NCCN National Comprehensive Cancer Network®

The NCCN

Uterine Neoplasms

Clinical Practice Guidelines in Oncology™

Benjamin E. Greer, MD; Wui-Jin Koh, MD; Nadeem Abu-Rustum, MD; Michael A. Bookman, MD; Robert E. Bristow, MD; Susana M. Campos, MD; Kathleen R. Cho, MD; Larry Copeland, MD; Marta Ann Crispens, MD; Patricia J. Eifel, MD; Warner K. Huh, MD; Wainwright Jaggernauth, MD; Daniel S. Kapp, MD, PhD; John J. Kavanagh, MD; John R. Lurain III, MD; Mark Morgan, MD; Robert J. Morgan, Jr., MD; C. Bethan Powell, MD; Steven W. Remmenga, MD; R. Kevin Reynolds, MD; Angeles Alvarez Secord, MD; William Small, Jr., MD; and Nelson Teng, MD, PhD

Overview

Adenocarcinoma of the endometrium is the most common malignancy in the female genital tract in the United States. An estimated 40,100 new diagnoses of uterine cancer and 7470 deaths from this disease will occur in 2008.[1] Uterine sarcomas are uncommon and account for approximately 1 in 12 of all uterine cancers.[2] These guidelines describe epithelial carcinomas and uterine sarcomas; each of these major categories contains specific histologic groups that require different management (see page 500).

By definition, these 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

Uterine Neoplasms Clinical Practice Guidelines in Oncology

Key Words

NCCN Clinical Practice Guidelines, uterine cancer, endometrial carcinoma, staging, surgery, chemotherapy, radiation therapy, hysterectomy, uterine sarcomas, nodal evaluation, brachytherapy (*JNCCN* 2009;7:498–531)

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

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

Please Note

These 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 these 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 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.

Disclosures for the NCCN Uterine Neoplasms Guidelines Panel

At the beginning of each NCCN guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Uterine Neoplasms Guidelines Panel members can be found on page 531. (To view the most recent version of these guidelines and accompanying disclosures, visit the NCCN Web site at www.nccn.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.nccn.org.

discussed among panel members during the process of developing these guidelines.

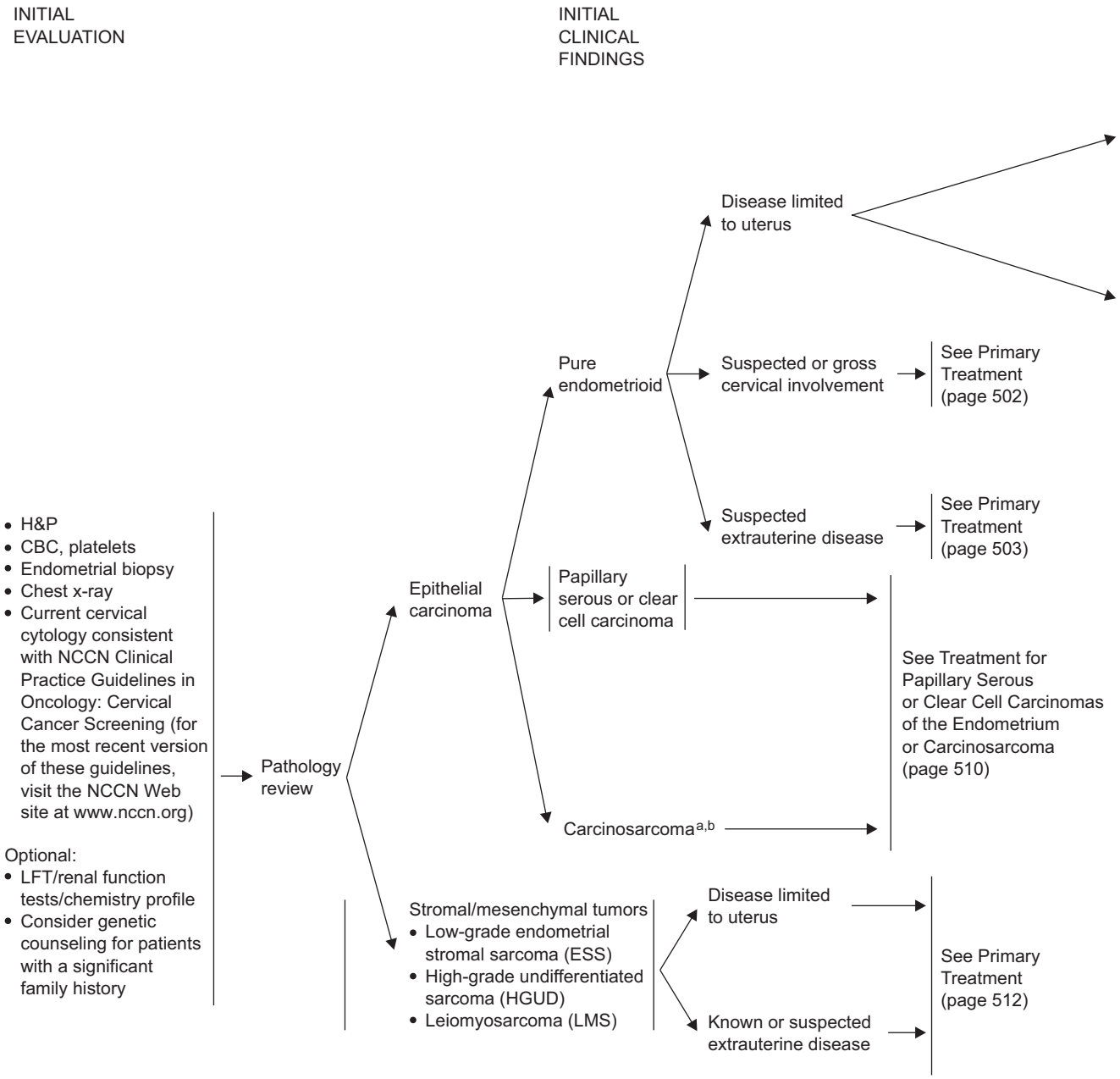
For patients with suspected uterine neoplasms, initial preoperative evaluation includes a history and physical examination, endometrial biopsy, chest radiograph, a CBC, and platelet count. A pathology review will determine whether patients have epithelial carcinoma (e.g., pure endometrioid cancer, papillary serous carcinoma, clear cell carcinoma, or carcinosarcoma, which is also known as malignant mixed Müllerian tumor); or stromal/mesenchymal tumors (e.g., low-grade endometrial stromal sarcoma [ESS], high-grade undifferentiated sarcoma [HGUD], or leiomyosarcoma [LMS]). If cervical involvement is suspected, cervical biopsy or MRI should be considered. Cervical cytology should be assessed using the NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer Screening (to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org).

Given the typical age group at risk for uterine neoplasms and the presence of comorbid illnesses, the blood chemistry profile and renal and liver function should also be measured in selected patients.

Endometrial Cancer

In approximately 75% of patients with adenocarcinoma of the endometrium, the invasive neoplasm is confined to the uterus at diagnosis. Many physicians believe that adenocarcinoma of the endometrium is a relatively benign disease, because the early symp-

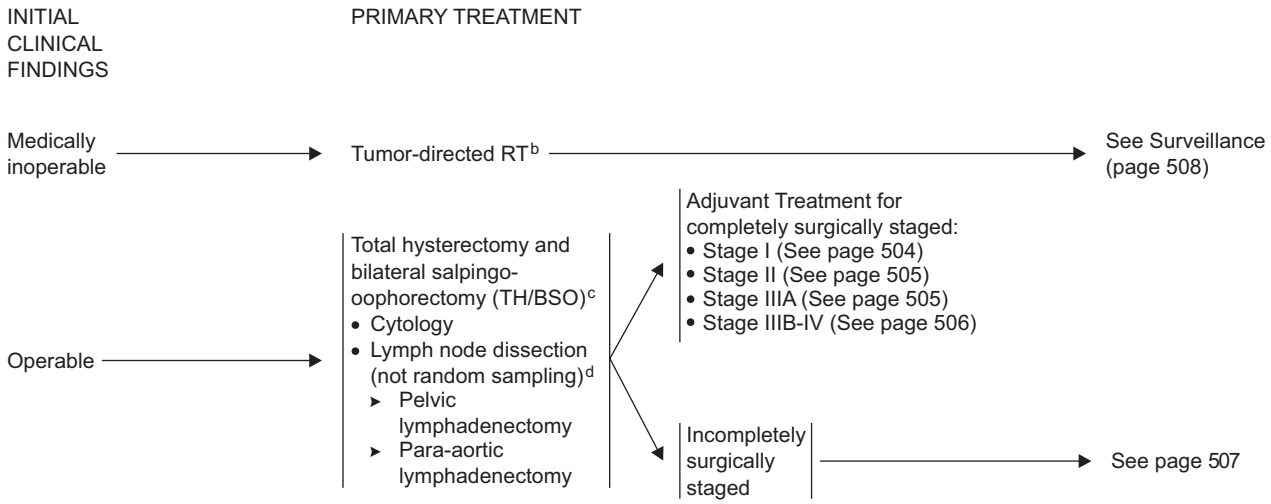
Text continues on p. 518



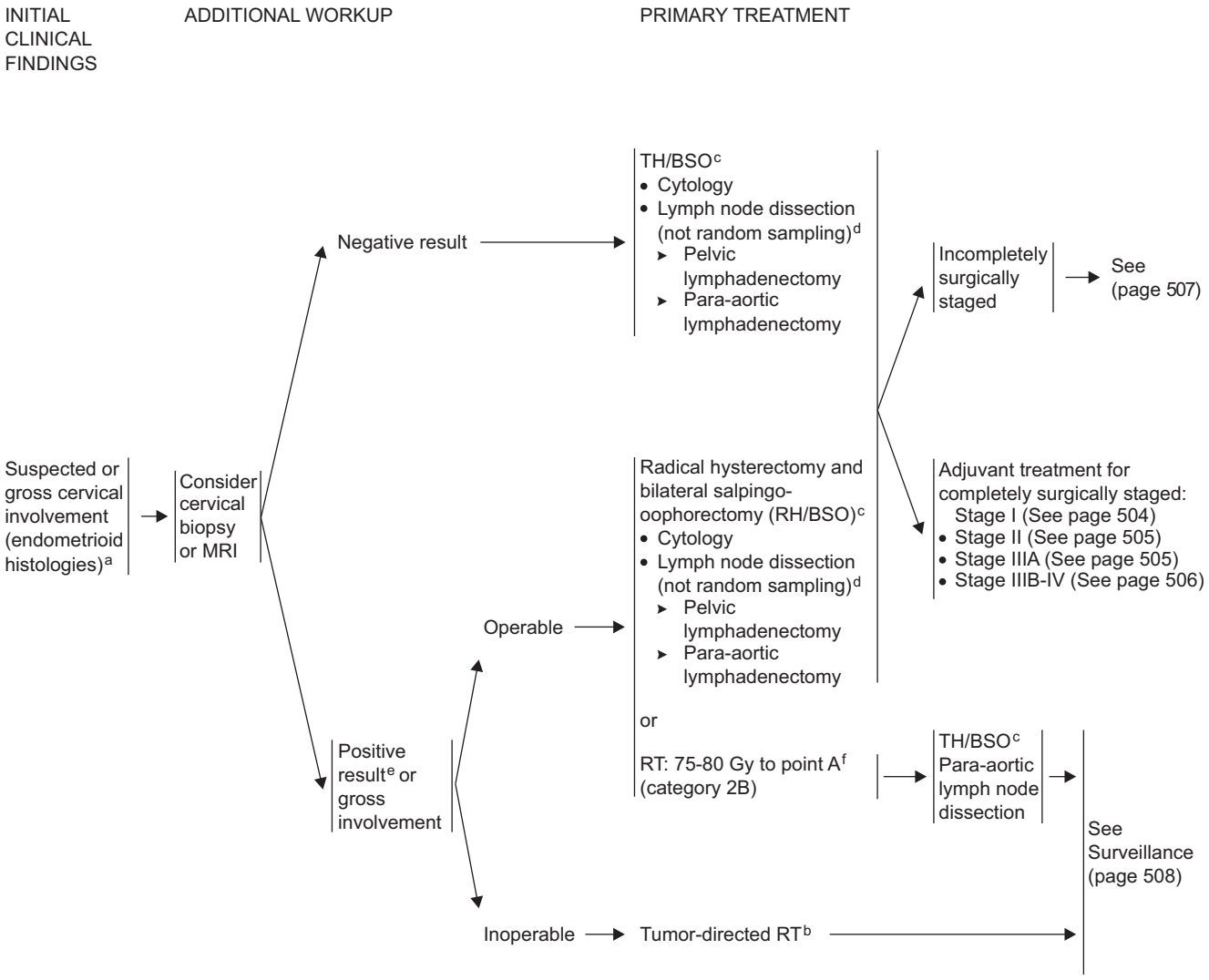
All staging in guideline is based on FIGO staging. (See staging table available online, in these guidelines, at www.nccn.org [ST-1].)

[a] Staged aggressively, should be treated as a high-grade endometrial cancer.
[b] Also known as malignant mixed mesodermal tumor or malignant mixed Müllerian tumor and including those with either homologous or heterologous stromal elements.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.

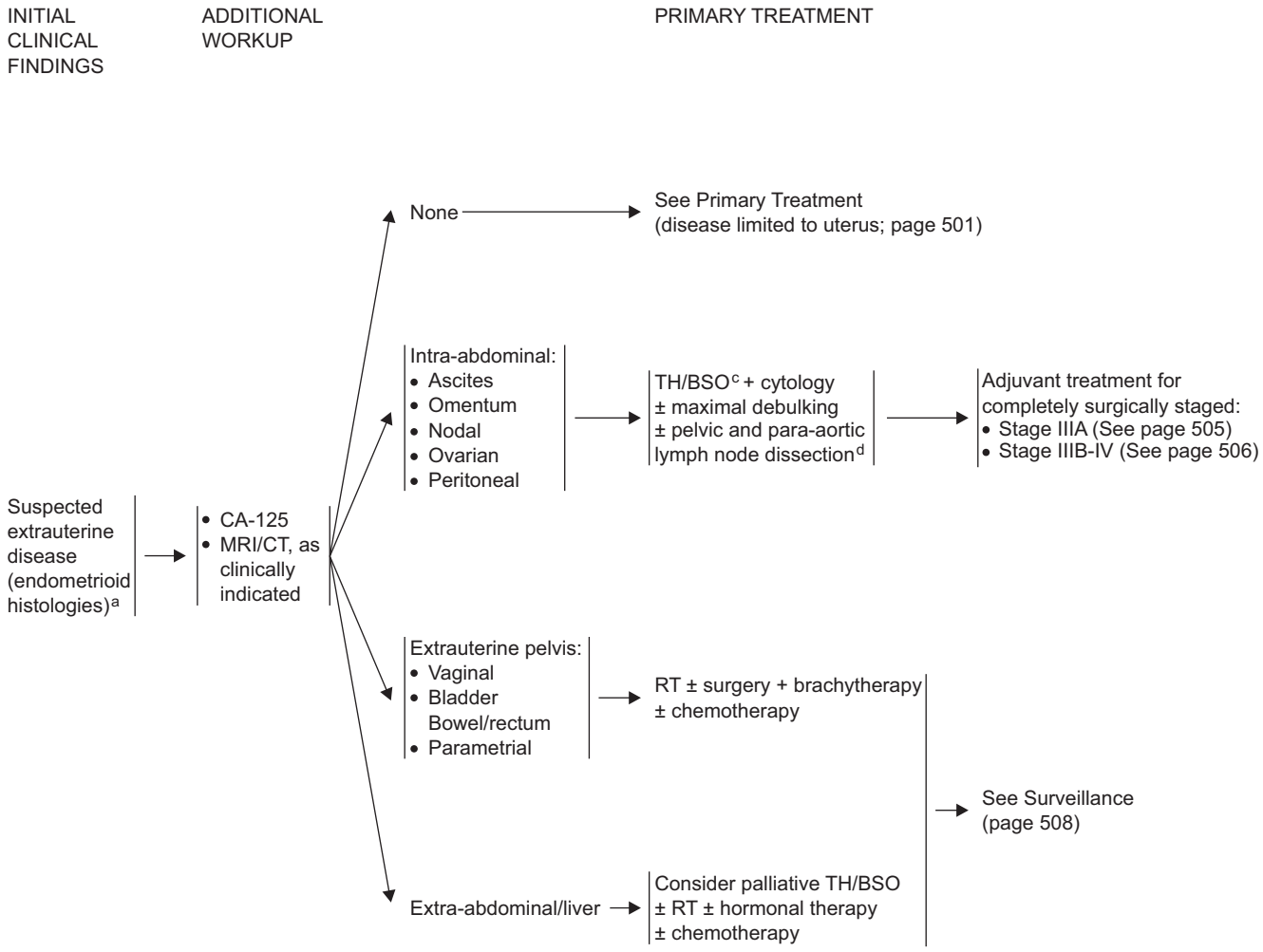


[a] See page 500 for clarification of uterine neoplasms.
[b] See Principles of Radiation Therapy (page 517).
[c] See Hysterectomy (page 511).
[d] American College of Obstetricians and Gynecologists practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstet Gynecol 2005;106:413-425.

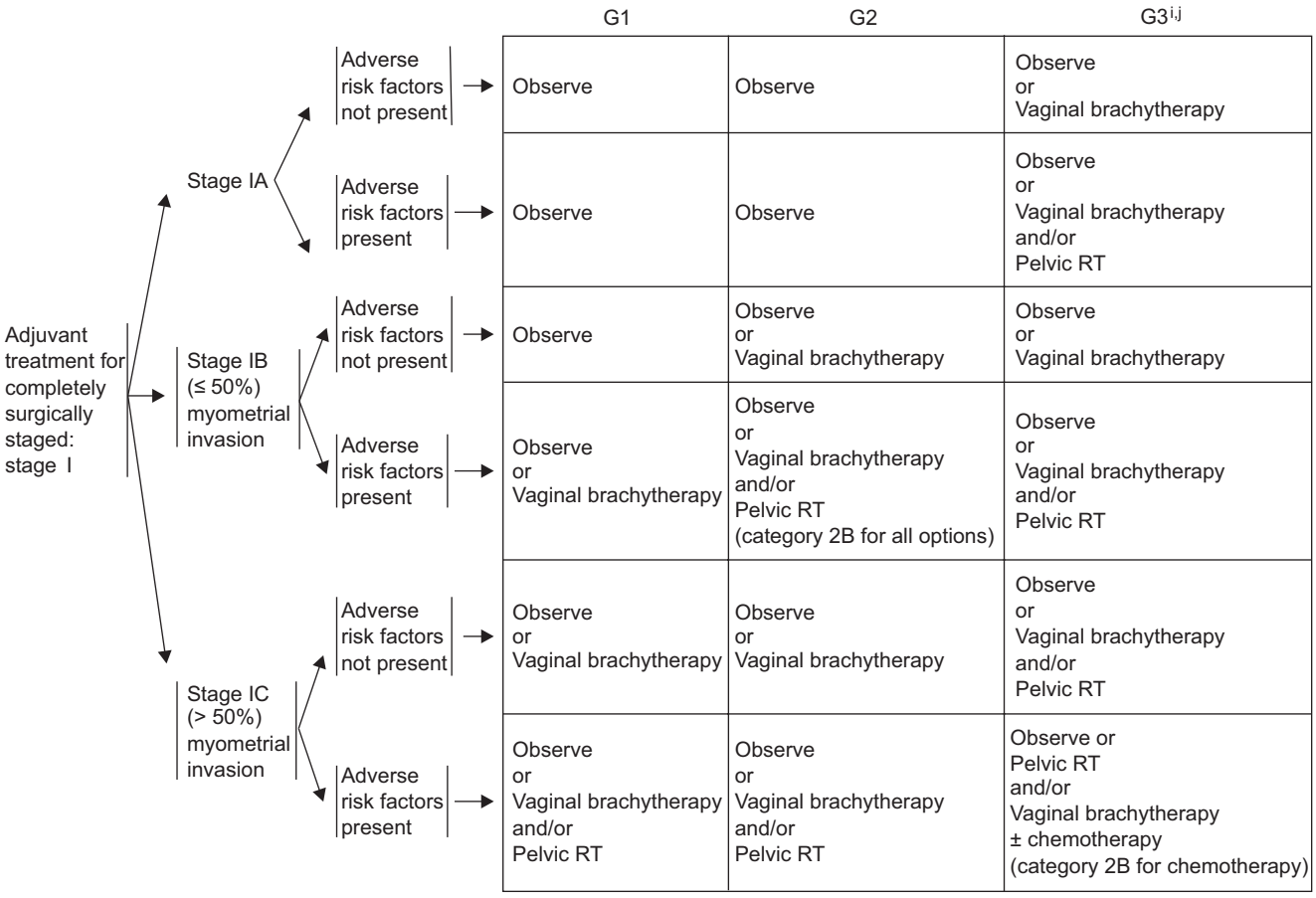


[a] See page 500 for clarification of uterine neoplasms.
[b] See Principles of Radiation Therapy (page 517).
[c] See Hysterectomy (page 511).
[d] American College of Obstetricians and Gynecologists practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstet Gynecol 2005;106:413-425.
[e] Clear demonstration of cervical stromal involvement.
[f] Based on summation of conventional external-beam fractionation and low-dose-rate brachytherapy equivalent.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.



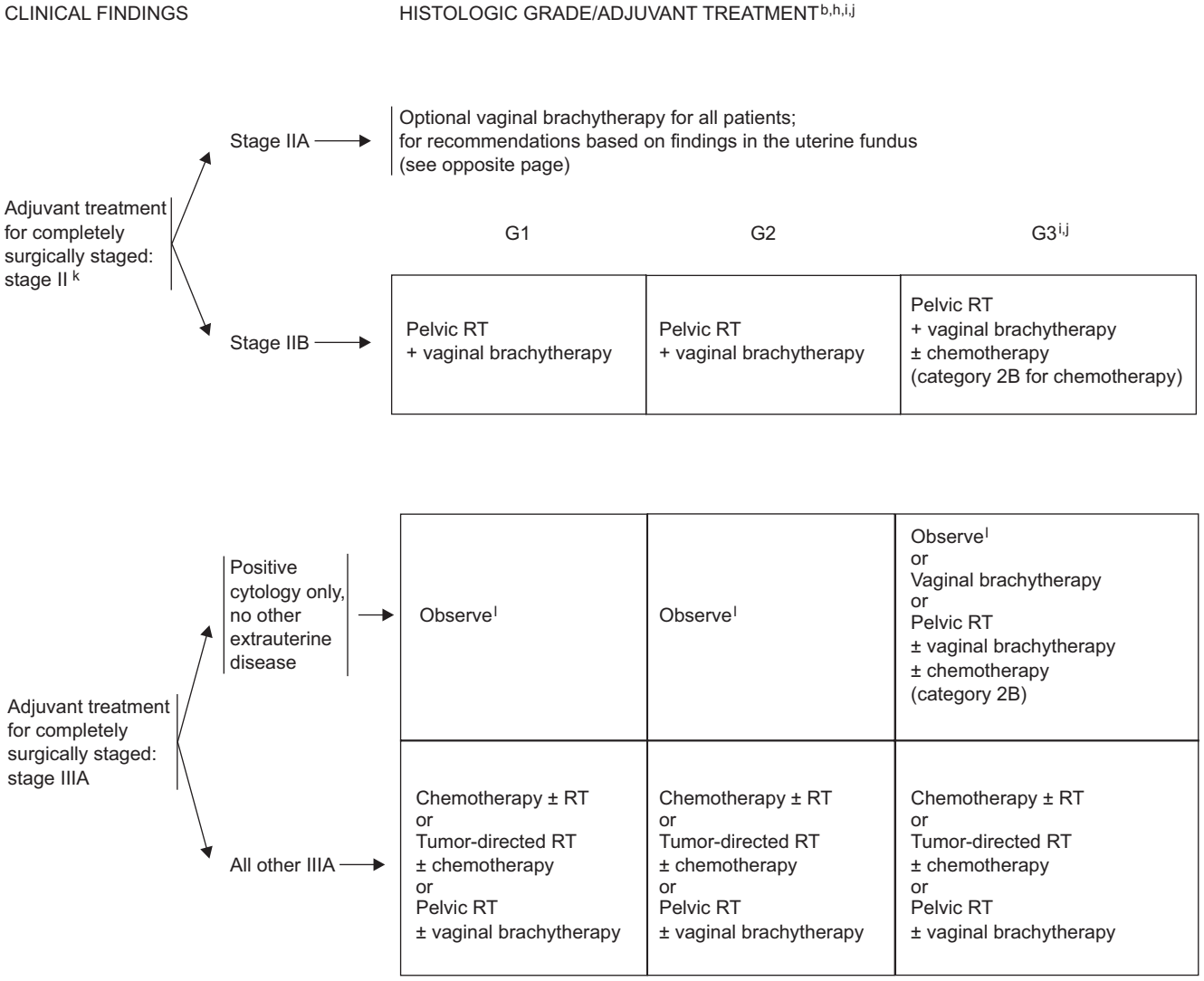
[a] See page 500 for clarification of uterine neoplasms.
[c] See Hysterectomy (page 511).
[d] American College of Obstetricians and Gynecologists practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstet Gynecol 2005;106:413-425.



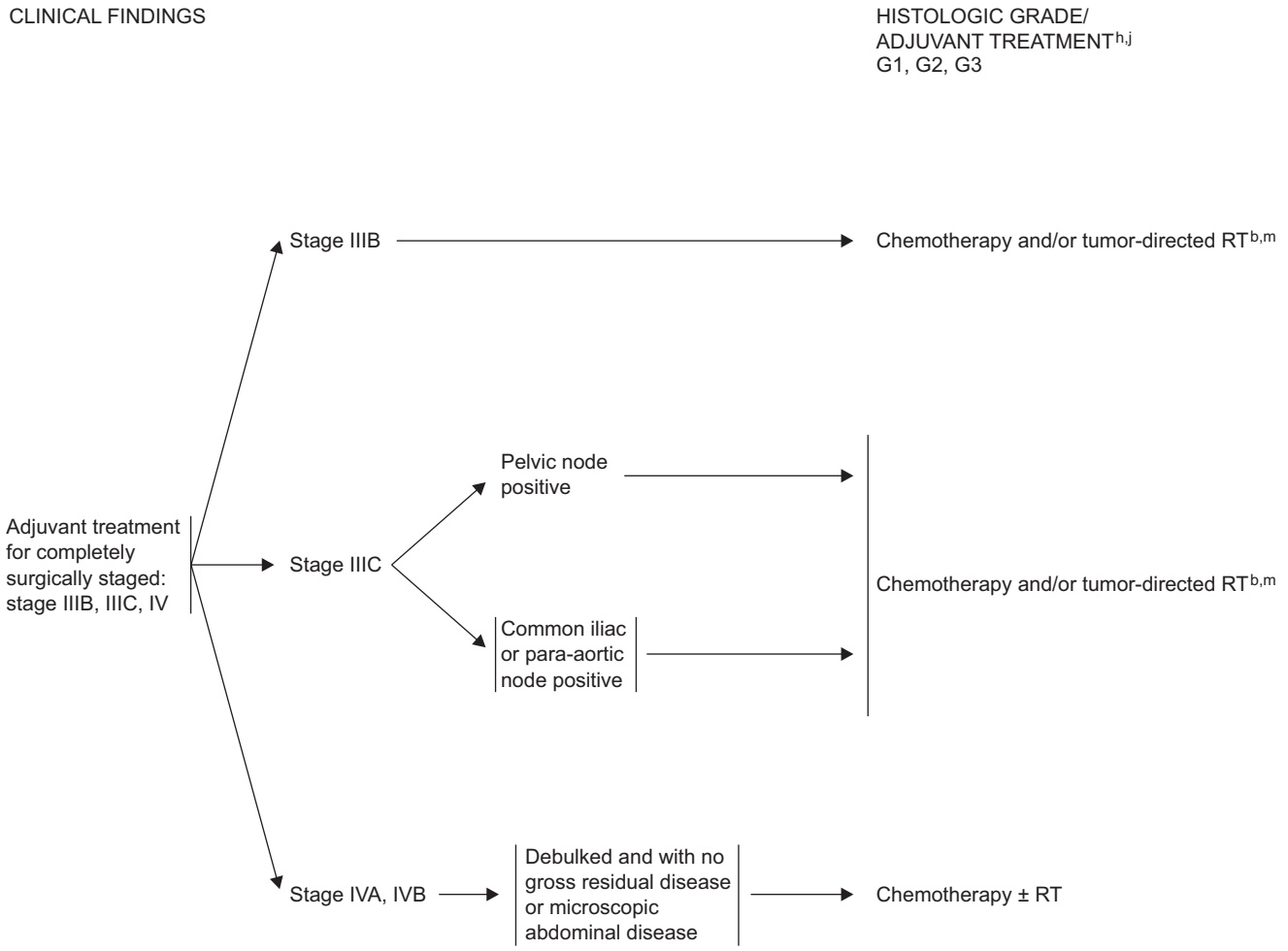
See Surveillance (page 508)

[b] See Principles of Radiation Therapy (page 517).
[g] Potential adverse risk factors include the following: age > 60 y, positive lymphovascular invasion, tumor size, lower uterine (cervical/glandular) involvement.
[h] Adjuvant therapy determinations are made on the basis of pathologic findings.
[i] The role of adjuvant chemotherapy in invasive high grade uterine confined disease is the subject of current studies. (ClinicalTrials.gov. Chemotherapy and Radiation Therapy Compared With Radiation Therapy Alone in Treating Patients With High-Risk Stage I, Stage II, or Stage III Endometrial Cancer. Available at: http://clinicaltrials.gov/ct/show/NCT00411138;jsessionid=2309E60C1051E921B4E2614F2BE708A4?order=9. Accessed March 30, 2009; and Hogberg T, Rosenberg P, Kristensen G, et al. A randomized phase-III study on adjuvant treatment with radiation (RT) ± chemotherapy (CT) in early-stage high-risk endometrial cancer (NSGO-EC-9501/EORTC 55991) [abstract]. J Clin Oncol 2007;25:Abstract 5503).
[j] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (page 511).

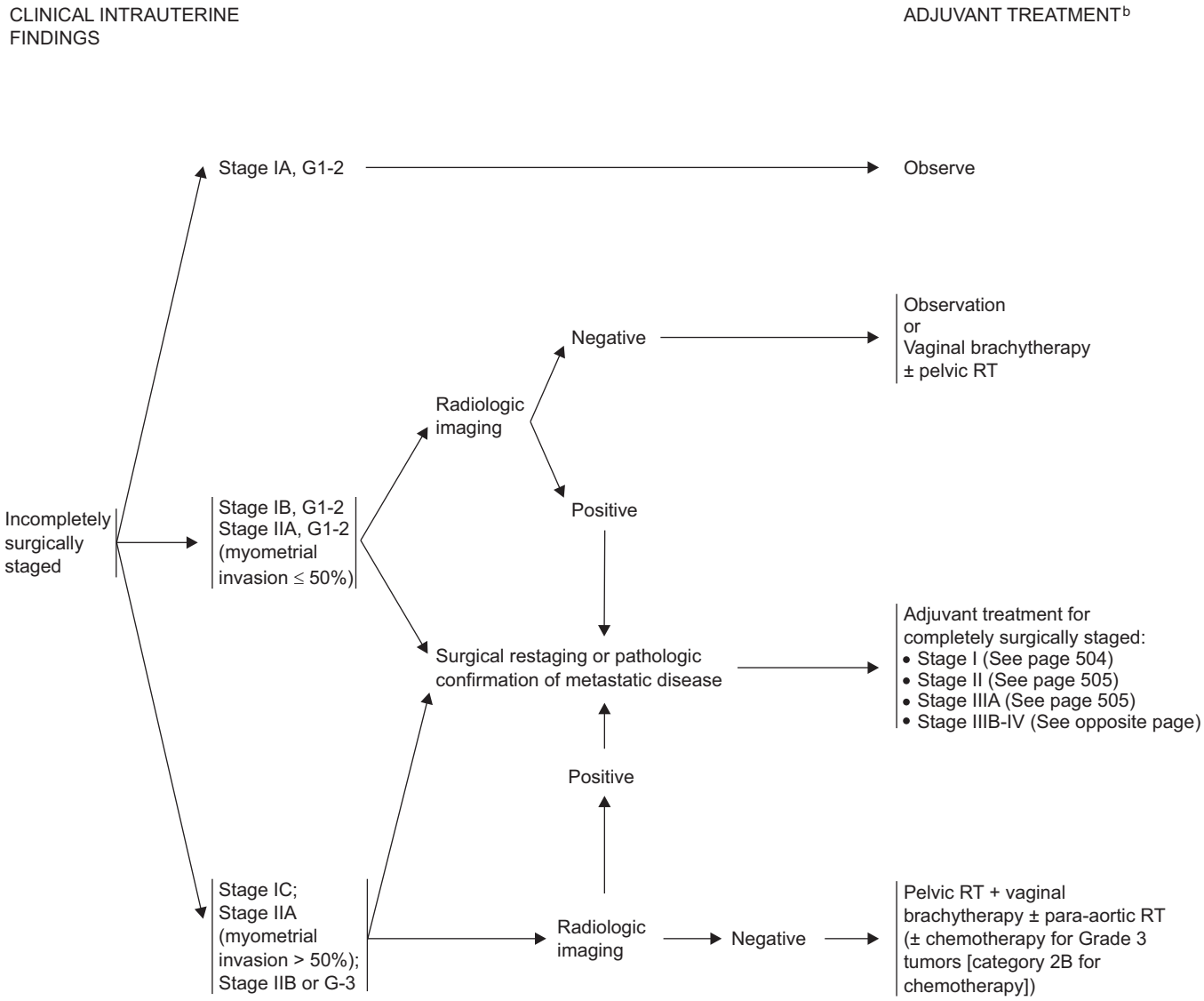
Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.



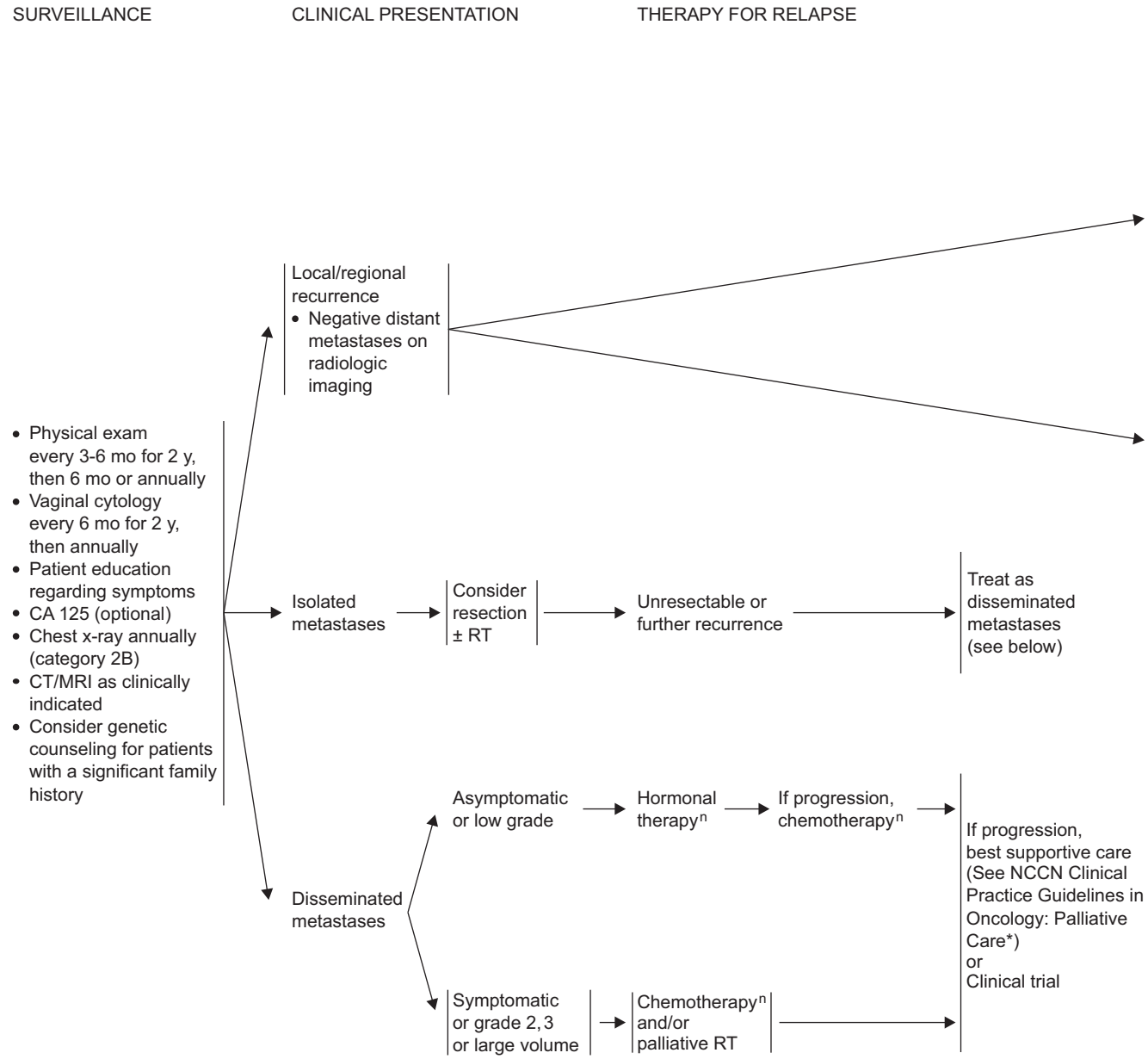
[b] See Principles of Radiation Therapy (page 517).
[h] Adjuvant therapy determinations are made on the basis of pathologic findings.
[i] The role of adjuvant chemotherapy in invasive high-grade uterine confined disease is the subject of current studies. (ClinicalTrials.gov. Chemotherapy and Radiation Therapy Compared With Radiation Therapy Alone in Treating Patients With High-Risk Stage I, Stage II, or Stage III Endometrial Cancer. Available at: http://clinicaltrials.gov/ct/show/NCT00411138;jsessionid=2309E60C1051E921B4E2614F2BE708A4?order=9. Accessed March 30, 2009; and Hogberg T, Rosenberg P, Kristensen G, et al. A randomized phase-III study on adjuvant treatment with radiation (RT) ± chemotherapy (CT) in early-stage high-risk endometrial cancer (NSGO-EC-9501/EORTC 55991) [abstract]. J Clin Oncol 2007;25:Abstract 5503).
[j] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (page 511).
[k] Observation or vaginal brachytherapy is an option for patients with stage II disease who are post primary radical hysterectomy with negative surgical margins and no evidence of extrauterine disease.
[l] Intrauterine risk factors may be treated following the guidelines on the opposite page and as seen above.



[b] See Principles of Radiation Therapy (page 517).
[h] Adjuvant therapy determinations are made on the basis of pathologic findings.
[j] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (page 511).
[m] Pelvic ± para-aortic lymph node RT based on surgical/pathologic findings.



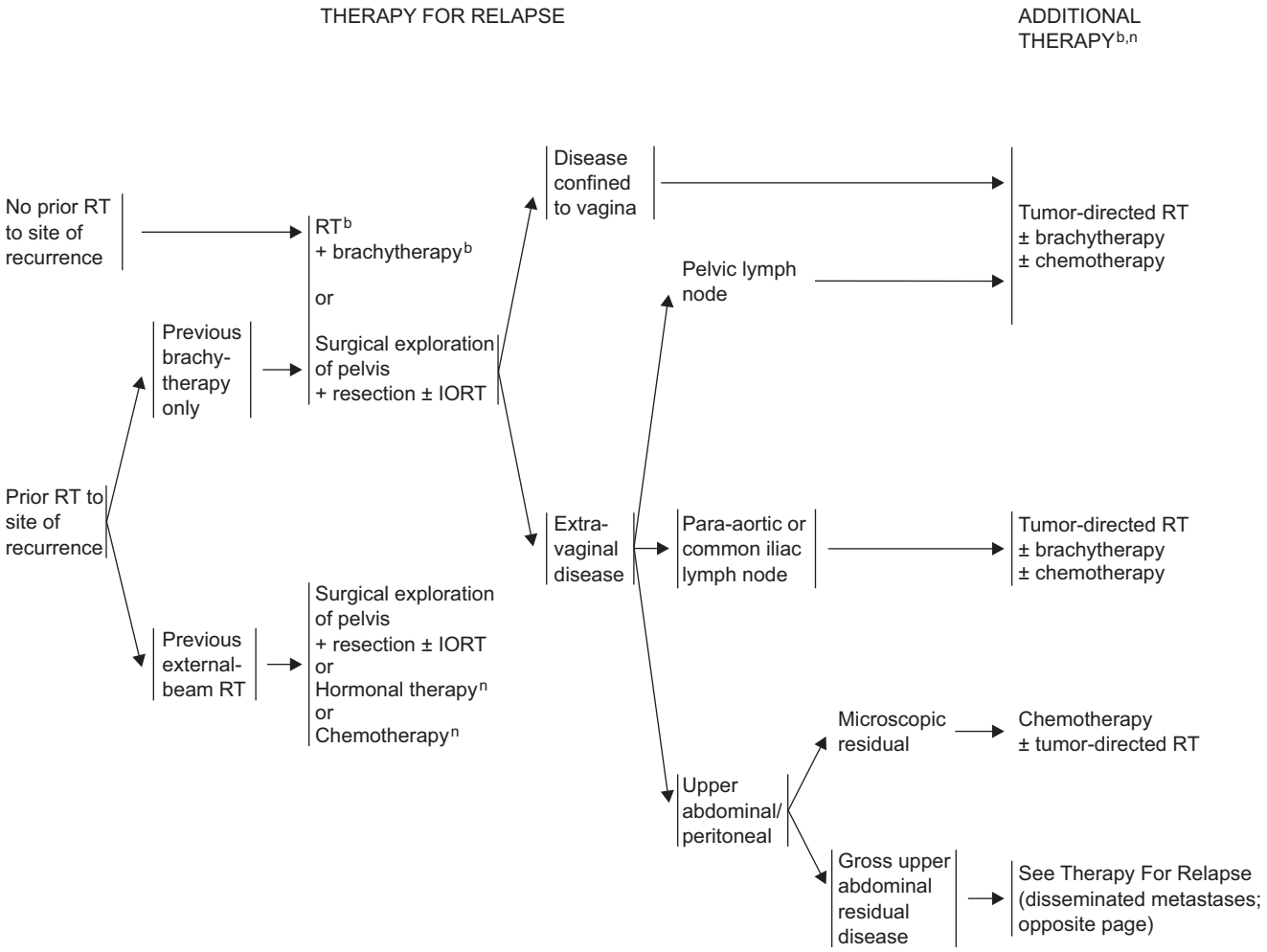
[b]See Principles of Radiation Therapy (page 517).



*For the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org

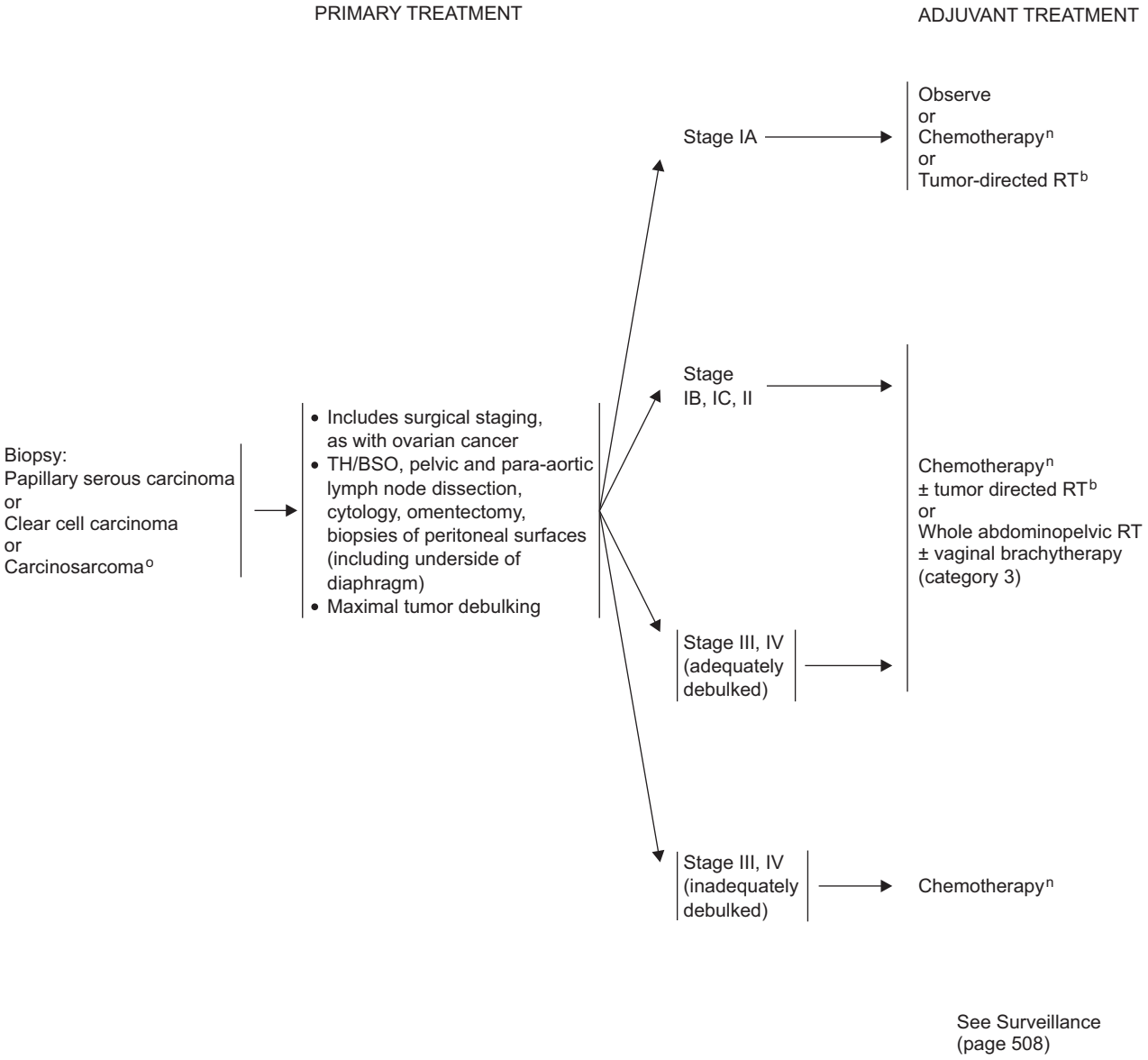
[n] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (page 511).

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.



[b] See Principles of Radiation Therapy (page 517).
[n] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (page 511).

PAPILLARY SEROUS OR CLEAR CELL CARCINOMA OF THE ENDOMETRIUM OR CARCINOSARCOMA[o]



[b] See Principles of Radiation Therapy (page 517).
[n] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (page 511).
[o] Also known as malignant mixed mesodermal tumor or malignant mixed Müllerian tumor and including those with either homologous or heterologous stromal elements.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.

HYSTERECTOMY

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

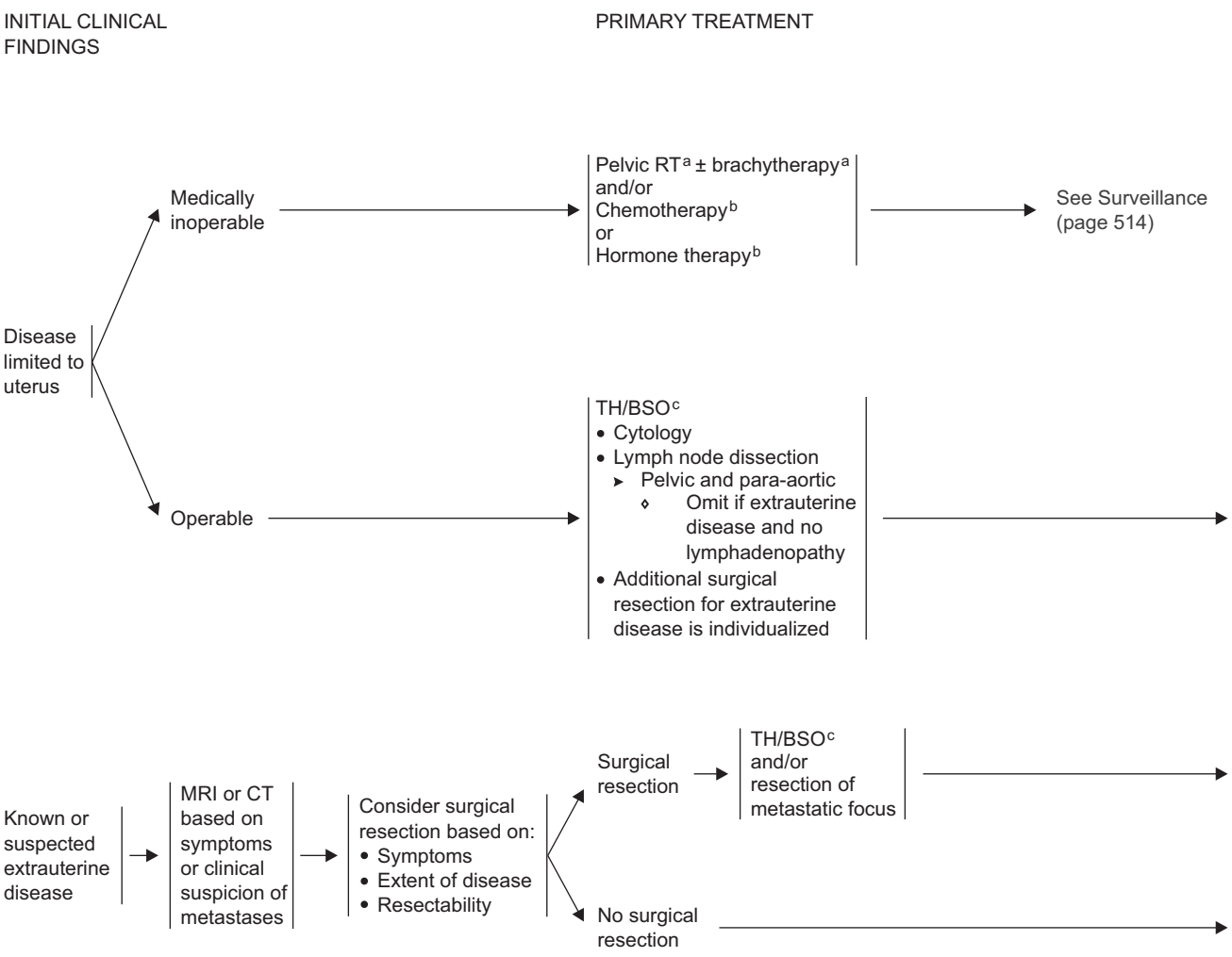
Pathologic assessment to include:
- Nodes
  - Level of nodal involvement (pelvic, common iliac, para-aortic)
- Peritoneal cytology
- Uterus
  - Ratio of depth of myometrial/stromal invasion to myometrial thickness
  - Cervical stromal or glandular involvement
  - Tumor size
  - Tumor location (fundus vs. lower uterine segment/cervix)
  - Histologic subtype with grade
  - Lymphovascular space invasion
  - Consider mismatch repair analysis to identify genetic problems
- Fallopian tubes/ovaries

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

HORMONAL THERAPY[1]
- Aromatase inhibitors
- Progestational agents
- Tamoxifen

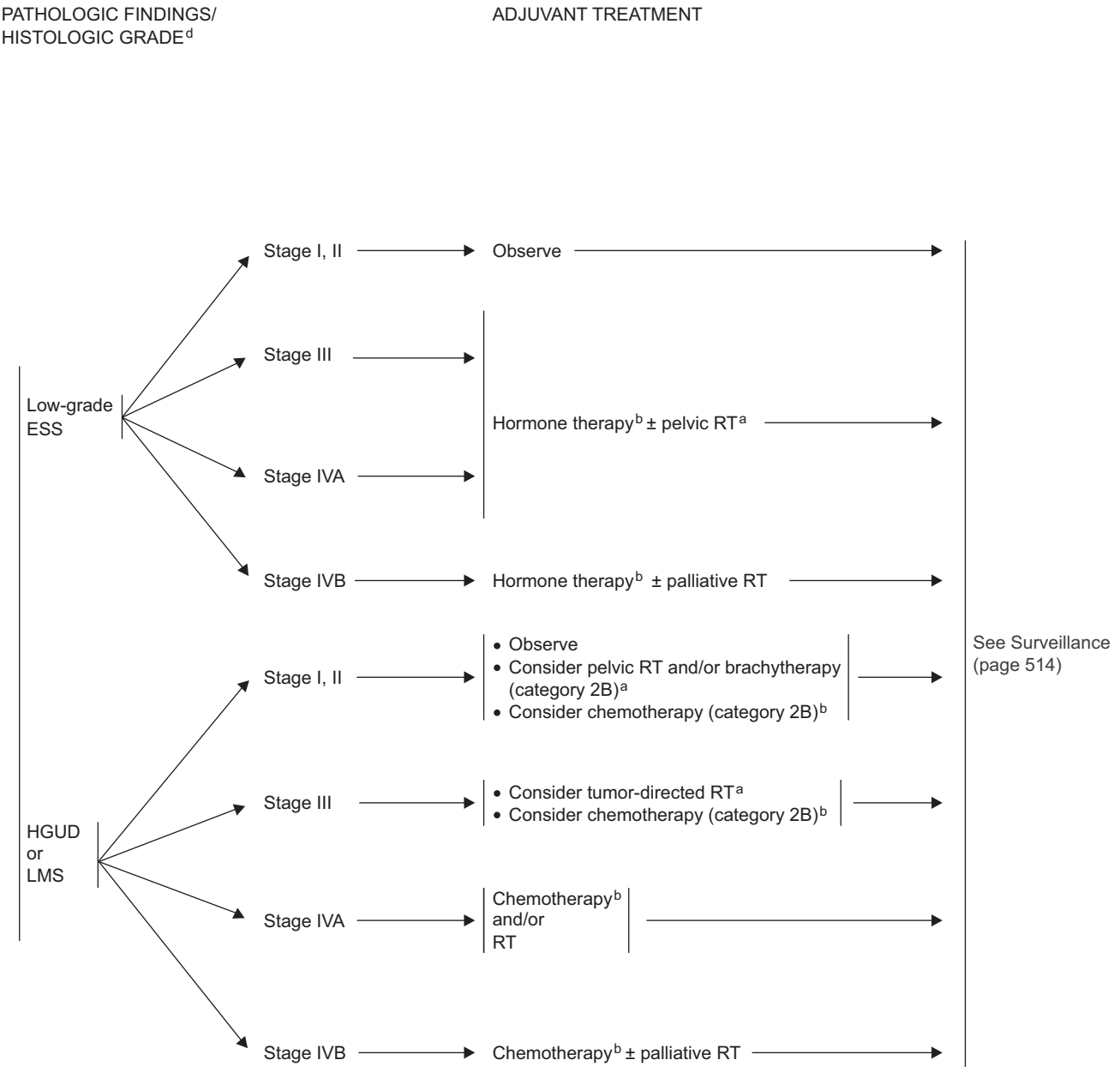
CHEMOTHERAPY REGIMENS[2]
(Multi-agent chemotherapy regimens preferred, if tolerated)
- Cisplatin/doxorubicin (category 1)
- Cisplatin/doxorubicin/paclitaxel (category 1)
- Ifosfamide plus paclitaxel (category 1 for carcinosarcoma)
- Carboplatin
- Carboplatin/paclitaxel
- Cisplatin
- Doxorubicin
- Paclitaxel
- Cisplatin/ifosfamide (for carcinosarcoma)
- Ifosfamide (for carcinosarcoma)

[1] Hormonal therapy is for endometrioid histologies only (i.e., not for papillary serous carcinoma, clear cell carcinoma, or carcinosarcoma).
[2] Chemotherapy regimens are for endometrioid histologies, papillary serous carcinoma, or clear cell carcinoma. A few of the agents can also be used for carcinosarcoma, as indicated.

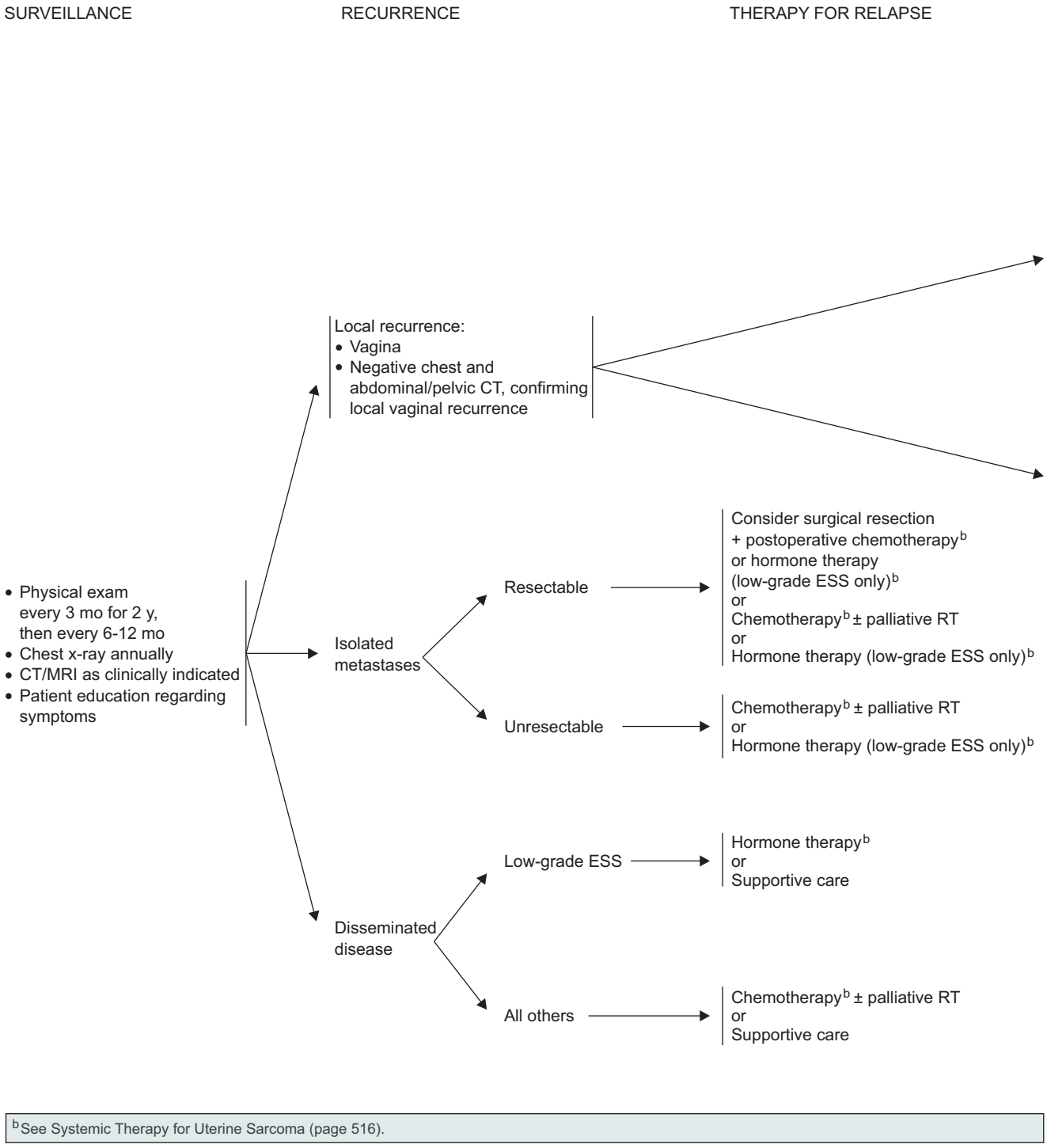


[a] See Principles of Radiation Therapy (page 517).
[b] See Systemic Therapy for Uterine Sarcoma (page 516).
[c] Oophorectomy/LND individualized for reproductive age patients. Fertility consultation as appropriate.

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.

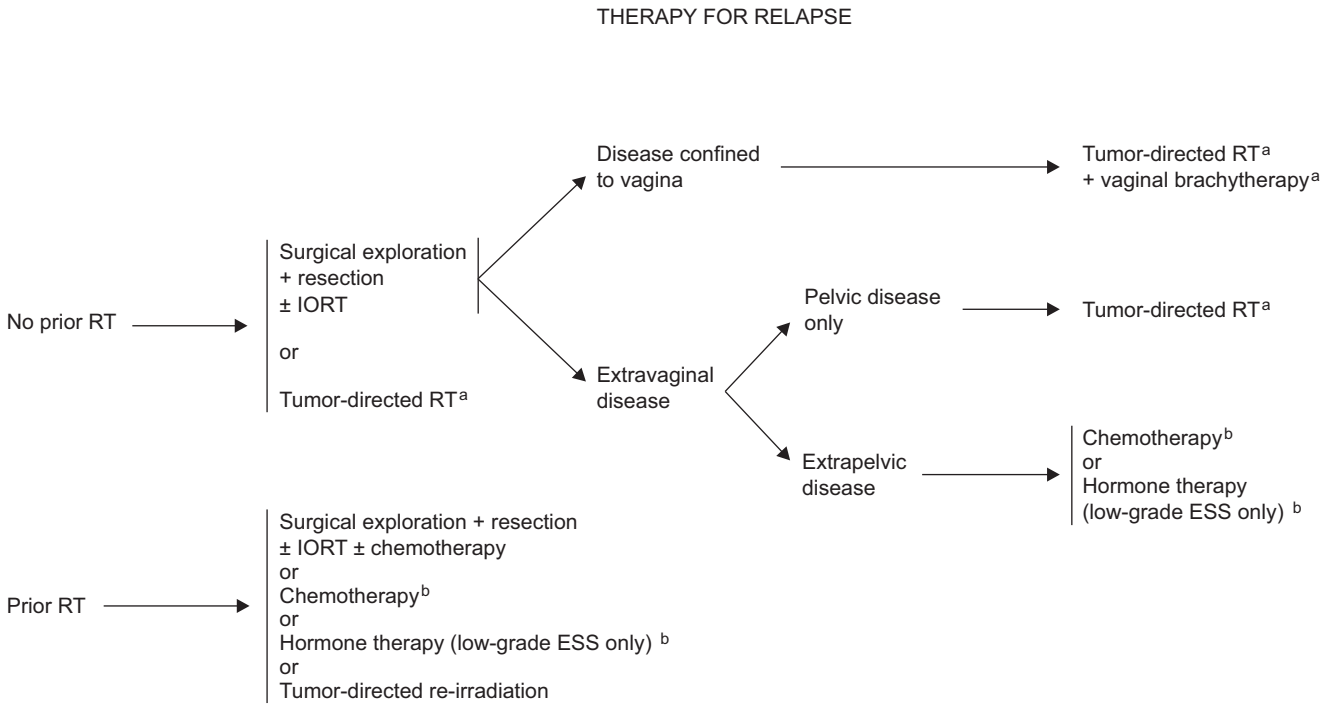


[a] See Principles of Radiation Therapy (page 517).
[b] See Systemic Therapy for Uterine Sarcoma (page 516).
[d] See Uterine Sarcoma Classification (page 516).



[b] See Systemic Therapy for Uterine Sarcoma (page 516).

Clinical trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise noted.



[a]See Principles of Radiation Therapy (page 517).
[b]See Systemic Therapy for Uterine Sarcoma (page 516).

SYSTEMIC THERAPY FOR UTERINE SARCOMA

CHEMOTHERAPY REGIMENS
(Clinical trials strongly recommended)

The following agents can be used as single agents or in combination, as clinically appropriate:

- Doxorubicin (most active single agent for LMS)
- Gemcitabine/docetaxel
- Single-agent dacarbazine, docetaxel, epirubicin, gemcitabine, ifosfamide, liposomal doxorubicin, and paclitaxel could also be considered (category 2B)

HORMONE THERAPY (low-grade ESS only)

- Medroxyprogesterone acetate
- Megestrol acetate
- Aromatase inhibitors (category 2B)
- GnRH analogs (category 2B)
- Tamoxifen (category 2B)

UTERINE SARCOMA CLASSIFICATION

- Endometrial stromal sarcoma[1]
- Undifferentiated sarcoma (high-grade undifferentiated sarcoma)[2] or pure heterologous sarcoma[3]
- Leiomyosarcoma[4]

[1] Endometrial stromal sarcomas displaying morphologic features of proliferative phase endometrial stroma and showing any mitotic index.
[2] High-grade stromas showing pleomorphism or anaplasia greater than that seen in proliferative phase endometrial stroma or completely lacking recognizable stromal differentiation; mitotic index almost always > 10 mf/10 hpf.
[3] Rare group of tumors including malignant fibrous histiocytoma, rhabdomyosarcoma, angiosarcoma, liposarcoma, chondrosarcoma, osteosarcoma, alveolar soft-part sarcoma, and other sarcomas with morphology comparable to extrauterine counterparts.
[4] Excludes smooth muscle tumors of uncertain malignant potential, epithelioid smooth muscle tumors, benign metastasizing leiomyomas, intravenous leiomyomatosis, diffuse leiomyomatosis; management in individual cases may be modified based on clinicopathologic prognostic factors, such as size (< or > 5 cm), mitotic activity (< or > 10 mf/10 hpf), age (< or > 50 years), and presence or absence of vascular invasion.

PRINCIPLES OF RADIATION THERAPY

- Tumor-directed RT refers to RT directed at sites of known or suspected tumor involvement and may include external-beam and/or brachytherapy. In general, tumor-directed external-beam RT (EBRT) is directed to the pelvis with or without the para-aortic region. Brachytherapy can be delivered to an intact uterus, either preoperatively or definitively; or, more commonly, to the vagina after hysterectomy. For the purposes of these guidelines, whole abdominal radiotherapy is not considered to be tumor-directed RT.

- Pelvic radiotherapy should target the gross disease (if present), the lower common iliacs, external iliacs, internal iliacs, parametrium, upper vagina, and presacral lymph nodes (in patients with cervical involvement). Extended-field radiotherapy 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 to 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 to 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 5-6 Gy x 2 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.

Text continued from p. 499

toms 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. Thus, endometrial cancer is often localized, yielding a generally high survival rate. However, data show that the mortality rate for uterine cancer has increased more rapidly than the incidence rate, which has remained stable over the past 20 years.[3] This increased mortality may be related to an increased rate of advanced-stage cancers and high-risk histologies (e.g., serous tumors). In addition, many women did not receive adequate staging. To further improve outcome for patients with this disease, physicians must identify high-risk patients and tailor treatment appropriately to provide the best long-term survival.

Diagnosis and Workup

Most patients (90%) with endometrial carcinoma have abnormal vaginal bleeding, usually during the postmenopausal period. The workup was previously described (see "Overview"). Diagnosis can usually be made through office endometrial biopsy.

Other ancillary tests (e.g., CT, MRI) are reserved for evaluating extrauterine disease as indicated by clinical symptoms, physical findings, or abnormal laboratory findings. In patients with extrauterine disease, a serum CA 125 assay may help monitor clinical response.[4,5] However, serum CA 125 levels may be falsely increased in women who have peritoneal inflammation/infection or radiation injury, normal in women with isolated vaginal metastases, and may not predict recurrence in the absence of other clinical findings.[6–8]

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 approximately 10%. Therefore, a negative endometrial biopsy in a symptomatic patient must be followed by a fractional dilation and curettage under anesthesia. Hysteroscopy may help evaluate the endometrium for lesions, such as a polyp, for patients who have persistent or recurrent undiagnosed bleeding.[9]

Endometrial Cancer Staging

The FIGO system is most commonly used for staging. The original 1970 criteria for staging endometrial cancer incorporated only information gained from presurgical evaluation (including physical examination, diagnostic fractional dilation, and curettage). Many patients at that time were not treated with primary surgery because of obesity or various other medical problems. Thus, the 1970 staging system is only used today in the rare instances of patients who are not surgical candidates.

Several studies in the biomedical literature have shown that clinical staging was inaccurate and did not reflect actual disease extent in 15% to 20% of patients.[10–12] 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 the Cancer Committee of FIGO modified its staging system to emphasize complete surgicopathologic assessment of data, such as histologic grade, myometrial invasion, and the extent and location of extrauterine spread (including retroperitoneal lymph node metastases; the staging table is available online, in these guidelines, at www.nccn.org [ST-1]).[13]

Primary Treatment

A pathology review will provide clinical findings of various endometrioid histologies, papillary serous carcinoma, clear cell carcinoma, 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. The pathologic assessment (see page 511) of the uterus should include 1) ratio of depth of myometrial/stromal invasion to myometrial thickness; 2) cervical stromal or glandular involvement; 3) tumor size; 4) tumor location (fundus vs. lower uterine segment/cervix); 5) histologic subtype with grade; 6) lymphovascular space invasion; and 7) consideration of mismatch repair analysis to identify genetic problems. The pathologic assessment of the nodes should include peritoneal cytology and level of nodal involvement (e.g., pelvic, common iliac, para-aortic). The pathologic assessment should also include the fallopian tubes and ovaries. The College of American Pathologists (CAP) protocol for endometrial carcinoma is a useful guide (http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2005/endometrium05_ckw.pdf).

Disease Limited to the Uterus: Most patients with endometrial cancer have stage I disease at presen-

tation. If medically operable, the recommended surgical procedure for staging a patient with endometrioid histologies clinically confined to the fundal portion of the uterus includes peritoneal lavage for cytology and total hysterectomy/bilateral salpingo-oophorectomy (TH/BSO) with dissection of pelvic and para-aortic lymph nodes (see page 501).[14] During surgery, the abdominal organs (including the diaphragm, liver, omentum, and pelvic and bowel peritoneal surfaces) should be carefully inspected and palpated. The pathologic information obtained provides an optimal basis for selecting adjuvant therapy. Pelvic and para-aortic lymphadenectomy and pathologic assessment of nodes are recommended for all patients, even those with disease confined to the uterus and for suspected or gross cervical involvement.[15–17] Recent data question the role of routine pelvic lymphadenectomy in early-stage endometrial carcinoma;[18,19] these findings remain a point of contention and are not currently reflected in North American practice.[14] For patients with surgical stage I (any grade) endometrial cancer, the 5-year overall survival rate is 88%.[20]

For medically inoperable patients, exclusive tumor-directed radiation therapy (RT) has been shown to be well-tolerated and effective and can provide some measure of pelvic control and long-term progression-free survival.[21]

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.[22] As the tumor grade increases, the accuracy of intraoperative evaluation of myometrial invasion decreases (i.e., assessment by 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.[23] A further indication for complete surgical staging is suggested in reports showing statistically improved survival in patients with complete node dissection versus no node dissection or limited node sampling, even after adjusting for other clinicopathologic variables.[24,25]

Suspected or Gross Cervical Involvement: For patients with suspected or gross cervical involvement, cervical biopsy or MRI should be considered (see page 502). If negative, patients are assumed to have disease limited to the uterus and are treated as previously described. For operable patients with cervical involvement, radical hysterectomy with bilateral salpingo-oophorectomy (RH/BSO), cytology, and dissection of pelvic and para-aortic lymph nodes are recommended. Alternatively, patients may undergo RT (75–80 Gy to point A; category 2B) followed by TH/BSO with para-aortic lymph node dissection. For medically inoperable patients, tumor-directed RT can provide long-term local control and cancer-specific survival rates (see "Principles of Radiation Therapy").[21]

Suspected Extrauterine Disease: If extrauterine disease is suspected, laboratory tests of CA 125 level or imaging studies (e.g., MRI, CT) are recommended if clinically indicated (see page 503). Patients with negative results are treated using the guidelines for disease limited to the uterus. Intra-abdominal disease (e.g., ascites or omental, nodal, ovarian, or peritoneal involvement) warrants surgical intervention using TH/BSO with cytology, selective pelvic and para-aortic lymph node dissection, and maximal debulking. Patients with extrauterine pelvic disease (e.g., vaginal, bladder, bowel/rectal, or parametrial involvement) are treated with RT and brachytherapy with or without surgery and chemotherapy. For extra-abdominal disease (e.g., liver involvement), palliative TH/BSO with or without RT, hormonal therapy, or chemotherapy can be considered.

Adjuvant Therapy

Definitive data are lacking regarding the effectiveness of adjuvant therapy in patients with uterine-confined disease. The basic concept underlying NCCN recommendations is the trend toward selecting more aggressive adjuvant therapy for patients as tumor grade and myometrial and/or cervical invasion worsen. Other pathologic factors that may influence the decision regarding adjuvant therapy in surgical stage I and II endometrial cancer include patient age, lymphovascular space invasion, tumor volume, and involvement of the lower uterine segment.

Three previously published trials have evaluated the role of pelvic RT in patients with endometrial carcinoma. In 2 of these trials, the patients were not formally staged;[26,27] however, patients were formally staged in the third trial.[28] The PORTEC-1 (Postoperative Radiation Therapy in Endometrial Carcinoma) trial was interpreted to show therapeutic benefit in selected patients with uterine-confined disease.[26,29] Although RT significantly decreased

locoregional recurrence, it did not increase overall survival.[30] The randomized trial by Aalders et al. [27] found that RT reduced vaginal recurrences but did not reduce distant metastases or improve survival, and the Gynecologic Oncology Group (GOG) 99 trial by Keys et al.[28] showed improvement in locoregional control, without overall survival benefit, for adjuvant pelvic RT. Both trials showed that most initial recurrences in patients with initial uterine-confined tumors were limited to the vagina, prompting increased use of vaginal brachytherapy alone as adjunctive treatment.[31]

To further assess the relative benefits of whole pelvic RT versus brachytherapy alone in uterine-confined disease, PORTEC-2 randomly assigned patients to these 2 modalities. PORTEC-2 showed excellent vaginal and pelvic control rates with both adjuvant radiation approaches, with no difference in overall survival. Given that vaginal brachytherapy is associated with significantly less toxicity than pelvic RT, experts have suggested that vaginal brachytherapy alone is a reasonable choice for most patients with uterine-confined endometrial cancer who are deemed candidates for adjuvant RT.[32] Notably, both PORTEC-1 and -2 specifically excluded patients with stage 1C grade 3 disease. A recent pooled randomized trial (ASTEC/EN.5) found that adjuvant pelvic RT alone did not improve survival in patients with intermediate- or high-risk early-stage endometrial cancer.[33]

A retrospective analysis of 21,249 women with endometrial cancer found that adjuvant pelvic RT only improved overall and relative survival in those with stage IC disease.[34] A meta-analysis of 5 randomized trials found that adjuvant pelvic RT for stage I disease was associated with a slight survival advantage in high-risk but not lower-risk patients.[35,36] The relative applications of brachytherapy and/or whole pelvic RT should be carefully tailored to a patient's pathologic findings.

Experts agree that patients with documented extrauterine disease are at increased risk for recurrence and require adjuvant therapy; however, the optimal form of adjuvant therapy has not been determined.[37] Whether adjuvant chemotherapy is beneficial in invasive high-grade uterine-confined disease is the subject of current studies (e.g., PORTEC-3). The Nordic trial closed early because of poor accrual; no overall survival benefit was shown between the chemotherapy/RT versus RT groups.[38] The Nordic trial had several limitations: 1) nodal staging of patients was optional, 2) patients with serous and clear cell histologies were enrolled, 3) the RT dose was lower (44 Gy) than currently recommended, and 4) chemotherapy could be given either before or after RT.[38] Treatment is often tailored to the surgically defined extent of disease. A point of historical controversy has been whether positive peritoneal cytology (stage IIIA) is an independent prognostic factor, after adjustment for other known risk factors.[39,40] Experts now generally agree that in the absence of other adverse pathologic features (high-grade tumors, deep myometrial invasion, papillary serous or clear cell histologies, or documented extrauterine disease), a positive peritoneal cytology may be a clinically inconsequential finding.

Radiotherapy Principles

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. 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. In these guidelines, whole abdominal RT is not considered tumor-directed RT (see page 517).

Pelvic RT should target the gross disease (if present); lower common, external, and internal iliacs; parametrium; upper vagina; and presacral lymph nodes (in patients with cervical involvement). Extended-field radiotherapy should include the pelvic volume and 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. EBRT doses for microscopic disease should be 45 to 50 Gy, and 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 or those with medically inoperable tumors, intrauterine brachytherapy boost after EBRT to a cumulative total dose of 75 to 80 Gy low-dose rate equivalent to the tumor volume (uterus) is generally recommended.

For patients who have undergone primary hysterectomy, vaginal brachytherapy (if used) 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 is often limited to the upper vagina. For high-dose–rate brachytherapy, when used as a boost after EBRT, 2 fractions of 5 to 6 Gy prescribed to the vaginal mucosa are commonly used. For high-dose rate vaginal brachytherapy alone, commonly used regimens include 3 fractions of 7 Gy prescribed at a depth of 0.5 cm from the vaginal surface, or 5 fractions of 6 Gy fractions prescribed to the vaginal surface.

Patients who undergo radiation are prone to vaginal stenosis, which can impair sexual function. Women can use vaginal dilators to prevent or treat this condition. Dilator use can begin 2 to 4 weeks after RT is completed and can be performed indefinitely.[41]

Completely Surgically Staged Patients: The imprecision of preoperative and intraoperative assessment of grade and myometrial invasion and the potential therapeutic benefit of lymph node dissection make the concept of intraoperative decision-based lymph node dissection difficult to apply prospectively with accuracy. Therefore, complete surgical staging to gather full pathologic and prognostic data on which to base decisions about adjuvant treatment should be advocated for all patients who do not have medical or technical contraindications to lymph node dissection.

Laparoscopic pelvic and para-aortic lymphadenectomy in association with total laparoscopic hysterectomy has been proposed as an alternative surgical approach; however, patients should be followed over long term to compare outcomes with those of traditional laparotomy. A randomized phase III trial (GOG-LAP2) evaluating this potentially less-invasive method assessed patients with clinical stage I to IIA disease is now closed.[42] Preliminary results from LAP2 indicate that positive cytology results, positive nodes, and FIGO staging results were similar between groups and that 24% of patients required conversion to laparotomy. Retrospective reviews of patients undergoing either laparoscopic hysterectomy or total abdominal hysterectomy found that morbidity rates were lower with laparoscopy and that survival and recurrence rates were similar.[43,44] Robotic surgery is being evaluated for treatment of patients with endometrial cancer.[45,46]

To assess the role of adjuvant radiation in patients with surgically staged endometrial cancer without extrauterine disease, the GOG completed a multicenter trial (99) that randomly assigned patients with stage IB, stage IC, and occult stage II disease (any grade) to pelvic RT versus observation alone after primary surgery. Initial analysis of the study showed a significant decrease in overall recurrences and an improvement in the 2-year progression-free interval favoring the radiated cohort, but overall survival was not statistically different between the groups.[28] Patterns of failure analysis in the GOG trial showed an intriguing finding: most of the initial pelvic recurrences in the observation group were limited to the vagina. This finding prompted the increased use of adjuvant vaginal brachytherapy alone for patients with tumors that are histologically confined to the uterus, despite the existence of other intrauterine risk features.[31,47–49] The GOG randomized trial has also been criticized for including patients with a broad range of relapse risk, including many who probably have excellent prognoses with surgery alone, hence diluting the possibility of detecting a benefit to adjuvant therapy.

Adequate surgical staging provides important information to assist in selection of adjuvant therapy for endometrial tumors. Patients with stage I endometrial cancer who are completely surgically staged are stratified by adverse risk factors (e.g., advanced age, lymphovascular invasion, tumor size, depth of invasion, involvement of lower uterine segment; see page 504). Observation is recommended for all patients with stage IA, G1 to 2 disease. However, vaginal brachytherapy is also recommended for stage IA, G3 disease if no adverse risk factors are present; observation or vaginal brachytherapy and/or pelvic RT is recommended for patients with adverse risk factors. Patients with stage IB, G2 to 3 disease without adverse risk factors can be observed or treated with vaginal brachytherapy; observation only is recommended for those with stage 1B, G1 disease. If adverse factors are present, observation or vaginal brachytherapy is recommended for patients with stage IB, G1 disease; however, options for stage 1B, G2 tumors include observation or vaginal brachytherapy with or without pelvic RT (category 2B for all options). For stage IB, G3 tumors with adverse risk factors, observation or vaginal brachytherapy and/or pelvic RT is recommended. For patients with

stage IC, G3 disease with adverse risk factors, observation or pelvic RT and/or vaginal brachytherapy with or without chemotherapy is recommended (category 2B for chemotherapy). For patients with stage IC, G1 to 2 disease with adverse risk factors, observation or vaginal brachytherapy and/or pelvic RT is recommended. Otherwise, if no adverse risk factors are present, observation or vaginal brachytherapy is recommended. However, observation or vaginal brachytherapy and/or pelvic RT is recommended for patients with IC, G3 disease.

Based on a prospective evaluation of surgicopathologic patterns of spread in endometrial cancer by the GOG and others, experts now recognize that much of the adverse prognosis associated with intrauterine risk factors is mediated through nodal involvement. The incidence of pelvic nodal metastases is 5% or less for grade 1 and 2 tumors with inner one-third myometrial invasion. For patients with outer-third infiltration, nodal disease was found in 19% of grade 2 and 34% of grade 3 cancers.[12,50] Given the wider acceptance of formal surgicopathologic evaluation and adoption of the 1988 FIGO staging classification (the staging table is available online, in these guidelines, at www.nccn.org [ST-1]), patients with clinical stage I and II disease with adverse intrauterine features who were once deemed at risk for nodal metastases are now upstaged to stage III and IV when extrauterine disease is documented. The implications of this stage migration should be considered when evaluating historical data.

Significant controversy centers on appropriate adjuvant therapy in patients with surgical stage I and II endometrial cancer, regardless of intrauterine features, for whom extrauterine disease has been clearly ruled out. In a large prospective study, the GOG reported a 92.7% 5-year survival rate for patients with surgical stage I cancer with no adverse risk factors other than grade and myometrial invasion (i.e., without extrauterine disease, isthmus/cervical involvement, or lymphovascular space invasion).[39] The practice of surgical staging has decreased the use of adjuvant therapy for stage I endometrial carcinoma.[51,52]

Optional vaginal brachytherapy is recommended for all patients with stage IIA disease (see page 504 for recommendations based on findings in the uterine fundus). The recommended treatment option for patients with stage IIB, G1 to 2 disease is pelvic RT and vaginal brachytherapy. For patients with stage IIB, G3 disease, chemotherapy may be added (category 2B for chemotherapy; see page 505). Observation or vaginal brachytherapy is also an option for those with stage II disease who had a radical hysterectomy with negative surgical margins and no evidence of extrauterine disease.

Patients with extrauterine disease confined to the lymph nodes or adnexa may be adequately treated with pelvic or extended-field RT.[53] Observation is recommended for noninvasive stage IIIA tumors confined to fundus or those with only positive cytology; G3 tumors can also be managed with vaginal brachytherapy or pelvic RT with or without vaginal brachytherapy or chemotherapy. For all other stage IIIA tumors, the recommended options include 1) tumor-directed RT with or without chemotherapy; 2) chemotherapy with or without RT; or 3) pelvic RT with or without vaginal brachytherapy (see page 505). A recent randomized phase III in patients with intermediate- and high-risk endometrial cancer (stages IC, G3–IIIA) compared cisplatin-based chemotherapy with pelvic radiation.[54–56] The study suggested similar outcomes with either modality but was hampered by insufficient power to detect a small but clinically significant difference.

Despite the histologic grade, patients with completely resected stage IIIB and IIIC are treated with chemotherapy and/or tumor-directed RT. After tumor debulking, chemotherapy with or without RT is recommended for stage IVA or IVB tumors with no gross residual disease or microscopic abdominal disease (see page 506).

For patients deemed at risk of peritoneal failure, whole abdominal RT in carefully selected cases seems to have provided therapeutic benefit in retrospective studies.[57,58] A randomized phase III GOG (122) trial assessed optimal adjuvant therapy for endometrial cancer with extrauterine disease. In this trial, patients with stage III and intra-abdominal stage IV disease who had minimal residual disease were randomly assigned to whole abdominopelvic RT versus 7 cycles of combined doxorubicin (60 mg/m^2) and cisplatin (50 mg/m^2) treatment, with an additional cycle of cisplatin (AP). This study showed that AP chemotherapy improved progression-free and overall survival compared with whole abdominopelvic RT; however, acute toxicity was greater in the AP chemotherapy arm.[59] This study established the role of adjuvant multiagent systemic chemotherapy in cura-

tive-intent patients with extrauterine disease spread. Recurrences were frequent, occurring in the pelvis and abdomen in both treatment arms. Approximately 52% of patients with advanced endometrial carcinoma experienced recurrences, indicating the need for further therapeutic improvement in this high-risk patient population.[59]

A follow-up study evaluated the role of chemotherapy intensification for this patient population. GOG 184 assessed combination chemotherapy (cisplatin and doxorubicin with or without paclitaxel) with more limited radiation fields (involved-field radiation to either pelvis or pelvis plus para-aortic nodes). Results indicate that the 3-drug regimen did not improve survival when compared with the 2-drug regimen after 3 years of follow-up and that the more intensive chemotherapy resulted in greater toxicity.[60]

Incompletely Surgically Staged Patients: For incompletely surgically staged patients, radiologic imaging is often required for stage IB, IC, IIA, and IIB tumors (see page 507). Positive radiologic findings necessitate surgical restaging or pathologic confirmation of metastatic disease. For patients with stage IB or IIA disease with myometrial invasion of 50% or less and with negative radiologic results, options include observation or vaginal brachytherapy with or without pelvic RT. The guidelines recommend that stage IA, G1 to 2 tumors be observed. Options for stage IB or IIA tumors with positive radiologic findings include surgical restaging or pathologic confirmation of metastatic disease, followed by adjuvant treatment (for patients who are completely surgically staged). Patients with more aggressive tumors (e.g., stage IC, stage IIA with myometrial invasion greater than 50%, stage IIB, or G3 tumors) are managed with radiologic imaging followed by either 1) surgical restaging or pathologic confirmation of metastatic disease followed by adjuvant treatment (for completely surgically staged) as indicated, or 2) pelvic RT and vaginal brachytherapy with or without para-aortic RT and/or with or without chemotherapy for grade 3 tumors (category 2B for chemotherapy) for negative radiologic findings.

Two randomized trials addressed the role of adjuvant pelvic RT in patients with nonformally staged uterine-confined endometrial cancer. The older Aalders et al.[27] trial and the more recent PORTEC-1 analysis showed improvement in pelvic control with adjuvant RT, but without a significant effect on overall survival.[26,29,30]

Hormone Replacement Therapy for Endometrial Cancers

Hypoestrogenism is associated with hot flashes, mood lability, vaginal dryness, pelvic soft tissue atrophy, osteoporosis, and an increased risk for cardiovascular disease. Estrogen replacement therapy in postmenopausal women has been shown to reduce or reverse these signs and symptoms. Because endometrial adenocarcinoma has historically been considered an estrogen-linked malignancy,[61,62] women successfully treated for this cancer have usually been denied estrogen replacement therapy for fear of inducing a higher relapse rate. However, estrogen replacement therapy for these patients remains controversial. That patients with endometrial cancer who undergo estrogen replacement therapy after hysterectomy have a higher relapse rate has never been proven. Several retrospective trials of estrogen replacement after treatment of early-stage endometrial cancer have shown no increase in tumor recurrence or cancer-related deaths.[63–65] However, estrogen replacement trials in postmenopausal women with no history of malignancy have shown a significantly increased risk for breast cancer.

Panel members agree 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. If adjuvant treatment is performed, a 6- to 12-month waiting period should occur before hormonal replacement therapy is initiated, and participation in clinical trials is strongly encouraged. Selective estrogen-receptor modulators (SERMs) may prove to be attractive options in hormone replacement therapy. For example, the SERM raloxifene does not exhibit a stimulatory effect on uterine or breast tissue but retains beneficial activity on bone and lipid metabolism. Unfortunately, raloxifene does not reduce vasomotor instability. Long-term comparisons between conjugated estrogens and SERMs for hormone replacement therapy are needed.

The primary treatment of endometrial cancer is usually hysterectomy. However, progesterone therapy has been used for young women with either atypical endometrial hyperplasia or grade 1 endometrial hyperplasia who desire fertility preservation and women who are very poor surgical candidates.[14,66,67]

Postoperative Surveillance

The panel recommends a postoperative surveillance protocol for endometrial cancer consisting

of a clinic visit with a physical examination every 3 to 6 months for 2 years, and then at 6-month to 1-year intervals (see page 508); patient education on symptoms of relapse is also recommended (see third paragraph in this section). Vaginal cytology is recommended every 6 months for 2 years, then annually. CA 125 levels are optional. Chest radiograph may be performed annually (category 2B). Genetic counseling can be considered to discuss significant family history. These recommendations recognize that the value of intensive surveillance has not been demonstrated in this disease, and ancillary testing is therefore not recommended.[68–71]

A review of the biomedical literature for routine intensive postoperative surveillance in patients with clinical stage I and II endometrial cancer showed an approximately 15% recurrence rate;[72] 58% of the patients had symptomatic recurrences. For most patients, disease recurred within 3 years of initial treatment.

All patients should receive verbal and written information on the symptoms of recurrent disease. Patients experiencing 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 delay until the 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 follow-up schedule and includes blood pressure determination, breast examination, mammography as clinically indicated, stool guaiac test, immunizations, and an opportunity to evaluate other health problems that often coexist in patients with endometrial cancer. Given the lack of prospective studies on the optimal frequency of posttherapy follow-up, the NCCN panel believes that the algorithm represents a reasonable surveillance scheme.

Treatment of Relapsed or Metastatic Disease

Patients with local or regional recurrences after surgical therapy can be evaluated for surgical exploration of the pelvis and resection and/or RT. Patients with recurrences confined to the pelvis after RT are unusual. Management of these patients is still controversial.

For patients previously treated with EBRT at the recurrence site, recommended therapy for relapse includes surgical exploration of the pelvis and resection with or without intraoperative radiotherapy (IORT); hormonal therapy; or chemotherapy. Radical surgery, such as pelvic exenteration, has been performed with reported survival rates approximating 20%.[73] However, these patients may not require pelvic exenteration; a more limited partial vaginectomy with or without IORT may be adequate.[74,75] Surgical exploration of the pelvis and abdominal resection may be performed with or without IORT in patients who did not undergo prior RT at the site of recurrence or who underwent previous brachytherapy only. RT with brachytherapy is another treatment option for these patients.

For recurrence confined to the vagina or with pelvic lymph node invasion, additional therapy is recommended, such as tumor-directed RT with or without brachytherapy or chemotherapy (see page 509). Vaginal recurrences treated with RT have reported survival rates of 40% to 50%, with significantly worse results if extravaginal extension or pelvic lymph node involvement is present.[76] Para-aortic or common iliac lymph node invasion is treated with tumor-directed RT with or without vaginal brachytherapy or chemotherapy. For upper abdominal or peritoneal recurrences, chemotherapy with or without tumor-directed RT is recommended for microscopic residual disease. However, for gross upper abdominal residual disease, more aggressive treatment for relapse is recommended, as outlined for disseminated metastases (see page 508). For resectable isolated metastases, surgical resection with or without RT should be considered. Further recurrences or unresectable isolated metastases are treated as disseminated metastases. The management of systemic disease is usually palliative (see NCCN Clinical Practice Guidelines in Oncology: Palliative Care; for the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org).

Hormonal Therapy: Hormonal therapy is for endometrioid histologies only (i.e., not for papillary serous carcinoma, clear cell carcinoma, or carcinosarcoma). Hormone therapy for metastatic disease involves mainly the use of progestational agents; tamoxifen and aromatase inhibitors are also being used. No particular drug, dose, or schedule has been found to be superior. The main predictors of response in the treatment of metastatic disease are well-differentiated tumors, a long disease-free interval, and the location and extent of extrapelvic (particularly pulmonary) metastases.

For asymptomatic or low-grade disseminated metastases, hormonal therapy with progestational agents has shown a good response for patients who have estrogen and progesterone receptor–positive disease.[77,78] Tamoxifen has a 20% response rate in those whose disease does not respond to standard progesterone therapy.[79,80] In a single-institution study, the SERM arzoxifene showed a response rate of approximately 28% in metastatic endometrial cancer;[81] an ongoing phase II trial is further assessing the efficacy of arzoxifene. Other hormonal modalities have not been well studied, and no benefit to adjuvant therapy with hormonal agents for treating endometrial cancer has been proven.[82] If disease progression is observed after hormonal therapy, cytotoxic chemotherapy can be considered. However, clinical trials or best supportive care (see NCCN Palliative Care Guidelines) is appropriate for patients with disseminated metastatic recurrence who experience a poor response to hormonal therapy and chemotherapy.

Therapy for relapse (e.g., chemotherapy and/or palliative RT) is recommended to relieve symptoms in patients with symptomatic, grade 2 to 3, or large-volume disseminated metastases. If patients experience treatment failure after 2 chemotherapy regimens, they can undergo best supportive care or enroll in an appropriate clinical trial.

Chemotherapy: Chemotherapy for endometrial cancer has been extensively studied. Single-agent therapy usually includes cisplatin, carboplatin, paclitaxel, and doxorubicin. Responses with these agents in advanced disease have ranged from 21% to 36%.

A phase III randomized trial (GOG 177) compared 2 combination chemotherapy regimens previously shown to have significant activity. This trial randomized 273 women with advanced/metastatic or recurrent endometrial carcinoma to cisplatin and doxorubicin or cisplatin, doxorubicin, and paclitaxel. The 3 drug regimen was associated with a slight improvement in survival (15 vs. 12 months) but with significantly increased toxicity.[83] The response rates with other multiagent chemotherapy regimens have ranged from 31% to 81%, but with relatively short durations. The median survival for patients in these trials remains approximately 1 year.[84,85]

Carboplatin and paclitaxel is an increasingly used regimen for advanced/metastatic or recurrent endometrial cancer based on ovarian studies; the response rate is approximately 40%, and overall survival is approximately 13 months.[86] Weekly low-dose paclitaxel and carboplatin also seems useful.[87] A phase III study (GOG 209) is currently assessing carboplatin and paclitaxel versus cisplatin, doxorubicin, paclitaxel, and filgrastim (granulocyte colony-stimulating factor [G-CSF]). Given current data, multiagent chemotherapy regimens are preferred for metastatic/recurrent disease if tolerated. Biologic and molecular therapies remain unproven for treating recurrent or metastatic endometrial carcinoma.

Papillary Serous Carcinomas, Clear Cell Carcinomas, and Carcinosarcomas

Uterine papillary serous carcinomas, clear cell carcinomas, and carcinosarcomas are considered more aggressive histologic variants of epithelial carcinoma, with a higher incidence of extrauterine disease at presentation.[88–90] Patterns of failure mimic those of ovarian cancer. Primary treatment includes TH/BSO with dissection of pelvic and para-aortic lymph nodes, peritoneal lavage for cytology, and maximal tumor debulking. Surgical staging for these tumor subtypes should follow the procedures performed for ovarian cancer, which include detailed examination of the entire abdominopelvic cavity and retroperitoneal spaces and appropriate biopsies (see page 510). Adjuvant therapy is highly individualized.[91–95]

Adjuvant therapy recommendations for stage IA include observation and/or chemotherapy, or tumor-directed RT.[96] Recommendations for stage 1B to II include chemotherapy with or without tumor-directed RT, or whole abdominopelvic RT with or without vaginal brachytherapy (category 3). Patients with adequately debulked stage III or IV disease can also undergo these procedures. Panel members disagreed about whether whole abdominal RT is appropriate.[97–100] Chemotherapy is recommended for patients with inadequately debulked stage III or IV disease.

The NCCN panel recently moved carcinosarcomas (i.e., malignant mixed Müllerian tumors) to the epithelial carcinoma guideline, because pathologists now believe they are metaplastic carcinomas.[90] Ifosfamide is the most active single agent for carcinosarcoma.[101,102] Combination cisplatin and ifosfamide was once a widely used active regimen. A recent phrase III trial showed that the combination of ifosfamide and paclitaxel was active for advanced carcinosarcoma with less toxicity than the cisplatin/ifosfamide regimen.[101]

Data on carcinosarcoma seem to consistently suggest that adjuvant pelvic RT provides a statistically significant reduction in the rate of local recurrences compared with surgery alone.[103–108] In some series, this local control improvement correlates with an improvement in survival, although other data show that lymphadenectomy confers greater benefit.[107–110] A phase III randomized GOG trial (150) involving patients with carcinosarcoma of the uterus assessed whole abdominal RT versus cisplatin and ifosfamide, but no difference in survival was seen between the groups.[111]

Uterine Sarcomas

Overview

Uterine sarcomas are generally categorized into low-grade ESS, HGUD, and LMS (see page 516). Consistent pathologic definitions of the various histologies continue to be refined. Stromal/mesenchymal tumors are subdivided into ESS (which are low-grade sarcomas) and HGUD (previously considered high-grade ESS).

Evaluation and Primary Therapy

It is necessary to determine if the sarcoma is confined to the uterus or if there is extrauterine disease. If medically operable, then hysterectomy (TH/BSO), with or without lymph node dissection, is the initial preferred treatment for uterine sarcomas (see page 512). Decisions regarding lymph node dissection should be individualized based on clinical scenarios and intraoperative findings. For medically inoperable sarcomas, options include 1) pelvic RT (with or without brachytherapy) and chemotherapy, 2) chemotherapy, or 3) hormone therapy (but only for low-grade ESS).

Low-Grade ESS: Hormone therapy is recommended for stages III to IV low-grade ESS (e.g., megestrol acetate, medroxyprogesterone, tamoxifen, gonadotropin-releasing hormone [GnRH] analogs, aromatase inhibitors [category 2B for last 3 agents]).[112] High-grade ESS is currently referred to as HGUD (see next section). Observation is recommended for stages I to II ESS (see page 513). Hormone therapy is also recommended for ESS that have recurred or are unresectable (see page 514).[112] Series of low-grade ESS suggest long disease-free intervals in the absence of specific therapy and offer less support for the use of adjuvant RT.[113] Adjuvant RT in ESS has been shown to reduce local recurrence rates but again with limited effect on survival.[114,115] Because of concerns about radiation exposure, frequent routine asymptomatic surveillance imaging is no longer recommended for young women after primary therapy for ESS.[116]

LMS and HGUD: LMS is often diagnosed after surgery. Currently, neither the AJCC nor FIGO staging systems are ideal for staging LMS; patients are often upstaged when using the AJCC staging system.[117]

The role of adjuvant radiotherapy in nonmetastatic disease is controversial. Most available data are retrospective, except for a recent phase III randomized trial.[103] Most retrospective studies suggest improved local pelvic control but no appreciable nor consistent improvement in overall survival given the propensity of metastatic extrapelvic disease to be a site of first or eventual recurrence.[118,119] In many series, the patients treated with adjuvant radiation were believed to have higher risk factors (e.g., larger tumors, deeper myometrial invasion), thus biasing the data against radiotherapy. However, a recent phase III randomized trial in stage I and II uterine sarcomas reported that postoperative pelvic radiotherapy did not improve overall survival for LMS compared with observation.[103] Thus, the use of adjuvant RT for local pelvic control is controversial. If used, adjuvant RT must be individualized and based on careful analysis of surgical pathologic findings.

The role of chemotherapy is even more poorly defined for patients with uterine-confined disease but has been considered because of the high risk of systemic relapse. For stage I and II LMS and HGUD that are completely resected, options for adjuvant therapy include 1) observation, 2) consider pelvic RT and/or brachytherapy (category 2B), or 3) consider chemotherapy (category 2B; see page 513).

Doxorubicin is the most active single agent for LMS.[120] Combination regimens, such as gemcitabine and docetaxel, have also been used.[121,122] Single-agent dacarbazine, docetaxel, liposomal doxorubicin, epirubicin, gemcitabine, ifosfamide, and paclitaxel can also be considered for advanced or metastatic disease (category 2B).[123–126] Enrollment in clinical trials is strongly recommended.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer J Clin 2008;58:71–96.
2. Olah K, Gee H, Blunt S, et al. Retrospective analysis of 318 cases of uterine sarcoma. Eur J Cancer 1991;27:1095–1099.
3. Ueda SM, Kapp DS, Cheung MK, et al. Trends in demographic and clinical characteristics in women diagnosed with corpus cancer and their potential impact on the increasing number of deaths. Am J Obstet Gynecol 2008;198:218.e1–6.
4. Duk JM, Aalders JG, Fleuren GJ, et al. CA 125: a useful marker in endometrial carcinoma. Am J Obstet Gynecol 1986;155:1097–1102.
5. Duk JM, Aalders JG, Fleuren GJ, et al. Tumor markers CA 125, squamous cell carcinoma antigen, and carcinoembryonic antigen in patients with adenocarcinoma of the uterine cervix. Obstet Gynecol 1989;73:661–668.
6. Patsner B, Orr JW Jr, Mann WJ Jr. Use of serum CA 125 measurement in posttreatment surveillance of early-stage endometrial carcinoma. Am J Obstet Gynecol 1990;162:427–429.
7. Rose PG, Sommers RM, Reale FR, et al. Serial serum CA 125 measurements for evaluation of recurrence in patients with endometrial carcinoma. Obstet Gynecol 1994;84:12–16.
8. Price FV, Chambers SK, Carcangiu ML, et al. CA 125 may not reflect disease status in patients with uterine serous carcinoma. Cancer 1998;82:1720–1725.
9. Gimpelson RJ, Rappold HO. A comparative study between panoramic hysterectomy with directed biopsies and dilatation and curettage: a review of 276 cases. Am J Obstet Gynecol 1998;158:489–492.
10. Boronow RC, Morrow CP, Creasman WT, et al. Surgical staging in endometrial cancer: clinical-pathologic findings of a prospective study. Obstet Gynecol 1984;63:825–832.
11. Cowles TA, Magrina JF, Masterson BJ, et al. Comparison of clinical and surgical-staging in patients with endometrial carcinoma. Obstet Gynecol 1985;66:413–416.
12. Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer: a Gynecologic Oncology Group study. Cancer 1987;60:2035–2041.
13. Benedet JL, Bender H, Jones H III, et al. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet 2000;70:209–262.
14. 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.
15. Mariani A, Dowdy SC, Cliby WA, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecol Oncol 2008;109:11–18.
16. Chan JK, Wu H, Cheung MK, et al. The outcomes of 27,063 women with unstaged endometrioid uterine cancer. Gynecol Oncol 2007;106:282–288.
17. Chan JK, Kapp DS. Role of complete lymphadenectomy in endometrioid uterine cancer. Lancet Oncol 2007;8:831–841.
18. ASTEC study group, Kitchener H, Swart AM, et al. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 2009;373:125–136.
19. Benedetti Panici P, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 2008;100:1707–1716.
20. Creasman WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. FIGO 6th annual report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet 2006;95(Suppl 1):S105–143.
21. Fishman DA, Roberts KB, Chambers JT, et al. Radiation therapy as exclusive treatment for medically inoperable patients with stage I and II endometrioid carcinoma of the endometrium. Gynecol Oncol 1996;61:189–196.
22. Daniel AG, Peters WA III. Accuracy of office and operating room curettage in the grading of endometrial carcinoma. Gynecol Oncol 1988;71:612–614.
23. Goff BA, Rice LW. Assessment of depth of myometrial invasion in endometrial adenocarcinoma. Gynecol Oncol 1990;38:46–48.
24. Kilgore LC, Partridge EE, Alvarez RD, et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. Gynecol Oncol 1995;56:29–33.
25. Havrilesky LJ, Cragun JM, Calingaert B, et al. Resection of lymph node metastases influences survival in stage IIIC endometrial cancer. Gynecol Oncol 2005;99:689–695.
26. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000;355:1404–1411.
27. Aalders J, Abeler V, Kolstad P, et al. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma. Clinical and histopathologic study of 540 patients. Obstet Gynecol 1980;56:419–427.
28. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92:744–751.
29. Creutzberg CL, van Putten WL, Warlam-Rodenhuis CC, et al. Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the Postoperative Radiation Therapy in Endometrial Carcinoma Trial. J Clin Oncol 2004;22:1234–1241.
30. Scholten AN, van Putten WL, Beerman H, et al. Postoperative radiotherapy for stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int J Radiat Oncol Biol Phys 2005;63:834–838.
31. Alektiar KM, Venkatraman E, Chi DS, Barakat RR. Intravaginal brachytherapy alone for intermediate-risk endometrial cancer. Int J Radiat Oncol Biol Phys 2005;62:111–117.
32. Nout RA, Putter H, Jürgenliemk-Schulz IM, et al. Vaginal brachytherapy versus external beam pelvic radiotherapy for high-intermediate risk endometrial cancer: results of the randomized PORTEC-2 trial [abstract]. J Clin Oncol 2008;26:Abstract LBA5503.
33. ASTEC/EN.5 Study Group, Blake P, Swart AM, et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet 2009;373:137–146.
34. Lee CM, Szabo A, Shrieve DC, et al. Frequency and effect of adjuvant radiation therapy among women with stage I endometrial adenocarcinoma. JAMA 2006;295:389–397.

35. Johnson N, Cornes P. Survival and recurrent disease after postoperative radiotherapy for early endometrial cancer: systematic review and meta-analysis. BJOG 2007;114:1313–1320.

36. Kong A, Johnson N, Cornes P, et al. Adjuvant radiotherapy for stage I endometrial cancer. Cochrane Database Syst Rev 2007;CD003916.

37. Koh WJ, Tran AB, Douglas JG, et al. Radiation therapy in endometrial cancer. Best Pract Res Clin Obstet Gynaecol 2001;15:417–432.

38. Hogberg T, Rosenberg P, Kristensen G, et al. A randomized phase-III study on adjuvant treatment with radiation (RT) ± chemotherapy (CT) in early-stage high-risk endometrial cancer (NSGO-EC-9501/EORTC 55991) [abstract]. J Clin Oncol 2007;25:Abstract 5503.

39. Morrow CP, Bundy BN, Kurman RJ, et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol 1991;40:55–65.

40. Kadar N, Homesley HD, Malfetano JH. Positive peritoneal cytology is an adverse factor in endometrial carcinoma only if there is other evidence of extrauterine disease. Gynecol Oncol 1992;46:145–149.

41. Owen Mumford. Best Practice Guidelines on the Use of Vaginal Dilators in Women Receiving Pelvic radiotherapy. Available at: http://www.owenmumford.com/en/download.asp?id=59. Accessed March 25, 2009.

42. Walker JL, Piedmonte M, Spirtos N, et al. Surgical staging of uterine cancer: randomized phase III trial of laparoscopy vs laparotomy—a Gynecologic Oncology Group study (GOG): preliminary results [Abstract]. J Clin Oncol 2006;24(Suppl 18):Abstract 5010.

43. Malur S, Possover M, Michels W, Schneider A. Laparoscopic-assisted vaginal versus abdominal surgery in patients with endometrial cancer—a prospective randomized trial. Gynecol Oncol 2001;80:239–244.

44. Obermair A, Manolitsas TP, Leung Y, et al. Total laparoscopic hysterectomy for endometrial cancer: patterns of recurrence and survival. Gynecol Oncol 2004;92:789–793.

45. Boggess JF, Gehrig PA, Cantrell L, et al. A comparative study of 3 surgical methods for hysterectomy with staging for endometrial cancer: robotic assistance, laparoscopy, laparotomy. Am J Obstet Gynecol 2008;199:360.e1–9.

46. Bandera CA, Magrina JF. Robotic surgery in gynecologic oncology. Curr Opin Obstet Gynecol 2009;21:25–30.

47. Chadha M, Nanavati PJ, Liu P, et al. Patterns of failure in endometrial carcinoma stage IB, grade 3 and IC patients treated with postoperative vaginal vault brachytherapy. Gynecol Oncol 1999;75:103–107.

48. Kong A, Powell M, Blake P. The role of postoperative radiotherapy in carcinoma of the endometrium. Clin Oncol (R Coll Radiol) 2008;20:457–462.

49. Solhjem MC, Petersen IA, Haddock MG. Vaginal brachytherapy alone is sufficient adjuvant treatment of surgical stage I endometrial cancer. Int J Radiat Oncol Biol Phys 2005;62:1379–1384.

50. Chi DS, Barakat RR, Palayekar MJ, et al. The incidence of pelvic lymph node metastasis by FIGO staging for patients with adequately surgically staged endometrial adenocarcinoma of endometrioid histology. Int J Gynecol Cancer 2008;18:269–273.

51. Gretz HF III, Economos K, Husain A, et al. The practice of surgical staging and its impact on adjuvant treatment recommendations in patients with stage I endometrial carcinoma. Gynecol Oncol 1996;61:409–415.

52. Ben-Shachar I, Pavelka J, Cohn DE, et al. Surgical staging for patients presenting with grade 1 endometrial carcinoma. Obstet Gynecol 2005;105:487–493.

53. Greven KM, Lanciano RM, Corn B, et al. Pathologic stage III endometrial carcinoma-prognostic factors and patterns of recurrence. Cancer 1993;71:3697–3702.

54. Susumu N, Sagae S, Udagawa Y, et al. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. Gynecol Oncol 2008;108:226–233.

55. Hogberg T. Adjuvant chemotherapy in endometrial carcinoma: overview of randomised trials. Clin Oncol (R Coll Radiol) 2008;20:463–469.

56. Fleming G. Adjuvant therapy for high-risk adenocarcinoma of the uterus. ASCO Educational Book 2008:230–233.

57. Gibbons S, Martinez A, Schray M, et al. Adjuvant whole abdominopelvic irradiation for high-risk endometrial carcinoma. Int J Radiat Oncol Biol Phys 1991;21:1019–1025.

58. Greer BE, Hamberger AD. Treatment of intraperitoneal metastatic adenocarcinoma of the endometrium by the whole-abdomen moving-strip technique and pelvic boost irradiation. Gynecol Oncol 1983;16:365–373.

59. Randall ME, Filiaci VL, Muss H, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol 2006;24:36–44.

60. Homesley HD, Filiaci V, Gibbons SK, et al. 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 [abstract]. 39th Annual Meeting of the Society of Gynecologic Oncologists; Tampa, FL; March 9, 2008. Abstract #1. Gynecol Oncol 2008;108:S2.

61. Smith DC, Prentice R, Thompson DJ, et al. Association of exogenous estrogen and endometrial cancer. N Engl J Med 1975;293:1164–1167.

62. Ziel HK, Finkle WD. Increased incidence of endometrial carcinoma among users of conjugated estrogens. N Engl J Med 1975;293:1167–1170.

63. Creasman WT, Henderson D, Hinshaw W, et al. Estrogen replacement therapy in the patient treated for endometrial cancer. Obstet Gynecol 1986;67:326–330.

64. Lee RB, Burke TW, Parke RC. Estrogen replacement therapy following treatment for stage I endometrial carcinoma. Gynecol Oncol 1990;36:189–191.

65. Chapman JA, DiSaia PJ, Osann K, et al. Estrogen replacement in surgical stage I and II endometrial cancer survivors. Am J Obstet Gynecol 1996;175:1195–1200.

66. Gotlieb WH, Beiner ME, Shalmon B, et al. Outcome of fertility-sparing treatment with progestins in young patients with endometrial cancer. Obstet Gynecol 2003;102:718–725.

67. Ramirez PT, Frumovitz M, Bodurka DC, et al. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. Gynecol Oncol 2004;95:133–138.

68. Podczaski E, Kaminski P, Gurski K, et al. Detection and patterns of treatment failure in 300 consecutive cases of "early" endometrial cancer after primary surgery. Gynecol Oncol 1992;47:323–327.

69. Shumsky AG, Stuart GC, Brasher PM, et al. An evaluation of routine follow-up of patients treated for endometrial carcinoma. Gynecol Oncol 1994;55:229–233.

70. Berchuck A, Anspach C, Evans AC, et al. Postsurgical surveillance of patients with FIGO stage I/II endometrial adenocarcinoma. Gynecol Oncol 1995;59:20–22.

71. Reddoch JM, Burke TW, Morris M, et al. Surveillance for recurrent endometrial carcinoma: development of a follow-up scheme. Gynecol Oncol 1995;59:221–225.

72. Greer BE, Goff BA, Koh WJ. Endometrial carcinoma. In: Johnson FE, Virgo KS, eds. Cancer Patient Follow-up. St. Louis: Mosby; 1997:357–377.

73. Barakat RR, Goldman NA, Patel DA, et al. Pelvic exenteration for recurrent endometrial cancer. Gynecol Oncol 1999;75:99–102.

74. Dowdy SC, Mariani A, Cliby WA, et al. Radical pelvic resection and intraoperative radiation therapy for recurrent endometrial cancer: technique and analysis of outcomes. Gynecol Oncol 2006;101:280–286.

75. Tran PT, Su Z, Hara W, et al. Long-term survivors using intraoperative radiotherapy for recurrent gynecologic malignancies. Int J Radiat Oncol Biol Phys 2007;69:504–511.

76. Poulsen MG, Roberts SJ. The salvage of recurrent endometrial carcinoma in the vagina and pelvis. Int J Radiat Oncol Biol Phys 1988;15:809–813.

77. Kauppila A. Oestrogen and progestin receptors as prognostic indicators in endometrial cancer. A review of the literature. Acta Oncol 1989;28:561–566.

78. Thigpen JT, Brady MF, Alvarez RD, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. J Clin Oncol 1999;17:1736–1744.

79. Quinn MA, Campbell JJ. Tamoxifen therapy in advanced/recurrent endometrial carcinoma. Gynecol Oncol 1989;32:1–3.

80. Thigpen T, Brady MF, Homesley HD, et al. Tamoxifen in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 2001;19:364–367.

81. Burke TW, Walker CL. Arzoxifene as therapy for endometrial cancer. Gynecol Oncol 2003;90(2 Pt 2):S40–46.

82. Quinn MA. Hormonal treatment of endometrial cancer. Hematol Oncol Clin North Am 1999;13:163–187.

83. Fleming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 2004;22:2159–2166.

84. Muss HB. Chemotherapy of metastatic endometrial cancer. Semin Oncol 1994;21:107–113.

85. Reddy SP, Kudelka AP, Gonzalez de Leon C, et al. Tumors of the uterine corpus. In: Pazdur R, ed. Medical Oncology: A Comprehensive Review. Huntington: PRR; 1996:407–416.

86. Sovak MA, Dupont J, Hensley ML, et al. Paclitaxel and carboplatin in the treatment of advanced or recurrent endometrial cancer: a large retrospective study. Int J Gynecol Cancer 2007;17:197–203.

87. Secord AA, Havrilesky LJ, Carney ME, et al. Weekly low-dose paclitaxel and carboplatin in the treatment of advanced or recurrent cervical and endometrial cancer. Int J Clin Oncol 2007;12:31–36.

88. Goff BA, Kato D, Schmidt RA, et al. Uterine papillary serous carcinoma: patterns of metastatic spread. Gynecol Oncol 1994,53:264–268.

89. Hendrickson MR, Longacre TA, Kempson RL. Uterine papillary serous carcinoma revisited. Gynecol Oncol 1994;54:261–263.

90. McCluggage WG. Uterine carcinosarcomas (malignant mixed Mullerian tumors) are metaplastic carcinomas. Int J Gynecol Cancer 2002;12:687–690.

91. Kelly MG, O'Malley DM, Hui P, et al. Improved survival in surgical stage I patients with uterine papillary serous carcinoma (UPSC) treated with adjuvant platinum-based chemotherapy. Gynecol Oncol 2005;98:353–359.

92. Thomas MB, Mariani A, Cliby WA, et al. Role of systematic lymphadenectomy and adjuvant therapy in stage I uterine papillary serous carcinoma. Gynecol Oncol 2007;107:186–189.

93. Goldberg H, Miller RC, Abdah-Bortnyak R, et al. Outcome after combined modality treatment for uterine papillary serous carcinoma: a study by the Rare Cancer Network (RCN). Gynecol Oncol 2008;108:298–305.

94. Hamilton CA, Cheung MK, Osann K, et al. The effect of adjuvant chemotherapy versus whole abdominopelvic radiation on the survival of patients with advanced stage uterine papillary serous carcinoma. Gynecol Oncol 2006;103:679–683.

95. Grice J, Ek M, Greer BE, et al. Uterine papillary serous carcinoma (UPSC): evaluation of long-term survival in 36 surgically staged patients. Gynecol Oncol 1998;69:69–73.

96. Havrilesky LJ, Secord AA, Bae-Jump V, et al. Outcomes in surgical stage I uterine papillary serous carcinoma. Gynecol Oncol 2007;105:677–682.

97. Mehta N, Yamada SD, Rotmensch J, Mundt AJ. Outcome and pattern of failure in pathologic stage I-II papillary serous carcinoma of the endometrium: implications for adjuvant radiation therapy. Int J Radiat Oncol Biol Phys 2003;57:1004–1009.

98. Murphy KT, Rotmensch J, Yamada SD, Mundt AJ. Outcome and patterns of failure in pathologic stages I-IV clear-cell carcinoma of the endometrium: implications for adjuvant radiation therapy. Int J Radiat Oncol Biol Phys 2003;55:1272–1276.

99. Sood BM, Jones J, Gupta S, et al. Patterns of failure after the multimodality treatment of uterine papillary serous carcinoma. Int J Radiat Oncol Biol Phys 2003;57:208–216.

100. Wolfson AH, Brady MF, Rocereto T, et al. A gynecologic oncology group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I-IV carcinosarcoma (CS) of the uterus. Gynecol Oncol 2007;107:177–185.

101. 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.

102. Sutton G, Kauderer J, Carson LF, et al. Adjuvant ifosfamide and cisplatin in patients with completely resected stage I or II carcinosarcomas (mixed mesodermal tumors) of the uterus: a Gynecologic Oncology Group study. Gynecol Oncol 2005;96:630–634.

103. Reed NS, Mangioni C, Malmström H, et al. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group study (protocol 55874). Eur J Cancer 2008;44:808–818.

104. Callister M, Ramondetta LM, Jhingran A, et al. Malignant mixed Müllerian tumors of the uterus: analysis of patterns of failure, prognostic factors, and treatment outcome. Int J Radiat Oncol Biol Phys 2004;58:786–796.

105. Chi D, Mychalczak B, Saigo P, et al. The role of whole-pelvic irradiation in the treatment of early-stage uterine carcinosarcoma. Gynecol Oncol 1997;65:493–498.

106. Knocke T, Weitmann H, Kucera H, et al. Results of primary and adjuvant radiotherapy in the treatment of mixed Mullerian tumors of the corpus uteri. Gynecol Oncol 1999;73:389–395.

107. Larson B, Silfversward C, Nilsson B, et al. Mixed mullerian tumours of the uterus—prognostic factors: a clinical and histopathologic study of 147 cases. Radiother Oncol 1990;17:123–132.

108. Gerszten K, Faul C, Kounelis S, et al. The impact of adjuvant radiotherapy on carcinosarcoma of the uterus. Gynecol Oncol 1998;68:8–13.

109. Dusenbery KE, Potish RA, Argenta PA, Judson PL. On the apparent failure of adjuvant pelvic radiotherapy to improve survival for women with uterine sarcomas confined to the uterus. Am J Clin Oncol 2005;28:295–300.

110. Nemani D, Mitra N, Guo M, Lin L. Assessing the effects of lymphadenectomy and radiation therapy in patients with uterine carcinosarcoma: a SEER analysis. Gynecol Oncol 2008;111:82–88.

111. Wolfson AH, Brady MF, Rocereto T, et al. A gynecologic oncology group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I-IV carcinosarcoma (CS) of the uterus. Gynecol Oncol 2007;107:177–185.

112. Pink D, Lindner T, Mrozek A, et al. Harm or benefit of hormonal treatment in metastatic low-grade endometrial stromal sarcoma: single center experience with 10 cases and review of the literature. Gynecol Oncol 2006;101:464–469.

113. Mansi J, Ramachandra S, Wiltshaw E, et al. Endometrial stromal sarcomas. Gynecol Oncol 1990;36:113–118.

114. Berchuck A, Rubin S, Hoskins W, et al. Treatment of endometrial stromal tumors. Gynecol Oncol 1990;36:60–65.

115. Weitmann H, Knocke T, Kucera H, et al. Radiation therapy in the treatment of endometrial stromal sarcoma. Int J Radiat Oncol Biol Phys 2001;49:739–748.

116. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. N Engl J Med 2007;357:2277–2284.

117. Zivanovic O, Iasonos A, Leitao MM, et al. Stage-specific survival of patients with uterine leiomyosarcoma: a comparison of FIGO and AJCC staging system [abstract]. J Clin Oncol 2008;26:Abstract 5554.

118. Giuntoli RN, Metzinger D, DiMarco C, et al. Retrospective review of 208 patients with leiomyosarcoma of the uterus: prognostic indicators, surgical management, and adjuvant therapy. Gynecol Oncol 2003;89:460–469.

119. Dusenbery KE, Potish RA, Judson P. Limitations of adjuvant radiotherapy for uterine sarcomas spread beyond the uterus. Gynecol Oncol 2004;94:191–196.

120. Sarcoma Meta-analysis Collaboration (SMAC). Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults. Cochrane Database Syst Rev 2000;CD001419.

121. Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J Clin Oncol 2002;20:2824–2831.

122. Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. Gynecol Oncol 2008;109:329–334.

123. Look KY, Sandler A, Blessing JA, et al. Phase II trial of gemcitabine as second-line chemotherapy of uterine leiomyosarcoma: a Gynecologic Oncology Group (GOG) study. Gynecol Oncol 2004;92:644–647.

124. Judson I, Radford JA, Harris M, et al. Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer 2001;37:870–877.

125. Sutton G, Blessing J, Hanjani P, et al. Phase II evaluation of liposomal doxorubicin (Doxil) in recurrent or advanced leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. Gynecol Oncol 2005;96:749–752.

126. Gallup DG, Blessing JA, Andersen W, et al. Evaluation of paclitaxel in previously treated leiomyosarcoma of the uterus: a gynecologic oncology group study. Gynecol Oncol 2003;89:48–51.

Individual Financial Disclosures of the NCCN Uterine Neoplasms Panel

Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Nadeem R. Abu-Rustum, MD	None	None	None	None	6/24/08
Michael A. Bookman, MD	None	Bristol-Myers Squibb Company; Eli Lilly and Company; Genentech, Inc.; GlaxoSmithKline; and Johnson & Johnson	None	Eli Lilly and Company; and Genentech, Inc.	7/28/08
Robert E. Bristow, MD	John's Hopkins University	Genzyme Corporation; and Oncotech	None	None	1/6/09
Susana M. Campos, MD, MPH	None	None	None	None	1/2/09
Kathleen R. Cho, MD	None	None	None	None	8/4/08
Larry Copeland, MD	Eli Lilly and Company; and Gynecologic Oncology Group	Eli Lilly and Company; MGI PHARMA, INC.; Onyx Pharmaceuticals, Inc.; and Pfizer Inc.	Gynecologic Oncology Group	None	7/26/08
Marta Ann Crispens, MD	None	None	None	None	5/21/08
Patricia J. Eifel, MD	None	None	None	None	10/8/08
Benjamin E. Greer, MD	None	None	None	None	12/22/08
Warner K. Huh, MD	GlaxoSmithKline; Merck & Co., Inc.; MGI PHARMA, INC.; and Takeda Pharmaceuticals North America, Inc.	GlaxoSmithKline; Intuitive Surgical, Inc.; and Merck & Co., Inc.	None	None	11/6/08
Wainwright Jaggernauth, MD	None	Bristol-Myers Squibb Company	None	None	7/23/08
Daniel S. Kapp, MD, PhD	None	None	None	None	7/23/08
John J. Kavanagh, MD	None	None	None	None	5/21/08
Wui-Jin Koh, MD	Gynecologic Oncology Group	None	None	None	7/23/08
John R. Lurain III, MD	None	None	None	None	9/5/08
Mark A. Morgan, MD	None	None	None	None	6/19/08
Robert J. Morgan, Jr., MD	NIH-CTEP	None	None	None	7/23/08
C. Bethan Powell, MD	None	None	None	None	9/11/08
Steven W. Remmenga, MD	None	None	None	None	7/23/08
R. Kevin Reynolds, MD	None	None	None	None	9/5/08
Angeles Alvarez Secord, MD	Bristol-Myers Squibb Company; GlaxoSmithKline; Precision Therapeutics, Inc.; and sanofi-aventis U.S.	Abraxis Oncology; Eli Lilly and Company; GlaxoSmithKline; Merck & Co., Inc.; and sanofi-aventis U.S.	None	Eli Lilly and Company	7/28/08
William Small, Jr., MD	Genentech, Inc.	Pfizer Inc.	None	None	8/3/08
Nelson Teng, MD, PhD	Gynecologic Oncology Group	None	None	None	1/2/09

The NCCN guidelines staff have no conflicts to disclose.