Adjuvant Radiotherapy in Endometrial Carcinoma

DAVID T. SHAEFFER, a MARCUS E. RANDALL b

a Therapeutic Radiologists, Inc., Kansas City, Missouri, USA; b Leo W. Jenkins Cancer Center, The Brody School of Medicine at East Carolina University, Greenville, North Carolina, USA

Key Words. Radiation • Endometrial cancer • Hysterectomy • Local-regional recurrence

Abstract
Endometrial cancer is a common female malignancy, affecting approximately 40,000 women per year. Despite the publication of several prospective randomized trials, there continues to be controversy regarding the use of adjuvant radiation therapy in endometrial cancer management. It is clear that most women with early-stage, low-risk disease will do well without adjuvant therapy. Intermediate-risk patients are at risk for local-regional relapse, and radiotherapy has been shown to effectively reduce this risk without significantly impacting overall survival. The absence of a clear impact on survival has resulted in a lack of consensus regarding the use of radiotherapy in intermediate-risk patients. At the same time, the patterns of failure in intermediate-risk patients have resulted in differing recommendations regarding appropriate radiotherapy targets. High-risk patients are at risk for both local and distant failure, and chemotherapy has been shown to improve outcome in these patients. High-risk patients are also at risk for local failure, and targeted radiotherapy may be appropriate. In this article, we discuss the controversies surrounding the use of adjuvant radiotherapy in endometrial cancer using an evidence-based approach.


Introduction
Endometrial cancer is the fourth most common female malignancy and is the most common gynecologic cancer. In 2004, an estimated 40,000 new cases occurred, accounting for approximately 6% of newly diagnosed female cancers. Endometrial cancer was estimated to have resulted in 3% of female cancer deaths in 2004 [1]. Surgery is the preferred initial treatment, and risk factors for local-regional recurrence have been established in both retrospective and prospective trials. Adjuvant radiotherapy options include pelvic radiation, vaginal brachytherapy, whole-abdomen radiation, and intraperitoneal radionuclide treatment. Radiotherapy decreases local recurrence rates in both uterine-confined and extraterine disease, but a significant impact on overall survival has not been demonstrated. Therefore, there continues to be controversy regarding the role of adjuvant radiation therapy in both uterine-confined and extraterine disease. In this article, we review the general therapeutic approach to endometrial cancer, with emphasis on the role of adjuvant radiotherapy in its management.
Surgery
Overall, approximately 80% of women with endometrial cancer present with disease localized to the uterus. An additional 20% have regional spread and/or distant metastatic disease [2]. A minority of patients presents with surgically unresectable disease and/or medical comorbidities that preclude surgery. These patients are often managed with preoperative or definitive radiotherapy; a full discussion of these techniques is beyond the scope of this article. Most patients undergo surgery, ideally consisting of exploratory laparotomy with biopsy of suspicious areas, peritoneal cytology, and extrafascial hysterectomy with bilateral salpingo-oophorectomy. Complete surgical staging also entails the sampling or dissection of pelvic and para-aortic lymph nodes. However, some patients have a sufficiently low risk for lymph node metastases that nodal staging can safely be omitted [3].

Adjuvant radiotherapy and chemotherapy recommendations are predicated on pathologic findings from surgery. In general, the greatest risk for the majority of patients with uterine-confined disease is to fail local-regionally, and adjuvant therapies are directed at reducing this risk. Patients with more advanced local disease or with spread beyond the uterus also have a high risk for distant failure, leading to the consideration of systemic therapy.

Adjuvant Therapy for Uterine-Confined Disease
After surgical-pathologic staging, most newly diagnosed endometrial cancer patients are found to have uterine-confined disease. The most important prognostic factor in endometrial cancer is stage, and the expected 5-year survival rates of patients with endometrial cancer are 87% for stage I and 76% for stage II. Most patients with stage I and II disease are cured after surgery, while certain subsets of patients are at higher risk for local-regional and distant relapse. Overall, the risk of local-regional failure after surgery with no adjuvant therapy in stage I and II disease ranges from minimal to up to 20% and is influenced by histologic grade, degree of myometrial invasion, and the presence of lymphovascular space invasion. Patients with stage IA, grade 1 or 2 disease and stage IB, grade 1 disease are at low risk for failure, and surgery alone is an adequate treatment. Failure patterns in patients with stage IA, grade 3 disease, a relatively rare subset, are poorly defined. However, surgical-pathologic data suggest that these patients are likely to be at low risk for lymph node metastases, and reasonable postsurgical options include vaginal brachytherapy and observation. The remainder of patients with stage I or II disease has historically been grouped into an “intermediate-risk” category and been the subject of prospective trials.

Randomized Trials in Stage I and II Disease
The Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC) trial (which did not use lymph node sampling) randomized 715 patients with grade 2 and 3 disease and <50% myometrial invasion (stage IB) as well as patients with ≥50% invasion (stage IC) and grade 1–2 disease to receive either pelvic radiotherapy or no further treatment. (Data from this and other trials discussed in this article are summarized in Table 1.) The PORTEC investigators felt that patients with >50% invasion and grade 3 disease represented a “higher-risk” subgroup presumed to benefit from pelvic radiotherapy, and these patients were excluded from the trial. The Gynecologic Oncology Group (GOG) performed a similar trial in patients with lymph node staging (GOG 99). That trial had a slightly different definition of intermediate risk, and included stage IB, stage IC, and occult stage II (involvement of the cervix) disease of all grades. Both of these trials demonstrated the ability of adjuvant radiation therapy to decrease pelvic and vaginal recurrences; local-regional relapse rates were 15% and 4% in treated versus nontreated patients, respectively, at 8 years in the PORTEC trial, and 9% versus 1.5%, respectively, at 4 years in the GOG trial [4, 5].

Overall survival, however, was not better for patients treated with radiotherapy in the PORTEC trial (71% with radiotherapy versus 77% with observation at 8 years, \( p = .18 \)) or in the GOG study (estimated 4-year survival rate of 92% in the radiotherapy arm versus 86% with observation, \( p = .557 \)). A third trial by Aalders et al. [6] randomized 540 clinical stage I patients after hysterectomy and vaginal brachytherapy to receive either pelvic radiotherapy or no further treatment. The local control rate was 2% with vaginal brachytherapy and pelvic radiotherapy versus 6.9% with vaginal brachytherapy alone [6]. Again, no survival benefit was seen with the addition of pelvic radiotherapy to vaginal brachytherapy.

Randomized Trials: Local Control Without Survival Advantage
There are many potential reasons for the lack of a survival advantage, including the predominance of patients with a relatively low risk for recurrence (discussed below), a high death rate from intercurrent disease, and the possibility of salvage for the most common site of recurrence (vaginal). For example, in the PORTEC study, there were 105 deaths in both arms; only 40% of the deaths were due to endometrial cancer. The GOG trial showed similar results, with approximately 50% of deaths in both arms attributable to causes other than endometrial cancer or treatment.

Another factor impacting survival in stage I and II disease is the local-regional failure pattern. In the con-
In the control arm of the PORTEC study, more than 70% of local-regional failures were in the vagina. As the initial site of failure, more than 70% of local failures in the control arm of the GOG study were in the vagina. The success of salvage therapy for vaginal relapses in the PORTEC study was reported by Creutzberg et al. [4] in 2003; they reported a 61% durable local control rate and an overall 49% salvage rate. Some patients failed distantly despite local control. Another report of salvage therapy for vaginal recurrences came from the MD Anderson Cancer Center in 2003. In 91 patients with isolated vaginal relapses, the 5-year local control rate was approximately 70% but, due to subsequent distant failure, the survival rate was only 49% [7]. The ultimate outcome of patients with vaginal failures in the GOG study has not been provided. However, in the final report, it was noted that approximately 60% of patients with vaginal relapse had not succumbed to their disease; details of disease-free status or salvage treatments were not provided. Taken together, these data suggest that roughly 50% of the patients who fail in the vagina can be salvaged.

Toxicity of Adjuvant Pelvic Radiotherapy

Adjuvant pelvic radiotherapy is associated with toxicity, which must be balanced against the benefit derived from its use. In general, patients experience acute gastrointestinal (frequency, diarrhea), genitourinary (frequency, dysuria), and hematologic toxicities with pelvic radiotherapy. The majority of the acute toxicity is self-limited [8], and treatment interruptions are relatively rare [9]. The PORTEC investigators found that pelvic radiotherapy, as expected, was associated with a higher risk for grade 1–2 late gastrointestinal (17% versus 1%) and genitourinary (8% versus 4%) toxicities [10]. Grade 3–4 toxicity was rare in both arms, but all grade 3–4 toxicities occurred in the radiotherapy arm (3% of patients). Obesity is a risk factor for endometrial cancer, and a two-field technique that generally delivers higher radiation dose to the bowel was associated with greater toxicity in the PORTEC study (p = .06). The reported toxicity from the PORTEC study is not applicable to patients undergoing lymph node staging, patients treated with doses >46 Gy, or patients receiving a vaginal brachytherapy boost; the use of a higher pelvic dose or additional therapies would likely increase the risk of adverse effects from treatment.

The GOG study reported results similar to those from the PORTEC study, with statistically significant differences in gastrointestinal, genitourinary, hematologic, and cutaneous toxicities between the treatment arms. As in the PORTEC study, most recorded toxicities were grade 1–2 in the radiotherapy group. Surgical staging did change the toxicity profile in the GOG study; patients in both the surgery and radiotherapy arms were noted to have lymphatic complications (primarily chronic lymphedema, occurring in 2.5% of the control patients and in 5% of the radiotherapy patients). This complication was not noted in patients from the PORTEC study, in which lymph node dissection was not used.

Low-Risk Stage I and II Patients

Both the PORTEC and GOG trials predominantly accrued patients at low risk for local-regional failure. In the absence

### Table 1. Prospective randomized trials of radiotherapy for uterine-confined disease

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of patients</th>
<th>Stage</th>
<th>Surgical treatment</th>
<th>Radiotherapy randomization</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aalders et al., [6]</td>
<td>540</td>
<td>I</td>
<td>TAH/BSO</td>
<td>Brachytherapy +/- pelvic RT</td>
<td>OS, no difference; LR, 7% versus 2%</td>
</tr>
<tr>
<td>PORTEC-1, [4]</td>
<td>715</td>
<td>IB, grade 2 or 3, or IC, grade 1 or 2</td>
<td>TAH/BSO</td>
<td>Pelvic RT, 46 Gy versus NFT</td>
<td>OS, no difference; LR, 15% versus 4%</td>
</tr>
<tr>
<td>GOG 99, [5]</td>
<td>488</td>
<td>IB, IC, or occult stage II, all grades</td>
<td>TAH/BSO + node dissection</td>
<td>Pelvic RT, 50 Gy versus NFT</td>
<td>OS, no difference; LR, 9% versus 1.5%</td>
</tr>
<tr>
<td>PORTEC-2</td>
<td>400</td>
<td>IC, grade 1 or 2, and IB, grade 3, with age &gt;60, or II A, grade 1 or 2, or IIIA, grade 3 (&lt;50% invasion)</td>
<td>TAH/BSO</td>
<td>Pelvic RT versus brachytherapy</td>
<td>Pending</td>
</tr>
<tr>
<td>NCIC EN 5</td>
<td>400</td>
<td>IA–IB, grade 3, or II–IIIA, all grades</td>
<td>TAH/BSO</td>
<td>Pelvic RT versus NFT</td>
<td>Pending</td>
</tr>
<tr>
<td>ASTEC</td>
<td>900</td>
<td>IA–B, grade 3, or II–IIIA, all grades, or papillary serous/ clear cell</td>
<td>TAH/BSO + node dissection</td>
<td>Pelvic RT versus NFT</td>
<td>Pending</td>
</tr>
</tbody>
</table>

**Abbreviations:** ASTEC, A Study in the Treatment of Endometrial Cancer; BSO, bilateral salpingo-oophorectomy; GOG, Gynecologic Oncology Group; LND, lymph node dissection; LR, local relapse; NCIC EN, National Cancer Institute of Canada Endometrial 5; NFT, no further treatment; OS, overall survival; PORTEC, Postoperative Radiation Therapy in Endometrial Carcinoma; RT, radiotherapy; TAH, total abdominal hysterectomy.
of lymphovascular space invasion (LVSI), the overall risk for lymph node disease and local-regional failure in patients with grade 1 or 2 disease and <50% myometrial invasion is relatively low. In their analysis of the GOG surgical-pathologic study, Morrow et al. [11] reported a 4.4% local-regional recurrence rate in 113 patients with inner- or middle-third invasion, grade 1 or 2 disease, and no LVSI. Approximately 30% of patients in the PORTEC study had stage IB, grade 2 disease. Nearly 60% of patients in the GOG 99 trial were stage IB, and approximately 80% had grade 1 or 2 disease. The inclusion of patients unlikely to benefit from adjuvant pelvic radiotherapy likely blunted the impact of treatment in both these trials.

Indeed, many series have reported an excellent outcome in stage IB patients with grade 1 or 2 disease without adjuvant radiation or with limited, targeted radiotherapy. In surgically staged patients, Straughn et al. [12] reported a 3.7% overall failure rate in 296 patients, with 64% of failures occurring in the vagina. Other series have reported similar outcomes in patients without surgical staging. For example, the Mayo clinic reported their experience in 261 patients with grade 1 or 2 and stage IB or lower disease treated with surgery alone. Overall, there was only a 2% isolated local recurrence rate without adjuvant radiation. Of the 126 patients not receiving lymphadenectomy, 2% failed locally. Other investigators have reported similar outcomes in surgically staged patients treated without adjuvant therapy [13, 14].

Given the low risk for pelvic failure, some have advocated vaginal brachytherapy alone in these patients. One of the largest series was reported by Alektiar et al. [15] from Memorial Sloan-Kettering Cancer Center; in 233 patients without surgical staging there was an overall 4% relapse rate. Only 2% of patients failed in the pelvis; the remainder failed either distantly or in the vagina. Other authors have reported similar results [16, 17]. Taken together, these data do not support the use of pelvic radiotherapy after surgery for these low-risk patients, defined as grade 1 or 2 disease with <50% myometrial invasion. Indeed, observation alone is appropriate for stage IB, grade 1 disease, and observation or vaginal brachytherapy is a reasonable treatment option after surgery in stage IB, grade 2 disease.

In addition to using grade and surgical stage to define low-risk patients, some groups have investigated the utility of incorporating DNA ploidy as a predictive factor. Based on previous work showing that ploidy is prognostic in patients with poorly differentiated tumors, Hogberg et al. [18], in a prospective study, assigned 355 stage I or II patients after surgery (with optional nodal staging) to either low- or high-risk categories based on DNA ploidy. High-risk stage I and II patients were defined as either stage IC or grade 3 with nondiploid tumors, and received adjuvant vaginal brachytherapy. The remaining patients were low risk, and were observed after surgery. In the low-risk group, there was an overall 6% local-regional failure rate and 1.4% distant failure rate. However, “low-risk” stage II patients had a significantly higher risk for failure with greater than one third failing, primarily in the vagina or pelvis. The model used in that study may predict for a group of stage I patients that can be safely observed; stage II patients and those identified as high risk likely benefit from adjuvant therapy.

Stage I and II Disease—Who Benefits from Adjuvant Pelvic Treatment?

All of the prospective studies made post hoc attempts to identify subgroups of patients at higher risk for recurrence. In the GOG study, a “high intermediate” group was defined by a combination of risk factors that included advanced age, LVSI, outer-third invasion, and moderate to high tumor grade. As the first site of failure, the control arm of the low intermediate risk group (which comprised approximately two thirds of the patients) had an observed failure rate of 5%, while the higher risk group had a 13% risk for local-regional failure. The high intermediate risk patients were also at risk for failing distantly, with a 48-month observed distant failure rate of 19% in the control arm. The PORTEC trial identified low-risk patients as those with superficially invasive, grade 1 or 2 tumors and <60 years of age; these patients had a 5% risk of local-regional relapse. High-risk patients included patients older than 60, patients with stage IC, grade 1 or 2 tumors, and patients with stage IB, grade 3 tumors. This group of patients had a 5-year local-regional relapse rate of 19%, with the majority of relapses occurring in the vagina. In the Aalders et al. [6] study, a subgroup analysis in patients with deep myometrial invasion revealed that the rate of pelvic relapse was lower in the radiotherapy-treated patients, at 6.6% versus 14.7%. In patients with both grade 3 disease and deep invasion, a 10% improvement in the cancer death rate was seen with the addition of pelvic radiotherapy, and the pelvic relapse rate was lower, at 4.5% versus 20%.

Stage IB, Grade 3 and Stage IC Disease

These subgroup analyses provide useful information regarding subgroups of patients at a relatively higher risk for local-regional failure. They do not, however, address the pattern of local failure, which can be used to tailor adjuvant therapeutic recommendations. For stage IB, grade 3 patients, there are limited observation data. These patients appear to be at a relatively low risk for pelvic nodal metastases, with Creasman et al. [19] showing an approxi-
mately 4%–9% rate of pelvic node metastases with grade 2 or 3 disease and greater than two thirds’ invasion. In the PORTEC study, there were 37 patients in the control arm with stage IB, grade 3 disease; the authors reported a 14% 5-year local-regional failure rate in those patients. All of the local failures occurred in the vagina [20]. Of note, these patients were as likely to fail distantly, with approximately 20% suffering a distant relapse in both the observation and radiotherapy arms. Straughn et al. [21] reported outcome in 29 patients with stage IB, grade 3 disease treated with surgery alone (including lymphadenectomy). They noted a crude 14% recurrence rate, with nearly all failures distant. Given the patterns of failure without radiotherapy and the low expected rate of pelvic node metastases, it may be reasonable to limit adjuvant radiotherapy to the vagina in these patients, especially in the setting of complete nodal staging.

In the GOG surgical-pathologic study, outer one-third invasion was associated with an 18% risk for pelvic lymph node disease, suggesting a need for pelvic treatment. Indeed, without surgical staging, Aalders et al. [6] showed that the pelvic failure rate was approximately 15% with deep myometrial invasion and 20% with deep invasion, grade 3 disease. Surprisingly, Creutzberg et al. [20] reported a relatively low pelvic failure rate in the control arm of the PORTEC study in stage IC, grade 1 and 2 patients. In the 67 patients not receiving radiotherapy, there was a 2% actuarial risk for pelvic relapse and a 10% risk for vaginal relapse after surgical staging, grade 1 tumors. For the 133 patients with stage IC, grade 2 tumors, there was a 6% risk for pelvic failure and a 13% risk for vaginal failure. There are limited data regarding outcome of surgically staged stage IC patients treated with observation alone. Straughn et al. [21] reported the largest series (121 patients) treated with full surgical staging and no adjuvant radiotherapy; there was a 12% overall failure rate with 6% of patients failing locally; again, the vast majority of these local-regional failures were in the vagina.

In this subset of patients with stage IC disease, pelvic radiotherapy may provide limited additional local control in the pelvis after surgical staging, and authors have reported results with brachytherapy alone [22]. In at least one study, the use of vaginal brachytherapy for observation was found to be cost-effective in these intermediate-risk patients, with a calculated cost per year of life saved of approximately $38,000 [23]. In the absence of surgical staging, however, the expected rate of nodal metastases and failure data from Aalders et al. [6] suggest that pelvic radiotherapy is needed. It should also be recognized that grade 3 patients are at a much higher risk for failing distantly, with approximately 20% of stage IB, grade 3 patients and 30% of stage IC, grade 3 patients failing distantly in the PORTEC study. As discussed below, chemotherapy is currently being investigated in a prospective fashion in at least one trial for patients with grade 3 disease.

### Stage II Disease and the Case of LVSI

Stage II disease accounts for approximately 5%–15% of endometrial cancer cases and has a poorer prognosis than stage I disease, with an approximately 75% 5-year overall survival rate. Historically, this stage of disease was often treated with preoperative radiotherapy followed by surgery. There is a relative paucity of data regarding local-regional failure patterns in surgically staged patients with cervical involvement not receiving radiotherapy. In general, treatment recommendations follow those of patients with stage IC disease, and adjuvant pelvic radiotherapy is recommended. In patients with full surgical staging, there is limited experience using brachytherapy alone without pelvic radiotherapy. Several small series have reported few or no local-regional failures with this approach in stage II disease [24, 25]. The need for routine pelvic radiotherapy in stage II disease is being investigated in the current PORTEC study, as discussed below.

The original GOG surgical-pathologic study found that LVSI placed patients at high risk for lymph node metastases. Other investigators have confirmed this [26], and the risk for lymph node disease with LVSI ranges from 20%–50% [27]. Even in the absence of other risk factors for lymph node metastases, the presence of LVSI places patients at a relatively high risk for nodal disease. Due to this, patients managed surgically without lymphadenectomy should be treated with pelvic radiotherapy in the presence of LVSI, regardless of other risk factors. The pelvic failure rate after lymphadenectomy in patients with LVSI is not well characterized, and the need for routine adjuvant pelvic radiotherapy in these patients is unknown.

### Ongoing Trials in Stage I and II Disease

Current trials are attempting to tailor radiotherapy to the area of highest risk, address the need for pelvic radiotherapy in higher risk patients, and address the distant failure rate seen with high-risk histologies. Ongoing trials in Stage I,II disease are outlined in Table 1. The newest PORTEC trial (PORTEC-2) randomizes intermediate-risk patients to receive either vaginal brachytherapy or pelvic radiotherapy. Patients eligible for this trial are those with stage IC, grade 1–2 disease and age >60; stage IIA, grade 1–2 disease and any age; stage IB, grade 3 and age >60; stage IIA, grade 3 with <50% myometrial invasion; and stage IIA grade 1–2 disease and age >60. As in the original PORTEC study, lymphadenectomy is not required. A current National
Stage III and IV Disease

Approximately 20% of patients with endometrial cancer present with or are found to have extrauterine disease at the time of surgery. Most of these patients present with stage III disease, which consists of disease confined to the pelvis or lymph nodes. Stage IV patients are those with either invasion of the bowel or bladder (stage IVA) or distant metastases (stage IVB) and comprise generally 5% of patients with endometrial cancer. Adjuvant radiotherapy options in stage IVB disease are usually directed at symptom management, and a detailed discussion of these patients is not covered here. Stage III patients are heterogeneous in terms of prognostics, with 5-year survival rates of 30%–70% (discussed below). Patients with this subset of disease can present with adnexal or serosal involvement or peritoneal cytology (stage IIIA), vaginal involvement (stage IIIB), or pelvic and/or para-aortic nodal disease (stage IIIC). Patients with vaginal involvement are usually managed with preoperative radiotherapy. A variety of therapies has been used in other stage III patients, including involved-field radiotherapy, whole-abdomen radiotherapy, chemotherapy alone, and combined chemoradiotherapy. Developing therapeutic recommendations for patients with advanced disease has been confounded by the presence of numerous small series using various regimens, the relative lack of prospective randomized trials, and the heterogeneous outcomes of patients with stage III disease.

Adjuvant Therapy for Stage III Disease

Evaluating risks and patterns of failure allows for some generalizations to be made regarding this group of patients. In the GOG surgical-pathologic study, the risk for relapse increased with an increasing number of extrauterine sites of disease. This has been found in other studies as well. For example, Greven et al. [28] reported on 126 patients with stage III disease; the risk for recurrence after pelvic radiotherapy correlated with increasing grade of disease and sites of extrauterine disease. That series also found a greater risk for abdominal failure in patients with multiple sites of extraperitoneal disease. Patients with more than two sites had a 31% abdominal failure rate versus 10% for those with one site and grade 1 disease. Mariani et al. [29] reported on patients with nodal disease alone versus those with nodal and other extrauterine disease. Patients with nodal disease alone had a 3-year cause-specific survival rate of 72%, versus 33% in patients with other extrauterine disease.

In addition to evaluating prognosis by number of extrauterine sites, it is instructive to consider each substage of disease. In stage IIIA disease, patients are found to have extrauterine disease limited to positive cytology, adnexal involvement, and/or uterine serosal involvement. In general, each of these pathologic findings has been associated with the presence of other extrauterine disease; isolated positive peritoneal cytology, adnexal involvement, or serosal involvement is relatively rare. However, the existing series of patients with these isolated pathologic findings do reveal some differences in outcome among these subgroups. In the GOG surgical-pathologic study, positive peritoneal cytology was found in 12% of patients. Of the patients with positive peritoneal cytology, approximately 50%–60% had evidence of extraperitoneal spread, and the prognosis for these patients is determined by the presence of other extrauterine disease. Isolated positive peritoneal cytology is rare, occurring in 5%–6% of patients, and its importance as a prognostic factor is probably minimal. Many series have reported a relatively favorable outcome in this subset of patients, especially in the absence of LVSI or high-grade disease [30]. For example, one recent series reported a >90% 3-year disease-free survival rate in 46 surgically staged patients with isolated peritoneal cytology; only three of those patients received adjuvant postoperative radiotherapy [31].

Adnexal involvement was found in 6% of patients in the
GOG surgical-pathologic study and was associated with a higher risk for pelvic and para-aortic metastases. Isolated adnexal involvement has been reported in several small series; most patients in those series received adjuvant pelvic radiotherapy, precluding any generalizations regarding local-regional failure patterns in observed patients. In general, patients with isolated adnexal involvement have a relatively favorable outcome, with a 5-year disease-free survival rate of approximately 60%–85% with the use of adjuvant radiotherapy [32, 33]. In contrast to adnexal involvement, patients with uterine serosal involvement usually have a poor prognosis. As with other subsets of stage IIIA disease, serosal involvement is commonly associated with disease spread to other pelvic and extrapelvic sites. Reports of patients with isolated serosal involvement are limited but show a poor outcome; one series noted a 42% 5-year disease-free survival rate in patients receiving pelvic radiotherapy [34].

Stage IIIC disease includes those patients with involvement of the pelvic or para-aortic lymph nodes. The GOG surgical-pathologic study found pelvic lymph node involvement in approximately 11% of stage I and occult stage II patients; para-aortic disease was found in approximately 5% of those patients. In that study, Morrow et al. [11] found that the risk for recurrence for patients with stage IIIC disease was influenced by additional risk factors, such as positive cytology, adnexal disease, and LVSI. With several risk factors present, 43%–63% of patients failed. Other investigators have confirmed the negative impact of other risk factors on prognosis in patients with stage IIIC disease [35]. In general, patients with pelvic-only lymph node disease have a better outcome, with reported 5-year survival rates of approximately 70% [36]. Patients with disease in the para-aortic nodal chain have a worse outcome, with reported 5-year survival rates of approximately 30%–40% with the use of extended-field adjuvant radiotherapy [37]. Of note, patients with stage IIIC disease limited to the pelvis and pathologically negative para-aortic nodes may also benefit from extended-field radiotherapy. Nelson et al. [36] reported on a small series of patients with this subset of disease; approximately 12% of patients failed in the para-aortic chain after receiving pelvic radiotherapy alone for pelvic-only stage IIIC disease.

### Formulating Therapeutic Recommendations in Extrauterine Disease

Patients with isolated peritoneal cytology involvement may have a favorable outcome without adjuvant treatment; treatment recommendations in these patients should be guided by other pathologic findings. In addition, patients with limited pelvic nodal disease or isolated adnexal disease have relatively favorable prognoses and have been historically managed with adjuvant pelvic or extended-field radiotherapy. However, recommendations for patients with all subsets of extrauterine disease will likely be strongly influenced by the recent reporting of the GOG 122 trial, the only modern randomized radiotherapy trial in this patient population. This trial randomized stage III and IV patients (without evidence of hematogenous metastases) after surgical staging and optimal debulking to receive either whole-abdomen radiotherapy or adjuvant chemotherapy [38]. At a median follow-up of 52 months, there was improvement in both progression-free and overall survival with the use of chemotherapy compared with whole-abdomen radiotherapy. This improvement resulted in a 13% predicted improvement in disease-free status and an 11% predicted improvement in percent alive at 24 months. Overall, approximately 55% of patients recurred, with the majority of initial failures occurring outside the pelvis in both treatment arms. After 2 years, the rates of initial failures in the pelvis were 21% for the whole-abdomen radiotherapy arm and 26% for the chemotherapy arm. The benefit of chemotherapy appeared to be in reducing distant recurrences as the site of first failure, from 18% with radiotherapy alone to 10% with systemic treatment. In this trial, chemotherapy was associated with significantly higher adverse effects. Grade 3–4 toxicities were primarily hematologic, gastrointestinal, and cardiac with the use of chemotherapy.

With the reporting of the GOG 122 trial, there appears to be little role for the use of whole-abdomen radiotherapy in stage III and IV endometrial cancer. However, the high local failure rates suggest a continued role for tailored radiotherapy fields in these patients. The recently completed GOG 184 study for patients with stage III and IV disease takes this approach. In that trial, patients were randomized to one of two chemotherapy arms after surgical staging and limited-volume radiotherapy. The GOG 122 trial showed significant toxicity with the use of adjuvant chemotherapy, and only approximately two thirds of patients were able to complete all cycles of adjuvant chemotherapy. Given this toxicity, it should be recognized that some subsets of stage III patients (limited pelvic adenopathy, isolated adnexal disease) who do not tolerate chemotherapy may have a relatively favorable outcome with pelvic or extended-field radiotherapy alone or, in the case of isolated peritoneal cytology, no adjuvant therapy, versus vaginal brachytherapy alone.

### Papillary Serous and Clear Cell Carcinoma

Papillary serous and clear cell carcinomas are aggressive histologies with a propensity for upper abdominal spread. Complete surgical staging is important in this disease, as up to 75% of patients with clinical stage I or II disease are upstaged with complete surgical staging [39].
therapeutic approaches in stage I and II disease include observation [40], chemotherapy and vaginal cuff brachytherapy [41], pelvic external-beam radiotherapy [42], whole-abdomen radiotherapy [43], systemic chemotherapy, and vaginal cuff brachytherapy and intraperitoneal phosphorus-32 [44]. The relative paucity of data and heterogeneity of published approaches limit the ability of radiation and gynecologic oncologists to make informed adjuvant treatment recommendations in patients with uterine-confined disease. In the absence of clear data, limited-volume adjuvant radiotherapy (pelvic or vaginal cuff brachytherapy) may be a reasonable option in these patients.

In patients with stage III or IV papillary serous and clear cell disease, adjuvant radiotherapy has traditionally consisted of whole-abdomen treatment [45]. The GOG performed a prospective single-arm study of whole-abdomen radiation in 165 patients with stage III or IV disease, including papillary serous and clear cell patients. For the papillary serous and clear cell variants, that trial showed a 33% survival rate at 3 years [46]. The recently reported GOG 122 study included papillary serous and clear cell variants (approximately 30% of entrants), and the overall trial results revealed an inferior outcome in patients receiving whole-abdomen radiotherapy when compared with those receiving adjuvant chemotherapy. Other investigators have noted a superior outcome using systemic therapy in stage III disease with high-risk histologies [47]. Given the results of these studies and the known patterns of failure, patients with advanced-stage papillary serous and clear cell carcinomas should be considered for systemic therapy, with or without tumor volume-directed radiation therapy.

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

The authors indicate no potential conflicts of interest.

---

**REFERENCES**


27 Cohn DE, Horowitz NS, Mutch DG et al. Should the presence of lympho-vascular space involvement be used to assign patients to adjuvant therapy following hysterectomy for unstaged endometrial cancer? Gynecol Oncol 2002;87:243–246.


