Abstract
Endometrial cancer is the most common malignancy of the female genital tract. It is typically a disease of postmenopausal women and often presents with postmenopausal vaginal bleeding. In 75% of cases, it is diagnosed at an early stage and is associated with better overall survival rates than many malignancies. The appropriate staging surgery for patients diagnosed with endometrial cancer is a total hysterectomy and bilateral salpingo-oophorectomy with pelvic and para-aortic lymphadenectomy. Adjuvant radiation therapy in early-stage disease is associated with decreased rates of locoregional recurrences but does not improve overall survival. The role of chemotherapy is not well established for early-stage disease. Treatment recommendations for locoregional recurrence of endometrial cancer after hysterectomy are poorly defined and include tumor-directed radiation therapy, and/or chemotherapy, and/or surgical resection. Because the current guidelines are not specific, they are confusing to clinicians. To illustrate this, this report presents a patient who was diagnosed with stage IA endometrial cancer and developed vaginal cuff recurrence 3 months after surgery. (JNCCN 2012;10:442–445)

Case Report
A 56-year-old gravida 12, para 7, morbidly obese woman with hypertension and stage IA endometrial cancer diagnosed in June 2011 was seen in a medical oncology clinic after local recurrence at the vaginal cuff. She initially presented in March 2011 with 3 months of vaginal bleeding. Endometrial biopsy revealed grade I endometrial cancer. She had attained menarche at 13 years of age and menopause at 54 years of age. She had no family history of malignancy, and does not use tobacco, alcohol, or illicit drugs.

In June 2011 she underwent laparoscopic total hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy. Pathology revealed FIGO grade 1–2 endometrioid adenocarcinoma measuring $4.2 \times 3.2 \times 1$ cm limited to the inner one-half of the myometrium. The ovaries and fallopian tubes were not involved with the malignancy. Left and right pelvic and para-aortic lymph nodes showed no evidence of malignancy in 26 examined nodes. She was pathologically staged as FIGO stage IA (pT1a pN0 Mx). She received no adjuvant therapy.

She returned 3 months later with recurrent vaginal bleeding. A 2-cm friable mass was visualized at the apex of the vaginal cuff on pelvic examination and was resected. Pathology showed a moderately differentiated endometrioid adenocarcinoma. Staging CT scans of the chest, abdomen, and pelvis showed no evidence of distant metastatic disease. She was evaluated through radiation oncology. Pelvic radiation followed by vaginal brachytherapy was recommended. She was referred to medical oncology for consideration of systemic therapy.

For treatment recommendations, the authors referred to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Uterine Neoplasms for the treatment of locoregional recurrence of endometrial cancer after hysterectomy (to view the most recent version of these guidelines visit the NCCN Web site at www.NCCN.org). The most im-
Recurrent Endometrial Cancer

Discussion

Endometrial cancer is the most common malignancy of the female genital tract in the United States, with an estimated 46,470 new cases in 2011, ranking fourth in cancer prevalence in women after breast, lung, and colorectal cancer. An estimated 8120 deaths result from this disease. Endometrial cancer is primarily a disease of postmenopausal women with a median age at diagnosis of 61 years. In a population-based analysis, 4% of the endometrial cancers occurred in women aged 40 years or younger. Endometrial cancer includes epithelial and nonepithelial tumors, such as sarcomas. Uterine sarcomas are highly aggressive and rare tumors, accounting for approximately 3% to 7% of uterine tumors. Among epithelial tumors, endometrioid histology is the most common subtype, present in 84% of patients. Poor prognostic subtypes, including papillary serous and clear cell carcinomas, represent the other 6%. Risk factors for endometrioid carcinomas include increased levels of exogenous or endogenous estrogens with unopposed progestins, older age, obesity, and diabetes mellitus. Postmenopausal vaginal bleeding is the most common presenting symptom. The diagnosis is typically made after an endometrial biopsy.

Endometrial cancer is diagnosed at an early stage, with uterine-confined disease in approximately 75% of cases. Several studies showed the inaccuracy of clinical staging, and the International Federation of Gynecology and Obstetrics (FIGO) therefore recommended surgical staging with pathologic evaluation for histologic grade, myometrial invasion, and extratubal spread, including lymph node metastasis. In January 2010, FIGO and the American Joint Committee on Cancer (AJCC) updated the staging for uterine neoplasms. Based on these changes, stage I tumors include those with uterine-confined disease. Stage IA tumors are those with less than 50% myometrial invasion and IB tumors are those with 50% or more myometrial invasion and/or involvement of the endocervical glandular portion of the cervix. Stage II disease includes tumors with cervical stromal invasion. Stage IIIC was subdivided into C1 with metastasis to pelvic lymph nodes and C2 with metastasis to para-aortic lymph nodes. Positive peritoneal lavage cytology no longer affects staging but should be reported separately.

Based on the NCCN Guidelines for Uterine Neoplasms, treatment of endometrial cancer is divided into 3 categories: uterine-confined disease, involvement of cervical stroma, and suspected extrauterine disease. Endometrioid tumors (all stages) have a 5-year survival rate of 83%, whereas stage I endometrioid tumors have a 90% 5-year survival rate. This discussion is limited to the current management of early-stage tumors and treatment failure with isolated local recurrence.

In medically operable patients, total hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymph node dissection is the recommended surgery for treatment and complete surgical staging. Adjuvant therapy recommendations for early-stage disease are based on high-risk prognostic factors predictive of increased risk of recurrence, including older age, histologic type, histologic grade, deep myometrial invasion, lymphovascular space invasion, large tumor size (> 2 cm), and involvement of lower uterine segment or cervix. Adjuvant radiotherapy is typically recommended, but the role of chemotherapy in these patients is not well established. Patients with stage IA and grade 1–2 tumors are considered low risk, with a 5% or less chance of locoregional recurrence. High-risk disease is defined as gross involvement of the cervix (stage II) or stage III or IV disease. The Gynecologic Oncology Group (GOG) has defined FIGO stage IB, stage II (occult involvement), and no evidence of lymph node involvement as intermediate-risk. The GOG 0099 trial further defined intermediate-risk disease, with high-intermediate risk defined as 1) at least 70 years of age with only 1 of the other risk factors (moderate to poorly differentiated tumor grade, presence of lymphovascular space involvement, and deep (> 2/3) myometrial invasion); 2) at least 50 years of
age with any 2 of the other risk factors; or 3) any age with all 3 of the other risk factors. All other patients in the intermediate-risk group were defined as low-intermediate risk.

Two studies, GOG 0099 and PORTEC, evaluated the role of adjuvant pelvic radiation therapy in patients with early-stage endometrial cancer after surgery, with or without complete surgical staging. Among patients who had not undergone prior radiation, pelvic-only recurrence (including vaginal, pelvic, and regional nodal) was seen in 8.9% in GOG 0099 and 14% in the PORTEC trial, and vaginal recurrence accounted for almost two-thirds of the pelvic recurrences. In both studies, pelvic radiation reduced local recurrences, with no statistical difference in overall survival or distant failure rate. The reported salvage rate of isolated vaginal recurrence with radiation is 65% to 80%, with a less than 50% salvage rate in those with pelvic or regional recurrences. Clearly, better strategies for the management of these patients with early-stage disease are necessary.

Two cooperative group trials are currently looking at systemic therapy in the early-stage, but intermediate- to high-risk population. The first is GOG 0249, a phase III trial of pelvic radiotherapy versus VBT followed by 3 cycles of chemotherapy. The second is RTOG 0921, a phase II trial of postoperative intensity-modulated radiation therapy with concurrent cisplatin and bevacizumab followed by 4 cycles of chemotherapy. Both of these trials use radiotherapy and are investigating the potential benefit of chemotherapy in regard to recurrence rates and overall survival for this high-risk group.

These provocative trials are specific to adjuvant therapy for intermediate- to high-risk early-stage disease, but optimal treatment for locoregional recurrence of endometrial cancer is also not well defined. Is radiation therapy enough or should chemotherapy be used? How should treatment differ in patients previously treated with radiation therapy? Should all recurrences be treated with chemotherapy?

Isolated vaginal recurrence is the most common treatment failure after surgery in patients with early-stage endometrial cancer. In a retrospective analysis of 50 patients with isolated vaginal recurrence treated with radiation therapy (combination of VBT and pelvic radiation therapy in patients with no prior radiation therapy, and VBT alone in patients with prior pelvic radiation therapy), the 5-year survival rate was 53%. This would suggest that even in patients who had no prior radiation therapy, treatment for locally recurrent disease with radiation therapy alone is not optimal. Treatment with chemotherapy in addition to radiation should be considered in an effort to improve the survival of these patients.

No consensus exists on the management of this patient population. Current guidelines are broad and include tumor-directed radiotherapy, and/or brachytherapy, and/or chemotherapy, and/or surgical resection. The GOG 0238 trial, a randomized trial evaluating pelvic radiation with or without concurrent weekly cisplatin in patients with endometrial cancer with pelvic-only recurrence, was aimed at studying whether pelvic radiation with concurrent chemotherapy would improve progression-free survival compared with pelvic radiation alone. The study continues but has had slow accrual nationally. Notably, this is a rare population with pelvic-only recurrence and no prior radiation therapy.

At the authors’ institution, all patients with recurrent disease are presented at the gynecologic malignancies multidisciplinary treatment planning conference. Each patient’s risk factors surrounding their original diagnosis and disease recurrence (e.g., location of recurrence, prior therapy) are evaluated in effort to tailor the treatment plan. For example, patients treated with radiation initially would routinely be offered chemotherapy as part of their treatment for recurrent disease. These patients are encouraged to participate in clinical trials, if eligible.

Conclusions

The likelihood of local recurrence in low-risk patients with stage IA, grade 1–2 endometrial cancer is quite low, estimated around 5% risk of local or regional recurrence. Further stratification of patients with locoregional recurrence according to site of recurrence (vaginal vs. pelvic), prior radiation therapy, and initial disease characteristics (size of tumor, histology, grade) may help focus the treatment guidelines for these patients. Ideally, randomized trials in the locoregional recurrent patient population looking at chemotherapy would help determine the benefit of systemic therapy and/or concurrent therapy with radiation. As more patients with early-stage endometrial cancer are treated with upfront adjuvant
chemotherapy (as in GOG 0249 and RTOG 0921), information will be gained regarding the impact on recurrence rates and survival. Excess toxicity with more aggressive upfront treatment will also have to be considered.

The authors counseled the patient on her overall prognosis with vaginal cuff recurrence, given no prior adjuvant therapy and the various treatment options available, including systemic chemotherapy. They concurred with the recommendation of pelvic radiation therapy followed by VBT. They also recommended consideration of systemic chemotherapy after radiation therapy given the overall poor survival of these patients treated with radiation alone. She refused chemotherapy because of concerns about added toxicity after radiation.

References