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Uterine Neoplasms, Version 1.2018

Clinical Practice Guidelines in Oncology

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Abstract

Endometrial carcinoma is a malignant epithelial tumor that forms in the inner lining, or endometrium, of the uterus. Endometrial carcinoma is the most common gynecologic malignancy. Approximately two-thirds of endometrial carcinoma cases are diagnosed with disease confined to the uterus. The complete NCCN Guidelines for Uterine Neoplasms provide recommendations for the diagnosis, evaluation, and treatment of endometrial cancer and uterine sarcoma. This manuscript discusses guiding principles for the diagnosis, staging, and treatment of early-stage endometrial carcinoma as well as evidence for these recommendations.

J Natl Compr Canc Netw 2018;16(2):170–199
doi: 10.6004/jnccn.2018.0006

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 for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview of Uterine Neoplasms

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 61,380 new uterine cancer cases will occur in 2017, with 10,920 deaths resulting from the disease.[1] Stromal or mesenchymal sarcomas are uncommon subtypes account-

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Uterine Neoplasms are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.**

Disclosures for the NCCN Uterine Neoplasms Panel

At the beginning of each NCCN Guidelines 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 199. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

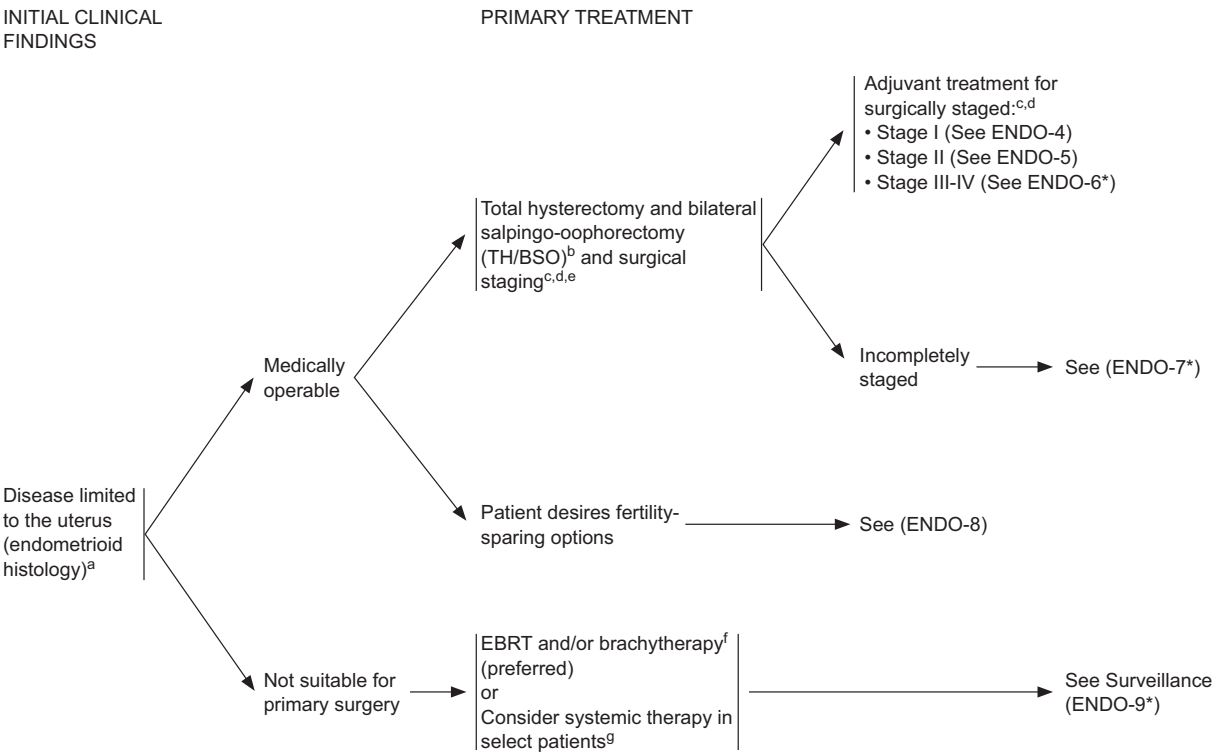
These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

ing for approximately 3% of all uterine cancers.[2,3] The NCCN Guidelines for Uterine Neoplasms describe malignant epithelial tumors and uterine sarcomas; each of these major categories contains specific histologic groups that require different management (see "Initial Clinical Findings" in the NCCN Guidelines for Uterine Neoplasms, available at NCCN.org).

Risk factors for uterine neoplasms include increased levels of estrogen (caused by obesity, diabetes, and high-fat diet), early age at menarche, nulliparity, late age at menopause, Lynch syndrome, older age (≥55 years), and tamoxifen use.[4–7] Thus, the incidence of endometrial cancer is increasing because of increased life expectancy and obesity. The "Summary of the Guidelines Updates" (available at NCCN.org) describes the most recent revisions to the algorithms, which have been incorporated into this revised Discussion text (see the NCCN Guidelines for Uterine Neoplasms). By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the NCCN panel during the process of developing these guidelines.

NOTE: This manuscript highlights only a portion of the NCCN Guidelines on Uterine Neoplasms. The guidelines appearing in this issue of *JNCCN* discuss important general principles and evidence for diagnosis, staging, and primary/adjuvant treatment of early-stage endometrial carcinoma. Please refer to the complete guidelines online at NCCN.org for recommendations for post-treatment surveillance of early-stage disease, in addition to diagnosis and management of

Text cont. on page 184.



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

[a]See UN-1* for clarification of uterine neoplasms.

[b]See Hysterectomy and Pathologic Evaluation (ENDO-B).

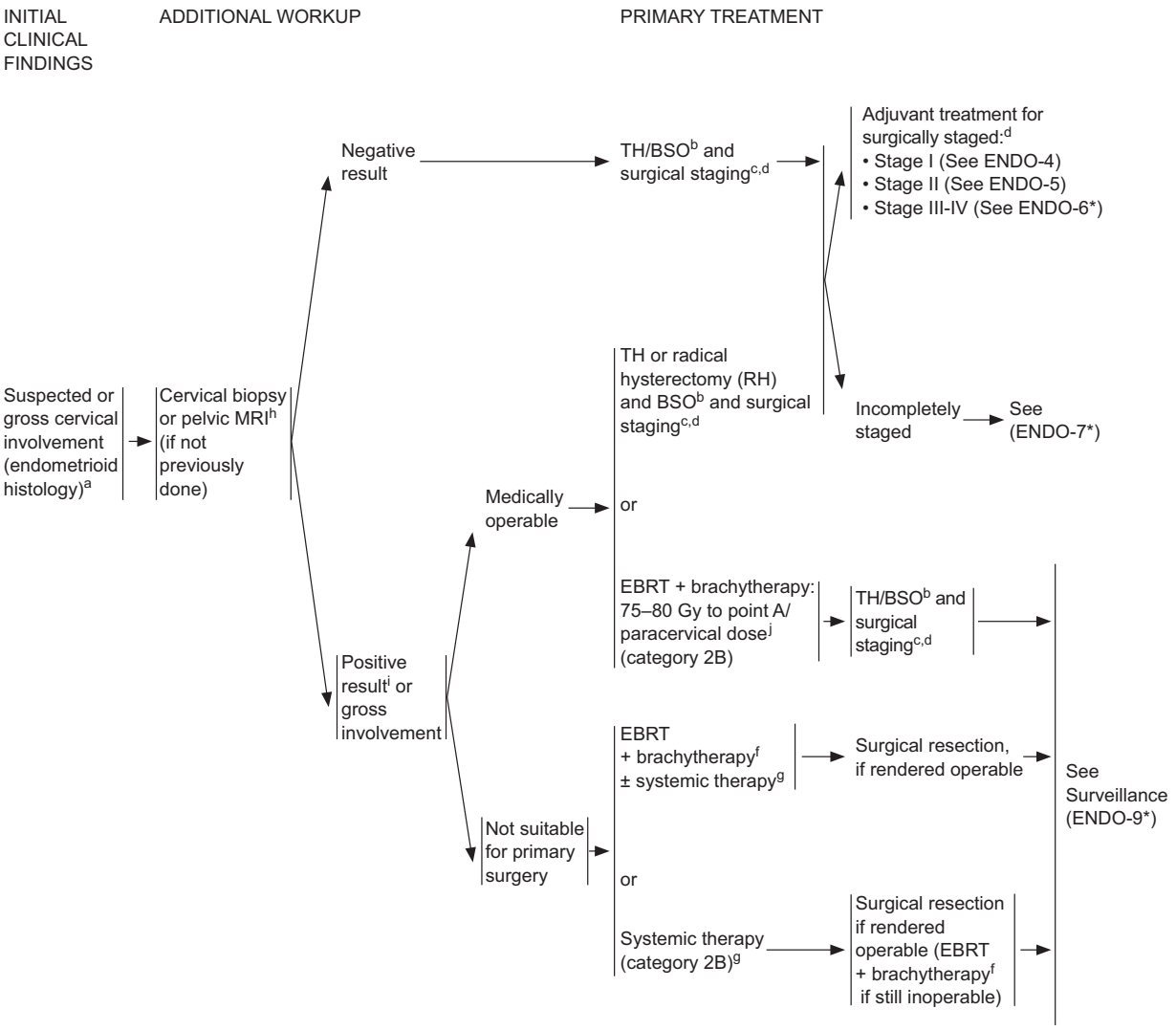
[c]Minimally invasive surgery (MIS) is the preferred approach when technically feasible. See Principles of Evaluation and Surgical Staging (ENDO-C).

[d]The degree of surgical staging to assess disease status depends on preoperative and intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).

[e]Ovarian preservation may be safe in select premenopausal women with early-stage endometrioid cancer.

[f]See Principles of Radiation Therapy for Uterine Neoplasms (UN-A*).

[g]See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-D).



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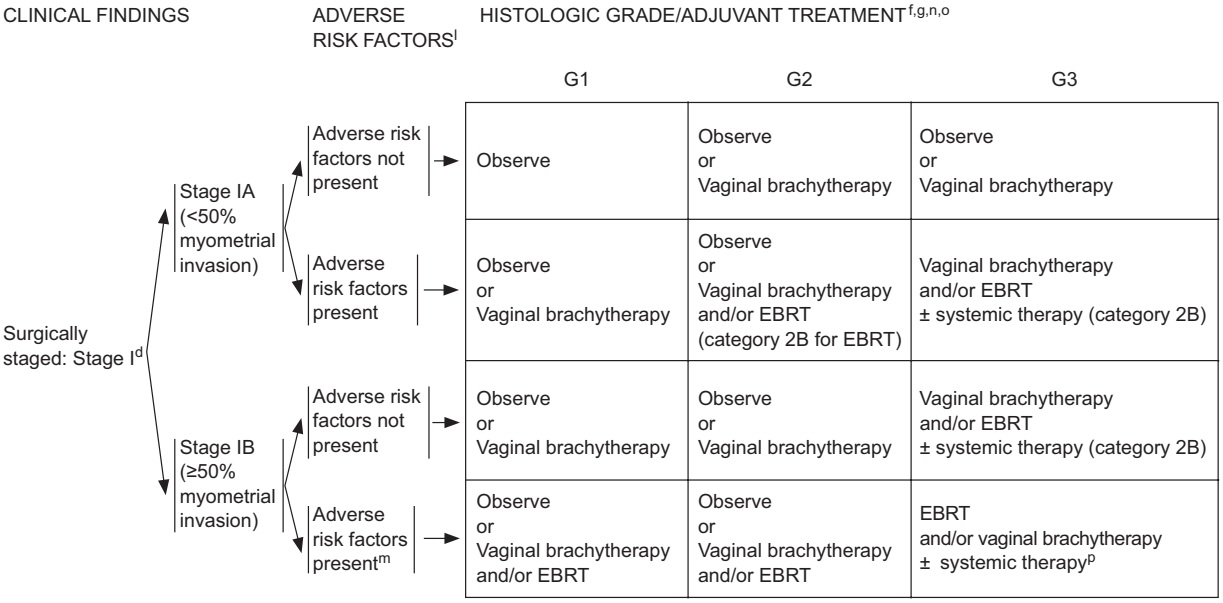
[g]See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-D).

[h]See Principles of Imaging for Endometrial Carcinoma (ENDO-A*).

[i]Clear demonstration of cervical stromal involvement.

[j]Based on summation of conventional external-beam fractionation and low-dose-rate brachytherapy equivalent.

All staging in guideline is based on updated 2010 FIGO staging. (See ST-1*)



See Surveillance (ENDO-9*)

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

[d]The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).

[f]See Principles of Radiation Therapy for Uterine Neoplasms (UN-A*).

[g]See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-D).

[l]Potential adverse risk factors include the following: age, positive lymphovascular invasion, tumor size, and lower uterine segment or surface cervical glandular involvement. See Discussion for additional information on adverse risk factors.

[m]Consider additional imaging if not previously done. See Principles of Imaging for Endometrial Carcinoma (ENDO-A*).

[n]Adjuvant therapy determinations are made on the basis of pathologic findings.

[o]Initiate EBRT as soon as the vaginal cuff is healed, preferably no later than 12 weeks after surgery.

[p]The role of adjuvant chemotherapy in invasive, high-grade, uterine-confined disease is the subject of current studies. Hormonal therapy is not used for high-grade disease.

All staging in guideline is based on updated 2010 FIGO staging. (See ST-1*)

CLINICAL FINDINGS	HISTOLOGIC GRADE/ADJUVANT TREATMENT[f,g,n,o]		
	G1	G2	G3
Surgically staged:[d] Stage II[m,q,r] →	Vaginal brachytherapy and/or EBRT	Vaginal brachytherapy and/or EBRT	EBRT ± vaginal brachytherapy ± systemic therapy[p] (category 2B for systemic therapy)

See Surveillance (ENDO-9*)

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

[d]The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).

[f]See Principles of Radiation Therapy for Uterine Neoplasms (UN-A*).

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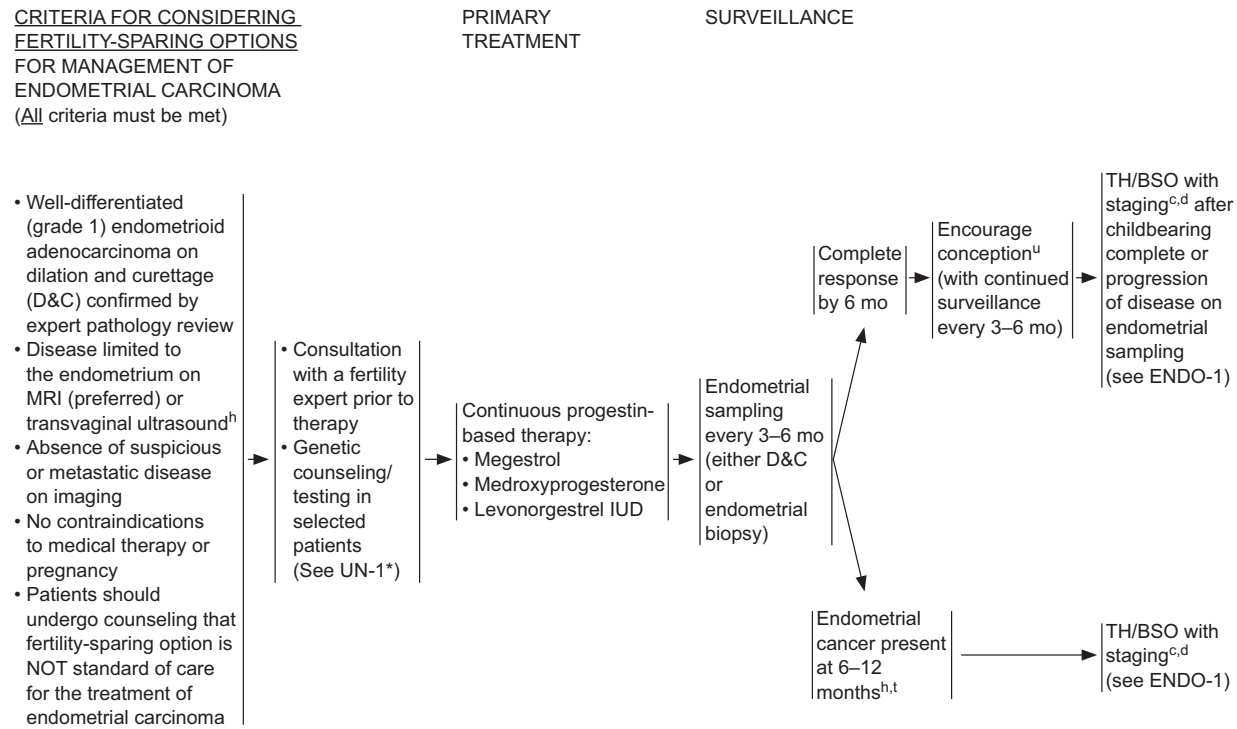
[n]Adjuvant therapy determinations are made on the basis of pathologic findings.

[o]Initiate EBRT as soon as the vaginal cuff is healed, no later than 12 weeks after surgery.

[p]The role of adjuvant chemotherapy in invasive high-grade uterine confined disease is the subject of current studies. Hormonal therapy is not used for high-grade disease.

[q]Observation or vaginal brachytherapy is also an option for patients with stage II disease who have had a radical hysterectomy with negative surgical margins and no evidence of extrauterine disease.

[r]The adverse fundal risk factors influencing therapy decisions for stage I disease (see ENDO-4) such as depth of myometrial invasion and LVSI may also impact the choice of adjuvant therapy for stage II disease.



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[h]See Principles of Imaging for Endometrial Carcinoma (ENDO-A*).

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[u]Endometrial sampling every 3 to 6 months and progestin-based therapy are recommended if patient is not in the active process of trying to conceive.

HYSTERECTOMY AND PATHOLOGIC EVALUATION[1,2]

TH/BSO: Total hysterectomy + bilateral salpingo-oophorectomy
RH: Radical hysterectomy

Pathologic assessment to include:

- Uterus
  - Ratio of depth of myometrial/stromal invasion to myometrial thickness
  - Cervical involvement (including depth of stromal invasion)
  - Tumor size
  - Tumor location (fundus vs. lower uterine segment/cervix)
  - Histologic subtype with grade
  - Lymphovascular space invasion
- Fallopian tubes/ovaries
- Peritoneal cytology[3]
- Nodes (when resected)
  - Level of nodal involvement (ie, pelvic, common iliac, para-aortic)
  - Size of metastasis (isolated tumor cells, micrometastasis, macrometastasis)
- Universal testing of endometrial carcinomas for MMR gene
  - Testing should be done on the final hysterectomy specimen (can be done on presurgical biopsy if hysterectomy not performed)
  - MLH1 loss should be further evaluated for promoter methylation to assess epigenetic process.
  - Genetic counseling and testing for all other MMR abnormalities
  - For those who are dMMR-negative or those who have not been screened, but who have strong family history of endometrial and/or colorectal cancer, genetic counseling and testing for patients is recommended. (See Lynch syndrome/HNPCC in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, available at NCCN.org)
- Estrogen receptor testing in setting of stage III, IV and recurrent disease

[1]American College of Obstetricians and Gynecologists practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstet Gynecol 2005;106:413-425.

[2]See Principles of Evaluation and Surgical Staging (ENDO-C).

[3]Although cytology by itself does not affect FIGO staging, cytology results should still be obtained because positive cytology is an adverse risk factor.

PRINCIPLES OF EVALUATION AND SURGICAL STAGING

Principles of Surgical Staging for Endometrial Cancer[1-15]

- TH/BSO, and lymph node assessment is the primary treatment of apparent uterine-confined endometrial carcinoma, unless patients desire (and are candidates for) fertility-sparing options (See ENDO-8).[1-3] Select patients with metastatic endometrial carcinoma are also candidates for hysterectomy. (See Hysterectomy and Pathologic Evaluation [ENDO-B])
- Endometrial carcinoma should be removed en bloc to optimize outcomes; intraperitoneal morcellation or tumor fragmentation should be avoided.
- TH/BSO and lymph node assessment may be performed by any surgical route (eg, laparoscopic, robotic, vaginal, abdominal), although 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 this setting 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.[4-9]
- The lymph node assessment includes evaluation of the nodal basins that drain the uterus, and often comprises a pelvic nodal dissection with or without aortic nodal dissection. This continues to be an important aspect of surgical staging in women with uterine-confined endometrial carcinoma, as the procedure provides important prognostic information that may alter treatment decisions.
- Pelvic lymph nodes from the external iliac, internal iliac, obturator, and common iliac nodes are frequently removed for staging purposes.
- Para-aortic nodal evaluation from the inframesenteric and infrarenal regions may also be utilized for staging in women with high-risk tumors such as deeply invasive lesions, high-grade histology, and tumors of serous carcinoma, clear cell carcinoma, or carcinosarcoma.
- Sentinel lymph node (SLN) mapping may be considered. (See pages 2–5 of ENDO-C)[15]
- Excision of suspicious or enlarged lymph nodes in the pelvic or aortic regions is important to exclude nodal metastasis.
- Some patients may not be candidates for lymph node dissection.
- Visual evaluation of the peritoneal, diaphragmatic, and serosal surfaces with biopsy of any suspicious lesions is important to exclude extrauterine disease.
- While peritoneal cytology does not impact staging, FIGO and AJCC nonetheless recommend that surgeons continue to obtain this during the TH/BSO.
- Omental biopsy is commonly performed in those with serous carcinoma, clear cell carcinoma, or carcinosarcoma histologies.

PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Principles of Sentinel Lymph Node (SLN) Mapping for Endometrial Cancer Staging[10-26]

- The role of SLN mapping in endometrial carcinoma is under evaluation. Prospective and retrospective studies demonstrate that compared to systemic lymphadenectomy, SLN mapping with ultrastaging may increase the detection of lymph node metastasis with low false-negative rates in women with apparent uterine-confined disease.[10-23,26] To date, no randomized trials evaluating this technique in endometrial carcinoma have been conducted. If SLN mapping is considered, the expertise of the surgeon and attention to technical detail is critical. Recent evidence indicate that sentinel node mapping may also be used in high-risk histologies (serous carcinoma, clear cell carcinoma, carcinosarcoma).[24,25]
- SLN mapping can be considered for the surgical staging of apparent uterine-confined malignancy when there is no metastasis demonstrated by imaging studies or no obvious extrauterine disease at exploration.
- A cervical injection with dye 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[10-12]).
- The combination of a superficial (1–3 mm) and 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 (Figure 1 on ENDO-C 3 of 5).
- Injection into the uterine cervix provides excellent dye penetration to the region of the uterine vessels and main uterine lymphatic trunks that condense in the parametria and appear in the broad ligament leading to pelvic and occasionally paraaortic 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 (Figure 2 on ENDO-C 3 of 5).
- 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 (Figure 3 on ENDO-C 3 of 5).
- 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% and Methylene Blue 1%, Patent Blue 2.5% sodium).
- Indocyanine green (ICG) recently emerged as a useful imaging dye that requires near-infrared camera for localization, provides a very high SLN detection rate, and is commonly used in many practices at the present time.[20,26]
- Low-volume nodal metastasis to SLN detected only by enhanced pathologic ultrastaging is another potential value to staging with SLN.[10,21-23]
- Key points to a successful SLN mapping is the adherence to the SLN algorithm, which requires the performance of a side-specific nodal dissection in cases of failed mapping and removal of any suspicious or grossly enlarged nodes regardless of mapping (Figure 4 on ENDO-C 4 of 5).[10-12,23,25]

PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Figure 1: Common cervical injection sites for mapping uterine cancer†

Figure 2: Most common location of SLNs (blue, arrow) following a cervical injection†

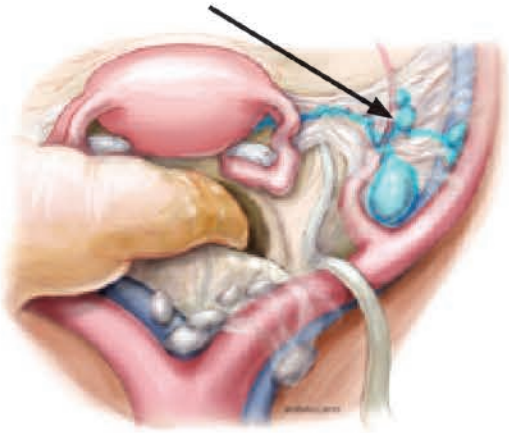
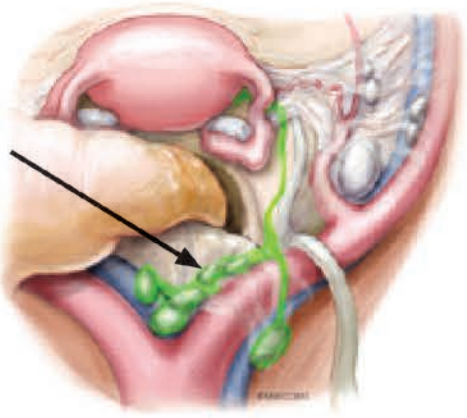


Figure 3: Less common location of SLNs (green, arrow) usually seen when lymphatic trunks are not crossing over the umbilical ligament but following the mesoureter cephalad to common iliac and presacral region†



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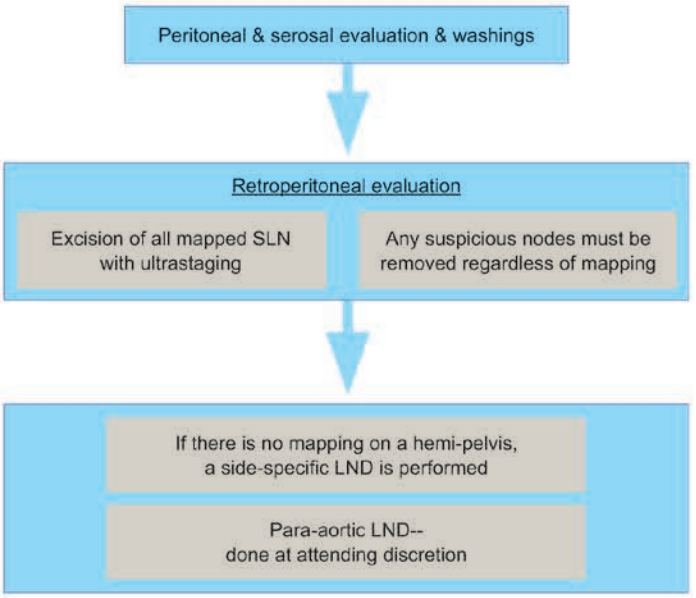
PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Figure 4: The SLN algorithm for surgical staging of endometrial cancer*



*Reproduced with permission from Barlin JN, Khoury-Collado F, Kim CH, et al. The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: Beyond removal of blue nodes. Gynecol Oncol 2012;125:531-535.

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PRINCIPLES OF EVALUATION AND SURGICAL STAGING
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SYSTEMIC THERAPY FOR RECURRENT, METASTATIC, OR HIGH-RISK DISEASE (STRONGLY ENCOURAGE PARTICIPATION IN CLINICAL TRIALS)

CHEMOTHERAPY REGIMENS*,**

- Multi-agent chemotherapy regimens (preferred, if tolerated)
  - Carboplatin/paclitaxel[1]
  - Cisplatin/doxorubicin[2]
  - Cisplatin/doxorubicin/paclitaxel[2,†]
  - Carboplatin/docetaxel[††]
  - Ifosfamide/paclitaxel (category 1 for carcinosarcoma)[3]
  - Cisplatin/ifosfamide (for carcinosarcoma)
  - Everolimus/letrozole (for endometrioid histology)
- Single agents
  - Cisplatin
  - Carboplatin
  - Doxorubicin
  - Liposomal doxorubicin
  - Paclitaxel[4]
  - Albumin-bound paclitaxel^
  - Pembrolizumab^^ (for MSI-H/dMMR tumors)
  - Topotecan
  - Bevacizumab[5,#]
  - Temsirolimus[6]
  - Docetaxel[††](category 2B)
  - Ifosfamide (for carcinosarcoma)

ADJUVANT TREATMENT FOR UTERINE-CONFINED DISEASE

- Carboplatin/paclitaxel (preferred)

HORMONE THERAPY[##]

- Megestrol/tamoxifen (alternating)
- Progestational agents
- Aromatase inhibitors
- Tamoxifen
- Fulvestrant

*Cisplatin, carboplatin, liposomal doxorubicin, paclitaxel, and docetaxel may cause drug reactions. (See NCCN Guidelines for Ovarian Cancer—Management of Drug Reactions [OV-C], available at NCCN.org)

**Chemotherapy regimens can be used for all carcinoma histologies. Carcinosarcomas are now considered and treated as high-grade carcinomas. However, ifosfamide-based regimens were previously used for carcinosarcomas.

†The cisplatin/doxorubicin/paclitaxel regimen is not widely used because of concerns about toxicity.

††Docetaxel may be considered for patients in whom paclitaxel is contraindicated.

^Albumin-bound paclitaxel is a reasonable substitute for patients with a hypersensitivity to paclitaxel if the skin testing to paclitaxel is negative. If the patient has a positive skin test to paclitaxel then the patient requires desensitization to paclitaxel. Albumin-bound paclitaxel is not a reasonable substitute for paclitaxel if the patient's skin test is positive.

^^For recurrent endometrial cancer, NCCN recommends MSI-H or dMMR testing if not previously done. Pembrolizumab is indicated for patients with MSI-H or dMMR tumors that have progressed following prior cytotoxic chemotherapy.

#Bevacizumab may be considered for use in patients who have progressed on prior cytotoxic chemotherapy.

##Hormonal therapy may be used for lower-grade endometrioid histologies only (ie, not for G3 endometrioid, serous carcinoma, clear cell carcinoma, or carcinosarcoma) preferably in patients with small tumor volume or an indolent growth pace.

SYSTEMIC THERAPY FOR RECURRENT, METASTATIC, OR HIGH-RISK DISEASE (References)

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Cont. from page 171.

advanced, metastatic, or recurrent endometrial carcinoma and uterine sarcoma.

Endometrial Cancer

In 2017, 67% of patients with adenocarcinoma of the endometrium were diagnosed with disease confined to the uterus at diagnosis.[1] Regional and distant disease comprised 21% and 8% of cases, respectively. Many physicians believe that adenocarcinoma of the endometrium is a more treatable malignancy because the early symptoms of irregular vaginal bleeding (in this predominantly postmenopausal patient population) 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 older age.

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 status, tumor size, lymphovascular space invasion (LVSI), and tumor involvement of the lower uterine segment.[10,11] To further improve outcome for patients with this disease, physicians need to identify high-risk patients and to tailor treatment appropriately to provide the best long-term survival. The panel suggests that gynecologic oncologists be involved in the primary management of all patients with endometrial cancer.

Genetic Factors

Most endometrial cancer is caused by sporadic mutations. However, hereditary genetic mutations cause endometrial cancer in about 5% of patients, which occurs 10 to 20 years before sporadic cancer.[12] Screening of the tumor for defective DNA mismatch repair (MMR) using immunohistochemistry and/or microsatellite instability (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).[12–18] Universal testing of endometrial tumors for defects in DNA MMR is recommended (eg, *MLH1*, *MSH2*, *MSH6*). *MLH1* loss should be further evaluated for promoter methylation to assess for an epigenetic process rather than a germline mutation.[16] Genetic counseling and testing is recommended for patients with all other MMR abnormalities and for patients without MMR defects but who have a significant family history of endometrial and/or colorectal cancer (See "Lynch Syndrome [Hereditary Non-Polyposis Colorectal Cancer]" in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal).

Women with Lynch syndrome are at a higher lifetime risk (up to 60%) for endometrial cancer; thus, close monitoring and discussion of risk-reducing strategies is recommended.[13,19,20] In relatives with Lynch syndrome but without endometrial cancer, a yearly endometrial biopsy is recommended to assess for cancer.[21,22] This strategy also enables select women to defer surgery (and surgical menopause) and to preserve fertility. Prophylactic hysterectomy/bilateral salpingo-oophorectomy (BSO) can then be done after childbearing is complete or sooner, depending on patient preference.[23,24] In addition, interventions to decrease the risk from colorectal cancer may also be appropriate (eg, annual colonoscopy).

Diagnosis and Workup

About 90% of patients with endometrial carcinoma have abnormal vaginal bleeding, most commonly in the postmenopausal period. Diagnosis can usually be made via an office endometrial biopsy.[25,26] The histologic information from the endometrial biopsy (with or without endocervical curettage) should be sufficient for planning definitive treatment. Office endometrial biopsies have a false-negative rate of about 10%. Thus, a negative endometrial biopsy in a symptomatic patient must be followed by a fractional dilation and curettage (D&C) under anesthesia.[25,27] Hysteroscopy may be helpful in evaluating the endometrium for lesions, such as a polyp, if the patient has persistent or recurrent undiagnosed bleeding.[28] Endometrial biopsy may not be accurate for diagnosing malignancies of the uterine wall such as mesenchymal tumors.

For detailed imaging recommendations by stage and planned treatment approach, see "Principles of Imaging" in the full NCCN Guidelines for Uterine Neoplasms at (available NCCN.org). Consideration of chest imaging (chest x-ray) is recommended. Oth-

er imaging tests such as CT, MRI, and/or PET/CT may be used to assess disease extent and to evaluate for metastatic disease as indicated based on clinical symptoms, physical findings, or abnormal laboratory findings.[29–34] In patients with extrauterine disease, a serum CA-125 assay may be helpful in monitoring clinical response.[35,36] However, serum CA-125 levels can be falsely increased in women who have peritoneal inflammation/infection or radiation injury, may be normal in women with isolated vaginal metastases, and may not predict recurrence in the absence of other clinical findings.[37–39] Currently, no validated screening test is available for endometrial carcinoma.[40,41]

Disease Staging

The FIGO (International Federation of Gynecology and Obstetrics) system is most commonly used for staging uterine cancer. The original 1970 criteria for staging endometrial cancer only used information gained from presurgical evaluation (including physical examination and diagnostic fractional D&C). At that time, many patients were not treated with primary surgery because of obesity or various other medical problems. Thus, the 1970 staging system is rarely used today (eg, when the patient is not a surgical candidate).

Several studies showed that clinical staging was inaccurate and did not reflect actual disease extent in 15% to 20% of patients.[42–44] 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 extrauterine spread (including retroperitoneal lymph node metastases).[45] FIGO updated and refined the surgical/pathologic staging criteria for uterine neoplasms in 2009.[46–49] Separate staging systems for malignant epithelial tumors and uterine sarcomas are now available (see the staging section of the algorithm). In 2017, the AJCC Cancer Staging Manual was updated (to take effect January 2018).[50]

The 2009 FIGO staging system streamlined stages I and II endometrial carcinoma. These revisions were made because the survival rates for some of the previous sub-stages were similar.[48] Stage IA is now less than 50% myometrial invasion, and stage IB is 50% or more myometrial invasion. Stage II only includes patients with cervical stromal invasion. Patients with uterine-confined disease and endocervical glandular involvement (mucosal involvement) without cervical stromal invasion are no longer considered stage II.[48] Stage IIIC is now subdivided into IIIC1 and IIIC2, because survival is worse with positive para-aortic nodes.[48] Although most of the previously published studies discussed in these NCCN Guidelines used the older 1988 FIGO staging system, these have been reinterpreted by the NCCN panel to reconcile with the 2009 staging system.

Peritoneal cytology no longer affects the 2009 FIGO staging, because it is not viewed by some authors as an independent risk factor.[49] However, FIGO and AJCC continue to recommend that peritoneal washings be obtained and results recorded, because positive cytology may add to the effect of other risk factors (see "Principles of Evaluation and Surgical Staging" on page 178 [ENDO-C]).[51,52]

Principles of Evaluation and Surgical Staging for Endometrial Carcinoma

Staging should be done by a team with expertise in imaging, pathology, and surgery. The amount of surgical staging that is necessary to determine disease status depends on preoperative and intraoperative assessment of findings by experienced surgeons. For the 2014 update, the NCCN panel added a new section on surgical staging (see "Principles of Evaluation and Surgical Staging" on page 178 [ENDO-C]). However, this surgical staging section only applies to malignant epithelial tumors and not to uterine sarcomas. Surgical staging with nodal assessment for apparent uterine-confined endometrial cancer is critical to accurately determine the initial FIGO stage. The NCCN sentinel lymph node (SLN) algorithm is recommended if sentinel node mapping is utilized.

Pathology: An expert pathology review will determine the specific epithelial histology of the tumor (ie, various endometrioid histologies, serous carcinoma, clear cell carcinoma, carcinosarcoma, undifferentiated carcinoma). The pathologic assessment of the uterus and the nodes is described in the algorithm; this assessment should also include the Fallopian tubes, ovaries, and peritoneal cytology. If nodal resection was performed, the level of nodal involve-

ment and size of metastasis should be determined. See "Hysterectomy and Pathologic Evaluation" in the algorithm (page 177 [ENDO-B]). The *Protocol for Examination of Specimens from Patients With Carcinoma of the Endometrium* from the College of American Pathologists (CAP) is a useful guide (http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2013/Endometrium_13protocol_3200.pdf). This CAP protocol was revised in October 2013 and reflects the updated FIGO/AJCC 2009 staging (ie, AJCC Cancer Staging Manual, 7th edition). Estrogen receptor testing is recommended in the setting of stage III, IV, or recurrent endometrioid carcinoma.

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.[53] Studies show that in 15% to 20% of cases, the preoperative grade (as assessed by endometrial biopsy or curettage) is upgraded on final fixed pathologic evaluation of the hysterectomy specimen.[54]

Lymphadenectomy: Previously, a full standard lymphadenectomy (ie, dissection and assessment of both pelvic and para-aortic nodes) was recommended for all patients; however, a more selective and tailored lymphadenectomy approach that may include the SLN algorithm is now recommended by the NCCN Panel to avoid systematic overtreatment.[55] No randomized trial data support routine full lymphadenectomy,[56] although some retrospective studies have suggested that it is beneficial.[57–59] Two randomized clinical trials from Europe reported that routine lymph node dissection did not improve the outcome of endometrial cancer patients, but lymphadenectomy did identify those with nodal disease.[60,61] However, these findings remain a point of contention.[62–64] 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.[65,66] 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) less than 50% myometrial invasion; 2) tumor less than 2 cm; and 3) well or moderately differentiated histology.[67,68] However, this may be difficult to accurately determine before final pathology results are available.

Another associated benefit of lymphadenectomy is the diagnosis of those with nodal metastases to guide appropriate adjuvant treatment to improve survival or decrease toxicity. However, one of the trials was not designed to address this question.[61] Therefore, there was no standardization of adjuvant treatment after staging surgery with lymphadenectomy. In fact, the use of lymphadenectomy did not translate into an increased use of adjuvant therapy. This may have contributed to the lack of difference in recurrence and survival in the two groups.

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.[44,67,69,70] There was a high rate of lymphatic metastasis above the inferior mesenteric artery, suggesting a need for systematic pelvic and para-aortic lymphadenectomy. Hence, para-aortic lymphadenectomy up to the renal vessels may be considered for selective high-risk situations, 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.[55]

In summary, lymph node dissection identifies patients requiring adjuvant treatment with radiation therapy (RT) and/or systemic therapy.[71] A subset of patients may not benefit from lymphadenectomy; however, it is difficult to preoperatively identify these patients because of the uncontrollable variables of change in grade and depth of invasion on final pathology. The NCCN Panel recommends that lymphadenectomy should be done for selected patients with endometrial cancer with para-aortic lymphadenectomy done as indicated for patients at high risk (see "Principles of Evaluation and Surgical Staging" on page 178 [ENDO-C]).[6] Lymphadenectomy is contraindicated for patients with uterine sarcoma. SLN mapping can be considered as an alternative to full lymphadenectomy in the setting of

apparent uterine-confined disease. The SLN surgical algorithm is described in the next section.

SLN Mapping: The section on surgical staging (see "Principles of Evaluation and Surgical Staging," page 178 [ENDO-C]) includes recommendations about SLN mapping. SLN mapping may be considered for patients with apparent uterine-confined endometrial cancer to assess whether they have metastatic pelvic lymph nodes.[72–76] In SLN mapping, dye is injected into the cervix, which travels to the sentinel nodes (see Figures 1–3 in "Principles of Evaluation and Surgical Staging," page 180).

A surgical SLN algorithm is proposed to decrease the false-negative rate (see Figure 4 in "Principles of Evaluation and Surgical Staging," page 181).[72,77] 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.[78,79] Because SLNs identify the primary lymphatic pathway, this increases the yield of finding metastatic disease during the mapping process. If SLN mapping fails, a reflex side-specific nodal dissection should be performed.[72,80] 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.[76,79–85] Recent findings also suggest that indocyanine green may be preferable to blue dyes.[85–89] Attention to detail and experience are critical to ensure optimal outcomes.

An updated literature review and consensus recommendations for SLN mapping in endometrial cancer were recently released by the Society of Gynecologic Oncology (SGO).[76] Close adherence to the NCCN SLN surgical algorithm was found to result in accurate prediction of pelvic lymph node metastasis with a less than 5% false-negative rate. Additionally, results were recently published from the FIRES trial, which compared SLN mapping to lymphadenectomy for endometrial cancer in the largest multicenter prospective study to date (n=385).[85] Mapping of at least 1 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).

Until recently, much of the data to support SLN mapping wasbased on single-institution studies. A systematic review of 17 studies with small cohorts (n>30 patients) revealed detection rates of 60% to 100%; detection rates for studies with larger cohorts (n>100) were at least 80%. Retrospective application of a surgical algorithm generated 95% sensitivity, 99% predictive value, and a 5% false-negative rate.[90] Another recent systematic review and meta-analysis of 55 studies with small cohorts (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.[89]

SLN mapping should be done in institutions with expertise in this procedure. If patients have apparent metastatic disease (based on imaging and surgical exploration), removal of nodes for staging purposes is not necessary because it will not change management.[29] The main contraindication for SLN mapping is uterine sarcoma. Historically, SLN mapping was controversial in patients with high-risk histology (eg, serous carcinoma, clear cell carcinoma, carcinosarcoma).[55,91] However, recently, 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.[80,92]

SLN Ultrastaging: Recent data highlight the potential significance and impact of SLN ultrastaging (ie, serial sectioning and immunohistochemistry) to improve the accuracy of detecting micrometastases. Ultrastaging of SLNs can reveal lymph node metastases undetected through conventional histology, and studies suggest that SLN ultrastaging leads to upstaging in 5% to 15% of patients.[75,78,82,84,90]

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.[93] 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 radiation therapy (EBRT) and chemotherapy at a higher rate than those with a negative SLN. In patients with a detected SLN, recurrence-free survival at 50 months was 84.7%, and no difference was detected between patients with and without a positive SLN ($P=.5$).[94]

In a cohort of 508 patients who underwent SLN mapping, ultrastaging detected 23 additional cases of micrometastasis that would have been missed by conventional hematoxylin and eosin staining.[95] A multicenter study of 304 women 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.[96]

Although these findings do not appear to be an artifact of uterine manipulation,[97] the implications and appropriate management of micrometastases or isolated tumor cells (ITCs) detected via SLN ultrastaging are not yet clear.[76,78,84,98–100] The prognostic significance of ITCs has been studied in breast cancer,[101] in which nodes containing ITCs are excluded from the positive node count per AJCC staging. Studies have recently begun to investigate the significance of ITCs discovered during SLN mapping in early-stage endometrial cancer.

A retrospective review examined 844 patients with endometrial cancer who underwent SLN mapping.[102] Most patients with ITCs, micrometastasis, and macrometastasis received adjuvant chemotherapy (83%, 81%, and 89%, respectively). Recurrence-free survival 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 recurrence-free survival (71%; $P<.001$).

A recent prospective observational study of 519 patients compared outcomes for patients with SLN macrometastasis, micrometastasis, and ITCs, taking into account adjuvant treatment.[103] 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 towards minimally invasive approaches to total hysterectomy (TH)/BSO and lymph node assessment in patients with early-stage endometrial cancer.[104] Although these procedures may be performed via any surgical route (eg, laparoscopic, robotic, vaginal, abdominal), the standard in those with apparent uterine-confined disease is to perform the procedure using a minimally invasive approach. Randomized trials, a Cochrane Database Systematic Review, and population-based surgical studies support that minimally invasive techniques are preferred in this setting 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.[104–110] 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.[106,110]

A randomized phase III trial evaluated laparoscopy for comprehensive surgical staging; patients (n=2616) with clinical stage I to IIA disease (GOG-LAP2) were assessed.[109,111] 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; $P<.0001$).[112,113] 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.[111] Laparoscopic staging was associated with improved postoperative quality of life across several parameters.[108]

Results were recently published from the LACE trial, which compared outcomes of patients with stage I endometrial carcinoma (n=760) who were randomized to undergo total abdominal or total laparoscopic hysterectomy.[105] 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.[114] However, laparotomy may still be required for certain clinical situations (eg, elderly patients, those with a very large uterus) or certain metastatic presentations.[109,115,116]

Robotic surgery is a minimally invasive technology that has been increasingly used in the surgical staging of early-stage endometrial carcinoma due to its potential advantages over laparotomy, especially for obese patients.[117–121] Prospective cohort and retrospective studies suggest that robotic approaches perform similarly to laparoscopy and result in comparable or improved perioperative outcomes.[121–124] Oncologic outcomes appear to be comparable to other surgical approaches, although longer-term outcomes are still being investigated.[125–127] 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.[121,122,128]

Costs for robotic equipment and maintenance remain high.[117,118,125–127,129,130] The SGO, American Association of Gynecologic Laparoscopists (AAGL), and American Congress of Obstetricians and Gynecologists (ACOG) have published guidelines or position statements about robotic surgery.[131–133] For recent reviews on the robotic-assisted surgery for gynecologic malignancies and associated cost issues, see articles by Sinno and Fader[134] and Gala et al. [135]

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.[136–139]

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 TH/BSO with surgical staging and lymph node assessment (see "Hysterectomy and Pathologic Evaluation" on page 177 [ENDO-B], and "Principles of Evaluation and Surgical Staging" on page 178 [ENDO-C] and in this discussion [page 185]).[62] When indicated, surgical staging is recommended to gather full pathologic and prognostic data on which to base decisions regarding adjuvant treatment for select patients who do not have medical or technical contraindications to lymph node dissection (see "Lymphadenectomy," page 186 and "SLN Mapping," page 187). Ovarian preservation may be safe in select premenopausal women with stage I endometrioid cancer.[140–142] 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; www.facs.org/quality-programs/cancer/ncdb/qualitymeasures).

During surgery, the intraperitoneal structures should be carefully evaluated, and suspicious areas should be biopsied. Although not specifically affecting staging, FIGO recommends that peritoneal cytology should be collected and results should be recorded. 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 lymphadenectomy—is useful when using the 2009 FIGO staging criteria, but its routine use has been questioned (see "Lymphadenectomy" on page 186).

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 "SLN Mapping" on page 187). Adherence to the NCCN SLN algorithm is critical.

Incomplete Surgical Staging: For patients with incomplete (ie, not thorough) surgical staging and high-risk intrauterine features, imaging is often recommended, especially in patients with higher grade and more deeply invasive tumors.[143,144] Surgical restaging, including lymph node dissection, can also be done.[67] Based on the imaging and/or surgical restaging results, recommended adjuvant treatment options are provided in the algorithm (see Adjuvant Treatment for "Incompletely Surgically Staged" on ENDO-7, available in these Guidelines 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 IA (noninvasive) disease who wish to preserve their fertility.[145–149] 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" on page 176 [ENDO-8]). The panel recommends consultation with a fertility expert. When considering fertility-sparing therapy, all of the criteria must be met as outlined in the algorithm (eg, no metastatic disease). Selected patients may require genetic counseling and testing. 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 uterine leiomyosarcoma).

Continuous progestin-based therapy may include megestrol acetate, medroxyprogesterone, or an intrauterine device containing levonorgestrel.[145,146,150] A durable complete response occurs in about 50% of patients.[145] 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.

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 the biopsies; or 3) if endometrial cancer is still present after 6 to 12 months of progestin-based therapy.[149,151] Although some young women who had subsequent negative endometrial biopsies after hormonal therapy were able to become pregnant (35%), their ultimate recurrence rate was high (35%).[145,148,152–154] 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 on fertility-sparing therapy.

In premenopausal women with stage IA to B endometrial cancer, data suggest that ovarian preservation is safe and not associated with an increased risk of cancer-related mortality; patients were followed up for 16 years.[140] Other studies also suggest that ovarian preservation may be safe in women with early-stage endometrial cancer.[141,142]

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" on page 173 [ENDO-2]).[143,144] If negative, patients are assumed to have disease that is limited to the uterus and are treated as previously described (see "Primary Treatment" on page 172 [ENDO-1]). It may be difficult to distinguish primary cervical carcinoma from stage II endometrial carcinoma. Thus, for operable patients with cervical involvement, TH or radical hysterectomy is recommended along with BSO, cytology (peritoneal lavage), and dissection of lymph nodes if indicated (see "Principles of Evaluation and Surgical Staging," page 178 [ENDO-C] and "Hysterectomy and Pathologic Evaluation," page 177 [ENDO-B]).[62] In these patients, radical or modified radical hysterectomy may improve local control and survival when compared with TH.[155,156] Alternatively, the patient may undergo EBRT and brachytherapy (category 2B) followed by TH/BSO and surgical staging. However, preoperative RT is a category 2B recommendation because the NCCN panel feels that upfront surgery is the preferred option for these patients.

Patients Not Suited for Primary Surgery: For uterine-confined disease not suitable for primary surgery, EBRT and/or brachytherapy is the preferred treatment approach. Initial systemic therapy can also be considered for select patients with uterine-confined tumors of endometrioid histology (eg, estrogen and progesterone receptor–positive [ER/PR-positive]). Patients receiving hormonal therapy alone should be closely monitored using endometrial biopsy (eg, consider endometrial biopsies every 3–6 months).[40,157]

Progesterone-based therapy has been shown to provide some benefit with low toxicity in patients with low-grade tumors.[158] Tamoxifen with alternating megestrol[159] and aromatase inhibitors has also been used.[160–163]

For suspected gross cervical involvement in patients who are not suited for primary surgery, EBRT and brachytherapy is an effective treatment that can provide some measure of pelvic control and long-term PFS (see "Principles of Radiation Therapy for Uterine Neoplasms," on page UN-A in these Guidelines at NCCN.org).[164–167] EBRT and brachytherapy should be administered with (or without) systemic therapy. If rendered operable, local treatment should follow. Systemic therapy alone is also a primary treatment option (category 2B), but should be followed by local treatment consisting of surgery if feasible (EBRT + brachytherapy if inoperable).

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 178 [ENDO-C]). 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).[168,169] Recommended adjuvant treatment is shown in the algorithm (see page 183 [ENDO-D]). Note that the treatment algorithm was revised in 2010 based on the updated FIGO staging.[48] 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 selecting more aggressive adjuvant therapy for patients as tumor grade and myometrial and/or cervical invasion worsen, because risk exists on a continuum.[170–172] 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 surface cervical glandular involvement. When administering adjuvant RT, it should be started as soon as the vaginal cuff has healed, 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, regardless of intrauterine features, if extrauterine disease has been clearly ruled out. In a large prospective study, the Gynecologic Oncology Group (GOG) reported that the 5-year survival rate for surgical stage I patients with no adverse risk factors other than grade and myometrial invasion (ie, without extrauterine disease, isthmus/cervical involvement, or LVSI) was 92.7%.[173] 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 option of *observation* in the NCCN Guidelines (see page 174 [ENDO-4]).[71,169,170,174–176] The NCCN panel recommends observation only for select patients with no residual disease in the hysterectomy specimen.

The recommended postoperative (ie, adjuvant) treatment options for patients with surgical stage II disease (using thorough surgical staging) are shown in the algorithm (see "Adjuvant Treatment" for stage II disease, page 175 [ENDO-5]). 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, observation or vaginal brachytherapy are options. As with stage I disease, the presence of adverse risk factors should be considered when selecting adjuvant therapy.[177]

In 2017, the panel removed observation as a recommended option in the adjuvant setting for patients with stage IA, grade 3 disease with additional risk factors and stage IB grade 3 disease without adverse risk factors. For patients with stage IA/IB, grade 3 disease (IA with adverse risk factors and IB without), systemic therapy was added as a category 2B option when performed along with the primary recommendation of vaginal brachytherapy and/or EBRT. For stage IB, grade 3 disease with adverse risk factors, the option of systemic therapy (in addition to EBRT and/or vaginal brachytherapy) was upgraded to a category 2A option.

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 RT did not improve OS in any of the trials. However, many of these trials had limitations because most of the patients were low risk (ie, they had low-risk intrauterine pathologic risk factors). Thus, the trials were underpowered for patients with high-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, 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 (Postoperative Radiation Therapy in Endometrial Carcinoma [PORTEC-1], Aalders).[178,179] In the third trial (ASTEC/EN.5), only 50% of the patients were thoroughly staged as part of a companion surgical protocol.[60,180] However, formal surgical staging was mandated for all patients in the fourth trial (GOG 99).[181] Note that these trials used the older staging system (ie, before 2009).

The PORTEC-1 trial suggested that external-beam pelvic RT provides a therapeutic benefit in selected patients with uterine-confined disease.[178,182] Although RT significantly decreased locoregional recurrence, it did not increase OS.[183] The Aalders' randomized trial found that RT reduced vaginal (ie, locoregional) recurrences but did not reduce distant metastases or improve survival.[179] A recent 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 a small improvement in pelvic control.[180] However, the ASTEC/EN.5 study is very controversial; 51% of the patients in the ASTEC observation group received vaginal brachytherapy.[64,184] The Keys' trial (GOG 99) showed that adjuvant pelvic RT improved locoregional control and relapse-free interval (ie, PFS), without OS benefit.[181] Both the GOG 99 and PORTEC-1 trials revealed that most of the initial recurrences for patients with initial uterine-confined tumors were limited to the vagina, prompting the increasing use of vaginal brachytherapy alone as adjunctive treatment.[181,185,186]

To help select a patient population who may benefit from adjuvant RT, the GOG 99 and PORTEC trials defined risk factors for women at high-intermediate risk (HIR) for recurrence.[178,181] These risk factors include age, in addition to deep myometrial invasion, grade, and LVSI. In GOG 99, women younger than 50 years had to have all 3 histologic risk factors to be considered HIR.[181] If they were 50 to 70 years, they were considered HIR if they had 2 histologic risk factors. Women 70 years or older were defined as HIR if they also had one risk factor. In PORTEC-1, women had to have 2 of 3 risk factors (ie, age >60 years, deep myometrial invasion, grade 3 histology) to be considered at HIR for recurrence.[178,185]

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.[187] Given that vaginal brachytherapy is associated with significantly less toxicity than pelvic RT, vaginal brachytherapy alone is a reasonable choice for most patients with uterine-confined endometrial cancer who are deemed candidates for adjuvant radiotherapy.[185–194] 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 1C and grade 3 endometrial carcinoma (2009 FIGO stage IB, grade 3);[48] thus, the use of adjuvant brachytherapy alone in the highest risk subset remains undetermined.

A recent trial (GOG 249) examined vaginal cuff brachytherapy and carboplatin/paclitaxel therapy (brachy+chemo) versus pelvic EBRT only in patients with high-risk, uterine-confined endometrial carcinoma (n=601). Unlike PORTEC-2, GOG 249 reported significantly increased rates of nodal recurrence (primarily pelvic) in the brachy+chemo arm versus the pelvic EBRT arm. No significant between-group differences in vaginal or distant recurrence rates were observed. However there were more ex-

travaginal pelvic failures in the brachy+chemo arm. At a median follow-up of 53 months, 3-year recurrence-free survival was 82% for both treatment arms; 3-year OS was 88% for the brachy+chemo 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.[195]

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 LVSI were highly predictive for locoregional relapse (LRR), distant relapse (DR), OS, and DFS, and treatment given (EBRT versus vaginal brachytherapy) was predictive for LRR and DFS.[168] 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 women with endometrial cancer found that adjuvant RT improved OS in those with high-risk disease.[196,197] In a meta-analysis of randomized trials, a subset analysis found that adjuvant pelvic RT for stage I disease was associated with a trend towards 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.[189,198–202]

Recently, results were published from a long-term follow-up study (median, 20.5 years) of 568 patients with early-stage endometrial carcinoma who were enrolled in the Aalders trial. The study compared long-term outcomes in women 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 younger than 60 years of age who received EBRT had increased incidence of secondary cancers and subsequent higher mortality rates.[189]

Adjuvant Systemic Therapy: Carboplatin/paclitaxel is the preferred regimen in the adjuvant setting for high-risk uterine confined disease.[205–207] 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 an appreciable risk of distant metastases.[181,182] Therefore, some clinicians suggested that adding systemic therapy to adjuvant RT may provide added therapeutic benefit (ie, decrease in distant metastases).[170,203] Studies have evaluated the role of systemic therapy in highest-risk uterine-confined disease.[203,204] PFS is improved with adjuvant sequential chemotherapy/RT.[203] 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.[203] We await final results from GOG 249.

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Individual Disclosures for Uterine Neoplasms Panel

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The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have an Employment/ Governing Board, Patent, Equity, or Royalty conflict:
David Cohn, MD: Society of Gynecologic Oncology
Kristin Bradley, MD: UpToDate, Inc.