Endometrial Cancer: Recent Developments in Evaluation and Treatment

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Endometrial carcinoma is the most common gynecologic malignancy in the United States. Most cases are diagnosed at an early stage. However, the outcome for women diagnosed with advanced-stage disease remains poor. The etiology of most endometrial carcinomas stems from the effects of excess estrogen, whether this comes from exogenous or endogenous sources. Differences in epidemiology and presentation suggest the existence of two forms of endometrial cancer: those related to and those unrelated to hormonal stimulation. Most women with endometrial cancer present with abnormal uterine bleeding; endometrial sampling is essential to exclude endometrial carcinoma in such patients. Endometrial cancer is surgically staged, and staging usually includes a hysterectomy and bilateral salpingo-oophorectomy. Lymphadenectomy also should be performed in selective cases to better assess disease spread and to evaluate the need for adjuvant therapy. Adjuvant treatment may include the use of radiation, progestins, or cytotoxic chemotherapeutic agents. Several clinical trials are underway to compare these treatment modalities, as well as to determine the optimal combination of active chemotherapeutic agents, such as doxorubicin, platinum agents, and paclitaxel (Taxol). [ONCOLOGY 13(12):1665-1675, 1999]

Introduction

In the United States, an estimated 37,400 women will develop uterine cancer in 1999 and an estimated 6,400 women will die of the disease.[1] The incidence of this cancer varies throughout the world, with more women in industrialized countries being afflicted. Carcinoma of the endometrium is the most common gynecologic malignancy among US women, who have a lifetime risk of developing the disease of approximately 2%.

Fortunately, the majority of cases of endometrial cancer are diagnosed at an early stage, when surgery alone may be adequate for cure. The rate of 5-year survival for women with stage I endometrial cancer is as high as 95%; however, the 5-year survival rate for women with stage III or IV disease is only 26%.[2] Great strides have been made in our understanding of endometrial cancer over the past decade. The etiologic role of estrogen therapies, including the use of hormone replacement and tamoxifen (Nolvadex), has been the focus of several studies. The protective benefits of oral contraceptive pills and progestin therapies have been well established. Surgical staging can be tailored to the individual patient, both by using the laparoscope to minimize surgical morbidity and by modifying the extent of tissue sampling based on histopathologic risk. For advanced or recurrent disease, more active chemotherapeutic agents are available as well, with many ongoing clinical trials.

Risk Factors

Unopposed Estrogens

Most of the risk factors for endometrial carcinoma are associated with increased estrogen exposure, either exogenous or endogenous. Examples of increased exogenous exposure include the use of estrogen replacement therapy or tamoxifen, while increased endogenous estrogen exposure may stem from obesity, anovulatory cycles, and estrogen-secreting tumors (Table 1).[3-5] Obesity and infertility are significant risk factors for the development of this cancer. Excessive adipose tissue is a site of conversion of androstenedione to estrone, as well as aromatization of androgens to estradiol. Nulliparity, by itself, probably does not increase the risk of endometrial cancer, but rather, the association lies with anovulatory cycles and the lack of a progestin effect during the luteal phase.

With respect to exogenous estrogen exposure, the risk of endometrial cancer is increased in women using combination hormone therapy, even when cyclical progestin therapy is added to an estrogen.
In a case-control study, Beresford et al found that women taking unopposed estrogens had a relative risk of endometrial cancer of 4.0 (95% confidence interval [CI], 3.1 to 5.1).[6] In women who took more than 5 years of hormone therapy that included a progestin for less than 10 days per month, the relative risk of endometrial cancer was 4.8 (95% CI, 2.0 to 11.4). Women who used hormone therapy with a progestin for 10 to 21 days per month had a relative risk of 2.7 (95% CI, 1.2 to 6.0). This study is limited by its retrospective case-control design, which relies on patient recall. However, it suggests the need for additional investigation.

The use of oral contraceptives has consistently been shown to decrease the risk of endometrial and ovarian cancer. The Cancer and Steroid Hormone (CASH) study demonstrated that women using combination oral contraceptives for at least 12 months had a 0.6 (95% CI, 0.3 to 0.9) relative risk of endometrial cancer, as compared with those who had never used oral contraceptives.[7] The protective effects of oral contraceptives were found to persist even 15 years after their use ceased. Current low-dose oral contraceptives prevent pregnancy primarily through a progestin effect. Similarly, the benefits of oral contraceptives in reducing endometrial cancer risk are also likely related to the effects of progestin in suppressing endometrial proliferation.

Family history also contributes to the risk of endometrial cancer. In women with the hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, endometrial cancer is the second most common malignancy, with an incidence of 20% to 40%.[8] A site-specific endometrial cancer syndrome has also been suggested from pedigree analysis and population-based studies.[9]

**Tamoxifen**

As the most commonly diagnosed cancer among US women, breast cancer has a far greater impact than endometrial cancer, the most common gynecologic malignancy. Tamoxifen, a nonsteroidal estrogen with antiestrogenic activity, is commonly used in the adjuvant treatment of women with breast cancer and as therapy for recurrent disease. Tamoxifen also recently received FDA approval for use in reducing the risk of breast cancer in high-risk women. The divergent activity of tamoxifen in different tissues is well recognized; it suppresses the growth of breast tissue (ie, acts as an estrogen antagonist) but stimulates the endometrial lining (ie, has estrogen-agonistic effects).

Both the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Stockholm Breast Cancer Study Group identified an increased risk for endometrial cancer among breast cancer patients treated with tamoxifen.[10,11] In one retrospective, case-control study from the Netherlands, use of tamoxifen for more than 2 years was associated with a 2.3-fold increased risk of endometrial cancer.[12] Conversely, another case-control study from Japan, which controlled for the total dose of tamoxifen exposure, did not find a significant increase in the incidence of subsequent endometrial cancer.[13] The consensus of most studies, however, is that there is a two- to threefold increased risk of endometrial cancer attributable to tamoxifen.[5] Despite initial reports, more recent studies do not confirm that tamoxifen use is associated with high-risk histology endometrial cancers.[11,14,15]

In tamoxifen-treated postmenopausal breast cancer patients, endometrial polyps are a common histopathologic finding. Lahti et al compared 51 postmenopausal women with breast cancer treated with tamoxifen (20 to 40 mg/d) for a median duration of 30 months to 52 breast cancer patients who were not treated with tamoxifen.[16] Endometrial thickening was markedly increased in the tamoxifen-treated women compared with the controls (mean thickness, 10.4 vs 4.2 mm), and polyps also occurred more frequently in the tamoxifen recipients (36% vs 10%). Similarly, Kedar et al performed a randomized, double-blind, placebo-controlled trial in which 51 of 111 postmenopausal women with breast cancer were treated with tamoxifen (20 mg/d) for a median duration of 22 months.[17] Again, greater endometrial thickening and more endometrial polyps were seen in the women randomized to tamoxifen. In addition, a proliferative process was noted in the endometrium of 90% of the tamoxifen-treated patients, as compared with 39% of the placebo-treated patients.

Endometrial cystic atrophy may also be a common process related to the estrogenic effect of tamoxifen that is not readily detected by curettage but is only diagnosed in patients undergoing hysterectomy.[18] In a cohort of 35 tamoxifen-treated postmenopausal women, endometrial polyps were found in 66% of patients. Endometrial cystic atrophy was noted in 9 of 11 patients who underwent hysterectomy, as compared with only 1 of 24 patients who underwent hysteroscopy and curettage.

Cystic atrophy may not always develop at the surface of the endometrium but may be present deeper within the uterine wall and, thus, still produce endometrial thickening on pelvic ultrasound. Sonohysterography may be helpful in differentiating between polyps and endometrial cystic atrophy in women with a thickened endometrium (see [Presentation and Diagnostic Evaluation] below).
In 1996, the American College of Obstetricians and Gynecologists (ACOG) issued a committee opinion regarding the role of tamoxifen in endometrial cancer. The committee concluded that although tamoxifen is associated with an increased risk of endometrial cancer, the benefits of treatment outweigh the risks. Although routine screening for endometrial cancer is not recommended for patients taking tamoxifen, many patients are being screened. Certainly, any abnormal bleeding or spotting should be investigated. Because of the high incidence of cystic atrophy, pelvic ultrasound may lead to false-positive results. Rather, endometrial biopsy is a more specific evaluation that may be combined with sonohysterography.

### Histopathology

Endometrial carcinomas are classified by histologic subtype (Table 2). By far, endometrioid adenocarcinomas are the most common subtype, occurring in 85% of patients. Endometrioid adenocarcinomas are characterized by a proliferation of endometrial glands without intervening stroma. Clear cell and serous carcinomas, representing 5% to 10% of endometrial cancers, are highly aggressive tumors that commonly present at a more advanced stage and with lymphatic invasion, and confer a much poorer prognosis. Endometrial hyperplasia is felt to be a precursor lesion to endometrial carcinoma. Hyperplasia with cytologic atypia, in particular, is associated with progression to well-differentiated adenocarcinoma, and is found in 30% to 40% of cases of endometrial carcinoma. Differences in epidemiology and presentation suggest two different forms of endometrial carcinoma. Type I endometrial carcinoma is estrogen-related, tends to be associated with hyperplasia, and typically presents as a low-grade endometrioid tumor. Type II endometrial carcinoma appears to be unrelated to estrogen or hyperplasia and tends to present with higher-grade or poor-prognostic cell types, such as papillary serous or clear cell tumors. Our current understanding of risk factors only helps to identify patients at risk for type I disease, although no effective screening tests are available for endometrial cancer. Most patients are still identified by symptoms of abnormal vaginal bleeding.

### Presentation and Diagnostic Evaluation

The hallmark symptom of endometrial carcinoma is abnormal uterine bleeding. All postmenopausal women who develop bleeding unrelated to hormone therapy should be evaluated to exclude endometrial carcinoma. Pre- and perimenopausal women with menometrorrhagia also should be evaluated for endometrial cancer, particularly if they have other risk factors, such as anovulation or obesity. Such an evaluation should be considered in asymptomatic postmenopausal women with endometrial cells on a Pap smear, particularly if atypical cells are present.

Screening has not proven to be effective in the early detection of endometrial cancer. Pap smears sample the exfoliated cells of the cervix but are inadequate for detecting endometrial disease. Endometrial biopsy is a less effective screening test in asymptomatic women due to its relative discomfort, the risk of equivocal results necessitating additional work-up, and the possibility of false-negative results.

Other tests that may aid in the evaluation of women at risk for endometrial carcinoma include the progesterone challenge test, transvaginal ultrasound, and sonohysterography. **Progesterone Challenge Test** The progesterone challenge test has been suggested as an inexpensive screening test for detecting women at risk for endometrial carcinoma. Classically, medroxyprogesterone acetate (10 mg) is administered for 10 days. Using a different regimen of injecting progesterone-in-oil, Hanna et al suggested that asymptomatic postmenopausal women who had withdrawal bleeding within 2 weeks were more likely to have hyperplastic changes of the endometrium. Likewise, of women known to have endometrial hyperplasia, 90% exhibited withdrawal bleeding. The progestin challenge test has never been evaluated in women with known endometrial cancer, and thus, its efficacy in this group of patients is unknown. **Transvaginal ultrasound** is a useful technique for evaluating the endometrium. A sagittal-view scan of the uterus allows for the measurement of double-wall endometrial thickness in an anteroposterior dimension from basalis layer to basalis layer, excluding any fluid within the cavity. In postmenopausal women, an endometrial thickness of < 4 to 5 mm is associated with a low risk for endometrial disease. A thicker lining should be evaluated further by endometrial sampling, either by office biopsy or dilatation and curettage, if indicated. **Sonohysterography** involves placement of fluid within the endometrial cavity to enhance
examination of the endometrial lining. As mentioned above, this technique may improve the delineation of endometrial polyps vs other pathologies that account for endometrial thickening.

**Pipelle Endometrial Sampling** The diagnosis of endometrial cancer is most easily made by office sampling. Pipelle endometrial sampling is simpler to perform and more acceptable to the patient than dilatation and curettage. Moreover, a prospective study found Pipelle endometrial sampling to have a sensitivity of 97.5% and a specificity of 83.3% in patients with known endometrial cancer.[25]

**Dilatation and curettage** still the constitute the gold standard of evaluation, and should be used in patients in whom endometrial biopsy findings are not diagnostic of cancer but still prompt high suspicion of its presence (eg, hyperplasia with atypia, necrosis, or pyometra).

### Preoperative Evaluation and Staging

Once a diagnosis of endometrial carcinoma has been made, preoperative evaluation includes a complete blood count, determination of serum electrolytes, renal panel, liver function tests, urinalysis, chest x-ray, and electrocardiogram. A computed tomographic (CT) scan is usually unnecessary unless extrapelvic disease is suspected.

Since 1988, endometrial carcinoma has been surgically staged according to the revised International Federation of Gynecology and Obstetrics (FIGO) classification system (Table 3). Risk of lymph node and distant metastases are associated with poor histology, increased tumor size and location, higher grade, depth of myometrial invasion, and lymphovascular space involvement.

In certain cases in which the risk of nodal spread is low, surgical staging can be limited to total hysterectomy and bilateral salpingo-oophorectomy (Table 4). In all cases, the uterine surgical specimen should be opened in the operating room to evaluate disease extent.

**Laparoscopic Staging** Minimally invasive surgical techniques using laparoscopic pelvic and para-aortic lymphadenectomy combined with vaginal hysterectomy may be an alternative to traditional laparotomy in selected patients.[26] Some limitations to this technique include the surgeon’s experience and patient factors, such as body habitus. The feasibility of laparoscopic staging is currently under investigation in Gynecologic Oncology Group (GOG) protocol number 9301, a phase III randomized study comparing laparoscopy to laparotomy in patients with clinical stage I and IIA disease.

### Treatment

The postoperative treatment plan should take into account the prognostic factors for risk of recurrent disease without adjuvant treatment.

**Low-Risk Patients**

Patients with well-differentiated endometrial carcinomas confined to the uterus or moderately differentiated endometrial carcinomas with only superficial invasion are considered to be at low risk for recurrence. In such low-risk patients, adjuvant therapy after hysterectomy is not recommended.

**Primary Progestin Therapy** In special circumstance, ie, young women who desire to maintain fertility, atypical hyperplasia and well-differentiated endometrial carcinomas may be treated with progestin therapy only. Randall and Kurman reported on a series of 12 women under the age of 40 years with well-differentiated endometrial cancer who were treated conservatively with high-dose progestins.[27] Of the 12 patients, 9 had documented regression of disease, and none exhibited disease progression.

**Hormone Replacement After Surgery** Whether to offer the patient hormone replacement therapy after surgery for endometrial cancer is still an area of controversy. A review of estrogen replacement in patients with stage I or II endometrial cancer found no difference in progression-free or overall survival associated with estrogen use.[28] Of note, 53% of patients treated with estrogen also received progestin therapy. In addition, patients treated with estrogen replacement had a lower-stage and lower-grade cancer, and also less depth of invasion, as compared with patients who did not receive estrogen.

Gynecologic Oncology Group protocol number 137, a randomized trial of conjugated estrogens vs placebo in patients with early-stage endometrial carcinomas currently in progress, hopefully will help to resolve this controversy.

**Intermediate-Risk Patients**

Patients with deeply invasive tumors confined to the uterus (with or without cervical involvement) are considered to be at intermediate risk for recurrence. The optimal therapy for this group of patients after surgical staging is still under evaluation.

**Brachytherapy** may be indicated in these intermediate-risk patients, at least to reduce the risk of...
vaginal cuff recurrence. To study the use of adjuvant brachytherapy, Orr et al treated 396 women with stage IA, grade 2-3, stage IB, or stage IC endometrial cancer with brachytherapy (6,000 cGy) to the upper vaginal cuff. The 5-year survival rate was 97%; all recurrences presented as distant disease.[29]

Pelvic radiation may also be of benefit in some intermediate-risk patients. Women with intermediate-risk (stage IB to occult IIB) endometrial cancer were studied in GOG protocol number 99, a randomized study comparing pelvic external-radiation therapy (5,040 cGy) vs no further treatment.[30] Of 390 evaluable patients, 96% of the patients treated with pelvic radiation remained disease free at 2 years, as compared with 88% of those given no further treatment (P= .003). Pelvic radiation significantly reduced vaginal and pelvic recurrences. However, since pelvic recurrences were treated relatively effectively with second-line therapy, survival differences were not statistically significant.

High-Risk Patients
Distant disease is present in 12% to 26% of patients with endometrial cancer at the time of diagnosis. Additional treatment with radiation and/or chemotherapy should be considered in these women with advanced-stage endometrial cancer, as well as in those with recurrent disease.

Role of Surgical Cytoreduction—Although the role of surgical tumor resection is relatively clear in early-stage endometrial cancer disease, the role of surgical cytoreduction in advanced-stage disease is more ambiguous. This is in contrast with ovarian cancer, in which cytoreduction of small-volume residual disease improves survival. This is probably because endometrial cancer is less sensitive to chemotherapy.

Nevertheless, Chi et al retrospectively studied three groups of endometrial cancer patients: those whose disease was optimally cytoreduced to < 2 cm, those whose tumor was suboptimally reduced (residual disease > 2 cm), and those with unresectable carcinomatosis.[31] Median survival in the optimally cytoreduced group (31 months) was longer than that in either the suboptimally cytoreduced or the unresectable group (12 and 3 months, respectively). Tumor biology may have contributed to the ability to cytoreduce disease. However, as in ovarian cancer, these preliminary data suggest that there may be a role for surgical cytoreduction in selected patients with advanced endometrial cancer.

Radiation Therapy—Endometrial cancer responds better to hysterectomy with or without adjuvant radiation therapy than to radiation alone. Adjuvant radiation is recommended for patients with lymph node involvement and for some patients with high-grade tumors. Both vaginal cuff radiation and pelvic radiation may reduce the likelihood of local recurrence. In patients with pelvic lymph node involvement alone, 5-year survival rates of 67% to 72% have been reported with postoperative whole-pelvic radiation therapy.[32,33] In patients with positive para-aortic nodal disease, extended-field radiation has yielded 5-year survival rates of 36% to 47%.

Systemic Therapy—Treatment of patients with disseminated endometrial carcinoma should be individualized, but both hormonal agents and cytotoxic chemotherapy play a role in the management of these patients.

Hormonal Agents—Progestin therapy has been shown to produce response rates of 15% to 25%. [4] Several progestins have been investigated and have resulted in similar response rates: hydroxyprogesterone caproate, 29%; medroxyprogesterone acetate, 22%; and megestrol acetate (Megace), 20%. The route of delivery does not appear to have an impact on response, and, therefore, an oral progestin is the agent of choice. A typical dose of megestrol acetate may range from 160 to 320 mg/d. The average duration of response with progestins is 4 months, with an average overall survival of 10 months.

Prognostic factors for response to progestin therapy include well-differentiated tumors, as well as tumors positive for estrogen and progesterone receptors, although progesterone receptor levels are more important prognostically than are estrogen receptors. Tamoxifen may also have activity in advanced and recurrent endometrial carcinoma and has been combined with progestins in several clinical trials. Preliminary results from a GOG study demonstrated a 32% response rate with tamoxifen and medroxyprogesterone acetate and a 26% response rate with tamoxifen and megestrol acetate.[unpublished data]

However, the combination of tamoxifen and progestins has not been shown to be more effective than single-agent therapy.

Gonadotropin-releasing hormone agonists also have been studied in patients with endometrial cancer. Jeyarajah et al reported on the use of leuprolide acetate (Lupron; 3.75 to 7.5 mg intramuscularly every 4 weeks) in 32 patients with recurrent endometrial cancer. This therapy produced a 28% response rate (two complete and seven partial responses).[34]
Cytotoxic chemotherapyː Both single-agent and combination chemotherapeutic regimens have been studied in patients with endometrial carcinoma. Although several agents have been shown to induce clinical responses, most of these responses were partial and of short duration. Doxorubicin, cisplatin (Platinol), and carboplatin (Paraplatin) all have shown activity as individual agents, yielding response rates of 21% to 28%.[4]
In a small series, a doxorubicin-based combination demonstrated a remarkably high response rate. Using the combination of cisplatin, doxorubicin, and cyclophosphamide (Cytoxan, Neosar), Burke et al reported a response rate of 45% in 87 evaluable patients with advanced or recurrent endometrial carcinoma; 12 patients had a complete response and 27 patients, a partial response. Progression-free survival was still relatively short at 4.8 months, however.[35] Gynecologic Oncology Group protocol number 107, a randomized, controlled trial, compared doxorubicin alone to doxorubicin combined with cisplatin every 3 weeks. Response rate was better in the combination group than in the doxorubicin-only group (42% vs 26%), as was progression-free survival (5.7 vs 3.8 months). However, overall survival did not differ significantly in the two groups. More recently, paclitaxel (Taxol) has been shown to be effective in advanced and recurrent endometrial cancer. Using paclitaxel at a dose of 250 mg/m² over 24 hours with granulocyte growth factor support, Ball et al reported a 36% response rate (four complete and six partial responses), a 3.8-month progression-free interval, and a 9.5-month overall survival time.[36] As a result of these findings, GOG protocol number 163 is randomizing patients with advanced or recurrent endometrial carcinoma to doxorubicin and cisplatin or to doxorubicin, paclitaxel infused over 24 hours, and granulocyte colony-stimulating factor (Neupogen) support. This trial recently closed to patient accrual, and results are expected within the next 2 years.
As more recognition has been given to the papillary serous and clear cell histologic subtypes of endometrial cancer, greater interest has focused on paclitaxel- and platinum-based combination regimens, similar to the regimens used in ovarian carcinoma. Many new agents with differing mechanisms of action are currently being studied by the GOG in endometrial cancer (Table 5).
Another ongoing GOG trial (protocol 122), is comparing the efficacy of combination chemotherapy vs whole-abdominal radiation therapy in patients with advanced-stage endometrial carcinoma debulked to < 2 cm residual disease.

Conclusions

Early-stage endometrial carcinoma is a very treatable disease. Identifying individuals at risk may provide opportunities for chemoprevention with oral contraceptives. Symptoms of abnormal uterine bleeding should be promptly evaluated, as should bleeding in any woman with excess estrogen effect, whether endogenous or exogenous. Once a histologic diagnosis of endometrial carcinoma has been made, surgical staging, when feasible, can determine the extent of disease and the presence or absence of risk factors. Risk of recurrence is based on stage and other prognostic factors, which dictate the need for additional treatment. Patients with early-stage disease may be treated by surgery alone. Intermediate-risk patients may benefit from adjunctive radiation therapy. The optimal treatment for individuals with high-risk or recurrent endometrial carcinoma has yet to be determined. Well-differentiated, hormone receptor-positive tumors may respond well to progestin therapy. Radiation therapy is beneficial in controlling retroperitoneal disease. Several active chemotherapeutic agents are also being studied. Doxorubicin, cisplatin, carboplatin, and paclitaxel seem to be effective as single agents as well as in combination. The optimal drug combination is still being defined.

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