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. Uterine sarcomas are uncommon and account for approximately 1 in 12 of all uterine cancers. 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

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.

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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-
INITIAL EVALUATION

- H&P
- CBC, platelets
- Endometrial biopsy
- Chest x-ray
- Current cervical cytology consistent with NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer Screening (for the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org)

Optional:
- LFT/renal function tests/chemistry profile
- Consider genetic counseling for patients with a significant family history

INITIAL CLINICAL FINDINGS

- Disease limited to uterus
- Pure endometrioid
- Suspected or gross cervical involvement
- Pathology review
- Papillary serous or clear cell carcinoma
- Suspected extrauterine disease
- Carcinosarcoma^a,b

Epithelial carcinoma

Disease limited to uterus

Stromal/mesenchymal tumors
- Low-grade endometrial stromal sarcoma (ESS)
- High-grade undifferentiated sarcoma (HGUD)
- Leiomyosarcoma (LMS)

Known or suspected extrauterine disease

See Treatment for Papillary Serous or Clear Cell Carcinomas of the Endometrium or Carcinosarcoma (page 510)

See Primary Treatment (page 503)

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.
INITIAL CLINICAL FINDINGS

Medically inoperable

Operable

Tumor-directed RT\textsuperscript{b}

Total hysterectomy and bilateral salpingo-oophorectomy (TH/BSO)\textsuperscript{c}
- Cytology
- Lymph node dissection (not random sampling)\textsuperscript{d}
  - Pelvic lymphadenectomy
  - Para-aortic lymphadenectomy

Adjuvant Treatment for completely surgically staged:
- Stage I (See page 504)
- Stage II (See page 505)
- Stage IIIA (See page 505)
- Stage IIIB-IV (See page 506)

Incompletely surgically staged

See page 507

See Surveillance (page 508)

\textsuperscript{a} See page 500 for clarification of uterine neoplasms.
\textsuperscript{b} See Principles of Radiation Therapy (page 517).
\textsuperscript{c} See Hysterectomy (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.
Suspected or gross cervical involvement (endometrioid histologies)a

Negative result

Positive result or gross involvement e

Operable

Radical hysterectomy and bilateral salpingo-oophorectomy (RH/BSO)

Cytology

Lymph node dissection (not random sampling)

Pelvic lymphadenectomy

Para-aortic lymphadenectomy

or RT: 75-80 Gy to point A (category 2B)

c
d
f

Inoperable Tumor-directed RTb

TH/BSO

Para-aortic lymph node dissection

See Surveillance (page 508)

Adjuvant treatment for completely surgically staged:

Stage I (See page 504)

Stage II (See page 505)

Stage IIIA (See page 505)

Stage IIIB-IV (See page 506)

Incompletely surgically staged

Suspected extrauterine disease (endometrioid histologies)a

None

See Primary Treatment (disease limited to uterus; page 501)

CA-125

MRI/CT, as clinically indicated

Intra-abdominal:

- Ascites
- Omentum
- Nodal
- Ovarian
- Peritoneal

TH/BSOc + cytology ± pelvic and para-aortic lymph node dissectiond

Extrauterine pelvis:

- Vaginal
- Bladder
- Bowel/rectum
- Parametrial

RT ± surgery + brachytherapy ± chemotherapy

Extra-abdominal/liver

Consider palliative TH/BSO ± RT ± hormonal therapy ± chemotherapy

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See page 500 for clarification of uterine neoplasms.

See Hysterectomy (page 511).


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Note: a, b, c, d, e, f correspond to specific references and clarifications provided in the NCCN Clinical Practice Guidelines in Oncology.

Adjuvant therapy determinations are made on the basis of pathologic findings. Potential adverse risk factors include the following: age > 60 y, positive lymphovascular invasion, tumor size, lower uterine (cervical/glandular) involvement. See Principles of Radiation Therapy (page 517).

See Surveillance (page 508)

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**ENDOMETRIAL CARCINOMA**


### CLINICAL FINDINGS

<table>
<thead>
<tr>
<th>Stage IA</th>
<th>Stage IB (≤ 50%) myometrial invasion</th>
<th>Stage IC (&gt; 50%) myometrial invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse risk factors present</td>
<td>Adverse risk factors not present</td>
<td>Adverse risk factors present</td>
</tr>
</tbody>
</table>

### ADVERSE RISK FACTORS

- Age > 60 y
- Positive lymphovascular invasion
- Tumor size
- Lower uterine (cervical/glandular) involvement

### HISTOLOGIC GRADE/ADJUVANT TREATMENT

<table>
<thead>
<tr>
<th>G1</th>
<th>G2</th>
<th>G3 i,j</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observe</td>
<td>Observe</td>
<td>Observe or Vaginal brachytherapy</td>
</tr>
<tr>
<td>Observe</td>
<td>Observe</td>
<td>Observe or Vaginal brachytherapy and/or Pelvic RT</td>
</tr>
<tr>
<td>Observe or Vaginal brachytherapy</td>
<td>Observe or Vaginal brachytherapy and Pelvic RT (category 2B for all options)</td>
<td>Observe or Vaginal brachytherapy and/or Pelvic RT</td>
</tr>
<tr>
<td>Observe or Vaginal brachytherapy</td>
<td>Observe or Vaginal brachytherapy</td>
<td>Observe or Vaginal brachytherapy and/or Pelvic RT</td>
</tr>
<tr>
<td>Observe or Vaginal brachytherapy and/or Pelvic RT</td>
<td>Observe or Vaginal brachytherapy and/or Pelvic RT</td>
<td>Observe or Pelvic RT and/or Vaginal brachytherapy ± chemotherapy (category 2B for chemotherapy)</td>
</tr>
</tbody>
</table>

See Principles of Radiation Therapy (page 517).

Potential adverse risk factors include the following: age > 60 y, positive lymphovascular invasion, tumor size, lower uterine (cervical/glandular) involvement.


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

Adjuvant treatment determinations are made on the basis of pathologic findings. See Principles of Radiation Therapy (page 517).


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Uterine Neoplasms Version 2:2009

ENDOMETRIAL CARCINOMA

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**CLINICAL INTRAUTERINE FINDINGS**

- **Stage IA, G1-2**
  - Observe
- **Stage IB, G1-2**
  - Positive: Radiologic imaging
  - Incompletely surgically staged
  - **Stage II A, G1-2**
    - (myometrial invasion ≤ 50%)
  - **Stage IC; Stage IIA**
    - (myometrial invasion > 50%)
    - Stage IIB or G-3
- **Stage IIA**
  - Radiologic imaging
  - Negative: Observation or Vaginal brachytherapy ± pelvic RT
  - Positive: Surgical restaging or pathologic confirmation of metastatic disease
  - Positive: Pelvic RT + vaginal brachytherapy ± para-aortic RT (± chemotherapy for Grade 3 tumors [category 2B for chemotherapy])

**ADJUVANT TREATMENT**

- **Stage IVA, IVB**
  - Chemotherapy ± RT
  - Debulked and with no gross residual disease or microscopic abdominal disease

**ADJUVANT TREATMENT**

- **Stage IIIB, IIIC**
  - Chemotherapy and/or tumor-directed RT
  - Pelvic node positive
  - Common iliac or para-aortic node positive

- **Stage IV**
  - Chemotherapy ± RT
  - Debulked and with no gross residual disease or microscopic abdominal disease

**ADJUVANT TREATMENT**

- **Incompletely surgically staged**
  - Stage I (See page 504)
  - Stage II (See page 505)
  - Stage IIIA (See page 505)
  - Stage IIIB-IV (See opposite page)

\[^b\] See Principles of Radiation Therapy (page 517).
**ENDOMETRIAL CARCINOMA**

<table>
<thead>
<tr>
<th>SURVEILLANCE</th>
<th>CLINICAL PRESENTATION</th>
<th>THERAPY FOR RELAPSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Physical exam every 3-6 mo for 2 y, then 6 mo or annually&lt;br&gt;- Vaginal cytology every 6 mo for 2 y, then annually&lt;br&gt;- Patient education regarding symptoms&lt;br&gt;- CA 125 (optional)&lt;br&gt;- Chest x-ray annually (category 2B)&lt;br&gt;- CT/MRI as clinically indicated&lt;br&gt;- Consider genetic counseling for patients with a significant family history</td>
<td>Local/regional recurrence&lt;br&gt;- Negative distant metastases on radiologic imaging</td>
<td>Treat as disseminated metastases (see below)</td>
</tr>
<tr>
<td>Isolated metastases</td>
<td>Consider resection ± RT</td>
<td>Unresectable or further recurrence</td>
</tr>
<tr>
<td>Disseminated metastases</td>
<td>Asymptomatic or low grade</td>
<td>Hormonal therapy(^n) If progression, chemotherapy(^n)</td>
</tr>
<tr>
<td></td>
<td>Symptomatic or grade 2, 3 or large volume</td>
<td>Chemotherapy(^n) and/or palliative RT</td>
</tr>
</tbody>
</table>

- *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.
## Uterine Neoplasms Version 2:2009

### Endometrial Carcinoma

#### Therapy for Relapse

<table>
<thead>
<tr>
<th>Disease</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial cancer in vagina</td>
<td>RT(^b) + brachytherapy(^b) or Surgical exploration of pelvis + resection ± IORT</td>
</tr>
<tr>
<td>Pelvic node</td>
<td>Tumor-directed RT ± brachytherapy ± chemotherapy</td>
</tr>
<tr>
<td>Para-aortic or common iliac lymph node</td>
<td></td>
</tr>
<tr>
<td>Microscopic residual</td>
<td>Chemotherapy ± tumor-directed RT</td>
</tr>
<tr>
<td>Gross upper abdominal residual disease</td>
<td>See Therapy For Relapse (disseminated metastases; opposite page)</td>
</tr>
<tr>
<td>Upper abdominal/ peritoneal</td>
<td></td>
</tr>
</tbody>
</table>

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\(^b\) See Principles of Radiation Therapy (page 517).

\(^n\) 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.
PAPILLARY SEROUS OR CLEAR CELL CARCINOMA OF THE ENDOMETRIUM OR CARCINOSARCOMA

Includes surgical staging, as with ovarian cancer:
- TH/BSO, pelvic and para-aortic lymph node dissection,
- Cytology, omentectomy,
- Biopsies of peritoneal surfaces (including underside of diaphragm)
- Maximal tumor debulking

**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**

- Aromatase inhibitors
- Progestational agents
- Tamoxifen

**CHEMOTHERAPY REGIMENS**

(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)

Hormonal therapy is for endometrioid histologies only (i.e., not for papillary serous carcinoma, clear cell carcinoma, or carcinosarcoma).

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.
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.

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UTERINE SARCOMA

PATHOLOGIC FINDINGS/HISTOLOGIC GRADE

<table>
<thead>
<tr>
<th>Stage I, II</th>
<th>Observe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III</td>
<td></td>
</tr>
<tr>
<td>Stage IVA</td>
<td></td>
</tr>
<tr>
<td>Stage IVB</td>
<td></td>
</tr>
</tbody>
</table>

ADJUVANT TREATMENT

<table>
<thead>
<tr>
<th>Low-grade ESS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I, II</td>
<td>Hormone therapy^b ± pelvic RT^a</td>
</tr>
<tr>
<td>Stage III</td>
<td>Hormone therapy^b ± palliative RT</td>
</tr>
<tr>
<td>Stage IVA</td>
<td></td>
</tr>
<tr>
<td>Stage IVB</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HGUD or LMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I, II</td>
</tr>
<tr>
<td>Stage III</td>
</tr>
<tr>
<td>Stage IVA</td>
</tr>
<tr>
<td>Stage IVB</td>
</tr>
</tbody>
</table>

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

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**Uterine Sarcoma**

**Surveillance**
- **Isolated metastases**
  - Physical exam every 3 mo for 2 y, then every 6-12 mo
  - Chest x-ray annually
  - CT/MRI as clinically indicated
- **Disseminated disease**
  - Patient education regarding symptoms

**Recurrence**
- **Local recurrence:**
  - Vagina
  - Negative chest and abdominal/pelvic CT, confirming local vaginal recurrence

**Therapy for Relapse**
- **Resectable**
  - Consider surgical resection + postoperative chemotherapy or hormone therapy (low-grade ESS only)
  - Chemotherapy ± palliative RT
  - Hormone therapy (low-grade ESS only)
- **Unresectable**
  - Surgical exploration + resection ± IORT or Tumor-directed RT
  - Tumor-directed re-irradiation

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*See Systemic Therapy for Uterine Sarcoma (page 516).*

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*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)
- Medroxyprogesterone acetate
- Megestrol acetate
- Aromatase inhibitors (category 2B)
- GnRH analogs (category 2B)
- Tamoxifen (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
- Undifferentiated sarcoma
  (high-grade undifferentiated sarcoma) or pure heterologous sarcoma
- Leiomyosarcoma

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 extraterine 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.
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 extraterine disease as indicated by clinical symptoms, physical findings, or abnormal laboratory findings. In patients with extraterine disease, a serum CA 125 assay may help monitor clinical response. 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.

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.

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. 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 extraterine spread (including retroperitoneal lymph node metastases; the staging table is available online, in these guidelines, at www.nccn.org [ST-1]).

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 extraterine 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 salpingooophorectomy (TH/BSO) with dissection of pelvic and para-aortic lymph nodes (see page 501). 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. Recent data question the role of routine pelvic lymphadenectomy in early-stage endometrial carcinoma; these findings remain a point of contention and are not currently reflected in North American practice. For patients with surgical stage I (any grade) endometrial cancer, the 5-year overall survival rate is 88%. 

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.

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. 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. 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.

**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”).

**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; however, patients were formally staged in the third trial. The PORTEC-1 (Postoperative Radiation Therapy in Endometrial Carcinoma) trial was interpreted to show therapeutic benefit in selected patients with uterine-confined disease. Although RT significantly decreased
locoregional recurrence, it did not increase overall survival. The randomized trial by Aalders et al. 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. 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.

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. Notably, both PORTEC-1 and -2 specifically excluded patients with stage IC 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.

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. 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. 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. 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. 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. 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. 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 extraterine 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 CTTreatment 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.  

**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. 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.  

Robotic surgery is being evaluated for treatment of patients with endometrial cancer. To assess the role of adjuvant radiation in patients with surgically staged endometrial cancer without extraperitoneal 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. 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. 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 IB, G1 disease. If adverse factors are present, observation or vaginal brachytherapy is recommended for patients with stage IB, G1 disease; however, options for stage IB, 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. 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 extraterine 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). The practice of surgical staging has decreased the use of adjuvant therapy for stage I endometrial carcinoma.

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 extraterine disease.

Patients with extraterine disease confined to the lymph nodes or adnexa may be adequately treated with pelvic or extended-field RT. 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. 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 IIIIB and IIC 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. A randomized phase III GOG (122) trial assessed optimal adjuvant therapy for endometrial cancer with extraterine disease. In this trial, patients with stage III and intra-abdominal stage IV disease who had minimal residual disease were randomly assigned to whole abdominal pelvic RT versus 7 cycles of combined doxorubicin (60 mg/m²) and cisplatin (50 mg/m²) treatment, with an additional cycle of cisplatin (AP). This study showed that AP chemotherapy improved progression-free and overall survival compared with whole abdominal pelvic RT; however, acute toxicity was greater in the AP chemotherapy arm. 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.

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.

**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. trial and the more recent PORTEC-1 analysis showed improvement in pelvic control with adjuvant RT, but without a significant effect on overall survival.

**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, 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. 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.

**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 progesterational 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 progesterational agents has shown a good response for patients who have estrogen and progesterone receptor–positive disease. Tamoxifen has a 20% response rate in those whose disease does not respond to standard progesterone therapy. In a single-institution study, the SERM arzoxifene showed a response rate of approximately 28% in metastatic endometrial cancer; 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. 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. 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.

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. Weekly low-dose paclitaxel and carboplatin also seems useful. 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. 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.

Adjuvant therapy recommendations for stage IA include observation and/or chemotherapy, or tumor-directed RT. Recommendations for stage IB 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. 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 metastatic carcinomas. Ifosfamide is the most active single agent for carcinosarcoma. Combination cisplatin and ifosfamide was once a widely used active regimen. A recent phase III trial showed that the combination of ifosfamide and paclitaxel was active for advanced carcinosarcoma with less toxicity than the cisplatin/ifosfamide regimen.
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. In some series, this local control improvement correlates with an improvement in survival, although other data show that lymphadenectomy confers greater benefit. A phase III randomized GOG trial 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.

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]). 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). 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. Adjuvant RT in ESS has been shown to reduce local recurrence rates but again with limited effect on survival. Because of concerns about radiation exposure, frequent routine asymptomatic surveillance imaging is no longer recommended for young women after primary therapy for ESS.

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.

The role of adjuvant radiotherapy in nonmetastatic disease is controversial. Most available data are retrospective, except for a recent phase III randomized trial. 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. 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. 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. Combination regimens, such as gemcitabine and docetaxel, have also been used. Single-agent dacarbazine, doctetaxel, liposomal doxorubicin, epirubicin, gemcitabine, ifosfamide, and paclitaxel can also be considered for advanced or metastatic disease (category 2B). Enrollment in clinical trials is strongly recommended.
References

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


### Individual Financial Disclosures of the NCCN Uterine Neoplasms Panel

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<td>Warner K. Huh, MD</td>
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<td>Daniel S. Kapp, MD, PhD</td>
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The NCCN guidelines staff have no conflicts to disclose.