Endometrial cancer is the most common type of female genital cancer in the United States, with an estimated 32,000 new cases and 5,600 deaths per year. During the first half of the 20th century, the incidence of cervical cancer was greater than that of endometrial cancer, but this trend reversed around the middle of the century. Endometrial cancer is a disease predominantly of postmenopausal women with the peak incidence occurring in the ages of 58 to 60 years. The following guidelines refer primarily to endometrioid endometrial adenocarcinomas, which represent the most common type and are associated with unopposed estrogen exposure, obesity, and the precursor lesions known as endometrial hyperplasia. In contrast, the serous and clear cell subtypes represent an entirely different clinical and pathologic entity, with associated poor prognosis, hormonal unresponsiveness, and without identifiable precursor lesions.

**Screening**

A screening test should be safe, inexpensive, have a high predictive value, and be able to diagnose the disease in a premalignant or early stage. By these criteria, there is no satisfactory screening method for endometrial carcinoma. The prevalence for endometrial carcinoma is 5 per 1,000 among asymptomatic women over age 45 years. Endometrial sampling and ultrasonography are screening modalities for this malignancy but do not meet screening test criteria. Cervical cytology will be abnormal in less than half of the endometrial carcinomas, while endometrial sampling (cytology or histology) has a higher degree of diagnostic reliability for both endometrial hyperplasia and carcinoma. Diagnosis by transvaginal ultrasound is based on endometrial thickness, with a 5-mm "cut-off" for normal thickness yielding the best predictive values in postmenopausal women.

Neither sampling nor sonography is an inexpensive screening method, and therefore, with the low prevalence in asymptomatic women, it is difficult to justify routine screening. Women with certain high-risk factors may, however, benefit from screening: age over 40 with abnormal uterine bleeding, massive obesity, history of endometrial hyperplasia, or unopposed estrogen or tamoxifen (Nolvadex) use. Since many women on tamoxifen have benign thickening of the endometrial lining, the screening recommendations for these women are still under investigation.

If one can adequately perform sampling (some patients have cervical stenosis or large fibroids that prevent adequate sampling), the risk of missing a cancer is very low. There is little evidence to justify the routine use of dilation and curettage (D&C) over office sampling, but D&C is indicated when faced with cervical stenosis. Hysteroscopy (office or operative) is a controversial screening modality that may offer superior sensitivity but at added costs.

**Diagnosis**

Microscopic analysis of endometrial tissue is required to make the diagnosis of endometrial carcinoma. The classical method for obtaining the tissue specimen is the fractional curettage. This consists of a circumferential endocervical canal scrape followed by a systematic, comprehensive endometrial curettage. The two specimens are submitted to the laboratory separately. Fractionating the curettage serves to detect an occult endocervical carcinoma and to determine if the endometrial carcinoma involves the cervix.

Today, office endometrial biopsy (EMB) with endocervical curettage (ECC), rather than a formal curetttement in the operating room, is the accepted first step in evaluating postmenopausal bleeding or suspected endometrial pathology. The EMB consists of multiple strokes with a suction or other curet, sampling as much of the uterine cavity as feasible. If the suspicion for cancer is high and the biopsy inconclusive, hysteroscopy may be employed to assist in making a correct diagnosis. When the cervical canal is stenotic or patient tolerance does not permit adequate office evaluation of the endometrium and endocervix, a curettage under anesthesia is necessary. Patients with postmenopausal bleeding whose pelvic examination is unsatisfactory may also be evaluated with...
transvaginal sonography to rule out concomitant adnexal pathology.

Staging

Clinical Staging
In 1988, the International Federation of Gynecology and Obstetrics (FIGO) staging for endometrial carcinoma was changed from a clinical to a surgical staging system (Table 1). Histopathologic factors and/or surgical findings determine the need for adjunctive therapies. However, clinical staging is still important in terms of preoperative evaluation and planning for surgery, and still correlates well with prognosis. The most important elements are the physical examination and the fractional curettage. In more than 75% of the cases there is no clinical evidence of extrauterine involvement. For these patients the only additional studies required are chest x-ray and the usual preoperative chemistries. Serum CA-125 may also be of value in following advanced disease. More extensive preoperative evaluation, such as MRI, CT scan, or barium enema, may be indicated for patients whose disease has features that put them at high risk for metastases (poorly differentiated, papillary serous, clear cell, or sarcomatous histology). Evaluation for metastases is indicated in patients with abnormal liver function tests, an elevated serum CA-125 value, clinical evidence of metastases, and parametrial or vaginal tumor extension. For locally advanced disease, cystoscopy and/or barium enema should be obtained. Bone and brain scans are not indicated in the absence of symptoms.

Hysteroscopy and hysterography have been used to determine the extent of tumor and its proximity to the cervix, but both have the theoretical potential to push cancer cells through the fallopian tubes or into uterine lymph-vascular spaces. Their use should be limited to cases in which a diagnosis is not forthcoming by the usual procedures. Transvaginal sonography may be helpful for evaluating the degree of myometrial invasion preoperatively. Magnetic resonance imaging may be a more accurate but less cost-effective technique.

Surgical-Pathologic Staging
The inherent inaccuracy of clinical staging for endometrial carcinoma has been a serious impediment to the selection of optimal therapy, and over the years has resulted in both overtreatment and undertreatment. The magnitude of clinical understaging is on the order of 15% to 25%. Node metastases, myometrial invasion, intraperitoneal implants, adnexal metastases, lymph-vascular space involvement (LVSI), and peritoneal cytology cannot be readily evaluated clinically. Up to 20% of tumors have a worse histologic grade based on the hysterectomy specimen than the curettage. In the Gynecologic Oncology Group (GOG) surgical-pathologic staging studies of endometrial carcinoma, 18% of the patients had demonstrable evidence of extrauterine spread, including 10% with pelvic and 7% with aortic node metastases. The metastasis rate to the pelvic and aortic chains ranges from 15% to 35% for grade 2 and 3 lesions with outer one-third myometrial invasion. Nonendometrioid histologic subtype, LVSI, and positive peritoneal cytology confer a worse prognosis. The role in treatment planning of tumor size, DNA ploidy, or molecular biological markers has not been established. Estrogen- and progesterone-receptor status remain standard prognostic and treatment planning variables.

Preoperative Radiation vs Surgical Staging
There are two approaches regarding the initial treatment of endometrial carcinoma. The classic approach is to administer preoperative irradiation followed by surgery. More recently, surgery with staging to determine the need for additional adjunctive therapy has gained wide acceptance. Both protocols have merit.

The preoperative irradiation approach calls for irradiation, either intracavitary brachytherapy or external radiation, prior to surgical procedures for high-risk lesions. In clinically stage I patients, intracavitary brachytherapy is the treatment of choice. Surgery may be performed within a day or two after completion of the brachytherapy. By this technique, the radiation does not significantly affect the pathologic evaluation of the tumor. External pelvic irradiation would be preferable only if there was gross cervical or parametrial involvement. Further therapy (external irradiation or chemotherapy) can be added if indicated after preoperative irradiation and surgical staging. The disadvantage of preoperative irradiation is that some patients will have less disease than believed and therefore would receive irradiation that was not necessary.

The surgical staging approach mandates washings and removal of the uterus, tubes, and ovaries with sampling of pelvic and para-aortic nodes. The decision for adjunctive therapy is based upon these findings. The disadvantage to this technique is that irradiation following surgery has a higher incidence of complications.

When one examines the complication and survival data from these two management protocols, they
are approximately the same. Therefore, either of these techniques is acceptable. However, it must be emphasized that both techniques require analysis of findings to determine if additional therapy is necessary.

**The Staging Procedure**

The abdomen is opened with a vertical, lower abdominal incision, and peritoneal washings are taken of the pelvis and abdomen. Careful exploration is then carried out looking and feeling for evidence of omental, liver, peritoneal, cul de sac, and adnexal metastases. The aortic and pelvic areas are palpated for nodal metastases. An extraperitoneal, total hysterectomy with bilateral salpingo-oophorectomy is then performed. No instruments should be placed on the uterus itself, and ligation or clipping of the distal tubes prevents possible tumor spillage during manipulation. Removal of the adnexa, even if they appear normal, is part of the therapy, since they may contain microscopic metastases. It is not necessary to remove a margin of vaginal cuff, nor does there appear to be any benefit from excising parametrial tissue in the usual case. In cases in which an endocervical primary cannot be ruled out with certainty and there is definite endocervical disease, a modified (Rutledge type II) radical hysterectomy may be the most prudent action in experienced hands. The entire cervix, in any case, is removed. The uterus is opened off the field to determine the extent of the growth. If the depth of invasion is not grossly evident, it may be determined by frozen-section analysis. Though an integral part of the FIGO staging system for endometrial carcinoma, the indications for lymph node sampling must always be evaluated in light of the risk to the patient and the likelihood of their involvement based on operative findings. The node-bearing retroperitoneum should first be evaluated with the peritoneum opened to identify enlarged or suspicious lymph nodes. If these are positive on frozen section, node dissection may be unnecessary unless clinically positive nodes can be excised with minimal risk to the patient.

Indications for aortic node sampling include: (1) suspicious aortic or common iliac nodes; (2) grossly positive adnexa; (3) grossly positive pelvic nodes; (4) any grade carcinoma with outer-half myometrial invasion; and (5) clear cell, papillary serous, or carcinosarcoma histologic subtypes. In the aortic region, a selective node dissection consists of removing the node-bearing tissue over the vena cava from the inferior mesenteric artery (IMA) origin down to the bifurcation of the common iliac artery. Left-sided para-aortic nodes should also be excised, as these may also harbor metastatic disease. Patients with aortic node metastases should have a postoperative CT scan of the liver and thorax prior to initiating radiotherapy. If the aortic node metastases are large or multiple, a scalene fat pad dissection is warranted, since node metastasis at this level would be a contraindication to aortic field radiation therapy.

Indications for pelvic node dissection include: (1) suspicious pelvic nodes; (2) aortic node sampling not feasible; (3) cases in which the nodal findings would be the basis for deciding whether the patient would receive postoperative radiation therapy. Pelvic node sampling consists of removing the node-bearing tissue from the medial aspect of the external iliac artery and vein, as well as the obturator fat pad superior to the obturator nerve.

**Treatment—All Stages**

Postoperatively, the decision to use adjuvant radiotherapy depends on the surgical-pathologic risk factors of tumor grade, depth of invasion, and node status. Patients with grade 3 lesions are candidates for postoperative pelvic radiation (4,000 to 5,000 rads at 170 to 180 rads/daily fraction). Grade 1 or 2 lesions with minimal myometrial invasion and no LVSI require no further therapy. Grade 1 and 2 lesions with no or only superficial myometrial invasion but endocervical extension may benefit from postoperative intravaginal ovoid brachytherapy. All other scenarios that confer higher risk warrant consideration for postoperative pelvic radiation. The management of patients with intermediate-depth/grade risk factors remains discretionary until recently completed randomized studies more clearly define the role of adjuvant radiotherapy in early-stage endometrial carcinoma.

If metastases to the aortic nodes are documented, extended-field radiotherapy is recommended in the absence of more widespread metastases. Some protocols are exploring more routine use of extended-field therapy when external-beam treatment is indicated. Vaginal cuff radiotherapy is not routinely administered in conjunction with postoperative external-beam radiotherapy. It is important to keep in mind that radiotherapy offers local or regional disease control, and the vast majority of endometrial cancer treatment failures and deaths involve disease outside the radiation fields. Since local recurrences can be cured with radiotherapy, the role of adjuvant radiotherapy in prolonging
overall survival in endometrial cancer is not well defined. Modifications of optimal therapy are permissible or even necessary at times. For instance, there are situations in which the low transverse incision is a reasonable choice. Vaginal hysterectomy with laparoscopic staging is appropriate therapy when applicable. However, vaginal hysterectomy alone is a compromise that should be used only in special cases because the adnexa may not be removable and exploration of the pelvis and abdomen is not possible. The most frequent indications are morbid obesity and the existence of a medical problem that is a contraindication to an abdominal operation. Thus, the vaginal approach becomes a choice intermediate between optimal surgery and no surgery.

**Stage II**

Patients with clinically occult stage II disease (a clinically normal cervix with microscopic cervical invasion on the ECC) are managed the same as stage I patients, except that pelvic and aortic node dissection is performed more often. When the cervix is clinically involved by tumor, whole-pelvic radiotherapy, intracavitary brachytherapy, and adjunctive extrafascial hysterectomy with selective aortic/common iliac node dissection comprise the usual treatment. Optimal surgical treatment of clinically overt cervical involvement requires a Wertheim radical hysterectomy (type II, modified, or type III, classical) with bilateral pelvic lymphadenectomy and selective aortic node dissection.

**Stage III**

Patients who have clinical stage III endometrial carcinoma by virtue of vaginal or parametrial extension are given pelvic radiation therapy after a thorough metastatic survey. When the therapy is complete, exploratory laparotomy is recommended for those patients whose disease seems to be resectable. Along with the hysterectomy and adnexectomy, surgical-pathologic staging is carried out to determine the extent of residual disease. Extended-field radiation therapy or systemic therapy with cytotoxic drugs or hormones is warranted in the presence of extrapelvic metastases. If tumor tissue is obtained for hormone receptor analysis, the choice between chemotherapy and hormone therapy can be facilitated. Patients placed in the clinical stage III category on the basis of an adnexal mass should undergo surgery without preoperative radiotherapy to determine the nature of the mass, to perform surgical-pathologic staging, and to carry out tumor reductive surgery. If the uterus is resectable, hysterectomy and adnexectomy should also be done.

**Stage IV**

Patients with clinical evidence of extrapelvic metastasis are usually most suitable for systemic hormonal or chemotherapy. Local irradiation is often beneficial, particularly to brain or bone metastases. Occasionally, pelvic radiotherapy or hysterectomy will be indicated to provide local tumor control and prevent bleeding or complications from pyometra, especially in the patient who is to undergo chemotherapy. The efficacy of whole-abdomen radiotherapy for endometrial cancer involving the peritoneal cavity is uncertain. It is most applicable to those cases having no macroscopic abdominal disease and no distant metastases. The remaining cases are managed the same as ovarian cancer: tumor reductive surgery and chemotherapy, unless the metastases contain high levels of hormone receptor protein, in which case progesterin or antiestrogen (tamoxifen) therapy is indicated.

**Special Considerations**

**Diagnosis Post-Hysterectomy**

The post-hysterectomy diagnosis of endometrial carcinoma can present a difficult management problem, especially if the adnexa have not been removed. This situation, which usually arises following vaginal hysterectomy for pelvic relaxation, can be averted by opening the excised uterus routinely in the operating room, with pathologic assessment as indicated. Recommendations for postoperative treatment are based on the known risk of extrauterine and extrapelvic disease related to histologic grade and myometrial penetration. Patients with deep myometrial invasion, grade 3 lesions, or LVSI are candidates for reoperation to remove the adnexa and perform surgical staging, as opposed to the empiric use of external-beam radiation. Grade 1 or 2 lesions with minimal myometrial invasion and no LVSI require no further therapy. The management of intermediate-depth/grade remains discretionary until recently completed randomized studies more clearly define the role of adjuvant radiotherapy.

**The Medically Inoperable Patient**

Severe cardiopulmonary disease and morbid obesity are the primary reasons a patient with...
endometrial carcinoma is deemed medically inoperable. Clinical judgment varies a great deal in these cases. Nevertheless, in every gynecologist’s experience, there will be patients for whom the risks of anesthesia and surgery are judged to exceed the likely benefits of even vaginal hysterectomy.

For patients with grade 1 lesions and a temporary contraindication to general anesthesia, or for those who are altogether unsuited to radiotherapy or surgery, high-dose progestins are the treatment of choice. All other patients should be treated with radiotherapy. If the uterus is small, tandem and ovoid brachytherapy alone may be appropriate. Patients with a large uterus probably stand a better chance of being cured using the Heyman packing technique.

Whenever radiation or hormonal therapy is administered as definitive treatment, the uterine lesion can be monitored with sonography or CT scan and serum CA-125 determinations. Endometrial biopsy or curettage should be performed after 3 months. If the tumor persists, the contraindications to surgery must be reassessed.

The Young Woman

The diagnosis of endometrial cancer during the reproductive years should always be viewed with skepticism, since the malignancy is uncommon and confusion with hyperplasia is frequent. The histologic distinction between atypical hyperplasia, which can be treated successfully with progestins, and well-differentiated carcinoma, which should be treated surgically, is to some extent subjective. When preservation of fertility is a significant clinical factor, the diagnosis of well-differentiated carcinoma should be based on endometrial curettings and consultation with an experienced pathologist.

Equivocal lesions are managed the same as atypical hyperplasia. When a diagnosis of carcinoma is confirmed, however, hysterectomy with removal of the adnexa is the treatment of choice unless the patient is willing to gamble that use of high-dose progestins and/or antiestrogen therapy may reverse a well-differentiated neoplasm. Thorough counseling and documentation of this decision are mandatory.

Malignant Peritoneal Cytology

The interpretation of peritoneal cytology is often difficult because reactive mesothelial cells take on the appearance of malignancy. Thus, adjuvant treatment for positive peritoneal cytology should not be undertaken without a cytopathology review. Even then, the management is controversial because there are insufficient data regarding recurrence risk and treatment results.

Patients with stage I, grade 1 endometrial carcinoma and positive pelvic cytology with scant cells may be considered for postoperative whole-abdominal radiation, intraperitoneal phosphorus-32 (32P), progestins, or no further treatment. If the yield of malignant cells is high, long-term gestational therapy should be instituted. For patients with lesions of histologic grade 2 or 3 and copious malignant cells on peritoneal cytology, whole-abdomen radiotherapy or chemotherapy should be considered. These patients are also suitable candidates for intraperitoneal 32P and adjuvant progestins and/or antiestrogens.

Recurrence

Localized recurrences are preferably managed by irradiation, surgery, or a combination of the two. In particular, large lesions should be excised whenever feasible. An isolated pelvic recurrence of any grade is potentially curable, especially when it appears more than 1 or 2 years after initial therapy. In this setting, extended or radical surgery, including exenteration, may be justified if the patient has already been irradiated. The results of pelvic exenteration, in properly selected cases, are similar to those obtained in cervical cancer.

Patients with nonlocalized, progesterone receptor-rich recurrent tumors more than 50 fmol/mg of cytosol protein) are candidates for progestin therapy: medroxyprogesterone acetate, 50 to 100 mg three times a day, or megestrol acetate, 80 mg two to three times a day. The progestin therapy is continued as long as the disease is static or in remission. The maximum clinical response may not be apparent for 3 or more months after initiating therapy.

Tamoxifen (Nolvadex) is currently being studied in conjunction with progestins in the treatment of advanced or recurrent endometrial cancer. Doxorubicin, cisplatin (Platinol), and perhaps paclitaxel (Taxol) are the most active agents. They produce objective responses in about 30% of patients, although the complete response (CR) rate is only 5% to 10%. Chemotherapy is recommended for patients with advanced or recurrent disease not amenable to cure by surgery and/or radiation therapy, those who have failed progestin therapy, or those who, based upon the known receptor status or tumor characteristics, are not expected to have
a progestin-responsive tumor. Treatment is continued for 6 to 12 cycles, provided that the patient continues to respond in terms of measurable tumor regression or declining CA-125 serum values. Reassessment laparotomy to document the completeness of response or to resect persistent disease may be indicated in selected cases or in a study setting.

The information in the Society of Gynecologic Oncologists clinical practice guidelines should not be viewed as a body of rigid rules. The guidelines are general and are intended to be adapted to many different situations, taking into account the needs and resources particular to the locality, the institution, or the type of practice. Variations and innovations that improve the quality of patient care are to be encouraged rather than restricted. The purpose of these guidelines will be well served if they provide a firm basis on which local norms may be built.

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References:

Selected Readings


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