

**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

# **Uterine Neoplasms**

Version 3.2017 — July 18, 2017

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## Uterine Neoplasms

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\*NCCN gratefully acknowledges the following NCCN Imaging Panel members for their contributions during the development of the Principles of Imaging pages (ENDO-A and UTSARC-A) in Version 1.2017 of the NCCN Guidelines for Uterine Neoplasms:

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To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical\\_trials/physician.html](#).

**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise specified.

See [NCCN Categories of Evidence and Consensus](#).

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# NCCN Guidelines Version 3.2017 Updates

## Uterine Neoplasms

Updates in Version 3.2017 of the NCCN Guidelines for Uterine Neoplasms from Version 2.2017 include:

### Uterine Sarcoma

#### UTSARC-B--Systemic Therapy for Uterine Sarcoma

- The combination “doxorubicin/olaratumab” was added as a systemic therapy option for the treatment of uterine sarcoma.

### MS-1

- The Discussion section was updated to reflect the changes in the algorithm.

Updates in Version 2.2017 of the NCCN Guidelines for Uterine Neoplasms from Version 1.2017 include:

### MS-1

- The Discussion section was updated to reflect the changes in the algorithm.

Updates in Version 1.2017 of the NCCN Guidelines for Uterine Neoplasms from Version 2.2016 include:

### Global changes

- A new section for “Principles of Imaging” that includes recommendations for “Initial Workup” and “Follow-up/Surveillance” was added to the Guidelines to clarify recommended imaging modalities. Recommendations for specific imaging modalities (ie, CT, PET, MRI) were removed from the algorithms and described in greater detail in the new imaging sections ([ENDO-A](#)) and ([UTSARC-A](#)).
- “Tumor-directed RT” was clarified as “*EBRT*” throughout the Guidelines.
- “Chemotherapy” changed to “*Systemic therapy*” throughout the Guidelines.

### UN-1

#### • Initial Evaluation:

- ▶ Third bullet revised: “*Expert pathology review with additional endometrial biopsy as clinically indicated.*” Previously “Expert pathology review” was in the second column and followed “Initial Evaluation”.
- ▶ Fourth bullet revised: “*Chest Imaging.*”
- ▶ New bullet added: “*Consider genetic evaluation ([See ENDO-B](#)).*”
- ▶ Optional
  - ◊ Bullet removed: “Consider genetic counseling/testing for patients (<50 y) and those with a significant family history of endometrial and/or colorectal cancer.”
- Footnote “a” is new: “*Initial preoperative evaluation for known or suspected malignancy.*”
- Footnote “b” revised: “...If there is suspicion of malignant mesenchymal sarcoma, fragmentation/*morcellation* should be avoided.” (Also for UTSARC-1)
- Footnote “c” is new: “See [Principles of Imaging for Endometrial Carcinoma \(ENDO-A\)](#) and [Principles of Imaging for Uterine Sarcoma \(UTSARC-A\)](#).”
- Footnote removed: “Recently, immunohistochemistry (IHC) and/or microsatellite instability (MSI) screening of all colorectal and endometrial cancers, regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for Lynch syndrome (LS). An infrastructure needs to be in place to handle the screening results. IHC and/or MSI screening is usually performed on epithelial tumors.”

[Continued](#) **UPDATES**



# NCCN Guidelines Version 3.2017 Updates

## Uterine Neoplasms

### Endometrial Carcinoma

#### ENDO-1

- Disease limited to the uterus (endometrioid histology); Not suitable for primary surgery: Primary Treatment recommendation revised, **"Tumor-directed RT EBRT and/or brachytherapy."**
- Footnote "c" is new: "Minimally invasive surgery (MIS) is the preferred approach when technically feasible. [See Principles of Evaluation and Surgical Staging \(ENDO-C\).](#)"
- Footnote removed: "Endometrial carcinoma should be removed en bloc to optimize outcomes; morcellation should be avoided."

#### ENDO-2

- Suspected or gross cervical involvement (endometrioid histology)
  - Additional Workup: Revised, "Consider cervical biopsy or *pelvic MRI (if not previously done).*"
  - Primary Treatment
    - ◊ Medically operable: Revised, "EBRT + *brachytherapy....*"
    - ◊ Not suitable for primary surgery:
      - Revised **"Tumor-directed RT EBRT + brachytherapy ± Chemotherapy-Systemic therapy."**
      - After "Systemic therapy (category 2B)," revised **"EBRT + brachytherapy if still inoperable."**
- Footnotes removed and added to the appendix sections:
  - "Endometrial carcinoma should be removed *en bloc* to optimize outcomes; morcellation should be avoided." included in [Principles of Surgical Staging and Evaluation \(ENDO-C\)](#)
  - "MRI performed with contrast unless contraindicated." included in the [Principles of Imaging \(ENDO-A\)](#)

#### ENDO-3

- Suspected extrauterine disease (endometrioid histology)
  - Additional Workup: Revised "CA-125 for *high risk sub-types* (optional)" and **"MRI/CT/PET, Imaging as clinically indicated (*if not previously done*)."**
  - Primary Treatment:
    - ◊ "Intra-abdominal" pathway: "TH/BSO + surgical staging/debulking (**may consider preoperative chemotherapy**)"
    - ◊ "Initially unresectable extrauterine pelvic disease" pathway: "RT + brachytherapy ± chemotherapy" changed to **"EBRT and/or brachytherapy ± chemotherapy systemic therapy or Chemotherapy-Systemic therapy."**
    - ◊ Extra-abdominal/liver pathway: Revised, **"May Consider palliative TH/BSO."**
  - Footnote removed: "CT and MRI performed with contrast throughout the guidelines unless contraindicated. Contrast not required for screening chest CT." included in the [Principles of Imaging \(ENDO-A\)](#)

#### ENDO-4

- New footnote "m" regarding "Adverse risk factors present" pathway added: **"Consider additional imaging if not previously done [See Principles of Imaging \(ENDO-A\).](#)"**





# NCCN Guidelines Version 3.2017 Updates

## Uterine Neoplasms

### Endometrial Carcinoma--continued

#### ENDO-6

##### • Adjuvant Treatment

- ▶ Stage IIIA disease "Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or EBRT ± vaginal brachytherapy" changed to "Systemic therapy *and/or* EBRT ± vaginal brachytherapy."
- ▶ Stage IIIB, IIIC1, IIIC2: "Chemotherapy and/or tumor-directed RT" changed to "Systemic therapy *and/or* EBRT ± vaginal brachytherapy."
- ▶ Stage IVA, IVB: "Chemotherapy ± RT" changed to "Systemic therapy *and/or* EBRT ± vaginal brachytherapy."

#### ENDO-8

##### • Surveillance after primary treatment with fertility sparing options; After, "Endometrial sampling every 3-6 mo...":

- ▶ Revised, "Endometrial cancer present at 6-9 6-12 months."
- ▶ "Consider MRI" added as an option before performing "TH/BSO with staging"

#### ENDO-9

##### • Surveillance recommendations revised

##### • CA-125 (optional) if initially elevated

- ▶ Patient education regarding symptoms of potential recurrence, periodic self-examinations, lifestyle, obesity, exercise, *sexual health (including vaginal dilator use and lubricants/moisturizers)*, smoking cessation, nutrition counseling, *potential long-term and late effects of treatment...*
- ▶ Bullet deleted: "Consider genetic counseling/testing for patients (<50 y) and those with a significant family history of endometrial and/or colorectal cancer and/or selected pathologic risk features ([See Lynch syndrome/HNPCC in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#))"
- ▶ Bullet deleted: "Patient education regarding sexual health, vaginal dilator use, and vaginal lubricants/moisturizers"

#### ENDO-10

##### • Local/regional recurrence; Previous external beam RT; Therapy for Relapse: Recommendation revised, "Surgical exploration + resection ± IORT (category 3 for IORT) *and/or* Hormone therapy or Chemotherapy Systemic therapy."

##### • "No Prior RT" and "Previous brachytherapy only" pathways: RT + brachytherapy changed to "EBRT ± brachytherapy."

#### ENDO-11 Serous or Clear Cell Carcinoma or Carcinosarcoma of the Endometrium;

- Additional workup: Second bullet revised, "MRI/CT/PET Imaging as clinically indicated" with a corresponding footnote to the new [Principles of Imaging \(ENDO-A\)](#) page.
- Primary Treatment: Removed "Included surgical staging as with ovarian cancer"
- Adjuvant Treatment
  - ▶ Stage IA: Revised "Tumor-directed RT EBRT ± vaginal brachytherapy"
  - ▶ Stage IB, II, III, IV: Revised "Chemotherapy ± Tumor-directed EBRT ± vaginal brachytherapy"



# NCCN Guidelines Version 3.2017 Updates

## Uterine Neoplasms

### **Endometrial Carcinoma--continued**

#### **ENDO-B--Hysterectomy and Pathologic Evaluation**

- Under "Pathologic Assessment to include:" the following revisions made:

- ▶ First bullet "Uterus":

- ◊ New sub-bullet added "*Universal testing of endometrial tumors for mismatch repair (MMR) gene.*"
- ◊ Sub-bullet deleted "Consider screening with IHC and MSI for inherited mismatch repair gene mutations in patients <50 y and those with a significant family history of endometrial and/or colorectal cancer and/or selected pathologic risk features to identify familial cancer syndromes, such as Lynch syndrome/HNPCC ([See Lynch syndrome/HNPCC in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#))"

- ▶ New bullets and sub-bullets added:

- ◊ *Universal testing of endometrial carcinomas for mismatch repair (MMR) gene*
  - *Testing should be done on the final hysterectomy specimen (can be done on presurgical biopsy if hysterectomy not performed)*
  - *MLH1 loss should be further evaluated for promoter methylation to assess epigenetic process.*
  - *Genetic counseling and testing for all other MMR abnormalities*
  - *Genetic counseling and testing for patients without MMR abnormalities, but who have a significant family history of endometrial and/or colorectal cancer ([See Lynch syndrome/HNPCC in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#))*

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

#### **ENDO-C--Principles of Evaluation and Surgical Staging**

##### **Page 1 of 5**

- This section was extensively revised.

##### **Page 2 of 5 Principles of Surgical Staging When SLN Mapping is Used**

- This section was extensively revised including edits to the following bullet : "SLN mapping (~~category 3~~) can be considered for the surgical staging of apparent uterine-confined malignancy when there is no metastasis demonstrated by imaging studies or no obvious extrauterine disease at exploration."





# NCCN Guidelines Version 3.2017 Updates

## Uterine Neoplasms

### Uterine Sarcoma

#### UTSARC-1

- Initial Clinical Findings: In the bottom pathway "Diagnosed any modality" was removed.
- Additional Evaluation: For both pathways revised, "~~CT chest/abdomen/pelvis or MRI or PET-CT Imaging~~" with corresponding footnote to the [Principles of Imaging \(UTSARC-A\)](#) page.

Footnote "b" revised: "~~CT and MRI performed with contrast throughout the guidelines unless contraindicated. Contrast not required for screening chest CT.~~ [See Principles of Imaging for Uterine Sarcoma \(UTSARC-A\).](#)"

#### UTSARC-4

- Surveillance:
  - ▶ Bullets revised and information included in the [Principles of Imaging \(UTSARC-A\)](#).
    - ◊ ~~CT Imaging (chest/abdomen/pelvis) every 3–6 mo for 2–3 y, then every 6 mo for next 2 y, then annually for high-grade sarcomas~~
    - ◊ ~~Consider other imaging (MRI/PET) as clinically indicated~~
  - ▶ Bullet revised: Patient education regarding symptoms of potential recurrence, lifestyle, obesity, exercise, nutrition, *sexual health, (including vaginal dilator use and lubricants/moisturizers)*, smoking cessation, nutrition counseling *and potential long-term and late effects of treatment...*
  - ▶ Bullet removed: "Patient education regarding sexual health, vaginal dilator use, and vaginal lubricants/moisturizers." and combined with bullet above.
- Under "Local recurrence," bullet revised and information included in the [Principles of Imaging \(UTSARC-A\)](#): "~~Chest and abdominal/pelvic CT Imaging~~ negative for metastatic disease."

#### UTSARC-5

- Radiologically isolated vaginal/pelvic recurrence, Therapy for Relapse:
  - ▶ "No Prior RT" pathway, revised the following treatment options
    - ◊ ~~"Tumor-directed RT EBRT ± brachytherapy ± systemic therapy"~~
    - ◊ After "Disease confined to vagina": "Consider ~~tumor-directed RT~~ adjuvant *EBRT ± brachytherapy* if not previously given."
  - ▶ "Prior RT" pathway: Revised, "~~Tumor-directed RT~~ *Selected* re-irradiation with *EBRT and/or brachytherapy*"

#### UTSARC-B--Systemic Therapy for Uterine Sarcoma

- Single-agent options: Eribulin changed from category 2A to category 2B.



# NCCN Guidelines Version 3.2017

## Uterine Neoplasms

### INITIAL EVALUATION<sup>a</sup>

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

### INITIAL CLINICAL FINDINGS

- H&P
- CBC (including platelets)
- Expert pathology review with additional endometrial biopsy as clinically indicated<sup>b</sup>
- Imaging<sup>c</sup>
- Consider genetic evaluation ([See ENDO-B](#))

- Optional:
- Liver function test (LFT)/renal function tests/chemistry profile

Malignant epithelial (carcinoma)

Pure endometrioid carcinoma

Serous carcinoma or  
Clear cell carcinoma or  
Carcinosarcoma<sup>d,e</sup>

Malignant mesenchymal (sarcoma)<sup>a</sup>

- Low-grade endometrial stromal sarcoma (ESS)
- High-grade ESS
- Undifferentiated uterine sarcoma (UUS)
- Uterine leiomyosarcoma (uLMS)

Disease limited to uterus

Suspected or gross cervical involvement

Suspected extrauterine disease

[See Primary Treatment \(ENDO-1\)](#)

[See Primary Treatment \(ENDO-2\)](#)

[See Primary Treatment \(ENDO-3\)](#)

[See Treatment for Serous or Clear Cell Carcinoma or Carcinosarcoma of the Endometrium \(ENDO-11\)](#)

[See Primary Treatment \(UTSARC-1\)](#)

<sup>a</sup>Initial preoperative evaluation for known or suspected malignancy.

<sup>b</sup>Preoperative imaging and biopsy may help to identify uterine sarcomas, although biopsy sensitivity is less than for endometrial cancer. If there is suspicion of malignant mesenchymal sarcoma, fragmentation/morcellation should be avoided.

<sup>c</sup>See [Principles of Imaging for Endometrial Carcinoma \(ENDO-A\)](#) and [Principles of Imaging for Uterine Sarcoma \(UTSARC-A\)](#).

<sup>d</sup>Staged as aggressive; should be treated as a high-grade endometrial cancer.

<sup>e</sup>Also known as malignant mixed mesodermal tumor or malignant mixed Müllerian tumor and including those with either homologous or heterologous stromal elements.

**Note:** All recommendations are category 2A unless otherwise indicated.

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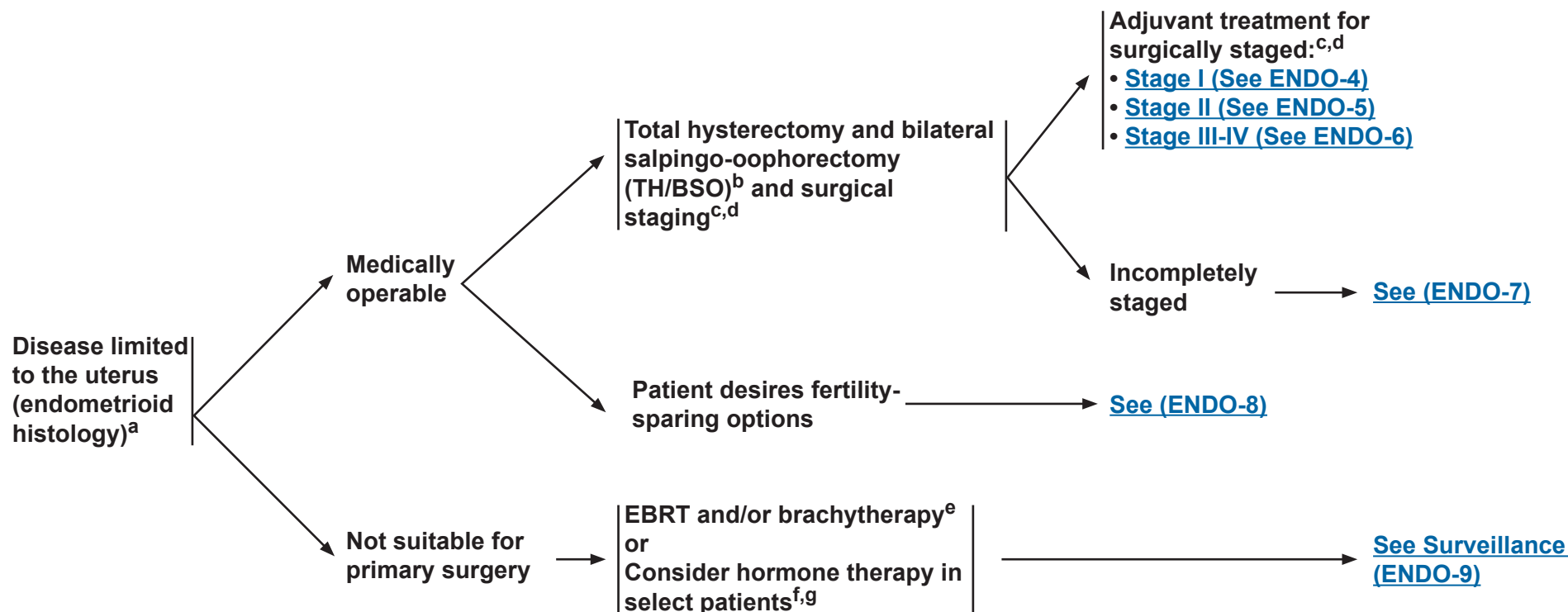


# NCCN Guidelines Version 3.2017

## Endometrial Carcinoma

### INITIAL CLINICAL FINDINGS

### PRIMARY TREATMENT



<sup>a</sup>[See \(UN-1\)](#) for clarification of uterine neoplasms.

<sup>b</sup>[See Hysterectomy and Pathologic Evaluation \(ENDO-B\)](#).

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

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

<sup>e</sup>[See Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\)](#).

<sup>f</sup>Patients should be closely monitored. Consider endometrial biopsies every 3 to 6 months.

<sup>g</sup>[See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease \(ENDO-D\)](#).

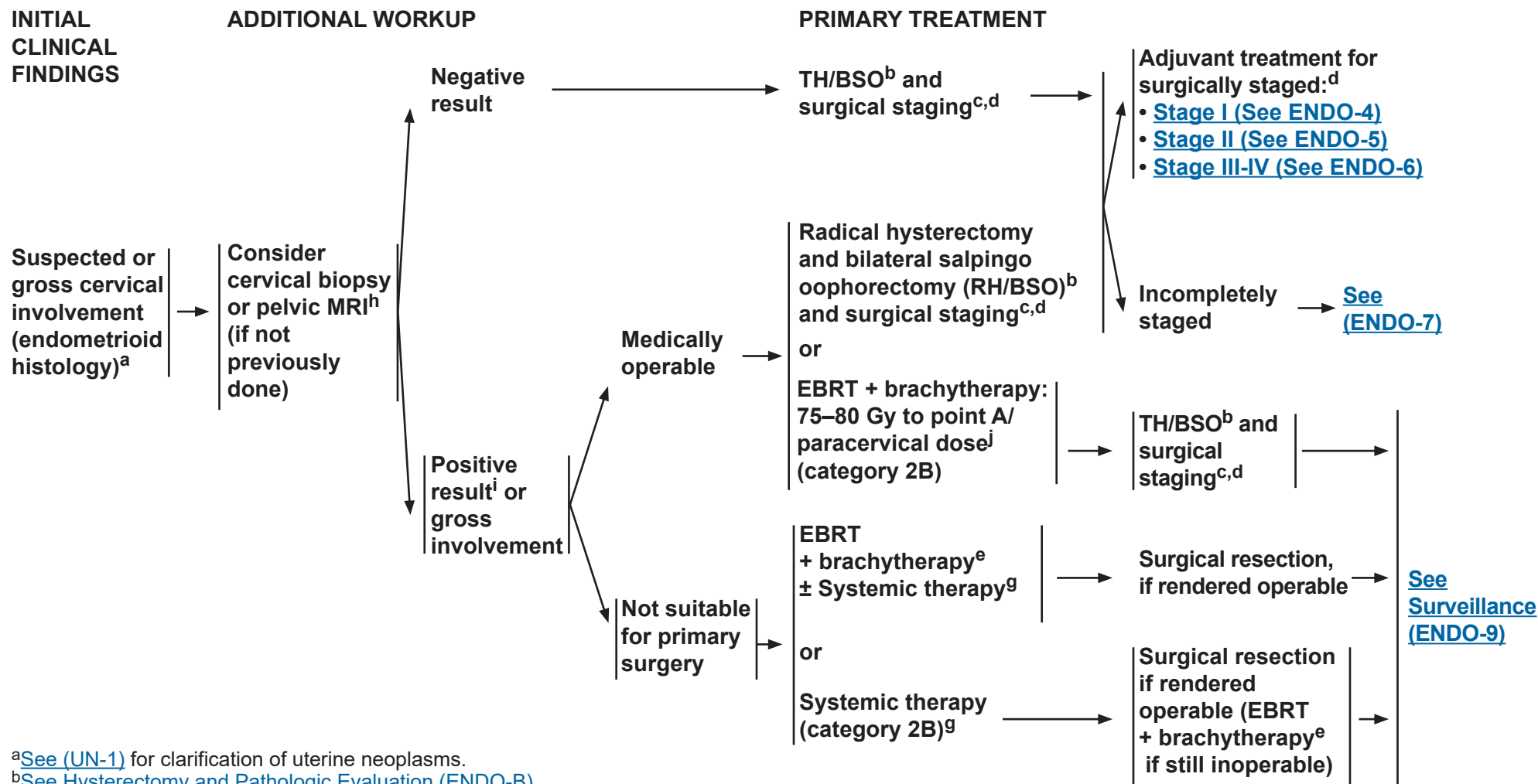
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# NCCN Guidelines Version 3.2017

## Endometrial Carcinoma



<sup>a</sup>See (UN-1) for clarification of uterine neoplasms.

<sup>b</sup>See [Hysterectomy and Pathologic Evaluation \(ENDO-B\)](#).

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

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

<sup>e</sup>See [Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\)](#).

<sup>g</sup>See [Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease \(ENDO-D\)](#).

<sup>h</sup>See [Principles of Imaging for Endometrial Carcinoma \(ENDO-A\)](#).

<sup>i</sup>Clear demonstration of cervical stromal involvement.

<sup>j</sup>Based on summation of conventional external-beam fractionation and low-dose-rate brachytherapy equivalent.

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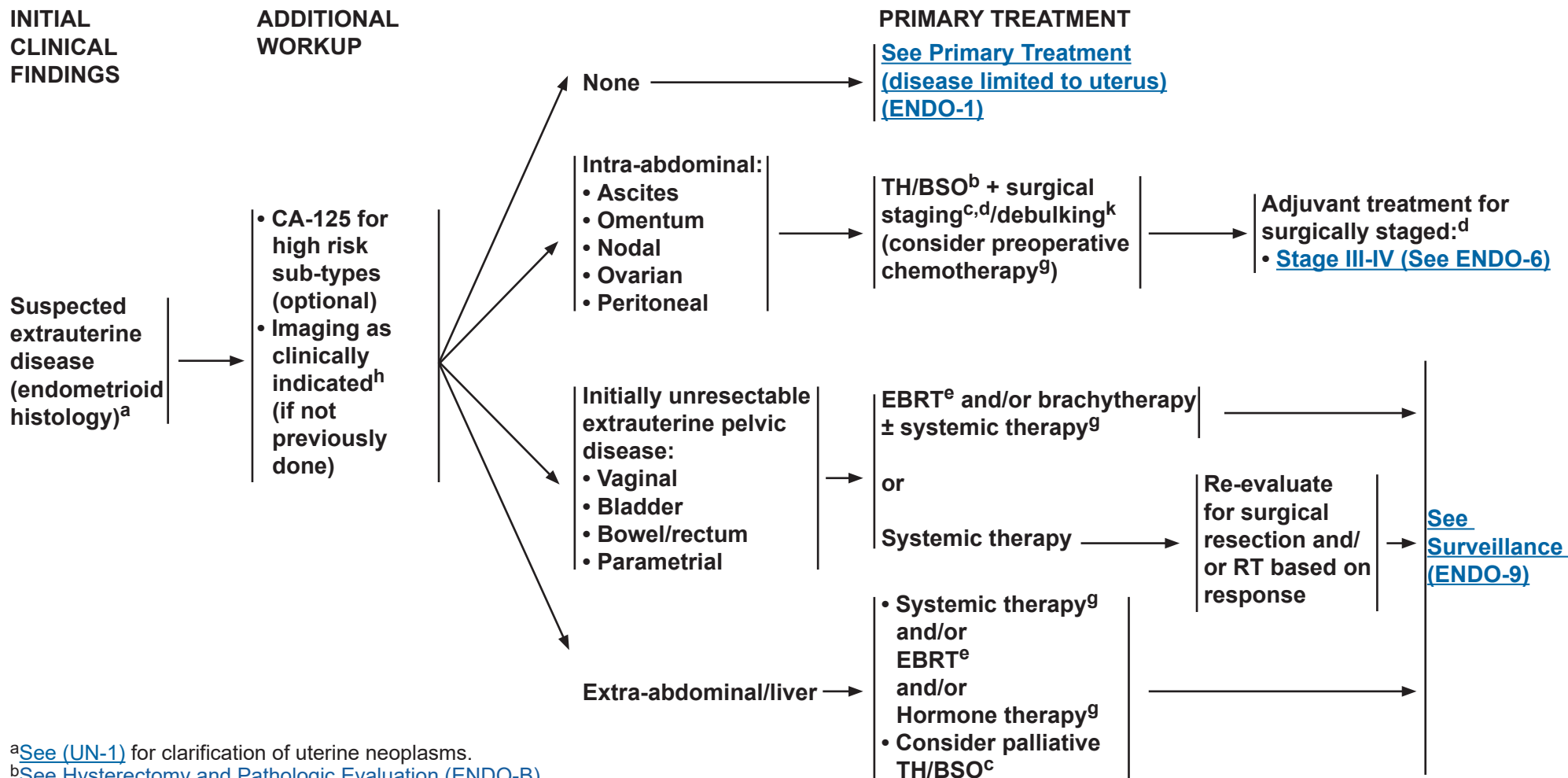


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## Endometrial Carcinoma

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<sup>a</sup>[See \(UN-1\)](#) for clarification of uterine neoplasms.

<sup>b</sup>[See Hysterectomy and Pathologic Evaluation \(ENDO-B\)](#).

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

<sup>d</sup>The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended.

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

<sup>e</sup>[See Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\)](#).

<sup>g</sup>[See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease \(ENDO-D\)](#).

<sup>h</sup>[See Principles of Imaging for Endometrial Carcinoma \(ENDO-A\)](#)

<sup>k</sup>The surgical goal is to have no measurable residual disease.

**Note:** All recommendations are category 2A unless otherwise indicated.

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



# NCCN Guidelines Version 3.2017

## Endometrial Carcinoma

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

### CLINICAL FINDINGS

### ADVERSE RISK FACTORS<sup>l</sup>

### HISTOLOGIC GRADE/ADJUVANT TREATMENT<sup>e,n,o</sup>

G1

G2

G3

Surgically staged: Stage I <sup>d</sup>	Stage IA (<50% myometrial invasion)	Adverse risk factors not present	Observe	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy
		Adverse risk factors present	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or EBRT (category 2B for EBRT)	Observe or Vaginal brachytherapy and/or EBRT
	Stage IB (≥50% myometrial invasion)	Adverse risk factors not present	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy	Vaginal brachytherapy and/or EBRT or Observe (category 2B for observation)
		Adverse risk factors present <sup>m</sup>	Observe or Vaginal brachytherapy and/or EBRT	Observe or Vaginal brachytherapy and/or EBRT	EBRT and/or vaginal brachytherapy ± systemic therapy <sup>g,p</sup> (category 2B for systemic therapy)

<sup>d</sup>The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended.

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

<sup>e</sup>[See Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\).](#)

<sup>g</sup>[See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease \(ENDO-D\).](#)

<sup>l</sup>See [Discussion](#) for information on adverse risk factors.

<sup>m</sup>Consider additional imaging if not previously done. [See Principles of Imaging for Endometrial Carcinoma \(ENDO-A\)](#)

<sup>n</sup>Adjuvant therapy determinations are made on the basis of pathologic findings.

<sup>o</sup>Initiate EBRT as soon as the vaginal cuff is healed, preferably no later than 12 weeks after surgery.

<sup>p</sup>The role of adjuvant chemotherapy in invasive, high-grade, uterine-confined disease is the subject of current studies. (Hogberg T, Signorelli M, de Oliveira CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur J Cancer 2010;46:2422-2431.) Hormonal therapy is not used for high-grade disease.

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[See Surveillance \(ENDO-9\)](#)





# NCCN Guidelines Version 3.2017

## Endometrial Carcinoma

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

### CLINICAL FINDINGS

### HISTOLOGIC GRADE/ADJUVANT TREATMENT<sup>e,g,n,o</sup>

Surgically staged:<sup>d</sup>  
Stage II<sup>m,q,r</sup>



G1	G2	G3
Vaginal brachytherapy and/or EBRT	Vaginal brachytherapy and/or EBRT	EBRT ± vaginal brachytherapy ± systemic therapy <sup>p</sup> (category 2B for systemic therapy)

<sup>d</sup>The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended.

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

<sup>e</sup>[See Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\).](#)

<sup>g</sup>[See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease \(ENDO-D\).](#)

<sup>m</sup>Consider additional imaging if not previously done. [See Principles of Imaging for Endometrial Carcinoma \(ENDO-A\)](#)

<sup>n</sup>Adjuvant therapy determinations are made on the basis of pathologic findings.

<sup>o</sup>Initiate EBRT as soon as the vaginal cuff is healed, no later than 12 weeks after surgery.

<sup>p</sup>The role of adjuvant chemotherapy in invasive high-grade uterine confined disease is the subject of current studies. (Hogberg T, Signorelli M, de Oliveira CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur J Cancer 2010;46:2422-2431.) Hormonal therapy is not used for high-grade disease.

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

<sup>r</sup>The adverse fundal risk factors influencing therapy decisions for stage I disease ([see ENDO-4](#)) may also impact the choice of adjuvant therapy for stage II disease.

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[See  
Surveillance  
\(ENDO-9\)](#)

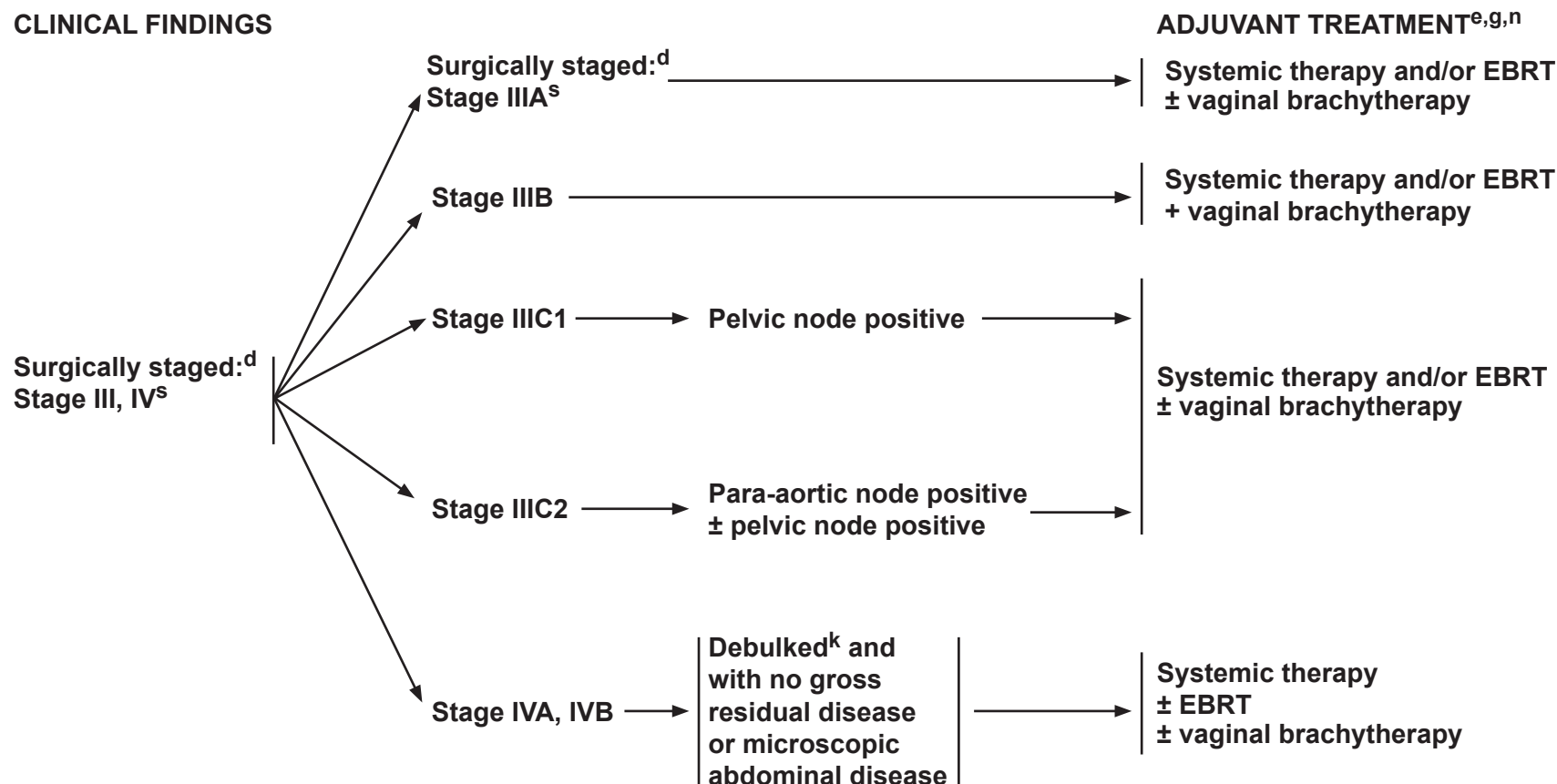


# NCCN Guidelines Version 3.2017

## Endometrial Carcinoma

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

### CLINICAL FINDINGS



<sup>d</sup>The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended.

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

<sup>e</sup>[See Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\).](#)

<sup>g</sup>[See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease \(ENDO-D\).](#)

<sup>k</sup>The surgical goal is to have no measurable residual disease.

<sup>n</sup>Adjuvant therapy determinations are made on the basis of pathologic findings.

<sup>s</sup>Additional imaging if not previously done. ([See Principles of Imaging ENDO-A](#))

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[See  
Surveillance  
\(ENDO-9\)](#)



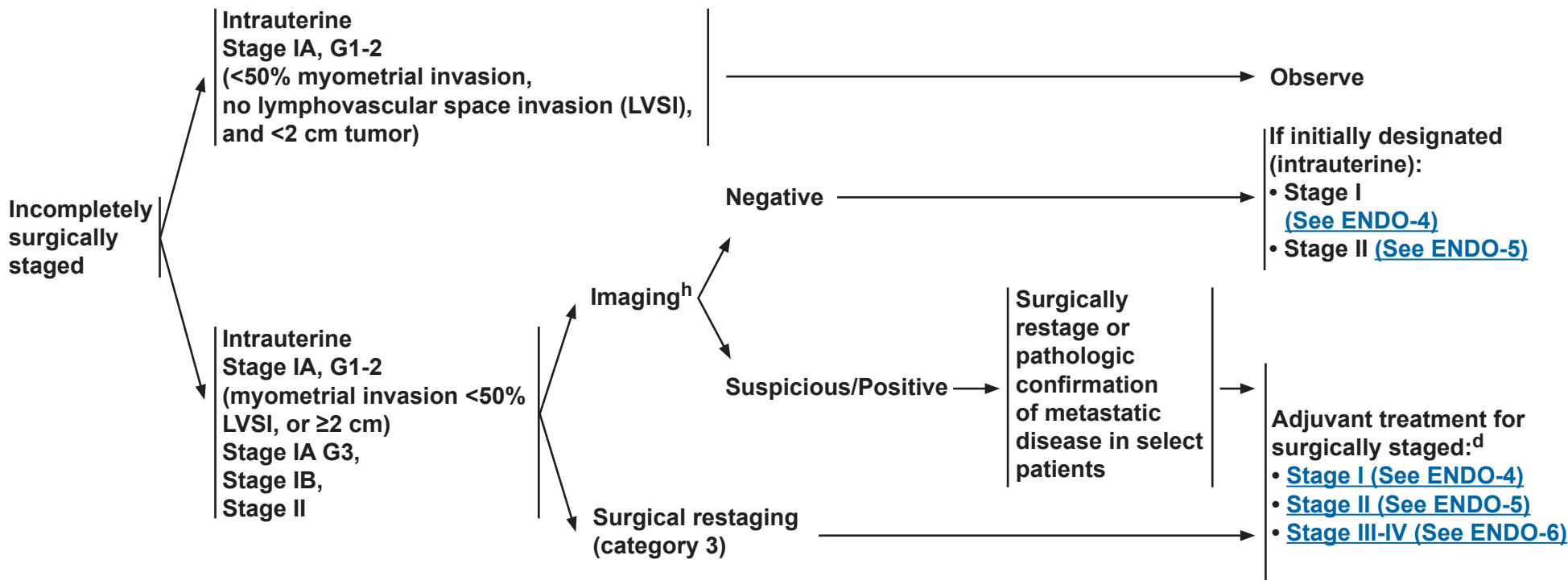
# NCCN Guidelines Version 3.2017

## Endometrial Carcinoma

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

### CLINICAL INTRAUTERINE FINDINGS

### ADJUVANT TREATMENT<sup>e,n</sup>



<sup>d</sup>The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended.

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

<sup>e</sup>[See Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\).](#)

<sup>h</sup>[See Principles of Imaging for Endometrial Carcinoma \(ENDO-A\)](#)

<sup>n</sup>Adjuvant therapy determinations are made on the basis of pathologic findings.

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[See Surveillance  
\(ENDO-9\)](#)

ENDO-7



# NCCN Guidelines Version 3.2017

## Endometrial Carcinoma

### CRITERIA FOR CONSIDERING FERTILITY-SPARING OPTIONS FOR MANAGEMENT OF ENDOMETRIAL CARCINOMA (All criteria must be met)

- Well-differentiated (grade 1) endometrioid adenocarcinoma on dilation and curettage (D&C) confirmed by expert pathology review
- Disease limited to the endometrium on MRI (preferred) or transvaginal ultrasound<sup>h</sup>
- Absence of suspicious or metastatic disease on imaging
- No contraindications to medical therapy or pregnancy
- Patients should undergo counseling that fertility-sparing option is NOT standard of care for the treatment of endometrial carcinoma

- Consultation with a fertility expert prior to therapy
- Genetic counseling/testing in selected patients (See UN-1)

Continuous progestin-based therapy:

- Megestrol
- Medroxyprogesterone
- Levonorgestrel IUD

Endometrial sampling every 3–6 mo (either D&C or endometrial biopsy)

Complete response by 6 mo

Encourage conception<sup>u</sup> (with continued surveillance every 3–6 mo)

TH/BSO with staging<sup>c,d</sup> after childbearing complete or progression of disease on endometrial sampling (see ENDO-1)

Endometrial cancer present at 6–12 months<sup>h,t</sup>

Consider MRI

TH/BSO with staging<sup>c,d</sup> (see ENDO-1)

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

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

<sup>h</sup>See Principles of Imaging for Endometrial Carcinoma (ENDO-A).

<sup>t</sup>Gunderson CC, Fader AN, Carson KA, Bristow RE. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. 2012 Gynecologic Oncology;125:477-482 and Hubbs JL, Saig RM, Abaid LN, et al. Systemic and local hormone therapy for endometrial hyperplasia and early adenocarcinoma. Obstet Gynecol 2013;121:1172-1180.

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

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# NCCN Guidelines Version 3.2017

## Endometrial Carcinoma

### SURVEILLANCE

- Physical exam every 3–6 mo for 2–3 y, then 6 mo or annually
- CA-125 if initially elevated
- Imaging as clinically indicated<sup>h</sup>
- Patient education regarding symptoms of potential recurrence, lifestyle, obesity, exercise, smoking cessation, sexual health (including vaginal dilator use and lubricants/moisturizers), nutrition counseling, potential long-term and late effects of treatment  
([See NCCN Guidelines for Survivorship](#) and [NCCN Guidelines for Smoking Cessation](#))

### CLINICAL PRESENTATION

Local/regional recurrence  
• Negative distant metastases on radiologic imaging<sup>h</sup>

Isolated metastases

Disseminated metastases

- Consider resection and/or EBRT<sup>e</sup> or Ablative therapy
- Consider hormone therapy<sup>g</sup> (category 2B)
- Consider chemotherapy<sup>g</sup> (category 3)

Low grade or Asymptomatic or ER/PR positive

Symptomatic or Grade 2, 3 or Large volume

### THERAPY FOR RELAPSE

[See Therapy For Relapse \(ENDO-10\)](#)

Not amenable to local treatment or Further recurrence

Treat as disseminated metastases (See below)

Hormone therapy<sup>g</sup>

If progression, systemic therapy<sup>g</sup>

If progression, Best supportive care ([See NCCN Guidelines for Palliative Care](#)) or Clinical trial

Systemic therapy<sup>g</sup> ± palliative EBRT<sup>e</sup>

<sup>h</sup>See [Principles of Imaging for Endometrial Carcinoma \(ENDO-A\)](#)

<sup>e</sup>See [Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\)](#).

<sup>g</sup>See [Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease \(ENDO-D\)](#).

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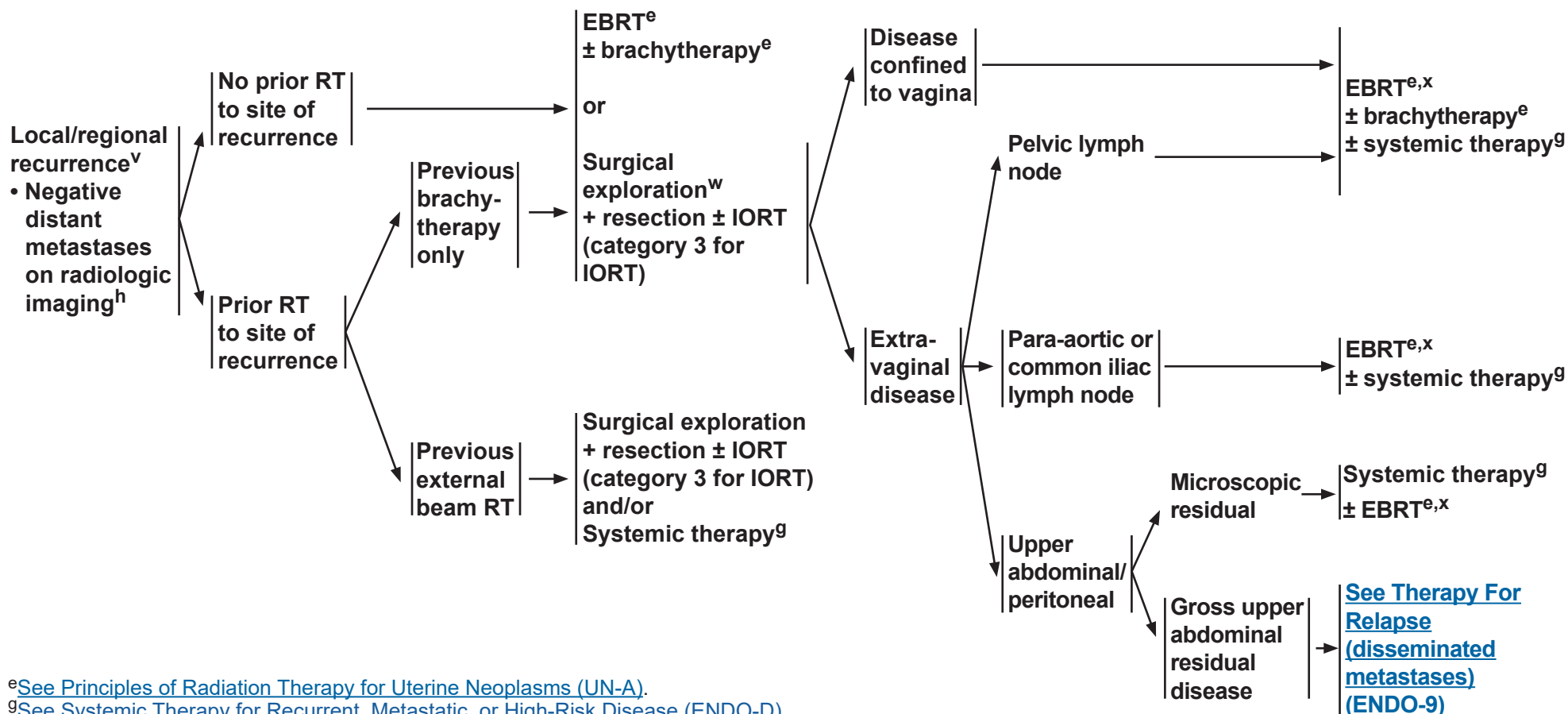
## Endometrial Carcinoma

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

### CLINICAL PRESENTATION

### THERAPY FOR RELAPSE

### ADDITIONAL THERAPY



<sup>e</sup>See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).

<sup>g</sup>See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-D).

<sup>h</sup>See Principles of Imaging for Endometrial Carcinoma (ENDO-A).

<sup>v</sup>May include patients with isolated common iliac or para-aortic lymph node recurrence.

<sup>w</sup>Consider preoperative EBRT in select patients.

<sup>x</sup>Post-resection consolidation EBRT can be considered in patients who were not previously radiated or who are deemed to have additional tolerance for radiation.

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# NCCN Guidelines Version 3.2017

## Endometrial Carcinoma

### SEROUS OR CLEAR CELL CARCINOMA OR CARCINOSARCOMA OF THE ENDOMETRIUM<sup>y</sup>

#### ADDITIONAL WORKUP

#### PRIMARY TREATMENT

#### ADJUVANT TREATMENT

Biopsy:  
Serous carcinoma  
or  
Clear cell carcinoma  
or  
Carcinosarcoma<sup>y</sup>

• CA-125  
(optional)  
• Imaging as  
clinically  
indicated<sup>h</sup>

• TH/BSO and surgical  
staging<sup>d</sup>  
• Consider maximal tumor  
debulking for gross  
disease

Stage IA

Observe<sup>z</sup>  
or  
Chemotherapy<sup>g</sup>  
± vaginal brachytherapy<sup>e</sup>  
or  
EBRT<sup>e</sup>  
± vaginal brachytherapy<sup>e</sup>

Stage IB, II, III, IV

Chemotherapy<sup>g</sup>  
± EBRT<sup>e</sup>  
± vaginal brachytherapy<sup>e</sup>

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

<sup>d</sup>The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended.

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

<sup>e</sup>[See Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\).](#)

<sup>g</sup>[See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease \(ENDO-D\).](#)

<sup>h</sup>[See Principles of Imaging for Endometrial Carcinoma \(ENDO-A\).](#)

<sup>y</sup>Also known as malignant mixed mesodermal tumor or malignant mixed Müllerian tumor. Carcinosarcomas are treated the same as poorly differentiated adenocarcinomas.

<sup>z</sup>Observation only for select patients with no residual disease in the hysterectomy specimen.

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[See Surveillance  
\(ENDO-9\)](#)



# NCCN Guidelines Version 3.2017

## Endometrial Carcinoma

### PRINCIPLES OF IMAGING<sup>a,1-9</sup>

#### Initial Workup

##### • Non-Fertility Sparing Treatment

- Chest imaging with plain radiography (chest x-ray). If an abnormality is seen then chest CT without contrast may be performed.
- Consider pelvic MRI to establish the origin of the tumor (endocervical vs. endometrial) and assess local disease extent.
- For high-grade carcinoma,<sup>b</sup> consider chest/abdominal/pelvic CT to evaluate for metastatic disease.
- For patients who underwent TH with incidental finding of endometrial cancer or incompletely staged with uterine risk factors,<sup>c</sup> consider chest/abdominal/pelvic CT to evaluate for metastatic disease.
- Consider whole body PET/CT if metastasis is suspected in select patients.
- Other initial imaging should be based on symptomatology and clinical concern for metastatic disease.<sup>d</sup>

##### • Fertility-Sparing Treatment

- Chest imaging with plain radiography (chest x-ray). If an abnormality is seen then chest CT without contrast may be performed.
- Pelvic MRI (preferred) to exclude myoinvasion and assess local disease extent; pelvic transvaginal ultrasound if MRI contraindicated.
- Consider whole body PET/CT if metastasis is suspected in select patients.
- Other imaging should be based on symptomatology and clinical concern for metastatic disease.<sup>e</sup>

#### Follow-up/Surveillance

##### • Non-Fertility Sparing Treatment

- Imaging should be based on symptomatology and clinical concern for metastatic disease.<sup>f</sup>
- For patients with treated FIGO stage III-IV disease optional chest/abdominal/pelvic CT every 6 months for the first 3 years and then every 6–12 months for the next 2 years.
- Consider whole body PET/CT if metastasis is suspected in select patients.

##### • Fertility-Sparing Treatment

- Consider repeating pelvic MRI for patients with persistent endometrial carcinoma after 6 months of failed medical therapy.
- Other imaging should be based on symptomatology and clinical concern for metastatic disease.<sup>g</sup>

<sup>a</sup>MRI and CT are performed with contrast throughout the guidelines unless contraindicated. Contrast is not required for screening chest CT.

<sup>b</sup>High-grade endometrial carcinoma includes: poorly differentiated endometrioid, serous, clear cell, undifferentiated carcinoma, and carcinosarcoma.

<sup>c</sup>Uterine risk factors identified post TH include: high-grade carcinomas (above criteria), myoinvasion >50%, cervical stromal involvement, LVI, tumor >2 cm.

<sup>d</sup>Indications may include abnormal physical exam findings; bulky uterine tumor; vaginal or extrauterine involvement; delay in presentation or treatment; and abdominal or pulmonary symptoms.

<sup>e</sup>These factors may include abnormal physical exam findings; bulky uterine tumor; vaginal or extrauterine involvement; delay in presentation or treatment; and abdominal or pulmonary symptoms.

<sup>f</sup>Indications may include abnormal physical exam findings such as vaginal involvement; palpable mass or adenopathy; and new pelvic, abdominal, or pulmonary symptoms.

<sup>g</sup>These factors may include abnormal physical exam findings such as bulky uterus, vaginal involvement, palpable mass or adenopathy, or new pelvic, abdominal, or pulmonary symptoms.

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# NCCN Guidelines Version 3.2017

## Endometrial Carcinoma

### PRINCIPLES OF IMAGING (References)

- <sup>1</sup>Salani R, Backes FJ, Fung MF, Holschneider CH, Parker LP, Bristow RE, Goff BA. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. *Am J Obstet Gynecol* 2011;204:466-478.
- <sup>2</sup>Haldorsen IS, Salvesen HB. What Is the Best Preoperative Imaging for Endometrial Cancer? *Curr Oncol Rep*. 2016 Apr;18(4):25.
- <sup>3</sup>Elit L, Reade CJ. Recommendations for Follow-up Care for Gynecologic Cancer Survivors. *Obstet Gynecol*. 2015 Dec;126 (6):1207-14.
- <sup>4</sup>Vargas HA, Akin O, Zheng J, Moskowitz C, Soslow R, Abu-Rustum N, Barakat RR, Hricak H. The value of MR imaging when the site of uterine cancer origin is uncertain. *Radiology*. 2011 Mar;258(3):785-92.
- <sup>5</sup>Sohaib SA, Houghton SL, Meroni R, Rockall AG, Blake P, Reznick RH. Recurrent endometrial cancer: patterns of recurrent disease and assessment of prognosis. *Clin Radiol*. 2007 Jan;62(1):28-34; discussion 35-6.
- <sup>6</sup>Hensley ML, Barrette BA, Baumann K, Gaffney D, Hamilton AL, Kim JW, Maenpaa JU, Pautier P, Siddiqui NA, Westermann AM, Ray-Coquard I. Gynecologic Cancer InterGroup (GCIG) consensus review: uterine and ovarian leiomyosarcomas. *Int J Gynecol Cancer*. 2014 Nov;24(9 Suppl 3):S61-6.
- <sup>7</sup>Lakhman Y, Katz SS, Goldman DA, Yakar D, Vargas HA, Sosa RE, Miccò M, Soslow RA, Hricak H, Abu-Rustum NR, Sala E. Diagnostic Performance of Computed Tomography for Preoperative Staging of Patients with Non-endometrioid Carcinomas of the Uterine Corpus. *Ann Surg Oncol*. 2016 Apr;23(4):1271-8.
- <sup>8</sup>Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, Marth C, Nout R, Querleu D, Mirza MR, Sessa C; ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer: diagnosis, treatment and follow-up. *Ann Oncol*. 2016 Jan;27(1):16-41.
- <sup>9</sup>Sala E, Rockall AG, Freeman SJ, Mitchell DG, Reinhold C. The added role of MR imaging in treatment stratification of patients with gynecologic malignancies: what the radiologist needs to know. *Radiology*. 2013 Mar;266(3):717-40.

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# NCCN Guidelines Version 3.2017

## Endometrial Carcinoma

### HYSTERECTOMY AND PATHOLOGIC EVALUATION<sup>1,2</sup>

**TH/BSO: Total hysterectomy + bilateral salpingo-oophorectomy**

**RH: Radical hysterectomy**

**Pathologic assessment to include:**

- Uterus
  - Ratio of depth of myometrial/stromal invasion to myometrial thickness
  - Cervical stromal or glandular involvement
  - Tumor size
  - Tumor location (fundus vs. lower uterine segment/cervix)
  - Histologic subtype with grade
  - Lymphovascular space invasion
  - Universal testing of endometrial tumors for mismatch repair (MMR) gene
- Fallopian tubes/ovaries
- Peritoneal cytology<sup>3</sup>
- Nodes (when resected)
  - Level of nodal involvement (ie, pelvic, common iliac, para-aortic)
- Universal testing of endometrial carcinomas for mismatch repair (MMR) gene
  - Testing should be done on the final hysterectomy specimen (can be done on presurgical biopsy if hysterectomy not performed)
  - MLH1 loss should be further evaluated for promoter methylation to assess epigenetic process.
  - Genetic counseling and testing for all other MMR abnormalities
  - Genetic counseling and testing for patients without MMR abnormalities, but who have a significant family history of endometrial and/or colorectal cancer ([See Lynch syndrome/HNPCC in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#))

<sup>1</sup>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.

<sup>2</sup>[See Principles of Evaluation and Surgical Staging \(ENDO-C\).](#)

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

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# NCCN Guidelines Version 3.2017

## Endometrial Carcinoma

### PRINCIPLES OF EVALUATION AND SURGICAL STAGING

#### Principles of Surgical Staging for Endometrial Cancer<sup>1-14</sup>

- Total hysterectomy, bilateral salpingo-oophorectomy (TH/BSO), and lymph node assessment is the primary treatment of apparent uterine-confined endometrial carcinoma, unless patients desire (and are candidates for) fertility-sparing options ([See ENDO-8](#)).<sup>1-3</sup> Select patients with metastatic endometrial carcinoma are also candidates for hysterectomy. ([See Hysterectomy and Pathologic Evaluation \[ENDO-B\]](#))
- Endometrial carcinoma should be removed en bloc to optimize outcomes; intraperitoneal morcellation or tumor fragmentation should be avoided.
- TH/BSO and lymph node assessment may be performed by any surgical route (eg, laparoscopic, robotic, vaginal, abdominal), although the standard in those with apparent uterine-confined disease is to perform the procedure via a minimally invasive approach. Randomized trials, a Cochrane Database Systematic Review, and population-based surgical studies support that minimally invasive techniques are preferred in this setting due to a lower rate of surgical site infection, transfusion, venous thromboembolism, decreased hospital stay and lower cost of care, without compromise in oncologic outcome.<sup>4-9</sup>
- The lymph node assessment includes evaluation of the nodal basins that drain the uterus, and often comprises a pelvic nodal dissection with or without aortic nodal dissection. This continues to be an important aspect of surgical staging in women with uterine-confined endometrial carcinoma, as the procedure provides important prognostic information that may alter treatment decisions.
- Pelvic lymph nodes from the external iliac, internal iliac, obturator, and common iliac nodes are frequently removed for staging purposes.
- Para-aortic nodal evaluation from the inframesenteric and infrarenal regions may also be utilized for staging in women with high-risk tumors such as deeply invasive lesions, high-grade histology, and tumors of serous carcinoma, clear cell carcinoma, or carcinosarcoma.
- Sentinel lymph node (SLN) mapping may be considered in select patients. ([See pages 2-4 of ENDO-C](#))
- Excision of suspicious or enlarged lymph nodes in the pelvic or aortic regions is important to exclude nodal metastasis.
- Some patients may not be candidates for lymph node dissection.
- Visual evaluation of the peritoneal, diaphragmatic, and serosal surfaces with biopsy of any suspicious lesions is important to exclude extrauterine disease.
- While peritoneal cytology does not impact staging, FIGO and AJCC nonetheless recommend that surgeons continue to obtain this during the TH/BSO.
- Omental biopsy is commonly performed in those with serous carcinoma, clear cell carcinoma, or carcinosarcoma histologies.

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[Continued](#)



# NCCN Guidelines Version 3.2017

## Endometrial Carcinoma

### PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

#### Principles of Sentinel Lymph Node (SLN) Mapping for Endometrial Cancer Staging<sup>10-22</sup>

- The role of SLN mapping in endometrial carcinoma is under evaluation. Prospective and retrospective studies demonstrate that compared to systemic lymphadenectomy, SLN mapping with ultrastaging may increase the detection of lymph node metastasis with low false-negative rates in women with apparent uterine-confined disease.<sup>10-22</sup> To date, no randomized trials evaluating this technique in endometrial carcinoma have been conducted. If SLN mapping is considered, the expertise of the surgeon and attention to technical detail is critical. The use of SLN mapping in high-risk histologies (serous carcinoma, clear cell carcinoma, or carcinosarcoma) should be undertaken with particular caution.
- SLN mapping can be considered for the surgical staging of apparent uterine-confined malignancy when there is no metastasis demonstrated by imaging studies or no obvious extrauterine disease at exploration.
- A cervical injection with dye has emerged as a useful and validated technique for identification of lymph nodes that are at high risk for metastases (ie, SLN in patients with early-stage endometrial cancer<sup>10-12</sup>).
- The combination of a superficial (1–3 mm) and deep (1–2 cm) cervical injection leads to dye delivery to the main layers of lymphatic channel origins in the cervix and corpus, namely the superficial subserosal, intermediate stromal, and deep submucosal lymphatic sites of origin (Figure 1 on [ENDO-C 3 of 5](#)).
- Injection into the uterine cervix provides excellent dye penetration to the region of the uterine vessels and main uterine lymphatic trunks that condense in the parametria and appear in the broad ligament leading to pelvic and occasionally paraaortic sentinel nodes.
- The uterine body lymphatic trunks commonly cross over the obliterated umbilical artery with the most common location of pelvic SLN being medial to the external iliac, ventral to the hypogastric, or in the superior part of the obturator region (Figure 2 on [ENDO-C 3 of 5](#)).
- A less common location is usually seen when the lymphatic trunks do not cross over the obliterated umbilical and move cephalad following the mesoureter; in these cases, the SLN is usually seen in the common iliac presacral region (Figure 3 on [ENDO-C 3 of 5](#)).
- The radiolabeled colloid most commonly injected into the cervix is technetium-99m (99mTc); colored dyes are available in a variety of forms (Isosulfan Blue 1% and Methylene Blue 1%, Patent Blue 2.5% sodium).
- Indocyanine green (ICG) recently emerged as a useful imaging dye that requires near-infrared camera for localization, provides a very high SLN detection rate, and is commonly used in many practices at the present time.<sup>19</sup>
- Low-volume nodal metastasis to SLN detected only by enhanced pathologic ultrastaging is another potential value to staging with SLN.<sup>10,20-22</sup>
- Key points to a successful SLN mapping is the adherence to the SLN algorithm, which requires the performance of a side-specific nodal dissection in cases of failed mapping and removal of any suspicious or grossly enlarged nodes regardless of mapping (Figure 4 on [ENDO-C 4 of 5](#)).<sup>10-12,22</sup>

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[Continued](#)



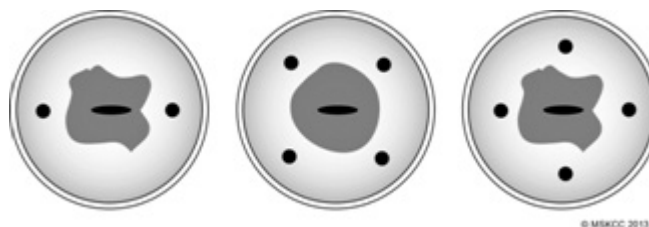


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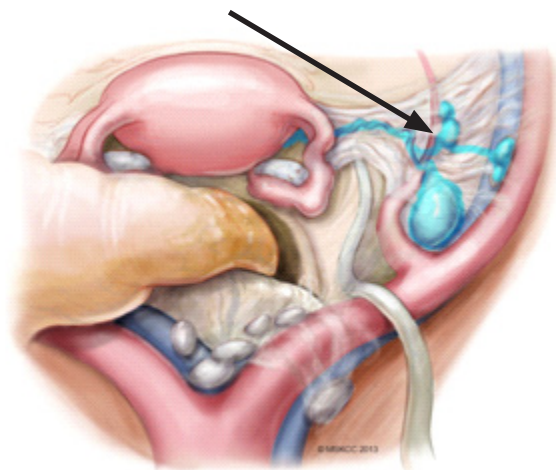
## Endometrial Carcinoma

### PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

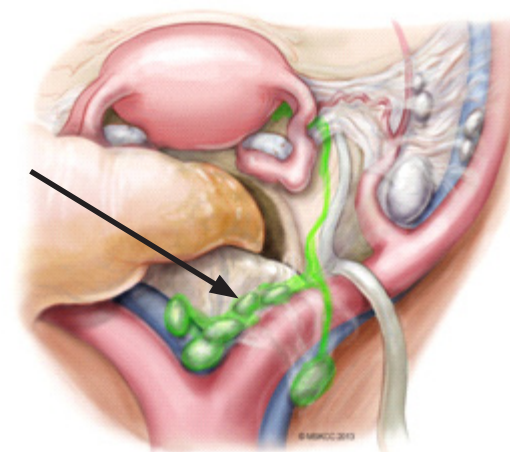
**Figure 1: Common cervical injection sites for mapping uterine cancer<sup>†</sup>**



**Figure 2: Most common location of SLNs (blue, arrow) following a cervical injection<sup>†</sup>**



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



<sup>†</sup>Figures 1, 2, and 3 are reproduced with permission from Memorial Sloan Kettering Cancer Center. © 2013, Memorial Sloan Kettering Cancer Center.

**Note:** All recommendations are category 2A unless otherwise indicated.

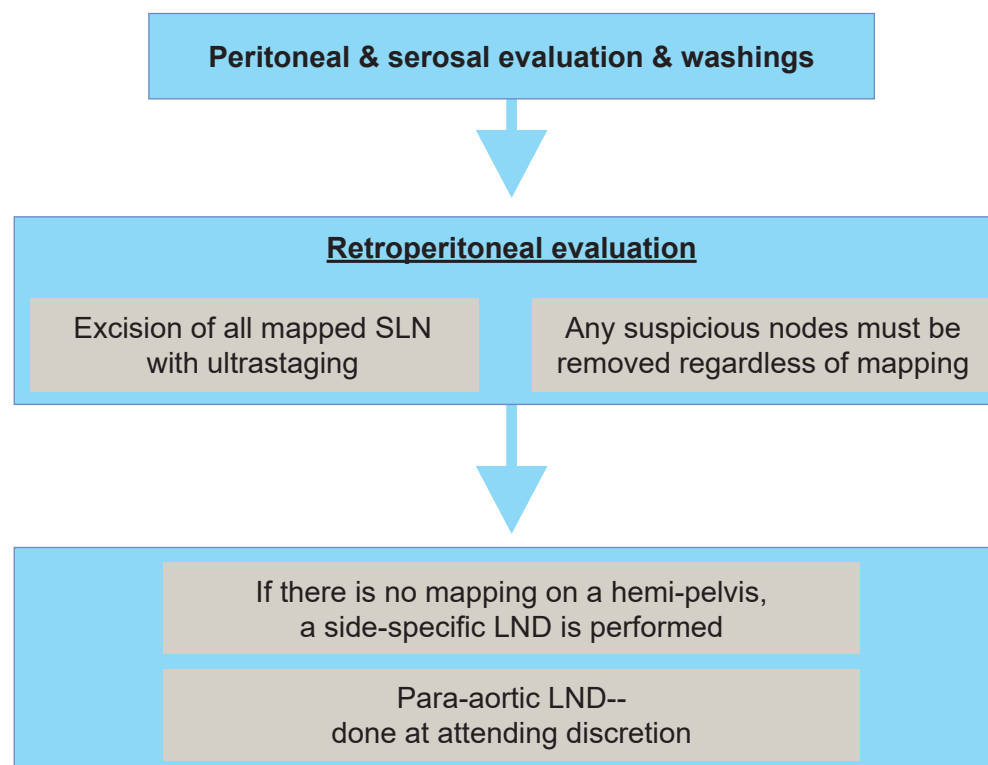
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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### PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

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



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

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# NCCN Guidelines Version 3.2017

## Endometrial Carcinoma

### PRINCIPLES OF EVALUATION AND SURGICAL STAGING

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# NCCN Guidelines Version 3.2017

## Endometrial Carcinoma

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

#### **CHEMOTHERAPY REGIMENS<sup>2,3</sup>**

- **Multi-agent chemotherapy regimens preferred, if tolerated**
  - ▶ Carboplatin/paclitaxel<sup>4</sup>
  - ▶ Cisplatin/doxorubicin<sup>5</sup>
  - ▶ Cisplatin/doxorubicin/paclitaxel<sup>5,6</sup>
  - ▶ Carboplatin/docetaxel<sup>7</sup>
  - ▶ Ifosfamide/paclitaxel (category 1 for carcinosarcoma)<sup>8</sup>
  - ▶ Cisplatin/ifosfamide (for carcinosarcoma)
- **Single agents**
  - ▶ Cisplatin
  - ▶ Carboplatin
  - ▶ Doxorubicin
  - ▶ Liposomal doxorubicin
  - ▶ Paclitaxel
  - ▶ Topotecan
  - ▶ Bevacizumab<sup>9</sup>
  - ▶ Temsirolimus<sup>10</sup>
  - ▶ Docetaxel<sup>7</sup> (category 2B)
  - ▶ Ifosfamide (for carcinosarcoma)

#### **HORMONE THERAPY<sup>1</sup>**

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

<sup>1</sup>Hormonal therapy may be used for lower grade endometrioid histologies only (ie, not for G3 endometrioid, serous carcinoma, clear cell carcinoma, or carcinosarcoma) preferably in patients with small tumor volume or an indolent growth pace.

<sup>2</sup>Cisplatin, carboplatin, liposomal doxorubicin, paclitaxel, and docetaxel may cause drug reactions.

(See [NCCN Guidelines for Ovarian Cancer--Management of Drug Reactions \[OV-C\]](#))

<sup>3</sup>Chemotherapy regimens can be used for all carcinoma histologies. Carcinosarcomas are now considered and treated as high-grade carcinomas. However, ifosfamide-based regimens were previously used for carcinosarcomas.

<sup>4</sup>Miller D, Filiaci V, Fleming G, et al. Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: a Gynecologic Oncology Group study [abstract]. Gynecol Oncol 2012;125:771.

<sup>5</sup>Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A Gynecologic Oncology Group study. Gynecol Oncol 2009;112:543-552.

<sup>6</sup>The cisplatin/doxorubicin/paclitaxel regimen is not widely used because of concerns about toxicity.

<sup>7</sup>Docetaxel may be considered for patients in whom paclitaxel is contraindicated.

<sup>8</sup>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.

<sup>9</sup>Bevacizumab may be considered for use in patients who have progressed on prior cytotoxic chemotherapy. (Aghajanian C, Sill MW, Darcy KM, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. J Clin Oncol 2011;29:2259-2265.)

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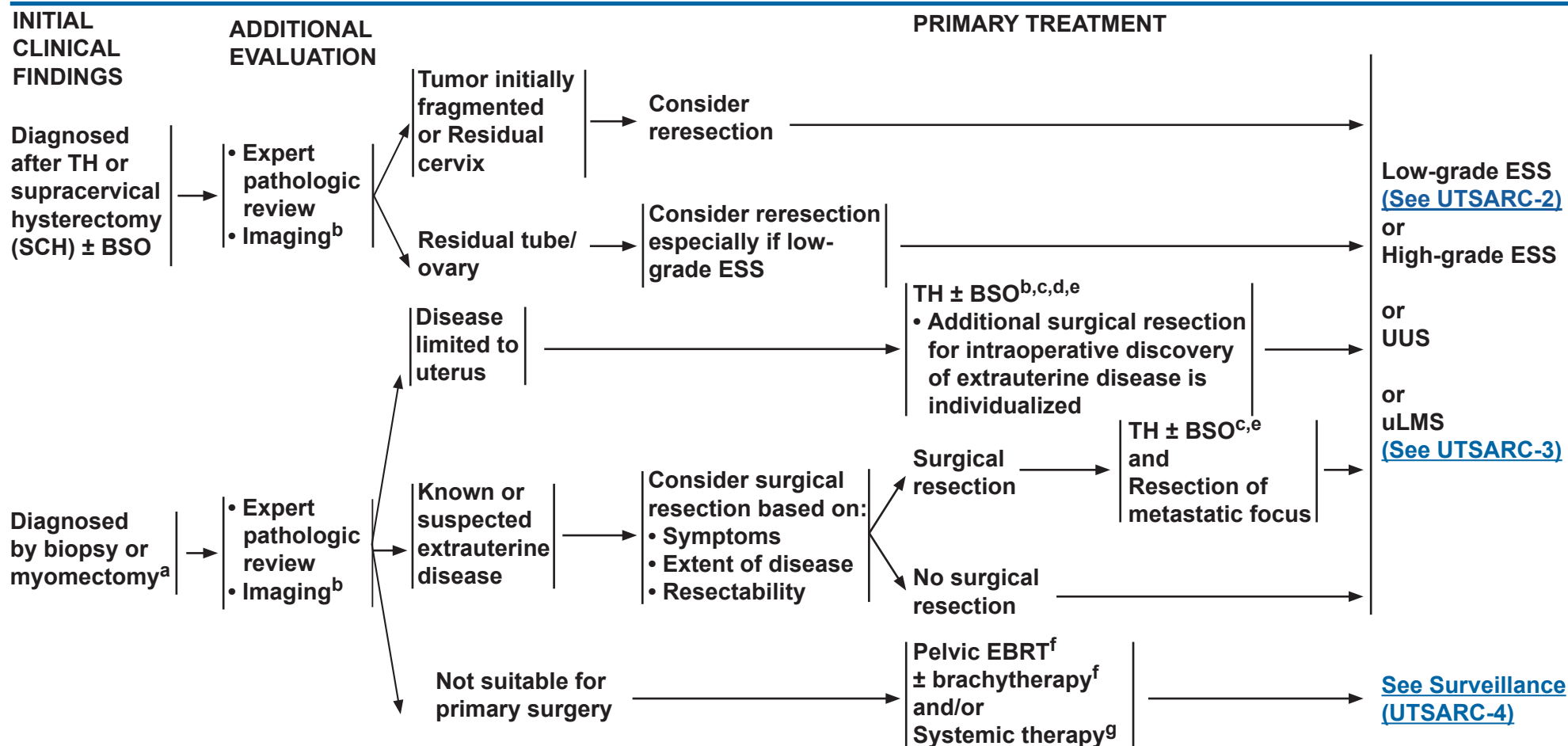


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## Uterine Sarcoma

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<sup>a</sup>Preoperative imaging and biopsy may help to identify uterine sarcomas, although biopsy sensitivity is less than for endometrial cancer. If there is suspicion of malignant mesenchymal sarcoma, fragmentation/morcellation should be avoided.

<sup>b</sup>See [Principles of Imaging for Uterine Sarcoma \(UTSARC-A\)](#).

<sup>c</sup>Oophorectomy individualized for reproductive-age patients.

<sup>d</sup>For incidental finding of uterine sarcoma after TH/BSO or fragmented specimen: Recommend imaging and consider additional surgical resection on an individual basis.

<sup>e</sup>Uterine sarcoma should be removed *en bloc* to optimize outcomes; morcellation should be avoided.

<sup>f</sup>See [Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\)](#).

<sup>g</sup>See [Systemic Therapy for Uterine Sarcoma \(UTSARC-B\)](#).

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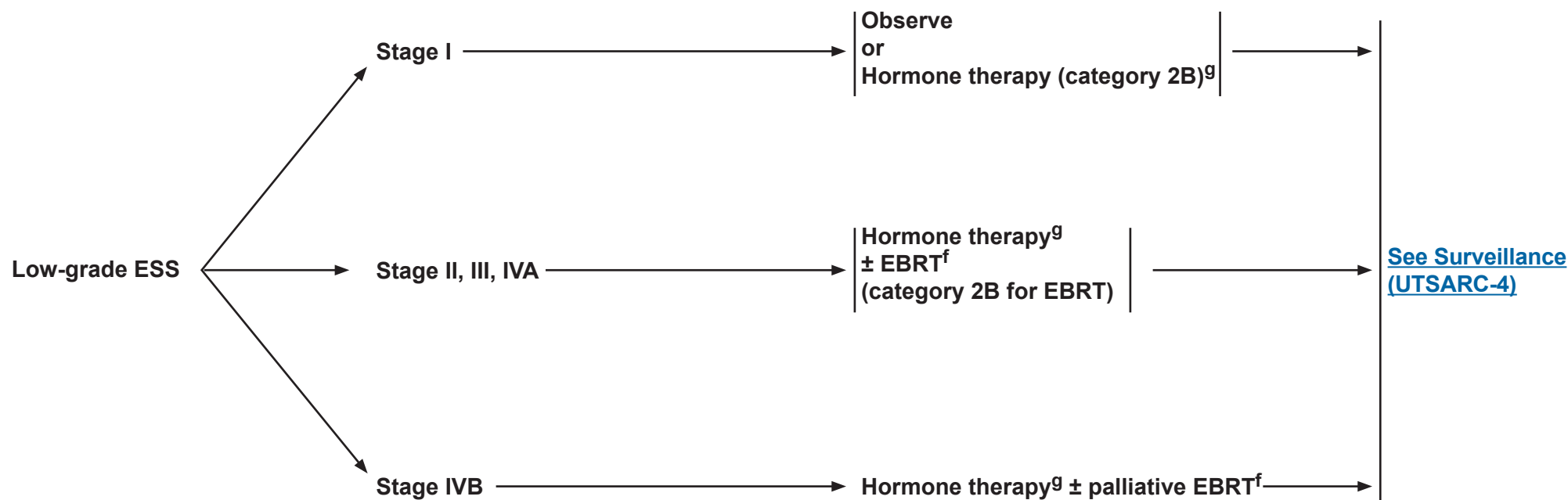
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## Uterine Sarcoma

### **PATHOLOGIC FINDINGS/ HISTOLOGIC GRADE<sup>h</sup>**

### **ADDITIONAL THERAPY**

(Consider observation for patients if no evidence of disease after primary surgery)



<sup>f</sup>[See Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\).](#)

<sup>g</sup>[See Systemic Therapy for Uterine Sarcoma \(UTSARC-B\).](#)

<sup>h</sup>[See Uterine Sarcoma Classification \(UTSARC-C\).](#)

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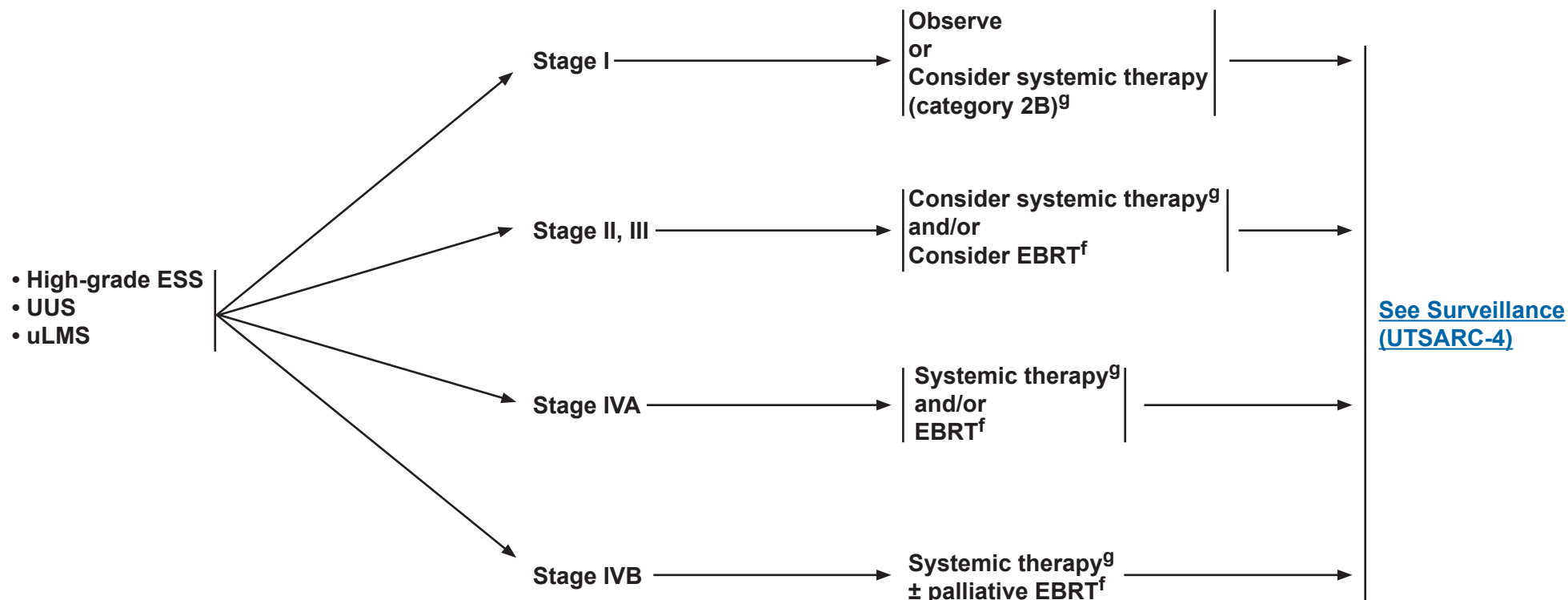


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## Uterine Sarcoma

### **PATHOLOGIC FINDINGS/ HISTOLOGIC GRADE<sup>h</sup>**

### **ADDITIONAL THERAPY**



<sup>f</sup>See [Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\)](#).

<sup>g</sup>See [Systemic Therapy for Uterine Sarcoma \(UTSARC-B\)](#).

<sup>h</sup>See [Uterine Sarcoma Classification \(UTSARC-C\)](#).

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# NCCN Guidelines Version 3.2017

## Uterine Sarcoma

### SURVEILLANCE

- H&P exam every 3 mo for 2 y, then every 6–12 mo
- Imaging<sup>b</sup>
- Patient education regarding symptoms of potential recurrence, lifestyle, obesity, exercise, nutrition, sexual health (including vaginal dilator use and lubricants/moisturizers), smoking cessation, nutrition counseling and potential long-term and late effects of treatment ([See NCCN Guidelines for Survivorship and NCCN Guidelines for Smoking Cessation](#))

### RECURRENCE

Local recurrence:  
• Vagina/pelvis  
• Imaging negative for metastatic disease<sup>b</sup>

Isolated  
metastases

Disseminated disease

### THERAPY FOR RELAPSE

[See Therapy For Relapse \(UTSARC-5\)](#)

Resectable

- Surgical resection or other local ablative therapy:
  - Consider postoperative systemic therapy<sup>g</sup>
  - Consider postoperative EBRT<sup>f</sup>

Unresectable

Systemic therapy<sup>g</sup> and/or  
Local therapy  
(EBRT<sup>f</sup> or local ablative therapy)

If response, consider surgery

Systemic therapy<sup>g</sup> ± palliative EBRT<sup>f</sup>  
or  
Supportive care

<sup>b</sup>[See Principles of Imaging for Uterine Sarcoma \(UTSARC-A\).](#)

<sup>f</sup>[See Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\).](#)

<sup>g</sup>[See Systemic Therapy for Uterine Sarcoma \(UTSARC-B\).](#)

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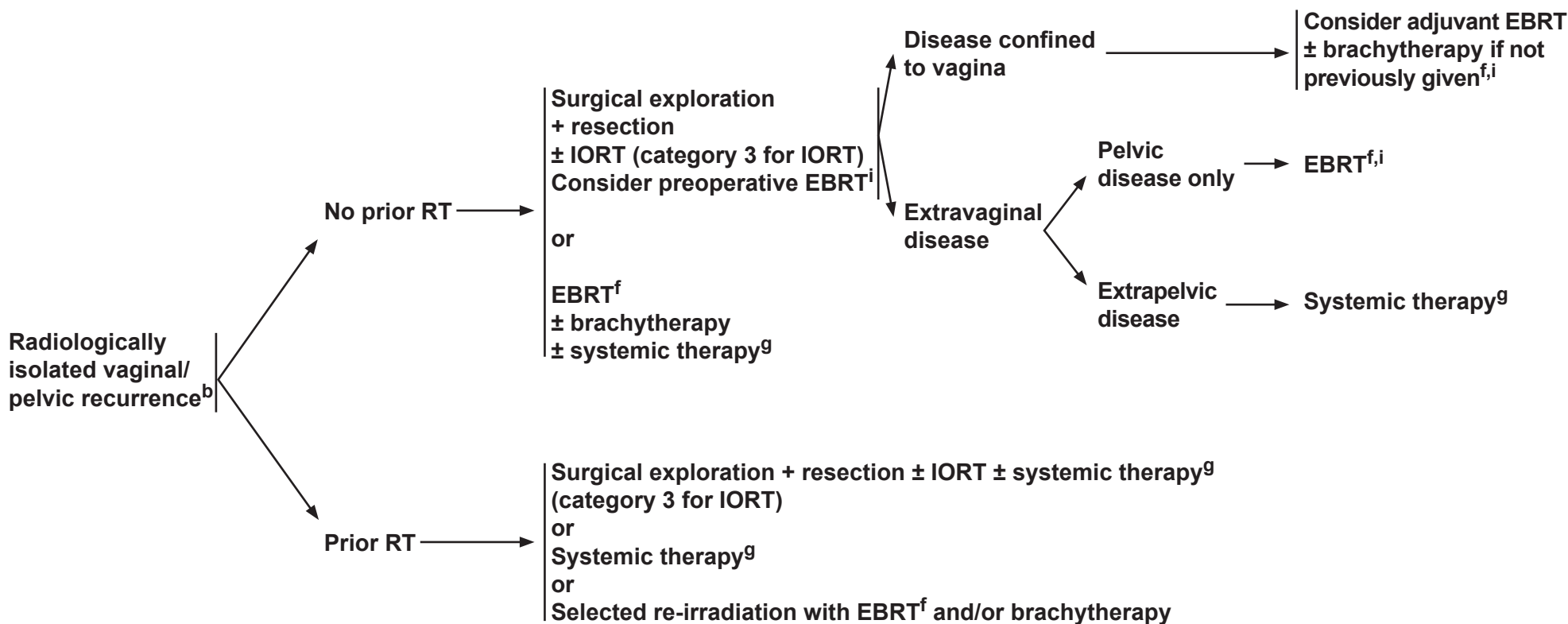


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## Uterine Sarcoma

### RECURRENCE

### THERAPY FOR RELAPSE



<sup>b</sup>See [Principles of Imaging for Uterine Sarcoma \(UTSARC-A\)](#).

<sup>f</sup>See [Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\)](#).

<sup>g</sup>See [Systemic Therapy for Uterine Sarcoma \(UTSARC-B\)](#).

<sup>i</sup>The use of preoperative EBRT would preclude postoperative EBRT.

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# NCCN Guidelines Version 3.2017

## Uterine Sarcoma

### **PRINCIPLES OF IMAGING<sup>a,1-9</sup>**

#### **Initial Workup**

- Chest/abdomen/pelvic CT.
- For patients who underwent TH with incidental finding of uterine sarcoma or incompletely resected uterus/adnexa (ie, supracervical hysterectomy, myomectomy, possible tumor fragmentation, intraperitoneal morcellation) perform chest/abdominal/pelvic CT or abdominal/pelvic MRI and chest CT without contrast to evaluate for metastatic disease.
- Consider pelvic MRI to evaluate local tumor extension or residual abnormality in cases where the uterus or adnexa were not resected or incompletely resected (supracervical hysterectomy, myomectomy, possible tumor fragmentation, intraperitoneal morcellation).
- Consider whole body PET/CT to clarify ambiguous findings.
- Other imaging should be based on symptomatology and clinical concern for metastatic disease.<sup>b</sup>

#### **Follow-up/Surveillance**

- Chest/abdominal/pelvic CT every 6 months for the first 3 years and then every 6–12 months for the next 2 years. Depending on histology grade and initial stage, consider annual to bi-annual imaging thereafter up to additional 5 years.<sup>c</sup>
- Optional abdominal/pelvic MRI and chest CT without contrast every 6 months for the first 3 years and then every 6–12 months for the next 2 years. Depending on histology, grade, and initial stage, consider annual to bi-annual imaging thereafter up to additional 5 years.<sup>c</sup>
- Consider whole body PET/CT if metastasis is suspected in select patients.
- Imaging should be based on symptomatology and clinical concern for metastatic disease.<sup>d</sup>

<sup>a</sup>MRI and CT are performed with contrast throughout the guidelines unless contraindicated. Contrast is not required for screening chest CT.

<sup>b</sup>Indications may include abnormal physical exam finding; bulky uterine tumor; vaginal or extrauterine involvement; delay in presentation or treatment; and abdominal or pulmonary symptoms.

<sup>c</sup>Follow-up imaging may be as frequent as every 3 months or change based on histology grade and/or stage of tumor.

<sup>d</sup>Indications may include abnormal physical exam findings such as vaginal involvement; palpable mass or adenopathy; and new pelvic, abdominal, or pulmonary symptoms.

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UTSARC-A  
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## Uterine Sarcoma

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# NCCN Guidelines Version 3.2017

## Uterine Sarcoma

### SYSTEMIC THERAPY FOR UTERINE SARCOMA<sup>1</sup> (Clinical trials strongly recommended)

#### Combination regimens:

- Docetaxel/gemcitabine  
(preferred for leiomyosarcoma)
- Doxorubicin/ifosfamide
- Doxorubicin/dacarbazine
- Doxorubicin/olaparatumab
- Gemcitabine/dacarbazine
- Gemcitabine/vinorelbine

#### Single-agent options:

- Dacarbazine
- Doxorubicin
- Epirubicin
- Eribulin (category 2B)
- Gemcitabine
- Ifosfamide
- Liposomal doxorubicin
- Pazopanib
- Temozolomide
- Trabectedin<sup>3</sup>
- Vinorelbine (category 2B)
- Docetaxel (category 3)

#### HORMONE THERAPY

(For Low-grade ESS or Hormone  
Receptor Positive (ER/PR) uLMS<sup>2</sup>):

- Medroxyprogesterone acetate  
(category 2B for ER/PR positive uLMS)
- Megestrol acetate  
(category 2B for ER/PR positive uLMS)
- Aromatase inhibitors
- GnRH analogs  
(category 2B for low-grade ESS and  
ER/PR positive uLMS)

<sup>1</sup>See [NCCN Guidelines for Ovarian Cancer--Management of Drug Reactions \[OV-C\]](#).

<sup>2</sup>These hormonal therapies may be considered for patients with uLMS that is ER/PR positive, preferably with small tumor volume or an indolent growth pace.

<sup>3</sup>For uLMS that has been treated with a prior anthracycline-containing regimen.

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# NCCN Guidelines Version 3.2017

## Uterine Sarcoma

### UTERINE SARCOMA CLASSIFICATION<sup>1</sup>

- Low-grade endometrial stromal sarcoma (ESS)<sup>2</sup>
- High-grade ESS<sup>3</sup>
- Undifferentiated uterine sarcoma (UUS)<sup>4</sup>
- Uterine leiomyosarcoma (uLMS)<sup>5</sup>

#### Other Rare Uterine Mesenchymal Sarcoma Subtypes: (see the [NCCN Guidelines for Soft Tissue Sarcoma](#))

- Adenosarcomas
- PEComas
- Rhabdomyosarcoma

<sup>1</sup>Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO Classification of Tumours of the Female Reproductive Organs, Volume 6, 2014.

<sup>2</sup>Low-grade endometrial stromal sarcomas (LGESS) are characterized by small cells with low-grade cytology and features resembling stromal cells in proliferative endometrium. Mitotic activity is usually low (<5 MF per 10 HPF).

<sup>3</sup>High-grade endometrial stromal sarcomas (HGESS) are characterized by small cells with high-grade cytology, frequent necrosis, and brisk mitotic activity (>10 MF per 10 HPF). HGESS can contain areas of conventional LGESS.

<sup>4</sup>Undifferentiated uterine sarcomas (UUSs) are characterized by cells with high-grade cytologic features lacking any resemblance to the stromal cells in proliferative endometrium or any other specific type of differentiation.

<sup>5</sup>Excludes smooth muscle tumors of uncertain malignant potential, epithelioid smooth muscle tumors, benign metastasizing leiomyomas, intravenous leiomyomatosis, and 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.

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### PRINCIPLES OF RADIATION THERAPY FOR UTERINE NEOPLASMS

- RT is directed at sites of known or suspected tumor involvement, and may include external beam RT (EBRT) and/or brachytherapy. Diagnostic imaging is often used to assess locoregional extent and to rule out distant metastases before administration of RT. In general, EBRT is directed to the pelvis with or without the para-aortic region. Brachytherapy can be delivered: 1) to an intact uterus, either preoperatively or definitively; or 2) more commonly, to the vagina after hysterectomy. For the purposes of these guidelines, whole abdominal 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, parametria, upper vagina/para-vaginal tissue, 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 utilized.
- Initiate brachytherapy as soon as the vaginal cuff is healed, preferably no later than 12 weeks after surgery. 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 two-thirds of the vagina.
  - ▶ For high-dose-rate brachytherapy, when used as a boost to EBRT, doses of 4 to 6 Gy x 2 to 3 fractions prescribed to the vaginal mucosa are commonly used.
  - ▶ For high-dose-rate vaginal brachytherapy alone, commonly used regimens include 7 Gy x 3 prescribed at a depth of 0.5 cm from the vaginal surface or 6 Gy x 5 fractions prescribed to the vaginal surface.
- Evidence supports the use of combined modality radiation and chemotherapy as adjuvant treatment for patients with extrauterine disease.<sup>1</sup>
- Palliative EBRT should be individualized to disease extent and patient performance status. Various dose/fractionation schemes can be considered. A common approach is 30 Gy in 10 fractions.

<sup>1</sup>Klopp A, Smith BD, Alektiar K, et al. The role of postoperative radiation therapy for endometrial cancer: executive summary of an american society for radiation oncology evidence-based guideline. Pract Radiat Oncol 2014;4:137-144.

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# NCCN Guidelines Version 3.2017 Staging Uterine Neoplasms

## Staging–Endometrial Carcinoma

**Table 1**

AJCC Tumor-Node-Metastases (TNM) and International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging Systems for Endometrial Cancer

**Primary Tumor (T)**

<b>TNM Categories</b>	<b>FIGO* Stages</b>	<b>Surgical-Pathologic Findings</b>
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis**		Carcinoma in situ (preinvasive carcinoma)
T1	I	Tumor confined to the corpus uteri
T1a	IA	Tumor limited to endometrium or invades less than one-half of the myometrium
T1b	IB	Tumor invades one-half or more of the myometrium
T2	II	Tumor invades stromal connective tissue of the cervix but does not extend beyond uterus#
T3a	IIIA	Tumor involves serosa and/or adnexa (direct extension or metastasis)##
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement##
	IIIC	Metastases to pelvic and/or para-aortic lymph nodes##
	IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
T4	IVA	Tumor invades bladder mucosa and/or bowel (bullous edema is not sufficient to classify a tumor as T4)

\*Either G1, G2, or G3

\*\*Note: FIGO no longer includes Stage 0 (Tis).

#Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.

##Positive cytology has to be reported separately without changing the stage.

**Regional Lymph Nodes (N)**

<b>TNM Categories</b>	<b>FIGO Stages</b>	<b>Surgical-Pathologic Findings</b>
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC1	Regional lymph node metastasis to pelvic lymph nodes (positive pelvic nodes)
N2	IIIC2	Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes

**Distant Metastasis (M)**

<b>TNM Categories</b>	<b>FIGO Stages</b>	<b>Surgical-Pathologic Findings</b>
M0		No distant metastasis
M1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes, intra-peritoneal disease, or lung, liver, or bone. It excludes metastasis to para-aortic lymph nodes, vagina, pelvic serosa, or adnexa)

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[Continued](#)



# NCCN Guidelines Version 3.2017 Staging Uterine Neoplasms

## Staging–Uterine Sarcoma

**Table 2**

AJCC Tumor-Node-Metastases (TNM) and International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging Systems for Uterine Sarcomas (includes Leiomyosarcoma and Endometrial Stromal Sarcoma)\*

### Leiomyosarcoma and Endometrial Stromal Sarcoma

#### Primary Tumor (T)

TNM Categories	FIGO Stages	Definition
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor limited to the uterus
T1a	IA	Tumor 5 cm or less in greatest dimension
T1b	IB	Tumor more than 5 cm
T2	II	Tumor extends beyond the uterus, within the pelvis
T2a	IIA	Tumor involves adnexa
T2b	IIB	Tumor involves other pelvic tissues
T3	III**	Tumor infiltrates abdominal tissues (not just protruding into the abdomen)
T3a	IIIA	One site
T3b	IIIB	More than one site
T4	IVA	Tumor invades bladder or rectum

**Note:** Simultaneous tumors of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors.

\*Carcinosarcomas should be staged as carcinomas of the endometrium ([See ST-1](#)).

\*\*In this stage, lesions must infiltrate abdominal tissues and not just protrude into the abdominal cavity.

#### Regional Lymph Nodes (N)

TNM Categories	FIGO Stages	Definition
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC	Regional lymph node metastasis

#### Distant Metastasis (M)

TNM Categories	FIGO Stages	Definition
M0		No distant metastasis
M1	IVB	Distant metastasis (excluding adnexa, pelvic, and abdominal tissues)

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## Discussion

### NCCN Categories of Evidence and Consensus

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

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

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

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

**All recommendations are category 2A unless otherwise noted.**

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## Uterine Neoplasms

### Overview

Adenocarcinoma of the endometrium (also known as endometrial cancer, or more broadly as uterine cancer or carcinoma of the uterine corpus) is the most common malignancy of the female genital tract in the United States. It is estimated that 61,380 new uterine cancer cases will occur in 2017, with 10,920 deaths resulting from the disease.<sup>1</sup>

Stromal or mesenchymal sarcomas are uncommon subtypes accounting for approximately 3% of all uterine cancers.<sup>2,3</sup> The NCCN Guidelines for Uterine Neoplasms describe malignant epithelial tumors and uterine sarcomas; each of these major categories contains specific histologic groups that require different management (see *Initial Clinical Findings* in the NCCN Guidelines for Uterine Neoplasms).

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

For patients with known or suspected uterine neoplasms, the initial preoperative evaluation/workup for known or suspected malignancy includes a history and physical examination, expert pathology review with additional endometrial biopsy as indicated, imaging, consideration

of genetic evaluation, and other studies (see *Initial Evaluation* and *Principles of Imaging* in the NCCN Guidelines for Uterine Neoplasms).<sup>8</sup> Preoperative imaging and biopsy may help to identify uterine sarcomas, although biopsy sensitivity is less than that for endometrial cancer. An expert pathology review will determine whether a patient has a malignant epithelial tumor or a stromal/malignant mesenchymal tumor. Epithelial tumor types include pure endometrioid cancer, uterine serous carcinoma, clear cell carcinoma, carcinosarcoma (also known as malignant mixed Müllerian tumor [MMMT]) and undifferentiated carcinoma. Stromal or mesenchymal tumor types (interchangeable terms) include uterine leiomyosarcoma (uLMS), endometrial stromal sarcoma (ESS), and undifferentiated uterine sarcoma (UUS, previously called high-grade undifferentiated endometrial sarcoma), adenosarcoma, and PEComa. Given the typical age group at risk for uterine neoplasms (ie, ≥55 years) and the presence of comorbid illnesses in older patients, it is prudent in selected patients to also measure renal and liver function.

Most endometrial cancer is caused by sporadic mutations. However, genetic mutations cause endometrial cancer in about 5% of patients, which occurs 10 to 20 years before sporadic cancer.<sup>9</sup> Screening for genetic mutations (eg, Lynch syndrome/hereditary non-polyposis colorectal cancer) should be considered in all patients with endometrial (and colorectal) cancer but especially in those younger than 50 years of age.<sup>7,9-11</sup> Genetic testing and counseling should be considered for patients younger than 50 years of age with endometrial cancer and those with a significant family history of endometrial and/or colorectal cancer.<sup>12-14</sup> If these patients have Lynch syndrome, they are at greater risk for a second cancer (eg, colorectal cancer, ovarian cancer).<sup>5,11,15</sup> In addition, their relatives may have Lynch syndrome.

Screening of the tumor for defective DNA mismatch repair (MMR) using immunohistochemistry and/or microsatellite instability (MSI) is used to identify which patients should undergo mutation testing for Lynch syndrome (see *Lynch Syndrome* in the NCCN Guidelines for Colorectal Cancer Screening).<sup>9,10,16,17</sup> Universal testing of endometrial tumors for defects in DNA MMR is recommended (eg, MLH1, MSH2, MSH6). MLH1 loss should be further evaluated for promoter methylation to assess for an epigenetic process rather than a germline mutation. Genetic counseling and testing is recommended for patients with all other MMR abnormalities and for patients without MMR defects but who have a significant family history of endometrial and/or colorectal cancer (See Lynch syndrome/HNPCC in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal).

Women with Lynch syndrome are at higher lifetime risk (up to 60%) for endometrial cancer; thus, close monitoring and discussion of risk reducing strategies is recommended.<sup>10,18,19</sup> In relatives with Lynch syndrome but without endometrial cancer, a yearly endometrial biopsy is recommended to assess for cancer.<sup>13,20</sup> This strategy also enables select women to defer surgery (and surgical menopause) and to preserve their fertility. Prophylactic hysterectomy/bilateral salpingo-oophorectomy (BSO) can then be done after childbearing is complete or sooner, depending on patient preference.<sup>21,22</sup> In addition, interventions to decrease the risk from colorectal cancer may also be appropriate (eg, annual colonoscopy).

### Endometrial Cancer

In approximately 70% of patients with adenocarcinoma of the endometrium, the invasive neoplasm is confined to the uterus at diagnosis.<sup>23</sup> Thus, endometrial cancer is often localized, yielding a generally high survival rate.<sup>24</sup>

Many physicians believe that adenocarcinoma of the endometrium is a more treatable malignancy because the early symptoms of irregular vaginal bleeding (in this predominantly postmenopausal patient population) often trigger patients to seek care when the disease is at an early and treatable stage. However, data show that the mortality rate for uterine cancer has increased more rapidly than the incidence rate.<sup>25</sup> This increased mortality may be related to an increased rate of advanced-stage cancers, high-risk histologies (eg, serous carcinomas), and patients being diagnosed at an older age. Analysis of SEER data suggests that survival is increased in patients who are younger, have early-stage disease, and have lower-grade disease.<sup>26</sup> In addition to grade and depth of myometrial invasion, other risk factors associated with poor prognosis include age, lymph node status, tumor size, lymphovascular space invasion (LVSI), and tumor involvement of the lower uterine segment.<sup>27,28</sup> To further improve outcome for patients with this disease, physicians need to identify high-risk patients and to tailor treatment appropriately to provide the best long-term survival. The panel suggests that gynecologic oncologists be involved in the primary management of all patients with endometrial cancer.

### Diagnosis and Workup

About 90% of patients with endometrial carcinoma have abnormal vaginal bleeding, most commonly in the postmenopausal period. The workup was previously described (see *Overview* in this Discussion). Diagnosis can usually be made by an office endometrial biopsy.<sup>29,30</sup> The histologic information from the endometrial biopsy (with or without endocervical curettage) should be sufficient for planning definitive treatment. Office endometrial biopsies have a false-negative rate of about 10%. Thus, a negative endometrial biopsy in a symptomatic patient must be followed by a fractional dilation and curettage (D&C) under anesthesia.<sup>29,31</sup> Hysteroscopy may be helpful in evaluating the



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endometrium for lesions, such as a polyp, if the patient has persistent or recurrent undiagnosed bleeding.<sup>32</sup> Endometrial biopsy may not be accurate for diagnosing malignancies of the uterine wall such as mesenchymal tumors.

For detailed imaging recommendations by stage and planned treatment approach, see *Principles of Imaging* in the NCCN Guidelines for Uterine Neoplasms. Chest imaging with plain radiography is recommended. Other imaging tests such as CT, MRI, and/or PET/CT may be used to assess disease extent and to evaluate for metastatic disease as indicated based on clinical symptoms, physical findings, or abnormal laboratory findings.<sup>33-38</sup> In patients with extrauterine disease, a serum CA 125 assay may be helpful in monitoring clinical response.<sup>39,40</sup> However, serum CA 125 levels may be falsely increased in women who have peritoneal inflammation/infection or radiation injury, may be normal in women with isolated vaginal metastases, and may not predict recurrence in the absence of other clinical findings.<sup>41-43</sup> Currently, there is no validated screening test for endometrial carcinoma.<sup>44,45</sup>

### Disease Staging

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

Several studies demonstrated that clinical staging was inaccurate and did not reflect actual disease extent in 15% to 20% of patients.<sup>46-48</sup> This reported understaging and, more importantly, the ability to identify

multiple prognostic factors with a full pathologic review made possible with surgical staging, motivated a change in the staging classification. Therefore, in 1988, FIGO modified its staging system to emphasize thorough surgical/pathologic assessment of data, such as histologic grade, myometrial invasion, and the extent and location of extrauterine spread (including retroperitoneal lymph node metastases).<sup>49</sup> FIGO and the AJCC updated and refined the surgical/pathologic staging criteria for uterine neoplasms in 2009.<sup>50-54</sup> Separate staging systems for malignant epithelial tumors and uterine sarcomas are now available (see Tables 1 and 2, respectively).

The 2009 staging system streamlined stages I and II endometrial carcinoma. These revisions were made because the survival rates for some of the previous sub-stages were similar.<sup>53</sup> Stage IA is now less than 50% myometrial invasion, and stage IB is 50% or more myometrial invasion. Stage II only includes patients with cervical stromal invasion. Patients with uterine-confined disease and endocervical glandular involvement (mucosal involvement) without cervical stromal invasion are no longer considered stage II.<sup>53</sup> Stage IIIC is now subdivided into IIIC1 and IIIC2, because survival is worse with positive para-aortic nodes.<sup>53</sup> While most of the previously published studies discussed in these NCCN Guidelines used the older 1988 FIGO staging system, these have been reinterpreted by the NCCN Panel to reconcile with the 2009 staging system.

Peritoneal cytology no longer affects the 2009 FIGO staging, because it is not viewed by some authors as an independent risk factor.<sup>54</sup> However, FIGO and AJCC continue to recommend that peritoneal washings be obtained and results recorded, because positive cytology may add to the effect of other risk factors (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).<sup>55,56</sup>



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

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

### Pathology

An expert pathology review will determine the specific epithelial histology of the tumor (ie, various endometrioid histologies, serous carcinoma, clear cell carcinoma, carcinosarcoma, undifferentiated carcinoma). The pathologic assessment of the uterus and the nodes is described in the algorithm; this assessment should also include the Fallopian tubes and the ovaries (see *Hysterectomy and Pathologic Evaluation* in the NCCN Guidelines for Endometrial Carcinoma). The *Protocol for Examination of Specimens from Patients With Carcinoma of the Endometrium* from the College of American Pathologists (CAP) is a useful guide

([http://www.cap.org/apps/docs/committees/cancer/cancer\\_protocols/2013/Endometrium\\_13protocol\\_3200.pdf](http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2013/Endometrium_13protocol_3200.pdf)) This CAP protocol was revised in October 2013 and reflects the updated FIGO/AJCC 2009 staging (ie, AJCC Cancer Staging Manual, 7<sup>th</sup> edition).

As the grade of the tumor increases, the accuracy of intraoperative evaluation of myometrial invasion decreases (ie, assessment by gross examination of fresh tissue). In one study, the depth of invasion was accurately determined by gross examinations in 87.3% of grade 1 lesions, 64.9% of grade 2 lesions, and 30.8% of grade 3 lesions.<sup>57</sup> 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.<sup>58</sup>

Additionally, recent data highlight the potential importance of ultrastaging (ie, serial sectioning and immunohistochemistry) to improve the accuracy of detecting micrometastases. In a cohort of 508 patients who underwent sentinel lymph node (SLN) mapping, ultrastaging detected 23 additional cases of micrometastasis that would have been missed by conventional hematoxylin and eosin staining.<sup>59</sup> A multicenter study of 304 women with presumed low- or intermediate-risk disease showed that SLN biopsy and ultrastaging detected metastatic SLNs in 3-fold greater number of patients than standard lymphadenectomy.<sup>60</sup>

### Lymphadenectomy

Previously, a full standard lymphadenectomy (ie, dissection and assessment of both pelvic and para-aortic nodes) was recommended for all patients; however, a more selective and tailored lymphadenectomy approach which may include the SLN algorithm is now recommended by the NCCN Panel to avoid systematic over-treatment.<sup>61</sup> No randomized trial data support routine full lymphadenectomy,<sup>62</sup> although some retrospective studies have suggested that it is beneficial.<sup>63-65</sup> Two randomized clinical trials from Europe reported that routine lymph node dissection did not improve the outcome of endometrial cancer patients, but lymphadenectomy did identify those with nodal disease.<sup>66,67</sup> However, these findings remain a point of contention.<sup>68-70</sup> To avoid over-interpretation of these results, it is





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important to address the limitations of these randomized studies, including selection of patients, extent of lymph node dissection, and standardization of postoperative therapy.<sup>71,72</sup> The other concerns include the lack of central pathology review, subspecialty of surgeons, and adequacy of statistical power.

Decisions about whether to perform lymphadenectomy, and, if done, to what extent (eg, pelvic nodes only or both pelvic and para-aortic nodes), can be made based on preoperative and intraoperative findings. Criteria have been suggested as indicative of low-risk for nodal metastases: 1) less than 50% myometrial invasion; 2) tumor less than 2 cm; and 3) well or moderately differentiated histology.<sup>73,74</sup> However, this may be difficult to accurately determine before final pathology results are available.

Another associated benefit of lymphadenectomy is the diagnosis of those with nodal metastases to guide appropriate adjuvant treatment to improve survival or decrease toxicity. However, one of the trials was not designed to address this question.<sup>67</sup> Therefore, there was no standardization of adjuvant treatment after staging surgery with lymphadenectomy. In fact, the use of lymphadenectomy did not translate into an increased use of adjuvant therapy. This may have contributed to the lack of difference in recurrence and survival in the two groups.

The question of whether to add para-aortic lymphadenectomy to pelvic node dissection has been debated. Prior studies have shown conflicting information regarding the risk of para-aortic nodal metastases in patients without disease in the pelvic nodes.<sup>48,73,75,76</sup> There was a high rate of lymphatic metastasis above the inferior mesenteric artery, suggesting a need for systematic pelvic and para-aortic lymphadenectomy. Hence, para-aortic lymphadenectomy up to the renal vessels may be considered for selective high-risk situations

including those with pelvic lymphadenectomy or high-risk histologic features. Many surgeons do not do a full lymphadenectomy in patients with grade 1 early-stage endometrial cancer.<sup>61</sup>

In summary, lymph node dissection identifies patients requiring adjuvant treatment with RT and/or systemic therapy.<sup>77</sup> A subset of patients may not benefit from lymphadenectomy; however, it is difficult to preoperatively identify these patients because of the uncontrollable variables of change in grade and depth of invasion on final pathology. At this point, pending further trials that seek to define the clinical benefit of lymphadenectomy, the NCCN Panel recommends that lymphadenectomy should be done for selected patients with endometrial cancer with para-aortic lymphadenectomy done as indicated for high-risk patients (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).<sup>6</sup> Lymphadenectomy is contraindicated for patients with uterine sarcoma.

### *Sentinel Lymph Node Mapping*

The new section on surgical staging (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma) includes recommendations about SLN mapping. SLN mapping is considered for patients with apparent uterine-confined endometrial cancer to assess whether they have metastatic pelvic lymph nodes.<sup>78-81</sup> In SLN mapping, dye is injected into the cervix, which travels to the sentinel nodes (see Figures 1–3 in *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma). A surgical SLN algorithm is proposed to decrease the false-negative rate (see Figure 4 in *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).<sup>78,82</sup> For example, suspicious or grossly enlarged nodes should be removed regardless of SLN mapping results. If mapping fails, a side-specific nodal dissection should be done.<sup>78</sup>



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In SLN mapping, the surgeon's expertise and attention to technical detail are critical. Patients may be able to avoid the morbidity of a standard lymphadenectomy with SLN mapping.<sup>83,84</sup> Because SLNs identify the primary lymphatic pathway, this increases the yield of finding metastatic disease during the mapping process.

SLN mapping may be most appropriate for those at low to intermediate risk for metastases and/or for those who may not tolerate a standard lymphadenectomy.<sup>84-88</sup> It is important to note that system-wide long-term outcomes data are not yet available for SLN mapping in endometrial cancer.<sup>89,90</sup>

Much of the data to support SLN mapping are based on single institution studies. A systematic review of seventeen studies with  $n > 30$  patients revealed detection rates of 60% to 100%; detection rates for studies with larger cohorts ( $n > 100$ ) were at least 80%. Retrospective application of a surgical algorithm generated 95% sensitivity, 99% predictive value, and a 5% false-negative rate.<sup>91</sup> Another recent systematic review and meta-analysis of 55 studies with  $n > 10$  patients ( $n = 4915$ ) generated an overall detection rate of 81% with a 50% bilateral pelvic node detection rate and 17% paraaortic detection rate.<sup>92</sup> Recent findings also suggest that indocyanine green may be preferable to colorimetric dyes.<sup>92-95</sup> Attention to detail and experience are critical to ensure optimal outcomes.

Ultrastaging of SLNs can reveal lymph node metastases undetected through conventional histology, and studies suggest that SLN ultrastaging leads to upstaging in 5% to 15% of patients.<sup>81,83,86,88,91</sup>

Although these findings do not appear to be an artifact of uterine manipulation,<sup>96</sup> the implications and appropriate management of micrometastases or isolated tumor cells (ITC) detected via SLN ultrastaging are not yet clear.<sup>83,88,97-99</sup> Future evaluation of prognosis may

need to separately examine patients with scattered ITCs versus patients with aggregated micrometastasis. The prognostic significance of ITCs has been studied in breast cancer<sup>100</sup> where nodes containing ITCs are excluded from the positive node count per AJCC staging.

In a retrospective analysis of patients with early-stage endometrial cancer ( $n = 780$ ) who underwent SLN mapping with lymphadenectomy versus lymphadenectomy alone, SLN mapping led to the detection of more metastasis (30.3% vs. 14.7%,  $P < .001$ ) and was associated with greater use of adjuvant therapy.<sup>101</sup> Long-term follow-up was reported from a prospective multicenter study in 125 patients with early-stage endometrial carcinoma who underwent SLN biopsy. Patients with a positive SLN underwent external beam radiation therapy (EBRT) and chemotherapy at a higher rate than those with a negative SLN. In patients with a detected SLN, recurrence-free survival at 50 months was 84.7%, and no difference was detected between patients with and without a positive SLN ( $P = .5$ ).<sup>102</sup>

SLN mapping should be done in institutions with expertise in this procedure. If patients have apparent metastatic disease (based on imaging and surgical exploration), removal of nodes for staging purposes is not necessary because it will not change management.<sup>33</sup> The main contraindication for SLN mapping is uterine sarcoma. Additionally, SLN mapping should be performed and interpreted with particular caution in patients with high-risk histology (eg, serous carcinoma, clear cell carcinoma, carcinosarcoma).<sup>61,103</sup> SLN mapping in patients with endometrial carcinosarcoma was recently reported with promising results.<sup>104</sup>

### **Minimally Invasive Procedures**

Over the past decade, practice has trended towards minimally invasive approaches to TH/BSO and lymph node assessment in patients with



early-stage endometrial cancer.<sup>105</sup> Although these procedures may be performed by any surgical route (eg, laparoscopic, robotic, vaginal, abdominal), the standard in those with apparent uterine-confined disease is to perform the procedure via a minimally invasive approach. Randomized trials, a Cochrane Database Systematic Review, and population-based surgical studies support that minimally invasive techniques are preferred in this setting due to a lower rate of surgical site infection, transfusion, venous thromboembolism, decreased hospital stay, and lower cost of care, without compromise in oncologic outcome.<sup>105-110</sup> Despite data showing that minimally invasive procedures result in lower perioperative complications and lower cost of care, racial and geographic disparities in access to minimally invasive surgical care have been observed.<sup>106,110</sup>

A randomized phase III trial evaluated laparoscopy for comprehensive surgical staging; patients (n = 2616) with clinical stage I to IIA disease (GOG-LAP2) were assessed.<sup>109,111</sup> Patients were randomly allocated 2:1 to laparoscopy or laparotomy. Results from LAP2 indicate that 26% of patients needed conversion to laparotomy because of poor visibility, metastatic cancer, bleeding, increased age, or increased body mass index. Detection of advanced cancer was not significantly different between the groups. However, significant differences were noted in removal of pelvic and para-aortic nodes (8% not removed with laparoscopy vs. 4% with laparotomy,  $P < .0001$ ).<sup>112,113</sup> Significantly fewer postoperative adverse events and shorter hospitalization occurred with laparoscopy compared with laparotomy. Recurrence rates were 11.4% for laparoscopy versus 10.2% for laparotomy. The 5-year overall survival (OS) rate was 84.8% for both arms of LAP2.<sup>111</sup> Laparoscopic staging was associated with improved postoperative quality of life across several parameters.<sup>108</sup>

Another randomized trial (n = 283) comparing laparoscopy versus laparotomy reported shorter hospital stay, less pain, and faster resumption of daily activities with laparoscopy.<sup>114</sup> However, laparotomy may still be required for certain clinical situations (eg, elderly patients, those with a very large uterus) or certain metastatic presentations.<sup>109</sup>  
 115,116

Robotic surgery is a minimally invasive technology that has been increasingly used in the surgical staging of early-stage endometrial carcinoma due to its potential advantages over laparotomy, especially for obese patients.<sup>117-121</sup> Prospective cohort and retrospective studies suggest that robotic approaches perform similarly to laparoscopy and result in comparable or improved perioperative outcomes.<sup>121-124</sup> Oncologic outcomes appear to be comparable to other surgical approaches, although longer-term outcomes are still being investigated.<sup>125-127</sup> In heavier patients, robotic surgery may result in less frequent conversion to laparotomy when compared with laparoscopic approaches and also appears to be safe and feasible in patients at higher anesthesiologic risk.<sup>121,122,128</sup>

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

### Primary Treatment

These NCCN Guidelines divide pure endometrioid cancer into three categories for delineating treatment: 1) disease limited to the uterus; 2)

suspected or gross cervical involvement; and 3) suspected extrauterine disease. Most patients with endometrial cancer have stage I disease at presentation, and surgery (with or without adjuvant therapy) is recommended for medically operable patients. As a general principle, endometrial carcinoma should be removed en bloc to optimize outcomes; intraperitoneal morcellation should be avoided.<sup>136-139</sup>

### ***Disease Limited to the Uterus***

To stage medically operable patients with endometrioid histologies clinically confined to the fundal portion of the uterus, the recommended surgical procedure includes total hysterectomy (TH)/BSO with surgical staging and lymph node assessment (see *Hysterectomy and Pathologic Evaluation*, and *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma and in this Discussion).<sup>68</sup>

When indicated, surgical staging is recommended to gather full pathologic and prognostic data on which to base decisions regarding adjuvant treatment for select patients who do not have medical or technical contraindications to lymph node dissection (see *Lymphadenectomy* and *Sentinel Lymph Node Mapping* in this Discussion). Minimally invasive surgery is the preferred approach when technically feasible and is considered a quality measure by the SGO and the American College of Surgeons ([www.sgo.org/quality-outcomes-and-research/quality-indicators](http://www.sgo.org/quality-outcomes-and-research/quality-indicators); [www.facs.org/quality-programs/cancer/ncdb/qualitymeasures](http://www.facs.org/quality-programs/cancer/ncdb/qualitymeasures)).

During surgery, the intraperitoneal structures should be carefully evaluated, and suspicious areas should be biopsied. While not specifically affecting staging, FIGO recommends that peritoneal cytology should be collected and results should be recorded. Enlarged or suspicious lymph nodes should be excised to confirm or rule out metastatic disease. Retroperitoneal node dissection with pathologic evaluation—in the absence of clinically apparent lymphadenectomy—is

useful when using the 2009 FIGO staging criteria, but its routine use has been questioned (see *Lymphadenectomy* in this Discussion).

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

### ***Incomplete Surgical Staging***

For patients with incomplete (ie, not thorough) surgical staging and high-risk intrauterine features, imaging is often recommended, especially in patients with higher grade and more deeply invasive tumors.<sup>140,141</sup> Surgical restaging, including lymph node dissection, can also be done.<sup>73</sup> Based on the imaging and/or surgical restaging results, recommended adjuvant treatment options are provided in the algorithm (see Adjuvant Treatment for *Incompletely Surgically Staged* in the NCCN Guidelines for Endometrial Carcinoma).

### ***Fertility-Sparing Therapy***

Although the primary treatment of endometrial cancer is usually hysterectomy, continuous progestin-based therapy may be considered for highly selected patients with Grade 1, stage IA (non-invasive) disease who wish to preserve their fertility.<sup>142-146</sup> Likewise, it may also be selectively used for young patients with endometrial hyperplasia who desire fertility preservation. The guidelines include an algorithm for fertility-sparing therapy in selected patients with biopsy-proven grade 1 (preferably by D&C), stage IA non-invasive endometrioid adenocarcinoma (see *Criteria for Considering Fertility-Sparing Options* in the NCCN Guidelines for Endometrial Cancer). The panel recommends consultation with a fertility expert. When considering fertility-sparing therapy, all of the criteria must be met as outlined in the



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algorithm (eg, no metastatic disease). Selected patients may require genetic counseling and testing. Patients should also receive counseling that fertility-sparing therapy is not the standard of care for the treatment of endometrial carcinoma. TH/BSO with surgical staging is recommended after childbearing is complete, if therapy is not effective, or if progression occurs. Fertility-sparing therapy is not recommended for high-risk patients (eg, those with high-grade endometrioid adenocarcinomas, uterine serous carcinoma, clear cell carcinoma, carcinosarcoma, and uLMS).

Continuous progestin-based therapy may include megestrol acetate, medroxyprogesterone, or an intrauterine device containing levonorgestrel.<sup>142,143,147</sup> A durable complete response occurs in about 50% of patients.<sup>142</sup> The use of progestin-based therapy should be carefully considered in the context of other patient-specific factors, including contraindications such as breast cancer, stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis, and smoking.

In patients receiving progestin-based therapies, the NCCN Panel recommends close monitoring with endometrial sampling (biopsies or D&C) every 3 to 6 months. TH/BSO with staging is recommended: 1) after childbearing is complete; 2) if patients have documented progression on the biopsies; or 3) if endometrial cancer is still present after 6 to 12 months of progestin-based therapy.<sup>146,148</sup> Although some young women who had subsequent negative endometrial biopsies after hormonal therapy were able to become pregnant (35%), their ultimate recurrence rate was high (35%).<sup>142,145,149-151</sup>

In premenopausal women with stage IA to B endometrial cancer, data suggest that ovarian preservation is safe and not associated with an increased risk of cancer-related mortality; patients were followed for 16

years.<sup>152</sup> Other studies also suggest that ovarian preservation may be safe in women with early-stage endometrial cancer.<sup>153,154</sup>

### ***Suspected or Gross Cervical Involvement***

For patients with suspected or gross cervical involvement (endometrioid histologies), cervical biopsy or pelvic MRI should be considered if not previously done (see *Additional Workup* in the NCCN Guidelines for Endometrial Carcinoma).<sup>140,141</sup> If negative, patients are assumed to have disease that is limited to the uterus and are treated as previously described (see *Primary Treatment* in the NCCN Guidelines for Endometrial Carcinoma). It may be difficult to distinguish primary cervical carcinoma from stage II endometrial carcinoma. Thus, for operable patients with cervical involvement, radical hysterectomy is recommended along with BSO, cytology (peritoneal lavage), and dissection of lymph nodes if indicated (see *Principles of Evaluation and Surgical Staging* and *Hysterectomy and Pathologic Evaluation* in the NCCN Guidelines for Endometrial Carcinoma).<sup>68</sup> In these patients, radical or modified radical hysterectomy may improve local control and survival when compared with TH.<sup>155,156</sup> Alternatively, the patient may undergo EBRT and brachytherapy (category 2B) followed by TH/BSO and surgical staging. However, preoperative RT is a category 2B recommendation because the NCCN Panel feels that upfront surgery is the preferred option for these patients.

### ***Patients Not Suited for Primary Surgery***

EBRT and brachytherapy with (or without) systemic therapy is an effective treatment that can provide some measure of pelvic control and long-term progression-free survival (PFS) (see *Principles of Radiation Therapy* in the NCCN Guidelines for Uterine Neoplasms).<sup>157-160</sup> If rendered operable, surgical resection should follow. Initial systemic therapy alone can also be considered (category 2B). Following systemic



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therapy, local treatment should still be utilized (ie, surgery if feasible, or EBRT + brachytherapy if still inoperable).

Hormonal therapy may be considered in selected patients with endometrioid histology (eg, estrogen and progesterone receptor–positive [ER/PR-positive] patients), who are not candidates for RT or surgery, if they are closely monitored (eg, consider endometrial biopsies every 3–6 months).<sup>44,161</sup> Progesterone-based therapy can provide some benefit with low toxicity in patients with low-grade tumors.<sup>162</sup> Tamoxifen with alternating megestrol may be used.<sup>163</sup> Aromatase inhibitors have also been used.<sup>164-167</sup>

### ***Suspected Extrauterine Disease***

If extrauterine disease (endometrioid histologies) is suspected, imaging studies are recommended if clinically indicated (see *Additional Workup* in the NCCN Guidelines for Endometrial Carcinoma). Patients with no extrauterine disease are treated using the guidelines for disease limited to the uterus. Intra-abdominal disease (ie, ascites; omental, nodal, ovarian, or peritoneal involvement) warrants surgical intervention using TH/BSO with cytology (peritoneal lavage), pelvic and para-aortic lymph node dissection if indicated, and surgical debulking. Consider preoperative systemic therapy. The surgical goal is to have no measurable residual disease; several studies support debulking.<sup>68,168-170</sup>

Patients with unresectable extrauterine pelvic disease (ie, vaginal, bladder, bowel/rectal, or parametrial involvement) are typically treated with EBRT and/or brachytherapy with (or without) systemic therapy, followed by re-evaluation of tailored surgery.<sup>171-174</sup> Systemic therapy alone can also be considered. Based on treatment response, patients should be re-evaluated for surgical resection and/or RT. For extra-abdominal disease (eg, liver involvement), recommended options

include systemic therapy and/or EBRT and/or hormone therapy. Palliative TH/BSO may be considered.

### **Adjuvant Therapy**

#### ***Uterine-Confined Disease***

Thorough surgical staging provides important information to assist in selection of adjuvant therapy for endometrial tumors (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma). Patients with stage I endometrial cancer who have thorough surgical staging are stratified by adverse risk factors (ie, age, positive LVSI, tumor size, depth of invasion, lower uterine [cervical/glandular] segment involvement).<sup>175,176</sup> Recommended adjuvant treatment is shown in the algorithm (see the NCCN Guidelines for Endometrial Carcinoma). Note that the treatment algorithm was revised in 2010 based on the updated FIGO/AJCC staging (7<sup>th</sup> edition).<sup>51,53</sup> However, by necessity, much of the discussion in this manuscript has been based on data from patients staged using the older FIGO/AJCC staging system. The implications of *stage migration* should be taken into account when evaluating historical data (see Table 1).

The basic concept underlying the recommendations in the NCCN Guidelines is the trend toward selection of more aggressive adjuvant therapy for patients as tumor grade and myometrial and/or cervical invasion worsen, because risk exists on a continuum.<sup>177-179</sup> In surgical stage I and II endometrial cancer, other pathologic factors that may influence the decision regarding adjuvant therapy include LVSI, patient age, tumor volume, depth of invasion, and lower uterine segment or surface cervical glandular involvement. When administering adjuvant RT, it should be initiated as soon as the vaginal cuff has healed, no later than 12 weeks after surgery.





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Significant controversy centers on how much adjuvant therapy is necessary in patients with surgical stage I endometrial cancer, regardless of intrauterine features, if extrauterine disease has been clearly ruled out. In a large prospective study, the Gynecologic Oncology Group (GOG) reported that the 5-year survival rate for surgical stage I patients with no adverse risk factors other than grade and myometrial invasion (ie, without extrauterine disease, isthmus/cervical involvement, or LVSI) was 92.7%.<sup>180</sup> The practice of surgical staging has led to a decrease in the use of adjuvant therapy for stage I endometrial carcinoma, which is reflected in the option of *observation* in the NCCN Guidelines (see section on adjuvant treatment in the NCCN Guidelines for Endometrial Carcinoma).<sup>77,176,177,181-183</sup>

The recommended postoperative (ie, adjuvant) treatment options for surgical stage II patients (using thorough surgical staging) are shown in the algorithm (see *Adjuvant Treatment for Stage II* in the NCCN Guidelines for Endometrial Carcinoma). The NCCN Panel generally agrees on the role of adjuvant therapy for patients with an invasive cervical component if extrafascial hysterectomy is performed. However, for patients with stage II disease who have had a radical hysterectomy with negative surgical margins and no evidence of extrauterine disease, observation or vaginal brachytherapy are options. As with stage I disease, the presence of adverse risk factors should be considered when selecting adjuvant therapy.<sup>184</sup>

In 2015, the panel removed observation as a recommended option in the adjuvant setting for patients with Stage IB, grade 3 disease with additional risk factors. Observation was changed from a category 2A recommendation to category 2B for patients with Stage IB, grade 3 disease with no additional risk factors. For the 2016 update of the guidelines, recommendations for Stage II, grades 2 and 3 disease were amended. For stage II, grade 2 disease, the revised recommendations

are vaginal brachytherapy and/or EBRT [formerly pelvic RT and vaginal brachytherapy]. For stage II, grade 3 disease, revised recommendations are EBRT with (or without) vaginal brachytherapy, with (or without) systemic therapy [formerly pelvic RT and vaginal brachytherapy, with (or without) systemic therapy].

### *Adjuvant RT*

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

Four trials have evaluated the role of adjuvant external-beam pelvic RT in patients with endometrial carcinoma. In 2 of these trials, the patients were not formally staged (Postoperative Radiation Therapy in Endometrial Carcinoma [PORTEC-1], Aalders).<sup>185,186</sup> In the third trial (ASTEC/EN.5), only 50% of the patients were thoroughly staged as part of a companion surgical protocol.<sup>66,187</sup> However, formal surgical staging was mandated for all patients in the fourth trial (GOG 99).<sup>188</sup> Note that these trials used the older staging system (ie, before 2009).

The PORTEC-1 trial suggested that external-beam pelvic RT provides a therapeutic benefit in selected patients with uterine-confined disease.<sup>185,189</sup> Although RT significantly decreased locoregional



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recurrence, it did not increase OS.<sup>190</sup> The Aalders' randomized trial found that RT reduced vaginal (ie, locoregional) recurrences but did not reduce distant metastases or improve survival.<sup>186</sup> A recent pooled randomized trial (ASTEC/EN.5) suggested that adjuvant pelvic RT alone did not improve either relapse-free survival (ie, PFS) or OS in patients with intermediate-risk or high-risk early-stage endometrial cancer, but there was a small improvement in pelvic control.<sup>187</sup> However, the ASTEC/EN.5 study is very controversial; 51% of the patients in the ASTEC observation group received vaginal brachytherapy.<sup>70,191</sup> The Keys' trial (GOG 99) showed that adjuvant pelvic RT improved locoregional control and relapse-free interval (ie, PFS), without OS benefit.<sup>188</sup> Both the GOG 99 and PORTEC-1 trials revealed that most of the initial recurrences for patients with initial uterine-confined tumors were limited to the vagina, prompting the increasing use of vaginal brachytherapy alone as adjunctive treatment.<sup>188,192,193</sup>

To help select a patient population who may benefit from adjuvant RT, the GOG 99 and PORTEC trials defined risk factors for women at high-intermediate risk (HIR) for recurrence.<sup>185,188</sup> These risk factors include age, in addition to deep myometrial invasion, grade, and LVSI. In GOG 99, women younger than 50 years had to have all 3 histologic risk factors to be considered HIR.<sup>188</sup> If they were 50 to 70 years, they were considered HIR if they had 2 histologic risk factors. Women 70 years or older were defined as HIR if they also had one risk factor. In PORTEC-1, women had to have 2 of 3 risk factors (ie, age >60 years, deep myometrial invasion, grade 3 histology) to be considered at HIR for recurrence.<sup>185,192</sup>

Due to concerns about potential toxicity of external-beam pelvic RT, the role of vaginal brachytherapy alone in uterine-confined disease has been evaluated. PORTEC-2 randomly assigned patients to

external-beam pelvic RT versus vaginal brachytherapy alone in uterine-confined disease. PORTEC-2 showed excellent and equivalent vaginal and pelvic control rates with both adjuvant radiation approaches and no difference in OS.<sup>194</sup> Given that vaginal brachytherapy is associated with significantly less toxicity than pelvic RT, vaginal brachytherapy alone is a reasonable choice for most patients with uterine-confined endometrial cancer who are deemed candidates for adjuvant radiotherapy.<sup>192-201</sup> The use of vaginal brachytherapy and/or whole pelvic RT should be carefully tailored to a patient's pathologic findings. Both PORTEC-1 and PORTEC-2 specifically excluded patients with 1998 FIGO stage 1C and grade 3 endometrial carcinoma (2009 FIGO stage IB, grade 3);<sup>51,53</sup> thus, the use of adjuvant brachytherapy alone in the highest risk subset remains undetermined. A recent trial (GOG 249) examined vaginal cuff brachytherapy followed by carboplatin/paclitaxel therapy versus EBRT only in patients with high-risk, uterine-confined endometrial carcinoma. Preliminary data suggest no significant difference in survival outcomes between the groups, although the brachytherapy/chemotherapy group experienced more acute toxicity.<sup>202</sup>

Analysis of pooled data from PORTEC-1 and PORTEC-2 ranked the predictive power of multiple variables on patient outcomes examined in these trials. Patient age, tumor grade, and LVSI were highly predictive for locoregional relapse (LRR), distant relapse (DR), OS, and disease-free survival (DFS), and treatment given (EBRT versus vaginal brachytherapy) were predictive for LRR and DFS.<sup>175</sup> The benefit of adjuvant EBRT in the highest risk spectrum of uterine-confined disease remains controversial. Most NCCN Panel Members feel that patients with deeply invasive grade 3 tumors should receive adjuvant treatment. Two large retrospective SEER analyses of women with endometrial cancer found that adjuvant RT improved OS in those with high-risk



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disease.<sup>203,204</sup> In a meta-analysis of randomized trials, a subset analysis found that adjuvant pelvic RT for stage I disease was associated with a trend towards a survival advantage in the highest-risk spectrum (eg, those with 1988 FIGO stage IC grade 3) but not in lower risk patients; however, other reviews have shown conflicting results.<sup>196,205-209</sup>

Recently, results were published from a long-term follow-up study (median 20.5 years) of 568 patients with early-stage endometrial carcinoma who were enrolled in the Aalders trial. The study compared long-term outcomes in women who received vaginal brachytherapy plus EBRT versus vaginal brachytherapy alone. The findings suggested no statistical difference in OS between the study groups, and in this cohort, patients younger than 60 years of age who received EBRT had increased incidence of secondary cancers and subsequent higher mortality rates.<sup>196</sup>

### *Adjuvant Systemic Therapy*

Patients with deeply invasive, grade 3, uterine-confined disease (2009 FIGO stage IB, grade 3 [formerly 1988 FIGO stage IC, grade 3]) have a relatively poor prognosis. Despite adjuvant therapy with pelvic RT, a significant number of patients continue to have an appreciable risk of distant metastases.<sup>188,189</sup> Therefore, some clinicians suggested that adding systemic therapy to adjuvant RT may provide added therapeutic benefit (ie, decrease distant metastases).<sup>177,210</sup> Studies have evaluated the role of systemic therapy in highest risk uterine-confined disease.<sup>210,211</sup> PFS is improved with adjuvant sequential chemotherapy/RT.<sup>210</sup> However, the NCCN Panel feels that adjuvant systemic therapy is a category 2B recommendation in this setting because an OS advantage has not been shown.<sup>210</sup> We await final results from GOG 249.

### **Advanced Stage/Extrauterine Disease**

There is a consensus that patients with documented extrauterine disease are at increased risk for recurrence and need adjuvant therapy; however, the optimal form of adjuvant therapy has yet to be determined.<sup>212-214</sup> Patients with extrauterine disease confined to the lymph nodes or the adnexa may be treated with pelvic or extended-field RT alone.<sup>215</sup> However, systemic therapy is regarded as the foundation of adjuvant therapy for patients with extrauterine disease.

For stage IIIA to IIIC disease, the recommended treatment options are systemic therapy and/or EBRT with (or without) vaginal brachytherapy. For stage IVA/IVB disease that is debulked with no gross residual disease or microscopic abdominal disease, systemic therapy forms the mainstay of treatment and can be combined with EBRT and/or vaginal brachytherapy.

Previously, whole abdominal RT was used for carefully selected patients deemed at risk for peritoneal failure, and RT appeared to have provided therapeutic benefit in retrospective studies.<sup>216,217</sup> A randomized phase III GOG (122) trial assessed optimal adjuvant therapy for patients with endometrial cancer who had extrauterine disease. In this trial, patients with stage III and intra-abdominal stage IV disease who had minimal residual disease were randomly assigned to whole abdominopelvic RT versus 7 cycles of combined doxorubicin (60 mg/m<sup>2</sup>) and cisplatin (50 mg/m<sup>2</sup>) treatment, with an additional cycle of cisplatin (AP). This GOG trial reported that AP chemotherapy improved PFS and OS when compared with whole abdominopelvic RT; however, acute toxicity (eg, peripheral neuropathy) was greater in the AP chemotherapy arm.<sup>172</sup>

The GOG 122 study established the role of adjuvant multiagent systemic chemotherapy for curative intent in patients with extrauterine





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disease. Thus, in the NCCN Guidelines, systemic therapy forms the established framework of adjuvant therapy for patients with stage III or IV disease. Whole abdominal RT as a single modality (as used in GOG 122) is considered inferior to chemotherapy and is no longer recommended. For the purposes of these guidelines, whole abdominal radiotherapy is not considered to be tumor-directed RT (see *Principles of Radiation Therapy* in the NCCN Guidelines for Uterine Neoplasms). Multimodality therapy is now the basis of randomized trials evaluating therapy (eg, GOG 258, PORTEC-3).

Recurrences were frequent in both treatment arms of GOG 122, occurring in the pelvis and abdomen. Approximately 52% of patients with advanced endometrial carcinoma had recurrences, indicating the need for further therapeutic improvement in this high-risk patient population.<sup>172</sup> A study found that combined modality adjuvant therapy (using chemotherapy and tumor-directed RT) may provide a therapeutic benefit when compared with other sequencing modalities (chemotherapy followed by RT or vice versa).<sup>174,218,219</sup>

A follow-up study evaluated the role of chemotherapy “intensification” for this patient population. The GOG 184 trial assessed combination chemotherapy (cisplatin and doxorubicin with [or without] paclitaxel) with more limited radiation fields (involved-field radiation either to the pelvis or to the pelvis plus para-aortic nodes). Results indicate that the 3-drug regimen did not improve survival when compared with the 2-drug regimen after 3 years of follow-up and that the more intensive chemotherapy resulted in greater toxicity (eg, hematologic toxicity, sensory neuropathy, myalgia).<sup>173</sup>

Adjuvant therapy options were compared in a multicenter retrospective analysis of 265 patients with optimally resected stage IIIC endometrial carcinoma. Compared with patients receiving adjuvant RT or adjuvant

RT plus chemotherapy, patients who received adjuvant chemotherapy had a 2.2 fold increased risk of recurrence and a 4.0 fold increased risk of death.<sup>214</sup> In a retrospective review of 116 patients with stage IIIC endometrial cancer, adjuvant RT significantly improved OS in patients with endometrioid histology, high-grade tumors, and positive para-aortic lymph nodes. Conversely, patients with low-grade tumors and non-endometrioid histology that received RT had similar OS compared with those who did not.<sup>220</sup> In a multicenter retrospective review of 73 patients with stage IIIA endometrial carcinoma, surgery followed by both chemotherapy and radiation therapy provided the highest 5-year OS.<sup>221</sup> A prospective study of 122 patients with fully resected locally advanced disease suggested a potential benefit of adjuvant chemoradiation followed by chemotherapy, with an estimated 5-year PFS and OS of 73% and 84%.<sup>222</sup> The role of adjuvant RT with systemic therapy for treating high-risk endometrial carcinoma remains an area of active investigation (eg, GOG 258, PORTEC-3).

### Radiotherapy Principles

RT has been a widely used modality in the treatment of patients with endometrial cancer; it clearly improves locoregional control.

*Tumor-directed RT* refers to RT directed at sites of known or suspected tumor involvement and may include EBRT and/or vaginal brachytherapy.<sup>178</sup> RT is described in detail in the algorithm, including target areas and doses for pelvic RT and brachytherapy (see *Principles of Radiation Therapy* in the NCCN Guidelines for Uterine Neoplasms).

Although adjuvant RT is typically not associated with high rates of severe morbidity,<sup>223</sup> studies have focused on subtle effects on quality of life (eg, diarrhea, bowel symptoms) that deserve further investigation.<sup>197,199,224</sup> In the PORTEC-2 trial, vaginal brachytherapy was associated with better quality of life when compared with EBRT without



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a significant detriment to outcome.<sup>197</sup> Therefore, many patients who were previously treated with adjuvant EBRT are now appropriately treated with vaginal brachytherapy; this recommendation is reflected in the NCCN Guidelines. Patients treated with RT are prone to vaginal stenosis, which can impair sexual function. Women can use vaginal dilators to prevent or treat vaginal stenosis. Dilator use can start 2 to 4 weeks after RT is completed and can be used indefinitely (<http://www.mskcc.org/cancer-care/patient-education/resources/improving-your-vaginal-health-after-radiation-therapy>).

### Post-Treatment Surveillance

The recommended post-treatment surveillance protocol for endometrial cancer is shown in the algorithm (see *Surveillance* in the NCCN Guidelines for Endometrial Carcinoma).<sup>33</sup> These recommendations recognize that the value of intensive surveillance has not been demonstrated in this disease; therefore, ancillary testing is not recommended.<sup>225,226</sup>

Patients with clinical stage I and stage II endometrial cancer have a recurrence rate of approximately 15%;<sup>24,226-228</sup> 50% to 70% of these patients are symptomatic. For most patients, disease recurs within 3 years of initial treatment. Because most recurrences are symptomatic, all patients should receive verbal and written information regarding the symptoms of recurrent disease.<sup>226</sup> Patients with bleeding (vaginal, bladder, or rectal), decreased appetite, weight loss, pain (in the pelvis, abdomen, hip, or back), cough, shortness of breath, and swelling (in the abdomen or legs) should seek prompt evaluation and not delay until the next scheduled appointment. As clinically indicated, imaging may be helpful in the detection of recurrence.

In the absence of recurrence, post-treatment surveillance provides psychosocial reassurance and improves quality of life for patients and their families. Health maintenance has been incorporated into the follow-up schedule (eg, blood pressure determination, breast examination, mammography as clinically indicated, stool guaiac test, immunizations). Patients should receive counseling and education regarding lifestyle, obesity, exercise, smoking cessation, sexual health, nutrition, and potential late or long-term effects of treatment (see the NCCN Guidelines for Survivorship, the NCCN Guidelines for Smoking Cessation, and <http://www.cancer.org/treatment/survivorshipduringandaftertreatment/index>).<sup>224,229-231</sup> Other health problems that often coexist in patients with endometrial cancer can also be evaluated during follow-up.

Given the lack of prospective studies regarding the optimal frequency of post-treatment follow-up, the NCCN Panel believes that the algorithm represents a reasonable surveillance scheme. The use of vaginal cytology is no longer recommended for asymptomatic patients consistent with the SGO guidelines.<sup>225,226,228,232</sup> Patients with stage I endometrial cancer have a low risk of asymptomatic vaginal recurrence (2.6%), especially after adjuvant brachytherapy, and vaginal cytology is not independently useful for detecting recurrences in this group of patients.<sup>233</sup> A recent multi-institutional review examined the utility of various surveillance methods in 254 patients with high-grade disease, revealing that symptoms led to the detection of the most recurrences (56%), followed by physical exam (18%), surveillance CT (15%), CA 125 (10%), and vaginal cytology (1%).<sup>234</sup>

### Hormone Replacement Therapy for Hypoestrogenism

After BSO, hypoestrogenism is associated with hot flashes, mood lability, vaginal dryness, pelvic soft tissue atrophy, osteoporosis, and an



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increased risk of cardiovascular disease. In postmenopausal women, estrogen replacement therapy was believed to reduce or reverse some of these signs and symptoms. However, women who have had BSO for endometrial adenocarcinoma have usually been denied estrogen replacement therapy for fear of inducing a higher relapse rate, because this cancer has historically been considered an estrogen-linked malignancy.<sup>235,236</sup> As such, estrogen replacement therapy for such patients remains controversial.

However, it has never been proven that relapse rates are higher in endometrial cancer patients who receive estrogen replacement therapy after hysterectomy. Several retrospective trials of estrogen replacement after treatment of early-stage endometrial cancer have shown no increase in tumor recurrence or cancer-related deaths.<sup>237-239</sup> In women with stage I to II endometrial cancer who had hysterectomy, a randomized trial of estrogen replacement therapy versus placebo did not find an increased rate of recurrence or new malignancy; the median follow-up was 35.7 months.<sup>240</sup> However, estrogen replacement trials in postmenopausal females without a history of malignancy have demonstrated a significantly increased risk of breast cancer.<sup>241</sup>

Initially, the Women's Health Initiative (WHI) Estrogen-Alone Trial in women who had hysterectomy (n = 10,739) reported that the risk of breast cancer and cardiovascular disease (eg, stroke) were increased and that estrogen replacement therapy was of concern; thus, the trial was stopped.<sup>242</sup> However, recent long-term follow-up data from this trial suggest that the risk from estrogen-alone replacement therapy (without progesterone) may not be as high in younger women (<60 years) who have had hysterectomy.<sup>243</sup>

The NCCN Panel agrees that estrogen replacement therapy is a reasonable option for patients who are at low risk for tumor recurrence,

but initiating such therapy should be individualized and discussed in detail with the patient.<sup>244,245</sup> If adjuvant treatment is carried out, there should be a 6- to 12-month waiting period before initiation of hormone replacement therapy, and participation in clinical trials is strongly encouraged. Selective estrogen-receptor modulators (SERMs) may prove to be attractive options for hormone replacement therapy.<sup>246,247</sup> Long-term comparisons between conjugated estrogens and SERMs for hormone replacement therapy are needed. Non-hormonal therapy may be considered in patients who are deemed poor candidates for hormone replacement therapy (eg, smokers, history of breast cancer, history of multiple strokes).<sup>248,249</sup>

### Treatment of Recurrent or Metastatic Disease

#### **Localized Disease**

Patients with local or regional recurrences can be evaluated for further treatment (see *Clinical Presentation* in the NCCN Guidelines for Endometrial Carcinoma). For recurrences confined to the vagina or the pelvis alone, second-line treatment (typically with RT and/or surgery or systemic therapy) can be effective. For patients with no prior RT exposure at the recurrence site or previous brachytherapy only, the panel recommends RT plus brachytherapy, or surgery. Isolated vaginal recurrences treated with RT have good local control and 5-year survival rates of 50% to 70%.<sup>250-252</sup> Prognosis is worse if there is extravaginal extension or pelvic lymph node involvement.<sup>251</sup>

After RT, it is unusual for patients to have recurrences confined to the pelvis. The management of such patients remains controversial. For patients previously treated with EBRT at the recurrence site, recommended therapy for isolated relapse includes: 1) surgery with (or without) intraoperative RT (IORT) (category 3 for IORT); 2) hormonal therapy; or 3) systemic therapy. In selected patients, radical surgery (ie,



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pelvic exenteration) has been performed with reported 5-year survival rates approximating 20%.<sup>253-256</sup>

Treatment for para-aortic or common iliac lymph node invasion and for upper abdominal or peritoneal recurrences is shown in the algorithm (see *Additional Therapy* in the NCCN Guidelines for Endometrial Carcinoma). However, for gross upper abdominal residual disease, more aggressive treatment for relapse is recommended, as outlined for disseminated metastases in *Therapy for Relapse* in the NCCN Guidelines for Endometrial Carcinoma. For resectable isolated metastases, consider surgical resection with or without RT or ablative therapy. Providers can also consider hormone therapy (category 2B) or systemic therapy (category 3). Further recurrences or disease not amenable to local therapy are treated as disseminated metastases. Palliative care measures should also be considered in management of patients with systemic disease (see the NCCN Guidelines for Palliative Care and <http://emedicine.medscape.com/article/270646-overview>).

### Systemic Disease

For patients with low-grade, asymptomatic, and hormone receptor–positive disseminated metastases, options include hormone therapy followed by systemic therapy on progression. Symptomatic, higher grade, or large volume metastases can be treated with systemic therapy with (or without) palliative RT. For persistent progression of disseminated metastases, best supportive care or enrollment in a clinical trial is recommended.

### Hormonal Therapy

The role of hormonal therapy in recurrent or metastatic cancer has been primarily evaluated in patients with endometrioid histologies only. Hormone therapy should only be considered for lower grade endometrioid histologies (ie, not for patients with grade 3 endometrioid,

serous, or clear cell carcinomas, or carcinosarcoma), and in patients with small tumor volume or indolent growth rate. Hormonal therapy is also used for selected patients with ESS (see section on *Uterine Sarcomas* in this Discussion). Hormonal agents for treating metastatic disease include megestrol with alternating tamoxifen, progestational agents alone, aromatase inhibitors, or tamoxifen alone.<sup>163-165,257-259</sup> No particular drug, dose, or schedule has been found to be superior. The main predictors of response in the treatment of metastatic disease are well-differentiated tumors, expression of ER/PR receptors, a long disease-free interval, and the location and extent of extrapelvic (particularly pulmonary) metastases.

For asymptomatic or low-grade disseminated metastases, hormonal therapy with progestational agents has shown good responses, particularly in patients with ER/PR-positive disease.<sup>167,260-262</sup> Tamoxifen has a 20% response rate in those who do not respond to standard progesterone therapy.<sup>263,264</sup> Tamoxifen has also been combined with progestational agents; however, a few patients had grade 4 thromboembolic events with this combination regimen.<sup>163,257,265</sup> In some patients, aromatase inhibitors (eg, anastrozole, letrozole) may be substituted for progestational agents or tamoxifen.<sup>166,167,262,266</sup>

Other hormonal modalities have not been well studied, and adjuvant therapy with hormonal agents has not been compared with cytotoxic agents.<sup>167,267</sup> If disease progression is observed after hormonal therapy, cytotoxic chemotherapy can be considered. However, clinical trials or best supportive care (see the NCCN Guidelines for Palliative Care) are appropriate for patients with disseminated metastatic recurrence who have a poor response to hormonal therapy and chemotherapy.





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### Systemic Therapy

Chemotherapy for endometrial cancer has been extensively studied.<sup>268,269</sup> Based on the current data, multiagent chemotherapy regimens are preferred for metastatic, recurrent, or high-risk disease, if tolerated. Single-agent therapy can also be used (see *Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease* in the NCCN Guidelines for Endometrial Carcinoma).

A phase III randomized trial (GOG 177) compared 2 combination chemotherapy regimens in women with advanced/metastatic or recurrent endometrial carcinoma. The 273 women were randomly assigned to 1) cisplatin, doxorubicin, and paclitaxel; or 2) cisplatin and doxorubicin. The 3-drug regimen was associated with improved survival (15 vs. 12 months,  $P < .04$ ) but with significantly increased toxicity (ie, peripheral neuropathy); therefore, it is not widely used.<sup>270,271</sup> These regimens are now category 2A in the NCCN Guidelines, because most panel members feel that carboplatin/paclitaxel is a less toxic regimen (see *Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease* in the NCCN Guidelines for Endometrial Carcinoma). The response rates with other multiagent chemotherapy have ranged from 31% to 81% but with relatively short durations. The median survival for patients in such trials remains approximately 1 year.<sup>268,269</sup>

Carboplatin and paclitaxel is an increasingly used regimen for advanced/metastatic or recurrent endometrial cancer; the response rate is about 40% to 62%, and OS is about 13 to 29 months.<sup>272-275</sup> A phase III trial (GOG 209) compared carboplatin and paclitaxel versus cisplatin, doxorubicin, paclitaxel, and filgrastim (granulocyte-colony stimulating factor).<sup>272</sup> Trial data presented at a national meeting show that oncologic outcomes are similar, but the toxicity and tolerability profile favor carboplatin/paclitaxel. Thus, the carboplatin/paclitaxel regimen is now the preferred approach for many patients. For patients in whom

paclitaxel is contraindicated, docetaxel can be considered in combination with carboplatin.<sup>276</sup>

If multiagent chemotherapy regimens are contraindicated, then single-agent therapy options include paclitaxel, cisplatin, carboplatin, doxorubicin, liposomal doxorubicin, topotecan, and docetaxel (category 2B for docetaxel) (see *Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease* in the NCCN Guidelines for Endometrial Carcinoma).<sup>167,277-279</sup> When single agents are used as first-line treatment, responses range from 21% to 36%.<sup>262,280</sup> When single agents are used as second-line treatment, responses range from 4% to 27%; paclitaxel is the most active in this setting.<sup>280</sup> Some oncologists have used liposomal doxorubicin, because it is less toxic than doxorubicin; the response rate of liposomal doxorubicin is 9.5%.<sup>281</sup> Docetaxel is recommended for use as a single agent; however, it is a category 2B recommendation because some panel members would not use docetaxel because it is less active (7.7% response rate) than other agents.<sup>162,282</sup>

New biologic and molecular therapies for the treatment of recurrent or metastatic endometrial carcinoma are being assessed in clinical trials.<sup>162,283</sup> Bevacizumab was shown to have a 13.5% response rate and OS rate of 10.5 months in a phase II trial for persistent or recurrent endometrial cancer.<sup>284</sup> Temsirolimus has been used as first-line or second-line therapy for recurrent or metastatic endometrial cancer and has a partial response rate of 4% in second-line therapy.<sup>285</sup> Based on these studies, the NCCN Panel considers bevacizumab or temsirolimus as appropriate single-agent biologic therapy for patients who have progressed on previous cytotoxic chemotherapy.<sup>283-286</sup> Everolimus combined with letrozole is also under investigation for recurrent disease with positive preliminary findings.<sup>287</sup>



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### Uterine Serous Carcinomas, Clear Cell Carcinomas, and Carcinosarcomas

#### Overview

Uterine serous carcinomas, clear cell carcinomas, and carcinosarcomas are considered more aggressive histologic variants of malignant epithelial tumors, with a higher incidence of extrauterine disease at presentation.<sup>288-295</sup> Carcinosarcomas are aggressive tumors that are staged as high-grade endometrial cancer (see Table 1).<sup>296,297</sup> Serous carcinomas, clear cell carcinomas, and carcinosarcomas are all considered high-risk histologies and high-grade by default, although they are staged using the same FIGO/AJCC staging system (ie, 7<sup>th</sup> edition) as endometrial cancers (see Table 1).<sup>51</sup>

Pathologists now believe that carcinosarcomas (also known as MMMTs) are metaplastic carcinomas and not uterine sarcomas; therefore, carcinosarcomas are included in the high-risk malignant epithelial tumors section of the NCCN Guidelines (see *Serous Carcinoma, Clear Cell Carcinoma, or Carcinosarcoma* in the NCCN Guidelines for Endometrial Carcinoma).<sup>292,295,298,299</sup> Even patients with apparent early-stage disease may have distant metastases. Thus, fertility-sparing therapy is not recommended for these aggressive tumors. If done, SLN mapping should proceed with particular caution.

Patients with uterine serous carcinoma, clear cell carcinoma, or carcinosarcoma may present with pelvic masses, abnormal cervical cytology, or ascites in addition to postmenopausal bleeding. Both the NCCN Panel and the SGO recommend that CA 125 and MRI or chest/abdominal/pelvic CT may be useful before surgery to assess if extrauterine disease is present; PET may also be useful.<sup>288</sup> Patterns of failure often mimic those of ovarian cancer.

#### Treatment

Multimodality therapy is typically recommended for these histologically aggressive tumors. Primary treatment includes TH/BSO with surgical staging, peritoneal lavage for cytology, omental and peritoneal biopsies, and consideration of maximal tumor debulking for gross disease (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).<sup>300</sup>

Adjuvant therapy is highly individualized.<sup>301-308</sup> For patients with stage IA without myometrial invasion, options include: 1) observation (if no residual disease in hysterectomy specimen); 2) systemic therapy with (or without) vaginal brachytherapy; or 3) EBRT with (or without) brachytherapy.<sup>309,310</sup> For all other patients with more advanced disease, systemic therapy with (or without) tumor-directed RT is the preferred option.<sup>290,302,306,311</sup> Adjuvant platinum/taxane-based therapy appears to improve survival in patients with uterine serous carcinoma and clear cell carcinoma, whereas ifosfamide/paclitaxel (category 1) is recommended for carcinosarcomas (see *Uterine Serous Carcinomas, Clear Cell Carcinomas, and Carcinosarcomas* in this Discussion and *Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease* in the NCCN Guidelines for Endometrial Carcinoma).<sup>288-290,312-314</sup>

Whole abdominopelvic RT with (or without) vaginal brachytherapy is no longer recommended as a primary treatment option for patients with advanced disease, because the NCCN Panel no longer feels that routine use of whole abdominal RT is appropriate.<sup>172,311,315</sup> Chemotherapy with (or without) RT appears to be more effective than RT alone.<sup>302</sup> Data are conflicting regarding the rate of abdominal recurrence in these patients.<sup>311,316-320</sup> Whole abdominal radiotherapy is not considered to be tumor-directed RT (see *Principles of Radiation Therapy* in the NCCN Guidelines for Uterine Neoplasms). As previously

mentioned, *tumor-directed RT* refers to RT directed at sites of known or suspected tumor involvement and may include EBRT with (or without) vaginal brachytherapy. In general, tumor-directed EBRT is directed to the pelvis with (or without) the para-aortic region.

Several studies have examined treatment paradigms for uterine serous or clear cell carcinoma. A recent phase II trial in patients with papillary serous carcinoma suggested favorable outcomes with concurrent pelvic RT and paclitaxel followed by additional rounds of adjuvant paclitaxel,<sup>321</sup> indicating the potential benefits of combined modality therapy.

Retrospective data were reviewed from 279 patients with serous or clear cell carcinoma who were treated at high-volume cancer centers. Adjuvant treatment (RT, systemic therapy, or chemoradiation) was associated with improved OS in stages IB-II disease but not stage IA disease (HR, 0.14; 95% CI, 0.02–0.78;  $P = .026$ ) disease.<sup>322</sup> Additionally, survival outcomes did not differ based upon surgical approach (robotic laparoscopy versus laparotomy).

Two multi-institutional retrospective reviews examined the impact of adjuvant therapy (vaginal brachytherapy,  $n = 103$ ; adjuvant pelvic radiation or chemotherapy,  $n = 115$ ) in patients with stage 1A uterine papillary serous carcinoma. In both cohorts, patients undergoing surgical staging/lymphadenectomy had greater PFS and OS than unstaged patients.<sup>323,324</sup> Vaginal brachytherapy reduced the vaginal recurrence rate but did not impact PFS or OS.<sup>323</sup> In unstaged patients, chemotherapy or pelvic RT were associated with greater PFS and OS, but no survival benefits were observed for adjuvant treatment in surgically staged patients.<sup>324</sup>

For treating carcinosarcoma, ifosfamide was historically considered the most active single agent.<sup>313,325,326</sup> A phase III trial for advanced carcinosarcoma showed that the combination of ifosfamide and

paclitaxel increased survival and was less toxic than the previously used cisplatin/ifosfamide regimen.<sup>313,327</sup> OS was 13.5 months with ifosfamide/paclitaxel versus 8.4 months with ifosfamide alone. Therefore, ifosfamide/paclitaxel is a category 1 recommendation in the NCCN Guidelines (see *Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease* in the NCCN Guidelines for Endometrial Carcinoma).<sup>313,315</sup> However, the toxicity of ifosfamide has led to investigation of better-tolerated regimens. A phase II trial suggests that paclitaxel/carboplatin is also a useful regimen for carcinosarcoma (response rate, 54%).<sup>328</sup> A GOG trial is currently assessing ifosfamide/paclitaxel versus carboplatin/paclitaxel.<sup>296</sup>

Data regarding carcinosarcoma suggest that adjuvant pelvic radiotherapy decreases the rate of local recurrences when compared with surgery alone.<sup>329-334</sup> This local control improvement in some series correlates with an improvement in survival, although other data show that lymphadenectomy confers greater benefit.<sup>333-336</sup> A phase III randomized trial (GOG 150) in patients with carcinosarcoma of the uterus showed a trend towards a decreased mortality rate for patients receiving cisplatin/ifosfamide vs. whole-abdominal RT ( $P = .085$ ), although these did not reach statistical significance in this underpowered trial.<sup>315,320</sup> A recent cohort study in women with early-stage MMMT suggests that postoperative chemotherapy improves PFS compared to RT or observation.<sup>296</sup>

## Uterine Sarcomas

### Overview

In 2017, an estimated 4910 cases of uterine sarcomas are anticipated.<sup>337</sup> Uterine sarcomas are malignant mesenchymal tumors that include ESS, UUS, and uLMS (see *Uterine Sarcoma Classification* in the NCCN Guidelines for Uterine Sarcoma). According to 2012





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systematic review of data from 1970 to 2011, uLMS was the most common subtype (63%), followed by ESS (21%) and less common subtypes such as UUS.<sup>338</sup> Even rarer subtypes of malignant mesenchymal tumors that can occur in the uterus include adenosarcoma, rhabdomyosarcoma (RMS), and perivascular epithelioid cell neoplasm (PEComa).<sup>339</sup> Carcinosarcomas were previously categorized and included in the sarcoma treatment algorithms until the mid-2000s, but are now considered and treated as high-grade epithelial tumors (carcinomas).<sup>292</sup> Screening for Lynch syndrome is not usually done for patients with malignant mesenchymal tumors.

ESSs are composed of cells resembling the endometrial stroma in the proliferative phase.<sup>339,340</sup> ESS displays a heterogenous mix of morphologic and genetic features. A significant proportion of these tumors (ie, up to half) harbor a *JAZF1-SUZ12* (formerly *JAZF1-JJAZ1*) gene fusion and present as lower grade, earlier stage tumors.<sup>341-344</sup> More recently, a higher-grade and more aggressively behaving ESS variant with a unique genetic rearrangement *YWHAЕ-FAM22A/B*, also known as *YWHAЕ-NUTM2A/B*, was identified.<sup>345,346</sup> These findings provided support for subdividing ESS into distinct low- and high-grade entities based on histopathology, clinical behavior, and patient outcomes. In light of new information, the World Health Organization (WHO) released an updated (4<sup>th</sup>) edition of the *WHO Classification of Tumours of Female Reproductive Organs*. The updated 2014 edition recognizes low-grade ESS and high-grade ESS as distinct histopathologic entities.<sup>347</sup>

Recent advances have expanded our understanding of the molecular features of these tumors, leading to the identification of genetic signatures that characterize some of the uterine sarcoma subtypes. At present, mesenchymal tumors are primarily diagnosed using histopathologic criteria, and the results of molecular studies are not

used in routine pathologic evaluation. However, molecular analysis (eg, identification of characteristic translocations) can help classify difficult cases and provide future therapeutic targets.

### Staging and Treatment

When evaluating suspected uterine sarcomas, biopsy may be helpful but is less sensitive than for endometrial cancers. The diagnosis of ESS and uLMS is often made after hysterectomy. The previous FIGO/AJCC staging systems for endometrial cancer were not appropriate for staging ESS and uLMS; patients were often upstaged when using the older AJCC staging system.<sup>348</sup> A new staging system for ESS and uLMS from FIGO/AJCC took effect in 2009 (see Table 2).<sup>51,349</sup> This updated staging system accounts for the differences between uterine sarcomas and endometrial cancers.

Confirmation of the type of mesenchymal malignancy by expert pathology review is critical. In addition, initial evaluation should include imaging of the chest/abdomen/pelvic by CT or combination MRI/CT. It is important to determine if the sarcoma is confined to the uterus or if extrauterine disease is present. Pelvic MRI can be used to evaluate local tumor extension or residual abnormality in cases where the uterus or adnexa were not resected or incompletely resected (ie, supracervical hysterectomy, myomectomy, possible tumor fragmentation, intraperitoneal morcellation). Whole-body PET/CT may be used to clarify ambiguous findings. If medically operable, then hysterectomy with (or without) BSO is the initial treatment of choice for uterine sarcomas (see *Primary Treatment* in the NCCN Guidelines for Uterine Sarcoma).<sup>350</sup>

Determining the ER/PR status on the primary tumor may also help in decision making for management of the ovaries particularly in young

premenopausal patients. In general, BSO is recommended for low-grade ESS or tumors expressing ER.

Uterine sarcoma should be removed en bloc to optimize outcomes; intraperitoneal morcellation is contraindicated.<sup>136-139</sup> For incidental diagnoses of uterine sarcoma after hysterectomy, or in the case of a fragmented specimen, imaging is recommended and re-exploration can be considered. The ovaries may be preserved in selected patients with early-stage uLMS who wish to retain hormonal function.<sup>351</sup> Additional surgical resection should be individualized based on clinical scenarios and intraoperative findings. Lymphadenectomy is controversial.<sup>2,339,351-354</sup> High-grade uterine sarcomas tend to show hematogenous metastases to the lungs; lymph node metastases are uncommon.

For medically inoperable sarcomas, options include: pelvic EBRT with (or without) brachytherapy and/or systemic therapy.

### **Low-Grade Endometrial Stromal Sarcoma**

If there is no evidence of disease after primary surgery (TH/BSO) for ESS, then observation can be considered (see *Additional Therapy* in the NCCN Guidelines for Uterine Sarcoma).<sup>352,353</sup> Observation (if menopause or prior BSO) or estrogen blockade (category 2B) is recommended for stage I ESS. Postoperative hormone therapy (estrogen blockade) is recommended for stages II to IV ESS. Adjuvant EBRT may be added for stage II-IVA (category 2B); palliative RT may be added for stage IVB.<sup>339,355,356</sup> Typical hormone therapy includes megestrol, medroxyprogesterone, or aromatase inhibitors; gonadotropin-releasing hormone [GnRH] analogs (category 2B) are also an option.<sup>339,351,357</sup> In 2014, tamoxifen was deleted from the NCCN Guidelines for ESS because it is contraindicated in women diagnosed with ESS or ER/PR-positive uLMS.<sup>351,356-358</sup> Hormone therapy is also

recommended for ESSs that have recurred or are unresectable (see *Therapy for Relapse* in the NCCN Guidelines for Uterine Sarcoma).<sup>357</sup>

Case series of patients with ESS suggest long disease-free intervals in the absence of specific therapy and raise questions about the use of adjuvant RT.<sup>359</sup> Adjuvant radiotherapy in ESS has been demonstrated to reduce local recurrence rates but again with limited effect on survival.<sup>360,361</sup> Because of concerns about radiation exposure, frequent routine surveillance imaging is no longer recommended for asymptomatic young women after primary therapy for ESS.<sup>362</sup>

Although hormone therapy is recommended for low-grade ESS, studies have not yet determined the optimal therapeutic approach for high-grade ESS. However, due to the more aggressive nature of these tumors (eg, those with YWHA-E-FAM22 rearrangements), the NCCN panel has recommended that high-grade ESS be treated according to the algorithms in place for uLMS and UUS.

### **High-Grade Endometrial Stromal Sarcoma, Leiomyosarcoma, and Undifferentiated Uterine Sarcoma**

The role of adjuvant radiotherapy in nonmetastatic disease is controversial. Most available data are retrospective except for a phase III randomized trial.<sup>329</sup> Most retrospective studies of adjuvant RT suggest an improvement in local pelvic control but no appreciable or consistent improvement in OS, given the propensity of metastatic extrapelvic disease as a site of first or eventual recurrence.<sup>363-366</sup> In many series, the patients treated with adjuvant radiation presumably had higher-risk factors (eg, larger tumors, deeper myometrial invasion), thus biasing the data against radiotherapy. However, a phase III randomized trial in stage I and II uterine sarcomas reported that postoperative pelvic radiotherapy did not improve OS for uLMS when compared with observation.<sup>329</sup> Therefore, routine postoperative RT is



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not recommended for stage I patients with uLMS and high-grade (undifferentiated) endometrial sarcoma.<sup>355</sup> If used in more advanced stages, adjuvant RT needs to be individualized and based on careful analysis of surgical pathologic findings.

The role of adjuvant systemic therapy is also poorly defined; however, adjuvant systemic therapy has been used because of the high risk of systemic relapse. Given the uncertainties regarding any adjuvant treatment for stage I uLMS and high-grade (undifferentiated) endometrial sarcoma, after complete resection options include: 1) observation; or 2) systemic therapy (category 2B), or 3) estrogen blockade if ER positive may be considered. Because of the increased risk profile in patients with completely resected stage II and III uLMS and high-grade (undifferentiated) endometrial sarcoma, the panel believes that it is appropriate to consider adjuvant systemic therapy and/or EBRT (see *Additional Therapy* in the NCCN Guidelines for Uterine Sarcoma).<sup>367</sup> In patients with incompletely resected or metastatic disease, systemic therapy with (or without) palliative EBRT is generally recommended.

An ongoing phase III randomized trial (GOG 277) is assessing the role of postoperative adjuvant chemotherapy (ie, gemcitabine/docetaxel followed by doxorubicin) versus observation in patients with high-grade stage I and II uLMS.<sup>368</sup>

If systemic therapy is used, gemcitabine/docetaxel (preferred for uLMS) is recommended for uterine sarcoma (see *Systemic Therapy* in the NCCN Guidelines for Uterine Sarcoma).<sup>340,369-373</sup> Other combination regimens include doxorubicin/ifosfamide, doxorubicin/dacarbazine, doxorubicin/olatumab, gemcitabine/dacarbazine, and gemcitabine/vinorelbine.<sup>326,374-377</sup>

Doxorubicin is an active single agent for uLMS and is less toxic than combination regimens.<sup>339,378</sup> Other single-agent options (category 2A unless otherwise noted) can also be considered for advanced or metastatic disease including dacarbazine, doxorubicin, epirubicin, gemcitabine, ifosfamide, liposomal doxorubicin, pazopanib, temozolomide, vinorelbine (category 2B), and docetaxel (category 3).<sup>339,340,369,374,375,379-395</sup> Aromatase inhibitors can be considered for ER/PR-expressing uLMS.<sup>396</sup>

In 2014, dacarbazine was changed to a category 2A recommendation (from a category 2B) because dacarbazine has been used as the standard arm in several phase II trials.<sup>374</sup>

In 2016, trabectedin and eribulin were both included in the guidelines. Data indicate that trabectedin may be useful in patients who have exhausted standard chemotherapy.<sup>397-400</sup> Recent phase III data revealed a 2.7-month PFS benefit versus dacarbazine in metastatic liposarcoma or leiomyosarcoma that progressed after anthracycline-based therapy; the study is ongoing to determine OS.<sup>401</sup> Following its October 2015 FDA approval, trabectedin was added to the guidelines as an option for unresectable or metastatic uLMS previously treated with an anthracycline-containing regimen. Eribulin was included based on results from a phase III trial comparing the survival benefit of eribulin and dacarbazine in 452 patients with advanced leiomyosarcoma or adipocytic sarcoma.<sup>402</sup> Median OS was 13.5 and 11.5 months for eribulin and dacarbazine, respectively (HR, 0.77; 95% CI, 0.62–0.95;  $P = .017$ ). Eribulin was designated as category 2B upon panel review of the mature trial data.

In 2017, the panel included combination therapy with doxorubicin and olatumab for use in uterine sarcoma. Olatumab blocks platelet-derived growth factor receptor alpha (*PDGFRA*). Phase II data



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from 133 patients with anthracycline-naïve, unresectable, or advanced/metastatic STS showed improved survival for olaratumab plus doxorubicin versus doxorubicin alone. When comparing olaratumab plus doxorubicin versus doxorubicin alone, median PFS was 6.6 months versus 4.1 months, respectively ( $P = .0615$ ). Median OS was 26.5 months versus 14.7 months, respectively ( $P = .0003$ ).<sup>377</sup>

### Post-Treatment Surveillance

The recommended post-treatment surveillance protocol for uterine sarcoma is depicted in the algorithm (see *Surveillance* in the NCCN Guidelines for Uterine Sarcoma). Imaging surveillance should include chest/abdominal/pelvic CT biannually for the first 3 years and then every 6 to 12 months for the next 2 years. Depending on histology, grade, and initial stage, annual to bi-annual imaging can be considered for an additional 5 years. Abdominal/pelvic MRI and chest CT can also be considered, with PET/CT or other imaging as needed to clarify findings or upon clinical concern for metastasis.

Patients should receive education regarding the symptoms of recurrent disease. Patients with bleeding (vaginal, bladder, or rectal), decreased appetite, weight loss, pain (in the pelvis, abdomen, hip, or back), cough, shortness of breath, and swelling (in the abdomen or legs) should seek prompt evaluation and not delay until the next scheduled appointment. As clinically indicated, imaging may be helpful in the detection of recurrence. Patients should be educated regarding healthy lifestyle, obesity, exercise, smoking cessation, nutrition, and potential long-term and late effects of treatment (see the NCCN Guidelines for Survivorship, NCCN Guidelines for Smoking Cessation, and <http://www.cancer.org/treatment/survivorshipduringandaftertreatment/in dex>).<sup>229-231</sup> The panel also recommends patient education regarding sexual health, vaginal dilator use, and vaginal lubricants or moisturizers.

### Treatment of Recurrent or Metastatic Disease

The recurrence rate is high in uLMS (50%–70%).<sup>2</sup> The guidelines provide recommendations based on tumor resectability and patients' prior RT exposure (see *Therapy for Relapse* in the NCCN Guidelines for Uterine Sarcoma). For treating local recurrence in patients without prior RT exposure, options include surgery with the option of IORT (category 3 for IORT) or EBRT ± vaginal brachytherapy, with (or without) systemic therapy. Hormone therapy is an option for patients with ESS. Preoperative EBRT can be considered. If surgery is performed, adjuvant EBRT with (or without) brachytherapy can be considered. Patients with local recurrence who have had prior RT exposure can be treated with: 1) surgery with the option of IORT and/or systemic therapy (category 3 for IORT); 2) systemic therapy; or 3) selected reirradiation with EBRT and/or brachytherapy. A recent retrospective analysis of patients with ESS suggested that cytoreductive resection improved OS in patients with recurrent lesions.<sup>403</sup> Systemic therapy with (or without) palliative EBRT or supportive care is recommended for metastatic disease.<sup>378</sup> For patients with isolated metastases, surgical resection or other ablative therapy (eg, radiofrequency ablation, stereotactic body RT) may be appropriate. Postoperative EBRT and/or systemic therapy can be considered. Systemic therapy and/or local therapy (tumor-directed EBRT or local ablative therapy) are reasonable options for patients with unresectable isolated metastases (see *Therapy for Relapse* in the NCCN Guidelines for Uterine Sarcoma).<sup>391,404-406</sup>

### Drug Reactions

Virtually all drugs have the potential to cause adverse hypersensitivity reactions, either during or after the infusion.<sup>407</sup> In gynecologic oncology treatment, drugs that more commonly cause adverse reactions include carboplatin, cisplatin, docetaxel, liposomal doxorubicin, and paclitaxel. Most of these drug reactions are mild infusion reactions (ie, skin



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reactions, cardiovascular reactions, respiratory or throat tightness), but more severe allergic reactions (ie, life-threatening anaphylaxis) can occur.<sup>408-410</sup> In addition, patients can have mild allergic reactions or severe infusion reactions. Infusion reactions are more common with paclitaxel.<sup>411</sup> Allergic reactions (ie, true drug allergies) are more common with platinum agents (ie, carboplatin, cisplatin).<sup>411,412</sup>

Management of drug reactions is discussed in the NCCN Guidelines for Ovarian Cancer.<sup>411</sup> It is important to note that patients who have had severe life-threatening reactions should not receive the implicated agent again unless under the care of an allergist or expert in managing drug reactions. If a mild allergic reaction has previously occurred and it is appropriate to administer the drug again, a desensitization regimen should be used even if the symptoms have resolved; various desensitization regimens have been published and should be followed.<sup>413-415</sup> Patients must be desensitized with each infusion if they previously had a reaction. Almost all patients can be desensitized (about 90%).<sup>407</sup> To maximize safety, it is prudent to desensitize patients in the intensive care unit.<sup>407</sup>





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