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Uterine Neoplasms, Version 1.2014

Clinical Practice Guidelines in Oncology

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Overview

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. An estimated 49,560 new uterine cancer cases will occur in 2013, with 8190 deaths resulting from the disease.[1] Uterine sarcomas (stromal/mesenchymal tumors) are uncommon malignancies, accounting for approximately 3% of all uterine cancers.[2] The NCCN Clinical Practice Guidelines

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. An estimated 49,560 new uterine cancer cases will occur in 2013, with 8190 deaths resulting from the disease. Uterine sarcomas (stromal/mesenchymal tumors) are uncommon malignancies, accounting for approximately 3% of all uterine cancers. The NCCN Guidelines for Uterine Neoplasms describe malignant epithelial carcinomas and uterine sarcomas; each of these major categories contains specific histologic groups that require different management. This excerpt of these guidelines focuses on early-stage disease. (*J Natl Compr Canc Netw* 2014;12:248–280)

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.

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 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 280. (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.

in Oncology (NCCN Guidelines) for Uterine Neoplasms describe malignant epithelial carcinomas and uterine sarcomas; each of these major categories contains specific histologic groups that require different management (see UN-1, page 250). This excerpt of the NCCN Guidelines for Uterine Neoplasms focuses on early-stage disease (ie, disease confined to the uterus), because this occurs more frequently (http://seer.cancer.gov/statfacts/html/corp.html). Fertility-sparing and non–fertility-sparing treatment options are described for those with early-stage disease. The complete version of these guidelines is available on the NCCN Web site (NCCN.org).

Risk factors for uterine neoplasms include increased levels of estrogen (caused by obesity, diabetes, high-fat diet), early age at menarche, nulliparity, late age at menopause, Lynch syndrome, older age (≥55 years), and tamoxifen use.[3–6] Thus, the incidence of endometrial cancer is increasing because of increased life expectancy and obesity.

For patients with suspected uterine neoplasms, the initial evaluation/workup includes a history and physical examination, endometrial biopsy, and other studies (see UN-1, page 250).[7] An expert pathology review will determine whether a patient has either 1) a malignant epithelial tumor (ie, pure endometrioid cancer, uterine serous adenocarcinoma, clear cell adenocarcinoma, or carcinosarcoma, which is also known as malignant mixed Müllerian tumor [MMMT]); or 2) a stromal/mesenchymal tumor (ie, uterine leiomyosarcoma [uLMS], endometrial stromal sarcoma [ESS], or high-grade [undifferentiated]

Text cont. on page 263.

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Specialties: ΩGynecologic Oncology; †Medical Oncology; ‡Hematology; §Radiotherapy/Radiation Oncology; ≠Pathology

INITIAL EVALUATION

- H&P
- CBC (including platelets)
- Endometrial biopsy
- Chest imaging

Optional:

- Liver function test (LFT)/renal function tests/chemistry profile
- Consider genetic counseling/testing for patients (<50 y) and those with a significant family history of endometrial and/or colorectal cancer[a] (See Lynch syndrome/HNPCC in NCCN Guidelines for Colorectal Cancer Screening; to view the most recent version of these guidelines, visit NCCN.org)

→ Expert pathology review

INITIAL CLINICAL FINDINGS

Malignant epithelial carcinoma

- Pure endometrioid carcinoma
  - Disease limited to uterus (endometrioid histologies) →
  - Suspected or gross cervical involvement → See Primary Treatment (ENDO-3*)
  - Suspected extrauterine disease → See Primary Treatment (ENDO-4*)
- Serous adenocarcinoma or Clear cell adenocarcinoma → See Treatment for Serous or Clear Cell Adenocarcinoma or Carcinosarcoma of the Endometrium (ENDO-11)
- Carcinosarcoma[c,d] → See Treatment for Serous or Clear Cell Adenocarcinoma or Carcinosarcoma of the Endometrium (ENDO-11)

Stromal/mesenchymal tumors

- Endometrial stromal sarcoma (ESS)[b]
- High-grade (undifferentiated) endometrial sarcoma[b]
- Uterine leiomyosarcoma (uLMS)

→ See Primary Treatment (UTSARC-1)

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

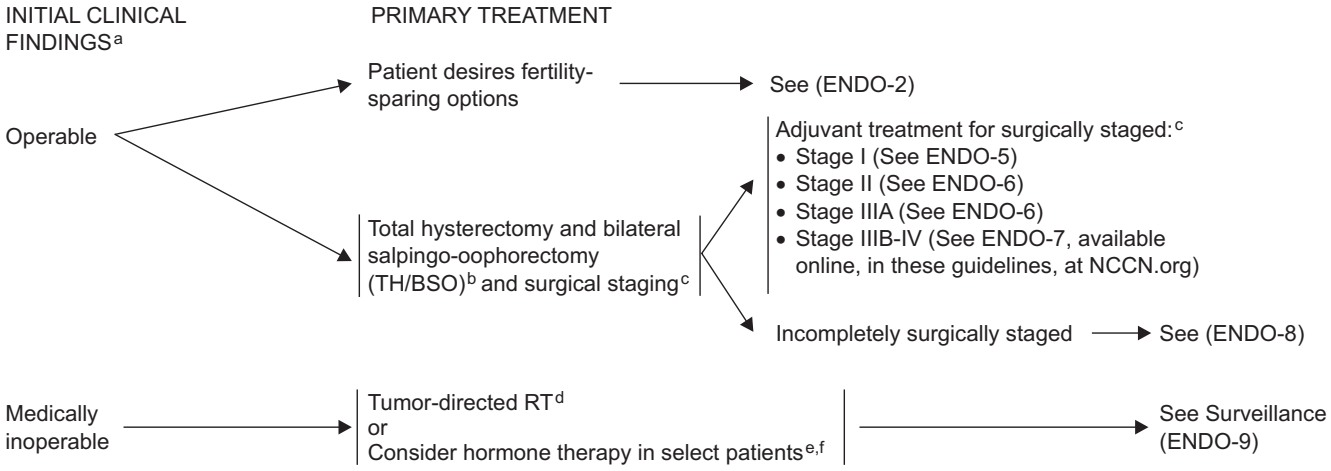
All staging in guideline is based on updated 2010 FIGO staging. (See ST-1* and ST-2*)

[a] Recently, immunohistochemistry (IHC) and/or microsatellite instability (MSI) screening of all colorectal and endometrial cancers, regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for Lynch syndrome (LS). An infrastructure needs to be in place to handle the screening results. IHC and/or MSI screening is usually performed on epithelial tumors and not stromal/mesenchymal endometrial tumors.

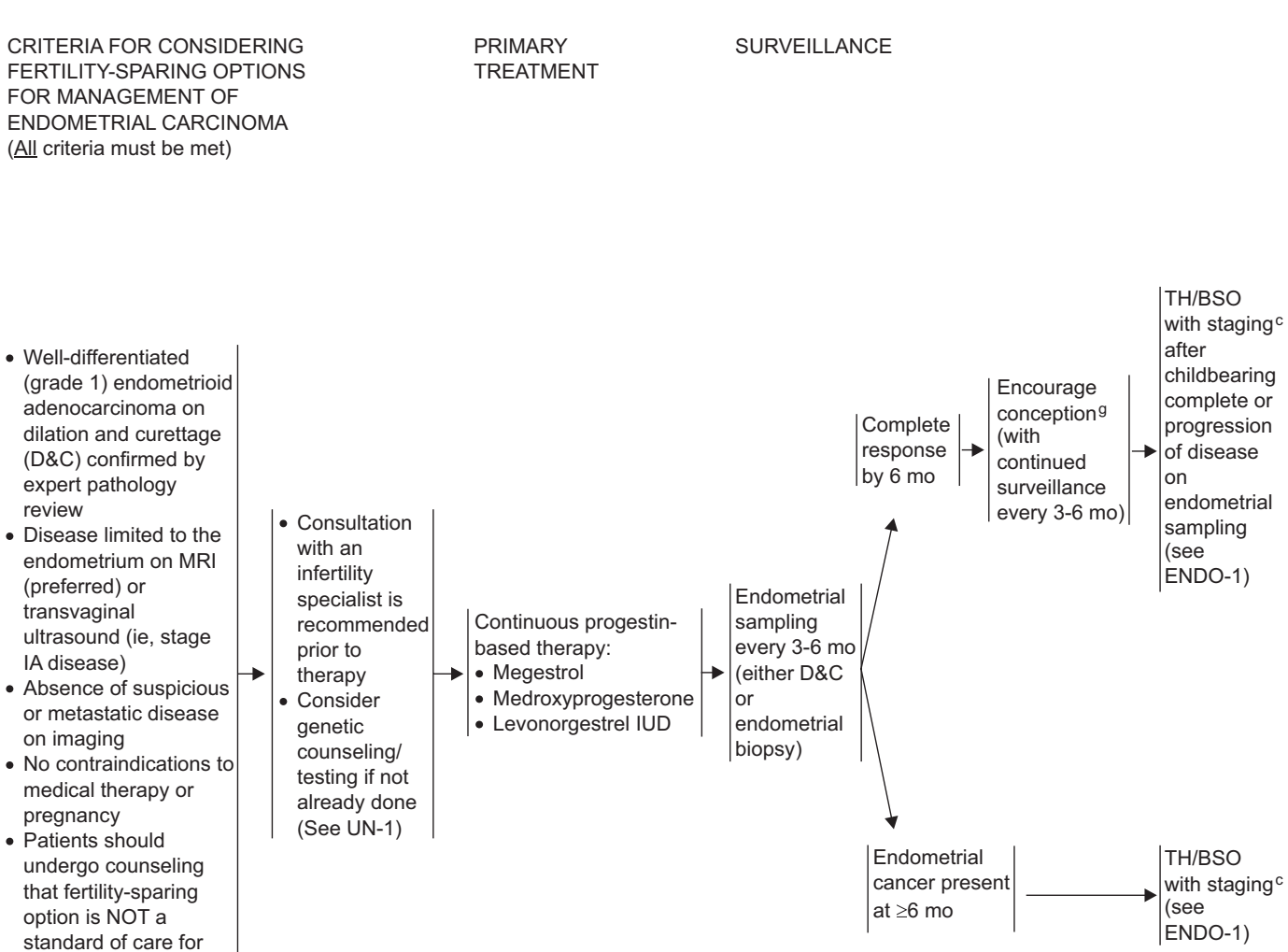
[b] By definition, ESS has low-grade cytologic features. High-grade subtypes of endometrial sarcomas (undifferentiated endometrial sarcomas in WHO classification) are still being defined.

[c] Staged as aggressive; should be treated as a high-grade endometrial cancer.

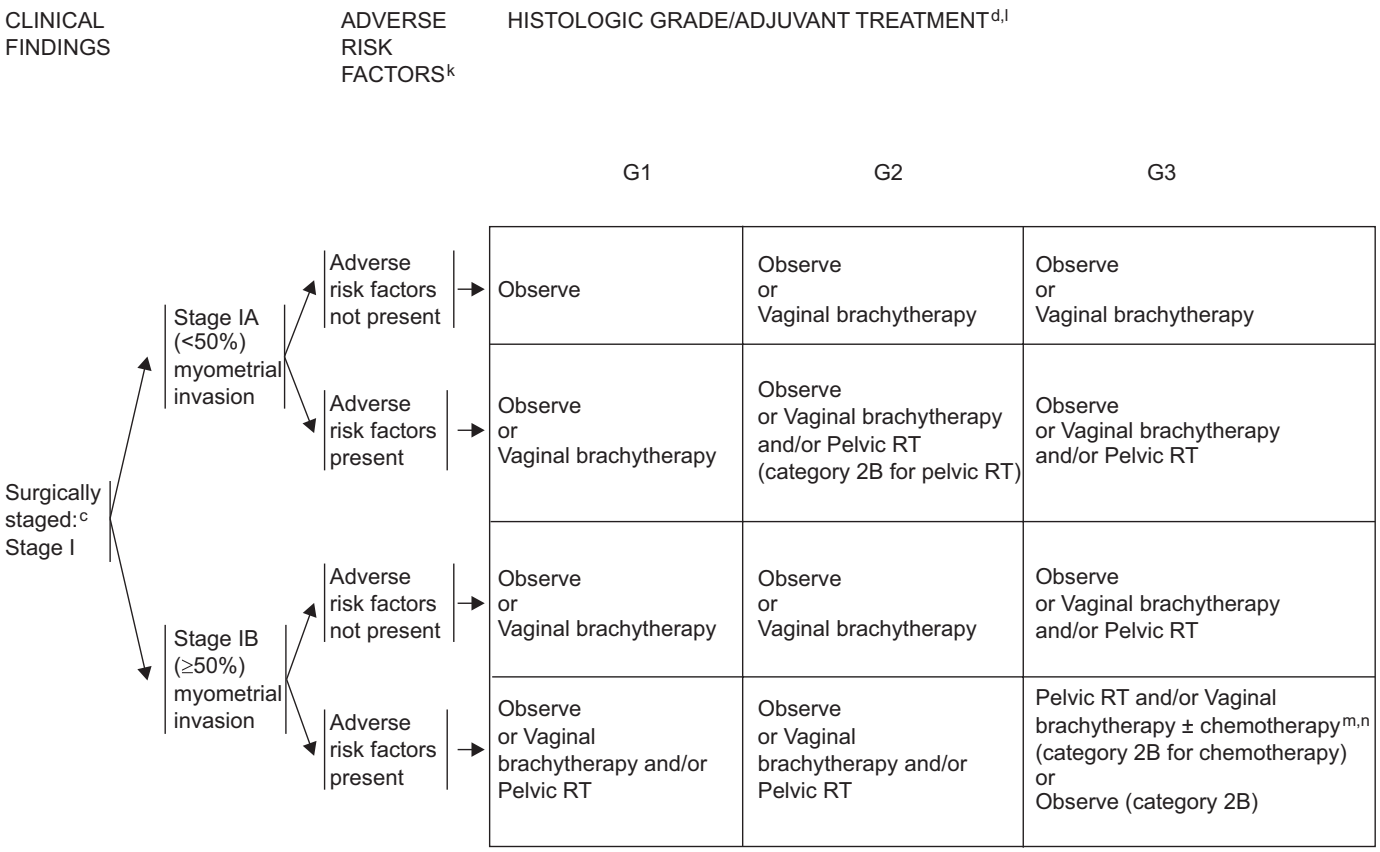
[d] Also known as malignant mixed mesodermal tumor or malignant mixed Müllerian tumor and including those with either homologous or heterologous stromal elements.



[a] See (UN-1) for clarification of uterine neoplasms.
[b] See Hysterectomy and Pathologic Evaluation (ENDO-A).
[c] 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-B).
[d] See Principles of Radiation Therapy (UN-A).
[e] Patients should be closely monitored. Consider endometrial biopsies every 3-6 months.
[f] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-C).



[c]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-B).
[g]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.



All staging in guideline is based on updated 2010 FIGO staging. (See ST-1; available online, in these guidelines, at NCCN.org)

[c] 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-B).
[d] See Principles of Radiation Therapy (UN-A).
[k] Potential adverse risk factors include the following: age, positive lymphovascular invasion, tumor size, and lower uterine (cervical/glandular) involvement.
[l] Adjuvant therapy determinations are made on the basis of pathologic findings.
[m] The role of adjuvant chemotherapy in invasive high-grade uterine confined disease is the subject of current studies. (Hogberg T, Signorelli M, de Oliveira CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur J Cancer 2010;46:2422-2431.)
[n] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-C).

CLINICAL FINDINGS	HISTOLOGIC GRADE/ADJUVANT TREATMENT[d,l,n]		
	G1	G2	G3
Surgically staged:[c] Stage II[o,p] →	Vaginal brachytherapy and/or pelvic RT	Pelvic RT + vaginal brachytherapy	Pelvic RT + vaginal brachytherapy ± chemotherapy[m,n] (category 2B for chemotherapy)
Surgically staged:[c] Stage IIIA →	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy

All staging in guideline is based on updated 2010 FIGO staging. (See ST-1; available online, in these guidelines, at NCCN.org)

[c] 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-B).
[d] See Principles of Radiation Therapy (UN-A).
[l] Adjuvant therapy determinations are made on the basis of pathologic findings.
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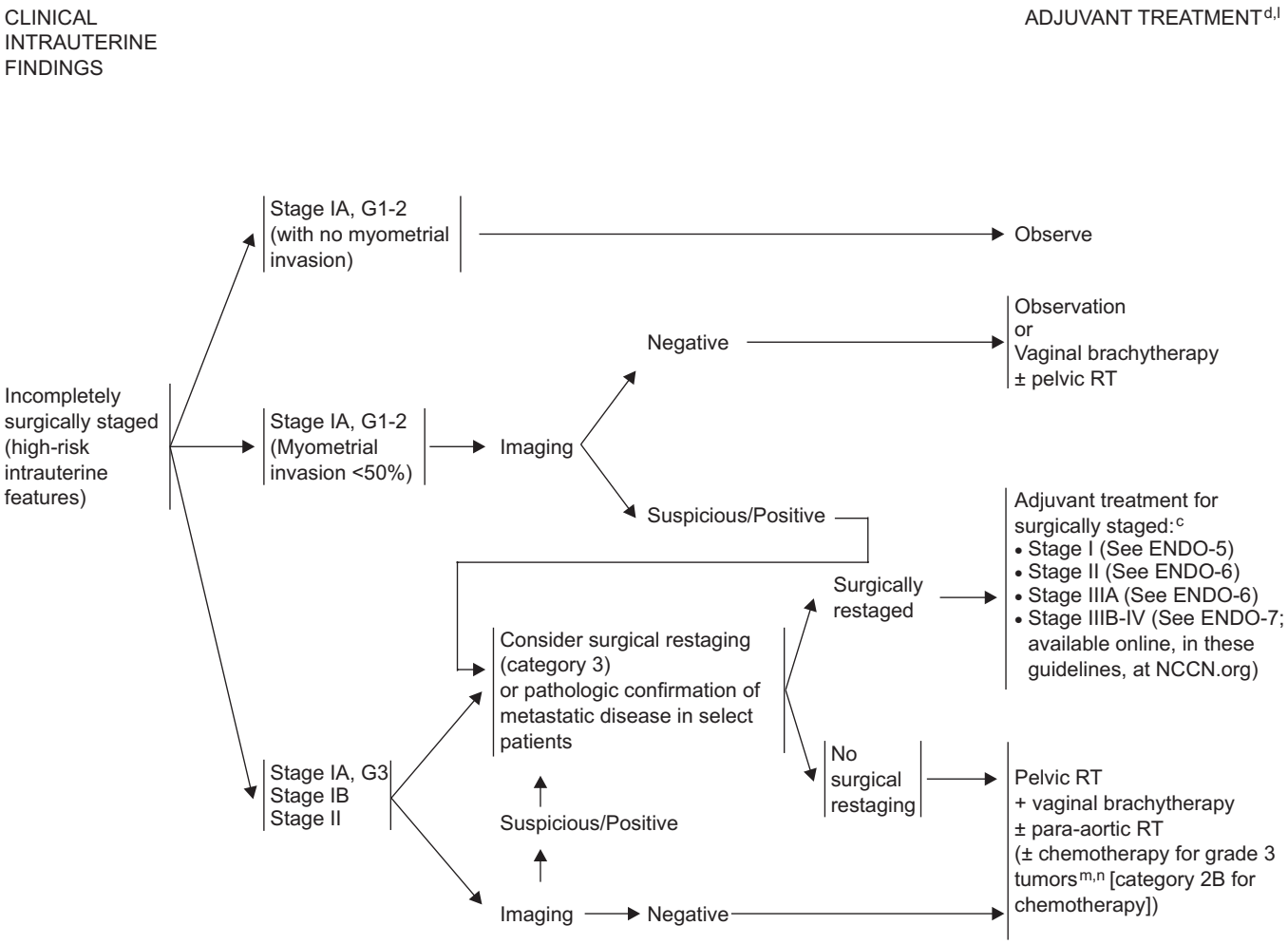
[n] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-C).
[o] Observation or vaginal brachytherapy is also an option for patients with stage II disease who have had a radical hysterectomy with negative surgical margins and no evidence of extrauterine disease.
[p] The adverse fundal risk factors influencing therapy decisions for stage I disease (see ENDO-5) may also impact the choice of adjuvant therapy for stage II disease.



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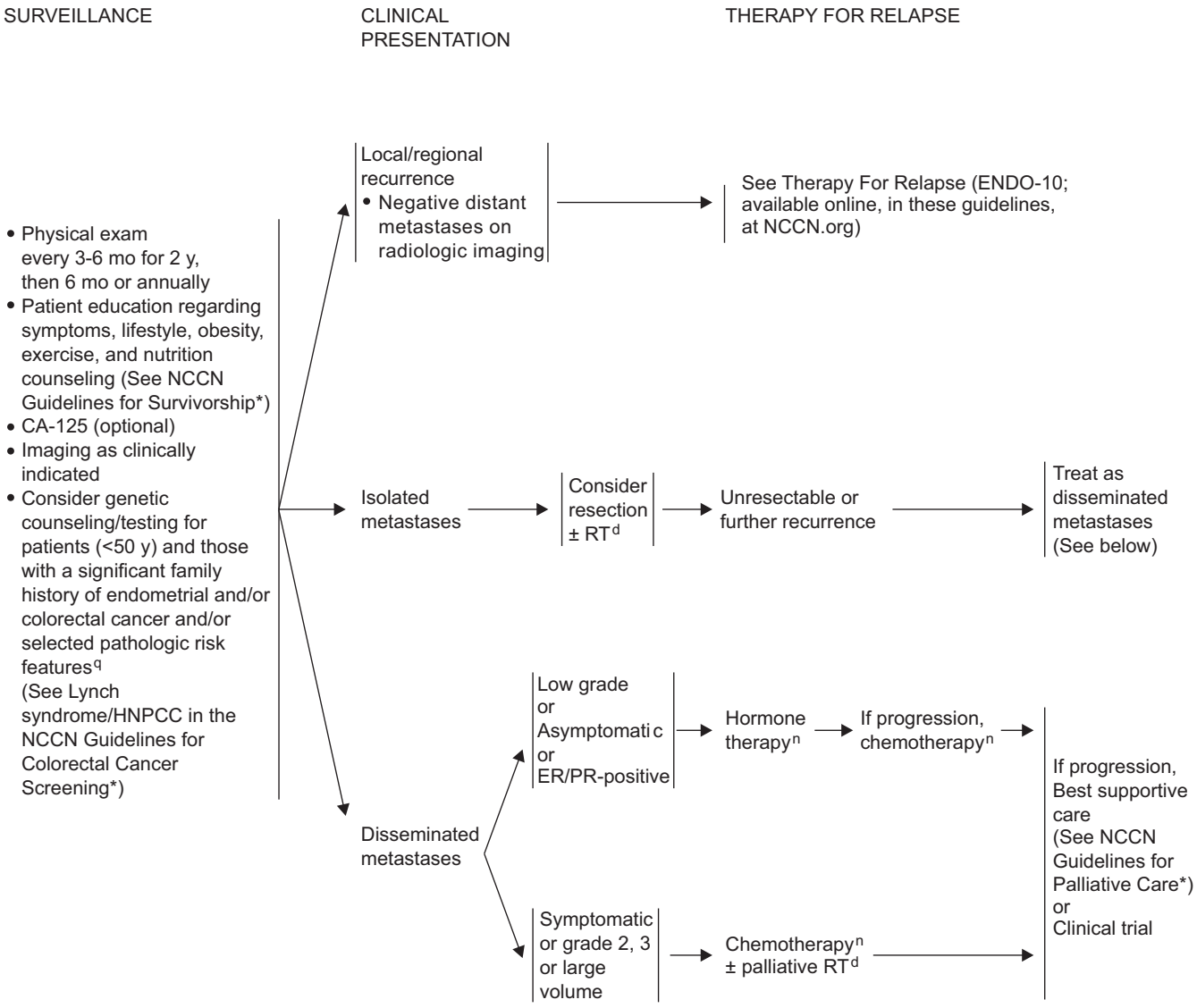
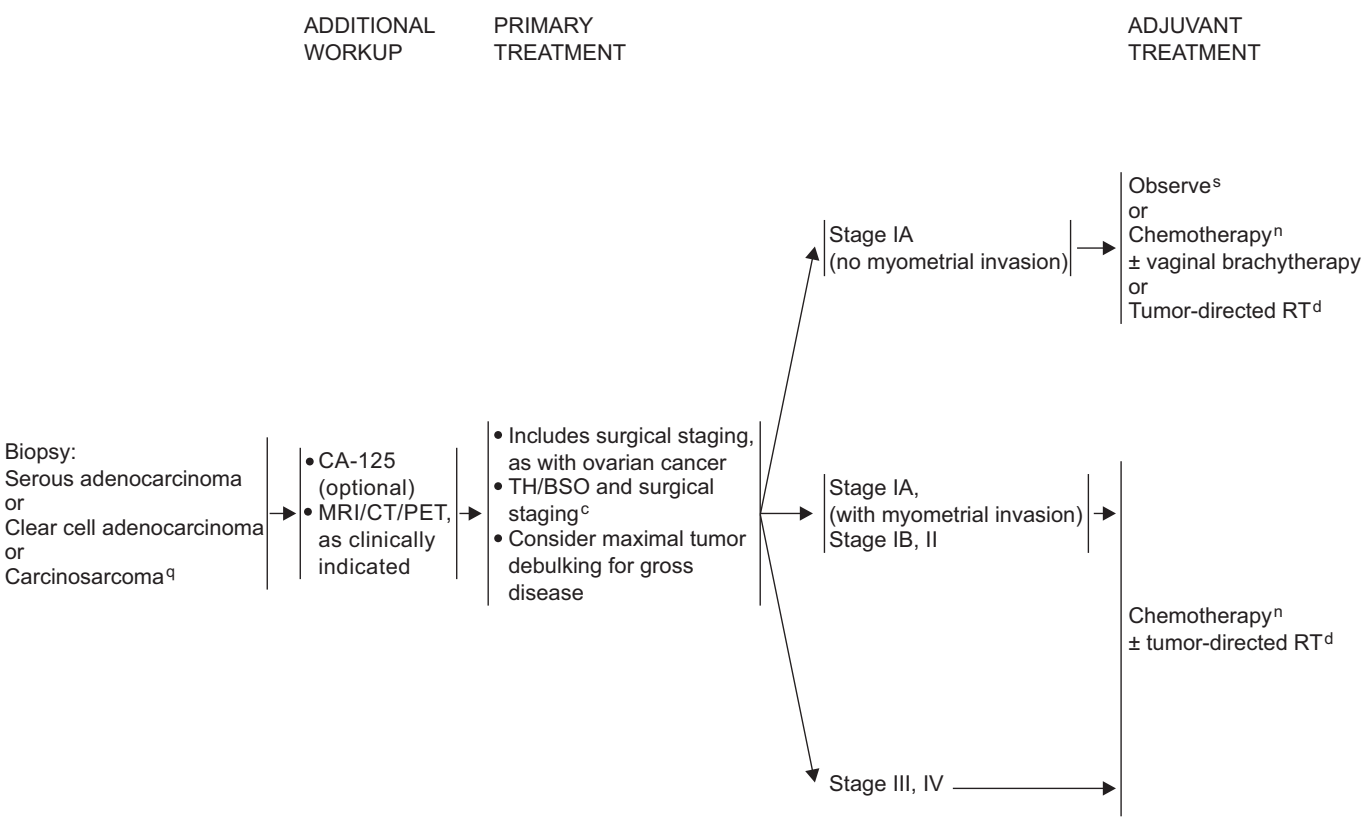
[n] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-C).



*To view the most recent version of these guidelines, visit NCCN.org.

[d]See Principles of Radiation Therapy (UN-A).
[n]See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-C).
[q]Recently, immunohistochemistry (IHC) and/or microsatellite instability (MSI) screening of all colorectal and endometrial cancers, regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for Lynch syndrome (LS). An infrastructure needs to be in place to handle the screening results. IHC and/or MSI screening is usually performed on epithelial tumors and not stromal/mesenchymal endometrial tumors.

SEROUS OR CLEAR CELL ADENOCARCINOMA OR CARCINOSARCOMA OF THE ENDOMETRIUM[r]



All staging in guideline is based on updated 2010 FIGO staging. (See ST-1; available online, in these guidelines, at NCCN.org)

[c]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-B).
[d]See Principles of Radiation Therapy (UN-A).
[n]See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-C).
[q]Recently, immunohistochemistry (IHC) and/or microsatellite instability (MSI) screening of all colorectal and endometrial cancers, regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for Lynch syndrome (LS).An infrastructure needs to be in place to handle the screening results. IHC and/or MSI screening is usually performed on epithelial tumors and not stromal/mesenchymal endometrial tumors.
[r]Also known as malignant mixed mesodermal tumor or malignant mixed Müllerian tumor. Carcinosarcomas are treated the same as poorly differentiated adenocarcinomas.
[s]Observation only for select patients with no residual disease in the hysterectomy specimen.

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 stromal or glandular involvement
  - Tumor size
  - Tumor location (fundus vs lower uterine segment/cervix)
  - Histologic subtype with grade
  - Lymphovascular space invasion
  - Consider screening with IHC and MSI for inherited mismatch repair gene mutations in patients <50 y and those with a significant family history of endometrial and/or colorectal cancer and/or selected pathologic risk features to identify familial cancer syndromes, such as Lynch syndrome/HNPCC[3]
    (See NCCN Guidelines for Colorectal Cancer Screening; to view the most recent version of these guidelines, visit NCCN.org)
- Fallopian tubes/ovaries
- Peritoneal cytology[4]
- Nodes (when resected)
  - Level of nodal involvement (ie, pelvic, common iliac, para-aortic)

[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-B).
[3] Recently, immunohistochemistry (IHC) and/or microsatellite instability (MSI) screening of all colorectal and endometrial cancers, regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for Lynch syndrome (LS). An infrastructure needs to be in place to handle the screening results. IHC and/or MSI screening is usually performed on epithelial tumors and not stromal/mesenchymal endometrial tumors.
[4] Although cytology by itself does not affect FIGO staging, cytology results should still be obtained because positive cytology is an adverse risk factor.

ENDO-A

PRINCIPLES OF EVALUATION AND SURGICAL STAGING

Principles of Surgical Staging for Endometrial Cancer[1-3]

- TH/BSO is the main treatment of apparent uterine confined endometrial cancer, unless patients are interested in and are candidates for fertility-sparing options (See ENDO-2). Many patients with locally advanced endometrial carcinoma are also candidates for TH/BSO. (See Hysterecomy and Pathologic Evaluation [ENDO-A])
- The hysterectomy and adnexectomy may be performed through laparotomy, vaginally, or via minimally invasive techniques such as laparoscopy or robotic surgery.
- 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 affect staging, FIGO and AJCC continue to recommend that it be obtained and reported.
- Omental biopsy is commonly performed in tumors with serous adenocarcinoma, clear cell adenocarcinoma, or carcinosarcoma histology.
- Excision of suspicious or enlarged lymph nodes in the pelvic or paraaortic regions is important to exclude nodal metastasis.
- Pelvic nodal dissection with pathologic evaluation continues to be an important part of the surgical staging for selected uterine confined endometrial cancer as it can identify 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 of select high-risk tumors such as deeply invasive lesions, high-grade histology, and tumors of serous adenocarcinoma, clear cell adenocarcinoma, or carcinosarcoma features.
- Sentinel lymph node (SLN) mapping may be considered (category 2B) in selected patients. (See pages 2-4 of ENDO-B, available online, in these guidelines, at NCCN.org)
- Some patients may not be candidates for lymph node dissection.

[1] American College of Obstetricians and Gynecologists. ACOG practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstet Gynecol 2005;106:413-425.
[2] Bakkum-Gamez JN, Gonzalez-Bosquet J, Laack NN, et al. Current issues in the management of endometrial cancer. Mayo Clin Proc 2008;83:97-112.
[3] Edge SB, Byrd DR, Compton CC. AJCC Cancer Staging Manual, 7th edition. New York: Springer; 2010.

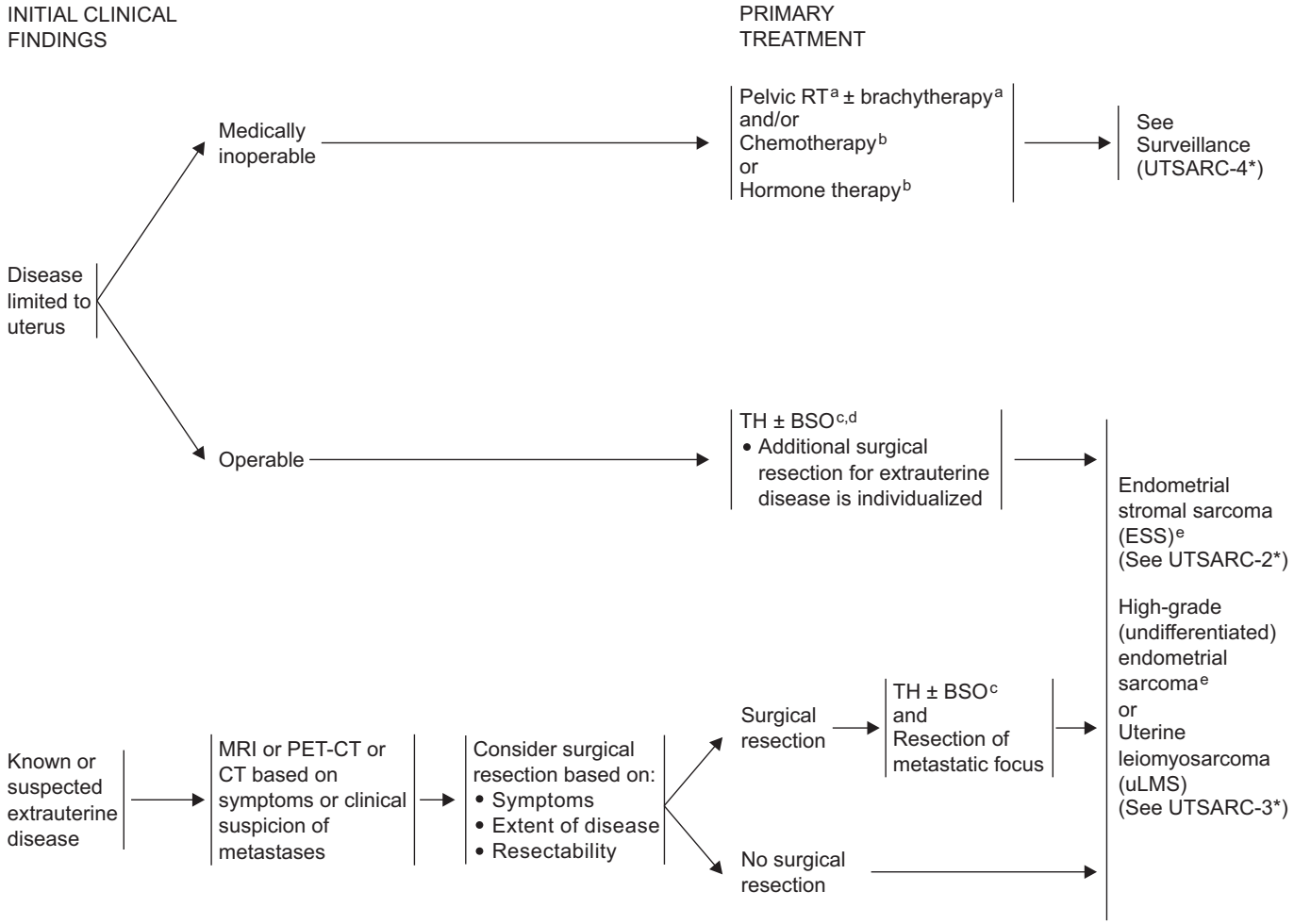
SYSTEMIC THERAPY FOR RECURRENT, METASTATIC, OR HIGH-RISK DISEASE
(STRONGLY ENCOURAGE PARTICIPATION IN CLINICAL TRIALS)

HORMONE THERAPY[1]
- Progestational agents
- Tamoxifen
- Aromatase inhibitors
- Megestrol/tamoxifen (alternating)

CHEMOTHERAPY REGIMENS[2,3]
- Multiagent chemotherapy regimens preferred, if tolerated
  - Carboplatin/paclitaxel[4]
  - Cisplatin/doxorubicin[5]
  - Cisplatin/doxorubicin/paclitaxel[5,6]
  - Carboplatin/docetaxel[7]
  - Ifosfamide/paclitaxel (category 1 for carcinosarcoma)[8]
  - Cisplatin/ifosfamide (for carcinosarcoma)
- Single agents
  - Cisplatin
  - Carboplatin
  - Doxorubicin
  - Liposomal doxorubicin
  - Paclitaxel
  - Topotecan
  - Bevacizumab[9]
  - Temsirolimus
  - Docetaxel[7] (category 2B)
  - Ifosfamide (for carcinosarcoma)

[1] Hormonal therapy is for endometrioid histologies only (ie, not for serous adenocarcinoma, clear cell adenocarcinoma, or carcinosarcoma).
[2] Cisplatin, carboplatin, liposomal doxorubicin, paclitaxel, and docetaxel may cause drug reactions. (See NCCN Guidelines for Ovarian Cancer--Management of Drug Reactions [OV-C]; to view the most recent version of these guidelines, visit NCCN.org.)
[3] 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.
[4] Miller D, Filiaci V, Fleming G, et al. Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: a Gynecologic Oncology Group study [abstract]. Gynecol Oncol 2012;125:Abstract 771.
[5] Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: a Gynecologic Oncology Group study. Gynecol Oncol 2009;112:543-552.
[6] The cisplatin/doxorubicin/paclitaxel regimen is not widely used because of concerns about toxicity.
[7] Docetaxel may be considered for patients in whom paclitaxel is contraindicated.
[8] Homesley HD, Filiaci V, Markman M, et al. Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:526-531.
[9] Bevacizumab may be considered for use in patients who have progressed on prior cytotoxic chemotherapy. (Aghajanian C, Sill MW, Darcy KM, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. J Clin Oncol 2011;29:2259-2265.)

ENDO-C



*To view the most recent version of these guidelines, visit NCCN.org.

All staging in guideline is based on updated 2010 FIGO staging. (See ST-2*)

[a] See Principles of Radiation Therapy (UN-A).
[b] See Systemic Therapy for Uterine Sarcoma (UTSARC-A*).
[c] Oophorectomy individualized for reproductive-age patients.
[d] For incidental finding of uterine sarcoma after TH/BSO: Recommend imaging and consider additional surgical resection on an individual basis.
[e] By definition, ESS has low-grade cytologic features. High-grade subtypes of endometrial sarcomas (undifferentiated endometrial sarcomas in WHO classification) are still being defined.

PRINCIPLES OF RADIATION THERAPY

- Tumor-directed RT refers to RT directed at sites of known or suspected tumor involvement, and may include external-beam RT (EBRT) and/or brachytherapy. Diagnostic imaging is often used to assess locoregional extent and to rule out distant metastases before administration of RT. In general, tumor-directed EBRT is directed to the pelvis with or without the para-aortic region. Brachytherapy can be delivered: 1) to an intact uterus, either preoperatively or definitively; or 2) more commonly, to the vagina after hysterectomy. For the purposes of these guidelines, whole abdominal RT is not considered to be tumor-directed RT.

- Pelvic RT should target the gross disease (if present), lower common iliacs, external iliacs, internal iliacs, parametria, upper vagina/para-vaginal tissue, and presacral lymph nodes (in patients with cervical involvement). Extended-field RT should include the pelvic volume and also target the entire common iliac chain and para-aortic lymph node region. The upper border of the extended field depends on the clinical situation but should at least be to the level of the renal vessels. External-beam doses for microscopic disease should be 45-50 Gy. Multiple conformal fields based on CT-treatment planning should be used.

- Brachytherapy doses for definitive therapy are individualized based on the clinical situation. For preoperative therapy in patients with gross stage IIB disease, in general, a total dose of 75-80 Gy low-dose rate equivalent to the tumor volume is recommended. For vaginal brachytherapy, the dose should be prescribed to the vaginal surface or at a depth of 0.5 cm from the vaginal surface; the dose depends on the use of EBRT.
  - The target for vaginal brachytherapy after hysterectomy should be limited to the upper vagina.
  - For high-dose rate brachytherapy, when used as a boost to EBRT, doses of 4-6 Gy x 2-3 fractions prescribed to the vaginal mucosa are commonly used.
  - For high-dose rate vaginal brachytherapy alone, commonly used regimens include 7 Gy x 3 prescribed at a depth of 0.5 cm from the vaginal surface or 6 Gy x 5 fractions prescribed to the vaginal surface.

UN-A

Text cont. from page 249.

endometrial sarcoma). Because this excerpt of the guidelines mainly focuses on early-stage malignant epithelial carcinoma, in-depth information about uterine sarcomas is not provided. Given the typical age group at risk for uterine neoplasms (ie, ≥55 years) and the presence of comorbid illnesses in older patients, it is prudent to also measure renal and liver function in selected patients.

Most endometrial cancer is caused by sporadic mutations. However, genetic mutations cause endometrial cancer in approximately 5% of patients, which occurs 10 to 20 years before sporadic cancer.[8] Screening for genetic mutations (eg, Lynch syndrome/hereditary nonpolyposis colorectal cancer [HNPCC]) should be considered in all patients with endometrial (and colorectal) cancer, but especially in those younger than 50 years.[6,8–10] Genetic testing and counseling should be considered for patients younger than 50 years with endometrial cancer and those with a significant family history of endometrial and/or colorectal cancer.[11–13] If these patients have Lynch syndrome, they are at greater risk for a second cancer (eg, colorectal cancer, ovarian cancer).[4,10,14] In addition, their relatives may have Lynch syndrome.

Screening of the tumor for defective DNA mismatch repair using immunohistochemistry and/or microsatellite instability (MSI) should be considered to identify which patients should undergo mutation testing for Lynch syndrome (see "Lynch Syndrome" in the NCCN Guidelines for Colorectal Cancer Screening; to view the most recent version of these guidelines, visit NCCN.org).[8,9,15,16] Immunohistochemistry and/or MSI is used to assess for defective DNA mismatch repair (eg, MLH1, MSH2, MSH6), which is associated with Lynch syndrome.[8] The Society of Gynecologic Oncology (SGO) also has useful criteria for determining which patients should have mutation testing (eg, young patients diagnosed with multiple Lynch syndrome-associated cancers, family members with similar cancers).[11,12] Some centers perform immunohistochemistry and/or MSI screening in all patients with colorectal and endometrial cancers to identify those at risk for Lynch syndrome, regardless of age at diagnosis or family history.[15,16] However, this screening is usually performed in patients with epithelial tumors, and not those with stromal or mesenchymal endometrial tumors.

Women with Lynch syndrome are at higher risk (60%) for endometrial cancer; thus, close monitoring is recommended.[9,17,18] In relatives with Lynch syndrome but without endometrial cancer, a yearly endometrial biopsy is recommended to assess for cancer.[12,19] This strategy also enables select women to defer surgery (and surgical menopause) and preserve their fertility. Prophylactic hysterectomy/bilateral salpingooophorectomy (BSO) can then be performed either after childbearing is complete or sooner, depending on patient preference.[20,21] In addition, interventions to decrease the risk of developing colorectal cancer may also be appropriate (eg, annual colonoscopy).

Endometrial Cancer

In approximately 75% of patients with adenocarcinoma of the endometrium, the invasive neoplasm is confined to the uterus at diagnosis.[22] Many physicians believe that adenocarcinoma of the endometrium is a relatively benign disease, because the early symptoms of irregular vaginal bleeding (in this predominantly postmenopausal patient population) often prompt patients to seek care when the disease is at an early and treatable stage. Thus, endometrial cancer is often localized, yielding a generally high survival rate.[23] However, data show that the mortality rate for uterine cancer has increased more rapidly than the incidence rate.[24] This increased mortality may be related to an increased rate of advanced-stage cancers, high-risk histologies (eg, serous adenocarcinomas), and patients being diagnosed at an older age. To further improve on outcome for patients with this disease, physicians must identify patients at high risk and tailor treatment appropriately to provide the best long-term survival. A recent analysis of SEER data suggests that survival is increased in patients who are younger, have early-stage disease, and have lower-grade disease.[25] It also recommended that gynecologic oncologists be involved in the primary management of patients with endometrial cancer.

Diagnosis and Workup

Approximately 90% of patients with endometrial carcinoma have abnormal vaginal bleeding, most commonly in the postmenopausal period. The workup was previously described (see "Overview," page 248). Diagnosis can usually be made based on an office endometrial biopsy.[26,27] The histologic information from the endometrial biopsy (with or without endocervical curettage) should be sufficient for plan-

ning definitive treatment. Office endometrial biopsies have a false-negative rate of approximately 10%. Thus, a negative endometrial biopsy in a symptomatic patient must be followed by a fractional dilation and curettage (D&C) under anesthesia.[26,28] Hysteroscopy may be helpful in evaluating the endometrium for lesions, such as a polyp, if the patient has persistent or recurrent undiagnosed bleeding.[29]

Other ancillary tests (ie, CT, MRI, and PET) are reserved for evaluating extrauterine disease as indicated by clinical symptoms, physical findings, or abnormal laboratory findings.[30–33] In patients with extrauterine disease, a serum CA125 assay may be helpful for monitoring clinical response.[34,35] However, serum CA125 levels may be falsely increased in women who have peritoneal inflammation/infection or radiation injury, or normal in women with isolated vaginal metastases, and may not predict recurrence in the absence of other clinical findings.[36–38] Currently, no validated screening test exists for endometrial carcinoma.[39,40]

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, 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).

However, several studies showed that clinical staging was inaccurate and did not reflect actual disease extent in 15% to 20% of patients.[41–43] 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 surgicopathologic assessment of data, such as histologic grade, myometrial invasion, and the extent and location of extrauterine spread (including retroperitoneal lymph node metastases).[44] FIGO and the AJCC updated and refined the surgical/pathologic staging criteria for uterine neoplasms in 2010.[45–49] Separate staging systems for malignant epithelial tumors and uterine sarcomas are now available (see Tables 1 and 2, respectively, in the complete version of these guidelines, available online at NCCN.org).

The 2010 staging streamlined stages I and II endometrial carcinoma. These revisions were made because the survival rates for some of the previous 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 endocervical glandular involvement without invasion are no longer upstaged.[48] Stage IIIC is now subdivided into IIIC1 and IIIC2, because survival is worse with positive paraaortic nodes.[48] Although most of the previously published studies discussed in these guidelines used the older 1988 FIGO staging system, these have been reinterpreted by the NCCN Uterine Neoplasms Panel to reconcile with the 2010 staging system.

An expert pathology review will determine the specific epithelial histology of the tumor (ie, various endometrioid histologies, serous adenocarcinoma, clear cell adenocarcinoma, or carcinosarcoma). These 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 (see UN-1, page 250). This shorter version of the NCCN Guidelines only discusses disease limited to the uterus. Pathologic assessment of the uterus and nodes is described in the algorithm; this assessment should also include the fallopian tubes and ovaries (see ENDO-A, page 258). Peritoneal cytology no longer affects the 2010 FIGO staging, because it is not viewed 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 ENDO-B, page 259).[50,51]

Staging should be performed 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 panel added a new section on surgical staging (see ENDO-B, page 259). Selected patients with apparent uterineconfined endometrial carcinoma may be considered (category 2B) for sentinel node biopsy (see "Sentinel Lymph Node Mapping" in the complete version of these

guidelines, available online at NCCN.org). However, this new surgical staging section only applies to malignant epithelial tumors and not to uterine sarcomas. The *Protocol for the Examination of Specimens From Patients With Carcinoma of the Endometrium* published by 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 2010 staging (ie, AJCC staging manual, 7th edition).

Most patients with endometrial cancer have stage I disease at presentation, and surgery (with or without adjuvant therapy) is recommended for medically operable patients. For patients with surgical stage I (any grade) endometrial cancer, the 5-year overall survival rate is 88% after treatment.[22]

Primary Treatment and Surgical Staging

Medically Operable Patients: For the staging of patients (if medically operable) with endometrioid histologies clinically confined to the fundal portion of the uterus, the recommended surgical procedure includes total hysterectomy (TH)/BSO with selective surgical staging (see ENDO-1, ENDO-A, and ENDO-B, pages 251, 258, and 259; see also "Minimally Invasive Procedures," page 266).[52] 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 Controversy," next column, and "Sentinel Lymph Node Mapping" in the complete version of these guidelines, available online at NCCN.org).

During surgery, the intraperitoneal structures should be carefully evaluated, and suspicious areas should be biopsied. Although it does not specifically affect 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 2010 FIGO staging criteria, but its routine use has been questioned (see "Lymphadenectomy Controversy," next section).

Lymphadenectomy Controversy: Previously, a full standard lymphadenectomy (ie, dissection and assessment of both pelvic and paraaortic nodes) was recommended for all patients; however, a more selective and tailored lymphadenectomy approach is now recommended by the panel to avoid systematic overtreatment.[53] No randomized trial data support routine full lymphadenectomy,[54] although some retrospective studies suggested that it is beneficial.[55–57] 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.[58,59] However, these findings remain a point of contention.[52,60,61] 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.[62,63] 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 so to what extent (eg, pelvic nodes only, or both pelvic and paraaortic nodes), can be made based on preoperative and intraoperative findings. The following 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[64,65]; however, these may be difficult to accurately determine before final pathology results are available.

Another associated benefit of lymphadenectomy is for diagnosing nodal metastases to help guide the selection of appropriate adjuvant treatment to improve survival or decrease toxicity. However, one of the 2 European randomized trials was not designed to address this question.[59] 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 between the 2 groups. 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.[66] As the grade of the tumor increases, the

accuracy of intraoperative evaluation of myometrial invasion decreases (ie, assessment based on gross examination of fresh tissue). In one study, the depth of invasion was accurately determined through gross examinations in 87.3% of grade 1 lesions, 64.9% of grade 2 lesions, and 30.8% of grade 3 lesions.[67]

The question of whether to add periaortic lymphadenectomy to pelvic node dissection has been debated. Prior studies have shown conflicting information regarding the risk of paraaortic nodal metastases in patients without disease in the pelvic nodes.[43,64,68,69] A high rate of lymphatic metastasis was seen above the inferior mesenteric artery, suggesting a need for systematic pelvic and paraaortic lymphadenectomy. Hence, periaortic lymphadenectomy up to the renal vessels may be considered for selected high-risk situations, including patients with pelvic lymphadenectomy or high-risk histologic features. Many surgeons do not perform a full lymphadenectomy in patients with grade 1 early-stage endometrial cancer.[53] Selected patients with apparent uterineconfined endometrial carcinoma may be candidates for sentinel node mapping (category 2B), which assesses the pelvic nodes and is a less morbid procedure than standard lymphadenectomy (see "Sentinel Lymph Node Mapping" in the complete version of these guidelines, available online at NCCN.org).

In summary, lymph node dissection identifies patients requiring adjuvant treatment with radiation therapy and/or chemotherapy.[70] A subset of patients may not benefit from lymphadenectomy; however, these patients are difficult to identify preoperatively because of the uncontrollable variables of change in grade and depth of invasion on final pathology. At this point, pending further trials that seek to define the clinical benefit of lymphadenectomy, the panel recommends that lymphadenectomy be performed for selected patients with endometrial cancer, with paraaortic lymphadenectomy performed as indicated for high-risk patients (see ENDO-B, page 259).[5] Lymphadenectomy is contraindicated for patients with uterine sarcoma. Sentinel node mapping may be considered (category 2B) for selected patients with apparent uterine-confined endometrial disease (see "Sentinel Lymph Node Mapping" in the complete version of these guidelines, available at NCCN.org).

Minimally Invasive Procedures: Laparoscopic pelvic and paraaortic lymphadenectomy in association with total laparoscopic hysterectomy is being used in many practices.[53,71,72] However, patients undergoing laparoscopy should be followed long term so the outcomes can be compared with those of traditional laparotomy.[73]

The randomized phase III trial GOGLAP2 evaluated laparoscopy for comprehensive surgical staging in patients with clinical stage I to IIA disease (n=2616).[73,74] Patients were randomly allocated 2:1 to either laparoscopy or laparotomy. Results from this trial indicated that 26% of patients required 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 among the groups. However, significant differences were noted in removal of pelvic and paraaortic nodes (8% not removed with laparoscopy vs 4% with laparotomy; $P<.0001$).[75,76] 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 rate was 84.8% for both arms of GOGLAP2.[74] Another randomized trial (n=283) comparing laparoscopy versus laparotomy reported shorter hospital stays, less pain, and faster resumption of daily activities with laparoscopy.[77] However, laparotomy may still be required for certain clinical situations (eg, elderly patients, patients with a very large uterus) or certain metastatic presentations.[73]

Robotic surgery is a minimally invasive technology that has been advocated by some as a feasible approach in the primary management of endometrial cancer.[71,72,78–85] Costs for equipment and maintenance remain high.[86] Given the recent introduction of robotic surgery, long-term outcomes are still pending.[87–90] However, because of its potential advantages over traditional laparoscopic approaches, it is rapidly becoming the preferred technique for minimally invasive surgery in endometrial cancer, especially for obese patients.[71,91] The SGO recently published a consensus statement about robotic surgery.[92]

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.[93,94] Surgical restaging, including lymph node dissection, can also be performed.[64] Recommended adjuvant treatment options are pro-

vided in the algorithm based on the imaging and/or surgical restaging results (see ENDO-8, page 255).

FertilitySparing Therapy: Although the primary treatment of endometrial cancer is usually hysterectomy, continuous progestin-based therapy may be considered for highly selected patients with stage IA disease who wish to preserve their fertility.[95–98] Likewise, it may also be selectively used for young patients with endometrial hyperplasia who desire fertility preservation. For the 2014 update, the panel added a new algorithm for fertility-sparing therapy in selected patients with biopsy-proven grade 1, stage IA endometrioid adenocarcinoma (see ENDO-2, page 252). When considering fertility-sparing therapy, all of the criteria must be met, as outlined in the algorithm (eg, no metastatic disease). Patients also need to 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 adenocarcinoma, clear cell adenocarcinoma, carcinosarcoma, or uLMS).

Continuous progestin-based therapy may include megestrol acetate, medroxyprogesterone, or an intrauterine device containing levonorgestrel.[95,96,99] A durable complete response occurs in approximately 50% of patients.[95] 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 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 based on biopsy results; or 3) if endometrial cancer is still present after 6 months of progestin-based therapy.[100] 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%).[95,98,101–103]

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 for 16 years.[104] Other studies also suggest that ovarian preservation may be safe in women with early-stage endometrial cancer.[105,106]

Medically Inoperable Patients: For medically inoperable patients, tumor-directed radiation therapy is a well-tolerated and effective treatment that can provide some measure of pelvic control and long-term progression-free survival (PFS) (see UN-A, page 262).[107–109] Hormonal therapy may be considered in selected patients with endometrioid histology (eg, patients who are estrogen receptor–positive and progesterone receptor–positive), who are not candidates for radiation therapy or surgery, if they are closely monitored (eg, consider endometrial biopsies every 3–6 months).[39,110] Progesterone-based therapy can provide some benefit with low toxicity in patients with low-grade tumors.[111] Tamoxifen with alternating megestrol may be used.[112] Aromatase inhibitors have also been used.[113–116]

Adjuvant Therapy: Thorough surgical staging provides important information to assist in the selection of adjuvant therapy for endometrial tumors (see ENDO-B, page 259). Patients with stage I endometrial cancer who undergo thorough surgical staging are stratified by adverse risk factors (ie, age, positive lymphovascular space invasion [LVSI], tumor size, and lower uterine [cervical/glandular] segment involvement). Recommended adjuvant treatment is shown in the algorithm (see ENDO-5, page 253). Note that the treatment algorithm was revised in 2010 based on the updated FIGO/AJCC staging (7th edition).[46,48] However, by necessity, much of the discussion in this manuscript has been based on the older FIGO/AJCC staging system. The implications of stage migration should be taken into account when evaluating historical data (see Table 1 in the complete version of these guidelines, available online at NCCN.org).

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 5year survival rate for patients with surgical stage I endometrial cancer with no adverse risk factors other than grade and myometrial invasion (ie, without ex-

trauterine disease, isthmus/cervical involvement, or LVSI) was 92.7%.[117] 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 these guidelines (see ENDO-5, page 253).[70,118–121]

Adjuvant Radiation Therapy: Several phase III trials have assessed adjuvant therapy in patients with uterine-confined disease. In summary, the use of adjuvant radiation therapy improves pelvic control in patients with selected risk factors (and may improve PFS), but radiation therapy did not improve overall survival 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 adenocarcinoma histologies.

The basic concept underlying the recommendations in these guidelines is the trend toward selection of more aggressive adjuvant therapy for patients as tumor grade and myometrial and/or cervical invasion worsen, because risk exists on a continuum.[118] In surgical stage I and II endometrial cancer, other pathologic factors that may influence the decision regarding adjuvant therapy include patient age, tumor volume, and involvement of the lower uterine segment.

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 (ie, Postoperative Radiation Therapy in Endometrial Carcinoma [PORTEC-1][122] and the trial by Aalders et al[123]). In the third trial (ASTEC/EN.5), only 50% of the patients were thoroughly staged as part of a companion surgical protocol.[58,124] However, formal surgical staging was mandated for all patients in the fourth trial (GOG-99).[125] Note that these trials used the older staging system (ie, before 2010).

The PORTEC-1 trial suggested that external-beam pelvic RT provides a therapeutic benefit in selected patients with uterine-confined disease.[122,126] Although radiation therapy significantly decreased locoregional recurrence, it did not increase overall survival.[127] The randomized trial by Aalders et al[123] found that radiation therapy reduced vaginal (ie, locoregional) recurrences but did not reduce distant metastases or improve survival. A recent pooled randomized trial (ASTEC/EN.5) suggested that adjuvant pelvic radiation therapy alone did not improve either relapse-free survival (ie, PFS) or overall survival in patients with intermediate-risk or high-risk early-stage endometrial cancer, but a small improvement in pelvic control was seen.[124] However, the ASTEC/EN.5 study is very controversial; 51% of the patients in the ASTEC observation group received vaginal brachytherapy.[61,128] The GOG-99 trial by Keys et al[125] showed that adjuvant pelvic radiation therapy improved locoregional control and relapse-free interval (ie, PFS), without conferring an overall survival benefit. Both the GOG-99 and PORTEC-1 trials revealed that most of the initial recurrences in patients with initial uterine-confined tumors were limited to the vagina, prompting the increasing use of vaginal brachytherapy alone as adjunctive treatment.[125,129,130]

To help select a patient population who may benefit from adjuvant radiation therapy, the GOG-99 and PORTEC-1 trials defined risk factors for women at high-intermediate risk (HIR) for recurrence.[122,125] 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.[125] If they were aged 50 to 70 years, they were considered HIR if they had 2 histologic risk factors. Women aged 70 years or older were considered HIR if they also had one risk factor. In PORTEC-1, women had to have 2 of 3 risk factors (age >60 years, deep myometrial invasion, grade 3 histology) to be considered at HIR for recurrence.[122,129]

Because of concerns about potential toxicity of external-beam pelvic radiation therapy, the role of vaginal brachytherapy alone in uterine-confined disease has been evaluated. PORTEC-2 randomly assigned patients to either external-beam pelvic radiation therapy or vaginal brachytherapy alone in uterine-confined disease. Results of this trial showed excellent and equivalent vaginal and pelvic control rates with both adjuvant radiation approaches, and no difference in overall survival.[131] Given that vaginal brachytherapy is associated with significantly less toxicity than pelvic radiation therapy, vaginal

brachytherapy alone is a reasonable choice for most patients with uterine-confined endometrial cancer who are deemed candidates for adjuvant radiation therapy.[129–137] The use of vaginal brachytherapy and/or whole pelvic radiation therapy should be carefully tailored to a patient's pathologic findings. Both PORTEC-1 and PORTEC-2 specifically excluded patients with 1998 FIGO stage IC, grade 3 endometrial carcinoma (2010 FIGO stage IB, grade 3)[46,48]; thus, the use of adjuvant brachytherapy alone in the highest-risk subset remains undetermined.

The benefit of adjuvant external-beam radiation therapy in the highest-risk spectrum of uterine-confined disease remains controversial. Most panel members feel that patients with deeply invasive grade 3 tumors should receive adjuvant treatment. However, given the lack of consistent absolute survival benefit, observation (category 2B) may be appropriate in selected cases. Two large retrospective SEER analyses of women with endometrial cancer found that adjuvant radiation therapy improved overall survival in those with high-risk disease.[138,139] In a meta-analysis of randomized trials, a subset analysis found that adjuvant pelvic radiation therapy 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.[133,140–143]

Adjuvant Chemotherapy: Patients with 1998 FIGO stage IC, deeply invasive, grade 3, uterine-confined disease have a relatively poor prognosis (revised to 2010 FIGO stage IB, grade 3). Despite adjuvant therapy with pelvic radiation therapy, a significant number of patients continue to have an appreciable risk of distant metastases.[125,126] Therefore, some clinicians suggested that adding chemotherapy to adjuvant radiation therapy may provide added therapeutic benefit (ie, decrease distant metastases).[118,144] Studies have evaluated the role of chemotherapy in highest-risk uterine-confined disease.[144,145] PFS is improved with adjuvant sequential chemotherapy/radiation therapy.[144] However, the panel feels that adjuvant chemotherapy is a category 2B recommendation in this setting because an overall survival advantage has not been shown.[144] The role of adjuvant chemotherapy in invasive high-grade, uterine-confined disease is being further studied (eg, GOG-249, PORTEC-3).

The recommended postoperative (ie, adjuvant) treatment options for patients with surgical stage II disease (using thorough surgical staging) are shown in the algorithm (see ENDO-6, page 254). The 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.

Radiotherapy Principles

Radiation therapy has been a widely used modality in the treatment of patients with endometrial cancer; it clearly improves locoregional control. Tumor-directed radiation therapy refers to radiation therapy directed at sites of known or suspected tumor involvement and may include external-beam radiation therapy (EBRT) and/or brachytherapy. Radiation therapy is described in detail in the algorithm, including target areas and doses for pelvic radiation therapy and brachytherapy (see UN-A, page 262).

Although adjuvant radiation therapy is typically not associated with high rates of severe morbidity,[146] studies have focused on its subtle effects on quality of life (eg, diarrhea, bowel symptoms) that deserve further investigation.[134,136] In the PORTEC-2 trial, vaginal brachytherapy was associated with better quality of life when compared with EBRT, without a significant detriment to outcome.[134] Therefore, many patients who were previously treated with adjuvant EBRT are now appropriately treated with vaginal brachytherapy, and this recommendation is reflected in these guidelines. Patients treated with radiation therapy are prone to vaginal stenosis, which can impair sexual function. Women can use vaginal dilators to prevent or treat vaginal stenosis. Dilator use can begin 2 to 4 weeks after radiation therapy is completed and can be used indefinitely (http://www.mskcc.org/patient_education/_assets/downloadsenglish/571.pdf).

Posttreatment Surveillance

The recommended posttreatment surveillance protocol for endometrial cancer is shown in the algorithm (see ENDO-9, page 256).[30] These recommendations recognize that the value of intensive surveillance has not been demonstrated in this disease; therefore, ancillary testing is not recommended.[147,148]

Patients with clinical stage I and II endometrial cancer have a recurrence rate of approximately 15%[23,148–150]; 50% to 70% of patients have symptomatic recurrences. For most patients, disease recurs within 3 years of initial treatment. Because most recurrences are symptomatic, all patients should receive verbal and written information regarding the symptoms of recurrent disease.[148] Patients with bleeding (vaginal, bladder, or rectal), decreased appetite, weight loss, pain (in the pelvis, abdomen, hip, or back), cough, shortness of breath, and swelling (in the abdomen or legs) should seek prompt evaluation and not wait until their next scheduled appointment.

In the absence of recurrence, posttreatment surveillance provides psychosocial reassurance and improves the quality of life for patients and their families. Health maintenance has been incorporated into the followup schedule (eg, blood pressure determination, breast examination, mammography as clinically indicated, stool guaiac test, immunizations), including lifestyle, obesity, exercise, and nutrition counseling (see the NCCN Guidelines for Survivorship [available online at NCCN.org] and http://www.cancer.org/treatment/survivorshipduringandaftertreatment/index).[151–153] Other health problems that often coexist in patients with endometrial cancer can also be evaluated during follow-up. Given the lack of prospective studies regarding the optimal frequency of posttreatment follow-up, the panel believes that the algorithm represents a reasonable surveillance scheme. For the 2014 update, the use of vaginal cytology is no longer recommended for asymptomatic patients, consistent with the SGO guidelines.[147,148,150,154] Patients with stage I endometrial cancer have a low risk of asymptomatic vaginal recurrence (2.6%), especially after adjuvant brachytherapy, and vaginal cytology is not independently useful for detecting recurrences in this group of patients.[155]

Hormone Replacement Therapy for Hypoestrogenism

After BSO, hypoestrogenism is associated with hot flashes, mood lability, vaginal dryness, pelvic soft tissue atrophy, osteoporosis, and an increased risk of cardiovascular disease. In postmenopausal women, estrogen replacement therapy was believed to reduce or reverse some of these signs and symptoms. However, women who have had BSO for endometrial adenocarcinoma have usually been denied estrogen replacement therapy for fear of inducing a higher relapse rate, because this cancer has historically been considered an estrogen-linked malignancy.[156,157] However, estrogen replacement therapy for these patients remains controversial.

It has never been proven that patients with endometrial cancer who receive estrogen replacement therapy after hysterectomy have a higher relapse rate. In fact, several retrospective trials of estrogen replacement after treatment of early-stage endometrial cancer have shown no increase in tumor recurrence or cancer-related deaths.[158–160] In women with stage I to II endometrial cancer who had hysterectomy, a randomized trial of estrogen replacement therapy versus placebo did not find an increased rate of recurrence or new malignancy; the median follow-up was 35.7 months.[161] However, estrogen replacement trials in postmenopausal women without a history of malignancy have shown a significantly increased risk of breast cancer.[162]

Initially, the Women's Health Initiative Estrogen-Alone Trial in women who had hysterectomy (n=10,739) reported that the risk of developing breast cancer and cardiovascular disease (eg, stroke) were increased and that estrogen replacement therapy was of concern; thus, the trial was stopped.[163] However, recent long-term follow-up data from this trial suggest that the risk from estrogen-alone replacement therapy (without progesterone) may not be as high in younger women (age <60 years) who have had hysterectomy.[164]

The panel agrees that estrogen replacement therapy is a reasonable option for patients who are at low risk for tumor recurrence, but initiating this therapy should be individualized and discussed in detail with the patient.[165,166] If adjuvant treatment is performed, there should be a 6- to 12-month waiting period before initiation of hormone replacement therapy, and participation in clinical trials is strongly encouraged. Selective estrogen-receptor modulators (SERMs) may prove to be attractive options for hormone replacement therapy.[167,168] Long-term comparisons between conjugated estrogens and SERMs for hormone replacement therapy are needed. Nonhormonal therapy may be considered in patients who are deemed poor candidates for hormone replacement therapy (eg, smokers, history of breast cancer, history of multiple strokes).[169,170]

Drug Reactions

Virtually all drugs have the potential to cause adverse hypersensitivity reactions, either during or after the infusion.[171] In gynecologic oncology treatment, drugs that more commonly cause adverse reactions include carboplatin, cisplatin, docetaxel, liposomal doxorubicin, and paclitaxel. Most of these responses are mild infusion reactions (ie, skin reactions, cardiovascular reactions, respiratory or throat tightness), but more severe allergic reactions (ie, life-threatening anaphylaxis) can occur.[172–174] In addition, patients can have mild allergic or severe infusion reactions. Infusion reactions are more common with paclitaxel.[175] Allergic reactions (ie, true drug allergies) are more common with platinum agents (ie, carboplatin, cisplatin).[175,176]

Management of drug reactions is discussed in the NCCN Guidelines for Ovarian Cancer (to view the most recent version of these guidelines, visit NCCN.org).[175] It is important to note that patients who have had severe life-threatening reactions should not receive the implicated agent again unless under the care of an allergist or expert in managing drug reactions. If a mild allergic reaction has previously occurred and it is appropriate to administer the drug again, a desensitization regimen should be used even if the symptoms have resolved; various desensitization regimens have been published and should be followed.[177–179] Patients must be desensitized with each infusion if they previously had a reaction. Almost all patients can be desensitized (≈90%).[171] To maximize safety, it is prudent to desensitize patients in the intensive care unit.[171]

Uterine Serous Adenocarcinomas, Clear Cell Adenocarcinomas, and Carcinosarcomas

Overview

Uterine serous adenocarcinomas, clear cell adenocarcinomas, and carcinosarcomas are considered more aggressive histologic variants of malignant epithelial tumors, with a higher incidence of extrauterine disease at presentation.[180–187] Carcinosarcomas are aggressive tumors that are staged as high-grade endometrial cancer (see Table 1 in the complete version of these guidelines, available online at NCCN.org).[188,189] Pathologists now believe that carcinosarcomas (also known as MMMTs) are metaplastic carcinomas and not uterine sarcomas; therefore, carcinosarcomas are included in the high-risk malignant epithelial tumors section of the NCCN Guidelines (see ENDO-11, page 257).[184,187,190,191] Even patients with apparent early-stage disease may have distant metastases. Thus, fertility-sparing therapy is not recommended for these aggressive tumors. If performed, sentinel lymph node mapping should proceed with particular caution (see the complete version of these guidelines).

Patients may present with pelvic masses, abnormal cervical cytology, or ascites in addition to postmenopausal bleeding. Both the NCCN Uterine Neoplasms Panel and the SGO recommend that CA-125 and MRI/CT may be useful before surgery to assess if extrauterine disease is present; PET may also be useful.[180] Serous adenocarcinomas, clear cell adenocarcinomas, and carcinosarcomas are all considered high-risk tumors (ie, grade 3), although they are staged using the same FIGO/AJCC staging system (ie, 7th edition) as endometrial cancers (see Table 1 in the complete version of these guidelines, available online at NCCN.org).[46] Patterns of failure often mimic those of ovarian cancer.

Treatment

Multimodality therapy is typically recommended for these histologically aggressive tumors. Primary treatment includes TH/BSO with surgical staging, peritoneal lavage for cytology, omental and peritoneal biopsies, and consideration of maximal tumor debulking for gross disease (see ENDO-B, page 259).[192]

Adjuvant therapy is highly individualized.[193–200] For patients with stage IA without myometrial invasion, options include observation, chemotherapy, or tumor-directed radiation therapy.[201] For all other patients with more advanced disease, chemotherapy with (or without) tumor-directed radiation therapy is the preferred option.[182,194,198,202] Adjuvant platinum/taxane-based therapy seems to improve survival in patients with uterine serous and clear cell adenocarcinoma, whereas ifosfamide/paclitaxel (category 1) is recommended for carcinosarcomas (see ENDO-C, page 260).[180-182,203–205] For the 2014 update, whole abdominopelvic radiation therapy with (or without) vaginal brachytherapy is no longer recommended as a primary treatment option for patients with advanced disease, because the panel no longer believes that routine use of whole abdominal radiation therapy is appropriate.[202,206,207] Chemotherapy with (or

without radiation therapy) seems to be more effective than radiation therapy alone.[194] Data are conflicting regarding the rate of abdominal recurrence in these patients.[202,208–212] Whole abdominal radiation therapy is not considered to be tumor-directed radiation therapy (see UN-A, page 262). As previously mentioned, *tumor-directed radiation therapy* refers to radiation therapy directed at sites of known or suspected tumor involvement and may include external-beam radiation therapy and/or brachytherapy. In general, tumor-directed external-beam radiation therapy is directed to the pelvis with (or without) the para-aortic region.

Ifosfamide was historically considered the most active single agent for carcinosarcoma.[204,213,214] A phrase 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.[204,215] Overall survival was 13.5 months with ifosfamide/paclitaxel versus 8.4 months with ifosfamide alone. Therefore, ifosfamide/paclitaxel is category 1 in these guidelines (see ENDO-C, page 260).[204] A phase II trial suggests that paclitaxel/carboplatin is also a useful regimen for carcinosarcoma (response rate, 54%).[216] A GOG trial is currently assessing ifosfamide/paclitaxel versus carboplatin/paclitaxel.[188]

Data regarding carcinosarcoma suggest that adjuvant pelvic radiation therapy decreases the rate of local recurrences when compared with surgery alone.[217–222] This improvement in local control reported in some series correlates with an improvement in survival, although other data show that lymphadenectomy confers greater benefit.[221–224] A phase III randomized trial (GOG-150) in patients with carcinosarcoma of the uterus assessed whole abdominal radiation therapy versus cisplatin/ifosfamide, but no difference was seen in survival between the groups.[207,212] A recent cohort study in women with early-stage MMMT suggests that postoperative chemotherapy improves PFS compared with radiation therapy or observation.[188]

Uterine Sarcomas

Uterine sarcomas are uncommon tumors (≈3% of all uterine neoplasms). Risk factors for uterine sarcomas include a history of pelvic radiation. Uterine sarcomas are stromal/mesenchymal tumors that are generally categorized into uLMS, ESS, and high-grade (undifferentiated) endometrial sarcoma (see "Uterine Sarcoma Classification" in the complete version of these guidelines, available online at NCCN.org). Most uterine sarcomas are LMS; ESS and high-grade (undifferentiated) endometrial sarcomas are rare (see UTSARC-1, page 261). Patients with stromal or mesenchymal tumors are not usually screened for Lynch syndrome. Because this guideline mainly focuses on early-stage malignant epithelial carcinoma, in-depth information about uterine sarcomas is not provided.

Pathologic definitions of the various histologies are undergoing revision.[2] By definition, ESS has low-grade cytologic features; JAZF1 rearrangements are common. However, high-grade subtypes of endometrial sarcomas (undifferentiated endometrial sarcomas in the WHO classification) are still being defined (eg, those with YWHAEFAM22 rearrangements).[225,226] Note that molecular subtyping is helpful, but not essential, for diagnosing undifferentiated endometrial sarcomas.

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Individual Disclosures of the NCCN Uterine Neoplasms Panel					
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