. The median age at diagnosis is 62 years [101]. Approximately 70% of endometrial cancer patients are diagnosed with localized disease, resulting in a 3-year survival of 95% in this subset of patients [1]. In addition, the mortality rate for endometrial cancer continues to decline; in 1991 the mortality rate was 4.18 per 100,000 and in 2005 it was 4.10 per 100,000 [1]. Risk factors for development of this disease include obesity, diabetes, hypertension, endogenous or exogenous excess estrogen, nulliparity, menopause, family history and endometrial hyperplasia.

**Treatment**

Most endometrial cancers in the USA are initially surgically staged according to the criteria established by the International Federation of Obstetrics and Gynecology (FIGO). FIGO announced that they had updated endometrial cancer staging in October 2009 [2]. Although most of the studies in this review use FIGO staging from 1988, it is important to recognize the new staging system because it will be used for future studies. The National Comprehensive Cancer Network (NCCN) and the American College of Obstetricians and Gynecologists (ACOG), standard definitive treatment includes a hysterectomy, bilateral salpingo–oophorectomy and pelvic/para-aortic lymph node dissection with pelvic washings and, for poor histologic types, an omental biopsy [3,102]. The value of pelvic/para-aortic lymph node dissection in the staging of endometrial cancer has been called into question by recent data published in A Study in the Treatment of Endometrial Cancer (ASTEC) and trials carried out by Panici et al. [4,5]. Management and adjuvant treatment after surgery depends upon a patient’s risk factors for recurrence. Options include vaginal vault brachytherapy, pelvic external-beam radiation therapy (EBRT) and/or chemotherapy. The most significant risk factors considered in any decision for adjuvant therapy include age of the patient, grade, histologic type (i.e., serous, clear cell or grade 2/3 endometrioid), depth of myometrial invasion, tumor extension beyond the uterus and lymphovascular space invasion. Depending on the number and severity of these risk factors, patients are categorized as being at low, intermediate, or high risk for recurrence (Table 1). Most controversy and debate is associated with the patients stratified to the intermediate-risk group.

In this article we will review the best level of evidence available for the use of radiation therapy within each risk stratum.

**Management after surgery**

**Should women with a low risk of recurrence receive adjuvant radiation therapy?**

Low-risk disease is defined as cancer that is confined to the uterus with little or no myometrial invasion and low-grade histologies (i.e., disease confined to the endometrium or with <50% myometrial invasion, grades 1 and 2). These patients have the lowest risk of recurrence and therefore are generally felt not to need any adjuvant treatment.

Historically, these patients have not received treatment because of their overall excellent survival and the fact that morbidity from treatment is greater than the expected benefit from therapy. This was further verified by the findings of prospective studies conducted between 1977 and 1983 by the Gynecologic Oncology Group (GOG 33), which investigated the patterns of failure for early-stage disease [6]. Of the women who had no myometrial invasion with grade 1 or 2 histology, none experienced recurrence [7]. In addition, a Cochrane review of the treatment for stage I endometrial cancer found a statistically significant greater risk for death in patients who had EBRT versus no treatment with low risk factors (i.e., disease confined to the endometrium, <50% myometrial invasion or grade 1/2) [8]. These data were confirmed again by meta-analysis of seven randomized trials by Johnson et al. showing that prophylactic EBRT could be harmful or ineffective in improving survival in women with low- or intermediate-risk cancer [9].

**Sorbe et al. (2009)**

A recent prospective trial evaluated patients diagnosed with stages 1A or IB using FIGO 1988 criteria with grade 1 or 2 histology. These patients were randomized to surgery plus intravaginal brachytherapy or surgery without adjuvant treatment. The study enrolled 645 patients and found no statistical difference in survival or local regional control with adjuvant treatment. The mean follow-up time was 68 months. A total of 26 (4%) recurrences were observed in the complete series and there...
was no difference between the two groups ($p = 0.114$). Acute and late side effects in both groups were few and mild [10]. Therefore, adjuvant treatment with radiation is not recommended in this group of patients and may expose women to unnecessary toxicity (level 1 evidence).

**Should women with an intermediate risk for recurrence receive adjuvant radiation therapy?**

Patients with disease confined to the uterus but with high risk factors for recurrence are defined as having intermediate risk. The inclusion criteria for this group vary slightly from trial to trial. These risk factors include, but are not limited to, age, lymphovascular space invasion, tumor size, cervical involvement and deep myometrial invasion. Despite multiple randomized studies, this group is still the most controversial with regard to adjuvant radiotherapy because it is not clear whether the benefit of treatment outweighs the risks (Table 2).

Aalders et al. (1980)

This trial was conducted before the introduction of FIGO staging, between 1968 and 1974. A total of 540 patients with clinical stage I endometrial cancers were entered into a prospective randomized clinical trial. All patients received vaginal brachytherapy and then were randomized to no further treatment or EBRT. The authors found a significant reduction in pelvic and vaginal recurrences in patients who received EBRT although these patients had more distant metastases. The 5-year overall survival (OS) was not improved by EBRT, although a more detailed analysis of the series concluded that patients with higher risk factors such as poorly differentiated tumors (grade 3), who have greater than 50% myometrial invasion might benefit from EBRT [11].


This multicenter trial randomized patients to external radiation therapy versus no therapy and included patients with stage IC grade 1, grade 2 with any invasion, and stage IB grade 3 (FIGO 1988 criteria). Following total abdominal hysterectomy salpingo–oophorectomy without routine lymphadenectomy patients ($n = 715$) were randomized to receive either EBRT or no further treatment. Both arms of patients were allowed to have vaginal brachytherapy. Median follow-up

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Inclusion criteria (FIGO 1988)</th>
<th>Method of staging</th>
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<th>Ref.</th>
</tr>
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<tbody>
<tr>
<td>Aalders et al.</td>
<td>540</td>
<td>Stage I (clinical stage)</td>
<td>Clinically</td>
<td>VBT + EBRT vs VBT alone</td>
<td>89 vs 91%; $p = NS$</td>
<td>2 vs 7%; $p &lt; 0.01$</td>
<td>[11]</td>
</tr>
<tr>
<td>PORTEC</td>
<td>714</td>
<td>Stage IB (G2/3); stage IC (G1/2)</td>
<td>Surgically, LND not required</td>
<td>No treatment vs EBRT</td>
<td>85 vs 81%; $p = 0.31$</td>
<td>14 vs 4%; $p &lt; 0.001$</td>
<td>[12]</td>
</tr>
<tr>
<td>GOG 99</td>
<td>392</td>
<td>Stage IB–II B (occult)</td>
<td>Surgically, LND required</td>
<td>No treatment vs EBRT (no VBT)</td>
<td>86 vs 92%; $p = 0.557$</td>
<td>12 vs 3%; $p = 0.007$ at 2 years</td>
<td>[13]</td>
</tr>
<tr>
<td>ASTEC/EN.5</td>
<td>906</td>
<td>Stage IA–II A</td>
<td>Surgically, LND not required</td>
<td>No treatment (51% VBT) vs EBRT (52% + VBT)</td>
<td>84 vs 84%; $p = 0.77$</td>
<td>6 vs 3%; $p = 0.02$</td>
<td>[14]</td>
</tr>
<tr>
<td>PORTEC-2</td>
<td>427</td>
<td>&gt;60 years of age stage IC G1/2, stage IB G3; any stage II A G3</td>
<td>Surgically, LND exclusion criteria</td>
<td>EBRT vs VBT</td>
<td>80 vs 84%; $p = 0.57$</td>
<td>2 vs 5%; $p = 0.17$</td>
<td>[16]</td>
</tr>
</tbody>
</table>

ASTEC: A Study in the Treatment of Endometrial Cancer; EBRT: External-beam radiation therapy; FIGO: International Federation of Gynecology and Obstetrics; G: Grade; GOG: Gynecologic Oncology Group; LND: Lymph node dissection; NS: Not significant; VBT: Vaginal brachytherapy.
was 52 months. The 5-year local regional recurrence rates were statistically different at 4% in the treatment group and 14% in the control group (p < 0.001). However, the 5-year OS rates were similar, (p = 0.31). This study identified significantly more complications in the EBRT group – 25% compared with 6% of controls. In a subgroup analysis, an age of 60 years and above and deep myometrial invasion were both identified as poor prognostic factors [12].

GOG 99 (2004)
Of the randomized studies, the GOG 99 study is the only study that required FIGO surgical staging. This Phase III trial included patients with intermediate-risk disease, defined as stage IB, IC, IIA (occult), and IIB (occult) of any grade, excluding papillary serous and clear cell histologies (FIGO 1988 staging criteria). A total of 448 women were randomized to adjuvant EBRT or no further treatment, and neither group received vaginal brachytherapy. The median follow-up was 68 months and the primary outcome was recurrence-free interval (RFI). The 24-month estimated cumulative incidence of recurrence was 3% for the EBRT group and 12% for the no adjuvant treatment group. The trial found that EBRT reduces the risk of recurrence by 58%, compared with the no adjuvant treatment group; however a statistical significance for survival was not found between the two groups. A subgroup analysis of the high-intermediate risk (HIR) patients was performed. HIR patients were defined as those with grade 2 or 3 histology, deep myometrial invasion (outer third) and lymphovascular space invasion; age 50 years or older with any two of these risk factors; or age of at least 70 years with any risk factor. This HIR group accounted for nearly 2/3 of the recurrences and 2/3 of the cancer-related deaths. This study was not powered to analyze this subgroup; however, they concluded that this trial provides strong evidence for the use of EBRT in patients who fall into this category [13].

ASTEC/EN.5 (2009)
The ASTEC/EN.5 trial is a pooled trial of two studies and may be flawed for this reason. These two trials, ASTEC and EN.5 were originally set up as individual trials that were later combined, secondary to insufficient recruitment in either trial. The trial was designed to evaluate the benefit of postoperative adjuvant EBRT in women with intermediate- and high-risk early-stage endometrial cancer. High risk was defined as papillary serous and clear cell subtypes, all other subtypes in IC (grade 3) and IIA (grade 3), and all women in stage IIB. Intermediate risk included subtypes other than papillary serious and clear cell, within stage IA and IB (grade 3), and stage IC and IIA (grades 1 and 2). FIGO 1988 staging criteria was used in this study. A total of 905 women were enrolled, and eligibility included stage IA/IB grade 3; IC all grades and papillary serous or clear cell histologies [14]. Briefly, the ASTEC trial was in two parts. The first randomization was to lymphadenectomy or not, and the second part was a randomization to receive postoperative radiation or not. Lymphadenectomy was not a requirement for randomization in EN.5 but was part of the original randomization in the first part of the ASTEC trial. Approximately half of the patients in both arms (EBRT vs no treatment) received vaginal brachytherapy. The trial found no evidence of a benefit from EBRT for early-stage endometrial cancer with intermediate or high risk of recurrence in terms of OS. In addition, the authors performed a meta-analysis using the data from GOG 99, PORTEC-1 and the current combined trial and found no significant difference in OS, or disease-specific survival regardless of the histologic risk group of the patient. However, EBRT did demonstrate a small reduction in isolated local recurrences. Controversy exists surrounding this trial, and some critics would cite methodological flaws, despite its large prospective randomized study design [15]. These limitations have been described as not including a para-aortic lymphadenectomy as part of the prescribed protocol, leading to inadequate lymphadenectomies in less than half of the patients. In addition, patients who had positive lymph nodes were still randomized to no treatment and there was possible selection bias in the nonrandomized nature of almost half of the patients from both arms receiving vaginal brachytherapy. Finally, there was a significant heterogeneity of inclusion criteria, especially when analyzing the adjuvant radiation portion of the study.

PORTEC-2 (2010)
This was the second trial in the PORTEC series. This noninferiority multicenter trial randomized patients with a HIR of endometrial cancer to vaginal brachytherapy or EBRT. FIGO 1988 staging was used in this trial and HIR was defined as age 60 years and above and stage IC grade 1 or 2 or stage IB grade 3, and any age with stage IIA grade 1,
2 or grade 3 with less than 50% invasion. A total of 427 patients were recruited to this trial between 2002 and 2006, with a median follow-up time of 45 months. Routine lymphadenectomy was not performed and was a basis for exclusion. There was no significant difference in OS and the 5-year loco-regional recurrence rate between treatment modalities. The estimated 5-year vaginal recurrence rates were 1.8% (95% CI) after vaginal brachytherapy and 1.6% (95% CI) after EBRT [16]. A second article from these data was published regarding the quality of life for patients enrolled in this study. Through validated questionnaires, vaginal brachytherapy was found to be preferred to EBRT with regard to quality of life. The EBRT group reported significant and clinically relevant higher levels of diarrhea and fecal leakage, which limited social and daily activities for the EBRT group (p < 0.001) [17].

The preponderance of data suggest that external beam radiotherapy does not improve OS but provides a small but real improvement in local control for patients with intermediate-risk disease. Vaginal brachytherapy appears equally effective, with an improved quality of life compared with EBRT (level 1 evidence).

**Should women with a high risk of recurrence receive adjuvant radiation therapy?**

Women who have endometrial cancer with a high risk for recurrence are defined as having myometrial invasion greater than 50% (grade 3), gross involvement of the cervix or advanced-stage disease. Other high-risk prognostic factors include lymphovascular space involvement and aggressive histologic types, papillary serous and clear cell. These histological types have a particularly poor prognosis, and are known to have a higher propensity for extra-abdominal and intraperitoneal spread. In addition, the majority of these tumors have extraterine spread at the time of presentation, therefore making these histological subtypes difficult to treat with radiation.

There are no randomized controlled trials that are specific to this exact subset of patients. Although, as described above, Aalders et al. analyzed a subset of patients with clinical stage IC grade 3 endometrial cancers and found that EBRT decreased the cancer-related death rate from 27.5 to 18.2% [11]. Significantly more deaths and recurrences were identified among patients with lymphovascular space invasion compared with those without (26.7 vs 9.1%, p = 0.01).

The GOG 99 trial, which was a randomized controlled trial but did not have the power to analyze the HIR subset of patients, demonstrated a 19% decrease in recurrence and a 0.73 relative hazard of death in the EBRT arm defined as HIR [13].

**Maggi et al. (2006)**

This randomized trial failed to show superiority of adjuvant chemotherapy over radiation. This trial enrolled 345 women with high-risk endometrial cancer. Most were stage III (approximately two-thirds), with the remaining being stage IC/grade 3 and stage II/grade 3 with more than 50% myometrial invasion (FIGO 1988 criteria). Patients were randomly assigned to adjuvant cisplatin, doxorubicin and cyclophosphamide versus EBRT. The median follow-up was 95.5 months. There were no significant differences between the two groups for OS or PFS [18].

**Hogberg et al. (2007)**

This randomized Phase III trial presented at ASCO in 2007 (abstract form) evaluated adjuvant treatment with radiation and chemotherapy versus radiation only in high-risk endometrial cancer. Patients with surgical stage I, II, IIA (positive for peritoneal fluid cytology only) or IIC (positive pelvic lymph nodes only) were eligible (FIGO 1988 criteria). Most patients had two or more risk factors: grade 3, deep myometrial invasion or DNA non diploidy. Serous, clear cell or anaplastic carcinomas were eligible regardless of risk factors. Lymphadenectomy was not required as part of surgical staging. Patients were randomized to EBRT ± vaginal brachytherapy with chemotherapy or to pelvic EBRT ± vaginal brachytherapy only. The study was terminated early, secondary to poor recruitment; 367 patients were evaluable. The median follow-up time was 3.5 years. Hazard ratio (HR) for progression free survival (PFS) was 0.58 in favor of EBRT and chemotherapy (95% CI: 0.34–0.89; p = 0.046). The authors concluded that EBRT plus chemotherapy was better than EBRT alone [19].

**Japanese GOG (2008)**

This was a randomized study that enrolled 475 patients with stage IC–IIIC endometrial carcinoma with deeper than 50% myometrial invasion (FIGO 1988 criteria). They were randomized to receive adjuvant EBRT or cyclophosphamide, doxorubicin and cisplatin. A pelvic lymphadenectomy was performed in 96.1% of the patients and a para-aortic lymphadenectomy was performed.
in 28.6%. The OS and PFS were not statistically different between the two arms. In their subgroup analysis of HIR patients, defined as stage IC greater than 70 years of age or grade 3, or stage II or IIIA with deeper than 50% myometrial invasion, they found that the chemotherapy group had a significantly higher PFS rate (HR: 0.44; 95% CI: 0.20–20.97; p = 0.24) and OS rate (HR: 0.24; 95% CI: 0.09–0.69; p = 0.006) [20].

Adjuvant radiation therapy is recommended for this group of patients. Although this was shown in a randomized controlled trial, it was not adequately powered. In addition, these patients may benefit from both chemotherapy and radiotherapy (level II evidence).

**Should women with advanced-stage disease receive adjuvant radiation therapy?**

The high rate of recurrence and poor survival in this population has been well documented [7,101]. Management with surgery alone for these patients is associated with poor survival. No prospective randomized trial has ever shown that adjuvant radiation in this patient population improves survival, although it has been shown to reduce the risk of local recurrence [21].

**GOG 122 (2006)**

GOG 122 was the first randomized Phase III trial demonstrating that chemotherapy offered a survival advantage over radiation therapy. A total of 422 patients with stage III or IV endometrial cancer (FIGO 1988 criteria) were entered into this trial and were randomly allocated to receive whole abdominal irradiation therapy (WAI) or chemotherapy (doxorubicin and cisplatin). Median follow-up time was 74 months. These authors found a significant OS and PFS in the patients who received chemotherapy versus WAI, plus volume-directed boost to the pelvis. The progression and death HR relative to the WAI arm, adjusted for stage, was 0.71 (95% CI: 0.55–0.91; p = 0.007) and 0.68 (95% CI: 0.52–0.89; p = 0.004) [22]. WAI is not often used in the treatment of advanced-stage endometrial cancer now.

**Secord et al. (2007)**

This retrospective analysis of patients using FIGO 1988 criteria with surgical stages III and IV identified 356 patients and evaluated their post-surgical therapies. A total of 48% received radiotherapy alone, 29% received chemotherapy alone, and 23% received both chemotherapy and radiation. Isolating the optimally debulked patients and after adjusting for stage, age and grade, the HR for death was 2.33 (95% CI: 1.12–4.86; p = 0.024) for chemotherapy alone and 2.64 (95% CI: 1.38–5.07; p = 0.004) for radiotherapy alone, when compared with a combined therapy regimen. Although this study is retrospective, it suggests that multimodality therapy with both chemotherapy and radiation may improve survival in this group of patients [23].

**Secord et al. (2009)**

Recently, many studies have evaluated the combination of EBRT and chemotherapy and its optimal sequencing. Chemotherapy alone has shown to have a high rate of pelvic recurrences [23–25]. Secord et al. performed a multicenter retrospective analysis of patients with surgical stages III and IV endometrial cancer (FIGO 1988 criteria) from 1993–2007. A total of 109 patients were identified who had received postoperative therapies. A total of 41% received chemotherapy followed by radiation and then further chemotherapy, 17% had radiation followed by chemotherapy, and 42% had chemotherapy followed by radiation. The authors found a significant difference between adjuvant treatment groups for both OS and PFS with those receiving the sequence of chemotherapy–radiation–chemotherapy; this group showed a superior 3-year OS of 88% and PFS of 69% versus both of the other groups; radiation–chemotherapy OS of 54% and PFS of 47% or chemotherapy–radiation OS of 57% and PFS of 52% [26].

**GOG 184**

This was a Phase III trial that included patients with advanced-stage endometrial carcinoma who had surgery and volume-directed radiation followed by cisplatin and doxorubicin with or without paclitaxel. They found that the addition of paclitaxel to cisplatin and doxorubicin following surgery and radiation was not associated with a significant improvement but did increase toxicity. These patients received volume-directed radiation followed by the different arms of chemotherapy [27]. This study is highlighted to show that approximately 80% of patients completed six cycles of chemotherapy using either drug regimen with acceptable tolerance of chemotherapy after full radiation.

Most patients with advanced-stage disease should receive chemotherapy and may benefit from adjuvant radiation therapy, although the optimal combination of chemotherapy and radiation therapy is still being researched (level II evidence).
Nonsurgical management in medically inoperable patients

How do you treat a medically inoperable patient?

The optimal treatment of endometrial cancer has been described above, although a small percentage of patients are deemed medically inoperable and can be treated with definitive radiation. There have been multiple retrospective studies analyzing the effectiveness of primary radiotherapy in this subset population. A SEER database review included 27,517 women from 1992–2002 with endometrial cancer; they found that 6% did not undergo surgery. There was a significant trend suggesting that women aged 65 years and over received surgical treatment less often than younger women. After adjustment for stage at diagnosis, histology and radiotherapy, the HRs for endometrial cancer-specific mortality were decreased when surgery was performed [28].

Conversely, a case–control study by Rose et al. retrospectively evaluated patients who were treated with primary radiation therapy [29]. The authors found that there was no statistical difference in survival in stage I and II patients treated by primary radiation versus surgically treated controls. Another study failed to show a difference between clinical stages I and II who were treated with primary radiation versus surgical management [30].

The optimal treatment for endometrial cancer is surgical staging, although if surgery is precluded secondary to comorbidities, primary radiotherapy is an option (level II).

Conclusion

Endometrial cancer is the most common gynecologic cancer in the USA [1]. Early-stage disease with a low risk for recurrence is highly curable with surgery alone. Women with an intermediate risk of recurrence benefit from radiation therapy with regard to local control, but not OS. The same pattern has been observed in patients within the HIR group, although risk factors to define this group are ongoing. A combination of chemotherapy and radiation may be the optimal treatment for patients with a high risk of recurrence. From initial data, advanced-stage therapy should be treated with both chemotherapy and radiation therapy.

Future perspective

Despite endometrial cancer being the most common and one of the most studied gynecologic cancers, optimal treatment remains unclear, particularly for the intermediate and HIRs groups. With recent randomized controlled trials we have learned more about optimal adjuvant treatment. Recently, PORTEC-2, as described above, shows that vaginal brachytherapy is as efficacious as whole pelvic radiation therapy with less toxicity. Hence we will probably be seeing increased use of vaginal brachytherapy alone for in this subgroup.

Currently there are many Phase III trials underway analyzing the use of radiotherapy in the treatment of high-risk endometrial cancers (Table 3). The gynecologic oncology group opened a study (GOG 249) in March of 2009 looking at adjuvant treatment for this group of patients with early stage endometrial cancer. This is a multi-institutional Phase III trial of pelvic radiation therapy without any chemotherapy versus vaginal cuff brachytherapy followed by three cycles of paclitaxel/carboplatin chemotherapy in patients with high-risk early-stage endometrial carcinoma. This study was designed to further delineate the difference between vaginal cuff brachytherapy and whole pelvic radiation. HIR is defined as the GOG 99 criteria for stage I–IIA. They are also including stage IIB occult and I–IIB with serous or clear cell carcinoma.

Table 3. Currently ongoing endometrial cancer randomized controlled trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Target accrual (n)</th>
<th>Stage</th>
<th>Method of staging</th>
<th>Arms of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 258</td>
<td>180</td>
<td>III; IVA</td>
<td>Surgically, LND required</td>
<td>Cis-volume-directed RT + C/T × 4 cycles vs C/T × 6 cycles</td>
</tr>
<tr>
<td>PORTEC-3</td>
<td>500</td>
<td>IIBG3 + LVS1; IC/IIAG3; IIB; IIA (only on cytology if grade 3) or IIC; IB–III serous or clear cell</td>
<td>Surgically, LND optional</td>
<td>Pelvic RT ± VBT (for cervical involvement) vs Cis/RT + C/T × 4 cycles</td>
</tr>
<tr>
<td>GOG 249</td>
<td>562 (planned sample size)</td>
<td>I–IIA + HIR; IIB: I–IIB serous/clear cell</td>
<td>Surgically, LND optional</td>
<td>Pelvic RT ± VBT (for cervical involvement) vs VBT + C/T × 3 cycles</td>
</tr>
</tbody>
</table>

Cis: Cisplatin; C/T: Carboplatin and paclitaxel chemotherapy; G: Grade; GOG: Gynecologic Oncology Group; HIR: High-intermediate risk; LND: Lymph node dissection; RT: Radiation therapy; VBT: Vaginal brachytherapy.
cell endometrial carcinoma regardless of risk factors. This study should give us more information regarding the optimal management of these higher risk patients.

GOG is evaluating the utility of radiation and chemotherapy in advanced-staged endometrial cancer. GOG 258 is a randomized Phase III trial of concurrent cisplatin and tumor volume-directed-irradiation followed by paclitaxel/carboplatin for four cycles versus paclitaxel/carboplatin for six cycles for optimally debulked advanced endometrial carcinoma. Is it better to treat this advanced cancer with systemic treatment or both chemotherapy and radiation? This study was designed to shed further light on this question.

An international group responsible for PORTEC and PORTEC-2 is now enrolling for PORTEC-3. This study is an international multicenter trial, that will randomize stage I or II endometrial with high-risk features or stage III who meet certain criteria to either external beam pelvic RT or concurrent cisplatin and radiotherapy followed by carboplatin and paclitaxel for four cycles. This study will establish a possible role of concurrent chemoradiation plus adjuvant chemotherapy in the treatment of this higher risk subgroup of endometrial cancer patients.

In the coming years we hope to see improvement in the treatment of high-risk and advanced-stage endometrial cancer through these collaborative studies.

Executive summary

**Should women with a low risk of recurrence receive adjuvant radiation therapy?**

- Adjuvant treatment with radiation is not recommended for patients with low-risk endometrial cancer and may expose women to unnecessary toxicity.

**Should women with an intermediate risk for recurrence receive adjuvant radiation therapy?**

- Most data suggest that external-beam radiotherapy does not improve overall survival but provides a small but real improvement in local control for patients with intermediate-risk disease.
- Vaginal brachytherapy appears equally effective, with an improved quality of life compared with EBRT in the high intermediate-risk group as described in the PORTEC-2 trial.

**Should women with a high risk of recurrence receive adjuvant radiation therapy?**

- Adjuvant radiation therapy is recommended for patients in the high-risk group diagnosed with endometrial cancer. Although this was shown in a randomized controlled trial, it was not adequately powered. In addition, these patients may benefit from both chemotherapy and radiotherapy. We await level 1 evidence for further guidance in this group of patients.

**Should women with advanced-stage disease receive adjuvant radiation therapy?**

- Most patients with advanced-stage disease should receive chemotherapy and may benefit from adjuvant radiation therapy, although the optimal combination of chemotherapy and radiation therapy is still being researched.

**How do you treat a medically inoperable patient?**

- The optimal treatment for endometrial cancer is surgical staging, although if surgery is precluded secondary to comorbidities, primary radiotherapy is an option.

Bibliography

Papers of special note have been highlighted as:
- of interest
- of considerable interest

3. New Federation of International Gynecologic Oncology (FIGO) staging system for endometrial cancer.
Identifies a high-intermediate-risk group in endometrial cancer.

Randomized trial analyzing the postoperative treatment of stage 1 endometrial cancer.

Identifies a high-intermediate-risk group in early-stage endometrial cancer.

Recent randomized controlled trial and meta-analysis on adjuvant radiation.

Recent randomized controlled trial of vaginal brachytherapy versus external-beam radiation therapy.

•• Randomized trial analyzing the postoperative treatment of stage 1 endometrial cancer.


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Evidence-based review of the utility of radiation therapy in the treatment of endometrial cancer

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.

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1. Which of the following best describes the typical patient presenting with abnormal uterine bleeding diagnosed with endometrial cancer?
   - A 50-year-old, multiparous perimenopausal woman
   - A 62-year-old, nulliparous, obese postmenopausal woman
   - A 71-year-old, nulliparous, thin postmenopausal woman
   - A 45-year-old, multiparous woman with premature menopause

2. A 58-year-old woman is diagnosed with advanced stage III endometrial cancer with over 50% endometrial invasion. Following surgery, which of the following adjuvant therapy regimens is likely to be associated with the best survival?
   - Radiation therapy-chemotherapy-radiation therapy
   - Chemotherapy-radiation therapy-chemotherapy
   - Radiation therapy-chemotherapy
   - High-dose radiation therapy only

3. In a woman diagnosed with inoperable endometrial cancer, which of the following is considered the best option for survival?
   - Chemotherapy
   - Chemotherapy and radiation therapy
   - Radiation therapy
   - No treatment