Contemporary Issues in the Management of Endometrial Cancer

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Cancer of the epithelial lining (endometrium) of the uterine corpus is the fourth most common malignancy in women and ranks seventh among causes of cancer deaths in females. Since 1972, endometrial cancer has been the most common female pelvic malignancy reported by the American Cancer Society, which estimates 36,100 newly diagnosed cases and 6,300 deaths in the United States in 1998.1

Factors influencing its prevalence are the declining incidence of cervical cancer because of widespread screening, prolonged life expectancy, and earlier diagnosis. Because 75% of cases occur in postmenopausal women who usually present with abnormal vaginal bleeding, most of these cancers are detected at an early stage when they are highly curable. Nonetheless, each year approximately 6,000 patients in the United States die of this disease. A great deal of attention has been paid to the possible induction of endometrial cancer by the antiestrogen tamoxifen, which has led to the development of new selective estrogen receptor modulators (SERMs).

Over the past decade the staging of endometrial cancer has evolved from an inaccurate method of clinically staging patients to a newly developed surgical staging system. Among contemporary surgical issues is the increasing use of minimal-access surgery, including laparoscopically assisted vaginal hysterectomy and lymph node sampling. Another area that continues to evolve is the role of postoperative adjuvant therapy, including radiation and chemotherapy. The optimal management of patients with metastatic or recurrent disease (or both) also continues to be defined.

The frequency and extent of follow-up visits and surveillance studies in patients with a history of endometrial cancer are being reassessed as a result of changes occurring throughout the country because managed care contracts are being awarded to low-cost providers. Hormones continue to play a prominent role in endometrial cancer. Controversy still exists regarding estrogen replacement therapy in the management of women with a history of endometrial cancer, and it is hoped that a large cooperative group trial currently under way will clarify this issue as we enter the next century.

Epidemiology

Endometrial cancer is primarily a disease of postmenopausal women, although 25% of these cancers occur in premenopausal patients and 5% occur in patients younger than 40 years.2,3 Two mechanisms are believed to be involved in the development of endometrial cancer. Type I cancers are associated with unopposed estrogen of either endogenous or exogenous origin (Table 1). Patient characteristics associated with type I cancers include obesity, nulliparity, diabetes, and hypertension. Increased expo-
sure to endogenous estrogen can be associated with chronic anovulation as occurs with Stein-Leventhal syndrome or estrogen-producing tumors such as granulosa cell tumors of the ovary. Peripheral conversion of androstenedione to estrone by extraglandular aromatization in adipose tissue accounts for the higher rate of endometrial cancer in obese women.

Administration of unopposed estrogen is associated with a four- to eightfold increased risk of developing endometrial carcinoma. These tend to be predominantly early-stage, low-grade, minimally invasive lesions that have a favorable prognosis. This risk can be abrogated almost completely by combining progesterone with estrogen to combat the carcinogenic effect of unopposed estrogen.

**Tamoxifen and Endometrial Cancer**

After the initial report by Killackey et al of endometrial cancer occurring in three breast cancer patients receiving antiestrogens, many studies have appeared implicating tamoxifen as a causal agent in the development of endometrial cancer.

Perhaps the strongest data initially implicating tamoxifen use in the subsequent development of endometrial cancer were published in 1989 by Fornander et al. These authors reviewed the frequency of new primary cancers as recorded in the Swedish Cancer Registry for a group of 1,846 postmenopausal women with early breast cancer who were included in a randomized trial of adjuvant tamoxifen. They noted a 6.4-fold increase in the relative risk of endometrial cancer in 931 tamoxifen-treated patients compared with 915 patients in the control group. The dose of tamoxifen in this study was 40 mg/day, and the greatest cumulative risk of developing endometrial cancer occurred after 5 years of tamoxifen use.

The most compelling data to date regarding the association between tamox-

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**Table 1**

| Characteristic                  | No. of Times Risk Increased |
|--------------------------------|----------------------------|
| Obesity                        |                            |
| 30–49 lb                       | 3.0                        |
| >50 lb                         | 10.0                       |
| Nulliparity                    | 2.0                        |
| Late menopause                 | 2.4                        |
| “Bloody” menopause             | 4.0                        |
| Diabetes mellitus              | 2.8                        |
| Hypertension                   | 1.5                        |
| Unopposed estrogen             | 4–8                        |
| Complex atypical hyperplasia   | 29.0                       |

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ifen use and the development of endometrial cancer are in the recent report published by Fisher et al\(^7\) of the findings of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial. These authors analyzed the rates of endometrial and other cancers in 2,843 patients with node-negative, estrogen receptor–positive invasive breast cancer randomly assigned to placebo or tamoxifen (20 mg/day) and 1,220 tamoxifen-treated patients registered in NSABP B-14 after randomization.

Two of the 1,424 patients assigned to receive placebo developed endometrial cancer; however, both had subsequently received tamoxifen for treatment of recurrent breast cancer. Fifteen patients randomized to tamoxifen treatment developed endometrial cancer. One of these patients never actually accepted tamoxifen therapy. Eight additional cases of uterine cancer occurred in the 1,220 tamoxifen-treated patients. Seventy-six percent of the endometrial cancers occurred in women aged 60 years or older. The mean duration of tamoxifen therapy was 35 months; 36% of the endometrial cancers developed within 2 years of therapy, and six occurred less than 9 months after treatment began, suggesting that some cancers may have been present before tamoxifen therapy started.

The average annual hazard rate for endometrial cancer was 0.2/1,000 in the placebo group and 1.6/1,000 in the randomized tamoxifen-treated group. The relative risk of an endometrial cancer occurring in the randomized, tamoxifen-treated group was 7.5. Similar results were seen in the 1,220 registered patients who received tamoxifen.

Any conclusions about the risk of tamoxifen treatment inducing endometrial cancer must weigh the benefits of tamoxifen in reducing breast cancer recurrence and new contralateral breast cancers. In the B-14 trial, the cumulative rate of breast cancer relapse per 1,000 was reduced from 227.8 in the placebo group to 123.5 in the randomized tamoxifen-treated group. In addition, the cumulative rate of contralateral breast cancer was reduced from 40.5 to 23.5. Taking into account the increased cumulative rate of endometrial cancer, the 5-year cumulative hazard rate in the tamoxifen-treated group was reduced 38%.

These results led the authors to conclude that the benefit of tamoxifen therapy for breast cancer outweighs the potential increase in endometrial cancer.

Screening for endometrial cancer in women with breast cancer taking tamoxifen has no proven benefit. The ultimate goal of any cancer screening program is to detect disease at an early stage when it is more curable. Because the stage, grade, and histology of tamoxifen-associated endometrial cancers appear similar to those of endometrial cancers occurring in the general population, prognosis of tamoxifen-associated endometrial cancers is generally good. Early detection probably will not improve outcome significantly.

A few tamoxifen-treated breast cancer patients could be expected to benefit from screening for endometrial cancer. Because the annual risk of endometrial cancer is 2/1,000 in this population and approximately 15% of these cancers will result in the patient’s death, annual screening could potentially decrease mortality in only 0.002 × 0.15, which is 0.0003, or 0.03%, of all tamoxifen-treated patients. Because approximately 80,000 women begin tamoxifen treatment annually, the cost of screening for endometrial cancer in this population may be prohibitively high.

For now, all women with breast cancer, regardless of whether they are receiving tamoxifen, should be encouraged to undergo an annual gynecologic evaluation. Endometrial sampling should be reserved for patients with any sign of abnormal vaginal bleeding, including spotting or brownish vaginal discharge.
Staging

Staging of endometrial cancer has evolved over the 25 years since the inaccurate clinical staging system proposed by the International Federation of Gynecology and Obstetrics (FIGO) in 1971.8

CLINICAL STAGING

In the 1971 FIGO system (Table 2), stage I is carcinoma confined to the corpus. It is divided into IA, in which the uterine cavity is 8 cm or less, and IB, in which the depth of the uterine cavity is more than 8 cm. Uterine depth is easily determined by sounding the uterus. Stage I cases are further subgrouped according to histologic differentiation. Grade 1 is highly differentiated carcinoma, grade 2 has partly solid areas, and grade 3 is predominantly solid or entirely undifferentiated carcinoma. Approximately 75% of patients with adenocarcinoma of the endometrium present with clinical stage I disease.

Stage II is carcinoma that has involved the corpus and cervix. In stage III, the carcinoma has extended outside the uterus but not outside the true pelvis. In stage IV, carcinoma has extended outside the true pelvis or has obviously involved the mucosa of the bladder or the rectum. This involvement must be proven by biopsy, because bullous edema does not permit a case to be allocated to stage IV. This clinical staging system is still applicable for cases that do not go to primary operative staging.

SURGICAL STAGING

Prognostic Factors

Because endometrial cancer is primarily treated surgically, in 1988 FIGO defined endometrial cancer as a surgically staged disease (Table 3),9 incorporating many of the prognostic factors reported in two large prospective staging trials by the Gynecologic Oncology Group (GOG) in

### Table 2

| Stage | Characteristics |
|-------|-----------------|
| I     | The carcinoma is confined to the corpus |
| IA    | The length of the uterine cavity is 8 cm or less |
| IB    | The length of the uterine cavity is more than 8 cm |
| II    | The carcinoma involves the corpus and cervix |
| III   | The carcinoma extends outside the uterus but not outside the true pelvis |
| IV    | The carcinoma extends outside the true pelvis or involves the bladder or rectum |

### Histologic Subtypes of Adenocarcinoma

- **G1**: Highly differentiated adenomatous carcinoma
- **G2**: Differentiated adenomatous carcinoma with partly solid areas
- **G3**: Predominantly solid or entirely undifferentiated carcinoma
Table 3

1988 International Federation of Gynecology and Obstetrics (FIGO) Clinical Staging for Corpus Cancer

| Stage | Characteristics |
|-------|-----------------|
| IA G1–3 | Tumor limited to endometrium |
| IB G1–3 | Invasion to less than half of myometrium |
| IC G1–3 | Invasion to more than half of myometrium |
| IIA G1–3 | Endocervical glandular involvement only |
| IIB G1–3 | Cervical stromal invasion |
| IIIA G1–3 | Tumor invades serosa or adenexae or peritoneal cytology positive |
| IIIB G1–3 | Vaginal metastases |
| IIIC G1–3 | Metastases to pelvic or paraaortic lymph nodes |
| IVA G1–3 | Tumor invades bladder and/or bowel mucosa |
| IVB | Distant metastases, including intraabdominal and/or inguinal lymph nodes |

Histopathology—Degree of Differentiation

Cases should be grouped by the degree of differentiation of the adenocarcinoma:

- G1: 5% or less of a nonsquamous or nonmorular solid growth pattern
- G2: 6%-50% of a nonsquamous or nonmorular solid growth pattern
- G3: More than 50% of a nonsquamous or nonmorular solid growth pattern

Notes on Pathologic Grading

Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade 1 or grade 2 tumor by 1.

In serous adenocarcinomas, clear-cell adenocarcinomas, and squamous cell carcinomas, nuclear grading takes precedence.

Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.

Rules Related to Staging

Because corpus cancer is now surgically staged, procedures previously used for determination of stages are no longer applicable, such as the finding of a fractional dilatation and curettage to differentiate between stages I and II.

A small number of patients with corpus cancer may be treated primarily with radiation therapy. If that is the case, the clinical staging adopted by FIGO in 1971 would still apply, but designation of that staging system would be noted.

Ideally, the width of the myometrium should be measured, along with the width of tumor invasion.
1984 and 1987. These studies helped to define the prognostic factors of endometrial carcinoma and the current treatment approach for patients with this disease.

In addition to evaluating the factors of age, race, and endocrine status, these studies confirmed that patient prognosis is directly related to the presence or absence of easily determinable uterine and extrauterine risk factors. The uterine factors were histologic cell type, tumor grade, depth of myometrial invasion, occult extension to the cervix, and vascular space invasion. The extrauterine prognostic factors are adnexal metastases, other extrauterine intraperitoneal spread, positive results of peritoneal cytologic studies, pelvic lymph node metastases, and aortic lymph node involvement.

Uterine size was previously believed to be a risk factor; however, recent information indicates that uterine size is not an independent risk factor but rather relates to cell type, grade, and myometrial invasion.

Cell type and grade are factors that can be determined before hysterectomy, although grade as determined by dilatation and curettage in some series has an overall 31% inaccuracy rate compared with grade determined by examination of the hysterectomy specimen, and grade 3 tumors have a 50% inaccuracy rate. Recognition of all the other factors requires an exploratory laparotomy, peritoneal fluid sampling, and hysterectomy with careful pathologic interpretation of all removed tissue.

**Surgical Procedure**

To stage by the FIGO criteria appropriately, the surgical procedure should minimally include an adequate abdominal incision (usually vertical), sampling of peritoneal fluid for cytologic evaluation (intraperitoneal cell washings), and abdominal and pelvic exploration with biopsy or excision of any extrauterine lesions suggestive of tumor.

Total abdominal hysterectomy and bilateral salpingo-oophorectomy are the standard operative procedures for carcinoma of the endometrium. The plane of excision lies outside the pubocervical fascia and does not require unroofing of the ureters. The ovarian and fallopian tubes are removed en bloc with the uterus.

In some cases, pelvic lymph node sampling is indicated. This consists of a sample of lymph nodes taken from the distal common iliac artery and from the external iliac artery and vein. A third sample of lymphatics is obtained from the group of nodes that lie along the obturator nerve. The surgeon tries to obtain an adequate sample of nodes from each anatomic site, but no attempt is made to perform a complete lymphadenectomy. Because lymph node sampling is not routinely done by the general gynecologist, identifying the subset of patients who benefit from selective lymphadenectomy is important and may require further surgical expertise from a gynecologic oncologist.

If no gross intraperitoneal tumor is noted at the time of laparotomy, pelvic and paraaortic lymph nodes should be sampled for the following indications: (1) invasion of more than half (the outer half) of the myometrium; (2) tumor presence (regardless of tumor grade) in the uterine isthmus or the cervix, adnexa, or other extrauterine sites; (3) presence of serous, clear-cell, undifferentiated, or squamous types; and (4) lymph nodes that are visibly or palpably enlarged.

If paraaortic node sampling is indicated, a sample can be obtained through a midline peritoneal incision over the common iliac arteries and aorta. Node sampling also can be done on the right by mobilizing the right colon medially and on the left by mobilizing the left colon medially. In each case, a sample of lymphatics and lymph nodes is resected along the upper common iliac vessels on either side and from the lower portion of the aorta and vena cava. On the left side, the
lymph nodes and lymphatics are slightly posterior to the aorta, and on the right side, they lie primarily in the vena caval fat bed.

After these procedures, the patient is surgically staged according to the 1988 FIGO criteria. The overall surgical complication rate after this type of staging is approximately 20%. The serious complication rate is 6%.11

**Lymph Node Sampling**

In the GOG study, 46% of the positive paraaortic lymph nodes were enlarged, and 98% of the cases with aortic node metastases came from patients with positive pelvic nodes, adnexal or intraabdominal metastases, or invasion of the outer third of the myometrium.11 These risk factors affected only 25% of the patients, yet they yielded most of the patients with positive paraaortic nodes. Overall, 5% to 6% of patients with a clinical stage I and II (occult) endometrial carcinoma have tumor spread to these lymph nodes.10

The key to the surgical management of patients with endometrial cancer is identifying patients at risk for retroperitoneal nodal metastasis because patients with pelvic and aortic disease can be salvaged with adjuvant radiotherapy. Postoperative irradiation to the pelvis and aortic area appears to be effective.

In the GOG study, 37 of 48 patients with positive paraaortic nodes received postoperative irradiation, and 36% remained tumor-free at 5 years.10 Potish and colleagues13 reported a 5-year survival rate of 47% in a smaller group of patients who were also treated with postoperative irradiation. Although this accounts for only 5% to 6% of patients with early-stage endometrial cancer, patients with metastatic spread to the paraaortic nodes must be identified because approximately 40% will be salvaged with extended-field radiotherapy.

Regardless of grade, lymph nodes need not be sampled for tumor limited to the endometrium because less than 1% of these patients have disease spread to pelvic or paraaortic lymph nodes. Frequently, the decision about lymph node sampling is difficult to make in patients whose only risk factor is invasion of the inner half of the myometrium, particularly if the grade is 2 or 3. This group has a 5% or less chance of node positivity. Lymph nodes should be sampled in these instances if any question exists about the degree of myometrial invasion. This includes invasion that approaches half the myometrial thickness in patients who are medically fit to undergo the sampling procedures.

The depth of myometrial invasion can be assessed easily at the time of surgery. The excised uterus is opened, preferably away from the operating table, and the depth of myometrial penetration and the presence of endocervical involvement is determined by clinical observation or by microscopic frozen section.14 Doering and colleagues15 reported a 91% accuracy rate for 148 patients in determining the depth of myometrial invasion by gross visual examination of the cut uterine surface.

Nine percent of patients with endometrial carcinoma have positive pelvic lymph nodes (stage IIIC).10 The incidence increases to 51%, 32%, and 25%, respectively, in patients with extrauterine metastases, adnexal involvement, and deep myometrial invasion. Patients with this as their only high-risk factor should be treated with postoperative whole-pelvic irradiation. In the GOG study, 13 (72%) of 18 patients are disease free at 5 years after treatment. Potish and others13 report a 5-year survival rate of 67% in a smaller series of similarly treated patients.

**Laparoscopic Surgery**

An alternative method of surgically staging patients with clinical stage I endometrial cancer is gaining in popularity. This approach combines laparoscopically as-
sisted vaginal hysterectomy with laparoscopic lymphadenectomy.

Childers and colleagues\textsuperscript{16} described their experience with this procedure in 59 patients with clinical stage I endometrial carcinoma. The laparoscopic procedure included a thorough inspection of the peritoneal cavity, collection of intraperitoneal washings, and laparoscopically assisted vaginal hysterectomy. Laparoscopic pelvic and aortic lymph node samples were obtained from all patients with grade 2 or 3 lesions and patients with grade 1 lesions who had more than 50\% myometrial invasion on frozen section. In two patients, laparoscopic lymphadenectomy was precluded by obesity.

Six patients noted to have intraperitoneal disease at laparoscopy underwent exploratory laparotomy. Two additional patients required laparotomy for complications, including a transected ureter and a cystotomy. The mean hospital stay was 2.9 days.

Laparoscopically assisted surgical staging is feasible in select groups of patients. However, it is not known whether it is applicable to all patients with clinical stage I disease. In particular, two groups of patients may not be ideal candidates because of their weight or the presence of intraabdominal adhesions. Paraortic lymphadenectomy is technically more difficult to do through the laparoscope. To obtain adequate exposure, the mesentery of the small bowel must be elevated into the upper abdomen, which becomes increasingly difficult to do as the patient's weight increases, especially for patients whose weight exceeds 180 pounds.\textsuperscript{17,18}

For patients who are eligible, the advantages of the laparoscopic approach include a reduction in length of hospitalization and fewer complications. Boike et al\textsuperscript{17} compared 23 patients who underwent laparoscopic management of endometrial cancer with 21 who underwent laparotomy during the same period. The laparoscopy group weighed significantly less than did the laparotomy group. No significant difference was found in the number of lymph nodes obtained from the pelvic or paraaortic regions in the two groups. The mean length of stay was 2.7 days for the laparoscopy group versus 5.9 days for the laparotomy group.

Although laparoscopically assisted vaginal hysterectomy with surgical staging may provide an alternative approach to the management of endometrial cancer, its equivalency in terms of cancer outcome to the standard laparotomy approach remains unproven, and the abdominal approach is still considered standard therapy. The GOG is conducting a randomized trial of these two approaches to help answer this question.

**Role of Postoperative Therapy**

The approach to postoperative treatment in patients with endometrial cancer is tailored to various prognostic factors (Table 4).

**LOW-RISK PATIENTS**

Patients with grade 1 or 2 lesions whose disease is confined to the endometrial cavity (stage IA) are considered low risk and do not appear to benefit from postoperative radiation. In the GOG experience no recurrences occurred in 72 of the patients who received no radiation compared with 19 who received either pelvic or vaginal radiation.\textsuperscript{11} One of five patients with a stage IA, grade 3 lesion who was not irradiated had a recurrence, but the number of these patients was too small for any firm conclusions to be drawn.

**INTERMEDIATE-RISK PATIENTS**

Patients with stage IB or stage IC and those with endocervical glandular (IIA) or stromal (IIB) involvement are considered to be at intermediate risk. Adjuvant pelvic radiation is of questionable benefit in this group of patients.

A randomized trial from the Norwegian Radium Hospital revealed no differ-
ence in survival between 277 patients with clinical stage I endometrial cancer treated with vaginal radium only and 263 patients who also received 4,000 rad of whole-pelvis radiation. Although the patients who received pelvic irradiation had a lower incidence of pelvic recurrences, this was offset by a higher frequency of distant failures. Pelvic radiation clearly improved survival only in patients with invasion of more than half the myometrial wall.

The GOG recently completed protocol 99, a randomized trial of no additional treatment versus 5,040 rad of pelvic radiotherapy in patients with intermediate-risk endometrial cancer. The estimated 2-year progression-free interval was 88% in the group with no treatment versus 96% in those given radiation. Most of the 17 recurrences in the no-treatment arm were pelvic (4) or vaginal (13).

Because most patients with recurrences were salvaged with radiation therapy, the study did not show any survival benefit to adjuvant radiation: 96% of patients who did not receive radiation initially. Toxicity was greater in the pelvic radiation group; therefore, perhaps the greatest therapeutic benefit would be with vaginal brachytherapy. Further studies of intermediate-risk patients are needed to answer this question.

The significance of positive results of peritoneal cytologic studies without extrauterine disease is unclear. The benefit of adjuvant therapy, including intraperitoneal chromic phosphate or other therapeutic modalities such as whole-abdominal radiation, is unproven. Many clinicians treat such patients with oral progestins.

**HIGH-RISK PATIENTS**

Patients with extrauterine disease, including intraperitoneal spread or spread to retroperitoneal lymph nodes, are considered high risk and benefit from adjuvant treatment. Patients with positive pelvic lymph nodes are treated with postoperative whole-pelvis radiation. In the GOG study, only 5 of 18 patients treated in this manner had recurrences.

Aortic nodal metastasis is an important prognostic factor. In the GOG

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**Table 4**  
Treatment Plan for Endometrial Cancer Using Surgical Staging

| Treatment Factors | Low Risk | Intermediate Risk | High Risk |
|-------------------|----------|-------------------|-----------|
| Stage             | IA, G1 & 2 | IA, G3 IB, IC (all G) 2A, 2B (all G) 3A (positive cytology) | 3A, 3B, 3C (all G) 4A, 4B (all G) |
| Postoperative treatment | None | Vaginal cuff radiation Pelvic radiation (questionable) | Vaginal cuff radiation Paraaortic radiation (positive aortic nodes) Abdominal radiation (intraabdominal spread) |

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experience, patients with grossly positive pelvic lymph nodes, gross adnexal metastasis, or invasion of the outer third of the myometrium had 55%, 43%, and 18% incidences of aortic node metastasis, respectively. Aortic nodal sampling is important in this group because approximately 40% of patients with aortic node metastases can be salvaged with adjuvant therapy. Of 48 patients in the GOG study with documented aortic nodal metastases, 37 received extended-field radiation therapy to include the paraaortic region, and 36% remained tumor-free at 5 years.

The ideal treatment for patients who present with intraabdominal disease remains to be determined. Patients with residual disease after surgery may benefit from whole-abdominal radiation or cytotoxic chemotherapy. The GOG is currently comparing whole-abdominal radiation with combination chemotherapy using cisplatin and doxorubicin in patients with stage III or IV disease and less than 2 cm of residual disease after surgery.

**Treatment of Recurrent Disease**

Various treatment strategies exist for patients with recurrent endometrial cancer. Aalders et al\(^\text{21}\) reported on 379 patients with recurrent disease treated at the Norwegian Radium Hospital. Local recurrence was noted in 50% of patients, distant recurrence in 28%, and both local and distant failure in 21%. The median time to recurrence was 14 months for patients with local recurrence and 19 months for those with distant metastases.

Approximately 40% of patients with isolated vaginal recurrences are salvageable with radiation therapy. Kuten et al\(^\text{22}\) noted a 40% progression-free 5-year survival in patients with an isolated vaginal recurrence treated with pelvic radiotherapy. In patients in whom the disease extended into the pelvis, however, this rate fell to 20%.

Hormonal therapy, including progestins and the antiestrogen tamoxifen, has proved useful in patients with recurrent endometrial cancer (Table 5). About 33% of patients with recurrent disease respond to progestins, and the highest responses are observed in patients with well-differentiated lesions that tend to be estrogen– and progesterone–receptor positive.

**Administration of unopposed estrogen is associated with an increased risk of developing endometrial carcinoma, which can be abrogated almost completely by combining progesterone with estrogen.**

In a review of 17 trials including a total of 1,068 patients, Kauppila et al\(^\text{23}\) noted a 34% response rate to progestins. Duration of response ranged from 16 to 28 months, and the average survival was 18 to 33 months.

Because progestins have low toxicity, many oncologists favor the use of these agents initially in patients with recurrent disease and reserve cytotoxic chemotherapy for treatment failures or symptomatic patients. A long disease-free interval (more than 2 or 3 years), well-differentiated histologic type, and positive estrogen or progesterone receptor status all have been associated with increased frequency of response to progestins. Response rates of approximately 22% have been noted with tamoxifen, and most responses occurred in women with well-differentiated tumors or those who had previously responded to progestins.
Cytotoxic chemotherapy is most often used for patients with advanced or recurrent disease who have failed hormonal therapy. Many chemotherapeutic agents have been tested in patients with endometrial cancer with varying results. Doxorubicin is considered the most active agent in endometrial cancer, with an overall response rate of approximately 26%.

Thigpen et al\(^{24}\) reported the GOG experience comparing doxorubicin with doxorubicin and cisplatin in patients with advanced or recurrent endometrial cancer. The combination had a higher overall response rate (45% versus 27%) and complete response rate (22% versus 8%) than did doxorubicin alone. At this point, the most active chemotherapeutic regimen for advanced endometrial cancer appears to be the combination of cisplatin and doxorubicin.

Paclitaxel (Taxol) appears to be a promising agent for the treatment of endometrial cancer. In a recent phase II trial conducted by the GOG, Ball and colleagues\(^{25}\) reported on 28 patients with recurrent or advanced endometrial cancer treated with 24-hour paclitaxel at a dose of 250 mg/m\(^2\) every 21 days. Patients who had received pelvic radiation previously were treated at an initial dose of 200 mg/m\(^2\). Complete responses were noted in four patients (14.3%) and partial responses in six (21.4%), for an overall response rate of 35.7%.

Currently, the GOG is evaluating paclitaxel in combination with doxorubicin compared with doxorubicin plus cisplatin.

### Postoperative Surveillance

The frequency and extent of follow-up visits and surveillance tests for patients with a history of gynecologic cancer traditionally have been based on arbitrary guidelines established and perpetuated at various institutions throughout the United States. The recent changes in medicine occurring throughout the country have led to a reevaluation of standard

### Table 5

| Progestin              | Average Dose | No. with CR+PR (%) | Response Range (%) | 95% Confidence Interval |
|------------------------|--------------|--------------------|--------------------|-------------------------|
| Hydroxyprogesterone caproate | 1–3 g IM q week | 198/674 (29)       | 9–34               | 26–33                   |
| Medroxyprogesterone acetate | 200–1,000 mg IM q wk or po qd | 164/746 (22)       | 14–53              | 19–25                   |
| Megestrol acetate      | 160–320 mg po qd | 42/206 (20)        | 11–56              | 15–27                   |
| Tamoxifen              | 20–40 mg     | 17/97 (18)         | 0–53               | 11–27                   |

CR = complete response; IM = intramuscularly; po = orally; PR = partial response; q = every; qd = every day.

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medical practices. Because managed care contracts now are awarded to low-cost providers, increased incentive exists to determine the most cost-effective manner of providing care.

Endometrial cancer is the most common gynecologic malignancy in the United States. Because most patients with endometrial cancer do well and no clear evidence exists that early detection of disease recurrence improves outcome, reevaluating the practice of routine intensive surveillance in women with a history of endometrial cancer has become necessary. Patients with medical complications, unexplained symptoms, or evidence of recurrent tumor require intense follow-up. Guidelines need to be set, however, for healthy, asymptomatic women who have been potentially cured and remain clinically free of disease.

In 1992, Barnhill and colleagues reported on the clinical surveillance programs used in the follow-up of gynecologic cancer patients based on the results of a survey of 94 members of the Society of Gynecologic Oncologists.

For an asymptomatic patient with no clinical evidence of disease, most respondents reported seeing patients in the clinic every 3 months for the first year after surgery, every 3 to 4 months the second year, every 6 months for the next 3 years, then annually thereafter. In most cases, physical examination included the breasts, abdomen, lymph node regions, and pelvis. In addition to performing a pelvic examination, 84% reported doing a Pap smear at each visit.

In terms of surveillance studies, 72% obtained annual chest radiographs for the first 2 years after surgery, and this decreased to approximately 50% for the next 3 years. Computed tomography (CT) scans were obtained annually by approximately 33% of respondents for the first 2 years after surgery, a figure that steadily declined after that. Although these follow-up practices are used widely, no rationale exists for any particular surveillance protocol based on examination sensitivity, cost-effectiveness, or survival benefit.

Several recent publications have addressed postsurgical surveillance in patients with endometrial cancer, trying to devise a more efficient and cost-effective method of following these patients. Specific attention was paid to the value of history and physical examination, Pap smears, chest radiographs, and level of the tumor marker CA-125 in detecting recurrent disease. A great deal can be learned from these studies and applied to the development of future strategies for following these patients.

HISTORY AND PHYSICAL EXAMINATION

Based on combined data from the four studies, 188 of 1,342 patients (14%) developed recurrent disease, 78 (42%) of whom had no associated symptoms. Eighty-one percent of all recurrences were detected by either symptoms or physical findings. In patients who were asymptomatic at the time of recurrence, approximately 52% had disease detected by physical examination. Therefore, only 37 patients (48% of 78) had their recurrent disease detected by other diagnostic tests.

Among symptomatic patients, the most common presenting complaint was pain, either abdominal or pelvic, followed by weight loss/lethargy and vaginal bleeding. Podczaski et al reported that only 2 of 23 symptomatic patients experienced abnormal bleeding, whereas 19 of 40 patients had vaginal bleeding in the series by Shumsky et al. Clearly, patient education regarding the signs and symptoms of recurrent disease should be incorporated into a surveillance program. Physicians should act promptly to evaluate symptomatic patients, with diagnostic tests being targeted toward the symptoms.

PAP SMEAR

According to Barnhill et al, 84% of asymptomatic patients being followed for
a history of gynecologic cancer undergo Pap smears at each visit. Again, reviewing the findings of the four published surveillance series, only 13 of the 188 patients (6.9%) with recurrent disease were found to have suggestive results of vaginal cytologic studies; however, this was an isolated finding not associated with an abnormal physical examination or symptoms in only 5 (2.7%) of these patients. Obtaining Pap smears routinely at each follow-up visit does not seem beneficial.

CHEST RADIOGRAPHS
Surveillance chest radiographs are obtained by most gynecologic oncologists during the first 2 years after surgery for early-stage endometrial cancer. Recurrent disease was detected by chest radiographs in 27 (14.4%) of the 188 patients reported in the pooled series.

Although chest radiographs can document the presence of distant recurrences, their impact is limited by the poor outcome of patients with pulmonary metastases. Most of these patients will succumb to their disease. The intent of routine surveillance is to detect the 10% to 15% of recurrences after primary treatment for endometrial cancer, with the hope that early initiation of therapy will improve the outcome. Because no effective systemic therapy exists for endometrial cancer and patients with pulmonary metastases have a poor prognosis, routine surveillance chest radiographs cannot be recommended.

CA-125 LEVEL
Elevated levels of the tumor-associated antigen CA-125 have been documented in patients with advanced and recurrent endometrial cancer and are correlated with the clinical course of disease.³¹

Rose et al³¹ noted that CA-125 levels were elevated in 19 of 33 (58%) patients with recurrent endometrial cancer. Reddoch et al³⁰ detected recurrence by an elevated serum CA-125 level in 6 of 23 (26%) asymptomatic patients. None of the patients achieved long-term survival, probably reflecting the association between an elevated CA-125 level and widespread disease. In view of the short lead time between CA-125 elevation and diagnosis of recurrence, the value of surveillance of CA-125 levels is limited and best reserved for patients with an elevated value at initial diagnosis.

RECOMMENDATIONS
Because most recurrences occur within the first 3 years after surgery, it is recommended that patients undergo pelvic examinations semiannually for 3 years, then annually thereafter. No evidence exists in the literature that surveillance with routine chest radiographs improves survival.

The studies cited earlier appear to indicate that routine Pap smears do not improve the outcome of patients with isolated vaginal recurrences. Based on these data, obtaining annual Pap smears appears to be of little benefit but may be reasonable during the first 3 years after surgery. Whether the smears should be continued annually after 3 years is debatable. Discontinuation of annual Pap smears after 3 years in favor of Pap smears at 3-year intervals may be considered. Serial CA-125 determinations should be done in patients with elevated levels at the time of diagnosis or with known extraterine disease, but no evidence exists that such monitoring improves patient outcome.

Postoperative follow-up also allows for the incorporation of a health maintenance program, including evaluation of blood pressure, breast examination, and assessment of stool guaiac level.

One important issue that needs to be addressed is the psychological support that routine follow-up visits provide for the cancer patient. The value of this support may be impossible to measure objectively. Less intensive surveillance can achieve substantial cost savings, but physicians need to continue providing emotional support and reassurance to
their patients. Combining patient education with interval nursing phone contact and prompt evaluation of symptoms may provide a more cost-effective method of practice while continuing to provide the emotional support that cancer patients need and deserve.

**Estrogen Replacement Therapy in Women with a History of Endometrial Cancer**

In the 1970s, reports in the medical literature began to link the use of exogenous estrogen to an increased incidence of endometrial cancer. However, these patients were found to have superficial, well-differentiated endometrial cancers that were highly curable. Furthermore, it was subsequently shown that the addition of progestational agents abrogated this increased risk.

Estrogen replacement offers important health benefits to women, including alleviation of hot flashes, prevention of osteoporosis, and protection from cardiovascular disease. The risk of major coronary disease for women who currently take estrogen was recently shown to be 56% of the risk for nonusers.

Despite the clearly proven benefits of estrogen replacement therapy, women with a history of endometrial carcinoma are usually denied this therapy because adenocarcinoma of the endometrium is considered an estrogen-dependent neoplasm. However, no scientific data exist to support the contention that estrogen replacement is dangerous for this group of patients.

Several retrospective studies have looked at the issue of estrogen replacement after surgical treatment of early-stage endometrial adenocarcinoma. In 1986, Creasman and colleagues reported on 221 patients with stage I endometrial cancer, of whom 47 (21%) received postoperative estrogen replacement for a median of 26 months. Estrogen was applied vaginally for 34 of these patients.

A multivariate analysis revealed no differences in tumor grade, myometrial invasion, nodal metastasis, or peritoneal cytologic findings among the 47 patients who received estrogen replacement therapy and the 174 who did not. In fact, the rate of recurrence was higher in the untreated group (15%) than in the treated group (2%), and 26 deaths occurred in the untreated group versus only one death in the group that received estrogen. The median time between surgery and initiation of estrogen replacement therapy was 15 months.

In 1990, Lee and associates reported on 44 patients with a history of stage I endometrial carcinoma who were selected to undergo estrogen replacement for a median of 64 months. No recurrent endometrial cancers or intercurrent deaths occurred in the treated group. In this study, 43% of patients waited 1 year before starting estrogen and 34% waited at least 2 years.

Because most endometrial cancer recurrences occur within the first 2 years after surgery, a selection bias exists in these two studies because many patients who would have had recurrent disease were not included in the study. Most recently, Chapman and colleagues compared 62 women with stage I or stage II endometrial cancer who received estrogen replacement after surgery with 61 who did not. The median interval to initiation of estrogen in this study was 8 months, and no increase in recurrences or deaths attributable to endometrial cancer occurred in the estrogen-treated group. These patients did have a greater incidence of early-stage disease but with less myometrial invasion than was seen in those who did not receive estrogen.

Although these studies do not prove the safety of estrogen replacement in this population, they do indicate that the safety of estrogen replacement therapy in women with a history of endometrial cancer should be determined in a
prospective randomized trial. Therefore, the GOG is undertaking a prospective randomized, double-blinded study of estrogen replacement therapy versus placebo for patients with surgical stages IA, IB, IIA, or IIB endometrial carcinoma. The study aims at accruing 2,206 patients who will receive treatment for 3 years and be followed for an additional 2 years.

To be eligible, patients must meet the following criteria:

1. Patients must have primary, histologically confirmed grades 1, 2, or 3 endometrial adenocarcinoma (endometrioid, villoglandular, mucinous, adenosquamous, papillary serous, clear cell, and not otherwise specified).

2. They must have had a total hysterectomy and bilateral salpingo-oophorectomy, their pelvic washings must have been examined, and they must be found to be surgical stage IA, IB, IIA (occult), or IIB (occult).

3. They must have at least one indication for estrogen replacement therapy, including hot flashes, vaginal atrophy, increased risk of cardiovascular disease based on age younger than 45 years at menopause or cardiovascular history; develop menopausal symptoms with bilateral salpingo-oophorectomy, or be at increased risk of osteoporosis based on personal or family history or physical characteristics.

4. They must have recovered from the effects of recent surgery and must be entered in the study within 12 weeks from time of surgery.

Patients considered ineligible include those with known or suspected carcinoma of the breast, patients with acute liver disease, those receiving any other form of hormonal therapy, and those with a history of thromboembolic disease.

This study should have the statistical ability to prove the safety of estrogen replacement in this population and lead to similar trials being conducted in women with breast cancer.

**Conclusion**

As we enter the next century, quality-of-life issues will play an increasing role in the management of patients with cancer. For the patient with early-stage endometrial cancer, prospective trials will help to define the need, or lack of need, for adjuvant therapy. Increasing knowledge of biomarkers of disease recurrence should help refine this area.

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