National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Uterine Neoplasms

Version 1.2014

NCCN.org

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Uterine Neoplasms

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NCCN Guidelines Panel Disclosures

Ω Gynecologic 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

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2014 Updates Uterine Neoplasms

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Updates in Version 1.2014 of the NCCN Guidelines for Uterine Neoplasms from Version 1.2013 include:

Global Changes

- The following tumor classifications were revised:
  - "Papillary serous" changed to "Serous adenocarcinoma."
  - "Clear cell carcinoma" changed to "Clear cell adenocarcinoma."
  - "High-grade undifferentiated sarcoma" changed to "High-grade (undifferentiated) endometrial sarcoma."
  - "Epithelial carcinoma" changed to "Malignant epithelial carcinoma."
  - "Pure endometrioid" changed to "Pure endometrioid carcinoma."
- Principles of Radiation; First bullet: The following sentence was added: "Diagnostic imaging is often used to assess locoregional extent and to rule out distant metastases before administration of RT." (UN-A)
- The Discussion has been updated to correspond with the changes in the algorithm. (MS-1)

Uterine Neoplasms

UN-1

- Initial Evaluation
  - The recommendation "Current cervical cytology consistent with NCCN Cervical Cancer Screening Guidelines." was removed.
  - Optional; Second bullet: Modified to "Consider genetic counseling/testing for ~~young~~ patients (< ~~55~~ 50 y) and those with..."
- Third column; Stromal/mesenchymal tumors; the decision points of "Disease limited to uterus" and "Known or suspected extrauterine disease" were removed.
- Footnote "a" was revised: "~~Screening with immunohistochemistry (IHC) should be considered in all patients, but especially in patients younger than 55 years. In relatives with Lynch syndrome, but without endometrial cancer, a yearly endometrial biopsy is recommended until a hysterectomy and bilateral salpingo-oophorectomy (BSO) are performed~~. Recently, immunohistochemistry (IHC) and/or microsatellite instability (MSI) screening of all colorectal and endometrial cancers, regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for Lynch syndrome (LS). An infrastructure needs to be in place to handle the screening results. IHC and/or MSI screening is usually performed on epithelial tumors and not stromal/mesenchymal endometrial tumors." Footnote "a" was also added to page ENDO-A.
- Footnote "b" was revised: "By definition, ESS ~~is low-grade histology~~ has low-grade cytologic features. High-grade subtypes of endometrial sarcomas (undifferentiated endometrial sarcomas in WHO classification) are still being defined." This footnote was also added to the Uterine Sarcoma algorithms (UTSARC-1).

Endometrial Carcinoma:

- ENDO-1
- Operable pathway; Primary Treatment:
  - The recommendation "Patient desires fertility-sparing options (See ENDO-2)" was added.
  - The recommendation was modified "Total hysterectomy and bilateral salpingo-oophorectomy (TH/BSO) and surgical staging." The sub-bullets of "Cytology" and "Pelvic and para-aortic lymph node dissection" and corresponding footnotes were removed from this page and placed in the "Principles of Surgical Evaluation and Staging" (ENDO-A). (Also for ENDO-3 and ENDO-4)
    - The next column was modified: "Adjuvant treatment for ~~completely~~ surgically staged..." (Also for ENDO-3, ENDO-4, ENDO-8)
- Footnote "c" is new to the algorithm: "The degree of surgical staging to assess disease status depends on preoperative and intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C)."

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Endometrial Carcinoma--continued

ENDO-1

- The following footnotes were removed:
  - Although peritoneal cytology by itself does not affect 2010 FIGO staging, cytology results should still be obtained and recorded.
  - See Discussion for routine lymphadenectomy.
  - Some patients may not be candidates for lymph node dissection.

ENDO-2

- A new section was added that provides recommendations for fertility-sparing treatment options for early-stage disease.

ENDO-4

- Additional Workup; Second bullet: Changed to "MRI/CT/PET, as clinically indicated."
- Intra-abdominal pathway; Primary Treatment: Recommendation modified, "TH/BSO and surgical staging ~~+ cytology +~~ surgical debulking ~~± pelvic and para-aortic lymph node dissection~~."

ENDO-5

- Clinical Findings: Modified to, "~~Completely~~ Surgically staged." (Also for ENDO-6 and ENDO-7)

ENDO-7

- Stage IIIC1 and Stage IIIC2; Adjuvant Treatment: Recommendation changed to "Chemotherapy ~~and/or~~ ± tumor-directed RT."

ENDO-8

- Third column: Modified to "~~Radiologic~~ imaging."
- After "Imaging" the finding "Positive" changed to "Suspicious/Positive."
- For Stage IA, G3; Stage IB; Stage II: The recommendation changed to "Consider surgical restaging (category 3) or pathologic confirmation of metastatic disease in select patients." After this recommendation, the following two decision points were added, "Surgically restaged" and "No surgical restaging."

ENDO-9

- Surveillance
  - Second bullet changed to "Patient education regarding symptoms, lifestyle, obesity, exercise, and nutrition counseling (see NCCN Guidelines for Survivorship)"

ENDO-9--(continued)

- Surveillance
  - Fourth bullet changed to "~~CT/MRI~~ Imaging as clinically indicated."
  - Fifth bullet changed to "Consider genetic counseling/testing for ~~young~~ patients (< ~~55~~ 50 y) and those with a significant family history of endometrial and/or colorectal cancer and/or selected pathologic risk features."
  - The following recommendations were removed: Vaginal cytology (category 3), Chest X-ray annually (category 2B).
- "Disseminated metastases" pathway: Recommendation modified to "Low grade or Asymptomatic or ER/PR positive."
- The following footnote was removed: "Screening with immunohistochemistry (IHC) should be considered in all patients, but especially in patients younger than 55 years."

ENDO-10

- Under "Therapy for Relapse": The recommendation was modified, "Surgical exploration of pelvis + resection ± IORT (category 3 for IORT)."

ENDO-11---Serous or Clear Cell Adenocarcinoma or Carcinosarcoma of the Endometrium

- The page title was revised for clarity.
- Additional Workup: Second bullet: Changed to "MRI/CT/PET, as clinically indicated."
- Primary Treatment:
  - Second bullet modified: "TH/BSO and surgical staging ~~, pelvic and para-aortic lymph node dissection, cytology, omentectomy, biopsies of peritoneal surfaces (including underside of diaphragm)~~."
  - Third bullet modified: "Consider maximal tumor debulking for gross disease."
- Adjuvant Treatment
  - Stage IA (no myometrial invasion)": Recommendation changed to, "Chemotherapy ± vaginal brachytherapy."
  - Stage III, IV: Recommendation changed to, "Chemotherapy ± tumor-directed RT ~~or Whole abdominopelvic RT (category 3) ± vaginal brachytherapy (category 3)~~."
- Footnote "q" was modified: "... or malignant mixed Müllerian tumor. ~~Most~~ Carcinosarcomas are treated the same as poorly differentiated adenocarcinomas."

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Endometrial Carcinoma--continued

ENDO-A---Hysterectomy and Pathologic Evaluation

- Page title changed to "Hysterectomy and Pathologic Evaluation."
- Pathologic assessment
  - Uterus; Last bullet: Modified to "Consider screening ~~disease~~ with IHC and MSI for inherited mismatch repair gene mutations in ~~young~~ patients < ~~55~~ 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."
  - "Nodes" changed to "Nodes (when resected)."

ENDO-B--Principles of Evaluation and Staging

- This is a new section that provides recommendations and techniques for surgical staging, sentinel lymph node mapping, and surgical evaluation for endometrial cancer.

ENDO-C---Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease

- Hormone Therapy; Last bullet changed to "Megestrol/tamoxifen (alternating)."
- Chemotherapy Regimens
  - Multi-agent chemotherapy:
    - Cisplatin/doxorubicin changed from category 1 to category 2A.
    - Cisplatin/doxorubicin/paclitaxel changed from category 1 to category 2A.
  - Single agents
    - Temsirolimus and Topotecan were added as options.
    - Bevacizumab changed from category 2B to category 2A.
- Footnote 6 is new the algorithm: "The cisplatin/doxorubicin/paclitaxel regimen is not widely used because of concerns about toxicity."

Uterine Sarcoma

UTSARC-1

- Primary Treatment: The recommendation: "TH/BSO" changed to "TH ± BSO" for "Disease limited to the uterus" and for "Known or suspected extrauterine disease."

UTSARC-2

- Endometrial stromal sarcoma; Additional Therapy:
  - The following statement was added under the column heading: "Consider observation for patients if no evidence of disease after primary surgery."

UTSARC-2--continued

- Endometrial stromal sarcoma; Additional Therapy:
  - Stage I: The recommendation was modified: "~~Observe or~~ Hormone therapy (category 2B)." "The option of "Observe" was removed here and included in the column heading.

UTSARC-3

- High-grade (undifferentiated) endometrial sarcoma and Uterine leiomyosarcoma; Additional Therapy:
  - Stage I: "Consider pelvic RT and/or brachytherapy (category 3)" was removed as a treatment option.

UTSARC-4

- Surveillance:
  - Second bullet modified: "Consider CT imaging (chest/abdomen/pelvis), every 3-6 mo for 2-3 y, then every 6 mo for next 2 y, then annually."
  - Third bullet modified: "Consider other imaging (MRI/PET) as clinically indicated."
- Therapy for Relapse; Isolated metastases; Resectable: The recommendation changed to "Surgical resection or other local ablative therapy..."

UTSARC-5

- Local recurrence; Therapy for relapse: The IORT recommendations for patients with or without prior RT changed from category 2A to category 3.

UTSARC-A Systemic Therapy for Uterine Sarcoma

- Chemotherapy Regimens
  - Combination regimens: Modified as "Docetaxel/gemcitabine (preferred for leiomyosarcoma)"
  - Single-agent options: Dacarbazine changed from category 2B to category 2A.
- Hormone Therapy (ESS only)
  - Aromatase inhibitors changed from category 2B to category 2A.
  - "Tamoxifen (category 3)" was removed as an option.

UTSARC-B Uterine Sarcoma Classification

- See the "Global Changes" for updates made to this page.

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

INITIAL EVALUATION

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

Optional:

- Liver function test (LFT)/renal function tests/chemistry profile
- Consider genetic counseling/testing for patients (<50 y) and those with a significant family history of endometrial and/or colorectal cancer[a] (See Lynch syndrome/HNPCC in NCCN Guidelines for Colorectal Cancer Screening)

→ Expert pathology review

INITIAL CLINICAL FINDINGS

Malignant Epithelial carcinoma

- Pure endometrioid carcinoma
  - Disease limited to uterus → See Primary Treatment (ENDO-1)
  - Suspected or gross cervical involvement → See Primary Treatment (ENDO-3)
  - Suspected extrauterine disease → See Primary Treatment (ENDO-4)
- Serous adenocarcinoma or Clear cell adenocarcinoma → See Treatment for Serous or Clear Cell Adenocarcinoma or Carcinosarcoma of the Endometrium (ENDO-11)
- Carcinosarcoma[c,d] → See Treatment for Serous or Clear Cell Adenocarcinoma or Carcinosarcoma of the Endometrium (ENDO-11)

Stromal/mesenchymal tumors

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

→ See Primary Treatment (UTSARC-1)

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

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

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

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

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

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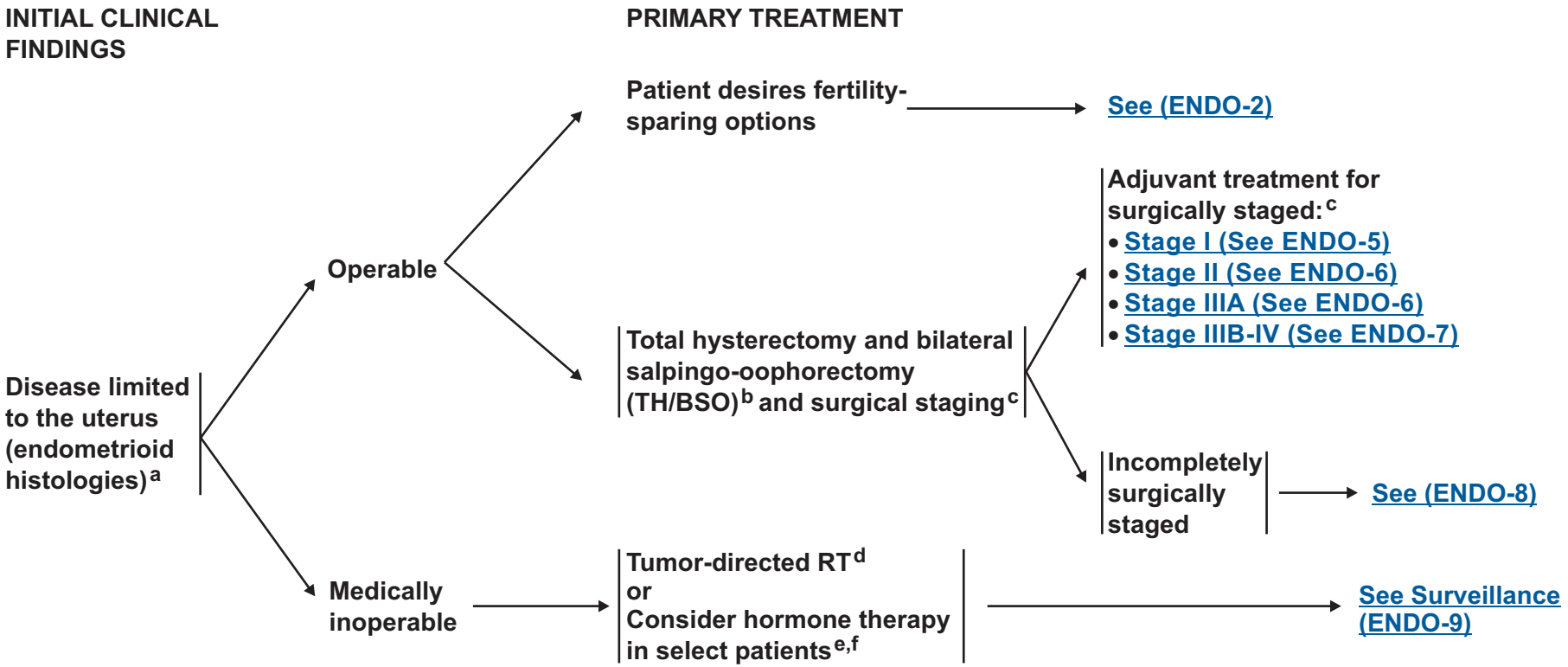

[a] See (UN-1) for clarification of uterine neoplasms.
[b] See Hysterectomy and Pathologic Evaluation (ENDO-A).
[c] The degree of surgical staging to assess disease status depends on preoperative and intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-B).
[d] See Principles of Radiation Therapy (UN-A).
[e] Patients should be closely monitored. Consider endometrial biopsies every 3 to 6 months.
[f] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-C).

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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 (ie, stage IA disease)
- 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 a standard of care for the treatment of endometrial carcinoma

→ **PRIMARY TREATMENT**

- Consultation with an infertility specialist is recommended prior to therapy
- Consider genetic counseling/testing if not already done (See UN-1)

→ Continuous progestin-based therapy:
- Megestrol
- Medroxyprogesterone
- Levonorgestrel IUD

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

SURVEILLANCE

→ Complete response by 6 mo → Encourage conception[g] (with continued surveillance every 3-6 mo) → TH/BSO with staging[c] after childbearing complete or progression of disease on endometrial sampling (see ENDO-1)

→ Endometrial cancer present at 6 months or later → TH/BSO with staging[c] (see ENDO-1)

[c] The degree of surgical staging to assess disease status depends on preoperative and intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-B).

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

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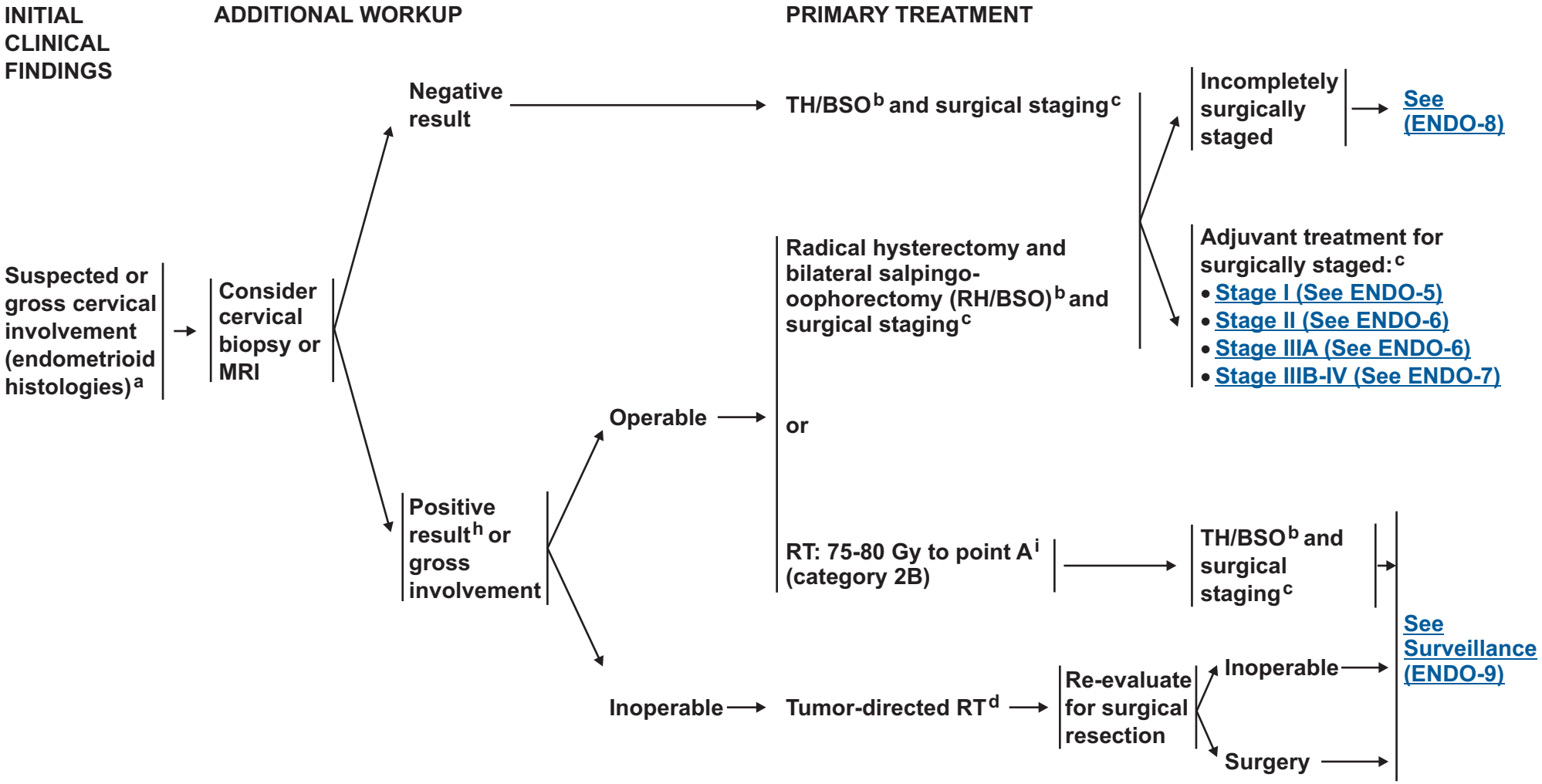

[a] See (UN-1) for clarification of uterine neoplasms.
[b] See Hysterectomy and Pathologic Evaluation (ENDO-A).
[c] The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-B).
[d] See Principles of Radiation Therapy (UN-A).
[h] Clear demonstration of cervical stromal involvement.
[i] Based on summation of conventional external-beam fractionation and low-dose-rate brachytherapy equivalent.

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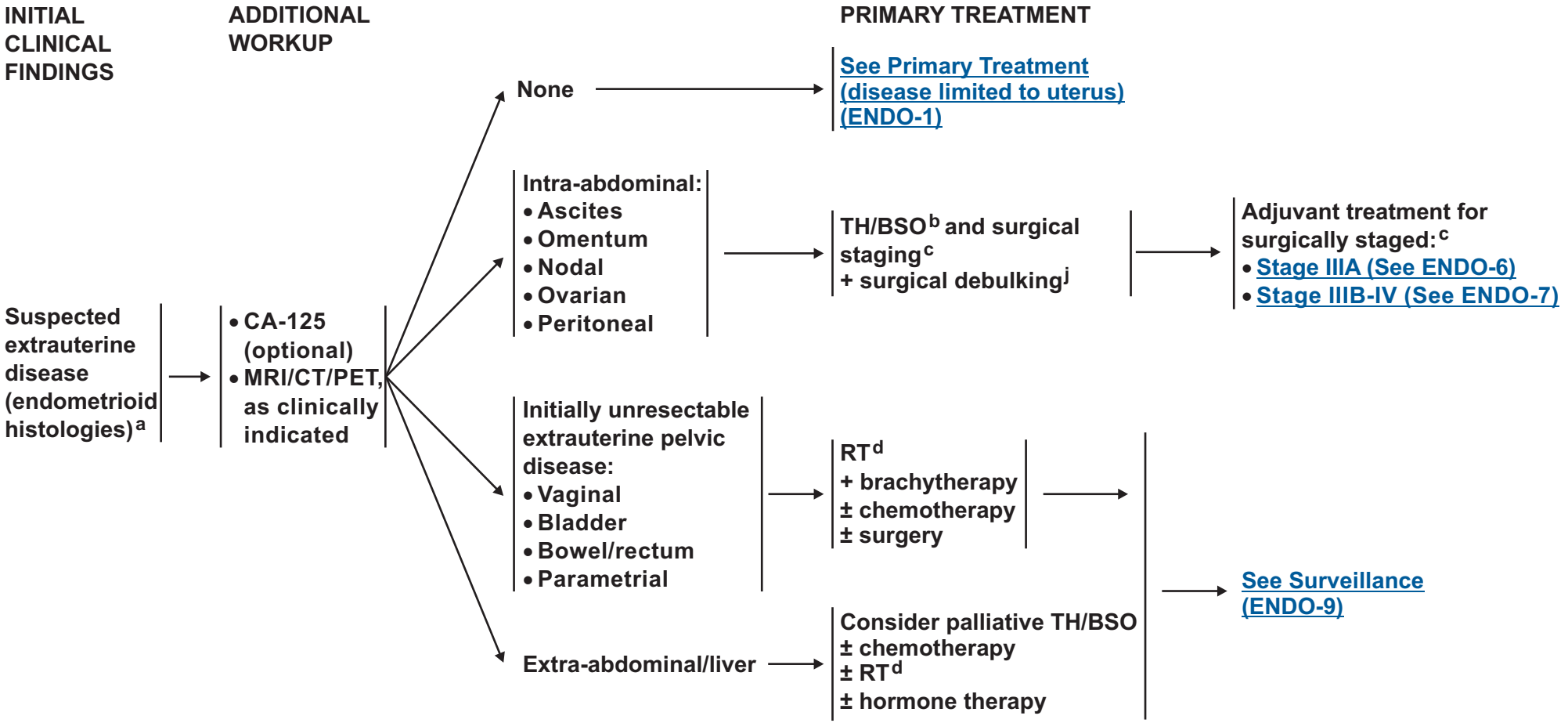

[a] See (UN-1) for clarification of uterine neoplasms.
[b] See Hysterectomy and Pathologic Evaluation (ENDO-A).
[c] The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-B).
[d] See Principles of Radiation Therapy (UN-A).
[j] The surgical goal is to have no measurable residual disease.

Note: All recommendations are category 2A unless otherwise indicated.
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All staging in guideline is based on updated 2010 FIGO staging. (See ST-1)

CLINICAL FINDINGS	ADVERSE RISK FACTORS[k]	HISTOLOGIC GRADE/ADJUVANT TREATMENT[d,l] G1	G2	G3
Surgically staged:[c] Stage I — 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 pelvic RT (category 2B for pelvic RT)	Observe or Vaginal brachytherapy and/or Pelvic RT
	Adverse risk factors not present	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or Pelvic RT
	Adverse risk factors present	Observe or Vaginal brachytherapy and/or Pelvic RT	Observe or Vaginal brachytherapy and/or Pelvic RT	Pelvic RT and/or Vaginal brachytherapy ± chemotherapy[m,n] (category 2B for chemotherapy) or Observe (category 2B)

[c] The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-B).

[d] See Principles of Radiation Therapy (UN-A).

[k] Potential adverse risk factors include the following: Age, positive lymphovascular invasion, tumor size, and lower uterine (cervical/glandular) involvement.

[l] Adjuvant therapy determinations are made on the basis of pathologic findings.

[m] The role of adjuvant chemotherapy in invasive high-grade uterine confined disease is the subject of current studies. (Hogberg T, Signorelli M, de Oliveira CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur J Cancer 2010;46:2422-2431.)

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

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See Surveillance (ENDO-9)

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

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

[c] The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-B).

[d] See Principles of Radiation Therapy (UN-A).

[l] Adjuvant therapy determinations are made on the basis of pathologic findings.

[m] The role of adjuvant chemotherapy in invasive high-grade uterine confined disease is the subject of current studies. (Hogberg T, Signorelli M, de Oliveira CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur J Cancer 2010;46:2422-2431.)

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

[o] Observation or vaginal brachytherapy is also an option for patients with stage II disease who have had a radical hysterectomy with negative surgical margins and no evidence of extrauterine disease.

[p] The adverse fundal risk factors influencing therapy decisions for stage I disease (see ENDO-5) may also impact the choice of adjuvant therapy for stage II disease.

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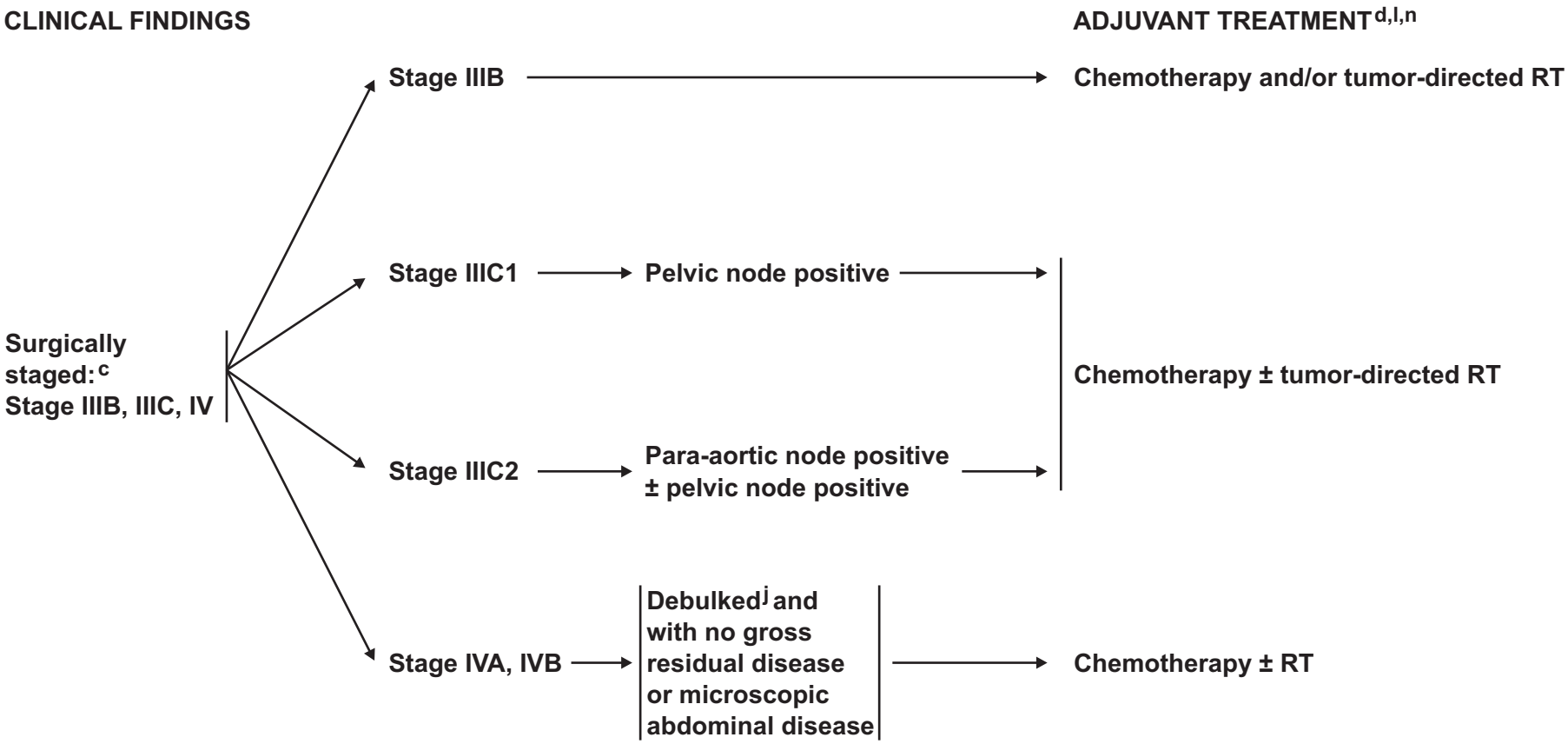
See Surveillance (ENDO-9)

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



[c] The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-B).

[d] See Principles of Radiation Therapy (UN-A).

[j] The surgical goal is to have no measurable residual disease.

[l] Adjuvant therapy determinations are made on the basis of pathologic findings.

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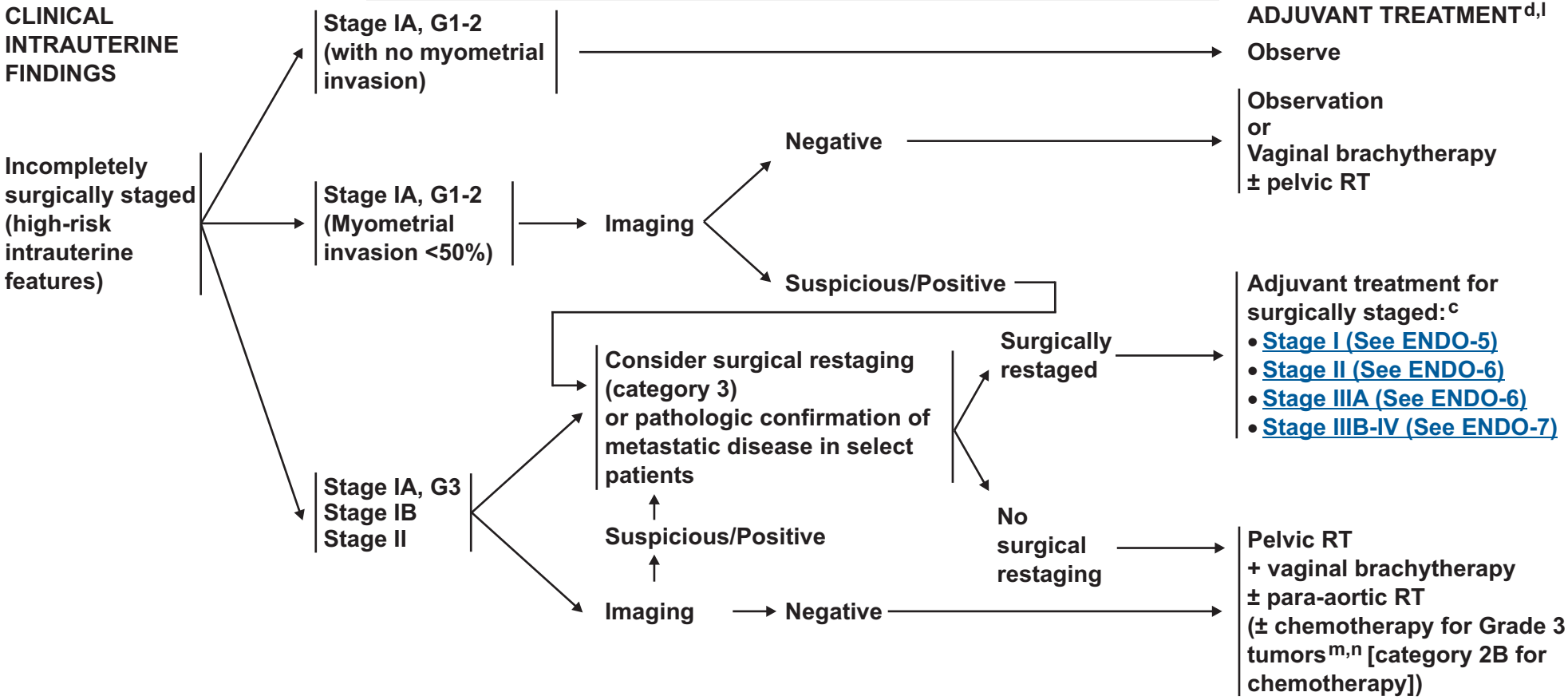
See Surveillance (ENDO-9)

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



[c] The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-B).

[d] See Principles of Radiation Therapy (UN-A).

[l] Adjuvant therapy determinations are made on the basis of pathologic findings.

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

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

See Surveillance (ENDO-9)

NCCN Guidelines Version 1.2014
Endometrial Carcinoma

SURVEILLANCE

- Physical exam every 3-6 mo for 2 y, then 6 mo or annually
- Patient education regarding symptoms, lifestyle, obesity, exercise, and nutrition counseling (See NCCN Guidelines for Survivorship)
- CA-125 (optional)
- Imaging as clinically indicated
- 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[q] (See Lynch syndrome/HNPCC in the NCCN Guidelines for Colorectal Cancer Screening)

CLINICAL PRESENTATION

- Local/regional recurrence
- Negative distant metastases on radiologic imaging

→ See Therapy For Relapse (ENDO-10)

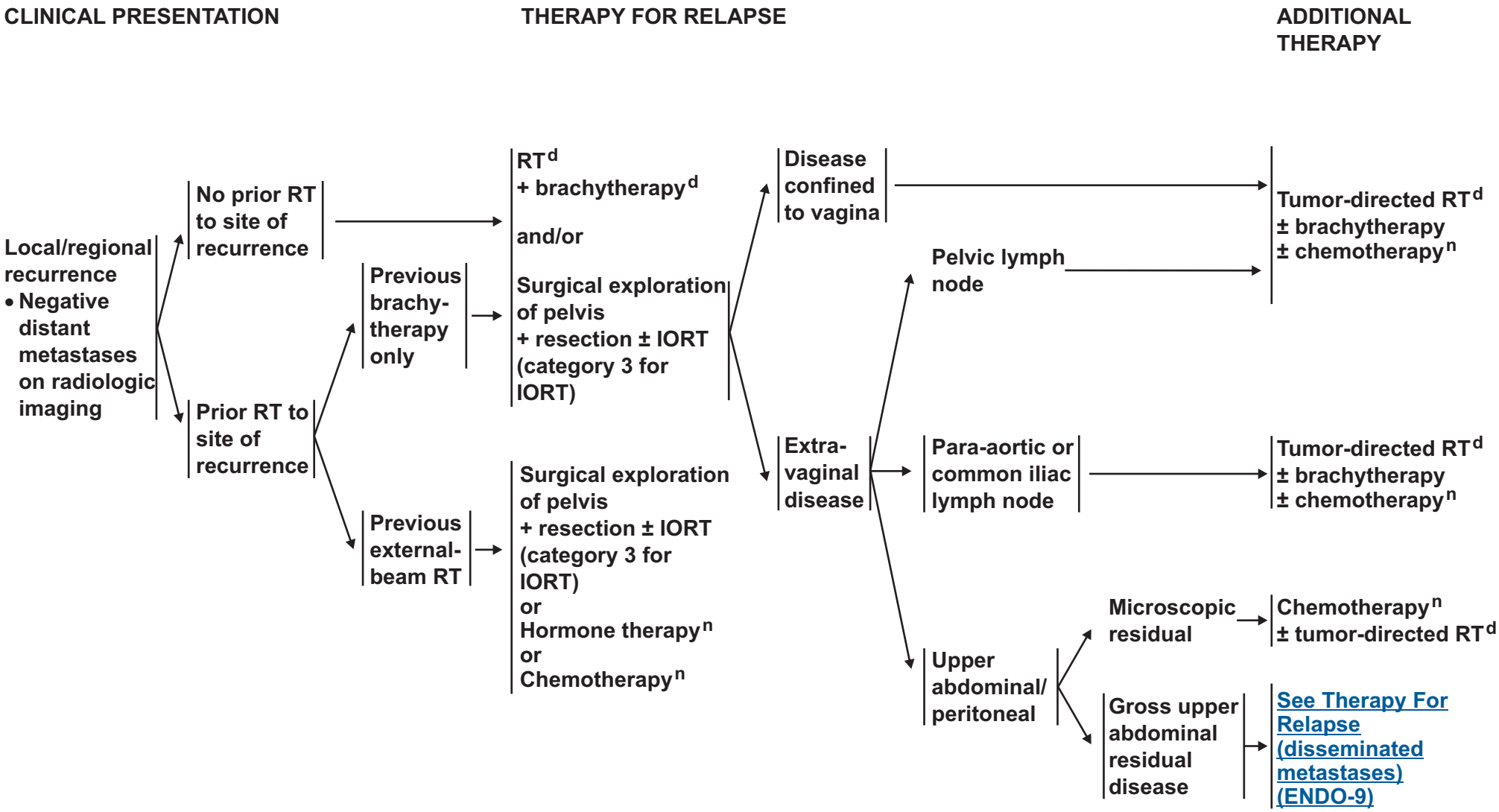
- Isolated metastases → Consider resection ± RT[d] → Unresectable or further recurrence → Treat as disseminated metastases (See below)
- Disseminated metastases
  - Low grade or Asymptomatic or ER/PR positive → Hormone therapy[n] → If progression, chemotherapy[n] → If progression, Best supportive care (See NCCN Guidelines for Palliative Care) or Clinical trial
  - Symptomatic or Grade 2, 3 or Large volume → Chemotherapy[n] ± palliative RT[d] → If progression, Best supportive care (See NCCN Guidelines for Palliative Care) or Clinical trial

[d] See Principles of Radiation Therapy (UN-A).

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

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

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



[d] See Principles of Radiation Therapy (UN-A).
[n] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-C).

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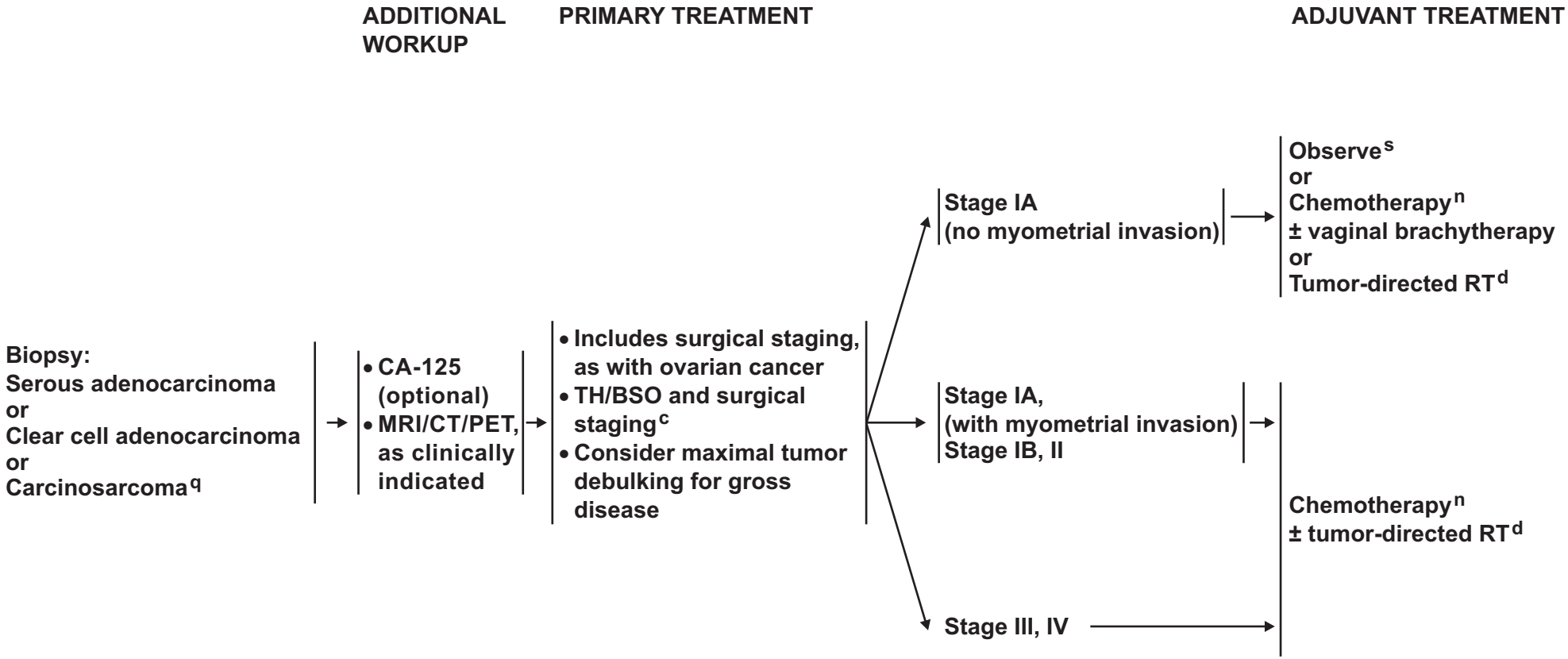
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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



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

[c] The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-B).

[d] See Principles of Radiation Therapy (UN-A).

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

[r] Also known as malignant mixed mesodermal tumor or malignant mixed Müllerian tumor. Carcinosarcomas are treated the same as poorly differentiated adenocarcinomas.

[s] Observation only for select patients with no residual disease in the hysterectomy specimen.

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

See Surveillance (ENDO-9)

HYSTERECTOMY AND PATHOLOGIC EVALUATION[1,2]

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

Pathologic assessment to include:

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

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

[2] See Principles of Evaluation and Surgical Staging (ENDO-B).

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

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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient 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[1-3]

- Total hysterectomy and bilateral salpingo-oophorectomy (TH/BSO) is the main treatment of apparent uterine confined endometrial cancer, unless patients are interested in and are candidates for fertility-sparing options (See ENDO-2). Many patients with locally advanced endometrial carcinoma are also candidates for TH/BSO. (See Hysterecomy and Pathologic Evaluation (ENDO-A))
- The hysterectomy and adnexectomy may be performed through laparotomy, vaginally, or via minimally invasive techniques such as laparoscopy or robotic surgery.
- Visual evaluation of the peritoneal, diaphragmatic, and serosal surfaces with biopsy of any suspicious lesions is important to exclude extrauterine disease.
- While peritoneal cytology does not affect staging, FIGO and AJCC continue to recommend that it be obtained and reported.
- Omental biopsy is commonly performed in tumors with serous adenocarcinoma, clear cell adenocarcinoma, or carcinosarcoma histology.
- Excision of suspicious or enlarged lymph nodes in the pelvic or paraaortic regions is important to exclude nodal metastasis.
- Pelvic nodal dissection with pathologic evaluation continues to be an important part of the surgical staging for selected uterine confined endometrial cancer as it can identify important prognostic information that may alter treatment decisions.
- Pelvic lymph nodes from the external iliac, internal iliac, obturator, and common iliac nodes are frequently removed for staging purposes.
- Para-aortic nodal evaluation from the inframesenteric and infrarenal regions may also be utilized for staging of select high-risk tumors such as deeply invasive lesions, high-grade histology, and tumors of serous adenocarcinoma, clear cell adenocarcinoma, or carcinosarcoma features.
- Sentinel lymph node (SLN) mapping may be considered (category 2B) in selected patients. (See pages 2-4 of ENDO-B)
- Some patients may not be candidates for lymph node dissection.

Continued

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

PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Principles of Sentinel Lymph Node (SLN) Mapping for Endometrial Cancer Staging

- The role of SLN mapping is currently being evaluated. No prospective randomized trials have been reported that evaluate this technique in endometrial cancer. 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 adenocarcinoma, clear cell adenocarcinoma, or carcinosarcomas) should be undertaken with particular caution.

- SLN mapping can be considered (category 2B) for the surgical staging of apparent uterine-confined malignancy when there is no metastasis demonstrated by imaging studies or no obvious extrauterine disease at exploration.

- A cervical injection with dye has emerged as a useful and validated technique for identification of lymph nodes that are at high risk for metastases (ie, SLN in patients with early-stage endometrial cancer[4-6]).

- 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-B 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-B 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-B 3 of 5).

- The radiolabeled colloid most commonly injected into the cervix is technetium-99m (^{99}mTc); 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.

- Low-volume nodal metastasis to SLN detected only by enhanced pathologic ultrastaging is another potential value to staging with SLN.[7-9]

- 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-B 4 of 5).[10-12]

Continued

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

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†

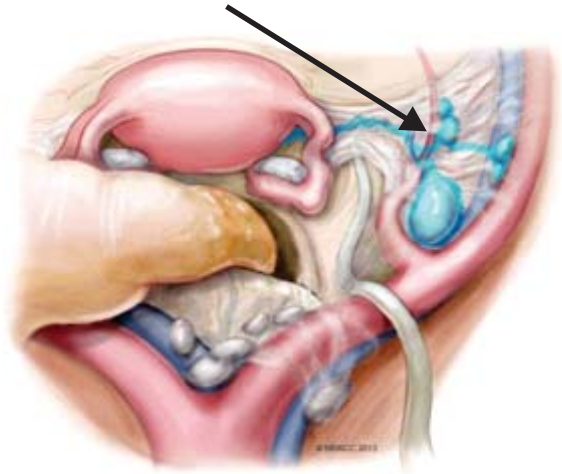
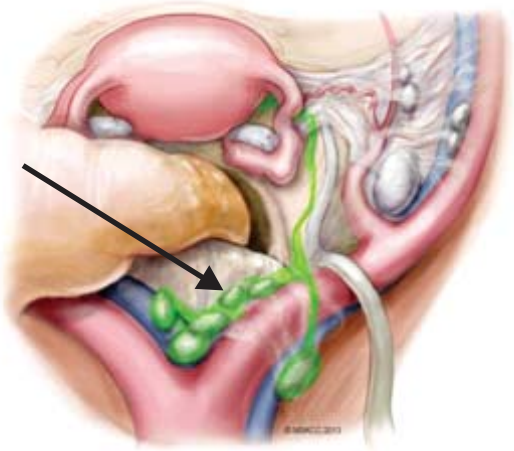


Figure 3: Less common location of SLNs (green, arrow) usually seen when lymphatic trunks are not crossing over the umbilical ligament but following the mesoureter cephalad to common iliac and presacral region†



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

Continued

Note: All recommendations are category 2A unless otherwise indicated.
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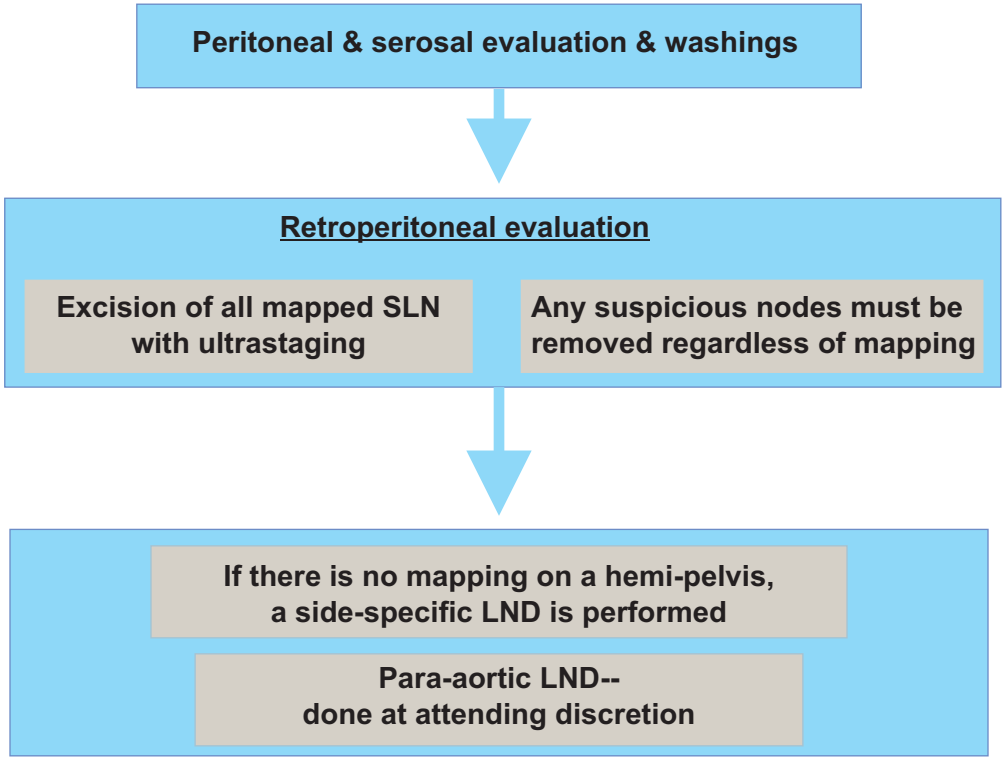
PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

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



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

Continued

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PRINCIPLES OF EVALUATION AND SURGICAL STAGING

[1]American College of Obstetricians and Gynecologists. ACOG practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstet Gynecol 2005;106:413-425.
[2]Bakkum-Gamez JN, Gonzalez-Bosquet J, Laack NN, et al. Current issues in the management of endometrial cancer. Mayo Clin Proc. 2008 Jan;83:97-112.
[3]Edge SB, Byrd DR, Compton CC. AJCC Cancer Staging Manual, 7th edition. New York: Springer; 2010.
[4]Abu-Rustum NR, Khoury-Collado F, Pandit-Taskar N, et al. Sentinel lymph node mapping for grade 1 endometrial cancer: is it the answer to the surgical staging dilemma? Gynecol Oncol 2009;113:163-169.
[5]Khoury-Collado F, Glaser GE, Zivanovic O, et al. Improving sentinel lymph node detection rates in endometrial cancer: how many cases are needed? Gynecol Oncol 2009;115:453-455.
[6]Khoury-Collado F, Murray MP, Hensley ML, et al. Sentinel lymph node mapping for endometrial cancer improves the detection of metastatic disease to regional lymph nodes. Gynecol Oncol 2011;122:251-254.
[7]Frimer M, Khoury-Collado F, Murray MP, et al. Micrometastasis of endometrial cancer to sentinel lymph nodes: is it an artifact of uterine manipulation? Gynecol Oncol 2010;119:496-499.
[8]Leitao MM Jr, Khoury-Collado F, Gardner G, et al. Impact of incorporating an algorithm that utilizes sentinel lymph node mapping during minimally invasive procedures on the detection of stage IIIC endometrial cancer. Gynecol Oncol 2013;129:38-41.
[9]Kim CH, Soslow RA, Park KJ, et al. Pathologic ultrastaging improves micrometastasis detection in sentinel lymph nodes during endometrial cancer staging. Int J Gynecol Cancer 2013;23:964-970.
[10]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.
[11]Vidal F, Leguevaque P, Motton S, Det al. Evaluation of the sentinel lymph node algorithm with blue dye labeling for early-stage endometrial cancer in a multicentric setting. Int J Gynecol Cancer 2013; 23:1327-1243.
[12]Abu-Rustum NR. The Increasing credibility of sentinel lymph node mapping in endometrial cancer. Ann Surg Oncol 2013;20:353-354.

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NCCN Guidelines Version 1.2014
Endometrial Carcinoma

NCCN Guidelines Index
Uteline Neoplasms TOC
Discussion

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

HORMONE THERAPY[1]

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

CHEMOTHERAPY REGIMENS[2,3]

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

[1] Hormonal therapy is for endometrioid histologies only (ie, not for serous adenocarcinoma, clear cell adenocarcinoma, or carcinosarcoma).

[2] Cisplatin, carboplatin, liposomal doxorubicin, paclitaxel, and docetaxel may cause drug reactions. (See NCCN Guidelines for Ovarian Cancer--Management of Drug Reactions [OV-C])

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

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

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

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

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

[8] Homesley HD, Filiaci V, Markman M, et al. Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:526-531.

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

Note: All recommendations are category 2A unless otherwise indicated.
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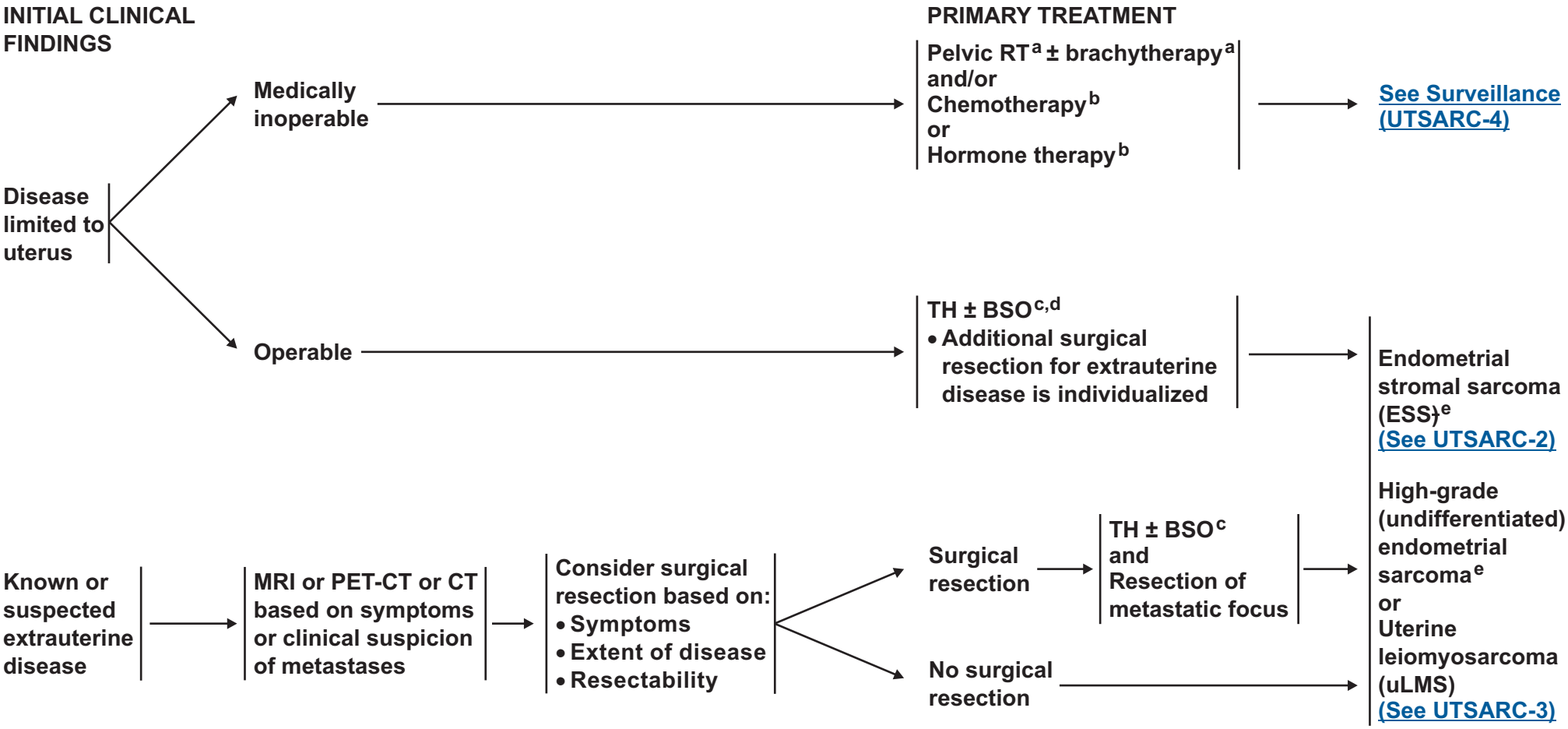
NCCN Guidelines Version 1.2014
Uterine Sarcoma

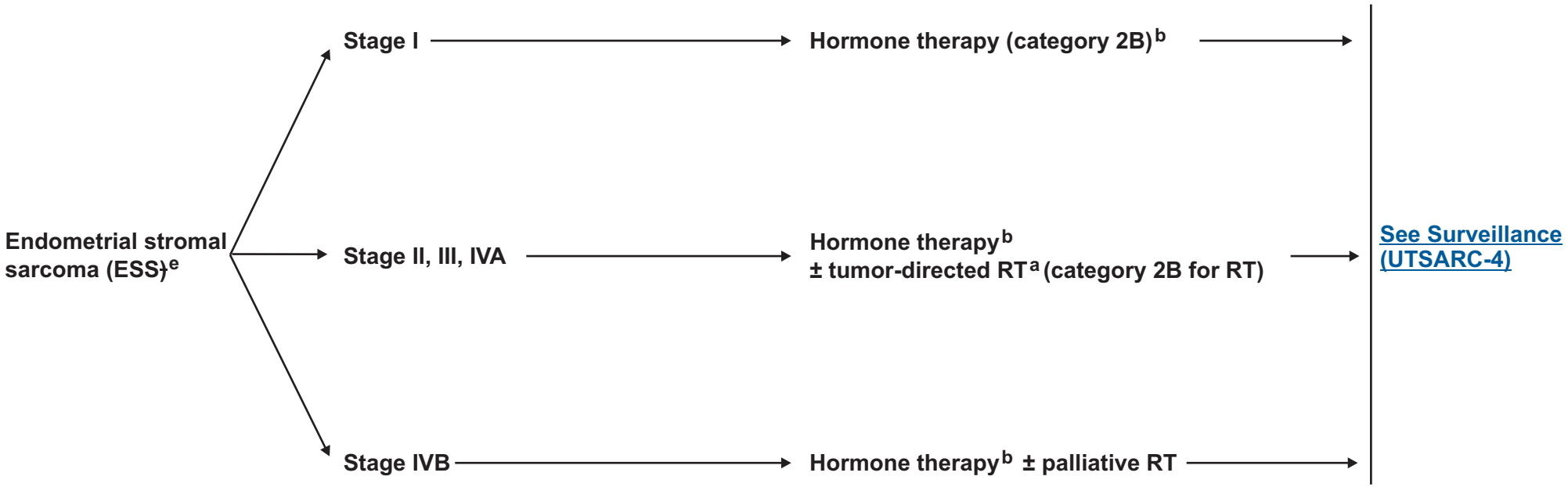
NCCN Guidelines Index
Uterine Neoplasms TOC
Discussion

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



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

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



[a] See Principles of Radiation Therapy (UN-A).
[b] See Systemic Therapy for Uterine Sarcoma (UTSARC-A).
[e] By definition, ESS has low-grade cytologic features. High-grade subtypes of endometrial sarcomas (undifferentiated endometrial sarcomas in WHO classification) are still being defined.
[f] See Uterine Sarcoma Classification (UTSARC-B).

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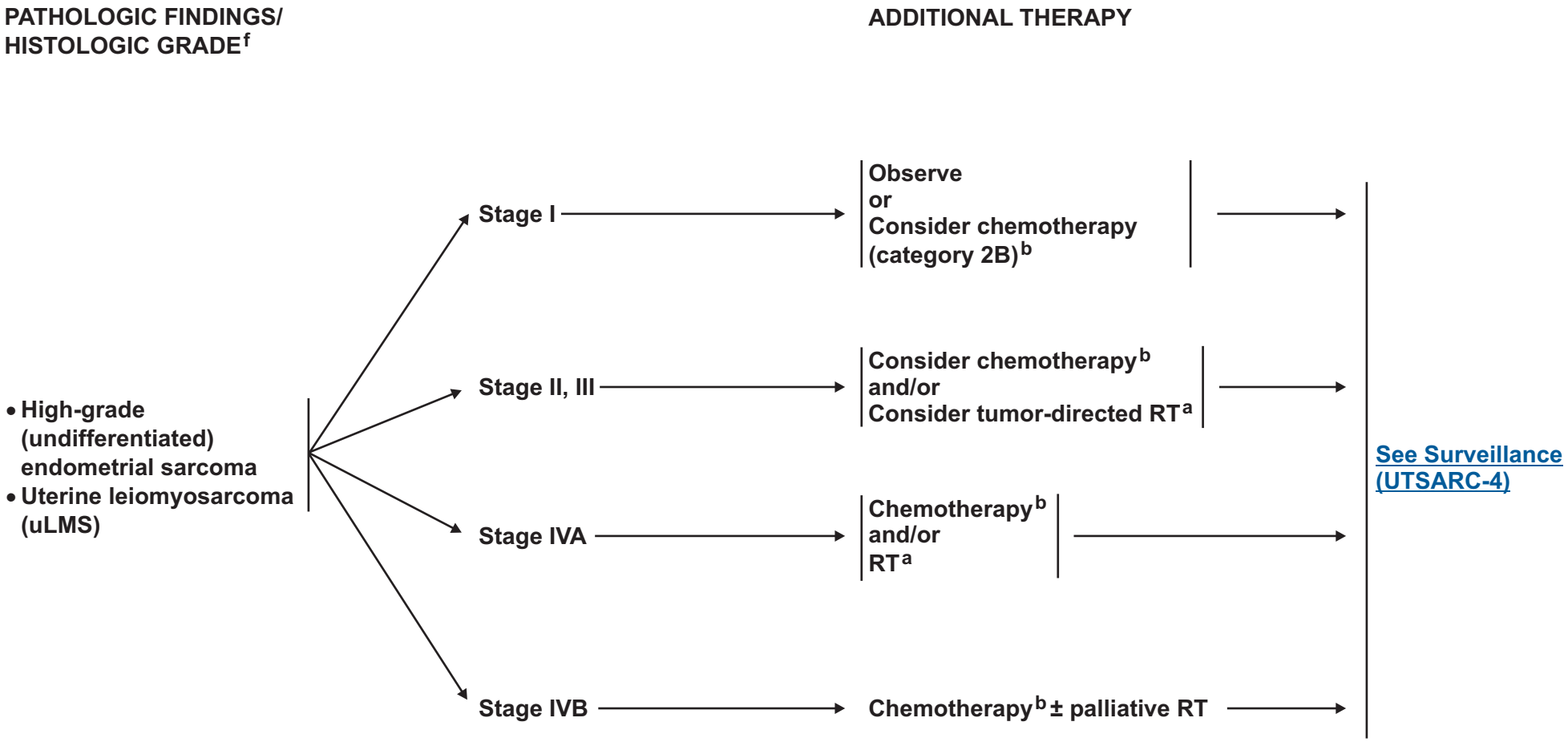

[a] See Principles of Radiation Therapy (UN-A).
[b] See Systemic Therapy for Uterine Sarcoma (UTSARC-A).
[f] See Uterine Sarcoma Classification (UTSARC-B).

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

NCCN Guidelines Version 1.2014
Uterine Sarcoma

NCCN Guidelines Index
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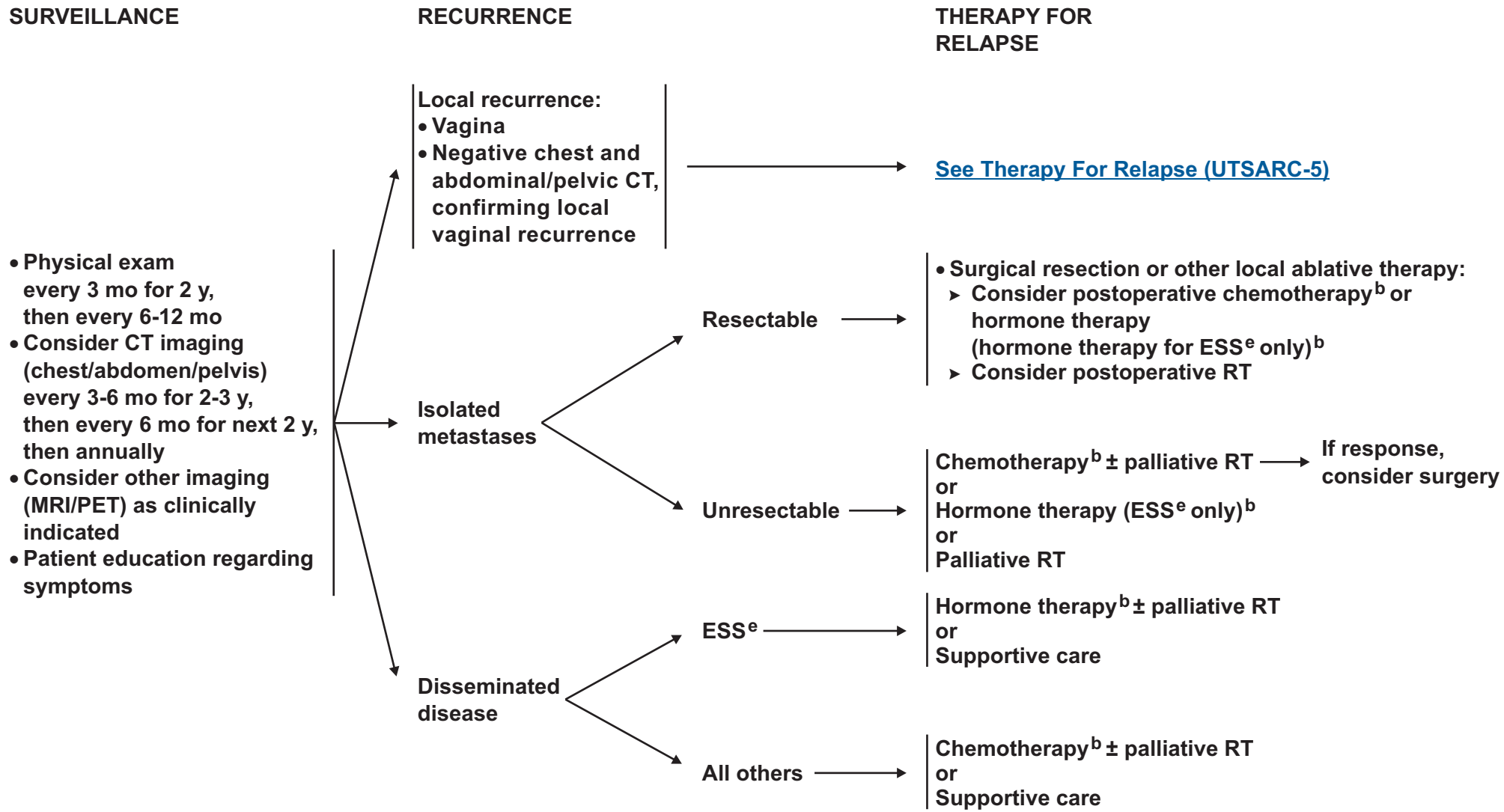
Discussion



[b] See Systemic Therapy for Uterine Sarcoma (UTSARC-A).

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

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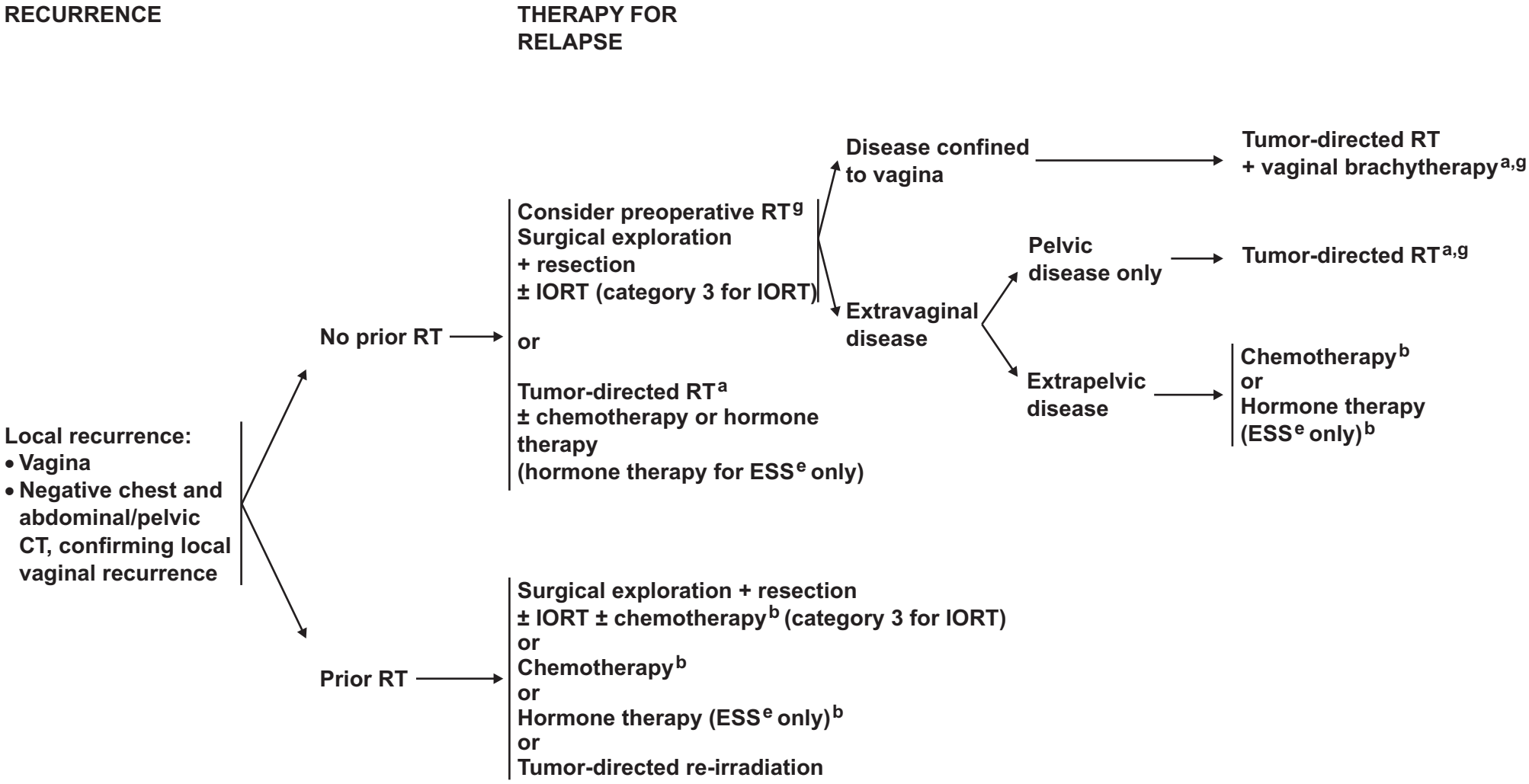

[a] See Principles of Radiation Therapy (UN-A).
[b] See Systemic Therapy for Uterine Sarcoma (UTSARC-A).
[e] By definition, ESS has low-grade cytologic features. High-grade subtypes of endometrial sarcomas (undifferentiated endometrial sarcomas in WHO classification) are still being defined.
[g] The use of preoperative RT would preclude postoperative RT.

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

SYSTEMIC THERAPY FOR UTERINE SARCOMA

CHEMOTHERAPY REGIMENS[1]
(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**
  - **Gemcitabine**
  - **Ifosfamide**
  - **Liposomal doxorubicin**
  - **Pazopanib**
  - **Temozolomide**
  - **Vinorelbine (category 2B)**
  - **Docetaxel (category 3)**

HORMONE THERAPY (ESS only)
- **Medroxyprogesterone acetate**
- **Megestrol acetate**
- **Aromatase inhibitors**
- **GnRH analogs (category 2B)**

[1] Liposomal doxorubicin and docetaxel may cause drug reactions (See NCCN Ovarian Cancer Guidelines--Management of Drug Reactions [OV-C]).

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

Back to Recurrence (UTSARC-4)

UTERINE SARCOMA CLASSIFICATION

- **Endometrial stromal sarcoma (ESS)[1]**
- **High-grade (undifferentiated) endometrial sarcoma[2]**
- **Uterine leiomyosarcoma (uLMS)[3]**

[1] Endometrial stromal sarcomas displaying morphologic features of proliferative phase endometrial stroma and showing any mitotic index. By definition, ESS is low-grade histology.

[2] High-grade sarcomas showing pleomorphism or anaplasia greater than that seen in proliferative phase endometrial stroma or completely lacking recognizable stromal differentiation; mitotic index is almost always >10 mf/10 hpf.

[3] Excludes smooth muscle tumors of uncertain malignant potential, epithelioid smooth muscle tumors, benign metastasizing leiomyomas, intravenous leiomyomatosis, diffuse leiomyomatosis; management in individual cases may be modified based on clinicopathologic prognostic factors, such as size (< or > 5 cm), mitotic activity (< or > 10 mf/10 hpf), age (< or > 50 years), and presence or absence of vascular invasion.

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

PRINCIPLES OF RADIATION THERAPY

- **Tumor-directed RT refers to RT directed at sites of known or suspected tumor involvement, and may include external beam RT (EBRT) and/or brachytherapy. Diagnostic imaging is often used to assess locoregional extent and to rule out distant metastases before administration of RT. In general, tumor-directed EBRT is directed to the pelvis with or without the para-aortic region. Brachytherapy can be delivered: 1) to an intact uterus, either preoperatively or definitively; or 2) more commonly, to the vagina after hysterectomy. For the purposes of these guidelines, whole abdominal 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.**

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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient 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)

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)

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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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 49,560 new uterine cancer cases will occur in 2013, with 8,190 deaths resulting from the disease.[1] Uterine sarcomas are uncommon malignancies accounting for approximately 3% of all uterine cancers.[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] An expert pathology review will determine whether a patient has either: 1) a malignant epithelial tumor (ie, pure endometrioid cancer, uterine serous adenocarcinoma, clear cell adenocarcinoma, or carcinosarcoma, which is also known as malignant mixed Müllerian tumor [MMMT]); or 2) a stromal/mesenchymal tumor (ie, uterine leiomyosarcoma [uLMS], endometrial stromal sarcoma [ESS], 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 [HNPCC]) 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 stromal or mesenchymal endometrial tumors.

Women with Lynch syndrome are at higher risk (60%) for endometrial cancer; thus, close monitoring is recommended.[9,17,18] In relatives with Lynch syndrome but without endometrial cancer, a yearly endometrial biopsy is recommended to assess for cancer.[12,19] This strategy also enables select women to defer surgery (and surgical menopause) and 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 75% of patients with adenocarcinoma of the endometrium, the invasive neoplasm is confined to the uterus at diagnosis.[22] Many physicians believe that adenocarcinoma of the endometrium is a relatively benign disease, because the early symptoms of irregular vaginal bleeding (in this predominantly postmenopausal patient population) often 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 adenocarcinomas), and patients being diagnosed at an older age. 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. A recent analysis of SEER data suggests that survival is increased in patients who are younger, have early-stage disease, and have lower grade disease.[25] It also 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.[26,27] 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.[26,28] Hysteroscopy may be helpful in evaluating the endometrium for lesions, such as a polyp, if the patient has persistent or recurrent undiagnosed bleeding.[29]

Other ancillary tests (ie, CT, MRI, PET) are reserved for evaluating extrauterine disease as indicated by clinical symptoms, physical findings, or abnormal laboratory findings.[30-33] In patients with extrauterine disease, a serum CA-125 assay may be helpful in monitoring clinical response.[34,35] 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.[36-38] Currently, there is no validated screening test for endometrial carcinoma.[39,40]

Staging

The FIGO (International Federation of Gynecology and Obstetrics) system is most commonly used for staging uterine cancer. The original 1970 criteria for staging endometrial cancer only used information gained from presurgical evaluation (including physical examination 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).

However, several studies demonstrated that clinical staging was inaccurate and did not reflect actual disease extent in 15% to 20% of patients.[41-43] This reported understaging and, more importantly, the ability to identify multiple prognostic factors with a full pathologic review made possible with surgical staging, motivated a change in the staging classification. Therefore, in 1988, FIGO modified its staging system to emphasize thorough surgico-pathologic assessment of data, such as histologic grade, myometrial invasion, and the extent and location of extrauterine spread (including retroperitoneal lymph node metastases).[44] FIGO and the AJCC updated and refined the surgical/pathologic staging criteria for uterine neoplasms in 2010.[45-49] Separate staging systems for malignant epithelial tumors and uterine sarcomas are now available (see Tables 1 and 2, respectively).

The 2010 staging streamlined stages I and II endometrial carcinoma. These revisions were made because the survival rates for some of the previous stages were similar.[48] Stage IA is now less than 50% myometrial invasion, and stage IB is 50% or more myometrial invasion. Stage II only includes patients with cervical stromal invasion. Patients with endocervical glandular involvement without invasion are no longer upstaged.[48] Stage IIIC is now subdivided into IIIC1 and IIIC2, because survival is worse with positive para-aortic nodes.[48] 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 2010 staging system.

Primary Treatment

An expert pathology review will determine the specific epithelial histology of the tumor (ie, various endometrioid histologies, serous adenocarcinoma, clear cell adenocarcinoma, carcinosarcoma). 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. 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). Peritoneal cytology no longer affects the 2010 FIGO staging, because it is not viewed as an independent risk factor.[49] However, FIGO and AJCC continue to recommend that peritoneal washings be obtained and results recorded, because positive cytology may add to the effect of other risk factors (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).[50,51]

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). Selected patients with apparent uterine-confined endometrial carcinoma may be considered (category 2B) for sentinel node biopsy (see *Sentinel Lymph Node Mapping* in the Discussion). However, this new surgical staging section only applies to malignant epithelial tumors and not to uterine sarcomas. 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 2010 staging (ie, AJCC Cancer Staging Manual, 7th edition).

Disease Limited to the Uterus

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

Medically Operable Patients

For the staging of a patient (if medically operable) with endometrioid histologies clinically confined to the fundal portion of the uterus, the recommended surgical procedure includes total hysterectomy (TH)/BSO with selective surgical staging (see *Primary Treatment, Hysterectomy and Pathologic Evaluation,* and *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma; see also *Minimally Invasive Surgery* in this Discussion).[52] When indicated, surgical staging is recommended to gather full pathologic and prognostic data on which to base decisions regarding adjuvant treatment for select patients who do not have medical or technical contraindications to lymph node dissection (see *Lymphadenectomy Controversy* 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 2010 FIGO staging criteria, but its routine use has been questioned (see *Lymphadenectomy Controversy* in this Discussion).

Lymphadenectomy Controversy

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.[53] No randomized trial data support routine full lymphadenectomy,[54] although some retrospective studies have suggested that it is beneficial.[55-57] Two randomized clinical trials from Europe reported that routine lymph node dissection did not improve the outcome of endometrial cancer patients, but lymphadenectomy did identify those with nodal disease.[58,59] However, these findings remain a point of contention.[52,60,61] To avoid overinterpretation of these results, it is important to address the limitations of these randomized studies, including selection of patients, extent of lymph node dissection, and standardization of postoperative therapy.[62,63] The other concerns include the lack of central pathology review, subspecialty of surgeons, and adequacy of statistical power.

Decisions about whether to do 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;[64,65] 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.[59] Therefore, there was no standardization of adjuvant treatment after staging surgery with lymphadenectomy. In fact, the use of lymphadenectomy did not translate into an increased use of adjuvant therapy. This may have contributed to the lack of difference in recurrence and survival in the two groups. Studies show that in 15% to 20% of cases, the preoperative grade (as assessed by endometrial biopsy or curettage) is upgraded on final fixed pathologic evaluation of the hysterectomy specimen.[66] As the grade of the tumor increases, the accuracy of intraoperative evaluation of myometrial invasion decreases (ie, assessment 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.[67]

The question of whether to add periaortic lymphadenectomy to pelvic node dissection has been debated. Prior studies have shown conflicting information regarding the risk of para-aortic nodal metastases in patients without disease in the pelvic nodes.[43,64,68,69] 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.[53] Selected patients with apparent uterine-confined endometrial carcinoma may be candidates for sentinel node mapping (category 2B), which assesses the pelvic nodes and is less morbid than standard lymphadenectomy (see *Sentinel Lymph Node Mapping* in this Discussion).

In summary, lymph node dissection identifies patients requiring adjuvant treatment with RT and/or chemotherapy.[70] 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 node mapping may be considered (category 2B) for selected patients with apparent uterine-confined endometrial disease (see *Sentinel Lymph Node Mapping* in this Discussion).

Surgical Staging

Minimally Invasive Procedures

Laparoscopic pelvic and para-aortic lymphadenectomy in association with total laparoscopic hysterectomy is being used in many practices.[53,71,72] However, patients having laparoscopy should be followed over a long term to compare their outcomes with those of

traditional laparotomy.[73] 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.[73,74] 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, $P<.0001$).[75,76] Significantly fewer postoperative adverse events and shorter hospitalization occurred with laparoscopy compared with laparotomy. Recurrence rates were 11.4% for laparoscopy versus 10.2% for laparotomy. The 5-year overall survival rate was 84.8% for both arms of LAP2.[74] Another randomized trial (n = 283) comparing laparoscopy versus laparotomy reported shorter hospital stay, less pain, and faster resumption of daily activities with laparoscopy.[77] However, laparotomy may still be required for certain clinical situations (eg, elderly patients, those with a very large uterus) or certain metastatic presentations.[73]

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

Incomplete Surgical Staging

For patients with incomplete (ie, not thorough) surgical staging and high-risk intrauterine features, imaging is often recommended, especially in patients with higher grade and more deeply invasive tumors.[93,94] Surgical restaging, including lymph node dissection, can also be done.[64] 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).

Sentinel Lymph Node Mapping

Sentinel lymph node (SLN) mapping may be considered (category 2B) for patients with apparent uterine-confined endometrial cancer to assess whether they have metastatic pelvic lymph nodes.[95-97] Because many NCCN Member Institutions do not routinely use SLN, it is a category 2B 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.[98] 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. Because SLNs identify the primary lymphatic pathway, this increases the yield of finding metastatic disease during the mapping process. 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).[95,99] 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.[95]

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.[100-102] It is important to note that system-wide long-term outcome data are not yet available for SLN mapping in endometrial cancer.[103,104] Data to support SLN mapping are based on single institution studies, and 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.[30] The main contraindication for SLN mapping is uterine sarcoma. SLN mapping should be done with particular caution in patients with high-risk histology (eg, serous adenocarcinoma, clear cell adenocarcinoma, carcinosarcoma).[53]

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.[105-108] Likewise, it may also be selectively used for young patients with endometrial hyperplasia who desire fertility preservation. For the 2014 update, the NCCN Panel added a new 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). When considering fertility-sparing therapy, all of the criteria must be met as outlined in the algorithm (eg, no metastatic disease). Patients also need to receive counseling that fertility-sparing therapy is not the standard of care for the treatment of endometrial carcinoma.

TH/BSO with surgical staging is recommended after childbearing is complete, if therapy is not effective, or if progression occurs. Fertility-sparing therapy is not recommended for high-risk patients (eg, those with high-grade endometrioid adenocarcinomas, uterine serous adenocarcinoma, clear cell adenocarcinoma, carcinosarcoma, and uLMS).

Continuous progestin-based therapy may include megestrol acetate, medroxyprogesterone, or an intrauterine device containing levonorgestrel.[105,106,109] A durable complete response occurs in about 50% of patients.[105] 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 months of progestin-based therapy.[110] 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%).[105,108,111-113]

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.[114] Other studies also suggest that ovarian preservation may be safe in women with early-stage endometrial cancer.[115,116]

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).[93,94] 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).[52] In these patients, radical or modified radical hysterectomy may improve local control and survival when compared with TH.[117,118] 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.

Medically Inoperable Patients

For medically inoperable patients, tumor-directed radiation therapy (RT) is a well-tolerated and 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).[119-121] 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).[39,122] Progesterone-based therapy can provide some benefit with low toxicity in patients with low-grade tumors.[123] Tamoxifen with alternating megestrol may be used.[124] Aromatase inhibitors have also been used.[125-128]

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.

The surgical goal is to have no measurable residual disease; several studies support debulking.[52,129-131] 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.[132-135] For extra-abdominal disease (eg, liver involvement), consider palliative TH/BSO followed by chemotherapy, RT, and/or hormonal therapy.

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 lymphovascular space invasion [LVSI], tumor size, lower uterine [cervical/glandular] segment involvement). 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).[46,48] However, by necessity, much of the discussion in this manuscript has been based on the older FIGO/AJCC staging system. The implications of *stage migration* should be taken into account when evaluating historical data (see Table 1).

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%.[136] 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 *Adjuvant Treatment for Stage I* in the NCCN Guidelines for Endometrial Carcinoma).[70,137-140]

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 adenocarcinoma histologies.

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.[137] In surgical stage I and II endometrial cancer, other pathologic factors that may influence the decision regarding adjuvant therapy include patient age, tumor volume, and involvement of the lower uterine segment.

Four trials have evaluated the role of adjuvant external-beam pelvic RT in patients with endometrial carcinoma. In 2 of these trials, the patients were not formally staged (Postoperative Radiation Therapy in Endometrial Carcinoma [PORTEC-1], Aalders).[141,142] In the third trial (ASTEC/EN.5), only 50% of the patients were thoroughly staged as part of a companion surgical protocol.[58,143] However, formal surgical staging was mandated for all patients in the fourth trial (Gynecologic Oncology Group [GOG] 99).[144] Note that these trials used the older staging system (ie, before 2010).

The PORTEC-1 trial suggested that external-beam pelvic RT provides a therapeutic benefit in selected patients with uterine-confined disease.[141,145] Although RT significantly decreased locoregional recurrence, it did not increase overall survival.[146] The Aalders' randomized trial found that RT reduced vaginal (ie, locoregional) recurrences but did not reduce distant metastases or improve survival.[142] 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.[143] However, the ASTEC/EN.5 study is

very controversial; 51% of the patients in the ASTEC observation group received vaginal brachytherapy.[61,147] The Keys' trial (GOG 99) showed that adjuvant pelvic RT improved locoregional control and relapse-free interval (ie, PFS), without overall survival benefit.[144] 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.[144,148,149]

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.[141,144] 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.[144] 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.[141,148]

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.[150] 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.[148-156] 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, grade 3 endometrial carcinoma (2010 FIGO stage IB, grade 3);[46,48] thus, the use of adjuvant brachytherapy alone in the highest risk subset remains undetermined.

The benefit of adjuvant external-beam 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. However, given the lack of consistent absolute survival benefit, observation (category 2B) may be appropriate in selected cases. Two large retrospective SEER analyses of women with endometrial cancer found that adjuvant RT improved overall survival in those with high-risk disease.[157,158] 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.[152,159-162]

Adjuvant Chemotherapy

Patients with 1998 FIGO stage IC, deeply invasive, grade 3, uterine-confined disease have a relatively poor prognosis (revised to 2010 FIGO stage IB, grade 3). Despite adjuvant therapy with pelvic RT, a significant number of patients continue to have an appreciable risk of distant metastases.[144,145] Therefore, some clinicians suggested that adding chemotherapy to adjuvant RT may provide added therapeutic benefit (ie, decrease distant metastases).[137,163] Studies have evaluated the role of chemotherapy in *highest risk* uterine-confined disease.[163,164] PFS is improved with adjuvant sequential chemotherapy/RT.[163] 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.[163] The role of adjuvant chemotherapy in invasive, high-grade, uterine-confined disease is being further studied (eg, GOG 249, PORTEC-3).

The recommended postoperative (ie, adjuvant) treatment options for 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.

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.[165-167] Patients with extrauterine disease confined to the lymph nodes or the adnexa may be treated with pelvic or extended-field RT alone.[168] 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).

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.[169,170] A randomized phase III GOG (122) trial assessed optimal adjuvant therapy for patients with endometrial cancer who had extrauterine disease. In this trial, patients with stage III and intra-abdominal stage IV disease who had minimal residual disease were randomly assigned to whole abdominopelvic RT versus 7 cycles of combined doxorubicin (60 mg/m^2) and cisplatin (50 mg/m^2) 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.[133]

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 (and is no longer recommended) to chemotherapy. 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).

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.[133] A study found that combined modality adjuvant therapy (using both chemotherapy and tumor-directed RT) may provide a therapeutic benefit when compared with other sequencing modalities (either chemotherapy followed by RT or vice versa).[135,171,172]

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).[134]

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. 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,[173] studies have focused on subtle effects on quality of life (eg, diarrhea, bowel symptoms) that deserve further investigation.[153,155] In the PORTEC-2 trial, vaginal brachytherapy was associated with better quality of life when compared with EBRT without a significant detriment to outcome.[153] 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 done indefinitely (http://www.mskcc.org/patient_education/_assets/downloads-english/571.pdf).

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).[30] These recommendations recognize that the value of intensive surveillance has not been demonstrated in this disease; therefore, ancillary testing is not recommended.[174,175]

Patients with clinical stage I and stage II endometrial cancer have a recurrence rate of approximately 15%;[23,175-177] 50% to 70% of patients have symptomatic recurrences. For most patients, disease recurs within 3 years of initial treatment. Because most recurrences are symptomatic, all patients should receive verbal and written information regarding the symptoms of recurrent disease.[175] 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.

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, and nutrition counseling (see the NCCN Guidelines for Survivorship) (http://www.cancer.org/treatment/survivorshipduringandaftertreatment/index).[178-180] 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. For the 2014 update, the use of vaginal cytology is no longer recommended for asymptomatic patients consistent with the SGO guidelines.[174,175,177,181] 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.[182]

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.[183,184] However, estrogen replacement therapy for such patients remains controversial.

It has never been proven that there is a higher relapse rate in endometrial cancer patients who receive estrogen replacement therapy after hysterectomy. Indeed, several retrospective trials of estrogen replacement after treatment of early-stage endometrial cancer have shown no increase in tumor recurrence or cancer-related deaths.[185-187] 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.[188] However, estrogen replacement trials in postmenopausal females without a history of malignancy have demonstrated a significantly increased risk of breast cancer.[189] 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.[190] 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.[191]

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.[192,193] 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.[194,195] 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).[196,197]

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. Isolated vaginal recurrences treated with RT have good local control and 5-year survival

rates of 50% to 70%,[198-200] although prognosis is worse if there is extravaginal extension or pelvic lymph node involvement.[199]

After RT, it is unusual for patients to have recurrences confined to the pelvis. The management of such patients is still 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%.[201-204]

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 (see *Therapy for Relapse* in the NCCN Guidelines for Endometrial Carcinoma). For resectable isolated metastases, consider surgical resection with or without RT. Further recurrences or unresectable isolated metastases 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) (http://emedicine.medscape.com/article/270646-overview).

Systemic Disease

Hormonal Therapy

The role of hormonal therapy in recurrent or metastatic cancer has been primarily evaluated in patients with endometrioid histologies only (ie, not for serous adenocarcinoma, clear cell adenocarcinoma, or carcinosarcoma). Hormonal therapy is also used for selected patients with ESS (see section on *Uterine Sarcomas* in this Discussion). Progestational agents are mainly used for metastatic disease; however, tamoxifen with alternating megestrol may be used.[124,205-207] Aromatase inhibitors are also being used.[125,126] 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.[128,208-210] Tamoxifen has a 20% response rate in those who do not respond to standard progesterone therapy.[211,212] Tamoxifen has also been combined with progestational agents; however, a few patients had grade 4 thromboembolic events with this combination regimen.[124,205,213] In some patients, aromatase inhibitors (eg, anastrozole, letrozole) may be substituted for progestational agents or tamoxifen.[127,128,210,214] Other hormonal modalities have not been well studied, and adjuvant therapy with hormonal agents has not been compared with cytotoxic agents.[128,215] 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.[216,217] 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 either 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.[218,219] Both 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.[216,217]

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.[220-223] A phase III trial (GOG 209) compared carboplatin and paclitaxel versus cisplatin, doxorubicin, paclitaxel, and filgrastim (granulocyte-colony stimulating factor [G-CSF]).[220] 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.[224]

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).[128,225-227] When single agents are used as first-line treatment, responses range from 21% to 36%.[210,228] When single agents are used as second-line treatment, responses range from 4% to 27%; paclitaxel is the most active in this setting.[228] Some oncologists have used liposomal doxorubicin, because it is less toxic than doxorubicin; the response rate of liposomal doxorubicin is 9.5%.[229] 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.[123,230]

New biologic and molecular therapies for the treatment of recurrent or metastatic endometrial carcinoma are being assessed in clinical trials.[123,231] Recently, 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.[232] Temsirolimus has been used as first-line or second-line therapy for recurrent or metastatic endometrial cancer and has a partial response rate of 4% in second-line therapy.[233] Based on these studies, the NCCN Panel considers bevacizumab or temsirolimus as appropriate single-agent biologic therapy for patients who have progressed on previous cytotoxic chemotherapy.[231,232]

Drug Reactions

Virtually all drugs have the potential to cause adverse hypersensitivity reactions, either during or after the infusion.[234] 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.[235-237] In addition, patients can have mild allergic reactions or severe infusion reactions. Infusion reactions are more common with paclitaxel.[238] Allergic reactions (ie, true drug allergies) are more common with platinum agents (ie, carboplatin, cisplatin).[238,239]

Management of drug reactions is discussed in the NCCN Guidelines for Ovarian Cancer.[238] 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.[240-242] Patients must be desensitized with each infusion if they previously had a reaction. Almost all patients can be desensitized (about 90%).[234] To maximize safety, it is prudent to desensitize patients in the intensive care unit.[234]

Uterine Serous Adenocarcinomas, Clear Cell Adenocarcinomas, and Carcinosarcomas

Overview

Uterine serous adenocarcinomas, clear cell adenocarcinomas, and carcinosarcomas are considered more aggressive histologic variants of malignant epithelial tumors, with a higher incidence of extrauterine disease at presentation.[243-250] Carcinosarcomas are aggressive tumors that are staged as high-grade endometrial cancer (see Table 1).[251,252]

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 Adenocarcinoma, Clear Cell Adenocarcinoma, or Carcinosarcoma* in the NCCN Guidelines for Endometrial Carcinoma).[247,250,253,254] 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 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.[243] Serous adenocarcinomas, clear cell adenocarcinomas, and carcinosarcomas are all considered high-risk tumors (ie, grade 3), although they are staged using the same FIGO/AJCC staging system (ie, 7th edition) as endometrial cancers (see Table 1).[46] Patterns of failure often mimic those of ovarian cancer.

Treatment

Multimodality therapy is typically recommended for these histologically aggressive tumors. Primary treatment includes TH/BSO with surgical staging, peritoneal lavage for cytology, omental and peritoneal biopsies, and consideration of maximal tumor debulking for gross disease (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).[255]

Adjuvant therapy is highly individualized.[256-263] For patients with stage IA without myometrial invasion, options include: 1) observation; 2) chemotherapy; or 3) tumor-directed RT.[264] For all other patients with

more advanced disease, chemotherapy with (or without) tumor-directed RT is the preferred option.[245,257,261,265] Adjuvant platinum/taxane-based therapy appears to improve survival in patients with uterine serous adenocarcinoma and clear cell adenocarcinoma, whereas ifosfamide/paclitaxel (category 1) is recommended for carcinosarcomas (see *Uterine Serous Adenocarcinomas, Clear Cell Adenocarcinomas, and Carcinosarcomas* in this Discussion and *Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease* in the NCCN Guidelines for Endometrial Carcinoma).[243-245,266-268]

For the 2014 update, 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.[133,265,269] Chemotherapy with (or without RT) appears to be more effective than RT alone.[257] Data are conflicting regarding the rate of abdominal recurrence in these patients.[265,270-274] 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.

Ifosfamide was historically considered the most active single agent for carcinosarcoma.[267,275,276] A phrase III trial for advanced carcinosarcoma showed that the combination of ifosfamide and paclitaxel increased survival and was less toxic than the previously used cisplatin/ifosfamide regimen.[267,277] 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).[267] A phase II trial suggests that paclitaxel/carboplatin is also a useful regimen for carcinosarcoma (response rate, 54%).[278] A GOG trial is currently assessing ifosfamide/paclitaxel versus carboplatin/paclitaxel.[251]

Data regarding carcinosarcoma suggest that adjuvant pelvic radiotherapy decreases the rate of local recurrences when compared with surgery alone.[279-284] This local control improvement in some series correlates with an improvement in survival, although other data show that lymphadenectomy confers greater benefit.[283-286] A phase III randomized trial (GOG 150) in patients with carcinosarcoma of the uterus assessed whole abdominal RT versus cisplatin/ifosfamide, but there was no difference in survival between the groups.[269,274] A recent cohort study in women with early-stage MMMT suggests that postoperative chemotherapy improves PFS compared to RT or observation.[251]

Uterine Sarcomas

Overview

Uterine sarcomas are uncommon tumors (about 3% of all uterine neoplasms). Risk factors for uterine sarcomas include history of pelvic radiation. Uterine sarcomas are stromal/mesenchymal tumors that are generally categorized into uLMS, ESS, and high-grade (undifferentiated) endometrial sarcoma (see *Uterine Sarcoma Classification* in the NCCN Guidelines for Uterine Sarcoma). Most uterine sarcomas are LMS; ESS and high-grade (undifferentiated) endometrial sarcomas are rare. Screening for Lynch syndrome is not usually done for patients with stromal or mesenchymal tumors.

Pathologic definitions of the various histologies are undergoing revision.[2] By definition, ESS has low-grade cytologic features; JAZF1

rearrangements are common. However, high-grade subtypes of endometrial sarcomas (undifferentiated endometrial sarcomas in the WHO classification) are still being defined (eg, those with YWHAE-FAM22 rearrangements).[287,288] Note that molecular subtyping is helpful but not essential for diagnosis of undifferentiated endometrial sarcomas.

Staging and Treatment

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.[289] A new staging system for ESS and uLMS from FIGO/AJCC took effect in 2010 (see Table 2).[46,290] This staging accounts for the fact that uterine sarcomas are different from endometrial cancers.

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). The ovaries may be preserved in selected patients with early-stage uLMS who wish to retain hormonal function.[291] Additional surgical resection should be individualized based on clinical scenarios and intraoperative findings. Lymphadenectomy is controversial.[2,291-295] High-grade uterine sarcomas tend to show hematogenous metastases to the lungs; lymph node metastases are uncommon. For medically inoperable sarcomas, options include: 1) RT and chemotherapy; 2) chemotherapy alone; or 3) hormone therapy (but only for ESS).

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).[292,293] Postoperative hormone therapy is recommended for stages II to IV ESS (category 2B for stage I only). Adjuvant RT may be added for stage II-IVA (category 2B); palliative RT may be added for stage IVB.[294,296,297] Typical hormone therapy includes megestrol, medroxyprogesterone, or aromatase inhibitors; gonadotropin-releasing hormone [GnRH] analogs (category 2B) are also an option.[291,294,298] For the 2014 update, tamoxifen was deleted from the NCCN Guidelines for ESS because tamoxifen is contraindicated in women diagnosed with ESS or ER/PR-positive uLMS.[291,297-299] Hormone therapy is also recommended for ESS that have recurred or are unresectable (see *Therapy for Relapse* in the NCCN Guidelines for Uterine Sarcoma).[298] Although hormone therapy is recommended for ESS, it is not clear what therapy should be used for the recently identified more aggressive subtypes (eg, YWHAE-FAM22 rearrangements).

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.[300] Adjuvant radiotherapy in ESS has been demonstrated to reduce local recurrence rates but again with limited effect on survival.[301,302] Because of concerns about radiation exposure, frequent routine surveillance imaging is no longer recommended for asymptomatic young women after primary therapy for ESS.[303]

Leiomyosarcoma and High-Grade (Undifferentiated) Endometrial Sarcoma

The role of adjuvant radiotherapy in nonmetastatic disease is controversial. Most available data are retrospective, except for a phase III randomized trial.[279] 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.[304-307] 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.[279] Therefore, routine postoperative RT is not recommended for stage I patients with uLMS and high-grade (undifferentiated) endometrial sarcoma.[296] 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 therapy (see *Additional Therapy* in the NCCN Guidelines for Uterine Sarcoma).[308] In patients with incompletely resected or metastatic disease, chemotherapy with (or without) RT is generally recommended. An ongoing phase III randomized trial (GOG 277) is assessing the role of postoperative adjuvant chemotherapy versus observation in patients with high-grade stage I and II uLMS.

If chemotherapy is used, gemcitabine/docetaxel (preferred for uLMS) is recommended for uterine sarcoma (see *Systemic Therapy* in the NCCN Guidelines for Uterine Sarcoma).[309-314] Other combination regimens include doxorubicin/ifosfamide, doxorubicin/dacarbazine, gemcitabine/dacarbazine, and gemcitabine/vinorelbine.[276,315,316] Doxorubicin is an active single agent for uLMS and is less toxic than combination regimens.[294,317]

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).[294,309,310,315,316,318-334] For the 2014 update, 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.[315] Data indicate that trabectedin may be useful in patients who have exhausted standard chemotherapy; overall survival was 13.9 months.[335-337] However, trabectedin is not currently available outside of a clinical trial. Enrollment in clinical trials is strongly recommended.

The recurrence rate is high in uLMS (50%–70%).[2] RT may be useful for local recurrence. Chemotherapy with (or without) palliative RT is recommended for metastatic disease;[317] surgical resection or other ablative therapy (eg, radiofrequency ablation, stereotactic body RT) may be appropriate for selected patients with isolated metastases (see *Therapy for Relapse* in the NCCN Guidelines for Uterine Sarcoma).[330,338]

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