

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Uterine Neoplasms

Version 1.2017 — November 21, 2016

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NCCN Guidelines Version 1.2017 Panel Members

Uterine Neoplasms

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*Wui-Jin Koh, MD/Co-Chair §
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

*Benjamin E. Greer, MD/Co-Chair Ω
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

*Nadeem R. Abu-Rustum, MD/Vice-Chair Ω
Memorial Sloan Kettering Cancer Center

Susana M. Campos, MD, MPH, MS †
Dana-Farber/Brigham and Women's
Cancer Center

Kathleen R. Cho, MD ≠
University of Michigan
Comprehensive Cancer Center

Hye Sook Chon Ω
Moffitt Cancer Center

Christina Chu, MD Ω
Fox Chase Cancer Center

David Cohn, MD Ω
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital and
Solove Research Institute

Marta Ann Crispens, MD Ω
Vanderbilt-Ingram Cancer Center

Don S. Dizon, MD †
Massachusetts General Hospital
Cancer Center

Oliver Dorigo, MD, PhD Ω
Stanford Cancer Institute

Patricia J. Eifel, MD §
The University of Texas
MD Anderson Cancer Center

Christine M. Fisher, MD, MPH §
University of Colorado Cancer Center

Peter Frederick, MD Ω
Roswell Park Cancer Institute

David K. Gaffney, MD, PhD §
Huntsman Cancer Institute
at the University of Utah

Suzanne George, MD/Liaison †
Dana-Farber/Brigham and Women's
Cancer Center

Ernest Han, MD, PhD Ω
City of Hope Comprehensive Cancer Center

Susan Higgins, MD §
Yale Cancer Center/Smilow Cancer Hospital

Warner K. Huh, MD Ω
University of Alabama at Birmingham
Comprehensive Cancer Center

John R. Lurain, III, MD Ω
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Andrea Mariani, MD Ω
Mayo Clinic Cancer Center

David Mutch, MD Ω
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

Christa Nagel, MD Ω
Case Comprehensive Cancer Center/University
Hospitals Seidman Cancer Center and Cleveland
Clinic Taussig Cancer Institute

Larissa Nekhlyudov, MD, MPH
Dana-Farber/Brigham and Women's Cancer Center

Amanda Nickles Fader, MD Ω
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Steven W. Remmenga, MD Ω
Fred & Pamela Buffett Cancer Center

R. Kevin Reynolds, MD Ω
University of Michigan
Comprehensive Cancer Center

Todd Tillmanns, MD Ω
St. Jude Children's Research Hospital/University of
Tennessee Health Science Center

Stefanie Ueda, MD Ω
UCSF Helen Diller Family
Comprehensive Cancer Center

Fidel A. Valea, MD Ω
Duke Cancer Institute

Emily Wyse
Patient Advocate

Catheryn M. Yashar, MD §
UC San Diego Moores Cancer Center

NCCN
Nicole McMillian, MS
Jillian Scavone, PhD

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Ω Gynecologic oncology
† Medical oncology
§ Radiotherapy/Radiation oncology
≠ Pathology
* Discussion Section Writing Committee

NCCN Guidelines Version 1.2017 Sub-Committees

Uterine Neoplasms

Principles of Imaging*

Nadeem R. Abu-Rustum, MD Ω/Lead
Memorial Sloan Kettering Cancer Center

Hye Sook Chon, MD Ω
Moffitt Cancer Center

Christina Chu, MD Ω
Fox Chase Cancer Center

Don S. Dizon, MD †
Massachusetts General Hospital
Cancer Center

Christine M. Fisher, MD, MPH §
University of Colorado Cancer Center

Suzanne George, MD/Liaison †
Dana-Farber/Brigham and Women's Cancer Center

David K. Gaffney, MD, PhD §
Huntsman Cancer Institute
at the University of Utah

Ernest Han, MD, PhD Ω
City of Hope Comprehensive
Cancer Center

Andrea Mariani, MD Ω
Mayo Clinic Cancer Center

Larissa Nekhlyudov, MD, MPH
Dana-Farber/Brigham and Women's Cancer Center

Fidel A. Valea, MD Ω
Duke Cancer Institute

*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:

Pamela DiPiro, MD φ
Dana-Farber/Brigham and Women's Cancer Center

Kristin Dittmar, MD φ
The Ohio State University Comprehensive Cancer Center
- James Cancer Hospital and Solove Research Institute

Ω Gynecologic oncology
† Medical oncology
§ Radiotherapy/Radiation oncology

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

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 1.2017 Updates

Uterine Neoplasms

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.”

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.”



NCCN Guidelines Version 1.2017 Updates

Uterine Neoplasms

Endometrial Carcinoma--continued

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 \(ENDO-A\).](#)"

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.*"



Endometrial Carcinoma--continued

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"



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."



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

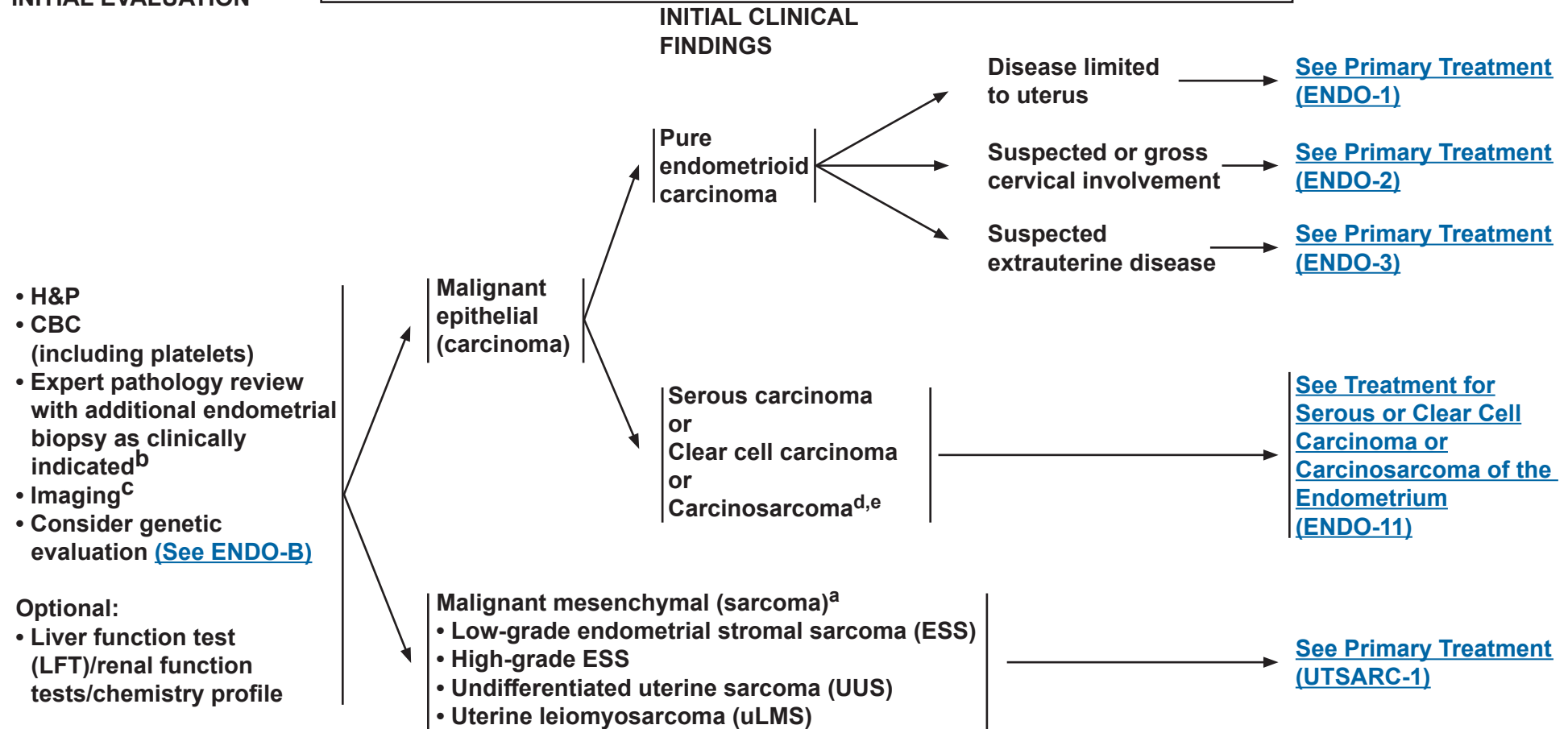
- Radiologically isolated vaginal/pelvic recurrence, Therapy for Relapse:
 - ▶ "No Prior RT" pathway, revised the following treatment options
 - ◇ ~~Tumor-directed RT EBRT ± brachytherapy ± systemic therapy~~
 - ◇ After "Disease confined to vagina": "Consider ~~tumor-directed RT~~ adjuvant EBRT ± brachytherapy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

UTSARC-A--Systemic Therapy for Uterine Sarcoma

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

INITIAL EVALUATION^a

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



^aInitial preoperative evaluation for known or suspected malignancy.

^bPreoperative 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.

^cSee [Principles of Imaging for Endometrial Carcinoma \(ENDO-A\)](#) and [Principles of Imaging for Uterine Sarcoma \(UTSARC-A\)](#).

^dStaged as aggressive; should be treated as a high-grade endometrial cancer.

^eAlso 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.
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.

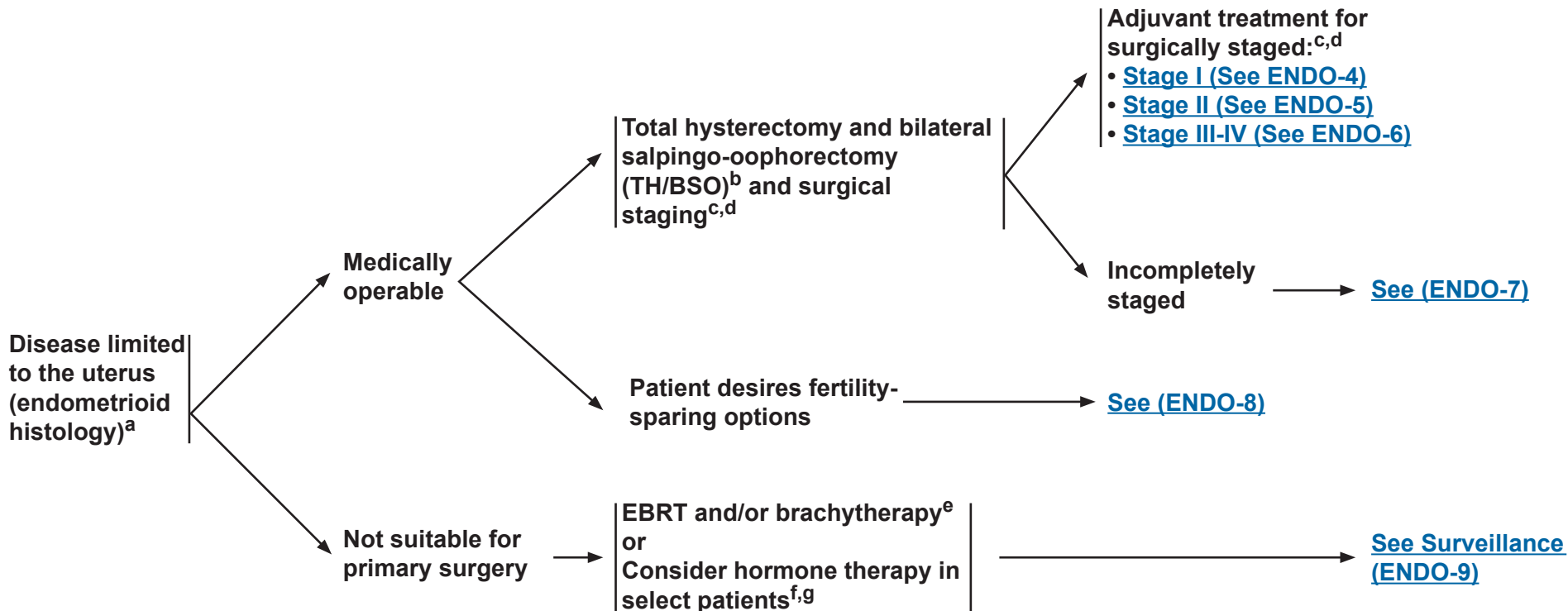


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Endometrial Carcinoma

INITIAL CLINICAL FINDINGS

PRIMARY TREATMENT



^aSee (UN-1) for clarification of uterine neoplasms.

^bSee [Hysterectomy and Pathologic Evaluation \(ENDO-B\)](#).

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

^dThe 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 \(ENDO-C\)](#).

^eSee [Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\)](#).

^fPatients should be closely monitored. Consider endometrial biopsies every 3 to 6 months.

^gSee [Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease \(ENDO-D\)](#).

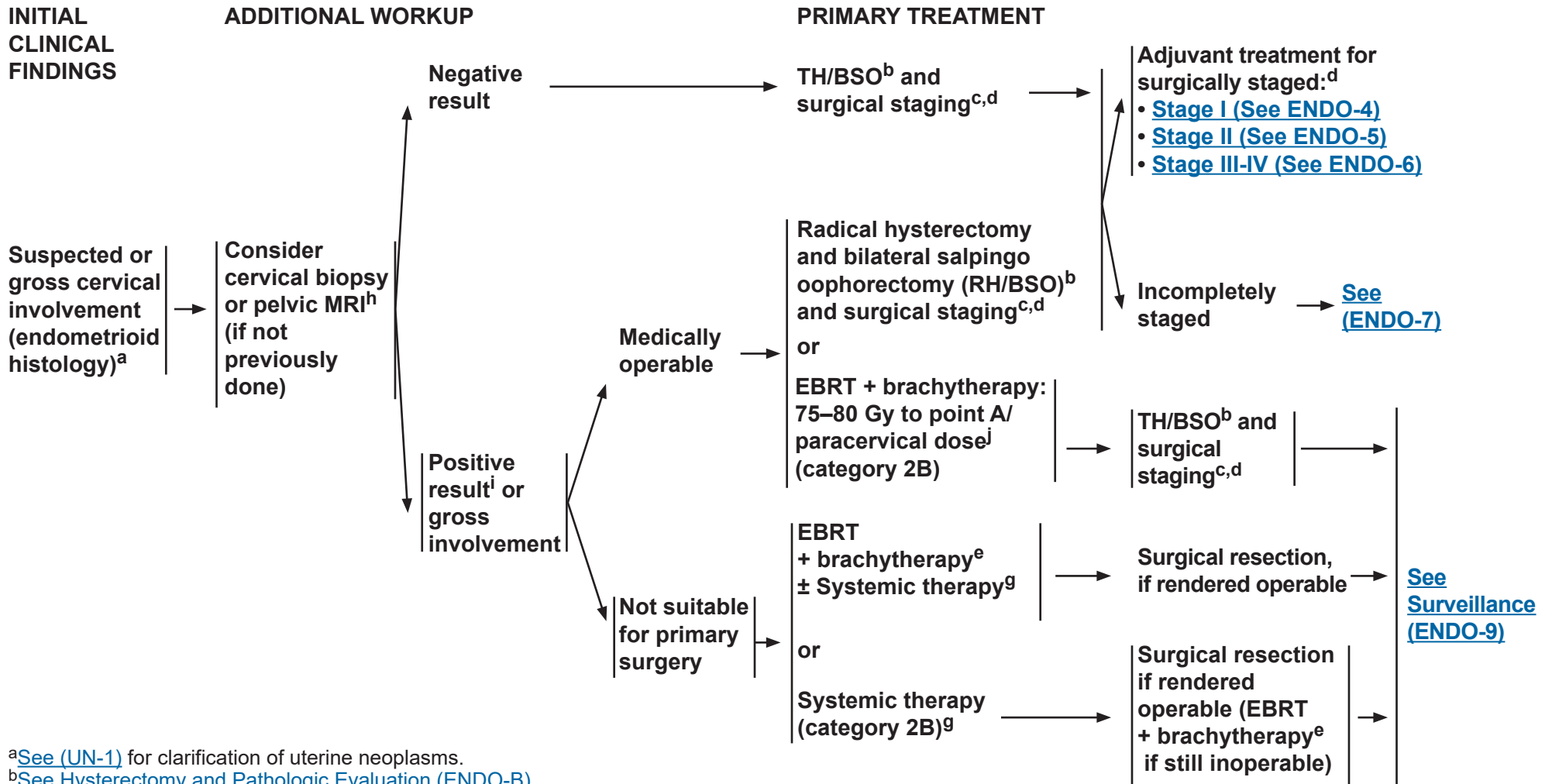
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NCCN Guidelines Version 1.2017

Endometrial Carcinoma



^aSee (UN-1) for clarification of uterine neoplasms.

^bSee [Hysterectomy and Pathologic Evaluation \(ENDO-B\)](#).

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

^dThe 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 \(ENDO-C\)](#).

^eSee [Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\)](#).

^gSee [Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease \(ENDO-D\)](#).

^hSee [Principles of Imaging for Endometrial Carcinoma \(ENDO-A\)](#).

ⁱClear demonstration of cervical stromal involvement.

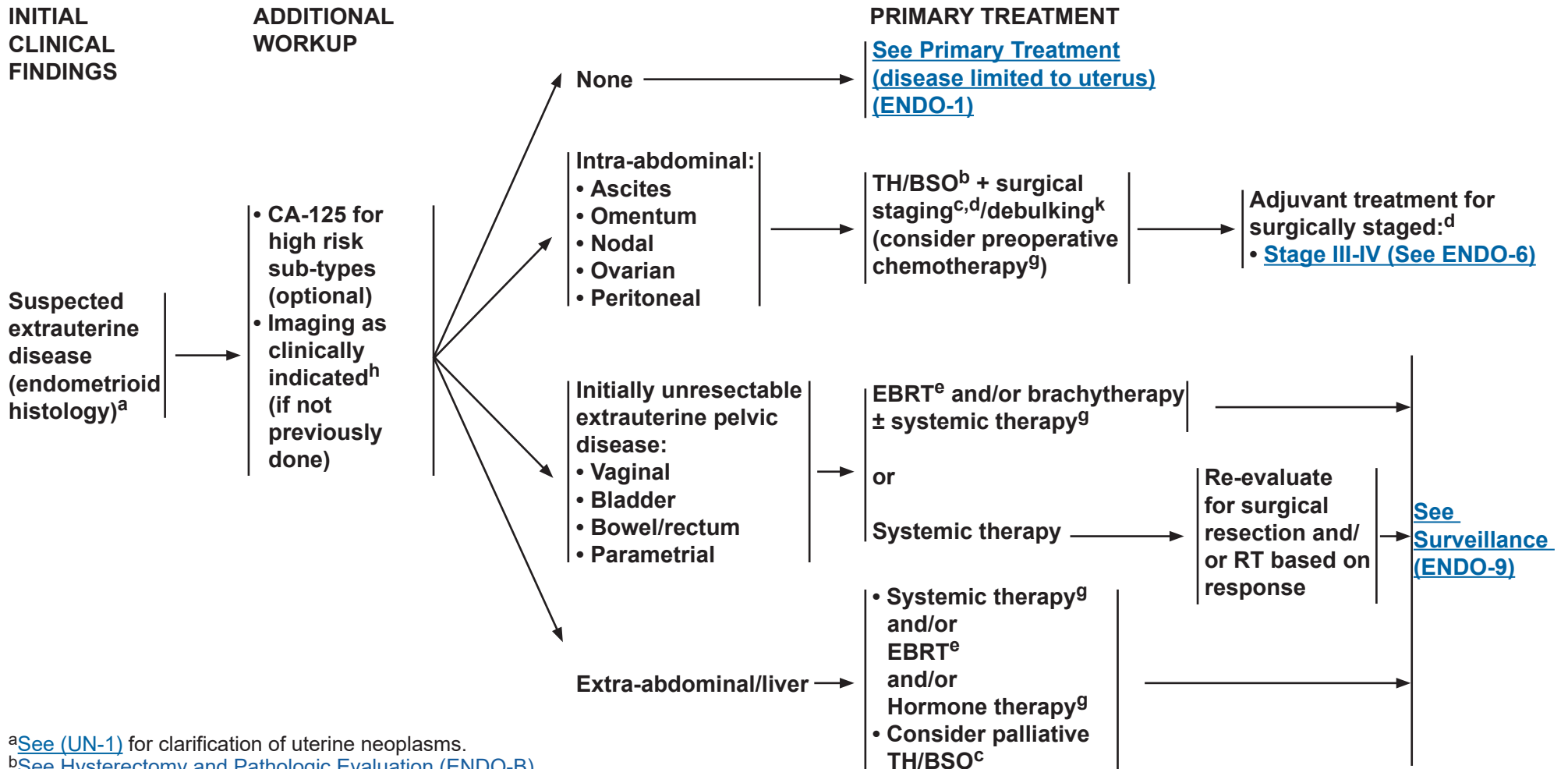
^jBased on summation of conventional external-beam fractionation and low-dose-rate brachytherapy equivalent.

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Endometrial Carcinoma



^aSee (UN-1) for clarification of uterine neoplasms.

^bSee [Hysterectomy and Pathologic Evaluation \(ENDO-B\)](#).

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

^dThe degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended.

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

^eSee [Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\)](#).

^gSee [Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease \(ENDO-D\)](#).

^hSee [Principles of Imaging for Endometrial Carcinoma \(ENDO-A\)](#)

^lThe surgical goal is to have no measurable residual disease.

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Endometrial Carcinoma

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

CLINICAL FINDINGS

ADVERSE RISK FACTORS^l

HISTOLOGIC GRADE/ADJUVANT TREATMENT^{e,n,o}

		HISTOLOGIC GRADE/ADJUVANT TREATMENT ^{e,n,o}			
		G1	G2	G3	
Surgically staged: Stage I ^d	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 ^m	Observe or Vaginal brachytherapy and/or EBRT	Observe or Vaginal brachytherapy and/or EBRT	EBRT and/or vaginal brachytherapy ± systemic therapy ^{g,p} (category 2B for systemic therapy)

^dThe degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended.

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

^fSee [Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\)](#).

^gSee [Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease \(ENDO-D\)](#).

^hSee [Discussion](#) for information on adverse risk factors.

^mConsider additional imaging if not previously done. See [Principles of Imaging for Endometrial Carcinoma \(ENDO-A\)](#).

ⁿAdjuvant therapy determinations are made on the basis of pathologic findings.

^oInitiate EBRT as soon as the vaginal cuff is healed, preferably no later than 12 weeks after surgery.

^pThe 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.

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.

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



NCCN Guidelines Version 1.2017

Endometrial Carcinoma

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

CLINICAL FINDINGS

HISTOLOGIC GRADE/ADJUVANT TREATMENT^{e,g,n,o}

	G1	G2	G3
Surgically staged: ^d Stage II ^{m,q,r} →	Vaginal brachytherapy and/or EBRT	Vaginal brachytherapy and/or EBRT	EBRT ± vaginal brachytherapy ± systemic therapy ^p (category 2B for systemic therapy)

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

^e[See Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\).](#)

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

^mConsider additional imaging if not previously done. [See Principles of Imaging for Endometrial Carcinoma \(ENDO-A\)](#)

ⁿAdjuvant therapy determinations are made on the basis of pathologic findings.

^oInitiate EBRT as soon as the vaginal cuff is healed, no later than 12 weeks after surgery.

^pThe 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.

^qObservation 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.

^rThe 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.

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

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

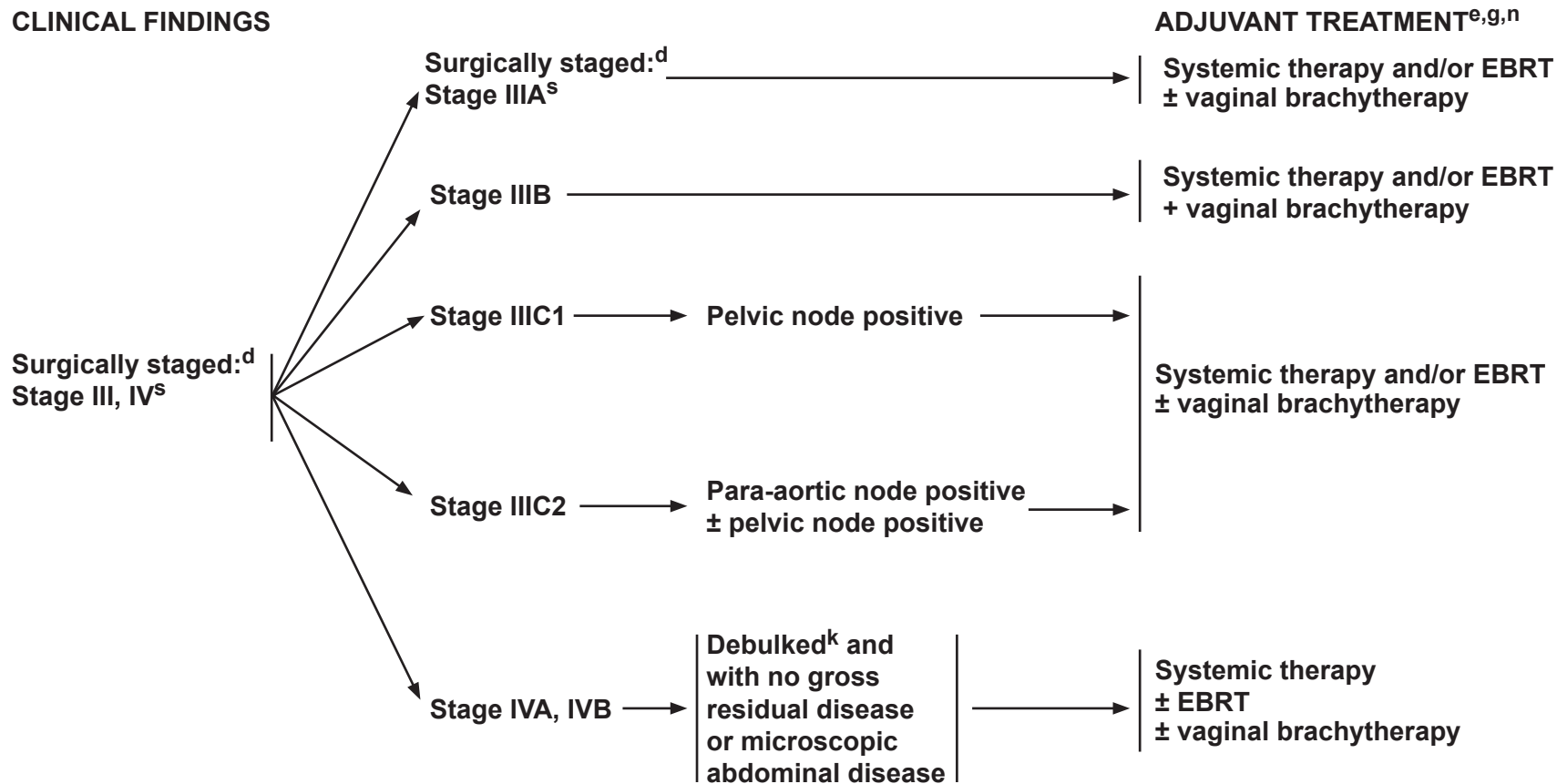


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Endometrial Carcinoma

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

CLINICAL FINDINGS



^dThe degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended.

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

^e[See Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\).](#)

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

^kThe surgical goal is to have no measurable residual disease.

ⁿAdjuvant therapy determinations are made on the basis of pathologic findings.

^sAdditional imaging if not previously done. ([See Principles of Imaging ENDO-A](#))

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.

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



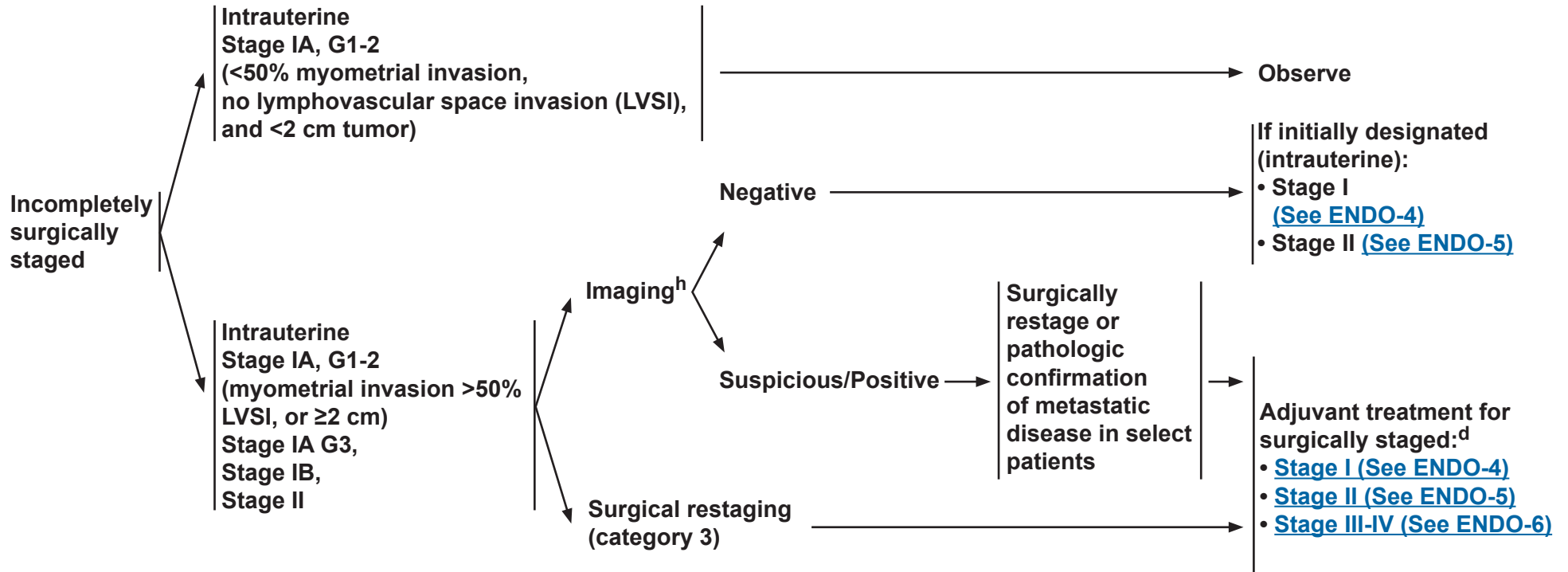
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Endometrial Carcinoma

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

CLINICAL INTRAUTERINE FINDINGS

ADJUVANT TREATMENT^{e,n}



^dThe degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended.

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

^e[See Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\).](#)

^h[See Principles of Imaging for Endometrial Carcinoma \(ENDO-A\)](#)

ⁿAdjuvant therapy determinations are made on the basis of pathologic findings.

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.

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

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^h
- 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^u (with continued surveillance every 3–6 mo)

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

Endometrial cancer present at 6–12 months^{h,t}

Consider MRI

TH/BSO with staging^{c,d} (see ENDO-1)

^cMinimally invasive surgery (MIS) is the preferred approach when technically feasible. See Principles of Evaluation and Surgical Staging (ENDO-C).

^dThe 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).

^hSee Principles of Imaging for Endometrial Carcinoma (ENDO-A)

^tGunderson 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.

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

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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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^h
 - 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^h

Isolated metastases

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

Disseminated metastases

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^g

If progression, systemic therapy^g

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

Systemic therapy^g ± palliative EBRT^e

or Clinical trial

^hSee [Principles of Imaging for Endometrial Carcinoma \(ENDO-A\)](#)

^eSee [Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\)](#).

^gSee [Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease \(ENDO-D\)](#).

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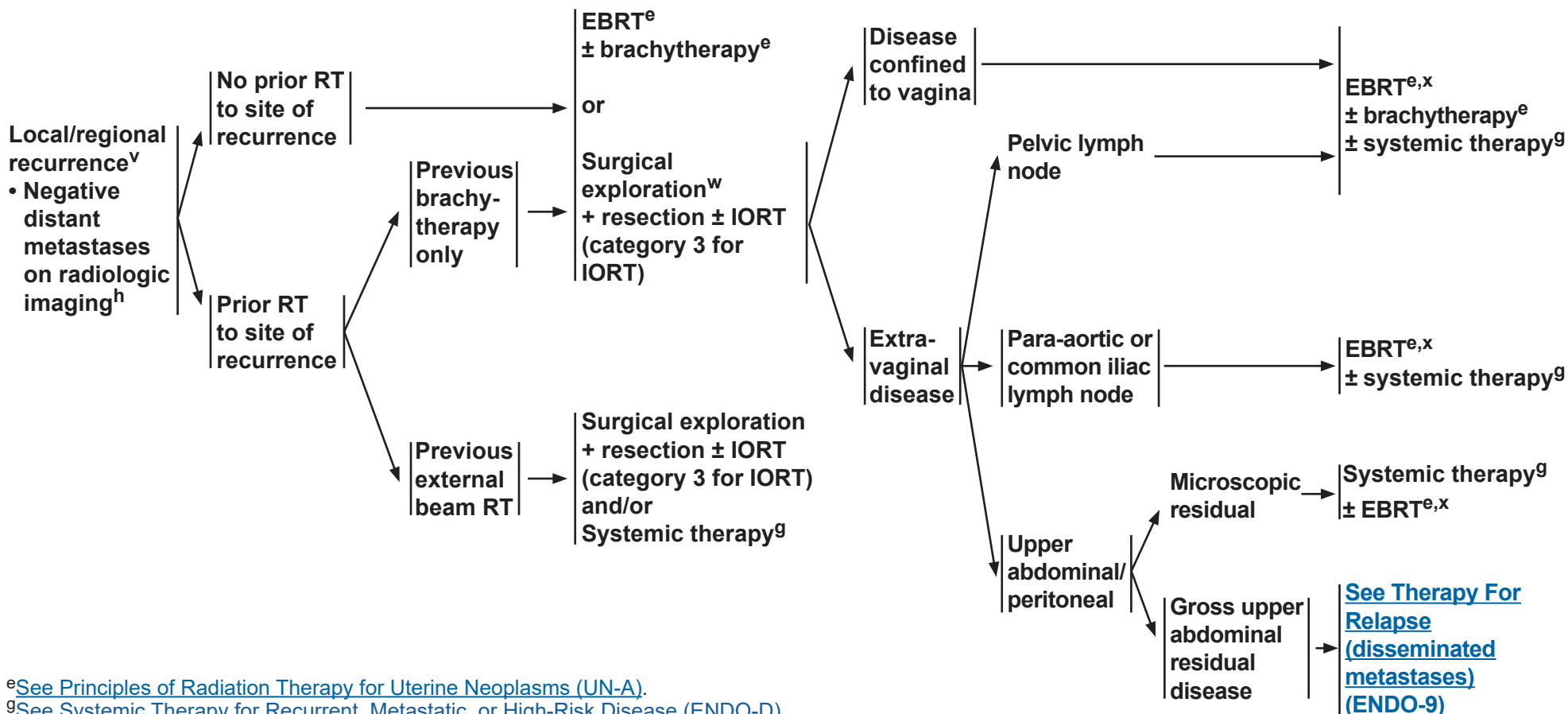
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Endometrial Carcinoma

CLINICAL PRESENTATION

THERAPY FOR RELAPSE

ADDITIONAL THERAPY



^eSee Principles of Radiation Therapy for Uterine Neoplasms (UN-A).

^gSee Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-D).

^hSee Principles of Imaging for Endometrial Carcinoma (ENDO-A)

^vMay include patients with isolated common iliac or para-aortic lymph node recurrence.

^wConsider preoperative EBRT in select patients.

^xPost-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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Endometrial Carcinoma

SEROUS OR CLEAR CELL CARCINOMA OR CARCINOSARCOMA OF THE ENDOMETRIUM^y

**ADDITIONAL
WORKUP**

PRIMARY TREATMENT

ADJUVANT TREATMENT

Biopsy:
Serous carcinoma
or
Clear cell carcinoma
or
Carcinosarcoma^y

- CA-125 (optional)
- Imaging as clinically indicated^h

- TH/BSO and surgical staging^d
- Consider maximal tumor debulking for gross disease

Stage IA

- Observe^z
- or
- Chemotherapy^g
- ± vaginal brachytherapy^e
- or
- EBRT^e
- ± vaginal brachytherapy^e

Stage IB, II, III, IV

- Chemotherapy^g
- ± EBRT^e
- ± vaginal brachytherapy^e

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

^dThe degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended.

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

^e[See Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\).](#)

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

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

^yAlso known as malignant mixed mesodermal tumor or malignant mixed Müllerian tumor. Carcinosarcomas are treated the same as poorly differentiated adenocarcinomas.

^zObservation only for select patients with no residual disease in the hysterectomy specimen.

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

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

PRINCIPLES OF IMAGING^{a,1-9}

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,^b 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,^c 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.^d

• 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.^e

Follow-up/Surveillance

• Non-Fertility Sparing Treatment

- ▶ Imaging should be based on symptomatology and clinical concern for metastatic disease.^f
- ▶ 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.^g

^aMRI and CT are performed with contrast throughout the guidelines unless contraindicated. Contrast is not required for screening chest CT.

^bHigh-grade endometrial carcinoma includes: poorly differentiated endometrioid, serous, clear cell, undifferentiated carcinoma, and carcinosarcoma.

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

^dIndications may include abnormal physical exam findings; bulky uterine tumor; vaginal or extrauterine involvement; delay in presentation or treatment; and abdominal or pulmonary symptoms.

^eThese factors may include abnormal physical exam findings; bulky uterine tumor; vaginal or extrauterine involvement; delay in presentation or treatment; and abdominal or pulmonary symptoms.

^fIndications may include abnormal physical exam findings such as vaginal involvement; palpable mass or adenopathy; and new pelvic, abdominal, or pulmonary symptoms.

^gThese factors may include abnormal physical exam findings such as bulky uterus, vaginal involvement, palpable mass or adenopathy, or new pelvic, abdominal, or pulmonary symptoms.

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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HYSTERECTOMY AND PATHOLOGIC EVALUATION^{1,2}

TH/BSO: Total hysterectomy + bilateral salpingo-oophorectomy

RH: Radical hysterectomy

Pathologic assessment to include:

- Uterus
 - ▶ Ratio of depth of myometrial/stromal invasion to myometrial thickness
 - ▶ Cervical stromal or glandular involvement
 - ▶ Tumor size
 - ▶ Tumor location (fundus vs. lower uterine segment/cervix)
 - ▶ Histologic subtype with grade
 - ▶ Lymphovascular space invasion
 - ▶ Universal testing of endometrial tumors for mismatch repair (MMR) gene
- Fallopian tubes/ovaries
- Peritoneal cytology³
- 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](#))

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

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

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

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.

**PRINCIPLES OF EVALUATION AND SURGICAL STAGING****Principles of Surgical Staging for Endometrial Cancer**¹⁻¹⁴

- 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](#)).¹⁻³ Select patients with metastatic endometrial carcinoma are also candidates for hysterectomy. ([See Hysterectomy and Pathologic Evaluation \[ENDO-B\]](#))
- Endometrial carcinoma should be removed en bloc to optimize outcomes; intraperitoneal morcellation or tumor fragmentation should be avoided.
- TH/BSO and lymph node assessment may be performed by any surgical route (eg, laparoscopic, robotic, vaginal, abdominal), although the standard in those with apparent uterine-confined disease is to perform the procedure via a minimally invasive approach. Randomized trials, a Cochrane Database Systematic Review, and population-based surgical studies support that minimally invasive techniques are preferred in this setting due to a lower rate of surgical site infection, transfusion, venous thromboembolism, decreased hospital stay and lower cost of care, without compromise in oncologic outcome.⁴⁻⁹
- The lymph node assessment includes evaluation of the nodal basins that drain the uterus, and often comprises a pelvic nodal dissection with or without aortic nodal dissection. This continues to be an important aspect of surgical staging in women with uterine-confined endometrial carcinoma, as the procedure provides important prognostic information that may alter treatment decisions.
- Pelvic lymph nodes from the external iliac, internal iliac, obturator, and common iliac nodes are frequently removed for staging purposes.
- Para-aortic nodal evaluation from the inframesenteric and infrarenal regions may also be utilized for staging in women with high-risk tumors such as deeply invasive lesions, high-grade histology, and tumors of serous carcinoma, clear cell carcinoma, or carcinosarcoma.
- Sentinel lymph node (SLN) mapping may be considered 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.
- Some patients may not be candidates for lymph node dissection.
- 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.

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.

[Continued](#)

PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED**Principles of Sentinel Lymph Node (SLN) Mapping for Endometrial Cancer Staging**¹⁰⁻²²

- The role of SLN mapping in endometrial carcinoma is under evaluation. Prospective and retrospective studies demonstrate that compared to systemic lymphadenectomy, SLN mapping with ultrastaging may increase the detection of lymph node metastasis with low false-negative rates in women with apparent uterine-confined disease.¹⁰⁻²² 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 cancer¹⁰⁻¹²).
- The combination of a superficial (1–3 mm) and deep (1–2 cm) cervical injection leads to dye delivery to the main layers of lymphatic channel origins in the cervix and corpus, namely the superficial subserosal, intermediate stromal, and deep submucosal lymphatic sites of origin (Figure 1 on [ENDO-C 3 of 5](#)).
- Injection into the uterine cervix provides excellent dye penetration to the region of the uterine vessels and main uterine lymphatic trunks that condense in the parametria and appear in the broad ligament leading to pelvic and occasionally paraaortic sentinel nodes.
- The uterine body lymphatic trunks commonly cross over the obliterated umbilical artery with the most common location of pelvic SLN being medial to the external iliac, ventral to the hypogastric, or in the superior part of the obturator region (Figure 2 on [ENDO-C 3 of 5](#)).
- A less common location is usually seen when the lymphatic trunks do not cross over the obliterated umbilical and move cephalad following the mesoureter; in these cases, the SLN is usually seen in the common iliac presacral region (Figure 3 on [ENDO-C 3 of 5](#)).
- The radiolabeled colloid most commonly injected into the cervix is technetium-99m (99mTc); colored dyes are available in a variety of forms (Isosulfan Blue 1% and Methylene Blue 1%, Patent Blue 2.5% sodium).
- Indocyanine green (ICG) recently emerged as a useful imaging dye that requires near-infrared camera for localization, provides a very high SLN detection rate, and is commonly used in many practices at the present time.¹⁹
- Low-volume nodal metastasis to SLN detected only by enhanced pathologic ultrastaging is another potential value to staging with SLN.^{10,20-22}
- Key points to a successful SLN mapping is the adherence to the SLN algorithm, which requires the performance of a side-specific nodal dissection in cases of failed mapping and removal of any suspicious or grossly enlarged nodes regardless of mapping (Figure 4 on [ENDO-C 4 of 5](#)).^{10-12,22}

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.

[Continued](#)

PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

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

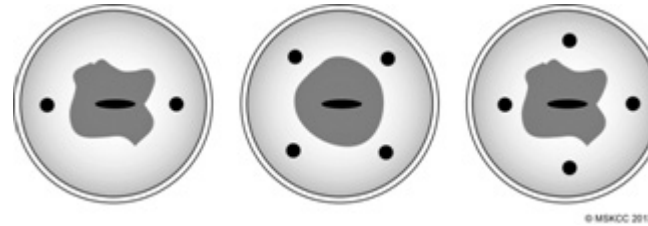


Figure 2: Most common location of SLNs (blue, arrow) following a cervical injection†

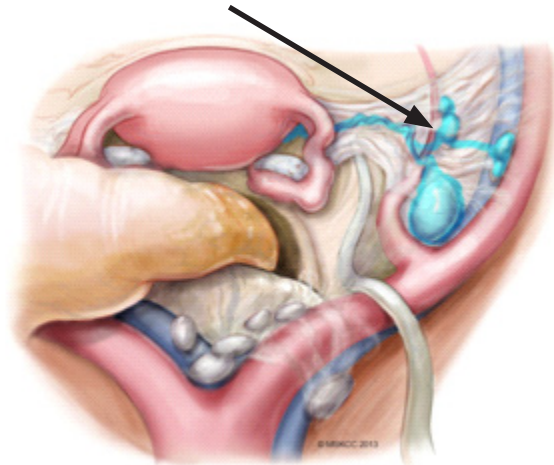
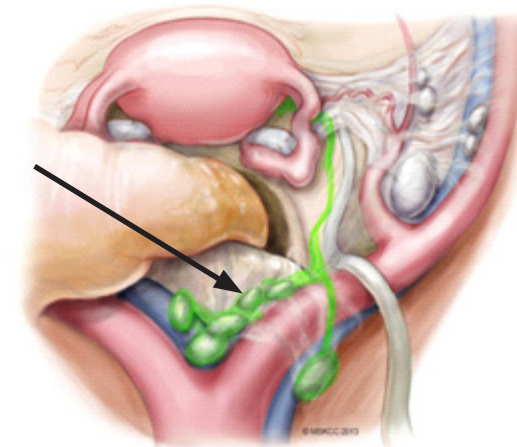


Figure 3: Less common location of SLNs (green, arrow) usually seen when lymphatic trunks are not crossing over the umbilical ligament but following the mesoreter cephalad to common iliac and presacral region†



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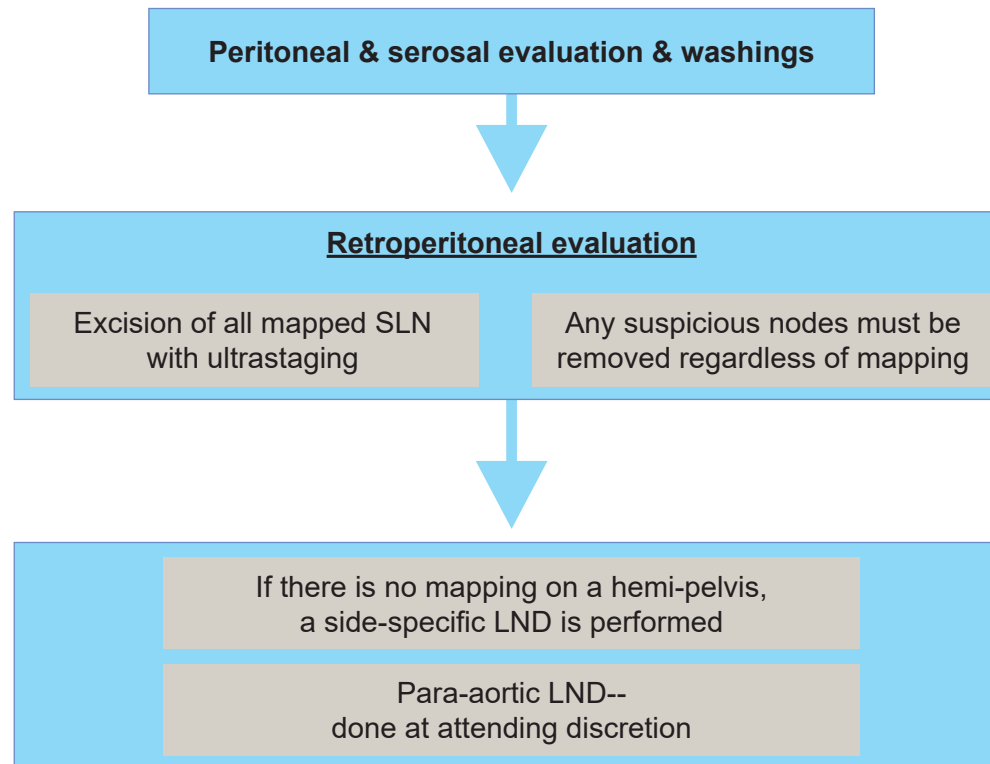
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[Continued](#)

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.

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

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[Continued](#)

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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 1.2017
Endometrial Carcinoma**SYSTEMIC THERAPY FOR RECURRENT, METASTATIC, OR HIGH-RISK DISEASE**
(STRONGLY ENCOURAGE PARTICIPATION IN CLINICAL TRIALS)**CHEMOTHERAPY REGIMENS**^{2,3}

- **Multi-agent chemotherapy regimens preferred, if tolerated**
 - ▶ Carboplatin/paclitaxel⁴
 - ▶ Cisplatin/doxorubicin⁵
 - ▶ Cisplatin/doxorubicin/paclitaxel^{5,6}
 - ▶ Carboplatin/docetaxel⁷
 - ▶ Ifosfamide/paclitaxel (category 1 for carcinosarcoma)⁸
 - ▶ Cisplatin/ifosfamide (for carcinosarcoma)
- **Single agents**
 - ▶ Cisplatin
 - ▶ Carboplatin
 - ▶ Doxorubicin
 - ▶ Liposomal doxorubicin
 - ▶ Paclitaxel
 - ▶ Topotecan
 - ▶ Bevacizumab⁹
 - ▶ Temsirolimus¹⁰
 - ▶ Docetaxel⁷ (category 2B)
 - ▶ Ifosfamide (for carcinosarcoma)

HORMONE THERAPY¹

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

¹Hormonal 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.

²Cisplatin, carboplatin, liposomal doxorubicin, paclitaxel, and docetaxel may cause drug reactions.

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

³Chemotherapy 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.

⁴Miller 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.

⁵Homesley 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.

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

⁷Docetaxel may be considered for patients in whom paclitaxel is contraindicated.

⁸Homesley 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.

⁹Bevacizumab 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.)

¹⁰Oza AM, Elit L, Tsao MS, et al. Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trials Group. J Clin Oncol 2011;29:3278-3285.

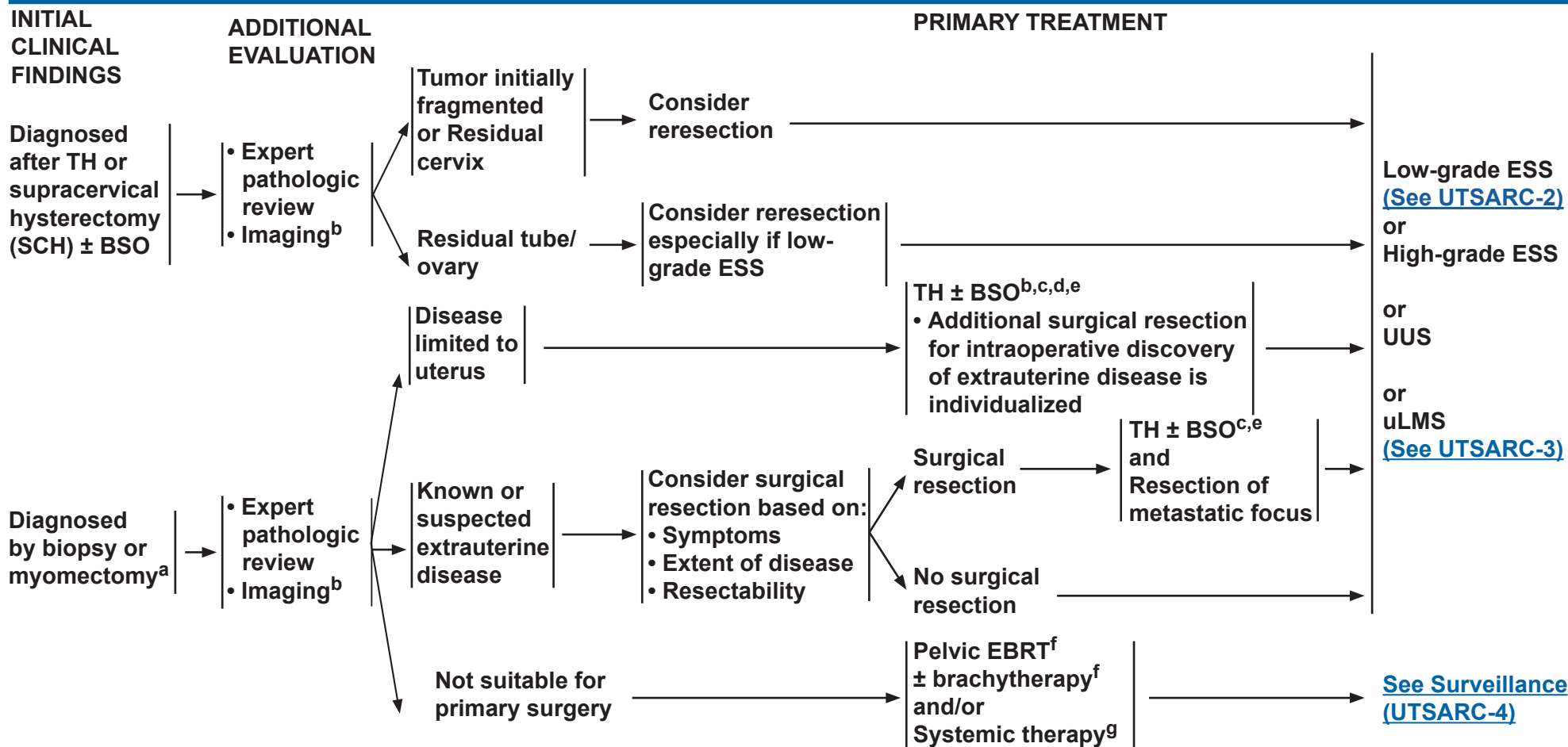
Note: All recommendations are category 2A unless otherwise indicated.

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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Uterine Sarcoma



^aPreoperative 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.

^bSee [Principles of Imaging for Uterine Sarcoma \(UTSARC-A\)](#).

^cOophorectomy individualized for reproductive-age patients.

^dFor incidental finding of uterine sarcoma after TH/BSO or fragmented specimen: Recommend imaging and consider additional surgical resection on an individual basis.

^eUterine sarcoma should be removed *en bloc* to optimize outcomes; morcellation should be avoided.

^fSee [Principles of Radiation Therapy for Uterine Neoplasms \(UN-A\)](#).

^gSee [Systemic Therapy for Uterine Sarcoma \(UTSARC-B\)](#).

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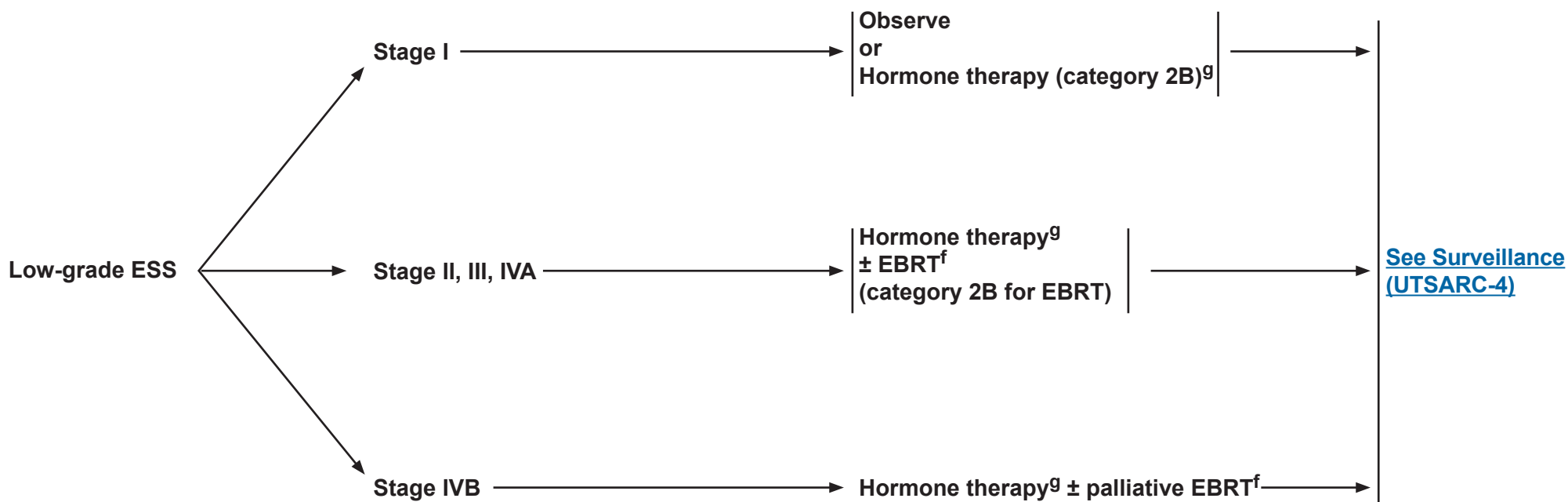


NCCN Guidelines Version 1.2017

Uterine Sarcoma

**PATHOLOGIC FINDINGS/
HISTOLOGIC GRADE^h**

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



^fSee Principles of Radiation Therapy for Uterine Neoplasms (UN-A).

^gSee Systemic Therapy for Uterine Sarcoma (UTSARC-B).

^hSee Uterine Sarcoma Classification (UTSARC-C).

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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.

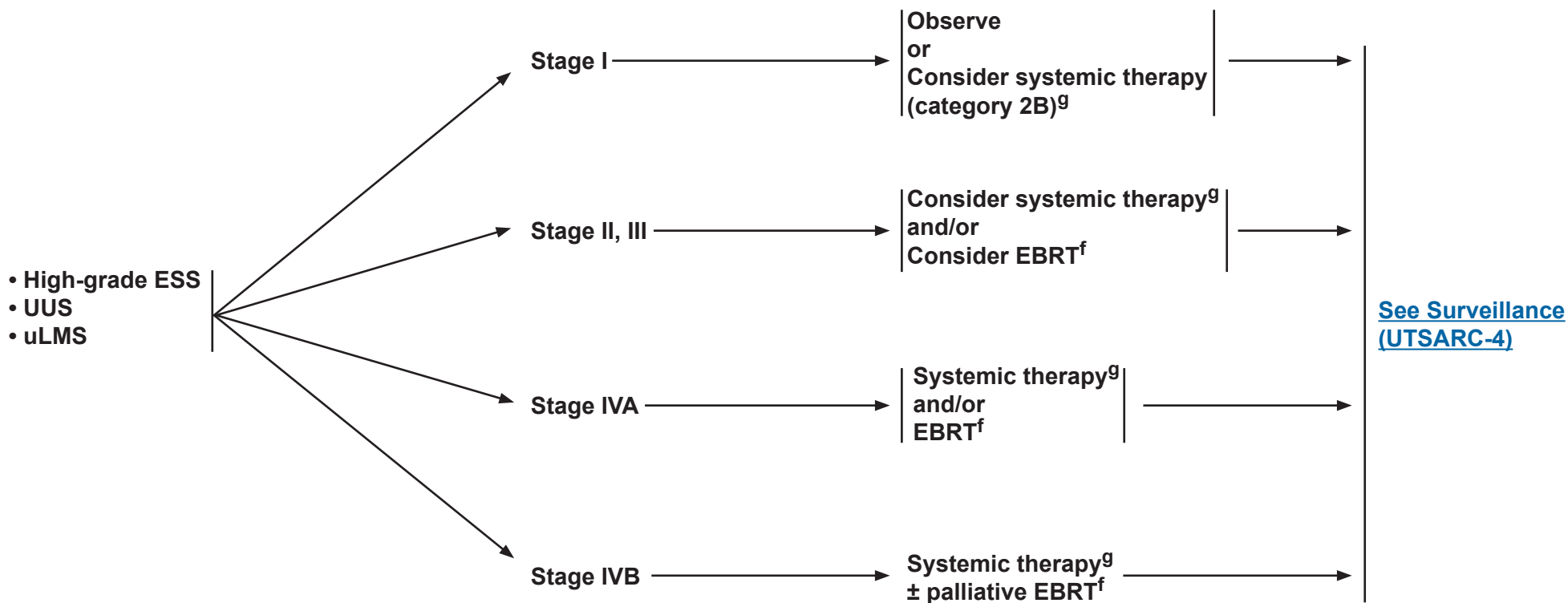


NCCN Guidelines Version 1.2017

Uterine Sarcoma

PATHOLOGIC FINDINGS/ HISTOLOGIC GRADE^h

ADDITIONAL THERAPY



^fSee Principles of Radiation Therapy for Uterine Neoplasms (UN-A).

^gSee Systemic Therapy for Uterine Sarcoma (UTSARC-B).

^hSee Uterine Sarcoma Classification (UTSARC-C).

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NCCN Guidelines Version 1.2017

Uterine Sarcoma

SURVEILLANCE

- H&P exam every 3 mo for 2 y, then every 6–12 mo
 - Imaging^b
- 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^b

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^g
 - ▶ Consider postoperative EBRT^f

Unresectable

Systemic therapy^g and/or Local therapy (EBRT^f or local ablative therapy)

If response, consider surgery

Systemic therapy^g ± palliative EBRT^f or Supportive care

^bSee Principles of Imaging for Uterine Sarcoma (UTSARC-A).

^fSee Principles of Radiation Therapy for Uterine Neoplasms (UN-A).

^gSee Systemic Therapy for Uterine Sarcoma (UTSARC-B).

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

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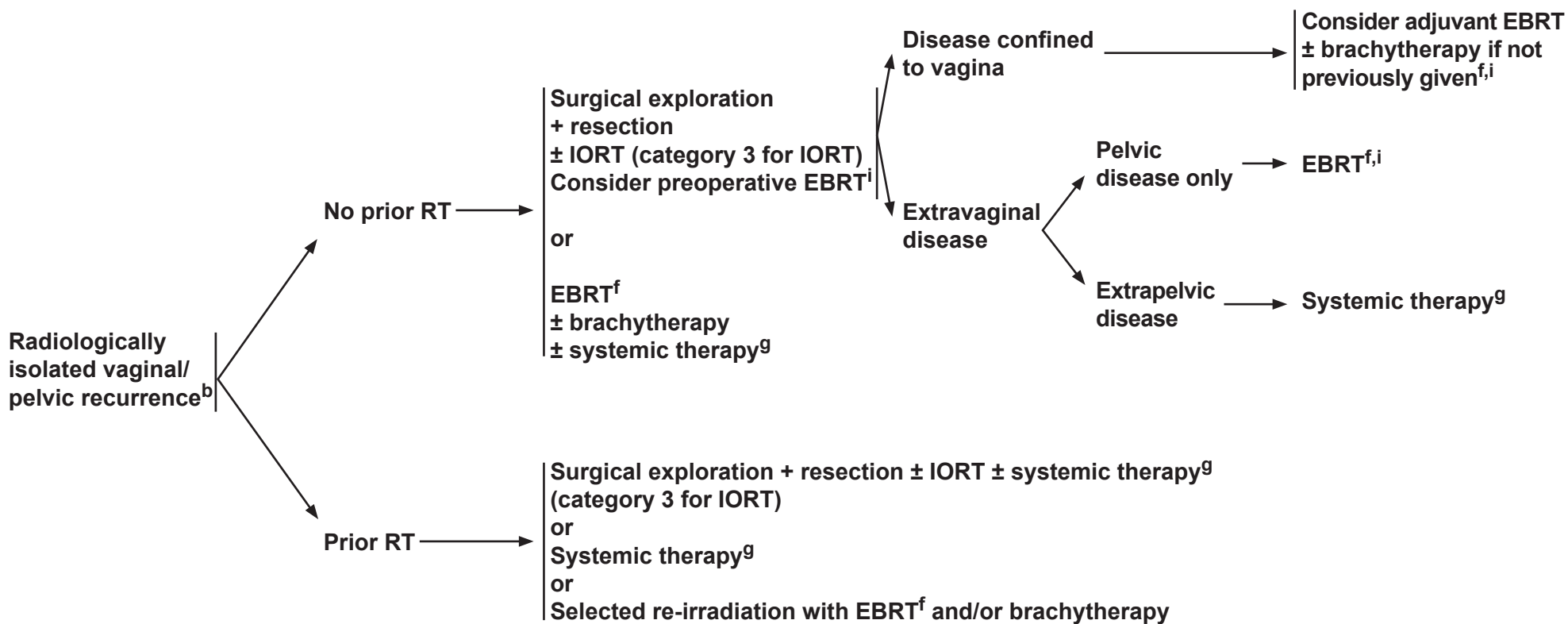


NCCN Guidelines Version 1.2017

Uterine Sarcoma

RECURRENCE

THERAPY FOR RELAPSE



^bSee Principles of Imaging for Uterine Sarcoma (UTSARC-A).

^fSee Principles of Radiation Therapy for Uterine Neoplasms (UN-A).

^gSee Systemic Therapy for Uterine Sarcoma (UTSARC-B).

ⁱThe use of preoperative EBRT would preclude postoperative EBRT.

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.



PRINCIPLES OF IMAGING^{a,1-9}

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.^b

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.^c
- 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.^c
- Consider whole body PET/CT if metastasis is suspected in select patients.
- Imaging should be based on symptomatology and clinical concern for metastatic disease.^d

^aMRI and CT are performed with contrast throughout the guidelines unless contraindicated. Contrast is not required for screening chest CT.

^bIndications may include abnormal physical exam finding; bulky uterine tumor; vaginal or extrauterine involvement; delay in presentation or treatment; and abdominal or pulmonary symptoms.

^cFollow-up imaging may be as frequent as every 3 months or change based on histology grade and/or stage of tumor.

^dIndications may include abnormal physical exam findings such as vaginal involvement; palpable mass or adenopathy; and new pelvic, abdominal, or pulmonary symptoms.

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.

[Continue](#)

UTSARC-A

1 OF 2



PRINCIPLES OF IMAGING (References)

- ¹Salani 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 Jun; 204(6):466-78.
- ²Haldorsen IS, Salvesen HB. What Is the Best Preoperative Imaging for Endometrial Cancer? *Curr Oncol Rep* 2016 Apr;18(4):25.
- ³Elit L, Reade CJ. Recommendations for Follow-up Care for Gynecologic Cancer Survivors. *Obstet Gynecol* 2015 Dec;126 (6):1207-14.
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Note: All recommendations are category 2A unless otherwise indicated.

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SYSTEMIC THERAPY FOR UTERINE SARCOMA¹
(Clinical trials strongly recommended)

Combination regimens:

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

Single-agent options:

- Dacarbazine
- Doxorubicin
- Epirubicin
- Eribulin (category 2B)
- Gemcitabine
- Ifosfamide
- Liposomal doxorubicin
- Pazopanib
- Temozolomide
- Trabectedin³
- Vinorelbine (category 2B)
- Docetaxel (category 3)

HORMONE THERAPY

**(For Low-grade ESS or Hormone
Receptor Positive (ER/PR) uLMS²):**

- 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)

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

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

³For uLMS that has been treated with a prior anthracycline-containing regimen.

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

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[Back to Recurrence
\(UTSARC-4\)](#)

UTERINE SARCOMA CLASSIFICATION¹

- Low-grade endometrial stromal sarcoma (ESS)²
- High-grade ESS³
- Undifferentiated uterine sarcoma (UUS)⁴
- Uterine leiomyosarcoma (uLMS)⁵

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

- Adenosarcomas
- PEComas
- Rhabdomyosarcoma

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

²Low-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).

³High-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.

⁴Undifferentiated 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.

⁵Excludes 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.¹
- 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.

¹Klopp 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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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.

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)

TNM Categories	FIGO* Stages	Surgical-Pathologic Findings
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)

TNM Categories	FIGO Stages	Surgical-Pathologic Findings
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)

TNM Categories	FIGO Stages	Surgical-Pathologic Findings
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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Reprinted from: Pecorelli S, Denny L, Ngan H, et al. Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet 2009;105:103-104. Copyright 2009, with permission from International Federation of Gynecology and Obstetrics.

[Continued](#)



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 issues
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)

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC. and

Reprinted from: D'Angelo E, Prat J. Uterine sarcomas: a review. Gynecol Oncol 2010;116:131-139. Copyright 2010, with permission from International Federation of Gynecology and Obstetrics.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 11/20/15

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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Discussion
update in
progress

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 54,870 new uterine cancer cases will occur in 2015, with 10,170 deaths resulting from the disease.¹

Uterine sarcomas are uncommon malignancies accounting for approximately 3% of all uterine cancers.^{1,2} 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.³⁻⁶ 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 suspected uterine neoplasms, the initial evaluation/workup includes a history and physical examination, endometrial biopsy, and other studies (see *Initial Evaluation* in the NCCN Guidelines for Uterine Neoplasms).⁷ 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, and carcinosarcoma (also known as malignant mixed Müllerian tumor [MMMT]). Stromal tumor types include uterine leiomyosarcoma (uLMS), endometrial stromal sarcoma (ESS), and undifferentiated uterine (previously called high-grade undifferentiated endometrial sarcoma). 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.⁸ 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.^{6,8-10} 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.¹¹⁻¹³ If these patients have Lynch syndrome, they are at greater risk for a second cancer (eg, colorectal cancer, ovarian cancer).^{4,10,14} In addition, their relatives may have Lynch syndrome.

Screening of the tumor for defective DNA mismatch repair using immunohistochemistry and/or microsatellite instability (MSI) should be considered to identify which patients should undergo mutation testing for Lynch syndrome (see *Lynch Syndrome* in the NCCN Guidelines for Colorectal Cancer Screening).^{8,9,15,16} Immunohistochemistry and/or MSI is used to assess for defective DNA mismatch repair (eg, MLH1, MSH2,

MSH6), which is associated with Lynch syndrome.⁸ The Society of Gynecologic Oncology (SGO) also has useful criteria for determining which patients should have mutation testing (eg, diagnosis of multiple Lynch syndrome cancers in young patients, family members with similar cancers).^{11,12} Some centers do immunohistochemistry and/or MSI screening in all patients with colorectal and endometrial cancer to identify those at risk for Lynch syndrome, regardless of age at diagnosis or family history.^{15,16} However, this screening is usually done in patients with epithelial tumors and not those with mesenchymal endometrial tumors.

Women with Lynch syndrome are at higher risk (60%) for endometrial cancer; thus, close monitoring is recommended.^{9,17,18} In relatives with Lynch syndrome but without endometrial cancer, a yearly endometrial biopsy is recommended to assess for cancer.^{12,19} This strategy also enables select women to defer surgery (and surgical menopause) and to preserve their fertility. Prophylactic hysterectomy/bilateral salpingo-oophorectomy (BSO) can then be done after childbearing is complete or sooner, depending on patient preference.^{20,21} 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.²² Many physicians believe that adenocarcinoma of the endometrium is a relatively benign disease because the early symptoms of irregular vaginal bleeding (in this predominantly postmenopausal patient population) often trigger patients to seek care when the disease is at an early and treatable stage. Thus, endometrial cancer is often localized, yielding a generally high survival rate.²³

However, data show that the mortality rate for uterine cancer has increased more rapidly than the incidence rate.²⁴ This increased mortality may be related to an increased rate of advanced-stage cancers, high-risk histologies (eg, serous 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.²⁵ In addition to grade and depth of myometrial invasion, other risk factors associated with poor prognosis include age, tumor size, lymphovascular space invasion (LVSI), and tumor involvement of the lower uterine segment.^{26,27} 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 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.^{28,29} 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.^{28,30} Hysteroscopy may be helpful in evaluating the endometrium for lesions, such as a polyp, if the patient has persistent or recurrent undiagnosed bleeding.³¹ Endometrial biopsy may not be accurate for diagnosing malignancies of the uterine wall such as mesenchymal tumors.

Other ancillary tests (ie, CT, MRI, PET) are reserved for evaluating extrauterine disease as indicated by clinical symptoms, physical findings, or abnormal laboratory findings.³²⁻³⁶ In patients with extrauterine disease, a serum CA-125 assay may be helpful in monitoring clinical response.^{37,38} 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.³⁹⁻⁴¹ Currently, there is no validated screening test for endometrial carcinoma.^{42,43}

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.⁴⁴⁻⁴⁶ 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 surgico-pathologic assessment of data, such as histologic grade, myometrial invasion, and the extent and location of extrauterine spread (including retroperitoneal lymph node metastases).⁴⁷ FIGO and the AJCC updated and refined the surgical/pathologic staging criteria for

uterine neoplasms in 2009.⁴⁸⁻⁵² 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 stages were similar.⁵¹ Stage IA is now less than 50% myometrial invasion, and stage IB is 50% or more myometrial invasion. Stage II only includes patients with cervical stromal invasion. Patients with endocervical glandular involvement without invasion are no longer upstaged.⁵¹ Stage IIIC is now subdivided into IIIC1 and IIIC2, because survival is worse with positive para-aortic nodes.⁵¹ 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 as an independent risk factor.⁵² 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).^{53,54}

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.

Pathology

An expert pathology review will determine the specific epithelial histology of the tumor (ie, various endometrioid histologies, serous carcinoma, clear cell carcinoma, carcinosarcoma). 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) This CAP protocol was revised in October 2013 and reflects the updated FIGO/AJCC 2009 staging (ie, AJCC Cancer Staging Manual, 7th 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.⁵⁵ 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.⁵⁶

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.⁵⁷ 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.⁵⁸

Finally, SLN ultrastaging led to upstaging in a subset of the cohort of 89 patients with presumed low- or intermediate-risk endometrial cancer, including patients whose positive SLNs went undiagnosed by conventional histology.⁵⁹ Ultrastaging of SLNs led to modifications to planned adjuvant therapy in about half of this cohort.

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 is now recommended by the NCCN Panel to avoid systematic over-treatment.⁶⁰ No randomized trial data support routine full lymphadenectomy,⁶¹ although some retrospective studies have suggested that it is beneficial.⁶²⁻⁶⁴ 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.^{65,66} However, these findings remain a point of contention.⁶⁷⁻⁶⁹ To avoid over-interpretation of these results, it is important to address the limitations of these randomized studies, including selection of patients, extent of lymph node dissection, and standardization of postoperative therapy.^{70,71} 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.^{72,73} 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.⁶⁶ 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 periaortic 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.^{46,72,74,75} There was a high rate of lymphatic metastasis above the inferior mesenteric artery, suggesting a need for systematic pelvic and para-aortic lymphadenectomy. Hence, periaortic 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.⁶⁰

In summary, lymph node dissection identifies patients requiring adjuvant treatment with RT and/or chemotherapy.⁷⁶ 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).⁵ 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 may be considered (category 3) for patients with apparent uterine-confined endometrial cancer to assess whether they have metastatic pelvic lymph nodes.⁷⁷⁻⁸⁰ 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).^{77,81} 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.⁷⁷

Because many NCCN Member Institutions do not routinely use SLN, it is a category 3 recommendation. 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.^{82,83} 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.⁸³⁻⁸⁷ It is important to note that system-wide long-term outcomes data are not yet available for SLN mapping in endometrial cancer.^{88,89}

Much of the data to support SLN mapping are based on single institution studies. Meta-analyses of the SLN mapping data in patients with endometrial cancer report a broad range in SLN detection rates and false negative rates.⁹⁰⁻⁹² A recent 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.⁹³

Ultrastaging of SLNs can reveal lymph node metastases undetected through conventional histology, and studies suggest that SLN ultrastaging leads to upstaging in 5%-15% of patients.^{80,82,85,87,93} However, the implications and appropriate management of micrometastases or isolated tumor cells (ITC) detected via SLN ultrastaging are not yet clear.^{82,87,92,94,95} Future evaluation of prognosis may need to separately examine patients with scattered ITCs versus patients with aggregated micrometastasis.

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 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 ($P = .5$).⁹⁶

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.³² The main contraindication for SLN mapping is uterine sarcoma. Additionally, SLN mapping should be done with particular caution in patients with high-risk histology (eg, serous carcinoma, clear cell carcinoma, carcinosarcoma).^{60,97}

Minimally Invasive Procedures

Laparoscopic pelvic and para-aortic lymphadenectomy in association with total laparoscopic hysterectomy is being used in many practices.^{60,98,99} However, patients having laparoscopy should be followed over a long term to compare their outcomes with those of traditional laparotomy.¹⁰⁰

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.^{100,101} 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, $P < .0001$).^{102,103} Significantly fewer postoperative adverse events and shorter hospitalization occurred with laparoscopy compared with laparotomy. Recurrence rates were 11.4% for laparoscopy versus 10.2% for laparotomy. The 5-year overall survival rate was 84.8% for both arms of LAP2.¹⁰¹

Another randomized trial (n = 283) comparing laparoscopy versus laparotomy reported shorter hospital stay, less pain, and faster resumption of daily activities with laparoscopy.¹⁰⁴ However, laparotomy may still be required for certain clinical situations (eg, elderly patients, those with a very large uterus) or certain metastatic presentations.¹⁰⁰

Recent meta-analyses of the data from studies comparing hysterectomy via laparoscopy versus laparotomy report reduced surgical complication rates and hospital stays for laparoscopic procedures.^{105,106} Survival outcomes were generally found to be comparable between both approaches in these analyses.

Robotic surgery is a minimally invasive technology that has been advocated by some as being a feasible approach in the primary management of endometrial cancer.^{98,99,107-114} Costs for equipment and maintenance remain high.¹¹⁵ Given the recent introduction of robotic surgery, long-term outcomes are still pending.¹¹⁶⁻¹¹⁹ However, due to its potential advantages over traditional laparoscopic approaches, providers may elect to use this technique for minimally invasive surgery in endometrial cancer, especially for obese patients.^{98,120} The 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.¹²¹⁻¹²³ For recent reviews on the robotic-assisted surgery for gynecologic malignancies and associated cost issues, see Sinno and Fader and Gala et al.^{124,125}

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; morcellation should be avoided.¹²⁶⁻¹²⁸

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 selective surgical staging (see *Hysterectomy and Pathologic Evaluation*, and *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma and in this Discussion).⁶⁷ 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).

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).

Selected patients with apparent uterine-confined endometrial carcinoma may be candidates for sentinel node mapping (category 3), which assesses the pelvic nodes and is less morbid than standard

lymphadenectomy (see *Sentinel Lymph Node Mapping* in this Discussion).

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.^{129,130} Surgical restaging, including lymph node dissection, can also be done.⁷² 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 stage IA disease who wish to preserve their fertility.¹³¹⁻¹³⁵ 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, stage IA 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 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.^{131,132,136} A durable complete response occurs in about 50% of patients.¹³¹ 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 9 months of progestin-based therapy.^{135,137} 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%).^{131,134,138-140}

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.¹⁴¹ Other studies also suggest that ovarian preservation may be safe in women with early-stage endometrial cancer.^{142,143}

Suspected or Gross Cervical Involvement

For patients with suspected or gross cervical involvement (endometrioid histologies), cervical biopsy or MRI should be considered (see *Additional Workup* in the NCCN Guidelines for Endometrial Carcinoma).^{129,130} 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).⁶⁷ In these patients, radical or modified radical hysterectomy may improve local control and survival when compared with TH.^{144,145} Alternatively, the patient may undergo RT (category 2B) followed by TH/BSO. 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

Tumor-directed radiation therapy (RT) with (or without) chemotherapy 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).¹⁴⁶⁻¹⁴⁸ If rendered operable, surgical resection should follow. Initial chemotherapy alone can also be considered (category 2B). Following chemotherapy, local treatment should still be utilized (ie, surgery if feasible, or RT).

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).^{42,149} Progesterone-based therapy can provide some benefit with low toxicity in patients with low-grade tumors.¹⁵⁰ Tamoxifen

with alternating megestrol may be used.¹⁵¹ Aromatase inhibitors have also been used.¹⁵²⁻¹⁵⁵

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. Preoperative chemotherapy can be considered.

The surgical goal is to have no measurable residual disease; several studies support debulking.^{67,156-158} Patients with unresectable extrauterine pelvic disease (ie, vaginal, bladder, bowel/rectal, or parametrial involvement) are typically treated with RT and brachytherapy with (or without) chemotherapy, followed by re-evaluation of tailored surgery.¹⁵⁹⁻¹⁶² Chemotherapy 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 chemotherapy and/or RT 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).^{163,164} 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 (7th edition).^{49,51} 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.^{165,166} 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.

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 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%.¹⁶⁷ 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 on ENDO-4 in the NCCN Guidelines for Endometrial Carcinoma).^{76,164,165,168-170}

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.¹⁷¹

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) chemotherapy [formerly pelvic RT and vaginal brachytherapy, with (or without) chemotherapy].

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 overall survival in any of the trials. However, many of these trials had limitations because most of the patients were low risk (ie, they had low-risk intrauterine pathologic risk factors). Thus, the trials were underpowered for patients with high-risk factors. It is recognized that in patients with uterine-confined disease, there is a spectrum of risk based on intrauterine pathologic findings. Adverse intrauterine pathologic risk factors include high-grade tumors, deep myometrial invasion (and consequently more advanced stage), LVSI, and serous or clear cell 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).^{172,173} In the third trial (ASTEC/EN.5), only 50% of the patients were thoroughly staged as part of a companion surgical protocol.^{65,174} However, formal surgical staging was mandated for all patients in the fourth trial (Gynecologic Oncology Group [GOG] 99).¹⁷⁵ 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.^{172,176} Although RT significantly decreased locoregional recurrence, it did not increase overall survival.¹⁷⁷ The Aalders' randomized trial found that RT reduced vaginal (ie, locoregional) recurrences but did not reduce distant metastases or improve survival.¹⁷³ A recent pooled randomized trial (ASTEC/EN.5) suggested that adjuvant pelvic RT alone did not improve either relapse-free survival (ie, PFS) or overall survival in patients with intermediate-risk or high-risk early-stage endometrial cancer, but there was a small improvement in pelvic control.¹⁷⁴ However, the ASTEC/EN.5 study is very controversial; 51% of the patients in the ASTEC observation group

received vaginal brachytherapy.^{69,178} The Keys' trial (GOG 99) showed that adjuvant pelvic RT improved locoregional control and relapse-free interval (ie, PFS), without overall survival benefit.¹⁷⁵ 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.^{175,179,180}

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.^{172,175} 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.¹⁷⁵ 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.^{172,179}

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 overall survival.¹⁸¹ 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.¹⁷⁹⁻¹⁸⁸ 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);^{49,51} 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.¹⁸⁹

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), overall survival (OS), and disease-free survival (DFS), and treatment given (EBRT versus vaginal brachytherapy) were predictive for LRR and DFS.¹⁶³ The benefit of adjuvant external-beam RT (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 overall survival in those with high-risk disease.^{190,191} 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.^{183,192-196}

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 overall survival 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.¹⁸³

Adjuvant Chemotherapy

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.^{175,176} Therefore, some clinicians suggested that adding chemotherapy to adjuvant RT may provide added therapeutic benefit (ie, decrease distant metastases).^{165,197} Studies have evaluated the role of chemotherapy in highest risk uterine-confined disease.^{197,198} PFS is improved with adjuvant sequential chemotherapy/RT.¹⁹⁷ However, the NCCN Panel feels that adjuvant chemotherapy is a category 2B recommendation in this setting because an overall survival advantage has not been shown.¹⁹⁷ 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.¹⁹⁹⁻²⁰¹ Patients with extrauterine disease confined to the lymph nodes or the adnexa may be treated with pelvic or extended-field RT alone.²⁰² However, chemotherapy is regarded as the foundation of adjuvant therapy for patients with extrauterine disease. For stage III tumors, the recommended options are shown in the algorithm (see *Adjuvant Treatment for Stage III* in the NCCN Guidelines for

Endometrial Carcinoma) and include chemotherapy and/or tumor-directed RT.

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.^{203,204} 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/m²) and cisplatin (50 mg/m²) treatment, with an additional cycle of cisplatin (AP). This GOG trial reported that AP chemotherapy improved PFS and overall survival when compared with whole abdominopelvic RT; however, acute toxicity (eg, peripheral neuropathy) was greater in the AP chemotherapy arm.¹⁶⁰

The GOG 122 study established the role of adjuvant multiagent systemic chemotherapy for curative intent in patients with extrauterine disease. Thus, in the NCCN Guidelines, chemotherapy 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.¹⁶⁰ 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).^{162,205,206}

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).¹⁶¹

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.²⁰¹ In a retrospective review of 116 patients with stage IIIC endometrial cancer, adjuvant RT significantly improved overall survival 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 overall survival compared with those who did not.²⁰⁷ 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.²⁰⁸ The role of adjuvant RT with chemotherapy 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 brachytherapy.¹⁶⁶ 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,²⁰⁹ studies have focused on subtle effects on quality of life (eg, diarrhea, bowel symptoms) that deserve further investigation.^{184,186} In the PORTEC-2 trial, vaginal brachytherapy was associated with better quality of life when compared with EBRT without a significant detriment to outcome.¹⁸⁴ 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).³² These recommendations recognize that the value of intensive surveillance has not been

demonstrated in this disease; therefore, ancillary testing is not recommended.^{210,211}

Patients with clinical stage I and stage II endometrial cancer have a recurrence rate of approximately 15%,^{23,211-213} 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.²¹¹ 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 the 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), including lifestyle, obesity, exercise, smoking cessation and nutrition counseling (see the NCCN Guidelines for Survivorship, the NCCN guidelines for Smoking Cessation, and <http://www.cancer.org/treatment/survivorshipduringandaftertreatment/index>).²¹⁴⁻²¹⁶ Patients should be educated regarding sexual health, vaginal dilator use, and vaginal lubricants or moisturizers. 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.^{210,211,213,217} 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.²¹⁸ 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%).²¹⁹

Hormone Replacement Therapy for Hypoestrogenism

After BSO, hypoestrogenism is associated with hot flashes, mood lability, vaginal dryness, pelvic soft tissue atrophy, osteoporosis, and an increased risk of cardiovascular disease. In postmenopausal women, estrogen replacement therapy was believed to reduce or reverse some of these signs and symptoms. However, women who have had BSO for endometrial adenocarcinoma have usually been denied estrogen replacement therapy for fear of inducing a higher relapse rate, because this cancer has historically been considered an estrogen-linked malignancy.^{220,221} 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.²²²⁻²²⁴ 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.²²⁵ However, estrogen replacement trials in postmenopausal females without a history of malignancy have demonstrated a significantly increased risk of breast cancer.²²⁶

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.²²⁷ 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.²²⁸

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.^{229,230} 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.^{231,232} 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).^{233,234}

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 chemotherapy [or hormonal 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%²³⁵⁻²³⁷. Prognosis is worse if there is extravaginal extension or pelvic lymph node involvement.²³⁶

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) chemotherapy. In selected patients, radical surgery (ie, pelvic exenteration) has been performed with reported 5-year survival rates approximating 20%.²³⁸⁻²⁴¹

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 chemotherapy (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 chemotherapy on progression. Symptomatic, higher grade, or large volume metastases can be treated with chemotherapy 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.^{151-153,242-244} 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.^{155,245-247} Tamoxifen has a 20% response rate in those who do not respond to standard progesterone therapy.^{248,249} Tamoxifen has also been combined with progestational agents; however, a few patients had grade 4

thromboembolic events with this combination regimen.^{151,242,250} In some patients, aromatase inhibitors (eg, anastrozole, letrozole) may be substituted for progestational agents or tamoxifen.^{154,155,247,251}

Other hormonal modalities have not been well studied, and adjuvant therapy with hormonal agents has not been compared with cytotoxic agents.^{155,252} 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.

Chemotherapy

Chemotherapy for endometrial cancer has been extensively studied.^{253,254} 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.^{255,256} 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.^{253,254}

Carboplatin and paclitaxel is an increasingly used regimen for advanced/metastatic or recurrent endometrial cancer; the response rate is about 40% to 62%, and overall survival is about 13 to 29 months.²⁵⁷⁻²⁶⁰ A phase III trial (GOG 209) compared carboplatin and paclitaxel versus cisplatin, doxorubicin, paclitaxel, and filgrastim (granulocyte-colony stimulating factor).²⁵⁷ 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.²⁶¹

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).^{155,262-264} When single agents are used as first-line treatment, responses range from 21% to 36%.^{247,265} When single agents are used as second-line treatment, responses range from 4% to 27%; paclitaxel is the most active in this setting.²⁶⁵ Some oncologists have used liposomal doxorubicin, because it is less toxic than doxorubicin; the response rate of liposomal doxorubicin is 9.5%.²⁶⁶ Docetaxel is recommended (category 2B) 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.^{150,267}

New biologic and molecular therapies for the treatment of recurrent or metastatic endometrial carcinoma are being assessed in clinical trials.^{150,268} Bevacizumab was shown to have a 13.5% response rate and overall survival rate of 10.5 months in a phase II trial for persistent or recurrent endometrial cancer.²⁶⁹ Temozolomide 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.²⁷⁰ Based on these studies, the NCCN Panel considers bevacizumab or temozolomide as appropriate single-agent biologic therapy for patients who have progressed on previous cytotoxic chemotherapy.²⁶⁸⁻²⁷¹ Everolimus combined with letrozole is also under investigation for recurrent disease with positive preliminary findings.²⁷²

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.²⁷³⁻²⁸⁰ Carcinosarcomas are aggressive tumors that are staged as high-grade endometrial cancer (see Table 1).^{281,282} 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, 7th edition) as endometrial cancers (see Table 1).⁴⁹

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).^{277,280,283,284} 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/CT may be useful before surgery to assess if extrauterine disease is present; PET may also be useful.²⁷³ 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).²⁸⁵

Adjuvant therapy is highly individualized.²⁸⁶⁻²⁹³ For patients with stage IA without myometrial invasion, options include: 1) observation (if no residual disease in hysterectomy specimen); 2) chemotherapy with (or without) vaginal brachytherapy; or 3) tumor-directed RT.²⁹⁴ For all other patients with more advanced disease, chemotherapy with (or without) tumor-directed RT is the preferred option.^{275,287,291,295} 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).^{273-275,296-298}

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.^{160,295,299}

Chemotherapy with (or without RT) appears to be more effective than RT alone.²⁸⁷ Data are conflicting regarding the rate of abdominal recurrence in these patients.^{295,300-304} 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 and/or 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,³⁰⁵ indicating the potential benefits of combined modality therapy.

Retrospective data was reviewed from 279 patients with serous or clear cell carcinoma who were treated at high-volume cancer centers.

Adjuvant treatment (RT, chemotherapy, or chemoradiation) was associated with improved OS in stages IB-II disease but not stage IA disease (HR, 0.14; 95% CI, 0.02 to 0.78; $p=0.026$) disease.³⁰⁶ 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.^{307,308} Vaginal brachytherapy reduced the vaginal recurrence rate but did not impact PFS or OS.³⁰⁷ 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.³⁰⁸

For treating carcinosarcoma, ifosfamide was historically considered the most active single agent.^{297,309,310} 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.^{297,311} Overall survival was 13.5 months with ifosfamide/paclitaxel versus 8.4 months with ifosfamide alone. Therefore, ifosfamide/paclitaxel is category 1 in the NCCN Guidelines (see *Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease in the NCCN Guidelines for Endometrial Carcinoma*).^{297,299} 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%).³¹² A GOG trial is currently assessing ifosfamide/paclitaxel versus carboplatin/paclitaxel.²⁸¹

Data regarding carcinosarcoma suggest that adjuvant pelvic radiotherapy decreases the rate of local recurrences when compared with surgery alone.³¹³⁻³¹⁸ This local control improvement in some series correlates with an improvement in survival, although other data show that lymphadenectomy confers greater benefit.³¹⁷⁻³²⁰ 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.^{299,304} A recent cohort study in women with early-stage MMT suggests that postoperative chemotherapy improves PFS compared to RT or observation.²⁸¹

Uterine Sarcomas

Overview

In 2015, an estimated 1600 cases of uterine sarcomas are anticipated (about 3% of all uterine neoplasms).^{1,2} Uterine sarcomas are malignant mesenchymal tumors that include endometrial stromal sarcoma (ESS), undifferentiated uterine sarcoma (UUS), and uterine leiomyosarcoma (uLMS) (see *Uterine Sarcoma Classification* in the NCCN Guidelines for Uterine Sarcoma). According to 2012 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.³²¹ Even rarer subtypes of malignant mesenchymal tumors that can occur in the uterus include adenosarcoma, rhabdomyosarcoma (RMS), and perivascular epithelioid cell neoplasm (PEComa).³²² Carcinosarcomas were previously categorized and included in the sarcoma treatment algorithms until the mid-2000's, but are now considered and treated as high-grade epithelial tumors (carcinomas).²⁷⁷ Screening for Lynch syndrome is not usually done for patients with malignant mesenchymal tumors.

Endometrial stromal sarcomas are composed of cells resembling the endometrial stroma in the proliferative phase.^{322,323} 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.³²⁴⁻³²⁷ More recently, a higher-grade and more aggressively-behaving ESS variant with a unique genetic

rearrangement *YWHAE-FAM22A/B*, also known as *YWHAE-NUTM2A/B*, was identified.^{328,329} 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 (4th) 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 histopathological entities.³³⁰

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 (e.g., 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.³³¹ A new staging system for ESS and uLMS from FIGO/AJCC took effect in 2009 (see Table 2).^{49,332} This updated staging system accounts for the differences between uterine sarcomas and endometrial cancers.

Evaluation should include expert pathologic review and imaging (ie, CT scan of the chest, abdomen, and pelvis; or MRI; or PET-CT). It is important to determine if the sarcoma is confined to the uterus or if

extrauterine disease is present. 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).³³³

Uterine sarcoma should be removed en bloc to optimize outcomes; morcellation is contraindicated.¹²⁶⁻¹²⁸ 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.³³⁴ Additional surgical resection should be individualized based on clinical scenarios and intraoperative findings. Lymphadenectomy is controversial.^{2,322,334-337} High-grade uterine sarcomas tend to show hematogenous metastases to the lungs; lymph node metastases are uncommon.

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

Low-Grade Endometrial Stromal Sarcoma

If there is no evidence of disease after primary surgery for ESS, then observation can be considered (see *Additional Therapy* in the NCCN Guidelines for Uterine Sarcoma).^{335,336} Postoperative hormone therapy is recommended for stages I to IV ESS (category 2A for stages II-IV; category 2B for stage I). Adjuvant tumor-directed RT may be added for stage II-IVA (category 2B); palliative RT may be added for stage IVB.^{322,338,339} Typical hormone therapy includes megestrol, medroxyprogesterone, or aromatase inhibitors; gonadotropin-releasing hormone [GnRH] analogs (category 2B) are also an option.^{322,334,340} 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.^{334,339-341} Hormone therapy is also recommended

for ESS that have recurred or are unresectable (see *Therapy for Relapse* in the NCCN Guidelines for Uterine Sarcoma).³⁴⁰

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.³⁴² Adjuvant radiotherapy in ESS has been demonstrated to reduce local recurrence rates but again with limited effect on survival.^{343,344} Because of concerns about radiation exposure, frequent routine surveillance imaging is no longer recommended for asymptomatic young women after primary therapy for ESS.³⁴⁵

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 YWHAE-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.³¹³ Most retrospective studies of adjuvant RT suggest an improvement in local pelvic control but no appreciable or consistent improvement in overall survival, given the propensity of metastatic extrapelvic disease as a site of first or eventual recurrence.³⁴⁶⁻³⁴⁹ 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 overall survival for uLMS when compared with observation.³¹³ Therefore,

routine postoperative RT is not recommended for stage I patients with uLMS and high-grade (undifferentiated) endometrial sarcoma.³³⁸ 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 chemotherapy is also poorly defined; however, adjuvant chemotherapy 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) chemotherapy (category 2B). 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 chemotherapy and/or RT (see *Additional Therapy* in the NCCN Guidelines for Uterine Sarcoma).³⁵⁰ In patients with incompletely resected or metastatic disease, chemotherapy with (or without) palliative RT 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.³⁵¹

If chemotherapy is used, gemcitabine/docetaxel (preferred for uLMS) is recommended for uterine sarcoma (see *Systemic Therapy* in the NCCN Guidelines for Uterine Sarcoma).^{323,352-356} Other combination regimens include doxorubicin/ifosfamide, doxorubicin/dacarbazine, gemcitabine/dacarbazine, and gemcitabine/vinorelbine.^{310,357-359}

Doxorubicin is an active single agent for uLMS and is less toxic than combination regimens.^{322,360} 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).^{322,323,352,357,358,361-377} Aromatase inhibitors can be considered for ER/PR-expressing uLMS.³⁷⁸

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.³⁵⁷

In 2016, eribulin and trabectedin were both included in the guidelines as category 2A recommendations for systemic therapy. 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.³⁷⁹ Median overall survival was 13.5 and 11.5 months for eribulin and dacarbazine, respectively (HR = 0.77, 95% CI 0.62–0.95; $P = 0.017$). Data have also indicated that trabectedin may be useful in patients who have exhausted standard chemotherapy.³⁸⁰⁻³⁸³ 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.³⁸⁴ Following its October 2015 FDA approval, trabectedin was added to the guidelines as an option for unresectable or metastatic uterine leiomyosarcoma previously treated with an anthracycline-containing regimen.

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). 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, and nutrition counseling (see the NCCN Guidelines for Survivorship, NCCN Guidelines for Smoking Cessation, and <http://www.cancer.org/treatment/survivorshipduringandaftertreatment/index>).²¹⁴⁻²¹⁶ 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%).² 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 tumor-directed RT with (or without) systemic therapy. Hormone therapy is an option for patients with ESS. Preoperative RT 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) tumor-directed reirradiation. A recent retrospective analysis of patients with ESS suggested that cytoreductive resection improved OS in patients with recurrent lesions.³⁸⁵ Systemic therapy with (or without) palliative RT or supportive care is recommended for metastatic disease.³⁶⁰ For patients with isolated metastases, surgical resection or other ablative therapy (eg, radiofrequency ablation, stereotactic body RT) may be appropriate. Postoperative RT and/or systemic therapy can be considered. Systemic therapy and/or local ablative therapy are

reasonable options for patients with unresectable isolated metastases (see *Therapy for Relapse* in the NCCN Guidelines for Uterine Sarcoma).^{373,386-388}

Drug Reactions

Virtually all drugs have the potential to cause adverse hypersensitivity reactions, either during or after the infusion.³⁸⁹ 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 reactions, cardiovascular reactions, respiratory or throat tightness), but more severe allergic reactions (ie, life-threatening anaphylaxis) can occur.³⁹⁰⁻³⁹² In addition, patients can have mild allergic reactions or severe infusion reactions. Infusion reactions are more common with paclitaxel.³⁹³ Allergic reactions (ie, true drug allergies) are more common with platinum agents (ie, carboplatin, cisplatin).^{393,394}

Management of drug reactions is discussed in the NCCN Guidelines for Ovarian Cancer.³⁹³ 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.³⁹⁵⁻³⁹⁷ Patients must be desensitized with each infusion if they previously had a reaction. Almost all patients can be desensitized (about 90%).³⁸⁹ To maximize safety, it is prudent to desensitize patients in the intensive care unit.³⁸⁹

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