Uterine Neoplasms, Version 1.2023

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ABSTRACT

Adenocarcinoma of the endometrium (also known as endometrial cancer, or more broadly as uterine cancer or carcinoma of the uterine corpus) is the most common malignancy of the female genital tract in the United States. It is estimated that 65,950 new uterine cancer cases will have occurred in 2022, with 12,550 deaths resulting from the disease. Endometrial carcinoma includes pure endometrioid cancer and carcinomas with high-risk endometrial histology (including uterine serous carcinoma, clear cell carcinoma, carcinosarcoma [also known as malignant mixed Mullerian tumor], and undifferentiated/de differentiated carcinoma). Stromal or mesenchymal sarcomas are uncommon subtypes accounting for approximately 3% of all uterine cancers. This selection from the NCCN Guidelines for Uterine Neoplasms focuses on the diagnosis, staging, and management of pure endometrioid carcinoma. The complete version of the NCCN Guidelines for Uterine Neoplasms is available online at NCCN.org.

NCCN GUIDELINES ADOPTION

The complete NCCN Guidelines for Uterine Neoplasms are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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Disclosures for the NCCN Uterine Neoplasms Panel

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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The complete NCCN Guidelines for Uterine Neoplasms Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Uterine Neoplasms Panel members can be found on page 209. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.
Overview

Endometrial carcinoma is a malignant epithelial tumor that forms in the inner lining, or endometrium, of the uterus. Risk factors for endometrial carcinomas include increased levels of estrogen (caused by obesity, diabetes, unopposed supplemental estrogen, and high-fat diet), early age at menarche, nulliparity, late age at menopause, Lynch syndrome, ages between 55 and 64 years, and tamoxifen use.\(^6\) Data show that almost 67% of patients with adenocarcinoma of the endometrium are diagnosed with disease confined to the uterus at diagnosis.\(^7\) Regional and distant disease comprise approximately 21% and 8% of cases, respectively.

Many physicians believe that adenocarcinoma of the endometrium is a more treatable malignancy because the early symptoms of metrorrhagia or postmenopausal vaginal bleeding often trigger patients to seek care when the disease is at an early and treatable stage. However, data show that the mortality rate for uterine cancer has increased more rapidly than the incidence rate.\(^8\) This increased mortality may be related to an increased rate of advanced-stage cancers, high-risk histologies (eg, serous carcinomas), and patients being diagnosed at an age \(\geq 65\) years. Analysis of SEER data suggests that survival is increased in patients who are younger, have early-stage disease, and have lower-grade disease.\(^9\) In addition to grade and depth of myometrial invasion, other risk factors associated with poor prognosis include age, lymph node involvement, tumor size, lymphovascular space invasion (LVSI), and lower uterine segment invasion.\(^10,11\) Depth of myometrial invasion is considered one of the critical criteria for evaluation of surgical-pathologic staging.\(^12,13\) To further improve outcomes for patients with this disease, physicians need to identify high-risk patients and to tailor treatment appropriately to provide the best long-term survival, including quality of life. The panel suggests that gynecologic oncologists be involved in the primary management of all patients with endometrial cancer.

Initial Evaluation

For patients with known or suspected uterine neoplasms, the initial preoperative evaluation/workup for known or suspected malignancy includes a history and physical examination, complete blood count (including platelets), consideration of liver function tests/renal function tests or chemistry profile, expert pathology review with additional endometrial biopsy as indicated, imaging, recommendation of genetic evaluation of tumor and for inherited cancer risk, and consideration of germline testing and/or multigene panel testing (see “Initial Evaluation” and “Principles of...
Imaging” in the NCCN Guidelines for Uterine Neoplasms, available at NCCN.org. Preoperative imaging and biopsy may help to identify uterine sarcomas, although biopsy sensitivity is less than that for endometrial cancer. An expert pathology review will determine whether a patient has a malignant epithelial tumor or a stromal/malignant mesenchymal tumor. Given the typical age group at risk for uterine neoplasms (i.e., ≥55 years) and the presence of comorbid illnesses, also see the NCCN Guidelines for Older Adult Oncology (available at NCCN.org).

Molecular Analysis and Genetic Factors

Most endometrial cancer (95%) is caused by sporadic (somatic) mutations. However, genetic mutations cause endometrial cancer in about 5% of patients, which occurs 10 to 20 years before sporadic cancer. Since there is increasing overlap in histopathologic features of these tumors, molecular analysis (e.g., identification of characteristic translocations and/or mutations) and subtype classification are useful in selecting appropriate therapies. The Cancer Genome Atlas (TCGA) study performed an integrated genomic, transcriptomic, and proteomic analysis of 373 endometrial carcinomas including low-grade endometrioid, high-grade endometrioid, and serous carcinomas for their molecular classification. The study identified 4 major clinically significant molecular subtypes with differing clinical prognosis: POLE (DNA polymerase epsilon) mutated, microsatellite instability-high (MSI-H), copy number low, and copy number high (associated with abnormal p53 expression/TP53 mutation). The POLE-mutated tumors harbor POLE exonuclease domain mutations. The copy number high group is the most aggressive subtype and requires multimodality treatment, which almost always includes chemotherapy. The MSI-H tumors have an intermediate prognosis but could be associated with other genetic cancer predisposition, and sensitivity to chemotherapy and immune checkpoint inhibition has been under investigation. Further studies have attempted to study the association of TCGA subgroups with histologic features such as tumor grade and histologic type.

The NCCN Guidelines for Uterine Neoplasms include a diagnostic algorithm for integrated genomic-pathologic classification of endometrial carcinomas based on the TCGA study and add that the decision to use molecular...
testing/classification depends on resource availability and each center’s multidisciplinary team. The panel encourages comprehensive genomic profiling via a validated and/or FDA-approved assay in the initial evaluation of uterine neoplasms to help facilitate cancer diagnoses. The panel also encourages ancillary studies of POLE mutation status, mismatch repair (MMR)/MSI, and aberrant p53 expression to complement the morphologic assessment of histologic tumor type. In addition, the panel includes consideration for NTRK gene fusion testing for metastatic or recurrent endometrial carcinoma, and for tumor mutational burden (TMB) testing through a validated and/or FDA-approved assay.

Screening of the tumor for defective DNA MMR using immunohistochemistry (IHC) and/or MSI is used to identify which patients should undergo mutation testing for Lynch syndrome (see “Lynch Syndrome” in the NCCN Guidelines for Colorectal Cancer Screening; available at NCCN.org).19–25 At a minimum, universal testing of endometrial tumors for defects in DNA MMR is recommended (e.g., MLH1, MSH2, MSH6, PMS2). MSI testing is recommended if MMR results are equivocal. Testing may be performed on the initial biopsy or dilation and curettage (D&C) material or the final hysterectomy specimen. MLH1 loss should be further evaluated for MLH1 promoter methylation to assess for a somatic epigenetic process rather than a germline mutation.22 Genetic counseling, molecular analysis, and testing are recommended for patients with all other MMR deficiencies. Patients with a significant family history of endometrial and/or colorectal cancer (even for those without MMR defects, who are MSI-stable, or those without screening) should be referred for genetic counseling and evaluation (See “Lynch Syndrome [Hereditary Non-Polyposis Colorectal Cancer]” in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, available at NCCN.org). Screening for genetic mutations should be considered, especially for patients <50 years of age.6,15,19,26 If these patients have Lynch syndrome, they are at a higher lifetime risk (≥60%) for endometrial cancer; thus, close monitoring and discussion of risk-reducing strategies is recommended.4,19,27 In addition, their relatives may have Lynch syndrome. For patients and family members with Lynch syndrome but without endometrial cancer, a yearly endometrial biopsy is recommended to assess for cancer.28,29 This strategy also enables select patients to defer surgery (and surgical menopause) and to preserve fertility. Prophylactic hysterectomy/bilateral salpingo-oophorectomy (BSO) is recommended after childbearing is complete.30,31 In addition, interventions to decrease the risk from colorectal cancer are recommended (e.g., annual colonoscopy).
Endometrial Carcinoma

**Diagnosis and Workup**
Currently, no validated screening test for endometrial carcinoma exists.大约90%的患者有子宫内膜癌史。约90%的患者在子宫内膜癌的Menopause期，通常在症状期。诊断一般可以通过官腔镜检查和活检，约10%的患者可诊断为良性。

**Imaging and Laboratory**
For detailed imaging recommendations by stage and planned treatment approach, see “Principles of Imaging” in the NCCN Guidelines for Uterine Neoplasms (available at NCCN.org). Consideration of preoperative EBRT in select patients. Consider preoperative EBRT in select patients.

### ENDOMETRIAL CARCINOMA

<table>
<thead>
<tr>
<th><strong>Clinical Presentation</strong></th>
<th><strong>Therapy for Relapse</strong></th>
<th><strong>Additional Therapy</strong></th>
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<tr>
<td><strong>Locoregional recurrence</strong></td>
<td>EBRT&lt;sup&gt;g&lt;/sup&gt; + brachytherapy&lt;sup&gt;g&lt;/sup&gt; ± systemic therapy&lt;sup&gt;h&lt;/sup&gt; or Surgical exploration + resection ± intraoperative RT (IORT) (category 3 for IORT)</td>
<td>EBRT&lt;sup&gt;k,l&lt;/sup&gt; + brachytherapy&lt;sup&gt;g&lt;/sup&gt; ± systemic therapy&lt;sup&gt;h&lt;/sup&gt;</td>
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<tr>
<td><strong>Prior RT to site of recurrence</strong></td>
<td>EBRT&lt;sup&gt;k,l&lt;/sup&gt; + brachytherapy&lt;sup&gt;g&lt;/sup&gt; ± systemic therapy&lt;sup&gt;h&lt;/sup&gt; or Surgical exploration + resection ± intraoperative RT (IORT) (category 3 for IORT)</td>
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<tr>
<td><strong>Previous brachytherapy only</strong></td>
<td>Pelvic lymph node</td>
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<td><strong>Previous EBRT</strong></td>
<td>Para-aortic or common iliac lymph node</td>
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<tr>
<td><strong>No prior RT to site of recurrence</strong></td>
<td>Locoregional disease&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>EBRT&lt;sup&gt;k,l&lt;/sup&gt; ± systemic therapy&lt;sup&gt;h&lt;/sup&gt;</td>
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<sup>9</sup> See Principles of Radiation Therapy for Uterine Neoplasms (JN-A*).
<sup>10</sup> See Systemic Therapy for Endometrial Carcinoma (ENDO-D).
<sup>11</sup> See Principles of Imaging (ENDO-G*).
<sup>12</sup> May include patients with isolated common iliac or para-aortic lymph node recurrence.
<sup>13</sup> Consider preoperative EBRT in select patients.
<sup>14</sup> Consider brachytherapy for locoregional disease with a vaginal component.
<sup>15</sup> Post-resection consolidation EBRT can be considered in patients who were not previously irradiated or who are deemed to have additional tolerance for radiation.

*Available online, in these guidelines, at NCCN.org.*

### Disease Staging
The FIGO system is most commonly used for staging uterine cancer. The original 1970 criteria for staging endometrial cancer only used information gained from the presurgical evaluation (including physical examination and diagnostic fractional D&C). The 1970 staging system is rarely used today (eg, reserved for when the patient is not a surgical candidate).

Several studies demonstrated that clinical staging was inaccurate and did not reflect actual disease extent in 15% to 20% of patients. This reported understaging and, more importantly, the ability to identify multiple prognostic factors with a full pathologic review made possible with...
surgical staging motivated a change in the staging classification. Therefore, in 1988, FIGO modified its staging system to emphasize thorough surgical/pathologic assessment of data, such as histologic grade, myometrial invasion, and the extent and location of extraperitoneal spread (including retroperitoneal lymph node metastases). FIGO updated and refined the surgical/pathologic staging criteria for uterine neoplasms in 2009. Separate staging systems for malignant epithelial tumors and uterine sarcomas are now available (see “Staging” section of the algorithm at NCCN.org). In 2017, the AJCC Cancer Staging Manual was further updated (which took effect in January 2018). The 2009 FIGO staging system streamlined stages I and II of endometrial carcinoma. These revisions were made because the survival rates for some of the previous substages were similar. Currently stage IA describes tumors with <50% myometrial invasion, and stage IB describes those with ≥50% myometrial invasion. Stage II describes patients with tumors that invade the cervical stroma. Patients with uterine-confined disease and endocervical glandular involvement (mucosal involvement) without cervical stromal invasion are no longer considered stage II. Stage IIIC is subdivided into IIIC1 (pelvic nodal involvement alone) and IIIC2 (para-aortic involvement ± pelvic node involvement), reflecting the inferior survival in those patients with positive para-aortic nodes. To maintain consistency, the NCCN panel has reinterpreted historical studies using the 1988 FIGO staging system to reconcile those studies with the 2009 staging system.

In the 2009 FIGO staging, the presence of positive peritoneal cytology no longer increases the disease stage, as its importance as an independent risk factor has been called into question. FIGO and AJCC continue to recommend that peritoneal washings be obtained and results be recorded (see “Principles of Evaluation and Surgical Staging,” next section).

**Principles of Evaluation and Surgical Staging for Endometrial Carcinoma**

Staging should be done by a team with expertise in imaging, pathologic evaluation, and surgery. The amount of surgical staging that is necessary to determine disease status depends on preoperative and intraoperative assessment by experienced surgeons. Pathologic nodal assessment for apparent uterine-confined endometrial cancer informs both stage and adjuvant therapy. However, if final pathology shows a noninvasive endometrioid histology, nodal assessment can be eliminated. The NCCN sentinel lymph node (SLN) algorithm is recommended if sentinel node mapping is used.
Pathology

An expert pathologic review determines the specific histotype of the tumor (endometrioid, serous, clear cell, carcinosarcoma, or undifferentiated/dedifferentiated). Morphologic evaluation of endometrial carcinoma to determine histologic type—especially in high-grade cancers—is challenging, and issues exist regarding diagnostic reproducibility. The pathologic assessment of the uterus and the nodes is described in the algorithm. The assessment of the uterus includes the hysterectomy type, specimen integrity, tumor site and size, histologic type and grade if applicable, myometrial invasion (depth of invasion in mm/myometrial thickness in mm), cervical stromal involvement, and LVSI. Pathologists may be asked to quantify LVSI. The current definition of substantial LVSI is ≥4 LVSI-involved vessels in ≥1 hematoxylin and eosin (H&E) slide (for clinically relevant LVSI in endometrial cancer).50

The pathologic assessment should also include assessment of involvement by other tissues such as the fallopian tubes, ovaries, vagina, parametrium, peritoneum, and omentum. The assessment of peritoneal/ascitic fluid cytology should also be obtained. If nodal resection was performed, the level of nodal involvement (ie, pelvic, common iliac, para-aortic) should be determined. SLNs should undergo ultrastaging for the detection of low-volume metastases. Ultrastaging commonly entails thin serial sectioning of the gross SLN and review of multiple H&E-stained sections with or without cytokeratin IHC for all blocks of SLN. There is no standard protocol for lymph node ultrastaging. See “Principles of Pathology” in the NCCN Guidelines for Endometrial Carcinoma (available at NCCN.org). The Protocol for the Examination of Specimens From Patients With Carcinoma and Carcinosarcoma of the Endometrium from the College of American Pathologists is a useful guide (available at https://cap.objects.frb.io/protocols/cp-femalereproductive-endometrium-18protocol-4100.pdf). This protocol was revised to reflect the updated pTNM requirements from the AJCC Cancer Staging Manual (8th edition) and 2015 FIGO Cancer Report.48,51

Estrogen receptor (ER) testing is recommended in the setting of stage III, IV, or recurrent endometrioid carcinoma. Evaluation of HER2 overexpression should also be considered. Rottmann et al52 recently showed that 16% of 80 gynecologic carcinosarcomas (including uterine carcinosarcoma) showed HER2 overexpression and amplification when using the 2013 ASCO/College of American Pathologists scoring system. Similar results were reported by several studies,53,54 including by Yoshida et al55 and
The panel recommends HER2 IHC testing (with reflex to HER2 fluorescence in situ hybridization for equivocal IHC) for possible treatment of advanced-stage or recurrent serous endometrial carcinoma or carcinosarcoma. HER2 IHC testing should also be considered in TP53-mutated/p53 abnormal endometrial carcinoma regardless of histotype.

As the grade of the tumor increases, the accuracy of intraoperative evaluation of myometrial invasion decreases (ie, assessment by gross examination of fresh tissue). In one study, the depth of invasion was accurately determined by gross examinations in 87.3% of grade 1 lesions, 64.9% of grade 2 lesions, and 30.8% of grade 3 lesions. Studies show that in 15% to 20% of cases, the preoperative grade (as assessed by endometrial biopsy or curettage) is upgraded on final pathologic evaluation of the hysterectomy specimen.

Lymphadenectomy

Previously, a full standard lymphadenectomy (ie, dissection and assessment of both pelvic and para-aortic nodes) was recommended for all patients; however, to decrease side effects, a more selective and tailored nodal evaluation approach that includes the SLN algorithm is recommended by the NCCN panel. No randomized trial data support routine full lymphadenectomy, although some retrospective studies have suggested that it is beneficial. Two randomized clinical trials from Europe reported that routine lymph node dissection did not improve the outcome of patients with endometrial cancer, but lymphadenectomy did identify those with nodal disease. However, these findings remain a point of contention. To avoid overinterpretation of these results, it is important to address the limitations of these randomized studies, including selection of patients, extent of lymph node dissection, and standardization of postoperative therapy. One of the trials did not standardize adjuvant treatment after staging surgery with lymphadenectomy and this has been identified as a weakness of the trial and may have contributed to the lack of difference in recurrence and survival in the 2 groups. The other concerns include the lack of central pathology review, subspecialty of surgeons, and adequacy of statistical power.

Decisions about whether to perform lymphadenectomy, and, if done, to what extent (eg, pelvic nodes only or both pelvic and para-aortic nodes), can be made based on preoperative and intraoperative findings. Criteria have been suggested as indicative of low risk for nodal metastases: (1) <50% myometrial invasion; (2) tumor <2 cm; and
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SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

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<tr>
<th>Chemoradiation Therapy</th>
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<tr>
<td><strong>Preferred Regimens</strong></td>
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<tr>
<td>- Cisplatin plus RT followed by carboplatin/paclitaxel[^1,2]</td>
<td>- <strong>Preferred Regimens</strong></td>
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<tr>
<td></td>
<td>- Carboplatin/paclitaxel[^3]</td>
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<td></td>
<td>- Carboplatin/paclitaxel/trastuzumab</td>
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<tr>
<td></td>
<td>(for stage II/III HER2-positive uterine serous carcinoma[^A,4])</td>
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<tr>
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<td>- Carboplatin/paclitaxel/trastuzumab</td>
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<tr>
<td></td>
<td>(for stage II/III HER2-positive carcinoma) (category 2B[^A,4])</td>
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[^1]: Available online, in these guidelines, at NCCN.org.

(3) well or moderately differentiated histology.[^60,70] However, this may be difficult to accurately determine before final pathology results are available. If expert gynecologic pathology is available, a frozen section to assess myoinvasion can be obtained and lymphadenectomy avoided if no myoinvasion or cervical invasion is identified.[^71]

Nodal evaluation will identify those patients with nodal metastases. Identification of metastatic disease guides appropriate adjuvant treatment that has been shown to improve survival and decrease locoregional recurrence.

The question of whether to add para-aortic lymphadenectomy to pelvic node dissection has been debated. Prior studies have shown conflicting information regarding the risk of para-aortic nodal metastases in patients without disease in the pelvic nodes.[^43,69,72-73] Para-aortic lymphadenectomy up to the renal vessels may be considered for selective patients, including those with pelvic lymphadenectomy or high-risk histologic features. Many surgeons do not do a full lymphadenectomy in patients with grade 1 early-stage endometrial cancer.[^60]

In summary, lymph node dissection identifies patients requiring adjuvant treatment with radiation therapy (RT) and/or systemic therapy.[^74] A subset of patients may not benefit from lymphadenectomy; however, it may be difficult to preoperatively identify these patients. The NCCN panel recommends that nodal evaluation be performed in patients with endometrial carcinoma, including para-aortic lymphadenectomy in high-risk patients (see “Principles of Evaluation and Surgical Staging,” page 186).[^5] SLN mapping is the preferred alternative to full lymphadenectomy in the setting of apparent uterine-confined disease. The SLN surgical algorithm is described subsequently. Lymphadenectomy is not recommended for patients with uterine sarcoma because metastasis to the nodes is unusual.

**SLN Mapping**

The section on surgical staging (see “Principles of Evaluation and Surgical Staging,” page 186) includes recommendations about SLN mapping. SLN mapping may be considered for patients without suspicion of metastatic disease by preoperative imaging and no obvious extraterine disease at exploration.[^75-79] In SLN mapping, dye is injected into the cervix, which travels to the sentinel nodes. This has emerged as a useful and validated technique for identification of lymph nodes that are at high risk for metastases (ie, SLN in patients with early-stage endometrial cancer).[^80] Superficial (1–3 mm) and optional deep (1–2 cm) cervical injection leads to dye delivery to the main layers of lymphatic channel origins in the cervix and corpus, namely the superficial subserosal, intermediate stromal, and deep
submucosal lymphatic sites of origin.81 Injection into the uterine cervix provides excellent dye penetration to the uterine vessels and main uterine lymphatic trunks that condense in the parametria and appear in the broad ligament leading to pelvic and occasionally para-aortic sentinel nodes. The uterine body lymphatic trunks commonly cross over the obliterated umbilical artery with the most common location of pelvic SLN being medial to the external iliac, ventral to the hypogastric, or in the superior part of the obturator region. A less common location is usually seen when the lymphatic trunks do not cross over the obliterated umbilical and move cephalad following the mesoureter; in these cases, the SLN is usually seen in the common iliac presacral region (see Figures 1–3 in “Principles of Evaluation and Surgical Staging,” page 187). The radiolabeled colloid most commonly injected into the cervix is technetium-99m (99mTc); colored dyes are available in a variety of forms (isosulfan blue, 1%; methylene blue, 1%; and patent blue, 2.5% sodium). Indocyanine green recently emerged as a useful imaging dye that requires a near-infrared camera for localization, provides a very high SLN detection rate, and is commonly used in many practices at the present time.82–86

A surgical SLN algorithm is proposed to decrease the false-negative rate in patients with apparent uterine-confined disease (see Figure 4 in “Principles of Evaluation and Surgical Staging,” page 188).75,87 SLN mapping may be most appropriate for those at low to intermediate risk for metastases and/or for those who may not tolerate a standard lymphadenectomy.79,81,88–93 SLN identification should always be done before hysterectomy, except in cases where a bulky uterus must be removed to allow access to iliac vessels and lymph nodes. For example, suspicious or grossly enlarged nodes should be removed regardless of SLN mapping results. In SLN mapping, the surgeon’s expertise and attention to technical detail are critical. Patients may be able to avoid the morbidity of a standard lymphadenectomy with SLN mapping.92,94 Because SLNs identify the primary lymphatic pathway, this increases the yield of finding metastatic disease during the mapping process. For cases of failed SLN mapping, reinjection of the cervix may be considered. However, if SLN mapping fails, a reflex side-specific nodal dissection should be performed and any suspicious or grossly enlarged nodes should be removed regardless of mapping.75,93

A literature review and consensus recommendations for SLN mapping in endometrial cancer were released by the Society of Gynecologic Oncology (SGO).79 Close adherence to the NCCN SLN surgical algorithm was found to result in accurate prediction of pelvic lymph node
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SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Recommended Regimens</th>
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<tr>
<td>- Megestrol acetate/tamoxifen (alternating)</td>
<td>- Medroxyprogesterone acetate/tamoxifen (alternating)</td>
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<td>- Everolimus/letrozole</td>
<td>- Progestational agents</td>
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<td>- Medroxyprogesterone acetate</td>
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<td>- Megestrol acetate</td>
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<td>- Aromatase inhibitors</td>
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<td>- Tamoxifen</td>
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<td>- Fulvestrant</td>
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Hormonal Therapy for Uterine limited Disease Not Suitable for Primary Surgery (ENDO-1)

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<tr>
<td>- Progestational agents</td>
<td>- Levonorgestral intrauterine device (IUD)</td>
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<tr>
<td>- Medroxyprogesterone acetate</td>
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<td>- Megestrol acetate</td>
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metastasis with a less than 5% false-negative rate.\textsuperscript{75} Additionally, results were published from the FIRES trial, which compared SLN mapping to lymphadenectomy for endometrial cancer in the largest multicenter prospective study to date (n=385).\textsuperscript{81} Mapping of at least one SLN was successful in 86% of patients; sensitivity was 97.2% (95% CI, 85.0–100), and negative predictive value was 99.6% (95% CI, 97.9–100).

A systematic review of 17 studies with n>30 patients revealed detection rates of 60% to 100%; detection rates for studies with larger cohorts (n>100) were ≥80%. Retrospective application of a surgical algorithm generated 95% sensitivity, 99% predictive value, and a 5% false-negative rate.\textsuperscript{95} Another systematic review and meta-analysis of 55 studies with n>10 patients (n=4915) generated an overall detection rate of 81% with a 50% bilateral pelvic node detection rate and 17% para-aortic detection rate.\textsuperscript{71} In a retrospective analysis of patients with early-stage endometrial cancer (n=780) who underwent SLN mapping with lymphadenectomy versus lymphadenectomy alone, SLN mapping led to the detection of more metastasis (30.3% vs 14.7%, \(P<.001\)) and was associated with greater use of adjuvant therapy.\textsuperscript{96} Long-term follow-up was reported from a prospective multicenter study in 125 patients with early-stage endometrial carcinoma who underwent SLN biopsy. Patients with a positive SLN underwent external beam RT (EBRT) and chemotherapy at a higher rate than those with a negative SLN. In patients with a detected SLN, recurrence-free survival (RFS) at 50 months was 84.7%, and no difference was detected between patients with and without a positive SLN (\(P=.5\)).\textsuperscript{97}

SLN mapping should be done in institutions with expertise in this procedure. If patients have apparent distant metastatic disease (based on imaging and/or surgical exploration), removal of nodes for staging purposes is not necessary because it will not change management.\textsuperscript{40,98} Historically, SLN mapping was controversial in patients with high-risk histology (eg, serous carcinoma, clear cell carcinoma, carcinosarcoma).\textsuperscript{60,99} However, SLN mapping in patients with high-risk histologies (ie, grade 3, serous, clear cell, carcinosarcoma) has been reported with promising results as a potential alternative to complete lymphadenectomy.\textsuperscript{93,100,101} A recent multi-institutional retrospective study concluded that SLN mapping versus SLN mapping with lymphadenectomy in high-risk endometrial cancer did not impact survival outcomes.\textsuperscript{102} A recent prospective, multicenter cohort study (SENTOR-trial) examined the diagnostic accuracy of SLN mapping versus lymphadenectomy for intermediate- and high-grade endometrial cancer in 156 patients. Of 27 patients
with nodal metastasis, SLN mapping correctly identified 26 of them (96% sensitivity; 95% CI, 81%–100%), thus concluding the acceptable accuracy of SLN mapping in high-grade endometrial cancer. More studies have suggested the value of using SLN mapping for surgical staging in high-grade endometrial cancer.

### SLN Ultrastaging

In general, SLN mapping allows for increased intraoperative surgical precision to identify nodes more likely to harbor metastasis combined with enhanced pathology protocols, which has been shown to increase the detection of nodal metastasis, which may alter stage and adjuvant therapy recommendations. Studies have suggested that SLN ultrastaging leads to upstaging in 5% to 15% of patients.

Ultrastaging typically includes 2 components: serial sectioning with review of multiple H&E-stained slides with or without cytokeratin IHC staining. Recent data highlight the potential significance and impact of SLN ultrastaging to improve the accuracy of detecting micrometastases.

In a cohort of 508 patients who underwent SLN mapping, ultrastaging detected 23 additional cases of micrometastasis that would have been missed by conventional H&E staining. A multicenter study of 304 patients with presumed low- or intermediate-risk disease showed that SLN biopsy and ultrastaging detected metastatic SLNs in a 3-fold greater number of patients than standard lymphadenectomy.

The implications and appropriate management of micrometastases and isolated tumor cells (ITCs), jointly referred to as low-volume metastases, detected via SLN ultrastaging are not yet clear. Studies have recently begun to investigate the significance of ITCs discovered during SLN mapping in early-stage endometrial cancer. The AJCC 8th edition cancer staging manual indicates that the lymph nodes with ITCs should be clearly reported even though they do not affect the overall staging. When ITCs are detected in the absence of macrometastasis and micrometastasis, the lymph node stage is designated as pN0(i+).

A retrospective review examined 844 patients with endometrial cancer that underwent SLN mapping. The majority of patients with ITCs, micrometastasis, and macrometastasis received adjuvant chemotherapy (83%, 81%, and 89%, respectively). RFS at 3 years was 90% for those with negative SLNs, 86% for ITCs, and 86% for micrometastasis. Only patients with SLN macrometastasis had significantly lower RFS (71%, P < .001).

A prospective observational study of 519 patients compared outcomes for patients with SLN micrometastasis,
micrometastasis, and ITCs, taking into account adjuvant treatment. Patients with SLN ITCs had a significantly better 3-year progression-free survival (PFS) compared with patients with SLN macrometastasis (95.5% vs 58.5%), and outcomes were similar between patients with negative SLNs, ITCs, and micrometastasis. Recurrence was detected in only 1 of 31 patients with ITCs (stage IB carcinosarcoma) and adjuvant treatment did not appear to influence outcomes. Based on these early data, it is unclear if patients with SLN ITCs would derive significant benefit from adjuvant treatment. Future evaluation of prognosis/outcome may need to prospectively examine the threshold for and impact of adjuvant therapy for patients with scattered ITCs.

Minimally Invasive Procedures
Over the past decade, practice has trended toward minimally invasive approaches to total abdominal hysterectomy (TH)/BSO and lymph node assessment in patients with early-stage endometrial cancer. Although these procedures may be performed by any surgical route (eg, laparoscopic, robotic, vaginal, abdominal), the standard in those with apparent uterine-confined disease is to perform the procedure via a minimally invasive approach. Randomized trials, a Cochrane Database Systematic Review, and population-based surgical studies support that minimally invasive techniques are preferred in the appropriate candidate due to a lower rate of surgical site infection, transfusion, venous thromboembolism, decreased hospital stay, and lower cost of care, without compromise in oncologic outcome. Despite data showing that minimally invasive procedures result in lower perioperative complications and lower cost of care, racial and geographic disparities in access to minimally invasive surgical care have been observed.

A randomized phase III trial evaluated laparoscopy for comprehensive surgical staging; patients (n=2,616) with clinical stage I to IIA disease (GOG-LAP2) were assessed. Patients were randomly allocated 2:1 to laparoscopy or laparotomy. Results from LAP2 indicate that 26% of patients needed conversion to laparotomy because of poor visibility, metastatic cancer, bleeding, increased age, or increased body mass index. Detection of advanced cancer was not significantly different between the groups. However, significant differences were noted in removal of pelvic and para-aortic nodes (8% not removed with laparoscopy vs 4% with laparotomy, P<.0001). Significantly fewer postoperative adverse events and shorter hospitalization occurred with laparoscopy compared with laparotomy. Recurrence rates were 11.4% for laparoscopy versus 10.2% for laparotomy. The 5-year overall survival (OS) rate was 84.8% for both arms of LAP2. Laparoscopic staging was associated with improved postoperative quality of life across several parameters.

The LACE trial compared outcomes of patients with stage I endometrial carcinoma (n=760) who were randomized to undergo TH or total laparoscopic hysterectomy, where half of the patients received concomitant lymphadenectomy. At a median follow-up of 4.5 years, disease-free survival (DFS) was 81.3% for laparotomy versus 81.6% for laparoscopy, with no significant differences observed between groups for recurrence and OS. Another randomized trial (n=283) comparing laparoscopy versus laparotomy reported shorter hospital stay, less pain, and faster resumption of daily activities with laparoscopy. A recent follow-up study of a multicenter randomized trial evaluated outcomes for total laparoscopic hysterectomy versus TH in 279 patients with early-stage, low-risk endometrial cancer who did not undergo concomitant lymphadenectomy and reported comparable disease recurrence and 5-year survival rates. The results were also similar to studies with lymphadenectomy. Laparotomy may still be required for certain clinical situations (eg, elderly patients, those with a very large uterus) or certain metastatic presentations.

Robotic surgery is a minimally invasive technology that has been increasingly used in the surgical staging of endometrial carcinoma due to its potential advantages over laparotomy, especially for patients who are overweight. Prospective cohort and retrospective studies suggest that robotic approaches perform similarly to laparoscopy and result in comparable or improved perioperative outcomes. Oncologic outcomes appear to be comparable to other surgical approaches, although longer-term outcomes (including quality of life) are still being investigated. In heavier patients, robotic surgery may result in less frequent conversion to laparotomy when compared with laparoscopic approaches and also appears to be safe and feasible in patients at higher anesthesiologic risk.

Costs for robotic equipment and maintenance remain high. The SGO, American Association of Gynecologic Laparoscopists, and American Congress of Obstetricians and Gynecologists have published guidelines or position statements about robotic surgery. For reviews on robotic-assisted surgery for gynecologic malignancies and associated cost issues, see Sinno and Fader and Gala et al.

Primary Treatment
These NCCN Guidelines divide pure endometrioid cancer into 3 categories for delineating treatment: (1) disease limited to the uterus; (2) suspected or gross cervical involvement; and (3) suspected extrauterine disease. Most patients with endometrial cancer have stage I disease at presentation, and surgery (with or without adjuvant therapy) is recommended for medically operable patients. As a general
principle, endometrial carcinoma should be removed en bloc to optimize outcomes; intraperitoneal morcellation should be avoided.152–155

**Disease Limited to the Uterus**

To stage medically operable patients with endometrioid histologies clinically confined to the fundal portion of the uterus, the recommended surgical procedure includes removal of the uterus and bilateral tubes and ovaries with lymph node and abdominal assessment (see “Principles of Evaluation and Surgical Staging,” pages 186 and 187 and “Lymphadenectomy,” page 188, and “Sentinel Lymph Node Mapping,” page 189).62 Ovarian preservation may be safe in select premenopausal patients with stage I endometrioid cancer.156–158 Minimally invasive surgery is the preferred approach when technically feasible and is considered a quality measure by the SGO and the American College of Surgeons (www.sgo.org/quality-outcomes-and-research/quality-indicators; https://www.facs.org/quality-programs/cancer-programs/national-cancer-database/quality-of-care-measures).

During surgery, the intraperitoneal structures should be carefully evaluated, and suspicious areas should be biopsied. While not specifically affecting staging, FIGO and AJCC recommend that peritoneal cytology should be collected and results should be recorded. Cytology results should not be taken in isolation to guide adjuvant therapy. Enlarged or suspicious lymph nodes should be excised to confirm or rule out metastatic disease. Retroperitoneal node dissection with pathologic evaluation—in the absence of clinically apparent lymphadenopathy—is useful when using the 2009 FIGO staging criteria, but its routine use has been questioned (see “Lymphadenectomy,” page 188). For patients with stage II disease, TH/BSO is the standard procedure. Radical hysterectomy should only be performed if needed to obtain negative margins.

Patients with apparent uterine-confined endometrial carcinoma are candidates for sentinel node mapping, which assesses the pelvic nodes bilaterally and may be less morbid than complete lymphadenectomy (see “Sentinel Lymph Node Mapping,” page 189). Adherence to the NCCN SLN algorithm is critical.

**Incomplete Surgical Staging**

For patients with incomplete surgical staging and high-risk intrauterine features, imaging is recommended, especially in patients with higher grade histologies.159,160 Surgical restaging, including lymph node dissection, can also be done.68 Based on the imaging and/or surgical restaging results, recommended adjuvant treatment options are provided in the algorithm (see “Adjuvant Treatment” of “Incompletely Surgically Staged,” available at NCCN.org).

**Fertility-Sparing Therapy**

Although the primary treatment of endometrial cancer is usually hysterectomy, continuous progestin-based therapy may be considered for highly selected patients with grade 1, stage I (noninvasive) disease who wish to preserve fertility.161–163 Likewise, it may also be selectively used for young patients with endometrial hyperplasia who desire fertility preservation. The guidelines include an algorithm for fertility-sparing therapy in selected patients with biopsy-proven grade 1 (preferably by D&C), stage IA noninvasive endometrioid adenocarcinoma (see “Criteria for Considering Fertility-Sparing Options,” available at NCCN.org). The panel recommends consultation with a fertility expert and genetic evaluation of tumor and evaluation for inherited cancer risk. When considering fertility-sparing therapy, all of the criteria must be met as outlined in the algorithm (eg, no metastatic disease) and a negative pregnancy test must be ensured. Patients should also receive counseling that fertility-sparing therapy is not the standard of care for the treatment of endometrial carcinoma. TH/BSO with surgical staging is recommended after childbearing is complete, if therapy is not effective, or if progression occurs. Fertility-sparing therapy is not recommended for high-risk patients (eg, those with high-grade endometrioid adenocarcinomas, uterine serous carcinoma, clear cell carcinoma, carcinosarcoma, and leiomyosarcoma).

Continuous progestin-based therapy may include megestrol acetate, medroxyprogesterone, or an intrauterine device containing levonorgestrel.161,162,166 A complete response occurs in about 50% of patients.161 The use of progestin-based therapy should be carefully considered in the context of other patient-specific factors, including contraindications such as breast cancer, stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis, and smoking. The panel also recommends counseling for weight management and lifestyle modification (see “Healthy Life-styles” and “Nutrition and Weight Management” in the NCCN Guidelines for Survivorship, available at NCCN.org).

In patients receiving progestin-based therapies, the NCCN panel recommends close monitoring with endometrial sampling (biopsies or D&C) every 3 to 6 months. TH/BSO with staging is recommended (1) after childbearing is complete; (2) if patients have documented progression on biopsy; or (3) if endometrial cancer is still present after 6 to 12 months of progestin-based therapy.165,167 Although some young patients who had subsequent negative endometrial biopsies after hormonal therapy were able to become pregnant (35%), the ultimate recurrence rate was high (35%).161,164–168 In patients with persistent endometrial carcinoma after 6 months of failed hormonal
therapy, the panel recommends pelvic MRI to exclude myoinvasion and nodal/ovarian metastasis before continuing fertility-sparing therapy.

In a study of premenopausal patients with stage IA to B endometrial cancer, median 16-year follow-up data suggest that ovarian preservation is safe and not associated with an increased risk of cancer-related mortality. Other studies also suggest that ovarian preservation may be safe in select patients.

Suspected or Gross Cervical Involvement
For patients with suspected or gross cervical involvement (endometrioid histologies), cervical biopsy or pelvic MRI should be performed if not done previously (see “Additional Workup,” page 183). If negative, patients are assumed to have disease that is limited to the uterus and are treated as previously described, although a radical hysterectomy may be performed when necessary to obtain negative margins. Distinguishing primary cervical carcinoma from stage II endometrial carcinoma may be difficult. Thus, for patients suitable for primary surgery, TH or radical hysterectomy is recommended along with BSO, cytology (peritoneal lavage), and evaluation of lymph nodes if indicated (see “Principles of Evaluation and Surgical Staging,” page 186). In these patients, radical or modified radical hysterectomy may improve local control and survival when compared with TH. Alternatively, the patient may undergo EBRT and brachytherapy (category 2B) followed by TH/BSO and surgical staging.

Suspected Extrauterine Disease
If extrauterine disease (endometrioid histologies) is suspected, imaging studies are recommended along with CA-125 testing (see “Additional Workup” in the algorithm [page 184]). ER testing is recommended in the setting of stage III or IV endometrioid tumors. Patients with no evidence of extrauterine disease are treated using the guidelines for disease limited to the uterus. Patients with abdominal- or pelvic-confined disease require surgical intervention using TH/BSO with surgical staging and surgical debulking with the goal to have no measurable residual disease; several studies support debulking. Consider preoperative chemotherapy. For distant visceral metastasis (eg, liver involvement), recommended options include systemic therapy with (or without) EBRT with (or without) TH/BSO and with (or without) SBRT. Ablative radiation can be considered for 1 to 5 metastatic lesions if disease is otherwise controlled (category 2B).

Disease Not Suited for Primary Surgery
For uterine-confined disease not suitable for primary surgery, EBRT and/or brachytherapy is the preferred treatment approach. Alternatively, progestational agents (such as medroxyprogesterone acetate and megestrol acetate) and levonorgestrel intrauterine device can also be considered for select patients (eg, estrogen and progesterone receptor-positive [ER/PR-positive]). Patients receiving hormonal therapy alone should be closely monitored by endometrial biopsy (eg, consider endometrial biopsies every 3–6 months).

For suspected gross cervical involvement in disease not suited for primary surgery, EBRT and brachytherapy is an effective treatment that can provide pelvic control and long-term PFS (see “Principles of Radiation Therapy,” in the NCCN Guidelines for Uterine Neoplasms, available at NCCN.org). EBRT and brachytherapy may be administered with or without platinum-based chemosensitization, depending on the clinical situation and medical fitness of the patient. If rendered operable, local treatment consisting of surgery should follow. Systemic therapy alone is also a primary treatment option (category 2B), but should be followed by EBRT plus brachytherapy if the patient remains inoperable.

Patients with unresectable extrauterine pelvic disease (ie, vaginal, bladder, bowel/rectal, nodal, or parametrial involvement) are typically treated with EBRT with (or without) brachytherapy with (or without) systemic therapy, followed by re-evaluation of tailored surgery. Systemic therapy alone can also be considered. Based on treatment response, patients should be re-evaluated for surgical resection and/or RT.

Adjuvant Therapy
Uterine-Confined Disease
Thorough surgical staging provides important information to assist in selection of adjuvant therapy for endometrial tumors (see “Principles of Evaluation and Surgical Staging,” page 186). Patients with stage I endometrial cancer who have thorough surgical staging are stratified by adverse risk factors (ie, age, positive LVSI, tumor size, and lower uterine segment or surface glandular involvement). Recommended adjuvant treatment is outlined in the algorithm (see the NCCN Guidelines for Endometrial Carcinoma at NCCN.org). Note that the treatment algorithm was revised in 2010 based on the updated FIGO staging. However, by necessity, much of the discussion in this manuscript has been based on data from patients staged using the older FIGO/AJCC staging system. The implications of stage migration should be considered when evaluating historical data.

The basic concept underlying the recommendations in the NCCN Guidelines is the trend toward selection of more aggressive adjuvant therapy for patients as tumor grade and myometrial and/or cervical invasion increase, as risk of systemic metastases increase. In surgical stage I and II endometrial cancer, other pathologic factors that may influence the decision regarding adjuvant therapy include LVSI, patient age, tumor volume, depth of
invasion, and lower uterine segment or cervical glandular involvement. When administering adjuvant RT, it should be initiated as soon as the vaginal cuff has healed, but no later than 12 weeks after surgery.

Significant controversy centers on how much adjuvant therapy is necessary in patients with surgical stage I endometrial cancer. The practice of surgical staging has led to a decrease in the use of adjuvant therapy for stage I endometrial carcinoma, which is reflected in the opinion of observation in the NCCN Guidelines for selected patients with low-risk features (see section on “Adjuvant Treatment,” in the NCCN Guidelines for Adjuvant Treatment of Endometrial Carcinoma, available at NCCN.org). The NCCN panel prefers observation for patients with stage IA, grade 1/2 disease, but strongly suggests treatment with adjuvant vaginal brachytherapy for those ≥60 years and/or those with LVSI. For patients with stage IA, grade 3 tumors, especially in those who have been surgically staged, vaginal brachytherapy is the preferred option, or observation can be considered if no myometrial invasion is present. If higher risk factors are present, ie, age ≥70 years or LVSI, EBRT can be considered as a category 2B option. For patients with stage IB, grade 1–2 disease, vaginal brachytherapy is preferred, although observation can be considered if no adverse risk factors are present. In these patients, the Postoperative Radiation Therapy in Endometrial Carcinoma (PORTEC)-2 trial, without evaluation of pelvic nodes, found pelvic recurrence to be low with vaginal brachytherapy alone. EBRT can be considered in grade 2 tumors if additional risk factors are present such as age ≥60 years and/or if LVSI is present. For stage IB, grade 3 disease with adverse risk factors, systemic therapy is added as a category 2B option (in addition to EBRT and/or vaginal brachytherapy).

The recommended postoperative (ie, adjuvant) treatment options for surgical stage II patients (using thorough surgical staging) are shown in the algorithm (see “Adjuvant Treatment,” for stage II in the NCCN Guidelines for Endometrial Carcinoma, at NCCN.org). The NCCN panel generally agrees on the role of adjuvant therapy for patients with an invasive cervical component if extrafascial hysterectomy is performed. However, for patients with stage II disease who have had a radical hysterectomy with negative surgical margins and no evidence of extrauterine disease, EBRT (preferred) and/or vaginal brachytherapy with (or without) systemic therapy (category 2B) are options. As with stage I disease, the presence of adverse risk factors (including depth of stromal invasion, grade, LVSI, and adverse fundal risk factors) should be considered when selecting adjuvant therapy for stage II disease.

**Adjuvant RT**

Several phase III trials have assessed adjuvant therapy in patients with uterine-confined disease. In summary, the use of adjuvant RT improves pelvic control in patients with selected risk factors (and may improve PFS), but has not been shown to improve OS. However, many of the earlier trials had limitations as the patients were primarily low risk (ie, they had low-risk intrauterine pathologic risk factors). It is recognized that in patients with uterine-confined disease, there is a spectrum of risk based on intrauterine pathologic findings. Adverse intrauterine pathologic risk factors include high-grade tumors, deep myometrial invasion (and consequently more advanced stage), LVSI (especially extensive), and serous or clear cell carcinoma histologies.

Four trials have evaluated the role of adjuvant external-beam pelvic RT in patients with endometrial carcinoma. In 2 of these trials, the patients were not formally staged (PORTEC-1, Aalders et al). In the third trial (ASTEC/EN.5), only 50% of the patients were thoroughly staged as part of a companion surgical protocol. However, formal surgical staging was mandated for all patients in the GOG 99 trial. Note that these trials used the older staging system (ie, before 2009).

The PORTEC-1 and GOG 99 trials suggest that external-beam pelvic RT provides a locoregional control benefit in selected patients with uterine-confined disease. Radiation was not shown to increase OS. It is important to note that the PORTEC 1 trial was powered to evaluate OS, although the GOG 99 trial was not. Similarly the Aalders et al randomized trial found that RT reduced vaginal (ie, locoregional) recurrences but did not reduce distant metastases or improve survival. A pooled randomized trial (ASTEC/EN.5) suggested that adjuvant pelvic RT alone did not improve either relapse-free survival (ie, PFS) or OS in patients with intermediate-risk or high-risk early-stage endometrial cancer, but there was an improvement in pelvic control. However, the ASTEC/EN.5 study is very controversial: 51% of the patients in the ASTEC observation group received vaginal brachytherapy. Vaginal brachytherapy has been shown to decrease vaginal recurrence, and in PORTEC 2 vaginal brachytherapy was compared in a prospective randomized trial with EBRT in low-risk patients. Vaginal brachytherapy alone was shown to sufficiently control the pelvis and was less toxic than full pelvic RT. As most pelvic recurrences are vaginal, inclusion of vaginal brachytherapy in the “observation” arm of the ASTEC/EN.5 study weakens any conclusions regarding pelvic radiation. The GOG 99 trial showed that adjuvant pelvic RT improved locoregional control and relapse-free interval (ie, PFS), without an OS benefit, although the study was not powered to evaluate OS. In both trials, pelvic radiation was found to be of greater benefit in patients >60 years with higher grade and more deeply invasive disease.

To help select the appropriate patient population that may benefit from adjuvant pelvic RT, the GOG 99 and PORTEC trials defined risk factors for patients at high-
intermediate risk (HIR) for recurrence, although the definition differed between these trials.197-199 Risk factors for recurrence identified in both trials included higher age, deep myometrial invasion (>50%), higher grade (grade 2 or 3, serous or clear cell), and LVS1 (especially extensive as defined in the PORTEC trials). Based on risk factors identified in GOG 99, HIR disease was defined as disease in patients <50 years with grade 2 or 3 disease, myometrial invasion greater than 50%, and LVS1.199 Patients 50 to 70 years of age were considered HIR if they had 2 of the 3 identified high-risk features. Patients ≥70 years were defined as HIR if they also had one risk feature present. Based on data from PORTEC-1, HIR patients were defined as having 2 of 3 risk factors (ie, age >60 years, deep myometrial invasion, grade 3 histology).197-204 LVS1 was not considered in the original PORTEC trials, but a subsequent retrospective evaluation demonstrated increased recurrence with extensive LVS1, as defined by the protocol.

Due to concerns about potential toxicity of external-beam pelvic RT, the role of vaginal brachytherapy alone in uterine-confined disease has been evaluated. PORTEC-2 randomly assigned patients to external-beam pelvic RT versus vaginal brachytherapy alone in uterine-confined disease. PORTEC-2 showed excellent and equivalent vaginal and pelvic control rates with both adjuvant radiation approaches and no difference in OS.195 Given that vaginal brachytherapy is associated with significantly less toxicity than pelvic RT, vaginal brachytherapy alone is a reasonable choice for patients with uterine-confined endometrial cancer as defined in the PORTEC 2 trial.195-204-212 The use of vaginal brachytherapy and/or whole pelvic RT should be carefully tailored to a patient’s pathologic findings. Both PORTEC-1 and PORTEC-2 specifically excluded patients with 1998 FIGO stage IC and grade 3 endometrial carcinoma (2009 FIGO stage IB, grade 3);46; thus, the use of adjuvant brachytherapy alone in this higher risk subset remains more controversial. PORTEC studies did not evaluate lymph nodes and, therefore, in the context of complete surgical staging and the lack of a survival benefit, the need for pelvic irradiation remains controversial in uterine-confined disease.

A meta-analysis evaluated results from studies that compared adjuvant postoperative EBRT with or without vaginal brachytherapy and vaginal brachytherapy alone in stage II endometrial cancer. EBRT plus vaginal brachytherapy significantly reduced locoregional recurrence versus vaginal brachytherapy alone. OS was comparable in both arms.213

The GOG 249 trial examined vaginal cuff brachytherapy and 3 cycles of carboplatin/paclitaxel therapy (3 cycles) versus pelvic EBRT only in patients with high-risk, uterine-confined endometrial carcinoma (n=601), including serous and clear cell carcinoma. GOG 249 reported significantly increased rates of nodal recurrence (primarily pelvic) in the brachytherapy plus chemotherapy arm compared with the pelvic EBRT arm. No significant between-group differences in vaginal or distant recurrence rates were observed. However, there were more extravaginal pelvic failures in the brachytherapy plus chemotherapy arm. At a median follow-up of 53 months, 3-year RFS was 82% for both treatment arms; 3-year OS was 88% for the brachytherapy plus chemotherapy cohort and 91% for the pelvic EBRT cohort. Acute toxicity was more common and severe for patients receiving brachytherapy with chemotherapy. No differences in late-onset toxicities were observed.214 Questions were raised whether 3 cycles of chemotherapy were sufficient to control distant disease.

Analysis of pooled data from PORTEC-1 and PORTEC-2 ranked the predictive power of multiple variables on patient outcomes examined in these trials. Patient age, tumor grade, and LVS1 were highly predictive for locoregional relapse, distant relapse, OS, and DFS, and treatment given (EBRT vs vaginal brachytherapy) was predictive for locoregional relapse and DFS.187 The benefit of adjuvant EBRT in the highest risk spectrum of uterine-confined disease remains controversial. Most NCCN panel members feel that patients with deeply invasive grade 3 tumors should receive adjuvant treatment. Two large retrospective SEER analyses of patients with endometrial cancer found that adjuvant RT improved OS in those with high-risk disease.215-216 In a meta-analysis of randomized trials, a subset analysis found that adjuvant pelvic RT for stage I disease was associated with a trend toward a survival advantage in the highest-risk spectrum (eg, those with 1988 FIGO stage IC, grade 3) but not in lower risk patients; however, other reviews have shown conflicting results.207,217-221

The long-term follow-up study (median 20.5 years) of 568 patients with early-stage endometrial carcinoma enrolled in the Aalders trial compared long-term outcomes in patients who received vaginal brachytherapy plus EBRT versus vaginal brachytherapy alone. The findings suggested no statistical difference in OS between the study groups, and in this cohort, patients <60 years of age who received EBRT had increased incidence of secondary cancers and subsequent higher mortality rates.207 Evaluation of secondary malignancies in the context of increased genetic susceptibility (eg, MSI-H) and radiation is ongoing.

Adjuvant Systemic Therapy
Patients with deeply invasive, grade 3, uterine-confined disease (2009 FIGO stage IB, grade 3 [formerly 1988 FIGO stage IC, grade 3]) have a relatively poor prognosis. Despite adjuvant therapy with pelvic RT, a significant number of patients continue to have a significant risk of distant metastases, and an optimal adjuvant therapy is still sought.189,200 Therefore, some clinicians suggested that adding systemic therapy to adjuvant RT may provide added therapeutic benefit (ie, decrease in distant metastases).189,222 Studies have evaluated
the role of systemic therapy in highest risk uterine-confined disease.222,223 PFS is improved with adjuvant sequential chemotherapy.222 However, the NCCN panel feels that adjuvant systemic therapy is a category 2B recommendation in this setting because an OS advantage has not been shown.222 The GOG-249 phase 3 trial evaluated the benefit of adjuvant pelvic RT versus vaginal cuff brachytherapy plus 3 cycles of paclitaxel/carboplatin combination in 601 patients with high-intermediate and high-risk early-stage endometrial cancer. The 5-year RFS and OS were similar in both groups and superiority of any of these treatments were not demonstrated. Acute toxicity was greater in the combination therapy.214

Advanced Stage/Extrauterine Disease

A consensus exists that patients with documented extra-uterine disease are at increased risk for recurrence and need adjuvant therapy; however, the optimal form of adjuvant therapy has yet to be determined.224,225 Patients with extrauterine disease confined to the lymph nodes or the adnexa may be treated with pelvic or extended-field RT alone or with chemotherapy (radiation is targeted to sites of nodal disease).226 However, systemic therapy is regarded as the foundation of adjuvant therapy for patients with extrauterine disease. The NCCN Guidelines include carboplatin/paclitaxel as the preferred option in the primary/adjuvant setting for advanced-stage disease or high-risk histologies.227–229

For stages III and IV disease, systemic therapy forms the mainstay of treatment and can be combined with EBRT with (or without) vaginal brachytherapy. The combination of therapies depends on assessment of both locoregional and distant metastatic risk. Combination therapy can be considered for stages IIIB and IIIC disease.

Previously, whole abdominal RT was used for carefully selected patients deemed at risk for peritoneal failure, and RT appeared to have provided therapeutic benefit in retrospective studies. However, it is considered too toxic and has largely been abandoned.230,231 A randomized phase III GOG (122) trial assessed optimal adjuvant therapy for patients with endometrial cancer who had extrauterine disease. In this trial, patients with stage III and intra-abdominal stage IV disease who had minimal residual disease were randomly assigned to whole abdominopelvic RT versus 7 cycles of combined doxorubicin (60 mg/m²) and cisplatin (50 mg/m²) treatment, with an additional cycle of cisplatin (AP). This GOG trial reported that AP chemotherapy improved PFS and OS when compared with whole abdominopelvic RT; however, acute toxicity (eg, peripheral neuropathy) was greater in the AP chemotherapy arm.184

The GOG 122 study established the role of adjuvant multiagent systemic chemotherapy for curative intent in patients with extrauterine disease. Thus, in the NCCN Guidelines, systemic therapy forms the established framework of adjuvant therapy for patients with stage III or IV disease. Whole abdominal RT as a single modality (as used in GOG 122) is considered inferior to chemotherapy and is too toxic; therefore, it is no longer recommended. For the purposes of these guidelines, whole abdominal RT is not considered to be tumor-directed RT (see “Principles of Radiation Therapy,” in the NCCN Guidelines for Uterine Neoplasms at NCCN.org).

Recurrences were frequent in both treatment arms of GOG 122, occurring in the pelvis and abdomen. Approximately 52% of patients with advanced endometrial carcinoma had recurrences, indicating the need for further therapeutic improvement in this high-risk population.184 A study found that combined modality adjuvant therapy (using chemotherapy and tumor-directed RT) may provide a therapeutic benefit when compared with single-modality adjuvant therapy.186,232,233

A follow-up study evaluated the role of chemotherapy “intensification” for this patient population. The GOG 184 trial compared 2 chemotherapy regimens (cisplatin and doxorubicin with or without paclitaxel) with tumor-directed radiation (involved-field radiation either to the pelvis or to the pelvis plus para-aortic nodes). Results indicate that the 3-drug regimen did not improve survival when compared with the 2-drug regimen after 3 years of follow-up and that the more intensive chemotherapy resulted in greater toxicity (eg, hematologic toxicity, sensory neuropathy, myalgia).185

In a retrospective review of 116 patients with stage IIIC endometrial cancer, adjuvant RT significantly improved OS in patients with endometrioid histology, high-grade tumors, and positive para-aortic lymph nodes. Conversely, patients with low-grade tumors and nonendometrioid histology who received RT had similar OS compared with those who did not.234 In a multicenter retrospective review of 73 patients with stage IIIA endometrial carcinoma, surgery followed by both chemotherapy and RT provided the highest 5-year OS.235 A prospective study of 122 patients with fully resected locally advanced disease suggested a potential benefit of adjuvant chemoradiation followed by chemotherapy, with an estimated 5-year PFS and OS of 73% and 84%.236 Adjuvant therapy options were compared in a multicenter retrospective analysis of 265 patients with optimally resected stage IIIC endometrial carcinoma. Compared with patients receiving adjuvant RT or adjuvant RT plus chemotherapy, patients who received adjuvant chemotherapy alone had a 2.2-fold increased risk of recurrence and a 4.0-fold increased risk of death.235

Multimodality therapy is now the basis of randomized trials evaluating therapy. The phase 2, RTOG 9708 trial assessed 46 patients for safety, toxicity, recurrence, and survival when chemotherapy (cisplatin/paclitaxel) was combined...
with adjuvant radiation in patients with high-risk endometrial cancer. The trial participants included patients with grade 2 or 3 endometrial adenocarcinoma with either >50% myometrial invasion, cervical stromal invasion, or pelvic-confined extrauterine disease. The OS and DFS favored the combined modality treatment.\(^{237}\)

The phase III, PORTEC-3 trial investigated the benefit of combined adjuvant chemotherapy and EBRT versus EBRT alone in 686 patients with endometrial cancer (stage I, grade 3 with deep invasion, LVSI, or both; stage II; stage III; or any patient with stage I to III serous or clear cell endometrial cancer). The 5-year OS was 81.4% (95% CI, 77.2–85.8) with chemoradiotherapy versus 76.1% (95% CI, 71.6–80.9) with radiotherapy alone (hazard ratio [HR], 0.70; 95% CI, 0.51–0.97; \(P=0.034\)) and 5-year failure-free survival was 76.5% (95% CI, 71.5–80.7) versus 69.1% (63.8–73.8; HR, 0.70; 95% CI, 0.522–0.94; \(P=0.016\)). Patients with serous cancers and with stage III disease were shown to benefit the most from the addition of systemic therapy. The combination treatment was also shown to be associated with more severe adverse events.\(^{238}\)

The GOG-258 phase III trial evaluated 707 patients with stage III or IVA, high-risk endometrial cancer who were randomly assigned 1:1 to receive chemoradiotherapy or chemotherapy only.\(^{240}\) This trial supported the benefit of using chemotherapy alone by concluding that the combined therapy was not associated with longer relapse-free survival when compared with chemotherapy alone (59% vs 58%, respectively). OS results are pending.

A follow-up molecular analysis was performed on the PORTEC-3 trial to study the impact of chemoradiotherapy for each molecular subtype using tissue samples from the trial participants. The tumors were classified into p53 abnormal, POLE, MMR-deficient (dMMR), or no specific molecular profile. The 5-year RFS with chemoradiotherapy versus RT alone was p53 abnormal, 59% versus 36%; POLE, 100% versus 97%; dMMR, 68% versus 76%; and 80% versus 68% for no specific molecular profile, suggesting that systemic therapy was beneficial for those patients with the p53 abnormal tumors.\(^{241}\) Results are awaited for an ongoing PORTEC-4a trial investigating molecular profile-based directed adjuvant treatment in high-risk endometrial cancer.\(^{242}\)

### Treatment of Recurrent or Metastatic Disease

#### Locoregional Recurrence

Patients with local or regional recurrences (negative for distance metastases on radiologic imaging) can be evaluated for further treatment (see “Clinical Presentation,” in the algorithm [page 185]). For recurrences confined to the vagina or the pelvis alone, second-line treatment (typically with RT and/or surgery or systemic therapy) can be effective, and selection depends on prior therapy. For patients with no prior RT exposure at the recurrence site, the panel recommends EBRT with (or without) brachytherapy and systemic therapy, or surgery with (or without) intraoperative RT (IORT) and systemic therapy. For patients previously treated with brachytherapy only at the recurrence site, surgery with (or without) IORT is recommended (category 3 for IORT).

For patients previously treated with EBRT at the recurrence site, recommended therapy for isolated relapse includes surgery with (or without) IORT (category 3 for IORT) ± systemic therapy. Use of RT in the context of recurrence depends on the site of recurrence (inside or outside the prior radiation field), and dose of prior therapy. Reirradiation is used only in the context of limited disease for palliation and lack of other options. In selected patients, radical surgery (ie, pelvic exenteration) has been performed with reported 5-year survival rates approximating 20%.\(^{243,246}\)

Isolated vaginal recurrences treated with RT have good local control and 5-year survival rates of 50%–70%.\(^{247,248}\) Prognosis is worse if there is extravaginal extension or pelvic lymph node involvement.\(^{247}\) After RT, it is unusual for patients to have recurrences confined to the pelvis. The management of such patients remains controversial.

Additional therapy options for disease confined to vagina or paravaginal soft tissues include EBRT with (or without) brachytherapy with (or without) systemic therapy. EBRT and systemic therapy are also included as options for the additional treatment of pelvic lymph node recurrence, para-aortic or common iliac lymph node invasion, and upper abdominal or peritoneal recurrences as shown in the algorithm (see “Additional Therapy,” in the algorithm, page 185).

#### Distant Metastases

For gross upper abdominal residual disease, more aggressive treatment of relapse is recommended, as outlined for disseminated metastases in “Therapy for Relapse” in the algorithm (page 185). For resectable isolated metastases, consider surgical resection and/or EBRT, or ablative therapy. Ablative RT can be considered for 1 to 5 metastatic lesions if the primary cancer has been controlled (category 2B).\(^{177}\) Providers can also consider systemic therapy (category 2B). Further recurrences or disease not amenable to local therapy are treated as disseminated metastases. Treatment options for disseminated metastases are systemic therapy with (or without) palliative EBRT. For persistent progression of disseminated metastases, best supportive care is recommended (see the NCCN Guidelines for Palliative Care at NCCN.org).

#### Hormonal Therapy

The role of hormonal therapy in recurrent or metastatic cancer has been primarily evaluated in patients with...
endometrioid histologies only. Hormonal therapy is typically used for lower-grade endometrioid histologies, preferably in patients with small tumor volume or an indolent growth pace. Hormonal agents for treating recurrent/metastatic disease include megestrol acetate with alternating tamoxifen, medroxyprogesterone acetate/tamoxifen (alternating), everolimus/letrozole combination, progestational agents (such as medroxyprogesterone acetate and megestrol acetate), aromatase inhibitors, tamoxifen alone, or fulvestrant.249–254 No particular drug, dose, or schedule has been found to be superior. The main predictors of response in the treatment of metastatic disease are well-differentiated tumors, expression of ER/PR receptors, a long disease-free interval, and the location and extent of extrapelvic (particularly pulmonary) metastases.

For asymptomatic or low-grade disseminated metastases, hormonal therapy with progestational agents has shown good responses, particularly in patients with ER/PR-positive disease.255–258 Tamoxifen has a 20% response rate in disease that does not respond to standard progesterone therapy.259 Tamoxifen has also been combined with progestational agents; however, a few patients had grade 4 thromboembolic events with this combination regimen.251,252,256 In some patients, aromatase inhibitors (eg, anastrozole, letrozole) may be substituted for progestational agents or tamoxifen.257

Everolimus combined with letrozole is recommended for recurrent disease of endometrioid histology. In the phase II trial, in patients with progressive or recurrent endometrial cancer who had received up to 2 prior therapies, the clinical benefit rate and objective response rate among 35 evaluable patients was 40% and 32%, respectively.261 In a following phase II study, patients (with or without prior chemotherapy) were treated either with the everolimus/letrozole combination or medroxyprogesterone acetate/tamoxifen regimen. Twenty-two percent of patients responded to the everolimus/letrozole therapy, while 25% showed a response with the medroxyprogesterone acetate/tamoxifen regimen.262 Median PFS was 6 months for the everolimus/letrozole arm and 4 months for the hormonal therapy arm. Median OS was 31 months and 17 months for the everolimus/letrozole and medroxyprogesterone acetate/tamoxifen arms, respectively. Higher PFS was observed in both arms for patients who had not received any prior chemotherapy.

Other hormonal modalities have not been well-studied, and adjuvant therapy with hormonal agents has not been compared with cytotoxic agents.257,263 If disease progression is observed after hormonal therapy, cytotoxic chemotherapy can be considered. However, clinical trials or best supportive care (see the NCCN Guidelines for Palliative Care, available at NCCN.org) are appropriate for patients with disseminated metastatic recurrence who have a poor response to hormonal therapy and chemotherapy.

### Systemic Therapy

Chemotherapy for endometrial cancer has been extensively studied.264,265 Based on the current data, multiagent chemotherapy regimens are preferred for advanced disease, if tolerated. The NCCN Guidelines for Endometrial Carcinoma recently updated the systemic therapy recommendation by including multiagent chemotherapy regimens such as carboplatin/paclitaxel, carboplatin/docetaxel, and carboplatin/paclitaxel/bevacizumab as first-line therapy options for the recurrent disease setting.

Other combination therapies such as cisplatin/doxorubicin, cisplatin/doxorubicin/paclitaxel, ifosfamide/paclitaxel (for carcinosarcoma), cisplatin/ifosfamide (for carcinosarcoma) are added as second-line or subsequent-therapy options. A phase III randomized trial (GOG 177) compared 2 combination chemotherapy regimens in females with advanced or recurrent endometrial carcinoma. The 273 participants were randomly assigned to (1) cisplatin/doxorubicin/paclitaxel; or (2) cisplatin/doxorubicin. The 3-drug regimen was associated with improved survival (15 vs 12 months; P<.04) but with significantly increased toxicity (ie, peripheral neuropathy); therefore, it is not widely used.266–268 These regimens are recommended as second-line options in the NCCN Guidelines, because most panel members feel that carboplatin/paclitaxel is a less toxic and preferred first-line option. The response rates with other multiagent chemotherapies have ranged from 31% to 81%, but with relatively short durations. The median survival for patients in such trials remains approximately 1 year.264–265

Carboplatin and paclitaxel is an increasingly used regimen for advanced or recurrent endometrial cancer; the response rate is about 40% to 62%, and OS is about 13 to 29 months.269–271 A phase III trial (GOG 209) compared carboplatin and paclitaxel versus cisplatin, doxorubicin, paclitaxel, and filgrastim (granulocyte colony-stimulating factor). Trial data show that oncologic outcomes are similar, but the toxicity and tolerability profile favor carboplatin/paclitaxel.272 Thus, the carboplatin/paclitaxel regimen is now the preferred approach for many patients. For patients in whom paclitaxel is contraindicated, docetaxel can be considered in combination with carboplatin.273

A phase II trial initially examined the addition of bevacizumab to carboplatin and paclitaxel among 15 patients with advanced or recurrent endometrial carcinoma.274 Although this study was closed early due to the initiation of a national trial, a retrospective analysis was performed to include data from an additional 27 patients who had received carboplatin/paclitaxel/bevacizumab for advanced or recurrent disease.275 Collective median PFS was 20 months with a median OS of 56 months. An overall response rate (ORR) of 82.8% was noted, with an 87.5% response rate among the subset of 8 patients who received this triplet as second-line therapy.
therapy after carboplatin/paclitaxel. Another phase II randomized study showed that the carboplatin/paclitaxel/bevacizumab combination improved OS from 29.7 to 40 months compared with the doublet regimen. Another meta-analysis of 3 studies also concluded similar results where the triplet combination increased the OS and PFS at >12 months with an ORR of 76%. If multiagent chemotherapy regimens are contraindicated, then single-agent subsequent-line therapy options included in the guidelines are cisplatin, carboplatin, doxorubicin, liposomal doxorubicin, paclitaxel, albumin-bound paclitaxel, topotecan, cabozantinib, and docetaxel (category 2B for docetaxel). When single agents are used as second-line treatment, responses range from 4% to 27%; paclitaxel is the most active in this setting. Some oncologists have used liposomal doxorubicin, because it is less toxic than doxorubicin; the response rate of liposomal doxorubicin is 9.5%. Docetaxel is recommended for use as a single agent; however, it is a category 2B recommendation because it is less active (7.7% response rate) than other agents. Bevacizumab was shown to have a 13.5% response rate and OS rate of 10.5 months in a phase II trial for persistent or recurrent endometrial cancer. Based on these studies, the NCCN panel considers bevacizumab as appropriate single-agent biologic therapy for patients who have progressed on previous cytotoxic chemotherapy.

In the advanced endometrial cancer cohort (n=24) of the phase Ib KEYNOTE-028 trial, durable antitumor responses were noted in a small subset of patients with programmed death ligand 1 (PD-L1)–positive tumors (3 partial response, 3 stable disease). Studies have also indicated that dMMR tumors are sensitive to programmed death receptor-1 (PD-1) blockade. Results were published from a study of patients with dMMR tumors of various disease sites. Among patients with dMMR endometrial carcinoma who received pembrolizumab (n=15), the objective response rate was 52% and the disease control rate was 73% (3 complete response, 5 partial response, and 3 stable disease). The FDA expanded pembrolizumab approval in 2017 to include treatment of unresectable or metastatic, MSI-H, or dMMR solid tumors that have progressed after prior treatment and that have no satisfactory alternative treatment options. In the following phase II Keynote-158 trial, pembrolizumab further demonstrated robust antitumor activity with encouraging survival outcomes in patients with advanced MSI-H/dMMR endometrial cancer and manageable adverse events. Pembrolizumab is included as a category 1 treatment option for MSI-H/dMMR endometrial tumors with a recommendation that recurrent endometrial tumors be tested for MSI-H or dMMR if not done previously. The FDA has also authorized the use of pembrolizumab in TMB-high tumors (>10 mutations/megabase [mut/Mb]). For TMB-H tumors, the panel recommends TMB-H testing if not previously done and has included pembrolizumab as a category 1 option for patients with unresectable or metastatic tumors with TMB-H (>10 mut/Mb), as determined by a validated and/or FDA-approved test, who have progressed after prior treatment and who have no satisfactory alternative treatment options.

Further studies have indicated that pembrolizumab monotherapy is less active in patients with MSI-stable or MMR-proficient (pMMR) disease versus MSI-H/dMMR disease. Only 16% to 31% of endometrial cancers are MSI-H/dMMR.

The Keynote-146 phase I/II trial showed that the combination of pembrolizumab/lenvatinib had a promising antitumor response in patients with advanced endometrial cancer regardless of their tumor MSI status. The Keynote-775 phase III trial randomly assigned 827 patients with pMMR (MSI-stable) advanced endometrial cancer to receive pembrolizumab/lenvatinib combination or chemotherapy (doxorubicin or paclitaxel). The median PFS for the pembrolizumab/lenvatinib arm was 7.2 versus 3.8 months for the chemotherapy arm (HR, 0.56; 95% CI, 0.47–0.66; P<.001). The median OS was also longer for the pembrolizumab/lenvatinib arm than for the chemotherapy arm (18.3 vs 11.4 months; HR, 0.62; 95% CI, 0.51–0.75; P<.001). Based on these data, the NCCN Guidelines in Endometrial Carcinoma include lenvatinib/pembrolizumab as a category 1 option for pMMR tumors for patients who have received prior platinum-based therapy.

Other anti-PD-1 inhibitors, such as dostarlimab and nivolumab, have also shown antitumor activity against MSI-H tumors. Dostarlimab is being evaluated in the ongoing GARNET phase I trial for patients with advanced endometrial cancer with dMMR/MSI-H disease. The ORR after 16.3 months was 43.5% with manageable safety profile. Dostarlimab is approved as monotherapy for the treatment of patients with recurrent or advanced dMMR/MSI-H endometrial cancer that has progressed on or after prior treatment with a platinum-containing regimen. Nivolumab monotherapy has also shown promising activity in endometrial carcinoma with dMMR tumors. The PD-L1 inhibitor, avelumab, have shown an ORR of 26.7% in advanced endometrial cancer with dMMR tumor as monotherapy. Dostarlimab, nivolumab, and avelumab are included as biomarker-directed options for recurrent dMMR/MSI-H endometrial tumors for those patients who have received prior systemic therapy. The NCCN panel also recommends larotrectinib or entrectinib for NTRK gene fusion-positive, recurrent/advanced endometrial tumors as a category 2B option.

The systemic therapy options for high-risk histologies recommended in the NCCN Guidelines include carboplatin/paclitaxel as a preferred, category 1 option for patients with carcinosarcoma histology. A randomized phase II study examined the addition of trastuzumab to
carboplatin/paclitaxel for patients with advanced or recurrent HER2/neu-positive uterine serous carcinoma.\textsuperscript{297} Among patients with stage I/III disease undergoing primary treatment (n = 41), median PFS was 17.9 versus 9.3 months for the experimental and control arms, respectively (P = .013). PFS for patients with recurrent disease (n = 17) was 9.2 versus 6.0 months (P = .003). The addition of trastuzumab appeared to improve PFS without increasing overall toxicity. The safety and tolerability of the trastuzumab combination was further evaluated in 61 patients in a recent phase II trial with PFS as the primary endpoint.\textsuperscript{308} The triplet therapy regimen carboplatin/paclitaxel/trastuzumab is recommended by the NCCN panel as a preferred option for HER2-positive uterine serous carcinoma or HER2-positive carcinosarcoma as: (1) primary therapy for stage I/III/IV disease; or (2) a first-line option for recurrent disease. The NCCN panel has designated the regimen a category 2B option for HER2-positive carcinosarcoma in both disease settings. This triplet regimen is recommended for patients who have not received any prior trastuzumab therapy. In second-line/subsequent therapy, the NCCN panel has included ifosfamide, ifosfamide/paclitaxel, and ifosfamide/cisplatin as options for carcinosarcoma only. For treating carcinosarcoma, ifosfamide was historically considered the most active single agent.\textsuperscript{299,300} A phase III trial for advanced carcinosarcoma showed that the combination of ifosfamide and paclitaxel increased survival and was less toxic than the previously used cisplatin/ifosfamide regimen.\textsuperscript{309,310} OS was 13.5 months with ifosfamide/paclitaxel versus 8.4 months with ifosfamide alone.\textsuperscript{299,302}

**Summary**

The management of endometrial cancer involves a multimodality treatment comprised of surgery and/or systemic therapy and radiotherapy depending on the histopathologic assessment of the tumor, and clinical presentation. The prognosis of the disease is mainly assessed by histopathologic characteristics including the grade, type, LVS1, and myometrial invasion. The NCCN Guidelines for Endometrial Cancer also include recommendations for molecular characterization of the tumor and encourages comprehensive genomic profiling, if feasible. The surgical staging of the disease impacts the prognosis and guides adjuvant treatment decisions, and is an integral part of management of the disease. Although surgery and/or radiotherapy is typically the standard procedure to treat early-stage endometrial cancer, more advanced stages or high-risk histologies of endometrial cancer are managed by a combination of radiotherapy and systemic therapy. The appropriate therapy also takes into account the clinical situation with consideration of the patient’s goals of care, especially in more advanced stages.

**References**


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## Individual Disclosures for the NCCN Uterine Neoplasms Panel

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The NCCN Guidelines Staff have no conflicts to disclose.

*The following individuals have disclosures relating to employment/governing board, patent, equity, or royalty:
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