REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Endometrial Cancer

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Unlike most other cancers in the United States, endometrial cancer is rising in both incidence and associated mortality[1] (Fig. 1). Obesity is one of the most important risk factors for this disease, and as rates of obesity have risen, rates of endometrial cancer have also increased. In the past several years, surgical treatment of endometrial cancer has been refined and now incorporates sentinel lymph-node mapping, along with the standard, minimally invasive removal of the uterus, fallopian tubes, and ovaries. Data from the Cancer Genome Atlas (TCGA) project have advanced our understanding of the biologic heterogeneity of endometrial cancer.[4-6] This new knowledge has opened up more options for targeted therapy for recurrent disease. Challenges remain, however, including a growing racial disparity in death rates. As obesity rates continue to rise in the United States, new approaches to both prevention and treatment are needed to address the rising numbers of cases of endometrial cancer and associated deaths.

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Epidemiology and Preventive Options

Obesity and conditions associated with metabolic syndrome, including diabetes and polycystic ovary syndrome, are risk factors for the development of endometrial cancer.[7-9] In addition, conditions involving excess estrogen, including estrogen-secreting tumors and hormone replacement with unopposed estrogen (i.e., estrogen therapy without progesterone), predispose women to endometrial cancer.[10,11] Tamoxifen, which has antiestrogenic effects in the breast and proestrogenic effects in the uterus, approximately doubles the risk of both endometrioid and nonendometrioid types of endometrial cancer, with up to four times the risk when tamoxifen is used for more than 5 years.[12,13] Factors that provide protection against endometrial cancer include parity (with an inverse association between parity and the risk of endometrial cancer) and oral contraceptive use.[14] Oral contraceptive use reduces the risk of endometrial cancer by 30 to 40%; longer use is associated with increased protection, which can persist even decades after cessation.[15]

In the United States, 57% of all endometrial cancers are attributable to obesity.[16] As compared with all other cancers, endometrial cancer has the strongest association with obesity. Women with a normal body-mass index (BMI) have a 3% lifetime risk of endometrial cancer, but for every 5-unit increase in the BMI, the risk of cancer increases by more than 50% (Fig. 1).[2,17] Endometrial cancer is increasingly being diagnosed in young obese women. Although the average age at diagnosis is 63 years, data from the Surveillance, Epidemiology, and End Results program from 1990 to the present show a sustained rise in cases among women under the age of 50 years.

Obese patients of childbearing age in whom endometrial cancer is diagnosed often wish to retain their ability to have children. Many of these women are anovulatory, which causes overstimulation of the endometrium due to excess estrogen and lack of progestin. The result is the development of a precancer called complex atypical hyperplasia (CAH) and of early endometrial cancer. A conservative alternative to hysterectomy for these women is the use of oral progestin or a

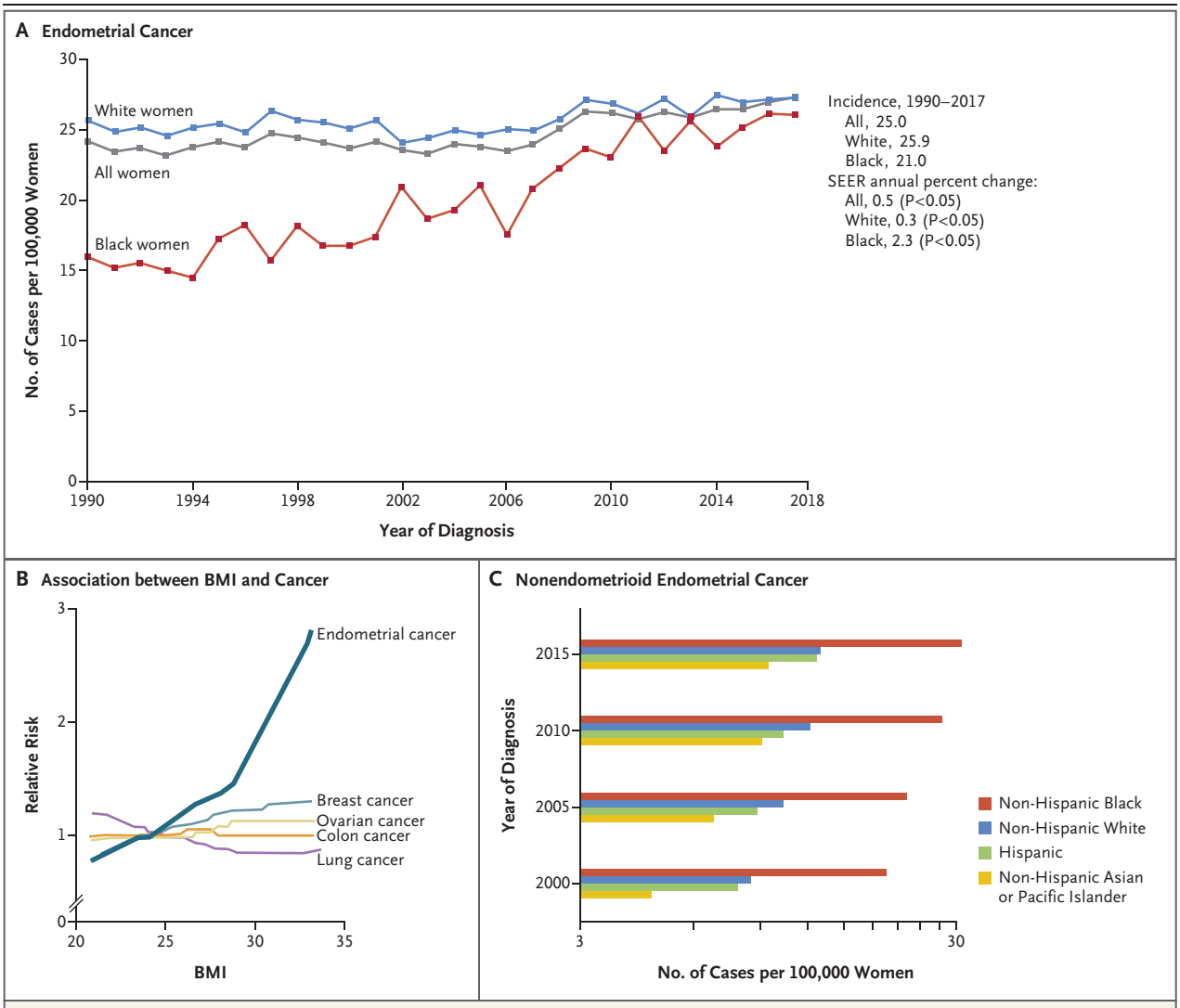


Figure 1. Association of Endometrial Cancer with Race and Body-Mass Index.

Panel A shows the age-adjusted incidence of endometrial cancer among Black women and White women on the basis of Surveillance, Epidemiology, and End Results (SEER) data from 1990 through 2017. Incidence (the number of cases per 100,000 women) was calculated with the use of SEER*Stat software, version 8.3.8, for incidence data. The incidence refers to cases of endometrioid and nonendometrioid endometrial cancer, age-adjusted to the U.S. standard population in 2000 (19 age groups); sarcomas are excluded. Panel B shows the association of obesity with cancer.[2] A higher body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) is associated with an increased risk of endometrial cancer. Among many cancers, endometrial cancer is the most strongly associated with obesity. Panel C shows the age-adjusted and hysterectomy-corrected incidence of nonendometrioid endometrial cancer according to race.[3] Although the incidence of this histologically more aggressive cancer is increasing in all races, the increase is most prominent among Black women.

progestin-containing intrauterine device (IUD).[18] In a meta-analysis that included women using mostly oral progestins, a complete response was seen in 65.8% of women with CAH and 48.2% of women with endometrial cancer; however, recurrence rates were 23.2% and 35.4%, respectively.[19] A recent prospective study of progestin-containing IUDs showed that 91% of women with CAH and 54% of women with endometrial cancer had a complete response at 12 months.[20] Women with higher-grade tumors or tumors invading the myometrium, as seen on magnetic resonance imaging, are not candidates for conservative management. The standard of care for such women is hysterectomy.

Women with the Lynch syndrome, diagnosed on the basis of a germline mutation in an *MLH1* or *MSH2* mismatch-repair gene, have a lifetime risk of endometrial cancer of 40 to 60%, with a median age at onset of 48 years, which is sub-

stantially younger than the median age at presentation in the general population (63 years).[21,22] Women with *MSH6* germline mutations have a similarly high risk of endometrial cancer, but with a median age at onset of 53 years. The Lynch syndrome accounts for approximately 3% of all endometrial cancers and 9% of endometrial cancers in women under the age of 50 years.[23,24]

Identification of the Lynch syndrome in patients with endometrial cancer has become increasingly important, since immune checkpoint blockade has been approved for the treatment of advanced disease with high microsatellite instability (MSI). Another factor favoring identification of patients with the Lynch syndrome is that they are at increased risk for colon cancer. Predictive genetic testing for family members, followed by screening and preventive options, should they test positive, allows this information to be "cascaded" beyond the original proband. Hysterectomy is a reasonable preventive option for women with the Lynch syndrome, with the decision and timing tailored to the individual patient.[25] As with colon cancer, many groups recommend screening of all patients with endometrial cancer, with the use of immunohistochemical tests for MLH1, MSH2, MSH6, and PMS2 or polymerase chain reaction–based MSI analysis or both types of testing (Fig. 2).[26,27]

The rates of endometrial cancer and associated mortality are rising among women of all backgrounds, but during the past decade, the rates have risen most sharply among Black women. Because Black women have higher rates of hysterectomy than White women, hysterectomy-adjusted rates of endometrial cancer highlight the disproportionate rise in incidence.[28-30] Of particular concern is the higher rate of increase among Black women of tumors with aggressive, nonendometrioid histologic features (Fig. 1). The cause of this increase in unclear. Although several studies have examined biologic differences in the endometrial cancers according to race, larger studies are needed to fully understand why Black women are at higher risk for the development of nonendometrioid tumors.[31,32] Even when adjusted for stage and histologic features, mortality rates remain highest among Black women. Access to appropriate care may also contribute to these differences.[33,34] Although older, thin Black women often present with uterine serous cancer, a population-based analysis showed that Black women under the age of 50 years, as compared with White women in the same age group, were more likely to present with higher-grade, nonendometrioid tumors, as well as later-stage tumors.[35] After adjustment for stage and histologic features, young Black women with early-stage tumors had a 24% higher likelihood of dying, as compared with their White counterparts. Urgent attention is needed to understand and address these disconcerting disparities.

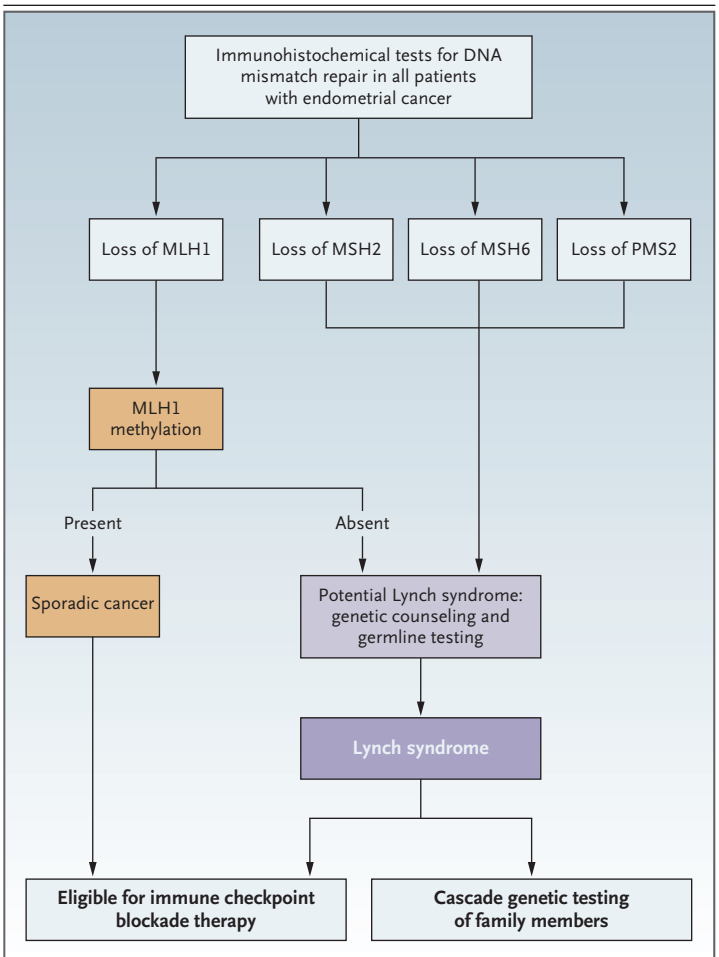


Figure 2. Use of DNA Mismatch-Repair Analysis in Endometrial Cancer to Guide Decisions about Treatment, Prevention, and Screening.

The results of DNA mismatch-repair analysis can have profound implications for subsequent cancer prevention and screening in the patient and the patient's family if the Lynch syndrome is detected. If the patient has advanced or recurrent endometrial cancer, mismatch-repair deficiency is targeted by treatment with immune checkpoint inhibitors approved by the Food and Drug Administration.

PATHOLOGICAL FEATURES

Endometrial carcinoma arises from the lining of the uterus and can broadly be divided into two

types: endometrioid, affecting approximately 80% of patients, and nonendometrioid, affecting approximately 20% of patients. In both premenopausal and postmenopausal patients, endometrioid tumors typically arise from endometrial CAH with epithelial atypia. Relative estrogen excess, such as that associated with obesity, the use of unopposed estrogen for hormone-replacement therapy, and estrogen-producing tumors (e.g., ovarian granulosa-cell tumors), predispose women to the development of endometrioid-type endometrial carcinoma. Nonendometrioid tumors, in contrast, have a hormone-independent pathogenesis and no known precursor lesions. They typically arise in older postmenopausal patients. Endometrioid carcinomas are graded with the International Federation of Gynecology and Obstetrics (FIGO) system on a scale of 1 to 3 according to the relative proportions of the glandular and solid-tumor components,[36] with grade 1 tumors having a solid-tumor component of less than 6%; grade 2, between 6 and 50%; and grade 3, more than 50%.[37] Grade 1 and grade 2 tumors are considered low grade and generally are associated with a good prognosis, whereas grade 3 tumors are associated with an intermediate-to-poor prognosis.

Nonendometrioid endometrial carcinomas include endometrial serous carcinoma, clear-cell carcinoma, and carcinosarcoma. Endometrial serous carcinoma is the most common of the nonendometrioid tumors and typically has a poor prognosis, with extrauterine disease in up to 37% of patients with no evidence of endometrial stromal or myometrial invasion.[38] Overall, the prognosis is worse with clear-cell carcinoma than with endometrial serous carcinoma,[3] although some studies have suggested that there are subgroups of women with clear-cell carcinoma who have longer survival.[39] Carcinosarcomas (or malignant mixed müllerian tumors) contain distinct malignant epithelial (carcinomatous) and malignant mesenchymal (sarcomatous) components. Pathologists regard carcinosarcoma as a high-grade metaplastic carcinoma. Its pattern of recurrence and metastasis mirrors that of carcinoma rather than that of sarcoma,[40] and clonality and mutation studies have shown that the carcinomatous and sarcomatous components derive from the same precursor.[41-44] Carcinosarcomas typically have worse outcomes than endometrioid, clear-cell, and serous carcinomas.[45,46]

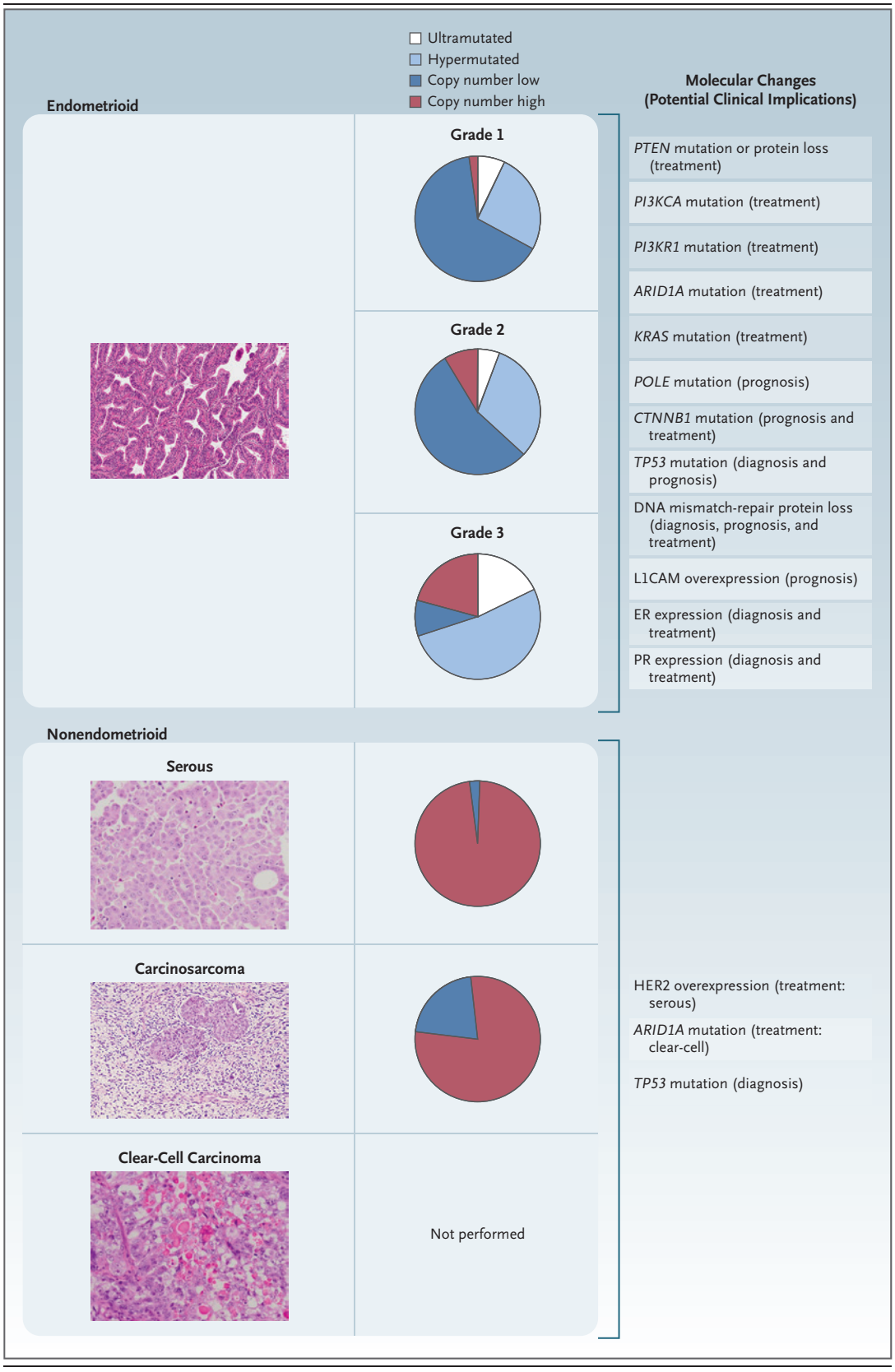
Figure 3 (facing page). Complex Interplay among the Type of Endometrial Cancer (Endometrioid or Nonendometrioid), Endometrioid Tumor Grade, and Molecular Changes in the Tumor.

Shown are molecular alterations in endometrioid and nonendometrioid cancers. Some molecular changes, especially alterations in the phosphatidylinositol 3-kinase (PI3K)–AKT pathway, are common across all endometrioid tumors and can even be detected in some nonendometrioid cases. Other molecular alterations, such as *CTNNB1* mutation and MLH1 loss due to *MLH1* gene methylation, are almost exclusively detected in endometrioid carcinomas. *TP53* mutations are especially enriched in nonendometrioid carcinomas and a subset of grade 3 endometrioid tumors. Although the Cancer Genome Atlas project and other genomic studies have led to a better molecular classification of these tumors, translation into clinical practice has lagged behind these efforts. Hematoxylin and eosin staining was used in the histologic images.

MOLECULAR CHARACTERIZATION

TCGA represents a National Cancer Institute–funded effort to comprehensively classify various types of cancer at a genomic level. The TCGA genomic data include next-generation sequencing of the whole exome, methylation profiles, microRNA profiles, gene expression analysis, and reverse-phase protein lysate arrays. Endometrioid carcinoma, endometrial serous carcinoma, and, to a lesser extent, carcinosarcoma have been characterized in TCGA (Fig. 3).[4] These data reaffirm the high incidence of phosphatidylinositol 3-kinase (PI3K)–AKT pathway mutations in the endometrioid type and show significant incidences of *CTNNB1*, *KRAS*, and *POLE* mutations. Cancers with *POLE* mutations, the smallest subset, are characterized by the highest number of mutations (ultramutated) and significantly longer survival.[4] The hypermutated group of cancers comprises primarily endometrioid carcinomas with high levels of MSI and a high mutation rate, but not as high as that of the ultramutated group.[4] The "copy-number–low" group accounts for the largest number of cases and is composed primarily of microsatellite-stable endometrioid carcinomas.[4]

The endometrial serous carcinomas are characterized by *TP53* mutations, an overall low mutation rate, and frequent copy-number alterations ("copy-number–high" group).[4] Much less is known about the molecular changes in endometrial clear-cell carcinoma. One study that in-



cluded whole-exome sequencing of 16 cases showed that clear-cell carcinoma is genomically heterogeneous, with a subset of tumors molecularly similar to endometrioid carcinoma, another subset genetically similar to serous carcinoma, a third subset with molecular findings common to both groups, and a fourth subset that is unique.[47]

In highlighting the genetic and clinical diversity of the endometrioid histotype, TCGA data have helped to refute the conventional wisdom that young, obese women have hormone-driven disease with a good prognosis. Although such patients certainly have a better prognosis than those with endometrial serous carcinoma, some patients have endometrioid cancers driven not by hormones but rather by activation of the WNT–β-catenin signaling pathway.[5,48] The higher-grade and advanced-stage endometrioid cancers are similarly heterogeneous; grade 3 endometrioid tumors with a more "immune driven" genotype have better outcomes.[5]

It is not possible to perform full, TCGA-scale genomic analyses for individual endometrial cancers in the clinical laboratory for patient care. A variety of more simplified schemes have been proposed. For example, DNA mismatch-repair deficiency, the presence of *CTNNB1* exon 3 mutation or *TP53* mutation, and p53 overexpression and null expression patterns on immunohistochemical analysis are each associated with poor survival in cases of endometrioid carcinoma. The survival effect of these gene mutations in endometrioid tumors may depend on the context. For example, *TP53* mutations are more common in grade 3 tumors, which are also associated with worse survival, than in other tumors. Therefore, it is likely that a patient with a *TP53*-mutated, grade 3 endometrioid tumor would have a shorter survival than a patient with a grade 1 tumor characterized by a *CTNNB1* mutation or a mismatch-repair deficiency. *POLE* mutation is associated with prolonged survival.[48-53] A challenge moving forward is to incorporate these prognostic indicators into routine patient care. The prospective Post-Operative Radiation Therapy in Endometrial Carcinoma 4a (PORTEC-4a) clinical trial in Europe is currently assessing simplified biomarker testing approaches in an adjuvant study that randomly assigns women with early-stage disease to vaginal brachytherapy or treatment based on a molecular risk profile.[54]

SURGICAL MANAGEMENT AND STAGING

Surgery is the mainstay of the initial management of endometrial cancer, and staging is based on pathological evaluation after surgery. Innovative surgical approaches have been especially important because many patients with endometrial cancer are obese and have clinically significant coexisting conditions. For most women with endometrial cancer, the current surgical approach includes laparoscopic or robotic removal of the uterus, cervix, fallopian tubes, and ovaries and a sentinel lymph-node evaluation. Two randomized surgical trials showed that a minimally invasive approach, as compared with the traditional open abdominal approach, was associated with significantly lower rates of postoperative complications and an improved short-term quality of life.[55,56] Long-term follow-up of patients in both studies, however, showed no significant difference in overall survival according to the initial surgical approach.[57,58]

For many years, standard lymphadenectomy of the pelvic and paraaortic nodes was performed as part of the initial surgical evaluation, with the development of lymphedema in more than 30% of patients and with short-term risks that included prolonged surgical times and increased blood loss.[59] In the past decade, a sentinel-lymph-node strategy has been developed and refined. Indocyanine green dye is injected into the cervix, then the bilateral sentinel lymph nodes are identified and removed (or a side-specific lymphadenectomy is performed if the sentinel node is not identified) and pathological ultrastaging of the sentinel nodes is conducted (Fig. 4).[59,60] To determine whether the sentinel-node strategy may miss positive pelvic nodes, a multicenter, prospective cohort study was conducted in which completion lymphadenectomy was performed after sentinel-node mapping. Among 385 women, 86% underwent successful mapping of at least one sentinel node, and the false negative rate was 2.8%.[61] In a similar study, which focused on patients with higher-risk disease, including grade 3 tumors and serous histologic features, 89% of the patients underwent successful mapping of at least one sentinel node, and the false negative rate was 4.3%.[62]

After initial surgery, endometrial cancer is

Primary Tumor (T)		
TNM system, T category	FIGO system	T criteria
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor confined to corpus uteri, including endocervical glandular involvement
T1a	IA	Tumor limited to the endometrium or invading less than half of the myometrium
T1b	IB	Tumor invading one half or more of the myometrium
T2	II	Tumor invading the stromal connective tissue of the cervix but not extending beyond the uterus Does not include endocervical glandular involvement
T3	III	Tumor involving serosa, adnexa, vagina, or parametrium
T3a	IIIA	Tumor involving the serosa, adnexa, or both (direct extension or metastasis)
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement
T4	IVA	Tumor invading the bladder mucosa, bowel mucosa, or both Bullous edema is not sufficient to classify a tumor as T4

Regional Lymph Nodes (N)		
TNM system, N category	FIGO system	N criteria
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node, ≤0.2 mm in diameter
N1mi	IIIC1	Regional lymph node micrometastasis (>0.2 mm to 2.0 mm in diameter) to pelvic lymph nodes
N1	IIIC1	Regional lymph node macrometastasis (>2.0 mm in diameter) to pelvic lymph nodes
N2mi	IIIC2	Regional lymph node micrometastasis (>0.2 mm to 2.0 mm in diameter) to paraaortic lymph nodes, with or without positive pelvic lymph nodes
N2	IIIC2	Regional lymph node macrometastasis (>2.0 mm in diameter) to paraaortic lymph nodes, with or without positive pelvic lymph nodes

Distant Metastasis (M)		
TNM system, M category	FIGO system	M criteria
cM0		No distant metastasis on clinical (c) assessment
cM1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes, lung, liver, or bone or intraperitoneal disease) Also includes metastasis to pelvic or paraaortic lymph nodes, vagina, uterine serosa, or adnexa
pM1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes, liver, or bone or intraperitoneal disease) microscopically confirmed on pathological (p) assessment Excludes metastasis to pelvic or paraaortic lymph nodes, vagina, uterine serosa, or adnexa

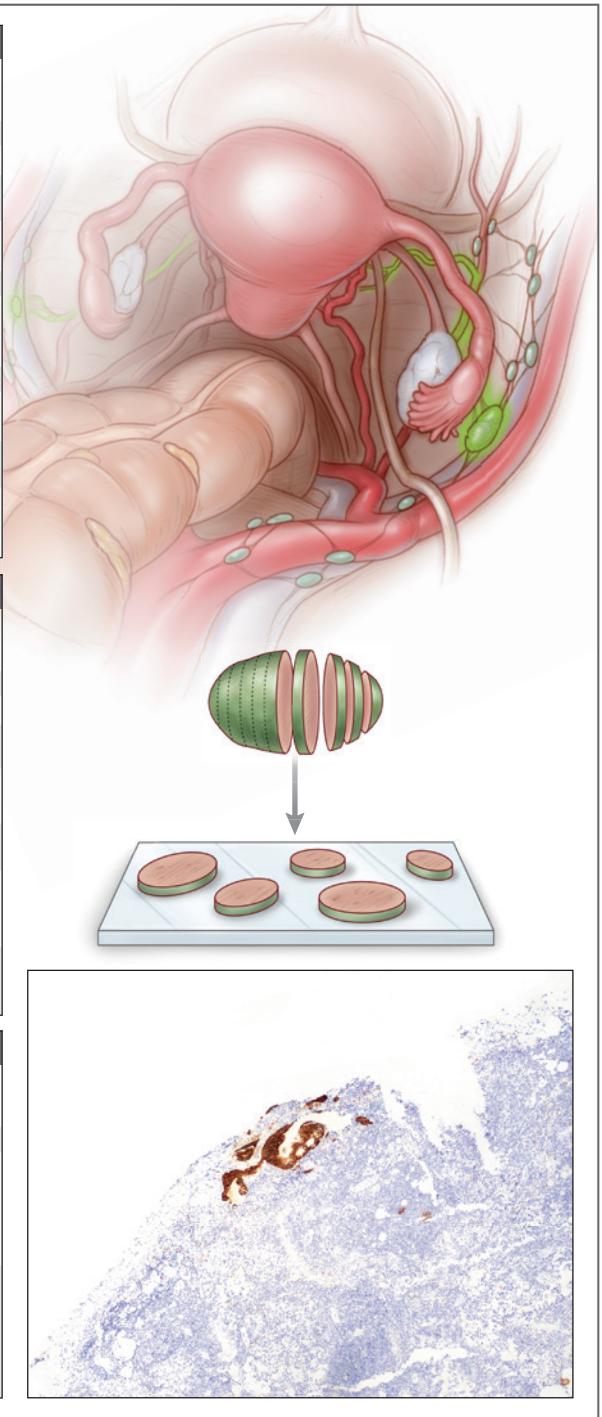


Figure 4. Staging Systems for Endometrial Cancer.

Staging is performed with the use of the International Federation of Gynecology and Obstetrics (FIGO) 2009 system and the tumor–node–metastasis (TNM) system. The sentinel-node strategy in endometrial cancer comprises injection of dye into the cervix; mapping of the nodes bilaterally (top image), with a side-specific lymphadenectomy if a sentinel node is not identified; serial sectioning of the sentinel node along its long axis (middle image), and microscopic evaluation with immunohistochemical staining for cytokeratin to help identify small clusters of cancer cells (bottom image).

staged with the use of the FIGO 2009 system (Fig. 4). The tumor–node–metastasis (TNM) system of the American Joint Committee on Cancer can also be used in conjunction with FIGO staging. In recognition of the widespread use of sentinel-node evaluation, classification of the size of the metastasis to the lymph node (isolated tumor cells, ≤0.2 mm; micrometastasis, >0.2 mm to 2.0 mm; and macrometastasis, >2.0 mm) is encouraged.

ADJUVANT THERAPY FOR EARLY-STAGE DISEASE

Close to 75% of patients with endometrial cancer have FIGO stage I disease, and 5-year overall survival rates exceed 90%.[63] Multiple prospective studies have tried to identify women with early-stage disease who are at highest risk for relapse and to develop effective adjuvant therapy. To date, however, no such strategy has been shown to improve overall survival.

Women with stage I endometrioid endometrial cancer, grade 1 or grade 2, and less than 50% myometrial invasion have a 97% survival rate and do not require adjuvant therapy.[26] The remaining patients with stage I disease can be categorized into low-intermediate-risk, high-intermediate-risk, and high-risk subgroups on the basis of age, tumor grade, histologic features, extent of myometrial invasion, and presence or absence of lymphovascular invasion, although there is no consensus on the specific criteria for the subgroups.[64,65] Because multiple studies have shown no survival benefit from adjuvant therapy in the high-intermediate-risk subgroup, an important advance has been a de-escalation of treatment and a shift away from whole-pelvis radiotherapy to vaginal brachytherapy or surveillance.[66]

Patients with early-stage but high-risk disease — those with grade 3 tumors and more than 50% invasion into the myometrium, regardless of lymphovascular invasion — have an increased risk of recurrence and have traditionally been offered pelvic radiation therapy. Two large prospective studies, the Gynecologic Oncology Group (GOG)–249 trial and PORTEC-3 (Postoperative Radiation Therapy in Endometrial Cancer 3), included early-stage, high-risk patients, but neither study showed a survival advantage for any strategy over pelvic irradiation in this subgroup.[67] Further limiting adjuvant therapy to vaginal-cuff brachytherapy is under study, especially for high-risk, early-stage patients who have undergone surgical staging.

An important subgroup of early-stage endometrial cancers is characterized by serous histologic features. Patients with these tumors have a high risk of distant spread, even when the disease is confined to the endometrium.[38,68] In addition, patients with stage I serous disease have an elevated risk of extrapelvic recurrence, and adjuvant therapy that includes systemic chemotherapy (carboplatin and paclitaxel) and vaginal brachytherapy is generally recommended, although no prospective, randomized trials have shown a survival benefit.[69,70] This regimen is also used for patients with rare, aggressive subtypes of early-stage tumors, such as carcinosarcoma.[71]

ADJUVANT THERAPY FOR NODE-POSITIVE DISEASE

Patients with node-positive disease in the pelvis or paraaortic region have a high risk of both local and distant recurrence, but the best adjuvant treatment for these patients remains controversial. The PORTEC-3 trial showed that patients with stage III disease who received chemoradiation therapy followed by four cycles of carboplatin and paclitaxel chemotherapy had better overall and 5-year recurrence-free survival rates than patients who underwent irradiation alone.[72,73] The GOG-258 trial showed no significant difference in relapse-free survival between patients receiving chemoradiation therapy followed by four cycles of carboplatin and paclitaxel and those receiving chemotherapy alone with six cycles of carboplatin and paclitaxel.[74] No consensus has emerged on the better treatment for node-positive disease, although a follow-up analysis of data from the PORTEC-3 study has suggested that molecular subtyping may inform future strategies. Patients enrolled in the PORTEC-3 study were classified according to TCGA subtype; patients with p53 abnormalities who received chemoradiation therapy plus chemotherapy had a significant relapse-free survival benefit, as compared with those treated with radiation therapy alone (59% vs. 36%, P=0.02), strongly suggesting that patients with p53 abnormalities benefit from the addition of chemotherapy. In addition, patients with *POLE* mutations had highly favorable outcomes in both groups (100% and 97%, respectively), suggesting that a de-escalation of adjuvant therapy could be considered.[75] Finally,

with sentinel-node evaluation, new questions about adjuvant therapy have emerged, including how to treat isolated tumor cells, micrometastases, and macrometastases.

THERAPEUTICS FOR ADVANCED AND RECURRENT DISEASE

Molecular characterization of endometrial tumors is becoming critical in directing treatment for advanced and recurrent disease. Assessment of estrogen receptor (ER) and progesterone receptor (PR) status, MSI analysis, and assessment of human epidermal growth factor receptor 2 (HER2) status for uterine serous cancers are essential in addition to histologic analysis; next-generation sequencing to identify somatic mutations may be useful information for potential enrollment in a clinical trial. For patients with uterine serous carcinomas that overexpress HER2, trastuzumab added to carboplatin and paclitaxel has been shown to prolong progression-free survival.[76] The effect of this three-drug regimen was greater in women with uterine serous carcinoma who were undergoing primary treatment than in those with recurrent disease. Currently, for all other recurrent endometrial cancers, combination chemotherapy with carboplatin and paclitaxel is considered the standard of care, with a median progression-free survival of 13 months and overall survival of 37 months.[77] Studies examining the addition of bevacizumab and other biologic agents to the chemotherapy backbone have shown no evidence of a benefit.[78,79] For women with advanced and recurrent uterine carcinosarcomas, first-line treatment is combination chemotherapy with carboplatin and paclitaxel.[71]

For women with advanced or recurrent endometrioid endometrial tumors that are grade 1 or 2 and positive for ER and PR, treatment with hormonal agents — specifically, progesterone — has been an option since it was first described by Kelley and Baker in 1961.[80] Unfortunately, no randomized trials have compared chemotherapy with hormonal therapy as first-line treatment. Clinically, chemotherapy can be used as first-line treatment for advanced and recurrent disease, and hormonal therapy is reserved for women with more limited performance status or for second- or third-line treatment. Although single-agent progestins — typically, medroxyprogesterone acetate or megestrol acetate — have been used, the results of clinical trials using combination therapies have suggested higher efficacy. Sequential administration of megestrol acetate and tamoxifen was associated with a 27% response rate, and for 53% of the women with a response, it lasted more than 20 months.[81] More recently, newer combinations of antihormonal and biologic agents have been shown to be effective and can be used as second- or third-line treatment for endometrioid endometrial cancers. The combination of everolimus and letrozole was shown to have an objective response rate of 32%.[82] In a follow-up, single-group study that added metformin to everolimus and letrozole, the objective response rate was 28%, with PR-positive patients having a 45% response rate.[83] On the basis of preliminary data from a randomized trial comparing everolimus and letrozole with the older combination of tamoxifen alternating with megestrol acetate, everolimus and letrozole had similar efficacy and a significantly lower risk of blood clots.[84] Single-agent aromatase inhibitors, fulvestrant, and tamoxifen can be considered, but monotherapy with these agents is generally associated with lower response rates than the combination treatments.

For second- and third-line treatment, evaluation of tumor DNA mismatch-repair function by determining MSI status helps guide the choice of targeted therapies. As part of a broad approval by the Food and Drug Administration (FDA) for all MSI tumors, pembrolizumab, an immune checkpoint inhibitor, is an effective option for second-line treatment in women with high-MSI endometrial cancer. In the KEYNOTE-158 study of single-agent pembrolizumab, 49 patients with high-MSI, recurrent endometrial cancer had an overall response rate of 57%, with 16% of the women having complete responses and 41% having partial responses.[85] Similar preliminary results of other, ongoing trials of immune checkpoint inhibitor drugs suggest that MSI status should be evaluated in all patients with recurrent endometrial cancer.

For patients with high-grade tumors that are not characterized by high MSI, a new combination of an oral targeted therapy — the multi–tyrosine kinase inhibitor lenvatinib — and pembrolizumab was recently granted accelerated FDA approval. In a single-group, phase 2 trial, the objective response rate was almost 40% at 24 months among unselected patients with recurrent endometrial cancer, and among the patients

with a response, 64.5% had a response that lasted for at least 12 months.[86] Responses occurred in patients who had tumors without high MSI and in patients with uterine serous cancers. Very few patients with high-MSI tumors were included in the study. However, the side effects of lenvatinib can be clinically significant, so close monitoring of patients is essential, with a dose reduction when needed.

For patients with a good performance status in whom second- or third-line treatment fails, standard-of-care options include bevacizumab, paclitaxel, and doxorubicin.[26] Somatic mutation testing with the use of next-generation sequencing can identify potentially actionable mutations for eligibility in clinical trials, including mutations in the PI3K pathway (which are frequently found in endometrioid tumors) or in homologous recombination repair pathways (which are frequently found in high-grade or serous tumors).

FUTURE DIRECTIONS

Although obesity and endometrial cancer are closely associated, endometrial cancer does not develop in all women who are obese, and not all women with endometrial cancer are obese, so identifying additional risk factors is critical. As the incidence of obesity and endometrial cancer continues to increase among younger women, new preventive and fertility-sparing options beyond the progestin-eluting IUD are needed. Even a simple strategy that focuses on educating women about the symptoms of endometrial cancer and its association with obesity can address the lack of public knowledge about this cancer.[87,88]

The increasing incidence of high-grade, clinically aggressive tumors among obese women suggests that the relationship between obesity and the development of endometrial cancer, which has long been attributed to a proestrogenic hormonal imbalance related to obesity, is more complex than previously thought. Expanding TCGA-type studies to delve into novel pathways that may be associated with obesity and endometrial cancer may lead to an improved biologic understanding. Similar analyses are critical for understanding why Black women are predisposed to higher-grade, more aggressive, nonendometrioid tumors. Finally, molecular diagnostics are now essential in the management of endometrial cancer. In the case of advanced and recurrent disease, recent FDA approvals have highlighted the importance of treatment with new agents that is based on histologic features and biomarkers. Refinement of adjuvant therapy for early-stage disease remains a challenge, but strategies that incorporate molecular markers of risk are currently being tested. To address the rising incidence of endometrial cancer and associated mortality, it is important to continue developing a biologic understanding of this disease, approaches to prevention, and targeted therapeutics.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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