Adenocarcinoma of the Endometrium: An Institutional Review

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The pathology, diagnosis, and management of endometrial cancer are reviewed.

Background: Many oncologists regard endometrial cancer as a relatively benign and easily treatable gynecologic tumor. Inadequate care can result in poor outcomes.

Methods: The authors review the epidemiology and pathology of the disease, and they compare disease characteristics and outcomes of FIGO staging with their own 11-year experience at a tertiary referral center.

Results: Patients referred to tertiary referral centers tend to present with more advanced stages of disease than those reported by FIGO, although the profile of histologic types is similar.

Conclusions: Prevention and early detection of endometrial cancer can minimize the impact of this disease. Complete staging and tumor removal including extrafascial hysterectomy with bilateral salpingo-oophorectomy, pelvic lymphadenectomy, and selective paraaortic lymphadenectomy are the cornerstones of surgical therapy.

Introduction

Adenocarcinoma of the endometrium ranks fourth in incidence among invasive tumors in women, following breast, lung, and colon cancers. In 1999, approximately 6,000 deaths will be caused by adenocarcinoma of the endometrium, and 35,000 new cases of this disease will be diagnosed. This death-to-diagnosis ratio of approximately 1 to 6 indicates a generally favorable prognosis. However, a prior American Cancer Society and SEER projection for 1986 indicated a death-to-diagnosis ratio of 1 to 12, so there is increasing concern about the virulence of this disease. For this reason, physicians and nurses should be aware of the epidemiological profile of the patient with adenocarcinoma of the endometrium and its precursors, the best methods of early detection, and the factors that influence the management of the individual patient.

Epidemiology

Adenocarcinoma of the endometrium is typically a disease of postmenopausal women with approximately 85% of the patients being over 50 years of age. With longer life expectancy for American women, the disease is becoming increasingly important. Menopause after age 52, nulliparity, obesity, diabetes, previous radiation, and the administration of unopposed estrogen and tamoxifen are the main factors that predispose to this type of cancer.

Patient Experience

During the 11-year period between 1987 and 1997, 290 patients with endometrial cancer were treated at our institution. A review of our experience with this group highlights key areas relating to diagnosis, pathology, management, and outcomes.

The modal age was 60 to 69 years, with only 43 (15%) of the 290 patients being under 40 years of age (Fig 1). The distribution of histologic subtypes of tumor is summarized in Table 1. The distribution of cases by stage is shown in Table 2. The greater proportion of patients with more advanced stages in our series in comparison to data from the International Federation of Gynecology and Obstetrics (FIGO) reflects the referral pattern to our institution. Fifty-one percent of our patients were treated with surgery only, 20% received surgery plus radiation, 10% had surgery and chemotherapy, 4% had surgery plus hormones, 2% were treated with radiation alone, and 13% received other therapy.

Fig 1.—Age at diagnosis of 290 patients with endometrial cancer seen at Moffitt Cancer Center (1987-1997).

Table 1. Endometrial Carcinoma: Histopathologic Subtypes Encountered at the
The majority of patients (87%) experienced no recurrence. Distant, local, and regional recurrences were seen in 7%, 0.7%, and 2% of patients, respectively. Eight patients (2.4%) were never disease-free. Table 3 summarizes the survival experience from our institution and compares it with pooled FIGO data.

### Pathology

**Precursors of Endometrial Carcinoma**

A range of hyperplastic lesions of the endometrium has long been recognized often in association with frank malignancy or in women considered at high risk for endometrial carcinoma. In 1900, Cullen suggested an etiologic relationship between endometrial hyperplasia and cancer, and reviews by Taylor and Novak and Yui supported this view. In 1947, Gusberg labeled the entire spectrum of hyperplastic lesions adenomatous hyperplasia, drew attention to their production by both endogenous and exogenous estrogenic stimulation, and emphasized their role as precursors of frank carcinoma. The first complete classification of endometrial hyperplasia was that of Hertig and Sommers published in 1949. Subsequent to these early studies, numerous authors have attempted to classify endometrial hyperplasias, but unfortunately, the results have been in a range of descriptive terminology, diagnostic labels, and treatment plans that "have conspired to confuse both the pathologist (in the formulation of meaningful diagnosis) and the gynecologist (in therapeutic decision making)."

In 1974, Vellios commented that the so-called "hyperplasias" of the endometrium would be more appropriately termed "dysplasias" in a manner analogous to lesions of the cervix. This led us to review the work of Richart on the classification of the precursors of invasive cervical carcinoma. He developed the unifying concept of cervical intraepithelial neoplasia (CIN) to replace the profusion of terms describing the precursors of invasive cervical cancer. Ruffolo et al proposed a similar classification for the precursors of endometrial carcinoma, labeling them GIN-I, GIN-II and GIN-III to signify glandular intraepithelial neoplasia, grades I, II, and III. GIN-I includes cystic hyperplasia and adenomatous hyperplasia without atypia (Fig 2). GIN-II includes adenomatous hyperplasia of moderate degree and atypical hyperplasia (Fig 3), and GIN-III includes severe atypical hyperplasia as described by Vellios and carcinoma in situ, as described by Hertig and Sommers (Fig 4). No classification is generally accepted, but whichever one is used, the presence or absence of atypia should be recognized because this parameter best reflects the subsequent cancer risk.
Histopathology of Endometrial Carcinoma

Carcinoma of the endometrium occurs in a number of subtypes, each varying in its propensity to create myometrial invasion and metastases. The relative frequencies of the various subtypes varies with time and from one institution to another. Table I shows the subtypes in our series.

**Adenocarcinoma** — Adenocarcinoma of endometrioid type is estrogen-dependent. It is the most common variety and accounts for approximately three fourths of patients in this series. Histopathologically, it is characterized by the proliferation of abnormal glands in an abnormal relationship to one another. Little or no stroma separates the glands. The lining epithelium may be infolded or slightly papillary. The cells are enlarged with variable numbers of mitotic figures. In accordance with the FIGO system established in 1988, three grades of adenocarcinoma are recognized: grade I is well differentiated (Fig 5), grade II is moderately differentiated with partly solid areas (Fig 6), and grade III is predominantly solid or entirely undifferentiated (Fig 7).

**Papillary Serous Carcinoma** — This tumor, which was present in 45 (16%) of our patients, has a poor prognosis. It is distinguished from clear cell carcinoma by the absence of a clear cell component. Its appearance is suggestive of ovarian carcinoma, and the tumor cells are supported on thin, fibrovascular cores forming delicate papillary fronds (Fig 8).

**Adenocarcinoma With Squamous Differentiation** — The first type of this neoplasm, formerly called adenoacanthoma, was present in only 1 (0.3%) of our 290 patients. It is an adenocarcinoma with areas of benign squamous epithelium that are usually scattered throughout the tumor but occasionally are localized (Fig 9). The second type, formerly called adenosquamous carcinoma, was found in 14 (5%) of our patients. This is characterized by the presence of both malignant glandular and malignant squamous elements (Fig 10). Adenosquamous carcinoma has a worse prognosis than adenoacanthoma.
Clear Cell Adenocarcinoma — This tumor was present in 9 (3%) of our patients. It consists of polygonal, hobnail-shaped, or flattened cells arranged in solid masses or in tubular, papillary, or cystic patterns (Fig 11).

Undifferentiated Carcinoma — This type, which was present in only 1 of our patients, carries a poor prognosis.

Secretory Adenocarcinoma — This tumor is characterized by a glandular pattern with cells forming uniform, subnuclear vacuolization similar to that seen in the luteal phase of the menstrual cycle.

Diagnosis

Postmenopausal bleeding should always be thoroughly investigated with cognizance that the Papanicolaou smear is positive in a minority of patients with adenocarcinoma of the endometrium (Fig 12). Women should be cautioned to contact their physician if postmenopausal bleeding occurs so that an adequate investigation can be undertaken. An endometrial biopsy will give the diagnosis in approximately 90% of patients. The Pipelle endometrial biopsy (Unimar Co, Wilton, Conn) provides excellent specimens. These devices should be used in conjunction with endocervical curettage to ensure that an endocervical lesion is not overlooked. If these biopsies are negative but the patient continues with perimenopausal or postmenopausal bleeding, then a fractional curettage of the uterus (endometrium and endocervix) is performed under general anesthesia. Hysteroscopy may be useful but should always be combined with fractional curettage to reduce diagnostic failure to a minimum. Ultrasound is as useful as magnetic resonance imaging in estimating the thickness of the endometrial stripe (over 8 mm is significant) and depth of invasion preoperatively, and it also is less expensive. Endometrial hyperplasia usually can be treated with progestational agents such as 20 mg of megestrol acetate given daily. The patients should be followed with endometrial biopsy and/or dilation and curettage every 6 months. Progression to severe atypia or cancer calls for hysterectomy.

Management

Treatment for adenocarcinoma of the endometrium depends on the FIGO stage (Table 4). The surgical keystone is total extrafascial abdominal hysterectomy with bilateral salpingo-oophorectomy. For accurate surgical staging, pelvic and paraaortic lymphadenectomy is performed. It is well recognized that node dissection is prognostically valuable, and Kilgore et al demonstrated that patients with endometrial cancer who underwent multiple-site pelvic node sampling had better survival than those who did not (P=0.002). When patients were classified as low-risk disease (corpus only) or high-risk disease (involving cervix, adnexa, uterine serosa, or positive washings), multiple-site nodal sampling again provided a significant advantage in survival compared with patients without node sampling (high risk P=0.0006, low risk P=0.026). Also, patients who received whole pelvic radiation for grade III lesions or who had deep myometrial invasion had better survival rates after multiple site pelvic node sampling than those in whom nodes were not sampled (P=0.0027). This survival advantage for patients having multiple site node sampling overall and for patients in high- and low-risk groups strongly suggests a therapeutic benefit. Adjuvant chemotherapy, hormonal therapy, or chemoradiotherapy may be logically directed in these high-risk patients, which comprised 40% of our cases (Table 2).

Table 4. FIGO Corpus Cancer Staging (1988)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA G1</td>
<td>Tumor limited to endometrium</td>
</tr>
<tr>
<td>IA G2</td>
<td>Inversion to &lt;1/2 myometrium</td>
</tr>
<tr>
<td>IA G3</td>
<td>Invasion to &gt;2 myometrium</td>
</tr>
<tr>
<td>IC G1</td>
<td>Endocervical glandular involvement only</td>
</tr>
<tr>
<td>IC G2</td>
<td>Endocervical glandular involvement only</td>
</tr>
<tr>
<td>IC G3</td>
<td>Endocervical glandular involvement only</td>
</tr>
</tbody>
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Many gynecologists are confident that they can treat patients with stage 1 endometrial carcinoma adequately. However, because few are capable of performing an adequate pelvic lymphadenectomy, patients are not being accurately staged according to the 1988 FIGO criteria. Thus many patients with stage 1 disease are being understaged. The patient should be referred to a gynecologic oncologist for treatment if the tumor stage is advanced or the tumor is poorly differentiated or if a high-risk histopathologic lesion such as a serous papillary, clear cell, or secretory carcinoma is detected at fractional curettage. Cases with cervical stromal involvement (stage IIB), if recognized, should also be referred because more extensive surgery involving radical hysterectomy, pelvic lymphadenectomy, and selective paraaortic lymphadenectomy will be required. During the operation, peritoneal washings are collected for cytology and the uterus is evaluated by frozen section to assess tumor type, grade and depth of invasion. Estrogen- and progesterone-receptor status should be evaluated to provide additional information on the permanent sections.

Nodal metastases are often associated with other high-risk features such as lymphatic or vascular involvement. These features are used to better assess prognosis and to assist in decisions regarding adjuvant treatments. At our center, only approximately 50% of our patients were treatable by surgery alone. All of these patients had an extravesical abdominal hysterectomy and pelvic and paraaortic selective node dissections unless contraindicated by such conditions as morbid obesity.

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Decisions regarding radiotherapy should follow complete surgical staging of the lesion in accordance with the 1988 FIGO staging classification. Preoperative radiotherapy is now rarely justified. If postoperative radiotherapy is to be given, a vaginal applicator should be used rather than external therapy in selected stage I patients. A vaginal applicator appears to provide a better therapeutic index, especially when the extravesical hysterectomy with bilateral salpingo-oophorectomy is accompanied by an extensive pelvic and paraaortic lymphadenectomy. This treatment is also less expensive than the external-beam approach.

Recurrence

Recurrence of endometrial carcinoma is most common in the high-risk cases and in premenopausal or younger (under 45 years) women. The incidence of ovarian metastases at presentation is approximately 30% for younger women compared with approximately 5% in women over 45 years of age. Since approximately 85% of recurrences occur within the first three years of treatment, patients are followed every two to three months for the first three years after treatment and thereafter at six-month intervals. The cornerstone of adequate follow-up is investigation of any history of vaginal bleeding, careful pelvic examination with a Papanicolaou smear at each visit, and annual chest radiograph and mammogram. An elevated serum CA-125 level of over 35 U/mL may be the first sign of recurrence in a patient with a stenosed upper vagina following radiotherapy because in these cases, vaginal bleeding is unlikely and pelvic examination is unsatisfactory. Routine computed tomography scans are not generally necessary but are considered if the clinical situation suggests recurrence. Fine-needle aspiration can confirm recurrence. Magnetic resonance imaging is expensive and rarely helpful in this situation.

Local recurrences are usually at the vault of the vagina and/or in the suburethral area. Localized recurrences in patients who have not received previous radiotherapy may be treated with radiotherapy. Metastases to bone can be treated with localized radiotherapy, which is highly effective in relieving pain. For pulmonary metastases, hormonal therapy with 80 to 320 mg/day of megestrol acetate (Megace) or 20 to 40 mg/day of tamoxifen should be tried. A complete response rate of approximately 20% has been reported with hormonal therapy. Hormonal therapy is probably most effective when the tumor tissues contain receptors. The value of 80 mg of megestrol acetate twice daily for three weeks, alternating with 20 mg of tamoxifen twice daily for three weeks, is being investigated in the Gynecologic Oncology Group protocol 153. In cases where levels are low, chemotherapy should be considered. If chemotherapy is to be used, it should be carried out by a gynecologic oncologist or a medical oncologist.

Discussion

Our overall survival results are slightly inferior to FIGO rates. This is partly explained by the fact that only 60% of our patients had stage I disease compared with 73% in the FIGO report. In addition, 24.5% of our patients were in the poor histopathologic prognosis categories (eg, papillary serous, adenosquamous, clear cell, and undifferentiated carcinomas). This also explains why only approximately 50% of our patients were treated with surgery alone.

Despite frequent warnings over many years, carcinoma of the endometrium remains an underrated tumor. Its management is often performed more casually than its virulence may warrant. That it is overall the least aggressive of gynecologic malignancies should not obscure the fact that for many women, this tumor is a cause of considerable morbidity from surgery and from radiation and chemotherapy used to supplement surgical treatment. Also, many patients who have what is generally assumed to be an easily curable, "early-stage" carcinoma die of the disease because gynecologic oncologists are not generally available to manage and accurately stage them.

Conclusions

The optimal treatment of early-stage endometrial carcinoma is still not fully defined. Known and as yet unrecognized prognostic factors must be sought by clinical and laboratory methods. New methods of therapy for extensive disseminated or recurrent disease must be carefully evaluated. All women with this cancer should have the benefit of consultation with a gynecologic oncologist before treatment begins. However, the key to reducing the mortality and morbidity of this disease is improved patient and physician education, which will result in earlier diagnosis and treatment.

References


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Back to Cancer Control Journal Volume 6 Number 4