The Role of Adjuvant Radiation in Endometrial Cancer

April 10, 2009
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Endometrial cancer is the most common gynecologic malignancy, with an estimated 40,100 cases and 7,470 deaths in 2008. This malignancy represents 6% of all cancers, and 3% of cancer deaths in women. Endometrial cancer is more prevalent in older women, with an incidence of 1 in 142 for women 40 to 59 years old, increasing to 1 in 81 women over 70 years old.[1] Median age at diagnosis is 62.[2] The mortality of endometrial cancer has decreased from 4.18 to 4.12 per 100,000 from 1991 to 2004.

ABSTRACT: Endometrial cancer treatment ideally begins with a staging procedure including abdominopelvic washing, total abdominal hysterectomy, bilateral salpingo-oophorectomy, and lymph node evaluation. Recommendations for postoperative adjuvant radiotherapy are determined by recurrence risk. Patients who have undergone staging and have early stage I disease and an absence of high-risk features for recurrence generally are treated with surgery alone. Intermediate-risk patients—those with high-risk stage I disease and some stage II patients—may benefit from adjuvant radiation therapy. Several randomized trials show that radiation therapy improves locoregional control among intermediaterisk patients. The optimal type of radiation therapy, whether vaginal brachytherapy or whole-pelvic radiation therapy, remains undetermined, though treatment decision can be guided by risk factors not encompassed by the current staging system. Patients with high-risk stage II disease and stage III disease generally receive external-beam radiotherapy, often in combination with chemotherapy. Chemotherapy alone in advanced-stage patients is a consideration, given the results of the Gynecologic Oncology Group (GOG)-122 trial.

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The general treatment approach to endometrial cancer therapy includes hysterectomy, salpingo-oophorectomy, and abdominopelvic washings (with or without lymph node dissection) as the primary therapy, with the use of postoperative radiation therapy (including vaginal brachytherapy, external-beam pelvic radiation therapy, extended-field irradiation, and wholeabdomen radiation therapy), hormonal therapy, and chemotherapy depending on pathologic criteria and patient-related factors. After surgical and pathologic staging is complete, patients can be roughly stratified into treatment groups based on risk. The first group—patients at low risk—includes those who have a high probability of cure and a low risk of recurrence without any additional treatment. The second group—patients with an intermediate risk—consists of those who have a higher rate of recurrence and lower rate of cure but who may or may not benefit from adjuvant radiation therapy. The third group—those at high risk—includes patients with a high recurrence rate for whom both chemotherapy and radiotherapy can be utilized to improve outcomes.

Low-Risk Disease
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Published on Physicians Practice (http://www.physicianspractice.com)

Low-risk patients are those with disease confined to the uterus and no adverse risk factors for recurrence, with no or little myometrial invasion of the tumor, and who have grade 1 or 2 histology. These patients have been shown to have an excellent cure rate without additional therapy. A prospective study of patterns of failure for early-stage disease was conducted between 1977 and 1983 (Gynecologic Oncology Group [GOG] protocol no. 33). The investigators found no recurrences among 72 patients with grade 1 and 2 tumors with no myometrial invasion who did not receive radiation therapy.[4] Another study showed only one recurrence after surgery alone in 127 patients with noninvasive cancer. The diagnosis of “recurrence” was clouded by the finding of an anaplastic carcinoma on the pelvic side wall in a patient who had initially presented with a grade 1 endometrioid adenocarcinoma, which the authors believed may have been a second primary.[5] Another study of patterns of recurrence with surgery alone noted vaginal recurrence rates of 4.4%, 5.7%, and 13.6% for normal, intermediate, and anaplastic histology, respectively. When stratifying by depth of invasion, recurrences were noted to be 3.7% with no myometrial invasion, 4.7% with superficial invasion, and 15.1% with deep invasion.[6] In the GOG-99 study, low-intermediate risk patients had a 4-year isolated local relapse rate of 5%.[7] Other investigators have described similar results with surgery alone in similar groups of low-risk patients.[8,9] Given the limited benefit, the risks and costs of adjuvant therapy are probably not warranted in this group.

Intermediate-Risk Disease

Intermediate-risk patients consist of those with disease confined to the uterus but who have a higher risk of recurrence based on patient- and tumor-related characteristics. These characteristics include age, lymphovascular space invasion (LVSI), and tumor size. Treatment recommendations are most varied in this group of patients, as seen in the National Comprehensive Cancer Network (NCCN) guidelines for cancer treatment.[10]

Several important risk factors for recurrence are not encompassed by our current staging system, including patient age, LVSI, and tumor size.[11-14] Younger women with endometrial cancer generally have a better prognosis. In an analysis of the GOG protocol 33 patients, 5-year relative survival rates were 96.3% for patients 40 years old or younger, 94.4% for patients 41 to 50 years old, 87.3% for patients 51 to 60 years old, 78% for patients 61 to 70 years old, 70.7% for patients 71 to 80 years old, and 53.6% for patients older than 80.[11] Another study estimated that for every 1-year increase in age, the recurrence risk increases by 7%.[12] LVSI is an independent risk factor for recurrence and death from all types of endometrial cancer.[11] Five-year survival in high-risk patients with endometrial cancer is 83.5% when considering those without LVSI, but only 64.5% in those with LVSI.[13] Tumor size has also correlated with lymph node metastases. Metastatic disease was noted in 4% of patients with tumors ≤ 2 cm, but 15% in patients with tumors > 2 cm, and 35% of patients with tumors involving the entire uterine cavity.[14]

Randomized Trials

| Table 1 |

Comparison of Intermediate-Risk Endometrial Carcinoma Trials

Five prospective randomized trials (Table 1) have attempted to delineate the role of adjuvant radiation therapy for intermediate-risk endometrial cancer.

- **Norwegian Trial**—The first of these randomized studies was the Norwegian trial by Aalders et al, which was published in 1980.[15] A total of 540 women with clinical stage I endometrial cancer who underwent hysterectomy and postoperative vaginal brachytherapy (60 Gy to the vaginal mucosal surface) were randomized to additional pelvic radiation therapy (40 Gy with a midline block after 20
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Gy) or observation. Pelvic radiation decreased vaginal and pelvic relapse rate (7% in the control group vs 2% in the pelvic radiation group at 5 years). However, the rate of distant metastases was higher in the pelvic radiation group (5% in the control group compared to 10% in the pelvic radiation group at 5 years), and the overall 5-year survival rate was not statistically different (89% vs 91%). On subset analysis, the patients with grade 3 tumors and > 50% myometrial invasion had non-statistically significant improvements in local control and survival after pelvic radiation therapy (18% vs 27% of deaths due to cancer).

- PORTEC-1 Trial—The Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1 trial was a randomized trial of surgery and postoperative radiation therapy vs surgery alone in 714 patients with stage I endometrial cancer. Patients had stage IA, grade 2/3; stage IB, grade 2/3; or stage IC, grade 1/2 disease. Lymph node sampling was not routinely performed, though suspicious lymph nodes were biopsied. Radiation therapy was given to a total dose of 46 Gy in 2-Gy fractions, with 177 patients treated with a four-field technique and 101 patients treated with anteroposterior/posteroanterior (AP/PA) opposed fields. The 5-year locoregional relapse rates were 4% in the radiation therapy group and 14% in the group receiving no further treatment (P < .001).[16] In an update of the study results with central pathology review, 10-year actuarial locoregional recurrence rates were 5% and 14%, respectively (P < .001), also favoring the radiation therapy group. The majority (75%) of locoregional recurrences in the observation arm were noted to be in the vagina or the vaginal vault. Risk factors for locoregional relapse were depth of invasion (less or more than half of the myometrium; P = .07), age (< 60, 60–70, and > 70; P = .007), International Federation of Gynecology and Obstetrics (FIGO) grade (P = .005), and radiation therapy (P < .0001). The investigators found no difference in overall survival.[17] Five-year grade 3/4 toxicity rates were 3% in the radiation therapy group and 0% in the control groups. Complication rates were improved in patients treated with a 4-field technique compared to those treated with an AP/PA technique.[18] The authors concluded that postoperative radiation therapy was not recommended in stage I patients less than 60 years old and patients with grade 2 tumors with superficial invasion.

- GOG-99 Trial—The next randomized trial, GOG-99, studied 392 patients with stage I/II endometrial carcinoma who underwent total abdominal hysterectomy–bilateral salpingooophorectomy (TAH-BSO) with lymphadenectomy followed by postoperative pelvic radiation therapy or no further therapy.[7] Patients had stage IB, IC, or occult II A/B disease. Radiation therapy consisted of wholepelvic radiation therapy to a total dose of 50.4 Gy. Estimated 2-year recurrence rates were 3% in the radiation therapy group and 12% in the group that received no additional therapy after surgery (P < .01). There were 18 pelvic or vaginal recurrences in the group that did not get adjuvant radiation therapy compared to three in the radiation therapy group, two of whom actually refused radiation therapy. Four-year survival rates (86% vs 92%) favored the radiation therapy group but this difference was not statistically significant.

An unplanned subset analysis was conducted for which patients were divided into high- and low-intermediate-risk groups based on four prognostic factors: age, high grade (grade 2 or 3), invasion of the outer one-third of the myometrium, and LVSI. High-intermediate-risk patients were at least 70 years old with one risk factor, at least 50 years old with two risk factors, or any age with all three risk factors. When examining recurrence with these risk factors taken into consideration, the relative hazard of recurrence among high-intermediaterisk patients who received radiation therapy was 0.42 (0.21–0.83) at 4 years. In other words, there was a 58% hazard reduction with the addition of radiation therapy. High-intermediaterisk patients, while making up 33% of patients, constituted...
67% of all recurrences. For survival analysis, the relative hazard associated with radiation therapy was 0.86 ($P > .05$), but for high-intermediate-risk patients, the hazard rate was 0.73 (0.43–1.26).

**ASTEC/EN.5 Trials**—The ASTEC (A Study in the Treatment of Endometrial Cancer) and EN.5 trials randomized 906 patients to adjuvant pelvic external-beam radiation therapy (40–46 Gy in 20–25 fractions) or no adjuvant external-beam radiation therapy. Vaginal brachytherapy could be used regardless of the external-beam randomization, and the total dose was 4 Gy in two fractions via high dose-rate radiation or 15 Gy via low dose-rate in the ASTEC trial—the EN.5 did not specify the brachytherapy. Treatment centers were required to decide in advance whether they would offer brachytherapy to all patients or to no patients. Brachytherapy was given to 54% of the patients in the external-beam radiation therapy arm and 53% of patients in the observation arm. Morbidity was 57% in the external-beam radiation therapy arm compared to 27% in the arm receiving no external-beam radiation therapy (no $P$ value available).[19]

Only 92% of patients randomized to the external-beam radiation therapy arm actually received external-beam radiation therapy, and only 82% of patients received at least 40 Gy of external-beam radiation therapy to the whole pelvis. With a median follow-up of 58 months, the 5-year hazard ratio for overall and disease-specific survival were not significantly different between the two groups. The 5-year hazard ratio for an isolated pelvic or vaginal recurrence was 0.46 (95% confidence interval = 0.24–0.89; $P = .02$), favoring the group that received radiation therapy, with recurrence incidences of 6.1% and 3.2% in the observation and external-beam radiation therapy arms, respectively. This trial shows a small improvement in locoregional control but no survival benefit. Limitations to the interpretation of the trial include low radiotherapy compliance, no discussion of radiotherapy quality assurance, the nonrandomized nature of brachytherapy use, and significant heterogeneity of inclusion criteria and staging.

**Additional Data**

**Pelvic Irradiation**—Adjuvant pelvic radiation therapy results in a clinically important decrease in locoregional recurrence in selected intermediate-risk endometrial cancer patients. While no improvement in survival was noted in the above trials with the addition of pelvic radiotherapy, competing morbidities in this patient population limit the power of even large studies over longer follow-up periods. The inclusion of low-risk patients and inadequate power may, in turn, limit the ability of these studies to detect small but important survival differences. For well-selected patients, improvement in local control may affect survival given that not all locoregional recurrences are salvaged. In addition, the substantial morbidity of salvage therapy should not be understated.

**SEER Analysis**—An analysis of the Surveillance, Epidemiology and End Results (SEER) database of the National Cancer Institute was conducted to evaluate the survival outcome of 21,249 patients treated for stage I endometrial cancer between 1988 and 2001.[20] Patients with N1 or M1 disease, as well as those without pathologic staging, were excluded. Approximately 19% of patients studied had radiation therapy. Of those who received radiation therapy, 89% had external-beam radiation therapy. On multivariate analysis with relative survival as an endpoint, use of radiation therapy showed a hazard ratio of 0.45 for IC, grade 1 patients ($P < .001$) and 0.74 for stage IC, grade 3/4 patients ($P = .009$).

**Vaginal Brachytherapy**—Since a large proportion of the locoregional recurrences are in the vagina or vaginal vault, some authors have hypothesized that postoperative vaginal brachytherapy alone may prevent the majority of locoregional recurrences. Many single-institution trials have shown acceptable locoregional control rates using vaginal brachytherapy alone.[21–29] Furthermore, since the addition of pelvic radiation therapy increases side effects, it would be beneficial to limit external-beam radiation therapy to those whose risk of recurrence is high, based on the risk factors noted above.

**PORTEC-2**—The PORTEC-2 trial, available at this time only in abstract form, was designed to compare postoperative external pelvic radiation therapy to postoperative vaginal brachytherapy. A total of 427 patients with high-intermediate risk endometrial cancer were randomized. High-intermediate risk was defined as: (1) age ≥ 60 and stage IC, grade 1/2; (2) age ≥ 60 and stage IB, grade 3; or (3) any age and stage IIA, grade 1/2, or grade 3 with < 50% myometrial invasion.

With a median follow-up of 34 months, 3-year actuarial vaginal relapse rates were 0.9% in the vaginal brachytherapy arm compared with 2.0% in the external-beam pelvic radiation therapy arm ($P = .97$). Pelvic relapse rate was 0.7% with external-beam radiation therapy and 3.6% with vaginal brachytherapy ($P = .03$). Distant recurrence rate, recurrence-free survival, and overall survival were not significantly different between the two arms. Three-year rates of vaginal, pelvic, and distant...
relapse as sites of first failure were 0%, 1.3%, and 6.4% in the vaginal brachytherapy group and 1.6%, 0.7%, and 6.0% in the pelvic radiation therapy group. There was no significant difference in recurrence-free or overall survival. The incidence of gastrointestinal grade 1 toxicities was 35% in the external-beam radiation therapy arm compared with 12% in the vaginal brachytherapy group. Grade 2 toxicity rates were 19% in the whole-pelvis radiation therapy group vs 7% in the vaginal brachytherapy group ($P \leq .001$). Grade 1 skin toxicity rates were 6% for the external-beam radiation therapy group and 1% for the vaginal brachytherapy group, and grade 2 toxicity rates were 3% and 0%, respectively ($P \leq .001$). The authors concluded that vaginal brachytherapy should be the treatment of choice for patients with high-intermediate risk of recurrence.[30]

**Local Recurrence** — Most of the above trials show an increased local recurrence rate without adjuvant radiation therapy in intermediate-risk patients. Five-year overall survival after local recurrence has been noted to range from 18% to 66%.[31-39] Of the 13 GOG-99 patients whose disease recurrence developed in the vagina alone, five had died from endometrial cancer by the time of publication.[7]

A retrospective review studied 91 patients treated with radiation therapy for vaginal recurrences at M.D. Anderson Cancer Center between 1960 and 1997. Approximately 74% of patients had stage I disease; 63% of these patients had not received radiation therapy as a part of their initial treatment plan. Of 91 patients, 80 received external-beam radiation therapy for their recurrence, with 52 also receiving brachytherapy. Eleven patients received brachytherapy alone. Local control rates were 82% and 75% at 2 and 5 years, respectively, and overall survival rates were 69% and 43% for the same time points. The local recurrence was not controlled in 18 patients, and 23 patients had treatment failure distantly as their next site of recurrence.[40] In general, outcomes are poorer in those who have a nonvaginal pelvic recurrence. Despite the possibility of salvaging some recurrences, the treatment of recurrence carries a significant morbidity. One recent study showed an 18% rate of grade 3/4 gastrointestinal toxicity and a 50% rate of grade 3 vaginal sequelae.[41]

The intermediate-risk group thus presents a clinical challenge. Secondary risk factors including age, LVSI, exact depth, grade, and possibly tumor size must be considered when making treatment decisions, so as to balance cure and complication rates. The benefit in locoregional control with the addition of radiation therapy must be balanced with the detriment to quality of life as a result of treatment. An additional quality-of-life concern is the morbidity associated with tumor recurrence and its treatment.

### High-Risk Disease

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<th>RECOMMENDATIONS</th>
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<tr>
<td><strong>Our group recommends:</strong></td>
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<tr>
<td>• Vaginal brachytherapy for most intermediate-risk patients</td>
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<td>• Radiation therapy combined with chemotherapy for patients with stage III disease</td>
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For patients who have endometrial cancer with a high risk of recurrence, adjuvant therapy should be considered. Patients in this group include those with stage IIB disease, evidence of cancer spread to the lymph nodes, pelvic disease outside of the uterus (ovaries or parametria), high-risk stage I disease (ie, grade 3 disease with deep myometrial invasion), and high-risk cell types such as papillary serous or clear cell histologies.

### Patterns of Recurrence: Observation

The data on patterns of recurrence with no additional therapy after surgery in patients with high-risk disease are scarce. In the study by Aalders et al, patients with stage IC, grade 3 tumors had a death rate of 27.5%.[15] Ayhan et al noted a 41% recurrence rate in a group of 68 surgically staged IIIA/IIIC patients who received no additional therapy. Nine patients (13%) had a local recurrence only, 13 (19%) had a distant recurrence only, and 6 (9%) had both local and distant recurrence. The total recurrence rate in the pelvis was 22%.[42]

### Patterns of Recurrence: Chemotherapy Alone
More information is available regarding the recurrence risk with chemotherapy alone. In a study of 43 patients with high-risk or advanced endometrial cancer who received chemotherapy alone, 29 patients (67%) relapsed, with 17 (39.5%) relapses in the pelvis and 23 (55.5%) outside of the pelvis. The 3-year actuarial pelvic relapse rate was 46.5%. The authors concluded that adjuvant radiation therapy should be used even in patients receiving postoperative chemotherapy.[43] The GOG-122 study randomized 396 stage III/IV patients treated with surgery (with maximal resection of disease to ≤ 2 cm) to postoperative chemotherapy or whole-abdominal radiation therapy. Among patients who received postoperative chemotherapy, the initial recurrence site was in the pelvis alone in 18%, in the abdomen in 14%, and included extra-abdominal or liver metastases in 18%.[44] Table 2 summarizes the data on locoregional recurrence in stage III patients treated with chemotherapy alone.

**Radiotherapy Options**—Several studies of patients with uterine-confined disease but higher risk of recurrence show a benefit of radiation therapy. In the Norwegian study, when examining the subset of patients with stage IC, grade 3 tumors, the addition of radiation therapy decreased the incidence of cancer-related death from 27.5% to 18.2%.[15] In the GOG-99 trial, the subset of patients in the high-intermediate risk group who received postoperative pelvic irradiation had a 19% decrease in recurrence and a 0.73 relative hazard of death.[7]

Patients who have disease outside of the uterus may also benefit from adjuvant radiation therapy, which has been given using whole-pelvis radiation therapy, extended-field radiation therapy, and whole-abdomen radiation therapy. In a study of 121 patients with stage III disease, the addition of pelvic radiation therapy improved 5-year survival from 50.3% to 68% ($P = .029$).[45] Extended-field irradiation—ie, extending the radiation therapy fields to include the common iliac and paraaortic lymph nodes—is used most often in patients with para-aortic metastasis. One series in a group of 40 surgically staged patients with para-aortic lymph node metastases reported a 47% 5-year survival with adjuvant extended-field radiation therapy. Only one severe complication was noted.[46] A previous series showed a 5-year survival of 10% in similar patients who did not receive extended-field radiation.[47]

### Case Report: How Would You Treat This 59-Year-Old Woman With Endometrial Cancer?

The patient is a 59-year-old woman who noted vaginal bleeding. Endometrial biopsy revealed grade 2 endometrial carcinoma, endometrioid type. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection, and peritoneal washings were performed.

Pathology revealed grade 2 endometrioid adenocarcinoma invading 11 of 24 mm of the myometrium. Lymphovascular space invasion was appreciated. Endocervical glands and stroma, ovaries, fallopian tubes, and peritoneal cytology were negative for tumor. Furthermore, 0 of 8 right pelvic lymph nodes, 0 of 7 left pelvic lymph nodes, 0 of 2 right para-aortic lymph nodes, and 0 of 2 left para-aortic lymph nodes were positive for metastatic disease.

Radiotherapy recommendations could include no additional therapy, pelvic radiotherapy, and/or vaginal brachytherapy. In cases such as these, vaginal brachytherapy is generally recommended by our group, for the following reasons:

This patient has stage IB, grade 2 disease and has an additional risk factor of lymphovascular space invasion. The patient would have been part of the high-intermediate group in the GOG-99 trial where there seemed to be significant benefit to pelvic radiotherapy. On the other hand, most pelvic recurrences in GOG-99 were vaginal, and PORTEC 2 notes similar outcomes for pelvic vs vaginal radiotherapy. In addition, the patient has been adequately staged with multiple single-institution
series, including our own, suggesting vaginal radiotherapy alone in this group of patients is adequate therapy. Pelvic radiotherapy is also associated with increased morbidity compared with vaginal brachytherapy. Therefore, for this patient, vaginal brachytherapy seems to provide a good balance between tumor control and morbidity.

Rose and colleagues reported the Massachusetts General Hospital experience of patients found to have para-aortic node metastases on lymph node dissection. A total of 26 patients were identified, of whom 17 received extended-field irradiation and 9 did not. Median survival time in the group that received extended-field radiation therapy was 27 months, compared to 13 months in the group given no adjuvant therapy \((P = .004)\). There was one treatment-related death in the extended-field irradiation group.[48]

Whole-abdominal irradiation has previously been used as a treatment option in patients with upper abdominal disease that has been completely excised or in those who are at a very high risk for intra-abdominal recurrence, such as those with papillary serous histology. The Stanford experience of whole-abdominal radiation in stage III/IV patients showed 3-year disease-free and overall survival rates of 79% and 89%, respectively.[49] Our institution’s experience showed a 5-year relapse-free survival rate of 70%, with a 5-year actuarial overall survival of 86%.[50]

The GOG-122 trial, as noted above, compared adjuvant whole-abdominal radiation therapy to adjuvant chemotherapy. With adjustment for stage, 5-year disease-free survival was predicted at 50% for the chemotherapy group compared to 38% in the whole-abdominal radiation therapy group. Overall survival also favored chemotherapy (hazard ratio = 0.68, \(P < .01\)). The 5-year actuarial pelvic control rate was 49% with adjuvant chemotherapy, but 74% with adjuvant radiation therapy \((P = .011)\). The combined locoregional and distant metastasis rate was not reported. However, the authors note that whole-abdominal radiation therapy “may not be the most effective RT approach.”[45]

- **Combined Chemoradiotherapy**— Given the improvement in disease-free survival seen with chemotherapy alone, but acknowledging the incidence of locoregional failures, the combination of chemotherapy and radiation therapy may be optimal.

Radiation Therapy Oncology Group (RTOG) 9708, a phase II study, was designed to assess the feasibility, toxicity, safety, recurrence patterns, and survival for high-risk patients receiving chemotherapy combined with adjuvant radiation therapy. Chemotherapy consisted of cisplatin at 50 mg/m\(^2\) on days 1 and 28 of radiation treatment followed by four additional courses of cisplatin at 50 mg/m\(^2\) and paclitaxel (175 mg/m\(^2\)). Radiation therapy consisted of 45 Gy in 25 fractions to the whole pelvis, followed by vaginal brachytherapy. A total of 46 patients were enrolled, and the median follow-up was 4.3 years. Four-year overall and disease-free survival rates for stage III patients were 77% and 72%. The investigators observed no recurrences for patients with stage IC, IIA, or IIB disease. The incidence of grade 3 toxicity was 16%, and of grade 4 toxicity, 5%.[51]
A phase III study conducted by the Nordic Society of Gynecologic Oncology–European Commission and European Organisation for Research and Treatment of Cancer (NSGOEC- 9501/EORTC 55991), randomized high-risk early-stage patients to adjuvant external- beam radiation therapy with a brachytherapy boost vs adjuvant chemoradiation therapy. The investigators found an estimated 7% absolute difference in progression-free survival favoring the combined-modality arm.[52] Table 2 shows outcome data for selected trials in patients with stage III disease.

Conclusions

Endometrial cancer is the most common gynecologic cancer in the United States.[53] Early-stage disease, in a large percentage of patients, is highly curable with surgery alone. Patients with uterine-confined disease and an intermediate risk of recurrence clearly benefit—in terms of local control— from the addition of radiotherapy. Ongoing evaluation of risk factors not included in staging is needed to clarify treatment recommendations. Until additional data are available, individual risk factors and competing morbidities should be considered when recommending adjuvant treatment. A combination of chemotherapy and radiotherapy may prove to be the preferred treatment algorithm in patients with a high risk of recurrence.

Financial Disclosure: The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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