National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Uterine Neoplasms

Version 3.2024 — September 20, 2024

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NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

NCCN Guidelines for Patients® available at www.nccn.org/patients

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NCCN Uterine Neoplasms Panel Members
Summary of the Guidelines Updates

Uterine Neoplasms
Uterine Neoplasms (UN-1)

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Uterine Neoplasms
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Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Updates in Version 3.2024 of the NCCN Guidelines for Uterine Neoplasms from Version 2.2024 include:

Endometrial Carcinoma

ENDO-D 1 of 4 Systemic Therapy for Endometrial Carcinoma

- Primary or Adjuvant Therapy (Stage I-IV)
  - Systemic Therapy; Preferred regimens: Carboplatin/paclitaxel/durvalumab (for stage III–IV dMMR tumors only) added as category 1 option.
  - Footnote "f" is new: For Stage III with measurable disease post surgery and stage IV with or without measurable disease.

ENDO-D 2 of 4

- Recurrent Disease
  - First-line Therapy for Recurrent Disease; Preferred regimens: Carboplatin/paclitaxel/durvalumab (for dMMR tumors only) added as category 1 option.
  - Footnote m is new: For adult patients with recurrent endometrial carcinoma with or without measurable disease.
  - Footnotes removed:
    - ◊ For stage IIIA, IIIB, or IIIC1 with measurable disease, stage IIIC1 with carcinosarcoma, clear-cell, serous, or mixed histology regardless of the presence of measurable disease; and stage IIIC2 or stage IV regardless of the presence of measurable disease.
    - ◊ For stage III or IVA with measurable disease or stage IVB with or without measurable disease

ENDO-D 4 of 4

- Reference 10 is new: Westin SN, Moore K, Chon HS, et al. Durvalumab plus carboplatin/paclitaxel followed by maintenance durvalumab with or without olaparib as first-line treatment for advanced endometrial cancer: The Phase III DUO-E trial. J Clin Oncol. 2023;42:283-299.

Updates in Version 2.2024 of the NCCN Guidelines for Uterine Neoplasms from Version 1.2024 include:

Endometrial Carcinoma

ENDO-D 2 of 4 Systemic Therapy for Endometrial Carcinoma

- Recurrent Disease; Second-line or Subsequent Therapy; Other Recommended Regimens
  - Cisplatin/gemcitabine added as an option with the following reference: Brown J, Smith JA, Ramondetta L, et al. Combination of Gemcitabine and Cisplatin Is Highly Active in Women With Endometrial Carcinoma: Results of a Prospective Phase 2 Trial. Cancer 2010;116:4973–4979.

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Updates in Version 1.2024 of the NCCN Guidelines for Uterine Neoplasms from Version 2.2023 include:

General
- Terminologies modified to advance the goals of equity, inclusion, and representation.
- Uterine leiomyosarcoma (uLMS) changed to *leiomyosarcoma (LMS)* throughout the guidelines.
- The term "cases" changed to "patients"

Uterine Neoplasms
UN-1
- Initial Evaluation revised
  - 2nd bullet: Complete blood count (CBC) (including platelets)*, liver function test [LFT], renal function tests, chemistry profile; and consider CA-125*
  - 5th bullet: Recommend ~~genetic~~ *molecular* evaluation of tumor and evaluation for inherited cancer risk (See ENDO-A *and UTSARC-A*)
  - 6th bullet: For ~~elderly~~ patients *who are older* with uterine cancer also see the NCCN Guidelines for Older Adult Oncology
  - 7th bullet: Consider germline ~~testing~~ and/or multigene panel testing
  - Bullet removed: Consider liver function test (LFT)/renal function tests/chemistry profile

Endometrial Carcinoma
ENDO-1
- Disease limited to uterus; Not suitable for primary surgery; Primary Treatment revised: Consider hormone therapy (including ~~progestin~~ levonorgestrel intrauterine device [IUD]) in select patients.
- Footnote b: ~~Patient declines surgery or is not suitable for surgery based on comorbidities~~. *Disease is not amenable to resection or patient is not suitable for surgery based on comorbidities*. (Also for ENDO-2, ENDO-3))
- Footnote f revised: Ovarian preservation may be safe in select ~~premenopausal~~ patients *who are premenopausal* with early-stage endometrioid cancer, normal-appearing ovaries, and no family history of breast/ovarian cancer or Lynch syndrome. Salpingectomy is recommended.

ENDO-2
- Suspected or gross cervical involvement; Primary Treatment
  - Suitable for primary surgery:
    - ◊ "TH *(preferred)* or radical hysterectomy (RH)..."
    - ◊ EBRT + brachytherapy changed to EBRT ± brachytherapy
      - – Recommendation revised: TH/BSO and surgical staging *4–12 weeks post RT*
  - Not suitable for primary surgery
    - ◊ EBRT + brachytherapy ± platinum-based chemosensitization changed to *EBRT ± brachytherapy*
      - – Recommendation revised: Surgical resection, if rendered operable *4–12 weeks post RT or Definitive RT if inoperable*
    - ◊ After Systemic therapy, recommendation revised as follows: Surgical resection if rendered operable (EBRT + brachytherapy if still inoperable) changed to Surgical resection if rendered operable *or* EBRT + brachytherapy if *still* inoperable

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UPDATES

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Updates in Version 1.2024 of the NCCN Guidelines for Uterine Neoplasms from Version 2.2023 include:

Endometrial Carcinoma-continued

ENDO-3
- Suspected extrauterine disease
  - Additional Workup; 2nd bullet revised: Imaging as clinically indicated ~~(if not previously done)~~
  - Not suitable for primary surgery; Locoregional disease; Primary Treatment:
    - ◊ Systemic therapy added as an option
    - ◊ After EBRT ± brachytherapy ± systemic therapy, recommendation revised: Re-evaluate for surgical resection *4–12 weeks post RT*

ENDO-7
- Incompletely surgically staged
  - Stage IA, G3 or brachytherapy; Stage IB, G1–2 and Age ≥60 y and no LVSI pathway recommendations revised
    - ◊ ~~Consider~~ Imaging
    - ◊ Imaging performed and negative ~~or Imaging not performed~~
  - Stage IA, G1–3 and LVSI; Stage IB, G1–2 and LVSI; Stage IB, G3 ± LVSI; Stage II pathway; Adjuvant treatment: *If not surgically restaged and substantial LVSI, consider EBRT ± brachytherapy* added as an option.

ENDO-8
- 2nd column; 2nd bullet revised: "Recommend ~~genetic~~ *molecular* evaluation of tumor and evaluation..."
- Primary Treatment: 1st bullet; 3rd arrow sub-bullet revised: Progestin Levonorgestrel IUD *(preferred for fertility preservation)*
- Complete response by 6 mo pathway;
  - Revised: Encourage conception (with continued surveillance/endometrial sampling every ~~6 mo~~ *6–12 mo* and consider..."
  - Last column recommendation revised: Ovarian preservation may be considered in select ~~premenopausal~~ patients *who are premenopausal*

ENDO-9
- Surveillance; 1st bullet revised: " Physical exam *(including pelvis)*..."

ENDO-10
- Locoregional recurrence;
  - Top pathway revised
    - ◊ No prior RT to site of recurrence *or previous vaginal brachytherapy only*
    - ◊ After "Locoregional disease,"
      - – Top pathway revised to Pelvic *or para-aortic* lymph node*(s)*
      - – Separate pathway for "Para-aortic or common iliac lymph node" removed
  - Bottom pathway revised
    - ◊ Prior *EB*RT to site of recurrence
    - ◊ Separate birfurcation for "Previous brachytherapy only" and "Previous EBRT" pathways removed

ENDO-11
- Serous carcinoma
  - Suitable for primary surgery; Primary Treatment; Top pathway revised to: No residual *uterine* disease *and negative surgical staging* (Also for ENDO-12)
  - Footnote revised: Disease is not amenable to resection~~, patient declines surgery,~~ or patient is not suitable for surgery based on comorbidities.

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Updates in Version 1.2024 of the NCCN Guidelines for Uterine Neoplasms from Version 2.2023 include:

Endometrial Carcinoma–continued

ENDO-A Principles of Pathology

ENDO-A 1 of 4

- Pathologic assessment for carcinoma
  - 6th bullet revised: HER2 immunohistochemistry (IHC) testing (with reflex to HER2 fluorescence in situ hybridization [FISH] for equivocal IHC) is recommended for ~~possible treatment of advanced-stage or recurrent~~ *all* serous ~~endometrial carcinoma or~~ *and* carcinosarcoma *tumors*. *Consider HER2 testing for p53 abnormal carcinomas regardless of histology*.
  - Last bullet revised: Estrogen receptor (ER) *and progesterone receptor (PR)* testing is recommended in the settings of stage III, stage IV, and recurrent disease.
  - New bullet added: Morphologic evaluation of endometrial carcinoma to determine histologic type—especially in high-grade cancers—is challenging and issues exist regarding diagnostic reproducibility.

ENDO-A 2 of 4 Principles of Molecular Analysis

- This page was significantly revised.

ENDO-A 3 of 4 Principles of Molecular Analysis

- Figure 1 was significantly revised.

ENDO-A 4 of 4

- New reference added: Rios-Doria E, Momeni-Boroujeni A, Friedman CF, et al. Integration of clinical sequencing and immunohistochemistry for the molecular classification of endometrial carcinoma. Gynecol Oncol 2023;174: 262-272.

ENDO-B Principles of Imaging

- Initial Workup; Fertility-Sparing Treatment; 1st arrow sub-bullet revised: "... transvaginal ultrasound if MRI is contraindicated *or unavailable*."
- Follow-up/Surveillance; Fertility-Sparing Treatment; 1st arrow sub-bullet revised: "... after 6–9 months of ~~failed medical therapy~~ *ineffective treatment*..."
- Suspected Recurrence or Metastasis: "Abdomen/pelvis *CT* and/or chest CT is recommended based on symptoms..."
- Footnote a revised: "MRI *is performed with and without contrast* and CT ~~are~~ *is* performed with contrast ~~throughout the guidelines~~ unless contraindicated

ENDO-D Systemic Therapy for Endometrial Carcinoma

ENDO-D 1 of 5

- Primary or Adjuvant Therapy (Stage I–IV)
  - Chemoradiation Therapy
    - ◊ New section added:
      - – Other Recommended Regimens (if cisplatin and carboplatin are unavailable)
        - Capecitabine/mitomycin
        - Gemcitabine
        - Paclitaxel
  - Systemic Therapy*:* Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive carcinosarcoma) changed from category 2B to category 2A.
- Footnote a is new: These agents may be considered when cisplatin and carboplatin are unavailable.
- Footnote d is new: Checkpoint inhibitors and/or monoclonal antibodies included in this regimen may be continued as maintenance therapy. Refer to the original study protocol for maintenance therapy dosing schedules. (Also for ENDO-D 2A of 4)

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Updates in Version 1.2024 of the NCCN Guidelines for Uterine Neoplasms from Version 2.2023 include:
Endometrial Carcinoma–continued
ENDO-D Systemic Therapy for Endometrial Carcinoma
ENDO-D 2 of 4
- First-line Therapy
  - Preferred: Carboplatin/paclitaxel/trastuzumab (for HER2-positive carcinosarcoma) changed from category 2B to category 2A.
  - Useful in Certain Circumstances (Biomarker-directed therapy: after prior platinum-based therapy including neoadjuvant and adjuvant): Section revised to separate regimens by mutation type
- Second-Line or Subsequent Line Therapy
  - Useful in Certain Circumstances (Biomarker-directed therapy)
    - Section revised to separate out regimens by mutation type
    - Fam-trastuzumab deruxtecan-nxki added for HER2-positive tumors (IHC 3+ or 2+)
    - NTRK gene fusion-positive tumors: Single agent Larotrectinib and Entrectinib changed from category 2B to category 2A.

ENDO-D 2A of 4
- The following footnote changes were made:
  - footnote e is new: For stage IIIA, IIIB, or IIIC1 with measurable disease, stage IIIC1 with carcinosarcoma, clear-cell, serous, or mixed histology regardless of the presence of measurable disease; and stage IIIC2 or stage IV regardless of the presence of measurable disease.
  - Footnote k: NCCN recommends TMB-H testing if not previously done. Pembrolizumab is indicated for patients with unresectable or metastatic tumors with TMB-H [≥10 mutations/megabase (mut/Mb)], as determined by ~~a validated and/or FDA-approved test~~ *an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory*, *whose disease has* ~~have~~ progressed following prior treatment and who have no satisfactory alternative treatment options.
  - Footnote q: Albumin-bound paclitaxel is a reasonable substitute for patients with a hypersensitivity to paclitaxel ~~if the skin testing to paclitaxel is negative. If the patient has a positive skin test to paclitaxel~~ *If a skin test is done, and is positive,* then the patient requires desensitization to paclitaxel. Albumin-bound paclitaxel is not a reasonable substitute for paclitaxel if the patient's skin test is positive.
  - Footnote r: Bevacizumab may be considered for use in patients ~~who have~~ *whose disease has* progressed on prior cytotoxic chemotherapy.

ENDO-D 3 of 4
- Hormonal Therapy for Recurrent or Metastatic Endometrial Carcinoma; New section added:
  - Useful in Certain Circumstances
    - ◊ ER-positive tumors
      - Letrozole/ribociclib
      - Letrozole/abemaciclib
- Table title revised: Hormonal Therapy for Uterine-Limited Disease Not Suitable for Primary Surgery *or for Those Desiring Uterine Preservation for Fertility*
  - Preferred regimens
    - ◊ Levonorgestrel IUD added. Previously it was listed under "Useful in Certain Circumstances"
  - Other Recommended Regimens (This is a new category); Progestational agents
    - ◊ Megestrol acetate added. Previously it was listed under "Preferred"
    - ◊ Medroxyprogesterone acetate added. Previously it was listed under "Preferred"

ENDO-D 4 of 4
- References updated to reflect changes in the algorithm

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Updates in Version 1.2024 of the NCCN Guidelines for Uterine Neoplasms from Version 2.2023 include:

Uterine Sarcoma
UTSARC-1
• Additional Evaluation; 1st bullet revised for both pathways: Expert pathologic review *and consider molecular testing*
• Footnote e is new: Disease is not amenable to resection, or patient is not suitable for surgery based on comorbidities.
• Footnote f revised: Oophorectomy is individualized for *patients of* reproductive *age* ~~patients~~. Favor BSO if ER/PR positive

UTSARC-2
• Adenosarcoma with SO; Stage II, III, IVA, IVB; Additional therapy revised: Consider systemic therapy *(recommended for residual measurable disease)*
• Footnote k is new: See Discussion. Nasioudis D, et al. Int J Gynecol Cancer 2019;29:126-132.

UTSARC-4
• Isolated metastases; Therapy for Relapse
  ▸ Resectable: Consider *preoperative or* postoperative EBRT
  ▸ Unresectable; After "Systemic therapy" recommendation revised: If response, consider surgery ± *EBRT*

UTSARC-A Principles of Pathology and Molecular Analysis
UTSARC-A 1 of 8
• Pathologic Assessment for Sarcoma
  ▸ 4th bullet revised: Peritoneal/ascitic fluid cytology *(if collected)*
• Molecular Analysis for Sarcoma
  ▸ 1st bullet revised: "*Recommend m*olecular profiling ~~is informative~~ in ~~many~~ *gynecologic* mesenchymal malignancies for accurate classification...".
  ▸ 2nd bullet revised: Comprehensive genomic profiling in setting of metastatic disease ~~with a validated and/or FDA-approved or CLIA-approved assay~~ *as determined by an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory,* is informative for predicting rare pan-tumor targeted therapy opportunities and should include at least *NTRK*, MSI, and TMB.
• Reference 2 updated

UTSARC-A 2 of 8
• Table 1 (Uterine Sarcoma Classifications)
  ▸ Conventional (spindle cell) LMS; Relevant Molecular Finding revised: "...*RB1*, ~~and~~ *PTEN*, *and BRCA2 mutation/loss*.

UTSARC-A 5 of 8
• Inflammatory Myofibroblastic Tumor (IMT): The term "cases" changed to "patients"

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Updates in Version 1.2024 of the NCCN Guidelines for Uterine Neoplasms from Version 2.2023 include:

UTSARC-B Principles of Imaging
UTSARC-B 1 of 2
- Follow-up/Surveillance
  - 1st bullet and 2nd bullets revised: "...Depending on histology grade and initial stage, consider *imaging* annual*ly* ~~to biannual~~ *or every other year* ~~imaging~~ thereafter up to an additional 5 years."
  - Footnote a revised: MRI i*s performed with and without contrast* and CT ~~are~~ *is* performed with contrast ~~throughout the guidelines~~ unless contraindicated. Contrast is not required for screening chest CT.

UTSARC-C Systemic Therapy for Uterine Sarcoma
UTSARC-C 1 of 3
- First-Line Therapy
  - Preferred regimens: Doxorubicin/trabectedin (for LMS) moved from the last bullet to the 3rd bullet.
  - Revised header: Useful in Certain Circumstances ~~(Biomarker-Directed Systemic Therapy)~~:
    - ◊ A new bullet was added for "Biomarker-directed therapy" and the sub-bullets were revised to separate the regimens by mutation type (Also for second-line or subsequent therapy)
- Footnote d revised: "... as determined by ~~a validated and/or FDA-approved test~~ *an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory*, that have progressed following prior treatment and have no satisfactory alternative treatment options."
- Footnote e is new: For oncogenic or likely oncogenic mutations in *BRCA2*, may refer to definitions at oncokb.org

UTSARC-C 3 of 3
- New References added:
  - Hensley ML, Chavan SS, Solit DB, et al. Genomic landscape of uterine sarcomas defined through prospective clinical sequencing. Clin Cancer Res 2020;26:3881-3888.
  - Shammas N, Yang T, Abidi A, et al. Clinical use of PARP inhibitor in recurrent uterine leiomyosarcoma with presence of a somatic BRCA2 mutation. Gynecol Oncol Rep 2022;42:101044.
  - Seligson ND, Kautto EA, Passen EN, et al. BRCA1/2 functional loss defines a targetable subset in leiomyosarcoma. Oncologist 2019;24:973-979.

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Updates in Version 1.2024 of the NCCN Guidelines for Uterine Neoplasms from Version 2.2023 include:

Uterine Neoplasms
UN-A Principles of Radiation Therapy for Uterine Neoplasms
UN-A 2 of 3
- General Treatment Information; Dosing Prescription Regimen – External Beam
  - 1st arrow sub-bullet revised: External-beam doses for microscopic disease should be 45–50 Gy. ~~Multiple conformal fields based on~~ CT treatment planning should be utilized, and ~~consideration for~~ intensity-modulated RT (IMRT) for normal tissue sparing ~~may be~~ *should be* considered, with appropriate attention to quality assurance (QA) and tissue interfraction mobility.
  - 6th bullet revised: " For *pelvic-confined* recurrent endometrial cancer without a prior history of radiation..."
  - New bullets added:
    - ◊ Treating with IMRT technique is preferred to minimize toxicities in definitive treatment of the pelvis with or without para-aortic treatment. Regular use of image-guided RT (IGRT) with orthogonal imaging and/or routine volumetric imaging (such as cone beam CT) at the time of treatment delivery is essential to ensure appropriate coverage of targets and sparing of normal tissues.
    - ◊ Postoperatively, if there is gross residual disease and the area(s) can be sufficiently localized, a boost can be added to a total dose of 60–70 Gy, respecting normal tissue sensitivity.

UN-B Principles Of Gynecologic Survivorship
- Physical Effects; New bullet added: Prior pelvic RT may contribute to bone loss and increase the risk of pelvic fractures. Consider bone density testing and prophylactic use of bisphosphonates, particularly in patients with osteoporosis.
- Clinical Approach; 4th Bullet revised: ~~For premenopausal patients, hormone replacement therapy should be considered.~~ *For treatment-related menopause, hormone therapy should be considered*.

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All staging in guideline is based on updated FIGO staging. (ST-1, ST-2, and ST-3)

INITIAL EVALUATION[a]

- History and physical (H&P)
- Complete blood count (CBC) (including platelets), liver function test [LFT], renal function tests, chemistry profile; and consider CA-125
- Expert pathology review with additional endometrial biopsy as clinically indicated[b,c]
- Imaging[d]
- Recommend molecular evaluation of tumor and evaluation for inherited cancer risk (ENDO-A and UTSARC-A)
- For patients who are older with uterine cancer also see the NCCN Guidelines for Older Adult Oncology
- Consider germline and/or multigene panel testing

INITIAL CLINICAL FINDINGS[c]

- Malignant epithelial (carcinoma)
  - Pure endometrioid carcinoma
    - Disease limited to uterus → Primary Treatment (ENDO-1)
    - Suspected or gross cervical involvement → Primary Treatment (ENDO-2)
    - Suspected extrauterine disease → Primary Treatment (ENDO-3)
  - High-risk endometrial carcinoma histology
    - Serous carcinoma → Primary Treatment (ENDO-11)
    - Clear cell carcinoma → Primary Treatment (ENDO-12)
    - Undifferentiated/dedifferentiated carcinoma → Primary Treatment (ENDO-13)
    - Carcinosarcoma[f,g] → Primary Treatment (ENDO-14)
- Malignant mesenchymal (sarcoma)[e]
  - Low-grade endometrial stromal sarcoma (ESS) or adenosarcoma
  - High-grade ESS
  - Undifferentiated uterine sarcoma (UUS)
  - Leiomyosarcoma (LMS)
  - Other sarcomas (eg, perivascular epithelioid cell tumor [PEComa])

  → Primary Treatment (UTSARC-1)

[a] Initial preoperative evaluation for known or suspected malignancy.
[b] Preoperative imaging and biopsy may help to identify uterine sarcomas, although biopsy sensitivity is less than for endometrial cancer. If there is suspicion of malignancy, fragmentation/morcellation should be avoided.
[c] See Principles of Pathology for Endometrial Carcinoma (ENDO-A) and Principles of Pathology for Uterine Sarcoma (UTSARC-A).
[d] See Principles of Imaging for Endometrial Carcinoma (ENDO-B) and Principles of Imaging for Uterine Sarcoma (UTSARC-B).
[e] Consider referral to a center of expertise that specializes in the treatment of malignant mesenchymal tumors (sarcoma).
[f] Should be treated as a high-grade endometrial cancer.
[g] 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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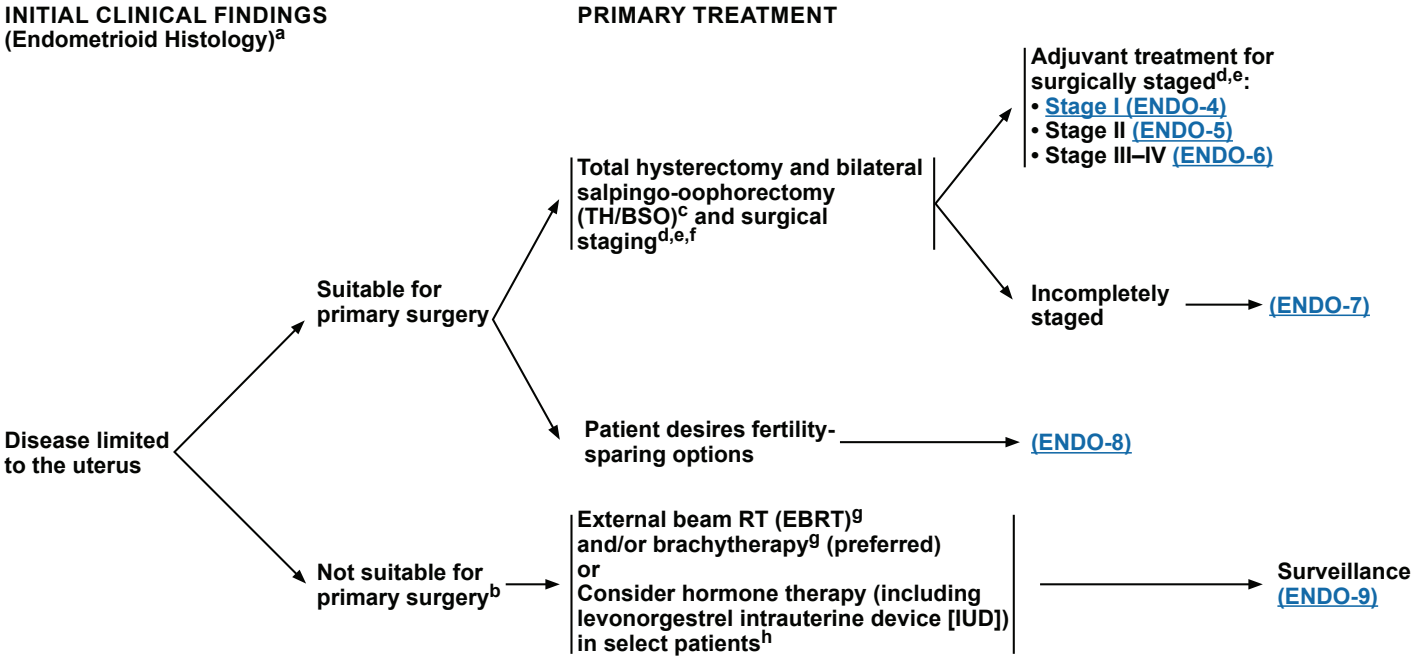

[a] (UN-1) for classification of uterine neoplasms.
[b] Disease is not amenable to resection or patient is not suitable for surgery based on comorbidities.
[c] Principles of Pathology and Molecular Analysis (ENDO-A).
[d] Minimally invasive surgery (MIS) is the preferred approach when technically feasible. See Principles of Evaluation and Surgical Staging (ENDO-C).
[e] 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).
[f] Ovarian preservation may be safe in select patients who are premenopausal with early-stage endometrioid cancer, normal-appearing ovaries, and no family history of breast/ovarian cancer or Lynch syndrome. Salpingectomy is recommended.
[g] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] Systemic Therapy for Endometrial Carcinoma (ENDO-D).

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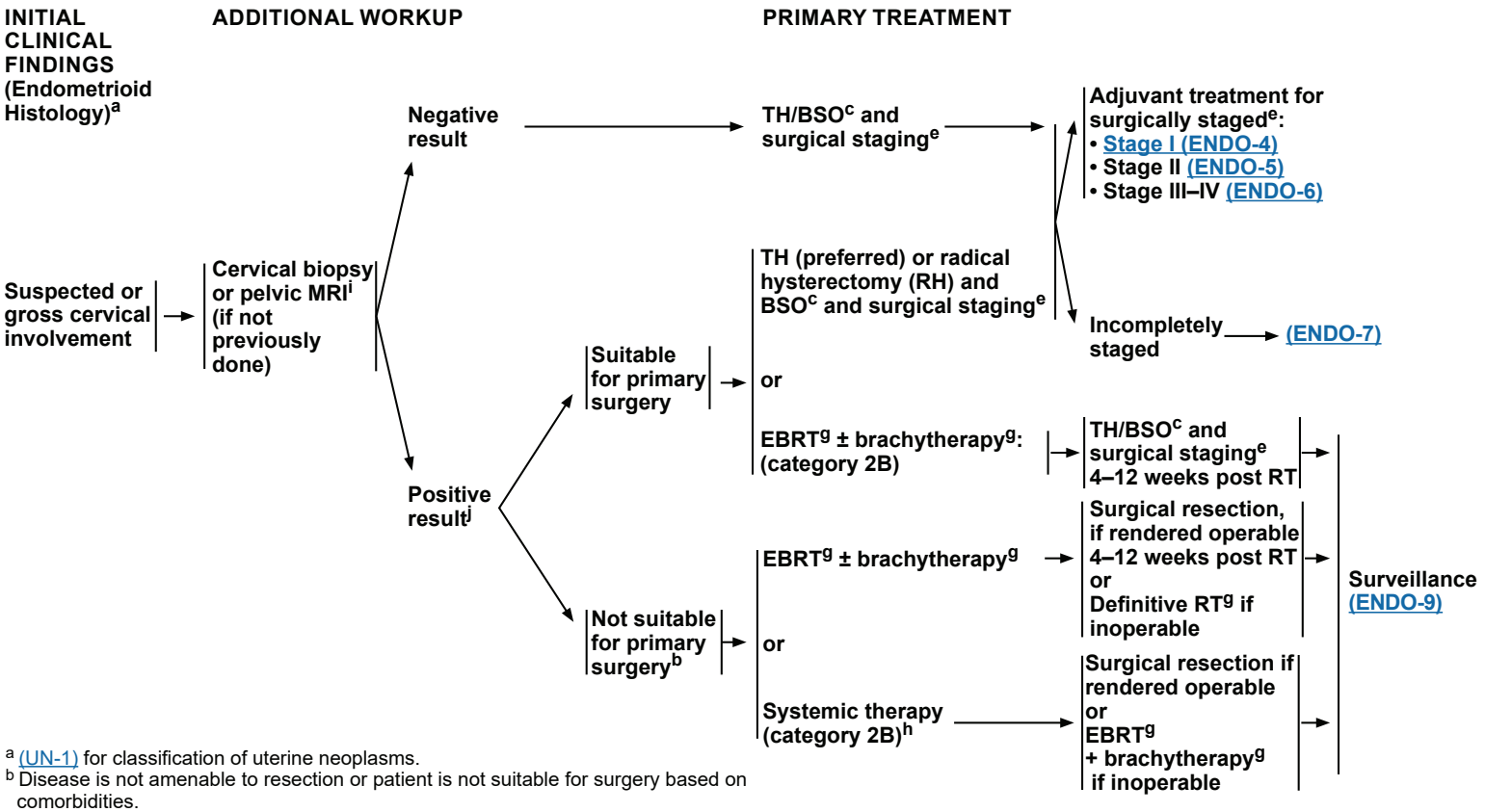

[a] (UN-1) for classification of uterine neoplasms.
[b] Disease is not amenable to resection or patient is not suitable for surgery based on comorbidities.
[c] Principles of Pathology and Molecular Analysis (ENDO-A).
[e] The degree of surgical staging to assess disease status depends on preoperative and intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).
[g] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] Systemic Therapy for Endometrial Carcinoma (ENDO-D).
[i] Principles of Imaging (ENDO-B).
[j] Clear demonstration of cervical stromal involvement.

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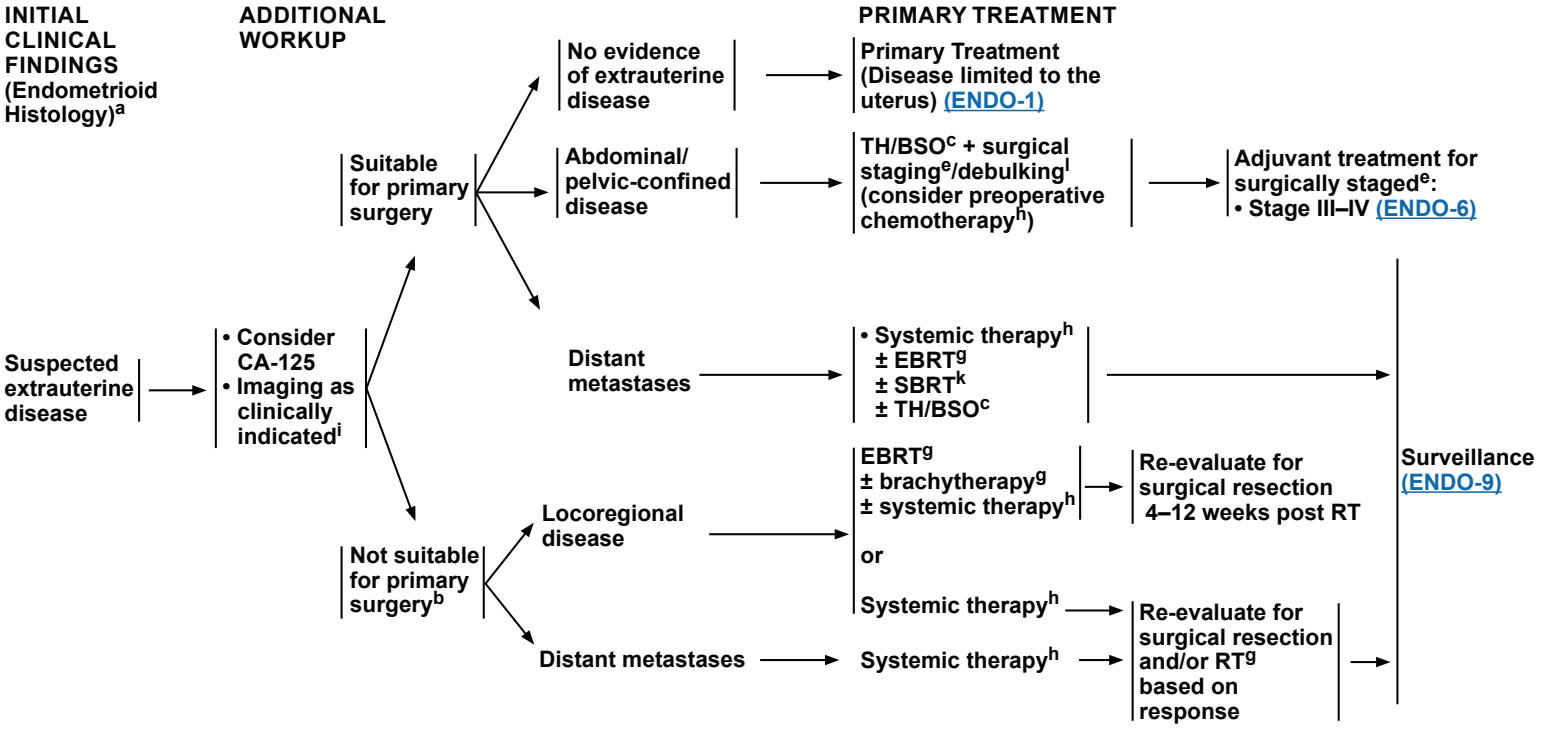

[a] (UN-1) for classification of uterine neoplasms.
[b] Disease is not amenable to resection or patient is not suitable for surgery based on comorbidities.
[c] Principles of Pathology and Molecular Analysis (ENDO-A).
[e] The degree of surgical staging to assess disease status depends on preoperative and intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).
[g] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] Systemic Therapy for Endometrial Carcinoma (ENDO-D).
[i] Principles of Imaging (ENDO-B).
[k] Consider ablative RT for 1–5 metastatic lesions if hysterectomy is performed (category 2B) (Palma DA, et al. Lancet 2019;393:2051-2058).
[l] The surgical goal is to have no measurable residual disease.

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

CLINICAL FINDINGS (Endometrioid Histology)[a]

HISTOLOGIC GRADE/ADJUVANT TREATMENT[g,h,m]

Surgically staged: Stage I[e] →

FIGO Stage	Histologic Grade	Adjuvant Treatment
IA	G1, G2	Observation preferred or Consider vaginal brachytherapy if lymphovascular space invasion (LVSI) and/or age ≥60 y[n]
	G3	Vaginal brachytherapy preferred or Consider observation if no myoinvasion or Consider EBRT if either age ≥70 y or LVSI (category 2B)
IB	G1	Vaginal brachytherapy preferred or Consider observation if age <60 y and no LVSI
	G2	Vaginal brachytherapy preferred or Consider EBRT if ≥60 y and/or LVSI or Consider observation if age <60 y and no LVSI
	G3	RT (EBRT and/or vaginal brachytherapy) ± systemic therapy (category 2B for systemic therapy)

[a] (UN-1) for classification of uterine neoplasms.
[e] 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).
[g] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] Systemic Therapy for Endometrial Carcinoma (ENDO-D).
[m] Initiate EBRT as soon as the vaginal cuff is healed, preferably no later than 12 weeks after surgery.
[n] Vaginal brachytherapy is strongly suggested if two risk factors are present.

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CLINICAL FINDINGS (Endometrioid Histology)[a]

HISTOLOGIC GRADE/ADJUVANT TREATMENT[g,h,m]

Surgically staged[e]: Stage II[o,p] →

FIGO Stage	Histologic Grade	Adjuvant Treatment
II	G1–G3	EBRT (preferred) and/or vaginal brachytherapy[q] ± systemic therapy (category 2B for systemic therapy)

Surveillance (ENDO-9)

[a] (UN-1) for classification of uterine neoplasms.
[e] 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).
[g] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] Systemic Therapy for Endometrial Carcinoma (ENDO-D).
[m] Initiate EBRT as soon as the vaginal cuff is healed, preferably no later than 12 weeks after surgery.
[o] Consider additional imaging if not previously done. See Principles of Imaging (ENDO-B).
[p] Adverse cervical risk factors including depth of stromal invasion, grade, LVSI, and adverse fundal risk factors influencing therapy decisions for stage I disease (ENDO-4), such as depth of myometrial invasion and LVSI, may also impact the choice of adjuvant therapy for stage II disease.
[q] Vaginal brachytherapy is also an option for grade 1 or 2, ≤50% myometrial invasion, no LVSI, and microscopic cervical invasion (Harkenrider MM, et al. Int J Radiat Oncol Biol Phys 2018;101:1069-1077).

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

CLINICAL FINDINGS (Endometrioid Histology)[a]	ADJUVANT TREATMENT[g,h]
Surgically staged[e]: Stage III, IV[r] →	Systemic therapy ± EBRT[s] ± vaginal brachytherapy[s]

[a] (UN-1) for classification of uterine neoplasms.
[e] 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).
[g] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] Systemic Therapy for Endometrial Carcinoma (ENDO-D).
[r] Additional imaging if not previously done. See Principles of Imaging (ENDO-B).
[s] Combination therapy depends on assessment of both locoregional and distant metastatic risk. Consider combination therapy for stage IIIB and IIIC disease.

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Surveillance (ENDO-9)

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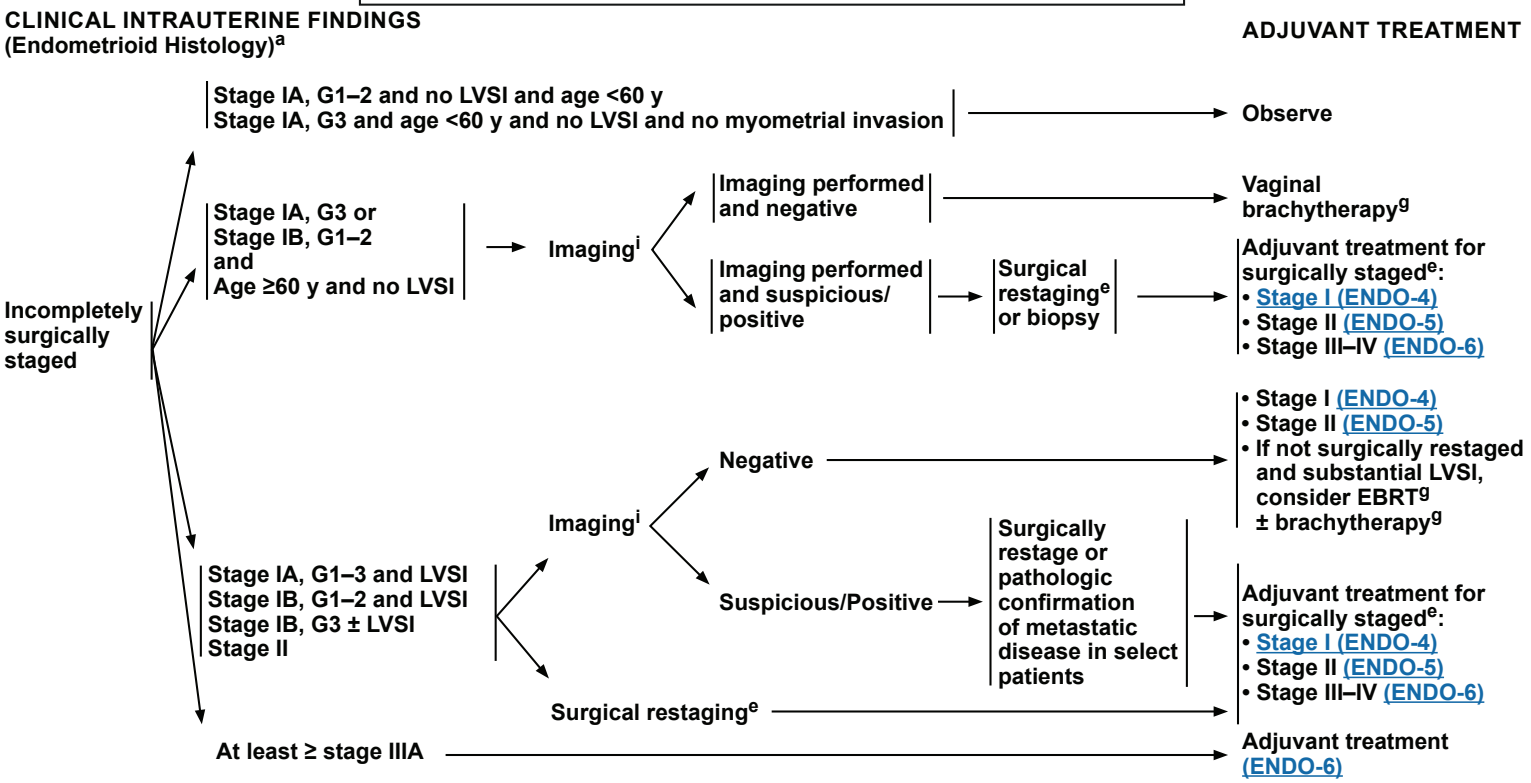

[a] (UN-1) for classification of uterine neoplasms.
[e] The degree of surgical staging to assess disease status depends on preoperative and intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).
[g] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[i] Principles of Imaging (ENDO-B).

Surveillance (ENDO-9)

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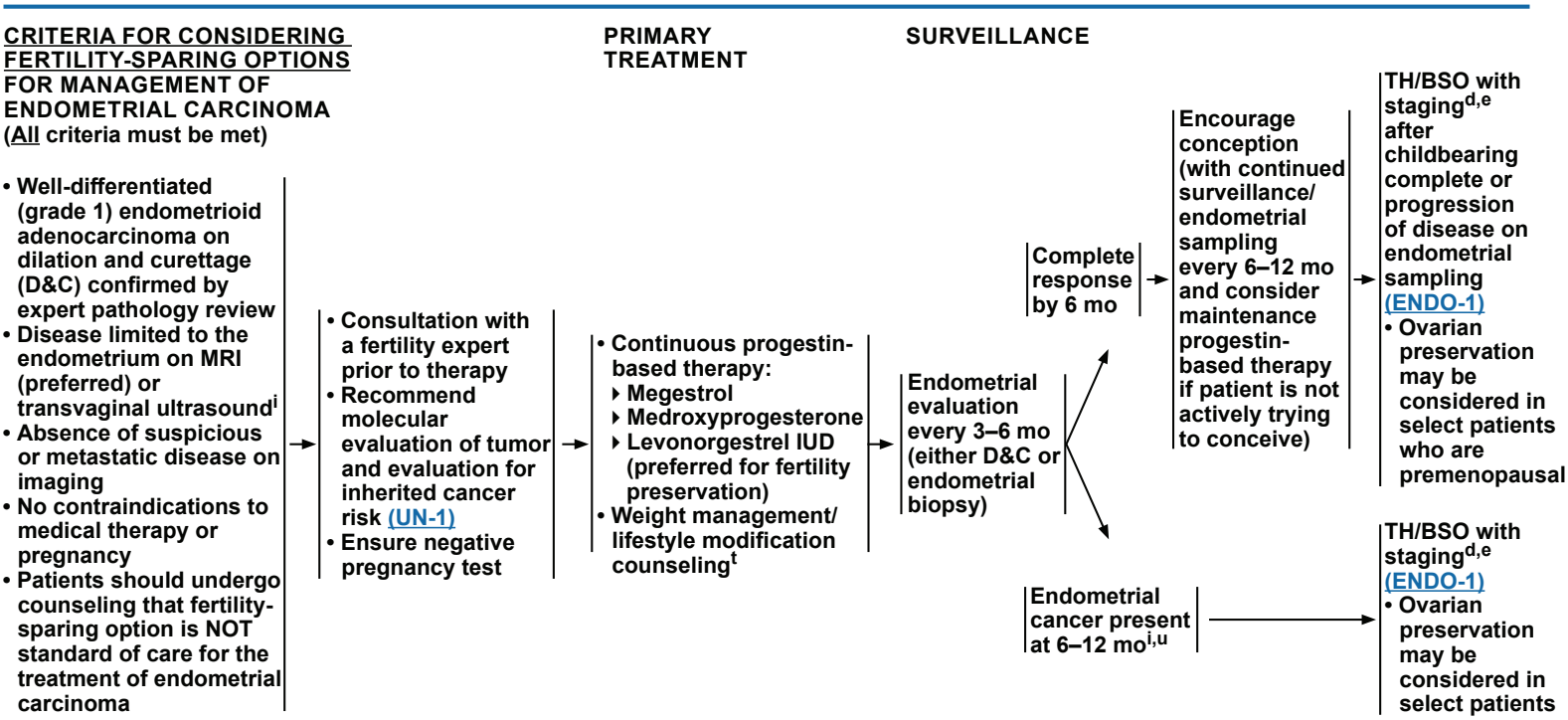

[d] MIS is the preferred approach when technically feasible. See Principles of Evaluation and Surgical Staging (ENDO-C).
[e] The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).
[i] Principles of Imaging (ENDO-B).
[t] See Healthy Lifestyles (HL-1) and Nutrition and Weight Management (SNWM-1) in the NCCN Guidelines for Survivorship.
[u] Gunderson CC, et al. Gynecol Oncol 2012;125:477-482 and Hubbs JL, et al. Obstet Gynecol 2013;121:1172-1180.

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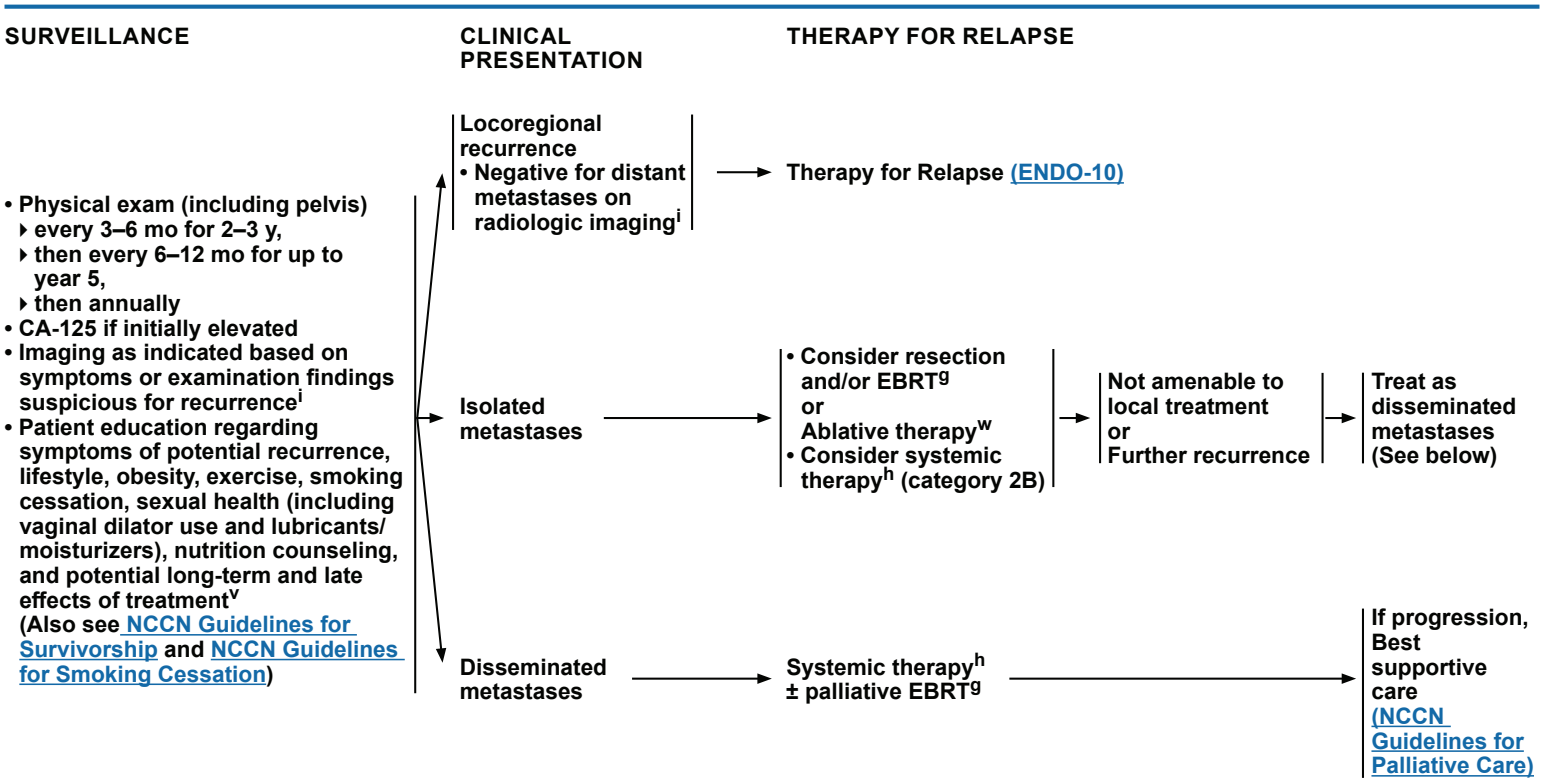

[g] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] Systemic Therapy for Endometrial Carcinoma (ENDO-D).
[i] Principles of Imaging (ENDO-B).
[v] Principles of Gynecologic Survivorship (UN-B).
[w] Consider ablative RT for 1–5 metastatic lesions if the primary cancer has been controlled (category 2B) (Palma DA, et al. Lancet 2019;393:2051-2058).

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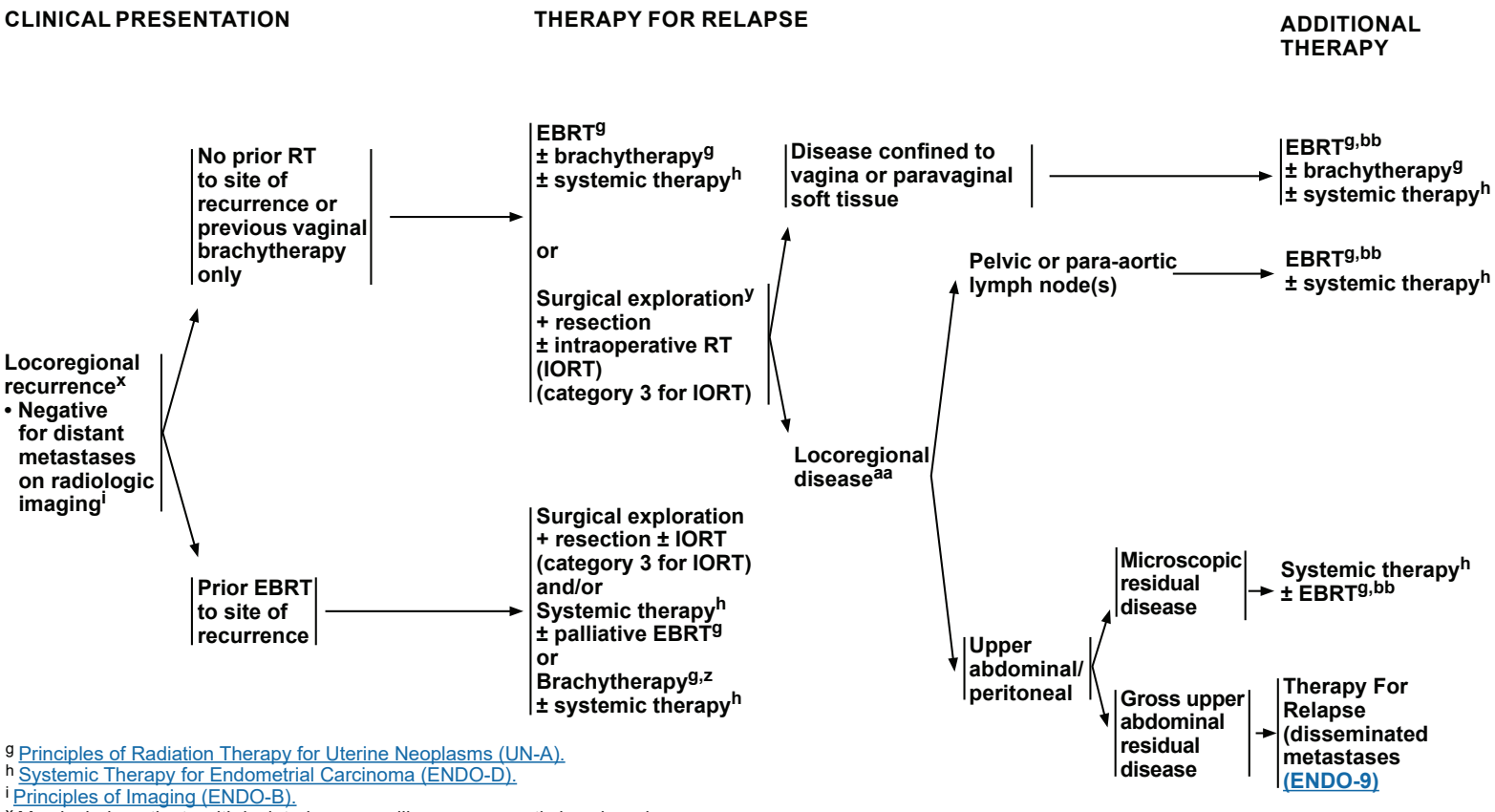

[g] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] Systemic Therapy for Endometrial Carcinoma (ENDO-D).
[i] Principles of Imaging (ENDO-B).
[x] May include patients with isolated common iliac or para-aortic lymph node recurrence.
[y] Consider preoperative EBRT in select patients.
[z] Recommended for small-volume vaginal and/or paravaginal disease.
[aa] Consider brachytherapy for locoregional disease with a vaginal component.
[bb] Post-resection consolidation EBRT can be considered in patients who were not previously irradiated or who are deemed to have additional tolerance for radiation.

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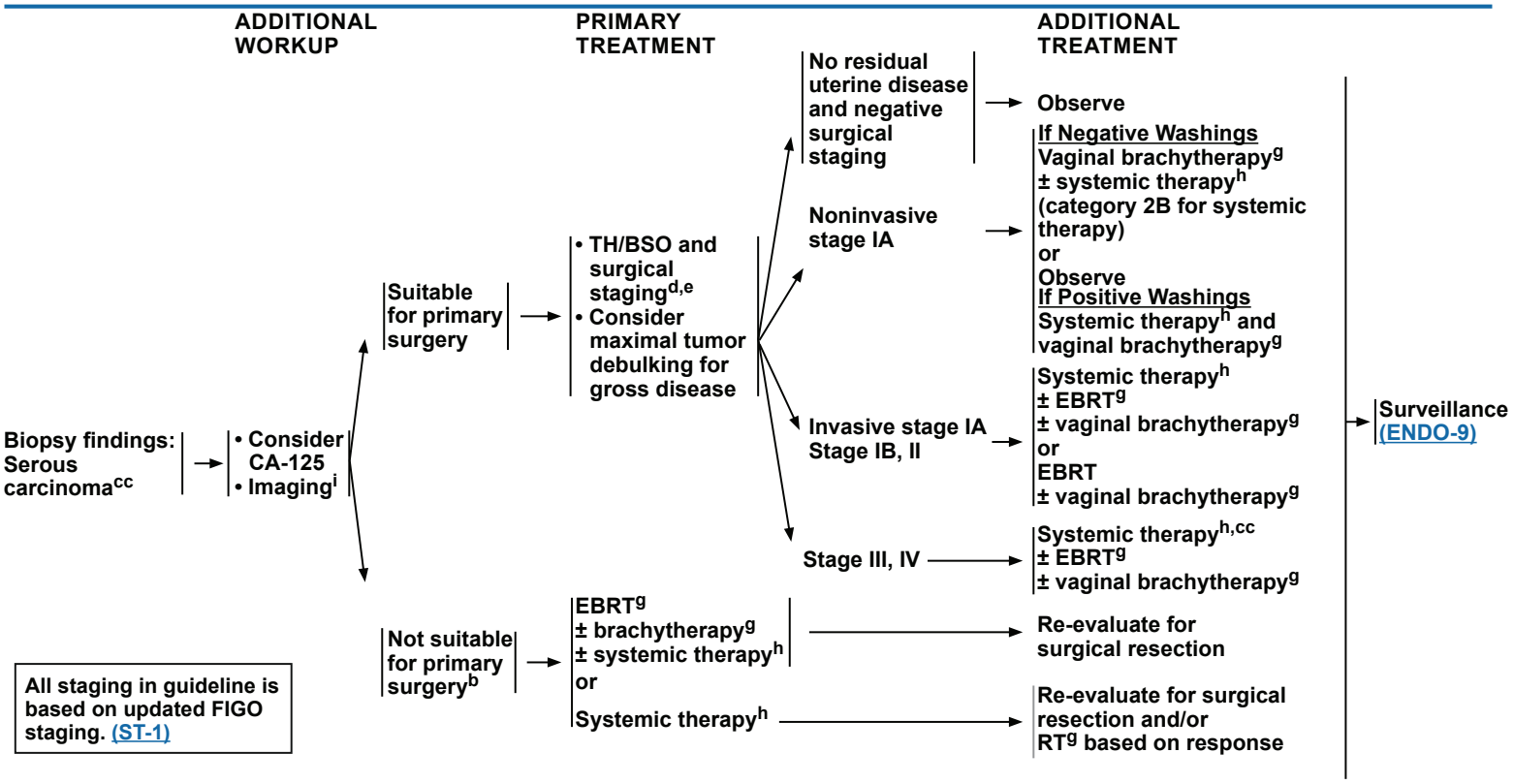

[b] Disease is not amenable to resection or patient is not suitable for surgery based on comorbidities.
[d] MIS is the preferred approach when technically feasible. See Principles of Evaluation and Surgical Staging (ENDO-C).
[e] The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).
[g] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] Systemic Therapy for Endometrial Carcinoma (ENDO-D).
[i] Principles of Imaging (ENDO-B).
[cc] HER2 testing is recommended for advanced or metastatic disease.

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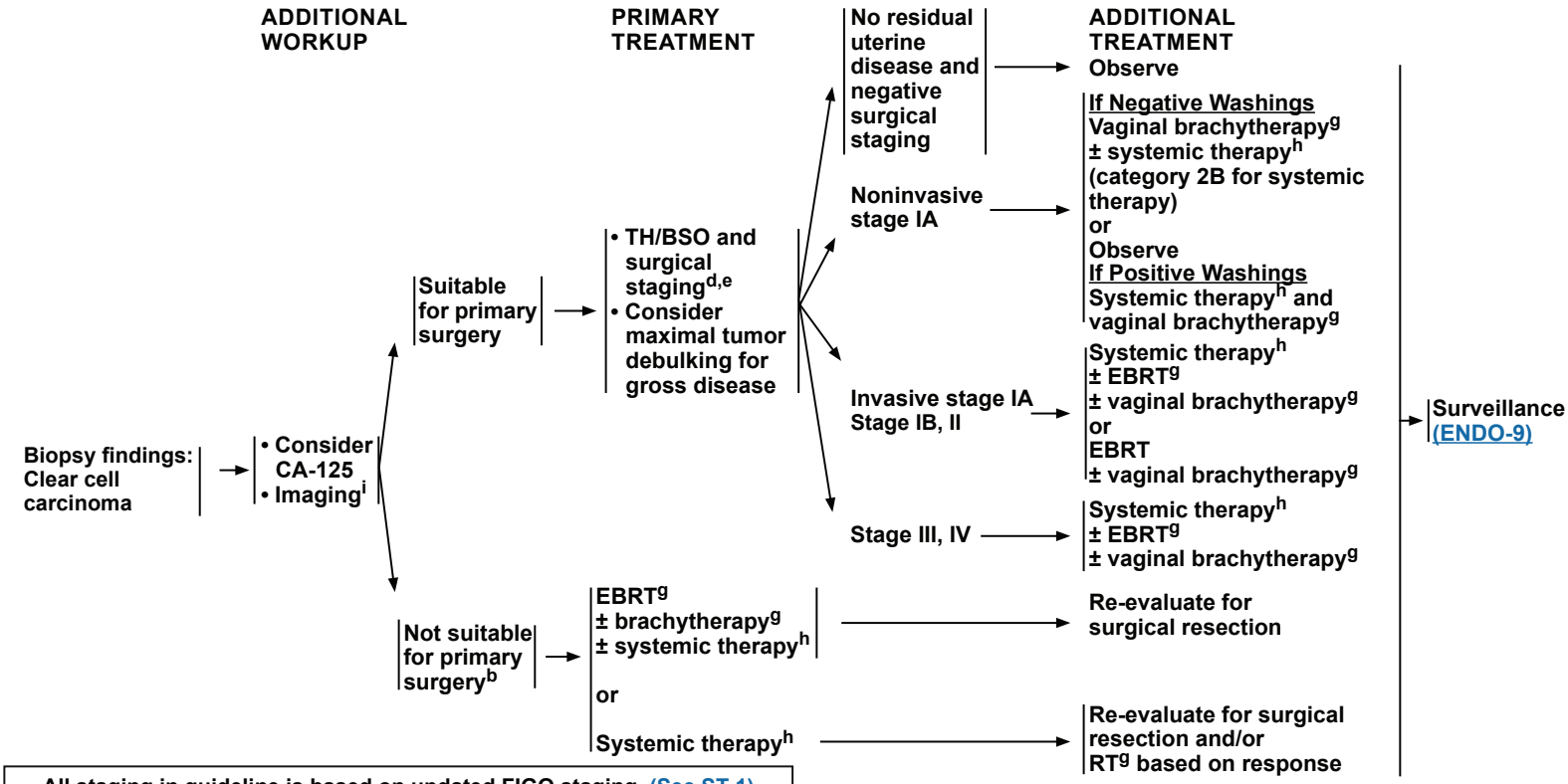

All staging in guideline is based on updated FIGO staging. (See ST-1)

[b] Disease is not amenable to resection or patient is not suitable for surgery based on comorbidities.
[d] MIS is the preferred approach when technically feasible. See Principles of Evaluation and Surgical Staging (ENDO-C).
[e] The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).
[g] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] Systemic Therapy for Endometrial Carcinoma (ENDO-D).
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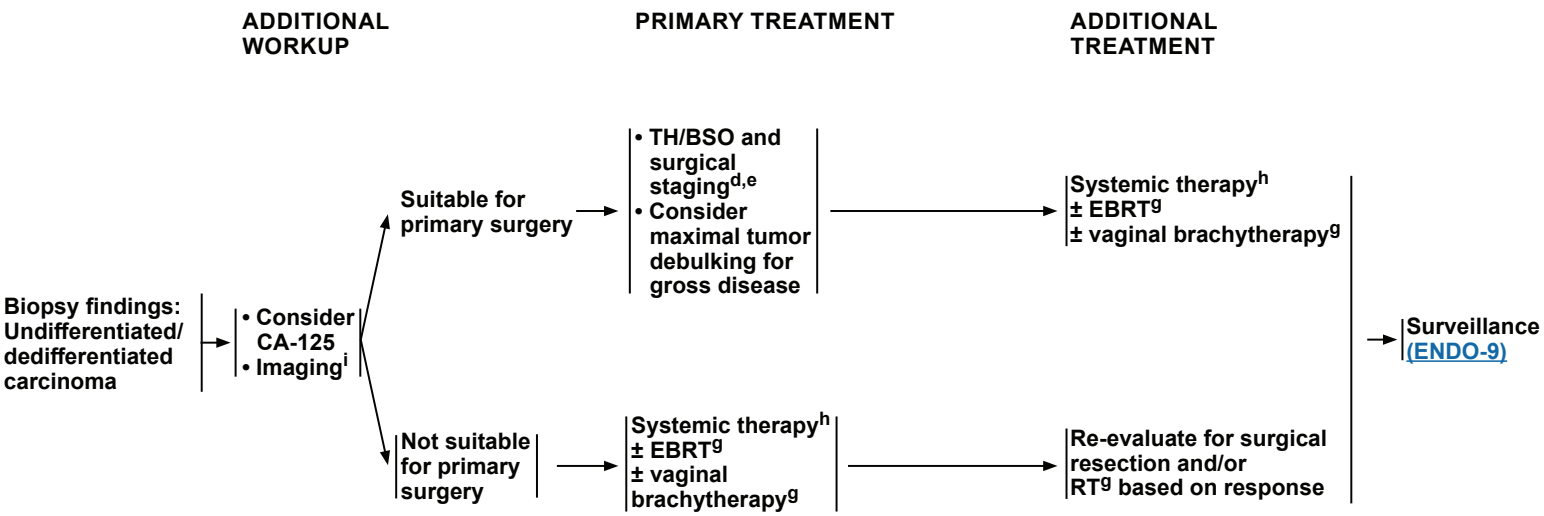
Endometrial Carcinoma: Undifferentiated/Dedifferentiated Carcinoma



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

[d] MIS is the preferred approach when technically feasible. See Principles of Evaluation and Surgical Staging (ENDO-C).
[e] The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).
[g] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] Systemic Therapy for Endometrial Carcinoma (ENDO-D).
[i] Principles of Imaging (ENDO-B).

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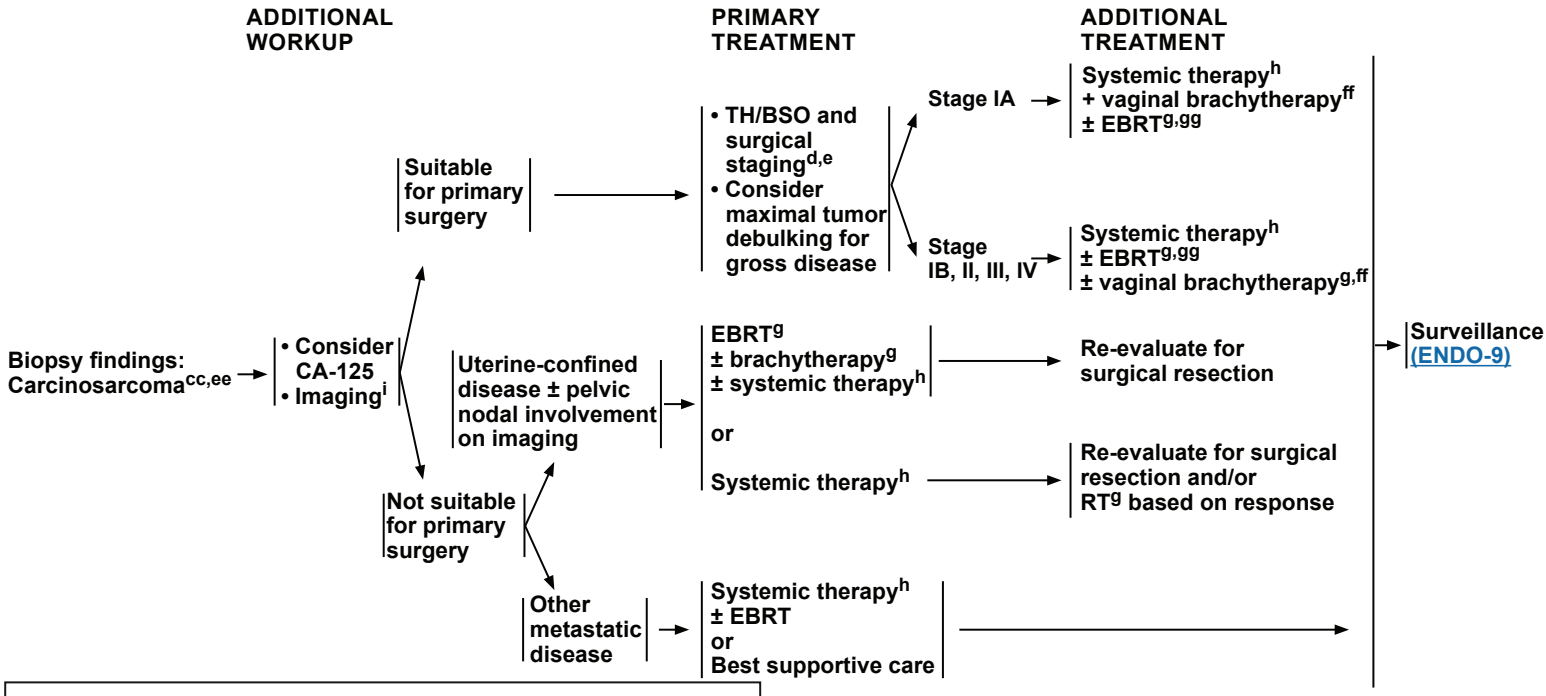

All staging in guideline is based on updated FIGO staging. (ST-1)

[d] MIS is the preferred approach when technically feasible. See Principles of Evaluation and Surgical Staging (ENDO-C).
[e] The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).
[g] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] Systemic Therapy for Endometrial Carcinoma (ENDO-D).
[i] Principles of Imaging (ENDO-B).

[cc] HER2 testing is recommended for advanced or metastatic disease.
[ee] Also known as malignant mixed mesodermal tumor or malignant mixed Müllerian tumor.
[ff] Initiation of chemotherapy within 3–6 weeks postoperatively should be considered. Vaginal brachytherapy can be interdigitated with chemotherapy starting 6 weeks postoperatively.
[gg] Consider EBRT if both high-grade epithelial components and sarcoma are dominant (>50% of sarcoma component in uterine tumor) (Matsuo K, et al. Surg Oncol 2018;27:433-440).

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PRINCIPLES OF PATHOLOGY[a,1,2,3]

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

Pathologic assessment for carcinoma (including carcinoma, carcinosarcoma, and neuroendocrine carcinoma):
- **Uterus**
  - **Hysterectomy type**
  - **Specimen integrity (intact, opened, morcellated, other)**
  - **Tumor site (endometrium, lower uterine segment, polyp)**
  - **Tumor size**
  - **Histologic type**
  - **Histologic grade (if applicable)**
  - **Myometrial invasion (depth of invasion in mm/myometrial thickness in mm)**
  - **Cervical stromal involvement[b]**
  - **LVSI[c]**
- **Other tissue/organ involvement (fallopian tubes, ovaries, vagina, parametrium, peritoneum, omentum, other)**
- **Peritoneal/ascitic fluid cytology[d]**
- **Lymph nodes (when resected)**
  - **Sentinel lymph nodes (SLNs) should undergo ultrastaging for detection of low-volume metastasis.[e]**
  - **Isolated tumor cells are staged N0(i+) and should not upstage patients, but should be considered in the discussion of adjuvant therapy.**
  - **Level of nodal involvement (ie, pelvic, common iliac, para-aortic)**
  - **Number of lymph nodes with isolated tumor cells, micrometastasis, macrometastasis**
  - **Thorough gross evaluation of the SLN tissue specimen is recommended to ensure that lymph node tissue is included. This could be performed either by the surgeon (depending on experience/comfort level with gross evaluation) or by seeking an intraoperative pathology consultation.**
- **Morphologic evaluation of endometrial carcinoma to determine histologic type—especially in high-grade cancers—is challenging and issues exist regarding diagnostic reproducibility.[4,5]**
- **HER2 immunohistochemistry (IHC) testing (with reflex to HER2 fluorescence in situ hybridization [FISH] for equivocal IHC) is recommended for all serous and carcinosarcoma tumors.[6-9] Consider HER2 testing for p53 abnormal carcinomas regardless of histology.**
- **Estrogen receptor (ER) and progesterone receptor (PR) testing is recommended in the settings of stage III, stage IV, and recurrent disease.**

[a] Principles of Evaluation and Surgical Staging (ENDO-C).
[b] Additional information including depth of invasion in mm/cervical wall thickness in mm may be requested by radiation oncologists to aid in the decision for EBRT.
[c] Pathologists may be asked to quantify LVSI. The current definition of substantial LVSI is four or more (LVSI-involved vessels in at least one hematoxylin and eosin [H&E] slide) for defining clinically relevant LVSI in endometrial cancer (Peters EEM, et al. Int J Gynecol Path 2022;41:220-226).
[d] Although cytology by itself does not affect FIGO staging, cytology results should still be obtained because positive cytology is an adverse risk factor.
[e] Ultrastaging commonly entails thin serial sectioning of the gross SLN and review of multiple H&E-stained sections with or without cytokeratin IHC for all blocks of SLN. There is no standard protocol for lymph node ultrastaging.

References
Continued

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PRINCIPLES OF MOLECULAR ANALYSIS

- **Molecular analysis of endometrial carcinoma has identified four clinically significant molecular subgroups associated with differing clinical prognoses: *POLE* mutations, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), no specific molecular profile (NSMP), and p53 abnormal.[10,11]**
- **Retrospective analyses indicate that these four molecular subgroups may respond to therapy differently and therefore may require escalation or de-escalation of therapy compared to previous guidelines. Prospective randomized trials are ongoing to determine the role of a molecular profile–guided treatment strategy in the management of high-intermediate-risk and high-risk endometrial carcinomas**
- **Ancillary studies for *POLE* mutations (hotspot mutations in the exonuclease domain), IHC staining for mismatch repair (MMR) or MSI testing, and p53 IHC are strongly encouraged to complement morphologic assessment regardless of histologic tumor type.[12]**
  See Figure 1: Pathology and Genomics in Endometrial Carcinoma (ENDO-A 3 of 4).
- **Comprehensive molecular profiling is strongly encouraged via an FDA-approved assay, or a validated test performed in a clinical laboratory improvement amendment (CLIA)-certified laboratory, in the initial evaluation of uterine neoplasms.**
- **For tumors that are POLE-mutated, MSI-H, or copy number high, clinical trial enrollment is strongly encouraged.**
- **Molecular testing may be performed on the initial biopsy or D&C material or the final hysterectomy specimen.**
- **Universal testing of endometrial carcinomas for MMR proteins is recommended.**
  - **MSI testing is recommended if results are equivocal.**
  - **MLH1 loss should be further evaluated for promoter methylation to assess for an epigenetic mechanism.**
  - **Genetic counseling, molecular analysis, and testing for all other MMR abnormalities is recommended.**
  - **For those who have a strong family history of endometrial and/or colorectal cancer, genetic counseling and testing are recommended regardless of MMR or MLH1 promoter methylation results [see Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer Syndrome) in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal].**
- **Consider *NTRK* gene fusion testing for metastatic or recurrent endometrial carcinoma.**
- **Consider tumor mutational burden (TMB) testing through an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory.[13]**

References
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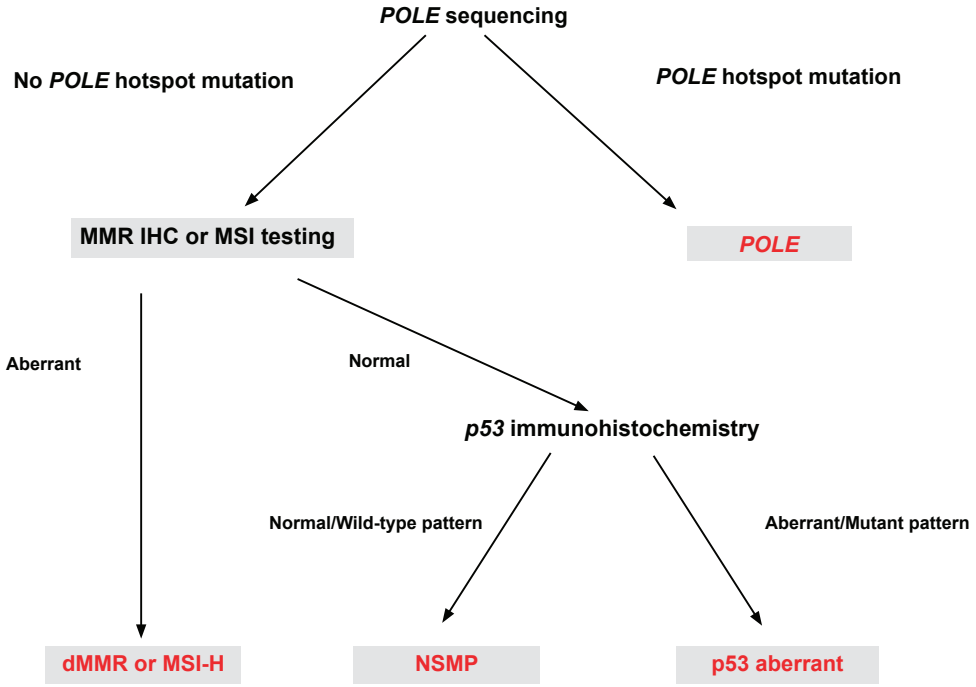
PRINCIPLES OF MOLECULAR ANALYSIS

FIGURE 1: PATHOLOGY AND GENOMICS IN ENDOMETRIAL CARCINOMA
(The decision to use molecular testing/classification depends on the availability of resources and the multidisciplinary team of each center.)[f,g]



[f] Adapted with permission from Murali R, Delair DF, Bean SM, et al. Evolving roles of histologic evaluation and molecular/genomic profiling in the management of endometrial cancer. J Nat Compr Canc Netw 2018;16:201-209.
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PRINCIPLES OF IMAGING[a,1-9]

Initial Workup

- **Non–Fertility-Sparing Treatment**
  - **Consider chest imaging (chest x-ray). If an abnormality is seen, then chest CT without contrast may be performed.**
  - **Consider pelvic MRI to establish the origin of the tumor (endocervical vs. endometrial) and assess local disease extent.**
  - **Consider preoperative pelvic ultrasound if uterine size is not clear on exam.**
  - **For high-grade carcinoma,[b] consider chest/abdomen/pelvis CT (preferred) to evaluate for metastatic disease.**
  - **For patients who underwent TH with incidental finding of endometrial cancer or whose cancer was incompletely staged (ENDO-7) with uterine risk factors,[c] consider chest/abdomen/pelvis CT to evaluate for metastatic disease.**
  - **Consider neck/chest/abdomen/pelvis/groin FDG-PET/CT if metastasis is suspected in select patients.**
  - **Other initial imaging should be based on symptomatology and clinical concern for metastatic disease.[d]**
- **Fertility-Sparing Treatment**
  - **Pelvic MRI (preferred) to exclude myoinvasion and assess local disease extent; pelvic transvaginal ultrasound if MRI is contraindicated or unavailable.**
  - **Consider chest imaging (chest x-ray). If an abnormality is seen, then chest CT without contrast may be performed.**
  - **Consider neck/chest/abdomen/pelvis/groin FDG-PET/CT if metastasis is suspected in select patients.**
  - **Other imaging should be based on symptomatology and clinical concern for metastatic disease.[e]**

Follow-up/Surveillance

- **Non–Fertility-Sparing Treatment**
  - **Imaging should be guided by patient symptoms, risk assessment, and clinical concern for recurrent or metastatic disease.[e]**
- **Fertility-Sparing Treatment**
  - **Repeat pelvic MRI (preferred) for patients with persistent endometrial carcinoma after 6–9 months of ineffective treatment, especially if considering further fertility-sparing approaches.**
  - **Other imaging should be based on symptomatology and clinical concern for metastatic disease.[e]**

Suspected Recurrence or Metastasis

- **Abdomen/pelvis CT and/or chest CT is recommended based on symptoms or physical exam findings.[e]**
- **Consider whole body FDG-PET/CT and/or abdomen/pelvis MRI in select patients as clinically indicated.**

[a] MRI is performed with and without contrast and CT is performed with contrast unless contraindicated. Contrast is not required for screening chest CT.
[b] High-grade endometrial carcinoma includes: poorly differentiated endometrioid, serous, clear cell, undifferentiated carcinoma, and carcinosarcoma.
[c] Uterine risk factors identified post TH include: high-grade carcinomas (above criteria), myoinvasion >50%, cervical stromal involvement, LVSI, and tumor >2 cm.
[d] Indications may include abnormal physical exam findings; bulky uterine tumor; vaginal or extrauterine involvement; delay in presentation or treatment; and abdominal or pulmonary symptoms.
[e] Indications may include abnormal physical exam findings such as vaginal tumor; palpable mass or adenopathy; and new pelvic, abdominal, or pulmonary symptoms.

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PRINCIPLES OF EVALUATION AND SURGICAL STAGING

Principles of Surgical Staging for Endometrial Cancer[1-15]

- **TH/BSO and lymph node assessment is the primary treatment for apparent uterine-confined endometrial carcinoma, unless patients desire (and are candidates for) fertility-sparing options (ENDO-8).[1-3] Select patients with metastatic endometrial carcinoma are also candidates for hysterectomy (Principles of Pathology and Molecular Analysis [ENDO-A]).**
- **Endometrial carcinoma should be removed en bloc to optimize outcomes; intraperitoneal morcellation or tumor fragmentation should be avoided.**
- **TH/BSO and lymph node assessment may be performed by any surgical route (eg, laparoscopic, robotic, vaginal, abdominal), although the standard in those with apparent uterine-confined disease is to perform the procedure via a minimally invasive approach. Randomized trials, a Cochrane Database Systematic Review, and population-based surgical studies support that minimally invasive techniques are preferred in this setting due to a lower rate of surgical site infection, transfusion, venous thromboembolism, decreased hospital stay, and lower cost of care, without compromise in oncologic outcome.[4-9]**
- **The lymph node assessment includes evaluation of the nodal basins that drain the uterus, and often comprises a pelvic nodal dissection with or without para-aortic nodal dissection. This continues to be an important aspect of surgical staging in patients with uterine-confined endometrial carcinoma, as the procedure provides important prognostic information that may alter treatment decisions.**
- **Pelvic lymph nodes from the external iliac, internal iliac, obturator, and common iliac nodes are frequently removed for staging purposes.**
- **Para-aortic nodal evaluation from the inframesenteric and infrarenal regions may also be utilized for staging in patients with high-risk tumors such as deeply invasive lesions, high-grade histology, and tumors of serous carcinoma, clear cell carcinoma, or carcinosarcoma.**
- **SLN mapping is preferred (see pages 2–6 of ENDO-C)[15]**
- **Excision of suspicious or enlarged lymph nodes in the pelvic or aortic regions is important to exclude nodal metastasis.**
- **Some patients may not be candidates for lymph node dissection.**
- **Visual evaluation of the peritoneal, diaphragmatic, and serosal surfaces with biopsy of any suspicious lesions is important to exclude extrauterine disease.**
- **While peritoneal cytology does not impact staging, FIGO and AJCC nonetheless recommend that surgeons continue to obtain this during the TH/BSO.**
- **Cytology results should not be taken in isolation to guide adjuvant therapy.**
- **Omental biopsy is commonly performed in those with serous carcinoma, clear cell carcinoma, or carcinosarcoma histologies.**
- **For stage II disease, TH/BSO is the standard procedure. RH should only be performed if needed to obtain negative margins.**

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PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Principles of Sentinel Lymph Node(s) Mapping for Endometrial Cancer Staging[10-26]

- **Prospective and retrospective studies demonstrate that compared to systemic lymphadenectomy, SLN mapping with ultrastaging may increase the detection of lymph node metastasis with low false-negative rates in patients with apparent uterine-confined disease.[10-23,26] If SLN mapping is considered, the expertise of the surgeon and attention to technical detail is critical. Recent evidence indicates that SLN mapping may also be used in high-risk histologies (ie, serous carcinoma, clear cell carcinoma, carcinosarcoma).[24,25]**
- **SLN mapping can be considered for the surgical staging of apparent uterine-confined malignancy when there is no metastasis demonstrated by imaging studies or no obvious extrauterine disease at exploration.**
- **A cervical injection with dye has emerged as a useful and validated technique for identification of lymph nodes that are at high risk for metastases (ie, SLN in patients with early-stage endometrial cancer[10-12]).**
- **Superficial (1–3 mm) and optional 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 (see Figure 1 on ENDO-C 4 of 6).[26]**
- **Injection into the uterine cervix provides excellent dye penetration to 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 (see Figure 2 on ENDO-C 4 of 6).**
- **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 (see Figure 3 on ENDO-C 4 of 6).**
- **The radiolabeled colloid most commonly injected into the cervix is technetium-99m (99mTC); colored dyes are available in a variety of forms (Isosulfan Blue 1%, Methylene Blue 1%, and Patent Blue 2.5% sodium).**
- **Indocyanine green (ICG) recently emerged as a useful imaging dye that requires a near-infrared camera for localization, provides a very high SLN detection rate, and is commonly used in many practices at the present time.[20,26,27]**
- **Low-volume nodal metastasis to SLN detected only by enhanced pathologic ultrastaging is another potential value to staging with SLN.[10,21-23]**
- **The key point 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 (see Figure 4 on ENDO-C 5 of 6).[10-12,23,25]**
- **For cases of failed SLN mapping, reinjection of the cervix may be considered.**
- **If there is no mapping on a hemi-pelvis, then a side-specific lymphadenectomy is recommended. However, if expert gynecologic pathology is available, a frozen section to assess myoinvasion can be obtained and lymphadenectomy can be avoided if no myoinvasion or cervical invasion is identified.**
- **SLN identification should always be done prior to hysterectomy, except in cases where a bulky uterus must be removed to allow access to iliac vessels and lymph nodes.**

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PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Principles of Sentinel Lymph Node(s) Mapping for Endometrial Cancer Staging (continued)[10-26]

- **SLNs are processed using ultrastaging, which typically includes two components: serial sectioning with review of multiple hematoxylin and eosin (H&E)-stained slides with or without cytokeratin IHC staining.**
  - **Protocols of serial sectioning and ultrastaging vary among gynecologic pathologists.[28] Comparison of two different ultrastaging protocols in endometrial cancer SLN did not reveal significant advantages when serial H&E sectioning and IHC staining were used.[29]**
- **Recent data highlight the potential importance of ultrastaging for detection of low-volume metastasis. In general, SLN mapping allows for increased intraoperative surgical precision to identify nodes more likely to harbor metastasis combined with enhanced pathology protocols, which has been shown to increase the detection of nodal metastasis, which may alter stage and adjuvant therapy recommendations.**
- **Lymph nodes with isolated tumor cells should be clearly reported. In endometrial cancer, when isolated tumor cells are detected in the absence of macrometastasis and micrometastasis, the lymph node stage is designated pN0(i+).[30]**

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PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Figure 1: Common cervical injection sites for mapping uterine cancer[a]

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

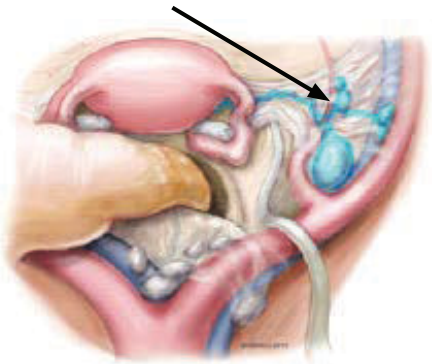
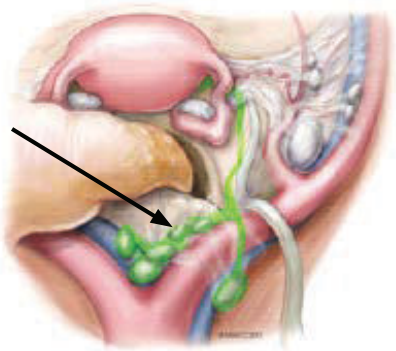


Figure 3: Less common location of SLNs (green, arrow) usually seen when lymphatic trunks are not crossing over the umbilical ligament but following the mesoureter cephalad to common iliac and presacral region[a]



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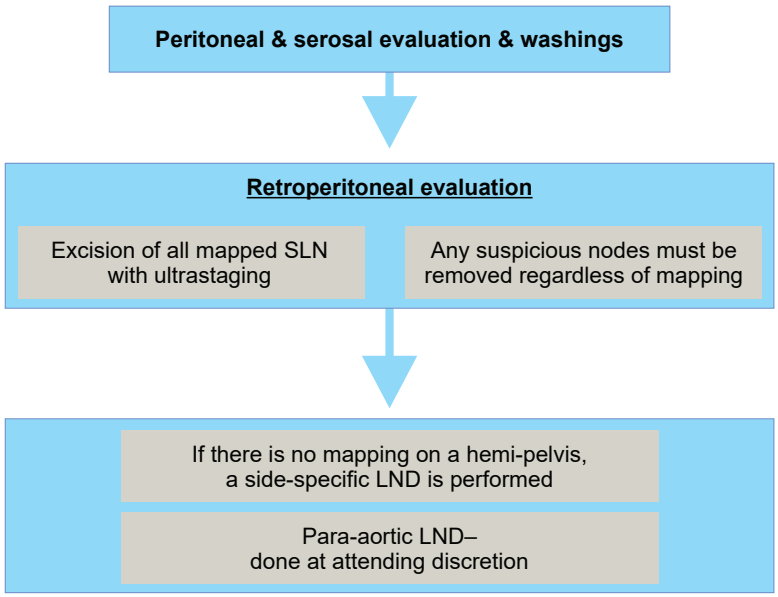
PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Figure 4: The SLN algorithm for surgical staging of endometrial cancer[b]



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SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Primary or Adjuvant Therapy (Stage I–IV)	
Chemoradiation Therapy	**Systemic Therapy**
Preferred Regimens • **Cisplatin plus RT followed by carboplatin/paclitaxel[1,2]** **Other Recommended Regimens[a]** **(if cisplatin and carboplatin are unavailable)** • **Capecitabine/mitomycin[3]** • **Gemcitabine[4]** • **Paclitaxel[5,6]**	**Preferred Regimens** • **Carboplatin/paclitaxel[7]** • **Carboplatin/paclitaxel/pembrolizumab (for stage III–IV tumors, except for carcinosarcoma) (category 1)[b,c,d,8]** • **Carboplatin/paclitaxel/dostarlimab-gxly (for stage III–IV tumors) (category 1)[c,d,e,9]** • **Carboplatin/paclitaxel/durvalumab (for stage III–IV dMMR tumors only) (category 1)[c,d,f,10]** • **Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive uterine serous carcinoma)[d,g,h,11]** • **Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive carcinosarcoma)[d,g,h,11]**

[a] These agents may be considered when cisplatin and carboplatin are unavailable.
[b] For stage III or IVA with measurable disease or stage IVB with or without measurable disease.
[c] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[d] Checkpoint inhibitors and/or monoclonal antibodies included in this regimen may be continued as maintenance therapy. Refer to the original study protocol for maintenance therapy dosing schedules.
[e] For stage IIIA, IIIB, or IIIC1 with measurable disease, stage IIIC1 with carcinosarcoma, clear-cell, serous, or mixed histology regardless of the presence of measurable disease; and stage IIIC2 or stage IV regardless of the presence of measurable disease.
[f] For stage III with measurable disease post surgery and stage IV with or without measurable disease.
[g] For patients who have not received prior trastuzumab therapy.
[h] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

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SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

RECURRENT DISEASE[i,j]	
First-Line Therapy for Recurrent Disease[k]	**Second-Line or Subsequent Therapy**
Preferred • Carboplatin/paclitaxel (category 1 for carcinosarcoma)[l,7] • Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma) (category 1)[c,d,m,8] • Carboplatin/paclitaxel/dostarlimab-gxly (category 1)[c,d,m,9] • Carboplatin/paclitaxel/durvalumab (for dMMR tumors only) (category 1)[c,d,m,10] • Carboplatin/paclitaxel/trastuzumab[d,h] (for HER2-positive uterine serous carcinoma)[g,11] • Carboplatin/paclitaxel/trastuzumab[d,h] (for HER2-positive carcinosarcoma)[g,11] **Other Recommended Regimens** • Carboplatin/docetaxel[n] • Carboplatin/paclitaxel/bevacizumab[d,o,12,13] **Useful in Certain Circumstances (Biomarker-directed therapy: after prior platinum-based therapy including neoadjuvant and adjuvant)** • MMR-proficient (pMMR) tumors ▸ Lenvatinib/pembrolizumab (category 1)[c,14] • TMB-H tumors[p] ▸ Pembrolizumab[c,15] • MSI-H/dMMR tumors[q] ▸ Pembrolizumab[c,16] ▸ Dostarlimab-gxly[c,17]	**Other Recommended Regimens** • Cisplatin/doxorubicin[18] • Cisplatin/doxorubicin/paclitaxel[r,18] • Cisplatin/gemcitabine[19] • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel[20] • Albumin-bound paclitaxel[s] • Topotecan • Bevacizumab[o,t,21] • Temsirolimus[22] • Cabozantinib • Docetaxel (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma)[23] • Cisplatin/ifosfamide (for carcinosarcoma) **Useful in Certain Circumstances (Biomarker-directed therapy)** • pMMR tumors ▸ Lenvatinib/pembrolizumab (category 1)[c,14] • TMB-H tumors[p,15] ▸ Pembrolizumab[c] • MSI-H/dMMR tumors[q] ▸ Pembrolizumab[c,16] ▸ Dostarlimab-gxly[c,17] ▸ Avelumab[c] ▸ Nivolumab[c,24] • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[25] • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib

Footnotes on ENDO-D 2A of 4

References

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SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA
FOOTNOTES FOR ENDO-D 2 OF 5

[c] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[d] Checkpoint inhibitors and/or monoclonal antibodies included in this regimen may be continued as maintenance therapy. Refer to the original study protocol for maintenance therapy dosing schedules.
[g] For patients who have not received prior trastuzumab therapy.
[h] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[i] Cisplatin, carboplatin, liposomal doxorubicin, paclitaxel, and docetaxel may cause drug reactions (see NCCN Guidelines for Ovarian Cancer–Management of Drug Reactions [OV-D]).
[j] Chemotherapy regimens can be used for all carcinoma histologies. Carcinosarcomas are now considered and treated as high-grade carcinomas.
[k] These agents can be used as second-line or subsequent therapy as clinically appropriate.
[l] Carboplatin/paclitaxel is preferred only for patients who have not received any prior systemic therapy. Can be considered as an option under the "Other Recommended Regimens" list if or when re-use is appropriate in the first-line setting for recurrent disease.
[m] For adult patients with recurrent endometrial carcinoma with or without measurable disease
[n] Docetaxel may be considered for patients in whom paclitaxel is contraindicated.
[o] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[p] NCCN recommends TMB-H testing if not previously done. Pembrolizumab is indicated for patients with unresectable or metastatic tumors with TMB-H [≥10 mutations/megabase (mut/Mb)], as determined by an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory, whose disease has progressed following prior treatment and who have no satisfactory alternative treatment options.
[q] For recurrent endometrial cancer, NCCN recommends MSI-H or dMMR testing if not previously done.
[r] The cisplatin/doxorubicin/paclitaxel regimen is not widely used because of concerns about toxicity.
[s] Albumin-bound paclitaxel is a reasonable substitute for patients with a hypersensitivity to paclitaxel If a skin test is done, and is positive, then the patient requires desensitization to paclitaxel. Albumin-bound paclitaxel is not a reasonable substitute for paclitaxel if the patient's skin test is positive.
[t] Bevacizumab may be considered for use in patients whose disease has progressed on prior cytotoxic chemotherapy.

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SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Hormonal Therapy for Recurrent or Metastatic Endometrial Carcinoma[u]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Megestrol acetate/tamoxifen (alternating) • Everolimus/letrozole	• Medroxyprogesterone acetate/tamoxifen (alternating) • Progestational agents ▸ Medroxyprogesterone acetate ▸ Megestrol acetate • Aromatase inhibitors • Tamoxifen • Fulvestrant	• ER-positive tumors ▸ Letrozole/ribociclib ▸ Letrozole/abemaciclib

Hormonal Therapy for Uterine-Limited Disease Not Suitable for Primary Surgery or for Those Desiring Uterine Preservation for Fertility (ENDO-1)[u]	
Preferred Regimens	**Other Recommended Regimens**
• Levonorgestrel IUD	• Progestational agents ▸ Megestrol acetate ▸ Medroxyprogesterone acetate

[u] Hormonal therapy is typically used for lower-grade endometrioid histologies, preferably in patients with small tumor volume or an indolent growth pace.

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SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA
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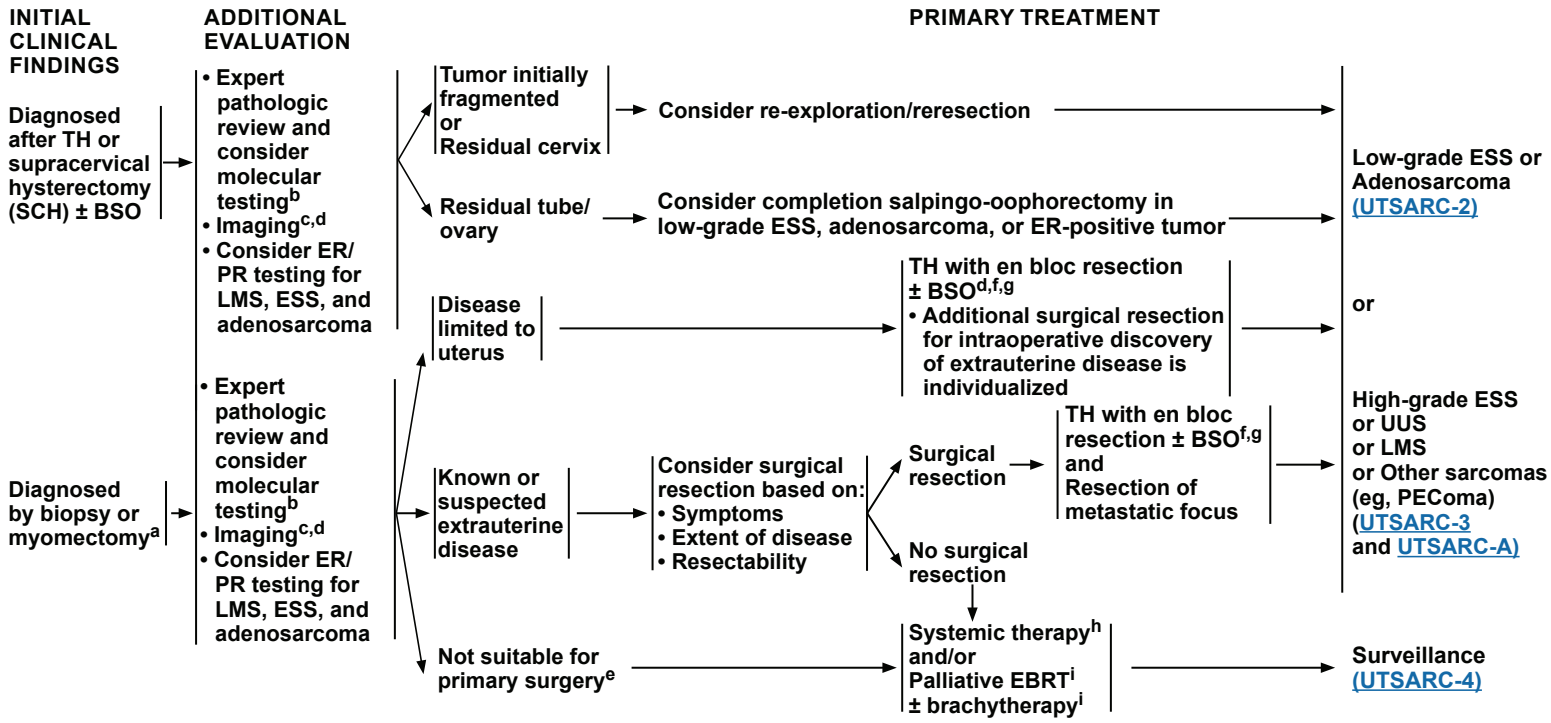

[a] Preoperative imaging and biopsy may help to identify uterine sarcomas, although biopsy sensitivity is less than for endometrial cancer. If there is suspicion of malignant mesenchymal sarcoma, fragmentation/morcellation should be avoided.
[b] Principles of Pathology and Molecular Analysis (UTSARC-A).
[c] Principles of Imaging (UTSARC-B).
[d] For incidental finding of uterine sarcoma after TH/BSO or fragmented specimen: recommend imaging and consider additional surgical resection on an individual basis.
[e] Disease is not amenable to resection, or patient is not suitable for surgery based on comorbidities.
[f] Oophorectomy is individualized for patients of reproductive age. Favor BSO if ER/PR positive.
[g] Morcellation should be avoided.
[h] Systemic Therapy (UTSARC-C).
[i] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).

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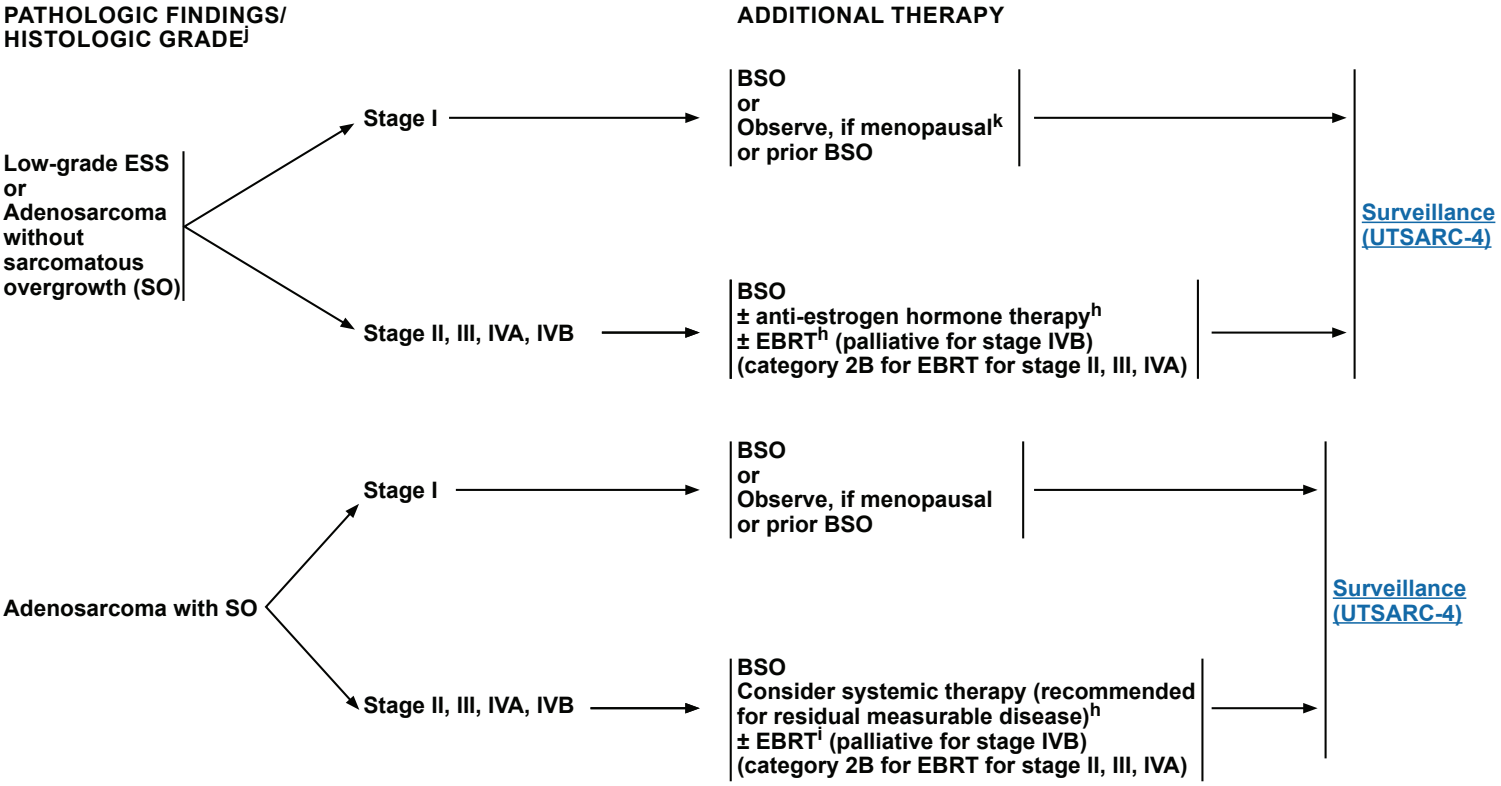

[h] Systemic Therapy (UTSARC-C).
[i] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[j] Principles of Pathology and Molecular Analysis (UTSARC-A 2 of 8).
[k] See Discussion. Nasioudis D, et al. Int J Gynecol Cancer 2019;29:126-132.

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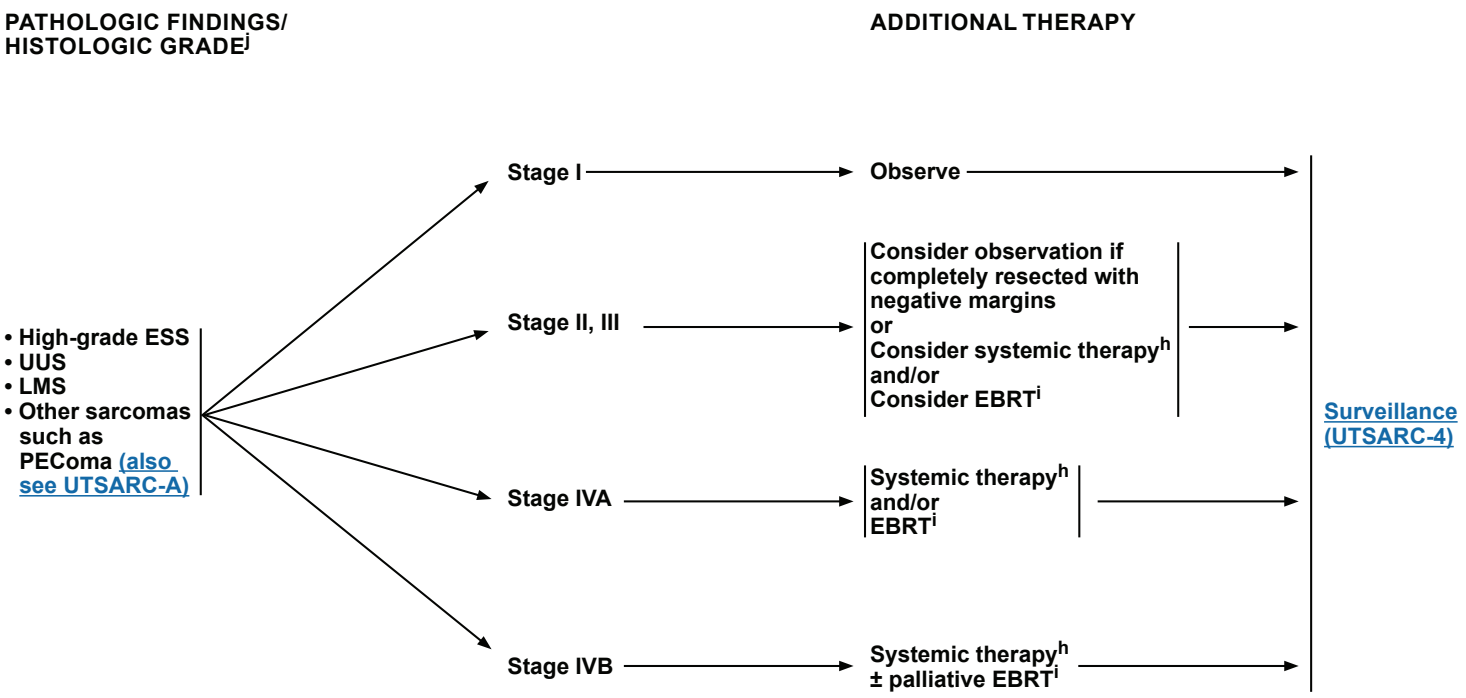

[h] Systemic Therapy (UTSARC-C).
[i] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[j] Principles of Pathology and Molecular Analysis (UTSARC-A 2 of 8).

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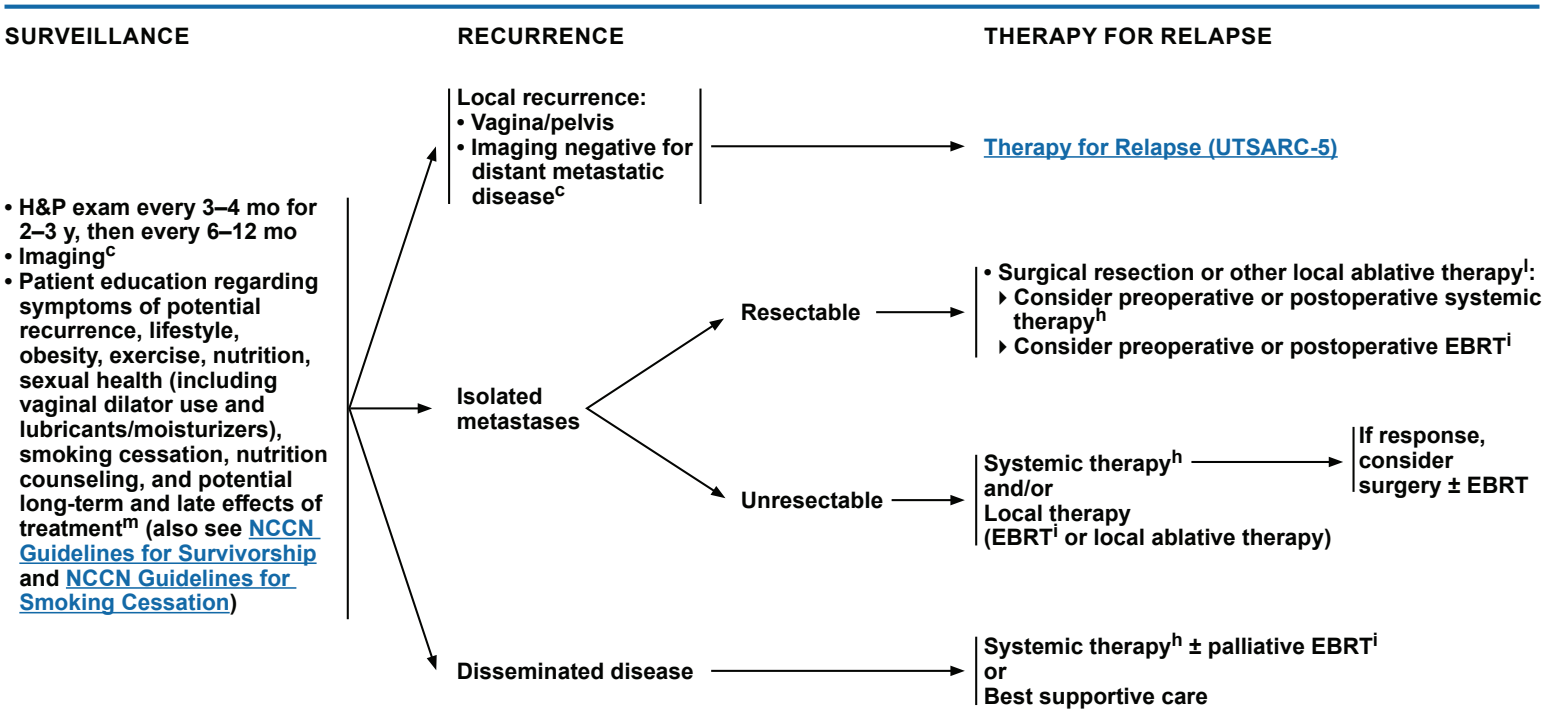

[c] Principles of Imaging (UTSARC-B).
[h] Systemic Therapy (UTSARC-C).
[i] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[l] Observation may be an option in select, completely resected cases with no evidence of disease on postoperative imaging.
[m] Principles of Gynecologic Survivorship (UN-B).

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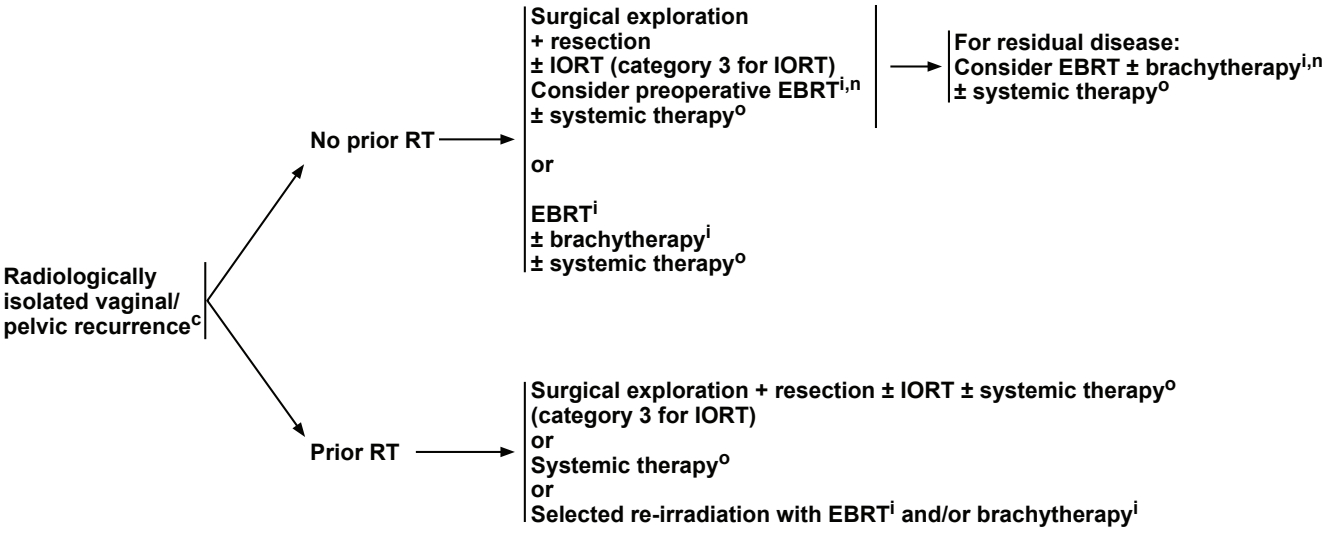
RECURRENCE | **THERAPY FOR RELAPSE**



[c] Principles of Imaging (UTSARC-B).
[i] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[n] The use of preoperative EBRT would preclude postoperative EBRT.
[o] For low-grade ESS or adenosarcoma without SO, the first choice of systemic therapy is anti-estrogen hormone therapy. See Systemic Therapy (UTSARC-C).

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PRINCIPLES OF PATHOLOGY AND MOLECULAR ANALYSIS[a,1,2]

Procedure:
- **TH ± BSO: Total hysterectomy ± bilateral salpingo-oophorectomy and en bloc resection of tumor**

Pathologic Assessment for Sarcoma (including LMS, adenosarcoma, ESS, and UUS):
- **Expert gynecologic pathology review is highly recommended**
- **Uterus**
  - **Hysterectomy type**
  - **Specimen integrity (intact, opened, morcellated, other)**
  - **Tumor size**
  - **Myometrial invasion (for adenosarcoma only)**
  - **Histologic type**
  - **Histologic grade (for adenosarcoma only)**
  - **LVSI**
- **Other tissue/organ involvement (fallopian tubes, ovaries, vagina, parametrium, peritoneum, omentum, other)**
- **Peritoneal/ascitic fluid cytology (if collected)**
- **Lymph nodes (when resected)**
  - **Level of nodal involvement[b] (ie, pelvic, common iliac, para-aortic)**
  - **Number of lymph nodes with metastasis**

Molecular Analysis for Sarcoma:
- **Recommend molecular profiling in gynecologic mesenchymal malignancies for accurate classification[3] (Table 1 [UTSARC-A 2 of 8]).**
- **Comprehensive genomic profiling in setting of metastatic disease as determined by an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory, is informative for predicting rare pan-tumor targeted therapy opportunities and should include at least *NTRK*, MSI, and TMB.**

Footnotes

[a] Also see Principles of Evaluation and Surgical Staging (ENDO-C).
[b] Routine node dissection is not required in the absence of clinical suspicion of nodal involvement.

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PRINCIPLES OF PATHOLOGY AND MOLECULAR ANALYSIS

Table 1

Uterine Sarcoma					
Tumor	**Hallmarks for Histologic Diagnosis**	**Relevant Molecular Finding**	**Tests Needed to Confirm Diagnosis**	**Relevant Prognostic Features**	**Other**
Conventional (spindle cell) Leiomyosarcoma (LMS)	Cellular spindle cell proliferation with interlacing long fascicles with two or more of the following: moderate to severe atypia, tumor cell necrosis, or mitotic index (MI) ≥10/10 high-power fields (HPFs).	Complex karyotypes are the hallmark of LMS. The most commonly altered genes include *TP53, ATRX, RB1*, *PTEN*, and *BRCA2* mutation/ loss.	Immunoexpression of smooth muscle markers such as desmin, smooth muscle actin (SMA), and/or caldesmon; however, tumors may have variable expression and even lose expression of one or more markers. Approximately 1/3 of LMS express ER/PR.	Prognosis is best predicted by stage. Morphology has not been shown to predict clinical behavior. Limited data suggest PR expression may be a positive prognostic marker in low-stage LMS.	
Epithelioid LMS[1]	Epithelioid morphology comprising >50% of the tumor with moderate to severe atypia and either tumor necrosis or MI >4/10 HPFs.	*PGR* fusions by FISH and/ or targeted RNA sequencing in a small subset with uniform nuclear atypia and rhabdoid features.	Immunoexpression of desmin, SMA, and/ or caldesmon without melanA expression is supportive. In some cases of epithelioid LMS, HMB-45 may be expressed.	Unknown	Epithelioid LMS may morphologically and immunohistochemically overlap with malignant PEComa for which there is no gold standard diagnostic test. Detection of pathogenic *TSC1/2* mutations by DNA sequencing may favor PEComa.

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PRINCIPLES OF PATHOLOGY AND MOLECULAR ANALYSIS

Table 1 (continued)

Uterine Sarcoma				
Tumor	**Hallmarks for Histologic Diagnosis**	**Relevant Molecular Finding**	**Tests Needed to Confirm Diagnosis**	**Relevant Prognostic Features**
Myxoid LMS[2,3]	Infiltrative spindle cell proliferation with variable myxoid matrix and tumor necrosis or any degree of atypia or MI ≥1/10 HPFs.	*PLAG1* fusion by FISH and/ or targeted RNA sequencing in a subset (~25%).	IHC panel of CD10, ER, PR, desmin, SMA, caldesmon, cyclinD1, and ALK is recommended to exclude morphologic mimics.	Unknown

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PRINCIPLES OF PATHOLOGY AND MOLECULAR ANALYSIS

Table 1 (continued)

Uterine Sarcoma				
Tumor	**Hallmarks for Histologic Diagnosis**	**Relevant Molecular Finding**	**Additional Confirmatory Tests**	**Relevant Prognostic Features**
Low-Grade Endometrial Stromal Sarcoma (ESS)[4-6]	Cytologically bland spindle cell neoplasm resembling proliferative endometrial stroma with distinctive finger-like myoinvasion and/or LVSI.	*JAZF1::SUZ12* fusion most common (>50%) followed by *JAZF1::PHF1, EPC1::PHF1,* and *MEAF6::PHF1* fusions; *MBTD1-CXorf67, BRD8::PHF1, EPC2::PHF1,* and *EPC1::SUZ12*.	CD10, ER positivity, PR positivity, and/or demonstration of a low-grade ESS-associated fusion by FISH and/or targeted RNA sequencing is confirmatory.	Stage is the most important prognostic factor.
High-Grade Endometrial Stromal Sarcoma (ESS)[4-12]	*YWHAE::NUTM2* fusion-positive tumors have a high-grade round cell component with delicate branching vasculature. Generally the MI is ≥10/10 HPFs. *YWHAE*-altered high-grade ESS may be associated with a low-grade fibrous or fibromyxoid spindle cell component with low MI. *ZC3H7B::BCOR* fusion-positive tumors have high-grade spindle cells embedded in myxoid matrix. *BCOR* internal tandem duplication (ITD)-positive tumors share morphologic features of *ZC3H7B::BCOR* fusion-positive tumors. Tongue-like infiltration and LVSI are present in all subtypes.	*YWHAE::NUTM2* fusion, *ZC3H7B::BCOR* fusion, or *BCOR* ITD.	IHC panel of CD10, ER, PR, cyclin D1, ± *BCOR* are recommended. Diffuse strong expression of cyclin D1 is present in all subtypes, and/or *BCOR* is strongly and diffusely expressed in the *YWHAE*-rearranged sarcomas but positive in only ~50% of the *BCOR*-altered sarcomas. CD10 is negative in the high-grade round cell component of altered subtype, but may be positive in *BCOR*-altered mutant subtypes. ER and PR are negative in the high-grade component of *YWHAE*-altered subtype, and variably positive in *BCOR*-altered tumors.	Slightly higher rate of lymph node involvement and trend towards worse outcomes when compared to low-grade ESS.
Undifferentiated Uterine Sarcoma (UUS)[12-15]	Infiltrative sheets of pleomorphic epithelioid and/or spindle cells.		This is essentially a diagnosis of exclusion, and thus there are no confirmatory tests. An IHC panel of CD10, cyclin D1, desmin, SMA, caldesmon, pan-CK, EMA, BRG1, INI1, pan-Trk, ALK, HMB45, melanA, SOX10, S100, CD34, and STAT6 is recommended to consider other tumor types. Absence of ESS-associated fusions by FISH and/or targeted RNA sequencing is recommended.	ER and/or PR expression may correlate with improved survival. MI ≥11/mm^2 is associated with decreased survival.

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References
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PRINCIPLES OF PATHOLOGY AND MOLECULAR ANALYSIS

Table 1 (continued)

Uterine Sarcoma				
Tumor	**Hallmarks for Histologic Diagnosis**	**Relevant Molecular Finding**	**Additional Confirmatory Tests**	**Relevant Prognostic Features**
Perivascular Epithelioid Cell Tumor (PEComa)[16-18]	Mesenchymal neoplasm comprised of perivascular epithelioid and/or spindled cells that coexpress melanocytic and muscle markers. The tumor cells can demonstrate variable cytologic atypia, mitotic activity, and melanin pigment in a background of thin-walled vascular spaces and sclerotic stroma. Proposed algorithms stratify tumors into uncertain malignant potential and malignant as outlined below. Uncertain malignant potential (<3 of the following: ≥5 cm size, high nuclear grade, >1 mitosis/50 mm^2, necrosis, vascular invasion). Malignant if ≥3 features (>5 cm, infiltrative growth, high nuclear grade, >1 mitosis/50 mm^2, necrosis, and vascular invasion).	Inactivating mutations of *TSC1/TSC2*, and fusions of *TFE3*, *RAD51B*, or *HTR4::ST3GAL1* can be seen. In situ hybridization to confirm rearrangement or fusion of *TFE3*, in *TFE3*–translocation-associated rumors.	Immunoexpression of cathepsin K, variable expression of melanocytic markers (HMB45 is most sensitive and MelanA is most specific), and at least one smooth muscle marker (SMA, desmin, and h-caldesmon). Keratins and hormone receptors can be variably expressed. Translocation-associated tumors show diffuse *TFE3* expression with weak to negative smooth muscle markers.	Tumor behavior is best predicted using tumor stratification into uncertain malignant potential and malignant subgroups. Treatment with mTOR inhibitors may be considered.[16,19]
Inflammatory Myofibroblastic Tumor (IMT)	Spindle cell neoplasm comprised of spindled cells with admixed inflammatory infiltrate (usually lymphoplasmacytic) in a myxoid stroma. Histologic patterns include myxoid hypocellular areas (resembling fasciitis), storiform or fascicular pattern with compact cellular areas with intersecting fascicles, and hyalinized dense collagenous matrix.	*ALK* rearrangements by FISH are seen in approximately 75% of patients. Common fusion partners include *IGFBP5*, *THBS1*, and *TIMP3*. *RANBP2-ALK* and *RRBP1::ALK* fusions are seen in aggressive IMT with epithelioid morphology. *ALK*-negative uterine IMTs are rare.	Immunoexpression of ALK (granular cytoplasmic) is sensitive and specific; seen in approximately 95% of patients and can be variable and focal. Immunoexpression of desmin, SMA, and/or caldesmon is common.	Typically benign and confined to the uterus; recurrence and extrauterine spread can occur. Tumors >7 cm with necrosis, lymphovascular invasion, severe cytologic atypia, and high MI behave aggressively as do peritoneal IMTs. *ALK*-rearranged tumor may respond to ALK inhibitors rather than general tyrosine kinase inhibitors.

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PRINCIPLES OF PATHOLOGY AND MOLECULAR ANALYSIS

Table 1 (continued)

Uterine Sarcoma					
Tumor	**Hallmarks for Histologic Diagnosis**	**Relevant Molecular Finding**	**Additional Confirmatory Tests**	**Relevant Prognostic Features**	**Other**
SMARCA4-Deficient Uterine Sarcoma (SDUS)	SDUS is characterized by sheets of epithelioid/rhabdoid cells associated with hyalinized matrix. LVSI, high MI, and necrosis are common. A small cell component or even spindled morphology may be focally present.	Biallelic *SMARCA4* inactivation	Absent CK expression and BRG1 loss (*SMARCA4*) and/or *SMARCA4* mutation detectable by DNA sequencing is helpful to support a diagnosis of SDUS, in the appropriate morphologic context.		Germline *SMARCA4* mutation testing should be considered.
New and Emerging Entities					
NTRK-Rearranged Sarcoma	Spindle cell neoplasm with fascicular, herringbone, or patternless growth. Entrapped glands may be present, sometimes with polypoid projections simulating adenosarcoma; however, there is typically no periglandular stromal condensation.	*NTRK1/2/3* fusions	Frequent positivity for CD34 and/or S100 (generally both but with variable extent). IHC for pan-TRK is typically positive, but this marker is not specific for the gene fusion.	Typically present with stage I disease; ~1/3 recur or metastasize. Targeted therapy against NTRK inhibitors has shown clinical benefit.	More commonly occurs in the uterine cervix.

References
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PRINCIPLES OF PATHOLOGY AND MOLECULAR ANALYSIS

Table 1 (continued)

Uterine Sarcoma					
Tumor	**Hallmarks for Histologic Diagnosis**	**Relevant Molecular Finding**	**Additional Confirmatory Tests**	**Relevant Prognostic Features**	**Other**
Uterine Tumor Resembling Ovarian Sex Cord Tumor (UTROSCT)[20-22]	Bland spindle cell proliferation with extensive sex cord-like differentiation and no endometrial stromal component.	*ESR1* or *GREB1* fusions in the majority of tumors.	Immunohistochemical expression of sex cord markers (inhibin, calretinin, SF1, FOXL2) and/or detection of *GREB1* or *ESR1* fusions by FISH *(NCOA1, NCOA2, NCOA3)* and/or targeted RNA sequencing is confirmatory.	Tumors have uncertain malignant potential with ~25% being malignant. Necrosis and MI ≥2/10 HPFs and/or presence of *GREB1* fusion may increase likelihood of malignant behavior.	
Rhabdomyosarcoma (RMS)[23-25]	Embryonal subtype consists of small primitive cells that may form a cambium layer in botryoid tumors; strap cells and fetal cartilage can be seen. Marked atypia defines the pleomorphic subtype. Alveolar subtype consists of small primitive cells growing in nests or alveoli.	*DICER1* mutations are present in up to 95% of embryonal RMS. *PIK3CA* and *TP53* mutations in pleomorphic tumors. *FOXO1* fusion in alveolar tumors.	IHC expression of myogenin and/or MyoD1 is confirmatory of rhabdomyosarcomatous differentiation. Extensive sampling must be performed to exclude carcinosarcoma or adenosarcoma with SO. FISH and/or targeted RNA sequencing for *FOXO1* fusion is recommended to confirm alveolar subtype.	Embryonal subtype has better prognosis than pleomorphic and alveolar subtypes. Age and stage are prognostic factors.	
Müllerian Adenosarcoma (MAS)[26-29]	Biphasic tumor with benign often metaplastic epithelium associated with an atypical usually low-grade spindle cell proliferation exhibiting phyllodes growth and periglandular stromal condensation. SO is defined by sarcoma comprising ≥25% of the tumor volume.	8q13 amplification and copy number gains of *MYBL1* in a subset; *NCOA2/3* fusions in a subset; rare *FGFR2*, *KMT2C*, *DICER1*, *ATRX*, and *TP53* mutations; *MDM2/CDK4* and *TERT* amplifications.	Ancillary testing is usually not required.	High grade, myoinvasion, and SO are poor prognostic factors. High-grade cytologic features may also portend a worse prognosis.	

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PRINCIPLES OF IMAGING[a,1-9]

Initial Workup

- **Chest/abdomen/pelvis CT**
- **For patients who underwent TH with incidental finding of uterine sarcoma or incompletely resected uterus/adnexa (ie, SCH, myomectomy, possible tumor fragmentation, intraperitoneal morcellation) perform chest/abdomen/pelvis CT or abdomen/pelvis MRI and chest CT without contrast to evaluate for metastatic disease.**
- **Consider pelvic MRI to evaluate local tumor extension or residual abnormality in cases where the uterus or adnexa were not resected or incompletely resected (ie, SCH, myomectomy, possible tumor fragmentation, intraperitoneal morcellation).**
- **Consider neck/chest/abdomen/pelvis/groin FDG-PET/CT to clarify ambiguous findings.**
- **Additional imaging should be based on symptomatology and clinical concern for metastatic disease.[b]**

Follow-up/Surveillance

- **Chest/abdomen/pelvis CT every 3–6 months for the first 3 years and then every 6–12 months for the next 2 years. Depending on histology grade and initial stage, consider imaging annually or every other year thereafter up to an additional 5 years.[c]**
- **Optional abdominal/pelvic MRI and chest CT without contrast every 3–6 months for the first 3 years and then every 6–12 months for the next 2 years. Depending on histology, grade, and initial stage, consider imaging annually or every other year thereafter up to an additional 5 years.[c]**
- **Consider neck/chest/abdomen/pelvis/groin FDG-PET/CT if metastasis is suspected in select patients.**
- **Additional imaging should be based on symptomatology and clinical concern for metastatic disease.[d]**

[a] MRI is performed with and without contrast and CT is performed with contrast unless contraindicated. Contrast is not required for screening chest CT.
[b] Indications may include abnormal physical exam finding, bulky uterine tumor, vaginal or extrauterine involvement, delay in presentation or treatment, and abdominal or pulmonary symptoms.
[c] Follow-up imaging may be as frequent as every 3 months or change based on histology grade and/or stage of tumor.
[d] Indications may include abnormal physical exam findings such as vaginal involvement; palpable mass or adenopathy; and new pelvic, abdominal, or pulmonary symptoms.

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SYSTEMIC THERAPY FOR UTERINE SARCOMA[a]
(Clinical trials strongly recommended)

Advanced, Recurrent/Metastatic or Inoperable Disease	
First-Line Therapy[b]	**Second-Line or Subsequent Therapy**
Preferred Regimens • Doxorubicin • Docetaxel/gemcitabine • Doxorubicin/trabectedin (for LMS)[1] • Doxorubicin/ifosfamide • Doxorubicin/dacarbazine **Useful in Certain Circumstances** • Biomarker-directed therapy ▸ *NTRK* gene fusion-positive tumors ◊ Larotrectinib ◊ Entrectinib ▸ IMT with ALK translocation ◊ Crizotinib[2] ◊ Ceritinib[3] ◊ Brigatinib[4,5] ◊ Lorlatinib ◊ Alectinib • PEComa ▸ Albumin-bound sirolimus	**Preferred Regimens** • Trabectedin[c] **Other Recommended Regimens** • Gemcitabine/dacarbazine • Gemcitabine/vinorelbine • Dacarbazine • Gemcitabine • Epirubicin • Ifosfamide • Liposomal doxorubicin • Pazopanib • Temozolomide • Eribulin (category 2B) **Useful in Certain Circumstances** • Biomarker-directed therapy ▸ TMB-H tumors[d] ◊ Pembrolizumab ▸ Consider PARP inhibitors for *BRCA*-altered LMS[e,6,7-9] ◊ Olaparib[10] ◊ Rucaparib ◊ Niraparib • PEComa ◊ Sirolimus ◊ Everolimus ◊ Temsirolimus

[a] NCCN Guidelines for Ovarian Cancer–Management of Drug Reactions (OV-D).
[b] If not used previously, first-line agents can be used as second-line or subsequent therapy as clinically appropriate.
[c] For LMS that has been treated with a prior anthracycline-containing regimen.
[d] For the treatment of patients with unresectable or metastatic TMB-high (TMB-H) [≥10 mut/Mb] tumors, as determined by an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory, that have progressed following prior treatment and have no satisfactory alternative treatment options.
[e] For oncogenic or likely oncogenic mutations in *BRCA2*, may refer to definitions at oncokb.org

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SYSTEMIC ENDOCRINE THERAPY FOR UTERINE SARCOMA[a]
(Clinical trials strongly recommended)

Anti-Estrogen Hormone Therapy for Low-Grade ESS or Adenosarcoma Without SO or Hormone Receptor-Positive (ER/PR) Uterine Sarcomas[f]	
Preferred Regimens • Aromatase inhibitors for low-grade ESS or adenosarcoma without SO[g]	**Other Recommended Regimens** • Aromatase inhibitors[g] (for ER/PR-positive uterine sarcomas) • Fulvestrant[g] • Megestrol acetate (category 2B for ER/PR-positive uterine sarcomas) • Medroxyprogesterone acetate (category 2B for ER/PR-positive uterine sarcomas) • GnRH analogs (category 2B for low-grade ESS, adenosarcoma without SO, and ER/PR-positive uterine sarcomas)

[a] NCCN Guidelines for Ovarian Cancer–Management of Drug Reactions (OV-D).
[f] These hormonal therapies may be considered for patients with uterine sarcomas that are ER/PR-positive, preferably with small tumor volume or an indolent growth pace.
[g] Ovarian ablation or suppression is needed in patients who are not postmenopausal. It is unknown if ovarian ablation or suppression is needed in order for fulvestrant to be effective in uterine sarcomas.

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PRINCIPLES OF RADIATION THERAPY FOR UTERINE NEOPLASMS

General Principles–Uterine Neoplasms

- **RT is directed at sites of known or suspected tumor involvement and may include EBRT and/or brachytherapy. Imaging is required to assess locoregional extent and to rule out distant metastases before administration of RT. In general, EBRT is directed to the pelvis with or without the para-aortic region. Brachytherapy can be delivered: 1) to an intact uterus, either preoperatively or definitively; or 2) more commonly, to the vagina after hysterectomy. For the purposes of these guidelines, whole abdominal radiotherapy is not considered to be tumor-directed RT.**
- **Chemoradiation can be given concurrently or sequentially.**

General Treatment Information

- **Target Volumes**
  - **Pelvic radiotherapy should target the gross disease (if present), the lower common iliacs, external iliacs, internal iliacs, obturators, 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 1–2 cm above the level of the renal vessels.**
  - **Pelvic tissues at risk, especially in the post-hysterectomy setting, can be highly variable depending on bowel and bladder filling. In this situation, the internal target volume (ITV), which encompasses the range of organ movement and deformation, is considered the clinical target volume (CTV), and should be fully covered in the treatment volume.**

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

Continued

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PRINCIPLES OF RADIATION THERAPY FOR UTERINE NEOPLASMS

General Treatment Information (continued)

- **Dosing Prescription Regimen – External Beam**
  - External-beam doses for microscopic disease should be 45–50 Gy. CT treatment planning should be utilized, and intensity-modulated RT (IMRT) for normal tissue sparing should be considered, with appropriate attention to quality assurance (QA) and tissue interfraction mobility.
  - Treating with IMRT technique is preferred to minimize toxicities in definitive treatment of the pelvis with or without para-aortic treatment. Regular use of image-guided RT (IGRT) with orthogonal imaging and/or routine volumetric imaging (such as cone beam CT) at the time of treatment delivery is essential to ensure appropriate coverage of targets and sparing of normal tissues.
  - Postoperatively, if there is gross residual disease and the area(s) can be sufficiently localized, a boost can be added to a total dose of 60–70 Gy, respecting normal tissue sensitivity.
  - For gross nodal disease, consider boost to 60–65 Gy while respecting normal tissue constraints.
  - For neoadjuvant radiation, doses of 45–50 Gy are typically used. One could consider adding 1–2 high dose-rate (HDR) insertions to a total dose of 75–80 Gy low dose-rate (LDR) equivalent, to minimize risk of positive or close margins at hysterectomy.
  - For pelvic-confined recurrent endometrial cancer without a prior history of radiation, fields would mirror adjuvant radiation. For reirradiation, fields should be limited to gross disease and target dose prescribed to maximize control while minimizing risk to normal tissues.
- **Dosing Prescription Regimen – Brachytherapy**
  - Initiate brachytherapy as soon as the vaginal cuff is healed, preferably 6–8 weeks after surgery but in general initiation of brachytherapy should not exceed 12 weeks. 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 no more than the upper two-thirds of the vagina; in cases of extensive LVSI or positive margins, a longer segment of the vagina may be treated.
    - For postoperative HDR vaginal brachytherapy alone, regimens include 6 Gy x 5 fractions prescribed to the vaginal surface, or 7 Gy x 3 fractions or 5.5 Gy x 4 fractions prescribed to 5 mm below the vaginal surface. While 7 Gy x 3 fractions prescribed at a depth of 0.5 cm from the vaginal surface is a regimen used by many, the use of smaller fraction sizes may be considered to potentially further limit toxicity in selected patients.
    - When HDR brachytherapy is used as a boost to EBRT, doses of 4–6 Gy x 2 to 3 fractions prescribed to the vaginal mucosa are commonly used.
  - For medically inoperable uterine cancer, risk of extrauterine spread determines the combination of EBRT plus brachytherapy or brachytherapy alone. Brachytherapy doses for definitive therapy are individualized based on the clinical situation. When available, image-guided therapy should be used. Based on the best available evidence, an Equivalent Dose in 2 Gy fractions (EQD2) D90 of at least 48 Gy should be delivered to the uterus, cervix, and upper 1–2 cm of vagina if brachytherapy alone is used, and should be increased to 65 Gy for the combination of EBRT and brachytherapy. If an MRI is used as part of planning, the target dose for the gross tumor volume (GTV) would be an EQD2 of ≥80 Gy.

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

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PRINCIPLES OF RADIATION THERAPY FOR UTERINE NEOPLASMS

General Treatment Information (continued)

- **Interstitial Brachytherapy**
  - **Interstitial brachytherapy is an advanced technique where multiple needles/catheters are inserted in the gross disease/target. Interstitial brachytherapy may be preferred to maximize dose to the target and minimize dose to the organs at risk (OARs) for cases where intracavitary brachytherapy is not possible, or anatomy favors interstitial brachytherapy. Three-dimensional treatment planning allows volumetric delineation of targets and OARs on CT and/or MRI with dose-volume histograms. Dose and fractionation depend on prior RT dose, target volume, and OAR doses.**

Stereotactic Radiosurgery (SRS) and Stereotactic Body RT (SBRT) for Metastatic Disease

- **SRS and SBRT are radiation treatment modalities that utilize advanced three-dimensional anatomic targeting accuracy to deliver precise, ablative, high-dose ionizing radiation. The therapy maximizes the cell-killing effect of ionizing radiation while minimizing radiation-induced injury in adjacent sensitive normal tissues. SRS and SBRT demand precise target localization, reproducibility of patient setup, and a sharp radiation dose gradient. SRS is delivered exclusively to intracranial targets while SBRT describes stereotactic therapy to extracranial targets. SRS and SBRT are delivered in 1 to 5 fractions of therapy with the expectation of durable control at the radiated site.**

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PRINCIPLES OF GYNECOLOGIC SURVIVORSHIP

Physical Effects

- **Gynecologic cancer treatment typically involves surgery, chemotherapy, hormone therapy, RT, and/or immunotherapy. These treatments cause acute, short-term, and long-term toxicities.**
- **Surgical approaches may be extensive and pose risks such as adhesion formation, which may cause pain and may contribute to small bowel obstruction, urinary or gastrointestinal complications (eg, incontinence, diarrhea), pelvic floor dysfunction (manifested by a variety of urinary, bowel, and/or sexual effects), and lymphedema.**
- **Chemotherapy agents vary, though commonly used regimens may pose a significant risk of neurotoxicity, cardiac toxicity, development of hematologic cancers, and cognitive dysfunction.**
- **Long-term estrogen deprivation may cause symptoms such as hot flashes, vaginal dryness, and bone loss.**
- **RT may cause long-term complications (eg, fibrosis, vulvovaginal atrophy) and may predispose patients to secondary cancers of the subcutaneous tissue, and/or underlying organs that are proximal to the radiation field.**
- **Prior pelvic RT may contribute to bone loss and increase the risk of pelvic fractures. Consider bone density testing and prophylactic use of bisphosphonates, particularly in patients with osteoporosis.**
- **Immunotherapy use is emerging, and to date, long-term effects of these treatments are unknown.**

Psychosocial Effects

- **Psychosocial effects after cancer may be psychological (eg, depression, anxiety, fear of recurrence, altered body image), financial (eg, return to work, insurance concerns), and/or interpersonal (eg, relationships, sexuality, intimacy) in nature.**

Clinical Approach

- **All gynecologic cancer survivors should receive regular general medical care that focuses on managing chronic disease, monitoring cardiovascular risk factors, providing recommended vaccinations, and encouraging adoption of a healthy lifestyle.**
- **In order to assess the late and long-term effects of gynecologic cancers, clinicians should comprehensively document the patient's history, conduct a thorough physical examination, and provide any necessary imaging and/or laboratory testing. All patients, whether sexually active or not, should be asked about genitourinary symptoms, including vulvovaginal dryness. Referral to appropriate specialty providers (eg, physical therapy, pelvic floor therapy, sexual therapy, psychotherapy) is recommended. As most treatments for gynecologic cancers will cause sexual dysfunction, early menopause, and infertility, special attention to the resultant medical and psychosocial implications is needed.**
- **Post-radiation use of vaginal dilators and moisturizers is recommended.**
- **For treatment-related menopause, hormone therapy should be considered.**
- **Communication and coordination with all clinicians involved in the care of survivors, including primary care clinicians, is critical. Providing cancer survivors with a summary of their treatment and recommendations for follow-up is recommended.**

Additional Guidance

- **NCCN Guidelines for Distress Management**
- **NCCN Guidelines for Smoking Cessation**
- **NCCN Guidelines for Survivorship**

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Staging–Uterine Carcinomas and Carcinosarcoma

Table 1
AJCC Tumor-Node-Metastases (TNM) and International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging Systems for Endometrial Cancer

Definitions for T, N, M

T	FIGO Stage	Primary Tumor
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	**I**	Tumor confined to the corpus uteri, including endocervical glandular involvement
T1a	**IA**	Tumor limited to the endometrium or invading less than half the myometrium
T1b	**IB**	Tumor invading one half or more of the myometrium
T2	**II**	Tumor invading the stromal connective tissue of the cervix but not extending beyond the uterus. Does NOT include endocervical glandular involvement
T3	**III**	Tumor involving serosa, adnexa, vagina, or parametrium
T3a	**IIIA**	Tumor involving the serosa and/or adnexa (direct extension or metastasis)
T3b	**IIIB**	Vaginal involvement (direct extension or metastasis) or parametrial involvement
T4	**IVA**	Tumor invading the bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)

Continued

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Table 1 **- Continued**

N	FIGO Stage	Regional Lymph Nodes
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	**IIIC1**	Regional lymph node metastasis to pelvic lymph nodes
N1mi	**IIIC1**	Regional lymph node metastasis (greater than 0.2 mm but not greater than 2.0 mm in diameter) to pelvic lymph nodes
N1a	**IIIC1**	Regional lymph node metastasis (greater than 2.0 mm in diameter) to pelvic lymph nodes
N2	**IIIC2**	Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes
N2mi	**IIIC2**	Regional lymph node metastasis (greater than 0.2 mm but not greater than 2.0 mm in diameter) to para-aortic lymph nodes, with or without positive pelvic lymph nodes
N2a	**IIIC2**	Regional lymph node metastasis (greater than 2.0 mm in diameter) to para-aortic lymph nodes, with or without positive pelvic lymph nodes

Suffix (sn) is added to the N category when metastasis is identified only by sentinel lymph node biopsy.

M	FIGO Stage	Distant Metastasis
M0		No distant metastasis
M1	**IVB**	Distant metastasis (includes metastasis to inguinal lymph nodes, intraperitoneal disease, lung, liver, or bone). (It excludes metastasis to pelvic or para-aortic lymph nodes, vagina, uterine serosa, or adnexa).

G	Histologic Grade
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated or undifferentiated

Table 2. **AJCC Prognostic Stage Groups**

	T	N	M
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC1	T1-T3	N1/N1mi/N1a	M0
Stage IIIC2	T1-T3	N2/N2mi/N2a	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

Continued

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Staging–Uterine Sarcoma

Table 3
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

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

N	FIGO Stage	Regional Lymph Nodes
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	**IIIC**	Regional lymph node metastasis

M	FIGO Stage	Distant Metastasis
M0		No distant metastasis
M1	**IVB**	Distant metastasis (excluding adnexa, pelvic, and abdominal tissues)

G	Histologic Grade
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated or undifferentiated

Table 4. **AJCC Prognostic Stage Groups**

	T	N	M
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T1-3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

Continued

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Staging–Uterine Sarcoma

Table 4

AJCC Tumor-Node-Metastases (TNM) and International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging Systems for Uterine Sarcomas (includes Müllerian adenosarcoma)

T	FIGO Stage	Primary Tumor
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	**I**	Tumor limited to the uterus
T1a	**IA**	Tumor limited to the endometrium/endocervix
T1b	**IB***	Tumor invades less than or equal to half myometrial invasion
T1c	**IC***	Tumor invades more than half myometrial invasion
T2	**II**	Tumor extends beyond the uterus, within the pelvis
T2a	**IIA**	Tumor involves adnexa
T2b	**IIB**	Tumor involves other pelvic tissues
T3	**III**	Tumor infiltrates abdominal tissues
T3a	**IIIA**	One site
T3b	**IIIB**	More than one site
T4	**IVA**	Tumor invades bladder or rectum

N	FIGO Stage	Regional Lymph Nodes
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	**IIIC**	Regional lymph node metastasis

M	FIGO Stage	Distant Metastasis
M0		No distant metastasis
M1	**IVB**	Distant metastasis (excluding adnexa, pelvic, and abdominal tissues)

G	Histologic Grade
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated or undifferentiated

Table 4. **AJCC Prognostic Stage Groups**

	T	N	M
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC	T1c	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T1-3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

*There is a discrepancy between the 2009 FIGO and 2017 AJCC staging documents in the tumor definitions for FIGO stages IB and IC. The NCCN Panel has chosen to use 2009 FIGO language as noted in Corrigendum to “FIGO staging for uterine sarcomas” [International Journal of Gynecology and Obstetrics (2009) 104:179].

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ABBREVIATIONS

BSO	bilateral salpingo-oophorectomy
CBC	complete blood count
CLIA	clinical laboratory improvement amendments
CTV	clinical target volume
D&C	dilation and curettage
dMMR	mismatch repair deficient
EBRT	external beam radiation therapy
EQD2	equivalent dose at 2 Gy
ESS	endometrial stromal sarcoma
FDG	fluorodeoxyglucose
FIGO	International Federation of Gynecology and Obstetrics
FISH	fluorescence in situ hybridization
GTV	gross tumor volume
H&E	hematoxylin and eosin
H&P	history and physical
HDR	high dose rate
HPF	high-power field
ICG	indocyanine green
IGRT	image-guided radiation therapy
IHC	immunohistochemistry
IMRT	intensity-modulated radiation therapy
IMT	inflammatory myofibroblastic tumor
IORT	intraoperative radiation therapy
ITD	internal tandem duplication
ITV	internal target volume
IUD	intrauterine device
LDR	low dose rate
LFT	liver function test
LMS	leiomyosarcoma
LND	lymphadenectomy
LVSI	lymphovascular space invasion
MAS	Müllerian adenosarcoma
MI	mitotic index
MIS	minimally invasive surgery
MMR	mismatch repair
MSI	microsatellite instability
MSI-H	microsatellite instability-high
mut/Mb	mutation/megabase
NSMP	no specific molecular profile
OARs	organs at risk
PEComa	perivascular epitheliod cell tumor
pMMR	mismatch repair proficient
QA	quality assurance
RH	radical hysterectomy
RMS	rhabdomyosarcoma
SBRT	stereotactic body radiation therapy
SDUS	SMARCA4-deficient uterine sarcoma
SCH	supracervical hysterectomy
SLN	sentinel lymph node
SMA	smooth muscle actin
SO	sarcomatous overgrowth
SRS	stereotactic radiosurgery
TH	total hysterectomy
TMB	tumor mutational burden
TMB-H	tumor mutational burden-high
UUS	undifferentiated uterine sarcoma
UTROSCT	uterine tumor resembling ovarian sex cord tumor

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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 indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

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Discussion

This discussion corresponds to the NCCN Guidelines for Uterine Neoplasms. Last updated: April 28th, 2023.

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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 65,950 new uterine cancer cases will occur in 2022, with 12,550 deaths resulting from the disease.[1] Stromal or mesenchymal sarcomas are uncommon subtypes accounting for approximately 3% of all uterine cancers.[2,3] 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, ages between 55 and 64 years, and tamoxifen use.[4-7] 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). The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. “Many exceptions to the rule” were discussed among the members of the panel during the process of developing these guidelines. Recommendations in the NCCN Guidelines® are category 2A unless otherwise noted.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of this version of the NCCN Guidelines for Uterine Neoplasms an electronic search of the PubMed database was performed to obtain key literature in uterine neoplasms published since the previous Guidelines update, using the following search terms: endometrial cancer or endometrial carcinoma or uterine sarcoma or endometrial stromal sarcoma or uterine leiomyosarcoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the panel

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during the Guidelines update process have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-fat-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Initial Evaluation

For patients with known or suspected uterine neoplasms, the initial preoperative evaluation/workup for known or suspected malignancy includes a history and physical examination, complete blood count (including platelets), expert pathology review with additional endometrial biopsy as indicated, imaging, recommendation of genetic evaluation of tumor and for inherited cancer risk, consideration of liver function tests (LFTs)/renal function tests or chemistry profile, and other studies (see *Initial Evaluation* and *Principles of Imaging* in the NCCN Guidelines for Uterine Neoplasms).[8] Preoperative imaging and biopsy may help to identify uterine sarcomas, although biopsy sensitivity is less than that for endometrial cancer. An expert pathology review will determine whether a patient has a malignant epithelial tumor or a stromal/malignant mesenchymal tumor. Epithelial tumor types include pure endometrioid cancer and carcinomas with high-risk endometrial histology (including uterine serous carcinoma, clear cell carcinoma, carcinosarcoma [also known as malignant mixed Müllerian tumor (MMMT)], and undifferentiated/dedifferentiated carcinoma). Stromal or mesenchymal tumor types (interchangeable terms) include uterine leiomyosarcoma (uLMS), endometrial stromal sarcoma (ESS), undifferentiated uterine sarcoma (UUS, previously called high-grade undifferentiated endometrial sarcoma), adenosarcoma, and perivascular epithelioid cell neoplasm (PEComa). Given the typical age group at risk for uterine neoplasms (ie, ≥55 years) and the presence of comorbid illnesses, also see the NCCN Guidelines for Older Adult Oncology available at https://www.nccn.org/professionals/physician_gls/pdf/senior.pdf.

Endometrial Cancer

Data show that almost 67% of patients with adenocarcinoma of the endometrium are diagnosed with disease confined to the uterus at diagnosis.[9] Regional and distant disease comprise approximately 21% and 8% of cases, respectively.

Many physicians believe that adenocarcinoma of the endometrium is a more treatable malignancy because the early symptoms of metrorrhagia or post-menopausal vaginal bleeding often trigger patients to seek care when the disease is at an early and treatable stage. However, data show that the mortality rate for uterine cancer has increased more rapidly than the incidence rate.[10] This increased mortality may be related to an increased

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rate of advanced-stage cancers, high-risk histologies (eg, serous carcinomas), and patients being diagnosed at an age ≥ 65 years. Analysis of SEER data suggests that survival is increased in patients who are younger, have early-stage disease, and have lower-grade disease.[11] In addition to grade and depth of myometrial invasion, other risk factors associated with poor prognosis include age, lymph node involvement, tumor size, lymphovascular space invasion (LVSI), and lower uterine segment invasion.[12,13] Depth of myometrial invasion is considered one of the critical criteria for evaluation of surgical-pathologic staging.[14,15] To further improve outcomes for patients with this disease, physicians need to identify patients who are at high-risk and to tailor treatment appropriately to provide the best long-term survival. The panel suggests that gynecologic oncologists be involved in the primary management of all patients with endometrial cancer.

Molecular Analysis and Genetic Factors

Most endometrial cancer (95%) is caused by sporadic (somatic) mutations. However, genetic mutations cause endometrial cancer in about 5% of patients, which occurs 10 to 20 years before sporadic cancer.[16] Since there is increasing overlap in histopathologic features of these tumors, molecular analysis (eg, identification of characteristic translocations and/or mutations) and subtype classification are useful in selecting appropriate therapies. The Cancer Genome Atlas (TCGA) study performed an integrated genomic, transcriptomic, and proteomic analysis of 373 endometrial carcinomas including low-grade endometrioid, high-grade endometrioid, and serous carcinomas for their molecular classification. The study identified four major clinically significant molecular subtypes with differing clinical prognosis: *POLE* (DNA polymerase epsilon) mutations, microsatellite instability-high (MSI-H), copy number low (wild type *p53*), and copy number high (abnormal *p53*). The *POLE* comprises tumors with *POLE* exonuclease domain mutations. The copy number high group is characterized by an elevated incidence of *TP53* alterations. These genomic classes are also associated with characteristic phenotypes. The endometrial cancers with *POLE* mutations are usually high-grade tumors with deep myometrial invasion and LVSI, and usually have a good prognosis.[17,18] The *p53* mutant is the most aggressive subtype and requires a multimodality treatment, especially chemotherapy. The MSI-H tumors have an intermediate prognosis, but could be associated with other genetic cancer predisposition, and sensitivity to chemotherapy has been under investigation. Further studies have attempted to study the association of TCGA subgroups with histologic features such as tumor grade and histologic type.[19]

The NCCN Guidelines for Uterine Neoplasms include a diagnostic algorithm for integrated genomic-pathologic classification of endometrial carcinomas based on the TCGA study and add that the decision to use molecular testing/classification depends on resource availability and each center's multidisciplinary team. The panel encourages comprehensive genomic profiling via a validated and/or FDA-approved assay in the initial evaluation of uterine neoplasms to help facilitate cancer diagnoses. The panel also encourages ancillary studies of *POLE* mutations, mismatch repair (MMR)/MSI, and aberrant *p53* expression to complement the morphologic assessment of histologic tumor type. In addition, the panel includes consideration for *NTRK* gene fusion testing for metastatic or recurrent endometrial carcinoma, and for tumor mutational burden (TMB) testing through a validated and/or FDA-approved assay.

Screening of the tumor for defective DNA MMR using immunohistochemistry (IHC) and/or MSI is used to identify which patients should undergo mutation testing for Lynch syndrome (see *Lynch Syndrome* in the NCCN Guidelines for Colorectal Cancer Screening available at https://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf).[16,20-26] At a minimum, universal testing of endometrial tumors for

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defects in DNA MMR is recommended (eg, *MLH1*, *MSH2*, *MSH6*). MSI testing is recommended if MMR results are equivocal. Testing may be performed on the initial biopsy or dilation and curettage (D&C) material or the final hysterectomy specimen. *MLH1* loss should be further evaluated for promoter methylation to assess for an epigenetic process rather than a germline mutation.[23] Genetic counseling, molecular analysis, and testing are recommended for patients with all other MMR abnormalities. Patients with a significant family history of endometrial and/or colorectal cancer (even for those without MMR defects, who are MSI-stable, or those without screening) should be referred for genetic counseling and evaluation (See *Lynch Syndrome [Hereditary Non-Polyposis Colorectal Cancer]* in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal available at https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf). Screening for genetic mutations should be considered, especially for patients <50 years of age.[7,16,20,27-30] If these patients have Lynch syndrome, they are at a higher lifetime risk (≤60%) for endometrial cancer; thus, close monitoring and discussion of risk-reducing strategies is recommended.[20,31,32, 5,27,33] In addition, their relatives may have Lynch syndrome. For patients and family members with Lynch syndrome but without endometrial cancer, a yearly endometrial biopsy is recommended to assess for cancer.[29,34] This strategy also enables select patients to defer surgery (and surgical menopause) and to preserve fertility. Prophylactic hysterectomy/bilateral salpingo-oophorectomy (BSO) is recommended after childbearing is complete.[35,36] In addition, interventions to decrease the risk from colorectal cancer are recommended (eg, annual colonoscopy).

Diagnosis and Workup

Currently, there is no validated screening test for endometrial carcinoma.[37,38] About 90% of patients with endometrial carcinoma have metrorrhagia, most commonly in the postmenopausal period. The workup was previously described above (see *Initial Evaluation*). Diagnosis can usually be made by an office endometrial biopsy, with a false-negative rate of about 10%.[39,40] Thus, a negative endometrial biopsy in a symptomatic patient must be followed by a fractional D&C under anesthesia.[39,41] Hysteroscopy may be helpful in evaluating the endometrium for lesions, such as a polyp, if the patient has persistent or recurrent bleeding.[42] Endometrial biopsy may not be accurate for diagnosing malignancies of the uterine wall such as mesenchymal tumors. The histologic information from the endometrial biopsy (with or without endocervical curettage) is sufficient for planning definitive treatment.

Imaging

For detailed imaging recommendations by stage and planned treatment approach, see *Principles of Imaging* in the NCCN Guidelines for Uterine Neoplasms. Consideration of preoperative chest imaging (chest x-ray) is recommended. Based on the fertility-sparing or non–fertility-sparing treatment criteria, other imaging tests such as CT, MRI, ultrasound (US), and/or FDG-PET/CT may be used to assess disease extent and to evaluate for metastatic disease as indicated based on clinical symptoms, physical findings, or abnormal laboratory findings.[43-49] In patients with extrauterine disease, a serum CA-125 assay may be helpful in monitoring clinical response.[50,51] However, serum CA-125 levels can be falsely increased in patients who have peritoneal inflammation/infection or radiation injury, may be normal in patients with isolated vaginal metastases, and may not predict recurrence in the absence of other clinical findings.[52-54]

Disease Staging

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

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fractional D&C). The 1970 staging system is rarely used today (eg, when the patient is not a surgical candidate).

Several studies demonstrated that clinical staging was inaccurate and did not reflect actual disease extent in 15% to 20% of patients.[55-57] This reported understaging and, more importantly, the ability to identify multiple prognostic factors with a full pathologic review made possible with surgical staging motivated a change in the staging classification. Therefore, in 1988, FIGO modified its staging system to emphasize thorough surgical/pathologic assessment of data, such as histologic grade, myometrial invasion, and the extent and location of extrauterine spread (including retroperitoneal lymph node metastases).[58] FIGO updated and refined the surgical/pathologic staging criteria for uterine neoplasms in 2009.[59-62] Separate staging systems for malignant epithelial tumors and uterine sarcomas are now available (see *Staging* section of the algorithm). In 2017, the AJCC Cancer Staging Manual was further updated (which took effect in January 2018).[63]

The 2009 FIGO staging system streamlined stages I and II of endometrial carcinoma. These revisions were made because the survival rates for some of the previous sub-stages were similar.[61] Currently stage IA describes tumors with less than 50% myometrial invasion, and stage IB describes those with 50% or more myometrial invasion. Stage II describes patients with tumors that invade the cervical stroma. Patients with uterine-confined disease and endocervical glandular involvement (mucosal involvement) without cervical stromal invasion are no longer considered stage II.[61] Stage IIIC is subdivided into IIIC1 (pelvic nodal involvement alone) and IIIC2 (para-aortic involvement +/- pelvic node involvement), reflecting the inferior survival in those patients with positive para-aortic nodes.[61] To maintain consistency, the NCCN Panel has reinterpreted historical studies using the 1988 FIGO staging system to reconcile those studies with the 2009 staging system.

In the 2009 FIGO staging the presence of positive peritoneal cytology no longer increases the disease stage, as its importance as an independent risk factor has been called into question.[62] However, FIGO and AJCC continue to recommend that peritoneal washings be obtained and results be recorded (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).[64]

Principles of Evaluation and Surgical Staging for Endometrial Carcinoma

Staging should be done by a team with expertise in imaging, pathologic evaluation, and surgery. The amount of surgical staging that is necessary to determine disease status depends on preoperative and intraoperative assessment by experienced surgeons. Pathologic nodal assessment for apparent uterine-confined endometrial cancer informs both stage and adjuvant therapy. However, if final pathology shows a noninvasive endometrioid histology, nodal assessment can be eliminated. The NCCN sentinel lymph node (SLN) algorithm is recommended if sentinel node mapping is utilized.

Pathology

An expert pathologic review determines the specific epithelial histology of the tumor (endometrioid, serous, clear cell, carcinosarcoma, or undifferentiated). Morphologic evaluation of endometrial carcinoma to determine histologic type—especially in high-grade cancers—is challenging and issues exist regarding diagnostic reproducibility. The pathologic assessment of the uterus and the nodes is described in the algorithm. The assessment of the uterus includes the hysterectomy type, specimen integrity, tumor site and size, histologic type and grade if applicable, myometrial invasion (depth of invasion in mm/myometrial thickness in mm), cervical stromal involvement, and LVSI. Pathologists may be asked to quantify LVSI. The current definition of substantial LVSI is 4 or more LVSI-involved vessels in at least one hematoxylin and eosin

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(H&E) slide (for clinically relevant LVSI in endometrial cancer).[65] The pathologic assessment should also include assessment of involvement by other tissues such as the fallopian tubes, ovaries, vagina, parametrium, peritoneum, and omentum. The assessment of peritoneal/ascitic fluid cytology should also be obtained. If nodal resection was performed, the level of nodal involvement (ie, pelvic, common iliac, para-aortic) should be determined. SLNs should undergo ultrastaging for the detection of low-volume metastases (LVMs). Ultrastaging commonly entails thin serial sectioning of the gross SLN and review of multiple H&E-stained sections with or without cytokeratin IHC for all blocks of SLN. There is no standard protocol for lymph node ultrastaging. See *Principles of Pathology* in the NCCN Guidelines for Endometrial Carcinoma. The *Protocol for the Examination of Specimens From Patients With Carcinoma and Carcinosarcoma of the Endometrium* from the College of American Pathologists (CAP) is a useful guide (https://cap.objects.frb.io/protocols/cp-femalereproductive-endometrium-18protocol-4100.pdf). This CAP protocol was revised to reflect the updated pTNM requirements from the AJCC Cancer Staging Manual (8th edition) and 2015 FIGO Cancer Report.[63,66]

Estrogen receptor (ER) testing is recommended in the setting of stage III, IV, or recurrent endometrioid carcinoma. Evaluation of human epidermal growth factor receptor 2 (HER2) overexpression should also be considered. Rottmann et al recently showed that 16% of 80 gynecologic carcinosarcomas (including uterine carcinosarcoma) showed HER2 overexpression and amplification when using the 2013 ASCO/CAP scoring system.[67] Similar results were reported by Jenkins et al, Yoshida et al, and others.[68-72] The panel recommends HER2 IHC testing (with reflex to HER2 fluorescence in situ hybridization [FISH] for equivocal IHC) for possible treatment for advanced-stage or recurrent serous endometrial carcinoma or carcinosarcoma. HER2 IHC testing should also be considered in *TP53*-aberrant endometrial carcinoma regardless of histotyping.

As the grade of the tumor increases, the accuracy of intraoperative evaluation of myometrial invasion decreases (ie, assessment by gross examination of fresh tissue).[73] 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.[74] 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.[75]

Lymphadenectomy

Previously, a full standard lymphadenectomy (ie, dissection and assessment of both pelvic and para-aortic nodes) was recommended for all patients; however, to decrease side effects, a more selective and tailored nodal evaluation approach that includes the SLN algorithm is recommended by the NCCN Panel.[76] No randomized trial data support routine full lymphadenectomy,[77] although some retrospective studies have suggested that it is beneficial.[78-80] Two randomized clinical trials from Europe reported that routine lymph node dissection did not improve the outcome of patients with endometrial cancer, but lymphadenectomy did identify those with nodal disease.[81,82] However, these findings remain a point of contention.[83-85] To avoid over-interpretation of these results, it is important to address the limitations of these randomized studies, including selection of patients, extent of lymph node dissection, and standardization of postoperative therapy.[86] One of the trials did not standardize adjuvant treatment after staging surgery with lymphadenectomy and this has been identified as a weakness of the trial and may have contributed to the lack of difference in recurrence and survival in the two groups.[80] The other concerns include the lack of central pathology review, subspecialty of surgeons, and adequacy of statistical power.

Decisions about whether to perform lymphadenectomy, and, if done, to what extent (eg, pelvic nodes only or both pelvic and para-aortic nodes),

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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.[87,88] However, this may be difficult to accurately determine before final pathology results are available. If expert gynecologic pathology is available, a frozen section to assess myoinvasion can be obtained and lymphadenectomy avoided if no myoinvasion or cervical invasion is identified.[89]

Nodal evaluation will identify those patients with nodal metastases. Identification of metastatic disease guides appropriate adjuvant treatment that has been shown to improve survival and decrease locoregional recurrence.

The question of whether to add para-aortic lymphadenectomy to pelvic node dissection has been debated. Prior studies have shown conflicting information regarding the risk of para-aortic nodal metastases in patients without disease in the pelvic nodes.[57,87,90,91] Para-aortic lymphadenectomy up to the renal vessels may be considered for selective patients, 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.[76]

In summary, lymph node dissection identifies patients requiring adjuvant treatment with radiation therapy (RT) and/or systemic therapy.[92] A subset of patients may not benefit from lymphadenectomy; however, it may be difficult to preoperatively identify these patients. The NCCN Panel recommends that nodal evaluation be performed in patients with endometrial carcinoma, including para-aortic lymphadenectomy in patients who are at higher-risk (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).[6] SLN mapping is the preferred alternative to full lymphadenectomy in the setting of apparent uterine-confined disease. The SLN surgical algorithm is described below.

Lymphadenectomy is not recommended for patients with uterine sarcoma as metastasis to the nodes is unusual.

Sentinel Lymph Node Mapping

The section on surgical staging (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma) includes recommendations about SLN mapping. SLN mapping may be considered for patients without suspicion of metastatic disease by preoperative imaging and no obvious extrauterine disease at exploration.[93-97] In SLN mapping, dye is injected into the cervix, which travels to the sentinel nodes. This 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).[98] Superficial (1–3 mm) and optional 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.[99] Injection into the uterine cervix provides excellent dye penetration to 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. 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 (see Figures 1–3 in *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma). The radiolabeled colloid most commonly injected into the cervix is technetium-99m (^{99m}Tc); colored dyes are available in a variety of forms (Isosulfan Blue 1%, Methylene Blue 1%, and Patent Blue 2.5% sodium). Indocyanine green (ICG) recently emerged as a useful imaging

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dye that requires a near-infrared camera for localization, provides a very high SLN detection rate, and is commonly used in many practices at the present time.[89,99-105]

A surgical SLN algorithm is proposed to decrease the false-negative rate in patients with apparent uterine-confined disease (see Figure 4 in *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).[93,106] 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.[97,99,107-112] SLN identification should always be done prior to hysterectomy, except in cases where a bulky uterus must be removed to allow access to iliac vessels and LNs. For example, suspicious or grossly enlarged nodes should be removed regardless of SLN mapping results. 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.[111,113] Because SLNs identify the primary lymphatic pathway, this increases the yield of finding metastatic disease during the mapping process. For cases of failed SLN mapping, reinjection of the cervix may be considered. However, if SLN mapping fails, a reflex side-specific nodal dissection should be performed and any suspicious or grossly enlarged nodes should be removed regardless of mapping.[93,112]

A literature review and consensus recommendations for SLN mapping in endometrial cancer were released by the Society of Gynecologic Oncology (SGO).[97] Close adherence to the NCCN SLN surgical algorithm was found to result in accurate prediction of pelvic lymph node metastasis with a less than 5% false-negative rate.[93] Additionally, results were published from the FIRES trial, which compared SLN mapping to lymphadenectomy for endometrial cancer in the largest multicenter prospective study to date (n = 385).[99] Mapping of at least one SLN was successful in 86% of patients; sensitivity was 97.2% (95% CI, 85.0–100), and negative predictive value was 99.6% (95% CI, 97.9–100).

A systematic review of 17 studies with n > 30 patients revealed detection rates of 60% to 100%; detection rates for studies with larger cohorts (n > 100) were at least 80%. Retrospective application of a surgical algorithm generated 95% sensitivity, 99% predictive value, and a 5% false-negative rate.[114] Another systematic review and meta-analysis of 55 studies with n > 10 patients (n = 4915) generated an overall detection rate of 81% with a 50% bilateral pelvic node detection rate and 17% paraaortic detection rate.[89] In a retrospective analysis of patients with early-stage endometrial cancer (n = 780) who underwent SLN mapping with lymphadenectomy versus lymphadenectomy alone, SLN mapping led to the detection of more metastasis (30.3% vs. 14.7%, $P < .001$) and was associated with greater use of adjuvant therapy.[115] Long-term follow-up was reported from a prospective multicenter study in 125 patients with early-stage endometrial carcinoma who underwent SLN biopsy. Patients with a positive SLN underwent external beam RT (EBRT) and chemotherapy at a higher rate than those with a negative SLN. In patients with a detected SLN, recurrence-free survival (RFS) at 50 months was 84.7%, and no difference was detected between patients with and without a positive SLN ($P = .5$).[116]

SLN mapping should be done in institutions with expertise in this procedure. If patients have apparent distant metastatic disease (based on imaging and/or surgical exploration), removal of nodes for staging purposes is not necessary because it will not change management.[43,49]

Historically, SLN mapping was controversial in patients with high-risk histology (eg, serous carcinoma, clear cell carcinoma, carcinosarcoma).[76,117] However, SLN mapping in patients with high-risk histologies (ie, grade 3, serous, clear cell, carcinosarcoma) has been reported with promising results as a potential alternative to complete

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lymphadenectomy.[112,118,119] A recent multi-institutional retrospective study concluded that SLN mapping versus SLN mapping with lymphadenectomy in high-risk endometrial cancer did not impact survival outcomes.[120] A recent prospective, multicenter cohort study (SENTOR-trial) examined the diagnostic accuracy of SLN mapping versus lymphadenectomy for intermediate- and high-grade endometrial cancer in 156 patients. Of 27 patients with nodal metastasis, SLN mapping correctly identified 26 of them (96% sensitivity; 95% CI; 81%–100%), thus concluding the acceptable accuracy of SLN mapping in high-grade endometrial cancer.[121] More studies have suggested the value of using SLN mapping for surgical staging in high-grade endometrial cancer.[122]

SLN Ultrastaging

In general, SLN mapping allows for increased intraoperative surgical precision to identify nodes more likely to harbor metastasis combined with enhanced pathology protocols, which has been shown to increase the detection of nodal metastasis, which may alter stage and adjuvant therapy recommendations. Studies have suggested that SLN ultrastaging leads to upstaging in 5% to 15% of patients.[96,108,110,113,114]

Ultrastaging typically includes two components: serial sectioning with review of multiple H&E-stained slides with or without cytokeratin IHC staining.[123] Recent data highlight the potential significance and impact of SLN ultrastaging to improve the accuracy of detecting micrometastases.[124]

In a cohort of 508 patients who underwent SLN mapping, ultrastaging detected 23 additional cases of micrometastasis that would have been missed by conventional H&E staining.[125] A multicenter study of 304 patients with presumed low- or intermediate-risk disease showed that SLN biopsy and ultrastaging detected metastatic SLNs in a 3-fold greater number of patients than standard lymphadenectomy.[126]

The implications and appropriate management of micrometastases and isolated tumor cells (ITCs), jointly referred to as LVM, detected via SLN ultrastaging are not yet clear.[97,110,113,127-131] Studies have recently begun to investigate the significance of ITCs discovered during SLN mapping in early-stage endometrial cancer. The AJCC 8th edition cancer staging manual indicates that the lymph nodes with ITCs should be clearly reported even though they do not affect the overall staging.[132] When ITCs are detected in the absence of macrometastasis and micrometastasis, the lymph node stage is designated as pN0(i+).

A retrospective review examined 844 patients with endometrial cancer that underwent SLN mapping.[133] The majority of patients with ITCs, micrometastasis, and macrometastasis received adjuvant chemotherapy (83%, 81%, and 89%, respectively). RFS at 3 years was 90% for those with negative SLNs, 86% for ITCs, and 86% for micrometastasis. Only patients with SLN macrometastasis had significantly lower RFS (71%, $P < .001$).

A prospective observational study of 519 patients compared outcomes for patients with SLN macrometastasis, micrometastasis, and ITCs, taking into account adjuvant treatment.[134] Patients with SLN ITCs had a significantly better 3-year progression-free survival (PFS) compared with patients with SLN macrometastasis (95.5% vs. 58.5%), and outcomes were similar between patients with negative SLNs, ITCs, and micrometastasis. Recurrence was detected in only 1 of 31 patients with ITCs (stage IB carcinosarcoma) and adjuvant treatment did not appear to influence outcomes. Based on these early data, it is unclear if patients with SLN ITCs would derive significant benefit from adjuvant treatment.[135] Future evaluation of prognosis/outcome may need to prospectively examine the threshold for and impact of adjuvant therapy for patients with scattered ITCs.

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Minimally Invasive Procedures

Over the past decade, practice has trended towards minimally invasive approaches to total abdominal hysterectomy (TH)/BSO and lymph node assessment in patients with early-stage endometrial cancer.[136] Although these procedures may be performed by any surgical route (eg, laparoscopic, robotic, vaginal, abdominal), the standard in those with apparent uterine-confined disease is to perform the procedure via a minimally invasive approach. Randomized trials, a Cochrane Database Systematic Review, and population-based surgical studies support that minimally invasive techniques are preferred in the appropriate candidate due to a lower rate of surgical site infection, transfusion, venous thromboembolism, decreased hospital stay, and lower cost of care, without compromise in oncologic outcome.[136-142] Despite data showing that minimally invasive procedures result in lower perioperative complications and lower cost of care, racial and geographic disparities in access to minimally invasive surgical care have been observed.[138,142]

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.[141,143] 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, $P < .0001$).[144,145] Significantly fewer postoperative adverse events and shorter hospitalization occurred with laparoscopy compared with laparotomy. Recurrence rates were 11.4% for laparoscopy versus 10.2% for laparotomy. The 5-year overall survival (OS) rate was 84.8% for both arms of LAP2.[143] Laparoscopic staging was associated with improved postoperative quality of life across several parameters.[140]

The LACE trial compared outcomes of patients with stage I endometrial carcinoma (n = 760) who were randomized to undergo TH or total laparoscopic hysterectomy (TLH), where half of the patients received concomitant lymphadenectomy.[137] At a median follow-up of 4.5 years, disease-free survival (DFS) was 81.3% for laparotomy versus 81.6% for laparoscopy, with no significant differences observed between groups for recurrence and OS. Another randomized trial (n = 283) comparing laparoscopy versus laparotomy reported shorter hospital stay, less pain, and faster resumption of daily activities with laparoscopy.[146] A recent follow-up study of a multicenter randomized trial evaluated outcomes for TLH versus TH in 279 patients with early-stage, low-risk endometrial cancer who did not undergo concomitant lymphadenectomy and reported comparable disease recurrence and 5-year survival rates. The results were also similar to studies with lymphadenectomy.[147] Laparotomy may still be required for certain clinical situations (eg, patients who are older, those with a very large uterus) or certain metastatic presentations.[141,148,149]

Robotic surgery is a minimally invasive technology that has been increasingly used in the surgical staging of endometrial carcinoma due to its potential advantages over laparotomy, especially for patients who are overweight.[150-154] Prospective cohort and retrospective studies suggest that robotic approaches perform similarly to laparoscopy and result in comparable or improved perioperative outcomes.[154-159] Oncologic outcomes appear to be comparable to other surgical approaches, although longer-term outcomes are still being investigated.[160-162] In certain patients, robotic surgery may result in less frequent conversion to laparotomy when compared with laparoscopic approaches and also appears to be safe and feasible in patients at higher anesthesiologic risk.[154,155,163]

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Costs for robotic equipment and maintenance remain high.[164 150,151,160-162,165] The SGO, American Association of Gynecologic Laparoscopists (AAGL), and American Congress of Obstetricians and Gynecologists (ACOG) have published guidelines or position statements about robotic surgery.[166-168] For reviews on the robotic-assisted surgery for gynecologic malignancies and associated cost issues, see Sinno and Fader and Gala et al.[169,170]

Primary Treatment

These NCCN Guidelines divide pure endometrioid cancer into three categories for delineating treatment: 1) disease limited to the uterus; 2) suspected or gross cervical involvement; and 3) suspected extrauterine disease. Most patients with endometrial cancer have stage I disease at presentation, and surgery (with or without adjuvant therapy) is recommended for patients who are medically operable. As a general principle, endometrial carcinoma should be removed en bloc to optimize outcomes; intraperitoneal morcellation should be avoided.[171-174]

Disease Limited to the Uterus

To stage patients who are medically operable with endometrioid histologies clinically confined to the fundal portion of the uterus, the recommended surgical procedure includes removal of the uterus and bilateral tubes and ovaries with lymph node and abdominal assessment (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma and in this Discussion and *Lymphadenectomy* and *Sentinel Lymph Node Mapping* in this Discussion).[83] Ovarian preservation may be safe in select patients who are premenopausal with stage I endometrioid cancer.[175-177] Minimally invasive surgery is the preferred approach when technically feasible and is considered a quality measure by the SGO and the American College of Surgeons (www.sgo.org/quality-outcomes-and-research/quality-indicators; https://www.facs.org/quality-programs/cancer-programs/national-cancer-database/quality-of-care-measures).

During surgery, the intraperitoneal structures should be carefully evaluated, and suspicious areas should be biopsied. While not specifically affecting staging, FIGO and AJCC recommend that peritoneal cytology should be collected and results should be recorded. Cytology results should not be taken in isolation to guide adjuvant therapy. 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 lymphadenopathy—is useful when using the 2009 FIGO staging criteria, but its routine use has been questioned (see *Lymphadenectomy* in this Discussion). For stage II patients, TH/BSO is the standard procedure. Radical hysterectomy should only be performed if needed to obtain negative margins.

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

Incomplete Surgical Staging

For patients with incomplete surgical staging and high-risk intrauterine features, imaging is recommended, especially in patients with higher grade histologies.[178,179] Surgical restaging, including lymph node dissection, can also be done.[87] 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).

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Fertility-Sparing Therapy
Although the primary treatment of endometrial cancer is usually hysterectomy, continuous progestin-based therapy may be considered for highly selected patients with grade 1, stage IA (noninvasive) disease who wish to preserve fertility.[180-184] Likewise, it may also be selectively used for young patients with endometrial hyperplasia who desire fertility preservation. The guidelines include an algorithm for fertility-sparing therapy in selected patients with biopsy-proven grade 1 (preferably by D&C), stage IA noninvasive endometrioid adenocarcinoma (see *Criteria for Considering Fertility-Sparing Options* in the NCCN Guidelines for Endometrial Carcinoma). The panel recommends consultation with a fertility expert and genetic evaluation of tumor and evaluation for inherited cancer risk. When considering fertility-sparing therapy, all of the criteria must be met as outlined in the algorithm (eg, no metastatic disease) and a negative pregnancy test must be ensured. Patients should also receive counseling that fertility-sparing therapy is not the standard of care for the treatment of endometrial carcinoma. TH/BSO with surgical staging is recommended after childbearing is complete, if therapy is not effective, or if progression occurs. Fertility-sparing therapy is not recommended for high-risk patients (eg, those with high-grade endometrioid adenocarcinomas, uterine serous carcinoma, clear cell carcinoma, carcinosarcoma, and uLMS).

Continuous progestin-based therapy may include megestrol acetate, medroxyprogesterone, or an intrauterine device (IUD) containing levonorgestrel.[180,181,185] A complete response occurs in about 50% of patients.[180] 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. The panel also recommends counseling for weight management and lifestyle modification (see *Healthy Lifestyles* and *Nutrition and Weight Management* in the NCCN Guidelines for Survivorship available at https://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf).

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 biopsy; or 3) if endometrial cancer is still present after 6 to 12 months of progestin-based therapy.[184,186] Although some young patients who had subsequent negative endometrial biopsies after hormonal therapy were able to become pregnant (35%), the ultimate recurrence rate was high (35%).[180,183,187-189] In patients with persistent endometrial carcinoma after 6 months of failed hormonal therapy, the panel recommends pelvic MRI to exclude myoinvasion and nodal/ovarian metastasis before continuing fertility-sparing therapy.

In a study of patients who are premenopausal and have stage IA to B endometrial cancer, median 16-year follow-up data suggest that ovarian preservation is safe and not associated with an increased risk of cancer-related mortality.[175] Other studies also suggest that ovarian preservation may be safe in select patients.[176,177]

Suspected or Gross Cervical Involvement
For patients with suspected or gross cervical involvement (endometrioid histologies), cervical biopsy or pelvic MRI should be performed if not done previously (see *Additional Workup* in the NCCN Guidelines for Endometrial Carcinoma).[178,179,190,191] If negative, patients are assumed to have disease that is limited to the uterus and are treated as previously described, although a radical hysterectomy may be performed when necessary to obtain negative margins. It may be difficult to distinguish primary cervical carcinoma from stage II endometrial carcinoma. Thus, for patients suitable for primary surgery, TH or radical hysterectomy is recommended along with BSO, cytology (peritoneal lavage), and

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evaluation of lymph nodes if indicated (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).[83] In these patients, radical or modified radical hysterectomy may improve local control and survival when compared with TH.[192,193] Alternatively, the patient may undergo EBRT and brachytherapy (category 2B) followed by TH/BSO and surgical staging.

Suspected Extrauterine Disease

If extrauterine disease (endometrioid histologies) is suspected, imaging studies are recommended along with CA-125 testing (see *Additional Workup* in the NCCN Guidelines for Endometrial Carcinoma). ER testing is recommended in the setting of stage III or IV endometrioid tumors. Patients with no evidence of extrauterine disease are treated using the guidelines for disease limited to the uterus. Patients with abdominal- or pelvic-confined disease require surgical intervention using TH/BSO with surgical staging and surgical debulking with the goal to have no measurable residual disease; several studies support debulking.[83,194-196] Consider preoperative chemotherapy.[197] For distant visceral metastasis (eg, liver involvement), recommended options include systemic therapy with (or without) EBRT with (or without) TH/BSO and with (or without) stereotactic body RT (SBRT). Ablative radiation can be considered for 1 to 5 metastatic lesions if disease is otherwise controlled (category 2B).[198]

Patients Not Suited for Primary Surgery

For uterine-confined disease not suitable for primary surgery, EBRT and/or brachytherapy is the preferred treatment approach. Alternatively, progestational agents (such as medroxyprogesterone acetate and megestrol acetate) and levonorgestrel IUD can also be considered for select patients (eg, estrogen and progesterone receptor–positive [ER/PR-positive]). Patients receiving hormonal therapy alone should be closely monitored by endometrial biopsy (eg, consider endometrial biopsies every 3–6 months).[37,199]

For suspected gross cervical involvement in patients who are not suited for primary surgery, EBRT and brachytherapy is an effective treatment that can provide pelvic control and long-term PFS (see *Principles of Radiation Therapy* in the NCCN Guidelines for Uterine Neoplasms).[200-203] EBRT and brachytherapy may be administered with or without platinum-based chemosensitization, depending on the clinical situation and medical fitness of the patient. If rendered operable, local treatment consisting of surgery should follow. Systemic therapy alone is also a primary treatment option (category 2B), but should be followed by EBRT + brachytherapy if the patient remains inoperable.

Patients with unresectable extrauterine pelvic disease (ie, vaginal, bladder, bowel/rectal, nodal, or parametrial involvement) are typically treated with EBRT with (or without) brachytherapy with (or without) systemic therapy, followed by re-evaluation of tailored surgery.[204-207] Systemic therapy alone can also be considered. Based on treatment response, patients should be re-evaluated for surgical resection and/or RT.

Adjuvant Therapy

Uterine-Confined Disease

Thorough surgical staging provides important information to assist in selection of adjuvant therapy for endometrial tumors (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma). Patients with stage I endometrial cancer who have thorough surgical staging are stratified by adverse risk factors (ie, age, positive LVSI, tumor size, and lower uterine segment or surface glandular involvement).[208,209] Recommended adjuvant treatment is outlined in the algorithm (see the NCCN Guidelines for Endometrial Carcinoma). Note that the treatment algorithm was revised in 2010 based on the updated FIGO staging.[61] However, by necessity, much of the discussion in this manuscript has been based on data from patients staged using the older

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FIGO/AJCC staging system. The implications of *stage migration* should be considered when evaluating historical data.

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 increase, as risk of systemic metastases increase.[210-212] In surgical stage I and II endometrial cancer, other pathologic factors that may influence the decision regarding adjuvant therapy include LVSI, patient age, tumor volume, depth of invasion, and lower uterine segment or cervical glandular involvement. When administering adjuvant RT, it should be initiated as soon as the vaginal cuff has healed, but no later than 12 weeks after surgery.

Significant controversy centers on how much adjuvant therapy is necessary in patients with surgical stage I endometrial cancer. 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 for selected patients with low-risk features (see section on *Adjuvant Treatment* in the NCCN Guidelines for Endometrial Carcinoma).[92,209,210,213-215] The NCCN Panel prefers observation for patients with stage IA, grade 1/2 disease, but strongly suggests treatment with adjuvant vaginal brachytherapy for those ≥60 years and/or those with LVSI. For patients with stage IA, grade 3 tumors, especially in those who have been surgically staged, vaginal brachytherapy is the preferred option, or observation can be considered if no myometrial invasion is present. If higher risk factors are present, ie, age ≥70 years or LVSI, EBRT can be considered as a category 2B option. For patients with stage IB, grade 1–2 disease, vaginal brachytherapy is preferred although observation can be considered if no adverse risk factors are present. In these patients, the PORTEC-2 trial, without evaluation of pelvic nodes, found pelvic recurrence to be low with vaginal brachytherapy alone.[216] EBRT can be considered in grade 2 tumors if additional risk factors are present such as age ≥60 years and/or if LVSI is present. For stage IB, grade 3 disease with adverse risk factors, systemic therapy is added as a category 2B option (in addition to EBRT and/or vaginal brachytherapy).

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, EBRT (preferred) and/or vaginal brachytherapy with (or without) systemic therapy (category 2B) are options. As with stage I disease, the presence of adverse risk factors (including depth of stromal invasion, grade, LVSI, and adverse fundal risk factors) should be considered when selecting adjuvant therapy for stage II disease.[217]

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 has not been shown to improve OS. However, many of the earlier trials had limitations as the patients were primarily low risk (ie, they had low-risk intrauterine pathologic 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 (especially extensive), and serous or clear cell carcinoma histologies.

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Four trials have evaluated the role of adjuvant external-beam pelvic RT in patients with endometrial carcinoma. In two of these trials, the patients were not formally staged (Postoperative Radiation Therapy in Endometrial Carcinoma [PORTEC-1], Aalders).[218,219] In the third trial (ASTEC/EN.5), only 50% of the patients were thoroughly staged as part of a companion surgical protocol.[81,220] However, formal surgical staging was mandated for all patients in the GOG 99 trial.[221] Note that these trials used the older staging system (ie, before 2009).

The PORTEC-1 and GOG 99 trials suggest that external-beam pelvic RT provides a locoregional control benefit in selected patients with uterine-confined disease.[218,222] Radiation was not shown to increase OS.[223] It is important to note that the PORTEC 1 trial was powered to evaluate OS, although the GOG 99 trial was not. Similarly the Aalders' randomized trial found that RT reduced vaginal (ie, locoregional) recurrences but did not reduce distant metastases or improve survival.[219] A pooled randomized trial (ASTEC/EN.5) suggested that adjuvant pelvic RT alone did not improve either relapse-free survival (ie, PFS) or OS in patients with intermediate-risk or high-risk early-stage endometrial cancer, but there was an improvement in pelvic control.[220] However, the ASTEC/EN.5 study is very controversial; 51% of the patients in the ASTEC observation group received vaginal brachytherapy. Vaginal brachytherapy has been shown to decrease vaginal recurrence, and in PORTEC 2 vaginal brachytherapy was compared in a prospective randomized trial with EBRT in low-risk patients. Vaginal brachytherapy alone was shown to sufficiently control the pelvis and was less toxic than full pelvic RT. As most pelvic recurrences are vaginal, inclusion of vaginal brachytherapy in the "observation" arm of the ASTEC/EN.5 study weakens any conclusions regarding pelvic radiation.[85,224] The Keys' trial (GOG 99) showed that adjuvant pelvic RT improved locoregional control and relapse-free interval (ie, PFS), without an OS benefit, although the study was not powered to evaluate OS.[221,225,226] In both trials pelvic radiation was found to be of greater benefit in patients >60 years with higher grade and more deeply invasive disease.

To help select the appropriate patient population that may benefit from adjuvant pelvic RT, the GOG 99 and PORTEC trials defined risk factors for patients at high-intermediate risk (HIR) for recurrence, although the definition differed between these trials.[218,221] Risk factors for recurrence identified in both trials included higher age, deep myometrial invasion (>50%), higher grade (grade 2 or 3, serous or clear cell), and LVSI (especially extensive as defined in the PORTEC trials). Based on risk factors identified in GOG 99, HIR disease was defined as patients <50 years with grade 2 or 3 disease, myometrial invasion greater than 50%, and LVSI.[221] Patients 50 to 70 years of age were considered HIR if they had 2 of the 3 identified high-risk features. Patients ≥70 years were defined as HIR if they also had one risk feature present. Based on data from PORTEC-1, HIR patients were defined as having 2 of 3 risk factors (ie, age >60 years, deep myometrial invasion, grade 3 histology).[218,225] LVSI was not considered in the original PORTEC trials, but a subsequent retrospective evaluation demonstrated increased recurrence with extensive LVSI, as defined by the protocol.

Due to concerns about potential toxicity of external-beam pelvic RT, the role of vaginal brachytherapy alone in uterine-confined disease has been evaluated. PORTEC-2 randomly assigned patients to external-beam pelvic RT versus vaginal brachytherapy alone in uterine-confined disease. PORTEC-2 showed excellent and equivalent vaginal and pelvic control rates with both adjuvant radiation approaches and no difference in OS.[216] Given that vaginal brachytherapy is associated with significantly less toxicity than pelvic RT, vaginal brachytherapy alone is a reasonable choice for patients with uterine-confined endometrial cancer as defined in the PORTEC 2 trial.[216,225-233] The use of vaginal brachytherapy and/or whole pelvic RT should be carefully tailored to a patient's pathologic findings.

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Both PORTEC-1 and PORTEC-2 specifically excluded patients with 1998 FIGO stage 1C and grade 3 endometrial carcinoma (2009 FIGO stage IB, grade 3);[61] thus, the use of adjuvant brachytherapy alone in this higher risk subset remains more controversial. PORTEC studies did not evaluate lymph nodes and, therefore, in the context of complete surgical staging and the lack of a survival benefit, the need for pelvic irradiation remains controversial in uterine-confined disease.

A meta-analysis evaluated results from studies that compared adjuvant postoperative EBRT with or without vaginal brachytherapy and vaginal brachytherapy alone in stage II endometrial cancer. EBRT + vaginal brachytherapy significantly reduced locoregional recurrence versus vaginal brachytherapy alone. OS was comparable in both arms.[234]

The GOG 249 trial examined vaginal cuff brachytherapy and 3 cycles of carboplatin/paclitaxel therapy (3 cycles) versus pelvic EBRT only in patients with high-risk, uterine-confined endometrial carcinoma (n = 601), including serous and clear cell carcinoma. GOG 249 reported significantly increased rates of nodal recurrence (primarily pelvic) in the brachytherapy plus chemotherapy arm compared with the pelvic EBRT arm. No significant between-group differences in vaginal or distant recurrence rates were observed. However, there were more extravaginal pelvic failures in the brachytherapy plus chemotherapy arm. At a median follow-up of 53 months, 3-year RFS was 82% for both treatment arms; 3-year OS was 88% for the brachytherapy plus chemotherapy cohort and 91% for the pelvic EBRT cohort. Acute toxicity was more common and severe for patients receiving brachytherapy with chemotherapy. No differences in late-onset toxicities were observed.[235] Questions were raised whether 3 cycles of chemotherapy were sufficient to control distant disease.

Analysis of pooled data from PORTEC-1 and PORTEC-2 ranked the predictive power of multiple variables on patient outcomes examined in these trials. Patient age, tumor grade, and LVSI were highly predictive for locoregional relapse (LRR), distant relapse (DR), OS, and DFS, and treatment given (EBRT vs. vaginal brachytherapy) was predictive for LRR and DFS.[208] The benefit of adjuvant EBRT in the highest risk spectrum of uterine-confined disease remains controversial. Most NCCN Panel Members feel that patients with deeply invasive grade 3 tumors should receive adjuvant treatment. Two large retrospective SEER analyses of patients with endometrial cancer found that adjuvant RT improved OS in those with high-risk disease.[236,237] 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.[228,238-242]

The long-term follow-up study (median 20.5 years) of 568 patients with early-stage endometrial carcinoma enrolled in the Aalders trial compared long-term outcomes in patients who received vaginal brachytherapy plus EBRT versus vaginal brachytherapy alone. The findings suggested no statistical difference in OS between the study groups, and in this cohort, patients <60 years of age who received EBRT had increased incidence of secondary cancers and subsequent higher mortality rates.[228] Evaluation of secondary malignancies in the context of increased genetic susceptibility (eg, MSI-H) and radiation is ongoing.

Adjuvant Systemic Therapy

Patients with deeply invasive, grade 3, uterine-confined disease (2009 FIGO stage IB, grade 3 [formerly 1988 FIGO stage IC, grade 3]) have a relatively poor prognosis. Despite adjuvant therapy with pelvic RT, a significant number of patients continue to have a significant risk of distant metastases, and an optimal adjuvant therapy is still sought.[221,222] Therefore, some clinicians suggested that adding systemic therapy to adjuvant RT may provide added therapeutic benefit (ie, decrease in distant metastases).[210,243] Studies have evaluated the role of systemic therapy in

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highest risk uterine-confined disease.[243,244] PFS is improved with adjuvant sequential chemotherapy.[243] However, the NCCN Panel feels that adjuvant systemic therapy is a category 2B recommendation in this setting because an OS advantage has not been shown.[243] The GOG-249 phase 3 trial evaluated the benefit of adjuvant pelvic RT versus vaginal cuff brachytherapy plus 3 cycles of paclitaxel/carboplatin combination in 601 patients with high-intermediate and high-risk early-stage endometrial cancer. The 5-year RFS and OS were similar in both groups and superiority of any of these treatments were not demonstrated. Acute toxicity was greater in the combination therapy.[245]

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.[246-248] Patients with extrauterine disease confined to the lymph nodes or the adnexa may be treated with pelvic or extended-field RT alone or with chemotherapy (radiation is targeted to sites of nodal disease).[249] However, systemic therapy is regarded as the foundation of adjuvant therapy for patients with extrauterine disease. The NCCN Guidelines include carboplatin/paclitaxel as the preferred systemic therapy option in the primary/adjuvant setting for advanced-stage disease or high-risk histologies.[250-252] The NCCN Guidelines recently added the pembrolizumab/carboplatin/paclitaxel and dostarlimab carboplatin/paclitaxel triplet regimens as Category 1, preferred, primary therapy options for stage III or IV disease based on the data from phase III NRG-GY018 and RUBY trials, respectively.[253,254] The pembrolizumab/carboplatin/paclitaxel regimen is recommended for stage III or IVA with measurable disease or for stage IVB with or without measurable disease. Since the NRG-GY018 trial did not include patients with carcinosarcoma histology, the NCCN Panel do not recommend the pembrolizumab/carboplatin/paclitaxel treatment option for patients with carcinosarcoma disease. The dostarlimab carboplatin/paclitaxel option is recommended for patients with stage IIIA, IIIB, or IIIC1 with measurable disease, stage IIIC1 with carcinosarcoma, clear-cell, serous, or mixed histology regardless of the presence of measurable disease; and stage IIIC2 or stage IV disease regardless of the presence of measurable disease.

For stages III and IV disease, systemic therapy forms the mainstay of treatment and can be combined with EBRT with (or without) vaginal brachytherapy. The combination of therapies depends on assessment of both locoregional and distant metastatic risk. Combination therapy can be considered for stages IIIB and IIIC disease.

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. However, it is considered too toxic and has largely been abandoned.[255,256] 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 OS when compared with whole abdominopelvic RT; however, acute toxicity (eg, peripheral neuropathy) was greater in the AP chemotherapy arm.[205]

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, systemic therapy forms the established framework of adjuvant therapy for patients with stage III or IV disease. Whole abdominal RT as a single modality (as used in GOG 122) is considered inferior to chemotherapy and is too toxic; therefore, it is no

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longer recommended. For the purposes of these guidelines, whole abdominal RT is not considered to be tumor-directed RT (see *Principles of Radiation Therapy* in the NCCN Guidelines for Uterine Neoplasms).

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.[205] A study found that combined modality adjuvant therapy (using chemotherapy and tumor-directed RT) may provide a therapeutic benefit when compared with single-modality adjuvant therapy.[207,257,258]

A follow-up study evaluated the role of chemotherapy "intensification" for this patient population. The GOG 184 trial compared two chemotherapy regimens (cisplatin and doxorubicin with [or without] paclitaxel) with tumor-directed radiation (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).[206]

In a retrospective review of 116 patients with stage IIIC endometrial cancer, adjuvant RT significantly improved OS in patients with endometriod histology, high-grade tumors, and positive para-aortic lymph nodes. Conversely, patients with low-grade tumors and non-endometrioid histology who received RT had similar OS compared with those who did not.[259] In a multicenter retrospective review of 73 patients with stage IIIA endometrial carcinoma, surgery followed by both chemotherapy and RT provided the highest 5-year OS.[260] A prospective study of 122 patients with fully resected locally advanced disease suggested a potential benefit of adjuvant chemoradiation followed by chemotherapy, with an estimated 5-year PFS and OS of 73% and 84%.[261] Adjuvant therapy options were compared in a multicenter retrospective analysis of 265 patients with optimally resected stage IIIC endometrial carcinoma. Compared with patients receiving adjuvant RT or adjuvant RT plus chemotherapy, patients who received adjuvant chemotherapy alone had a 2.2-fold increased risk of recurrence and a 4.0-fold increased risk of death.[248]

Multimodality therapy is now the basis of randomized trials evaluating therapy. The phase 2, RTOG 9708 trial assessed 46 patients for safety, toxicity, recurrence, and survival when chemotherapy (cisplatin/paclitaxel) was combined with adjuvant radiation in patients with high-risk endometrial cancer. The trial participants included patients with grade 2 or 3 endometrial adenocarcinoma with either >50% myometrial invasion, cervical stromal invasion, or pelvic-confined extrauterine disease. The OS and DFS favored the combined modality treatment.[262]

The phase 3, PORTEC-3 trial investigated the benefit of combined adjuvant chemotherapy and EBRT versus EBRT alone in 686 patients with endometrial cancer (stage I, grade 3 with deep invasion, LVSI, or both; stage II; stage III; or any patient with stage I to III serous or clear cell endometrial cancer). The 5-year OS was 81.4% (95% CI, 77.2–85.8) with chemoradiotherapy versus 76.1% (95% CI, 71.6–80.9) with radiotherapy alone (HR, 0.70; 95% CI, 0.51–0.97; $P = .034$) and 5-year failure-free survival was 76.5% (95% CI, 71.5–80.7) versus 69.1% (63.8–73.8; HR, 0.70; 95% CI, 0.522–0.94; $P = .016$).[263,264] Patients with serous cancers and with stage III disease were shown to benefit the most from the addition of systemic therapy. The combination treatment was also shown to be associated with more severe adverse events.[265]

The GOG-258 phase 3 trial evaluated 707 patients with stage III or IVA, high-risk endometrial cancer who were randomly assigned 1:1 to receive chemoradiotherapy or chemotherapy only.[266] This trial supported the benefit of using chemotherapy alone by concluding that the combined therapy was not associated with longer relapse-free survival when

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compared with chemotherapy alone (59% vs. 58%, respectively). OS results are pending.

A follow-up molecular analysis was performed of the PORTEC-3 trial to study the impact of chemoradiotherapy for each molecular subtype using tissue samples from the trial participants. The tumors were classified into *p53* abnormal, *POLE*, MMR-deficient (dMMR), or no specific molecular profile. The 5-year RFS with chemoradiotherapy versus RT alone was *p53* abnormal, 59% versus 36%; *POLE*, 100% versus 97%; dMMR, 68% versus 76%; and 80% versus 68% for no specific molecular profile, suggesting that systemic therapy was beneficial for those patients that were *p53* abnormal.[267] Results are awaited for an ongoing PORTEC-4a trial investigating molecular profile-based directed adjuvant treatment in high-risk endometrial cancer.[268]

High-Risk Endometrial Carcinoma Histologies

Overview

Uterine serous carcinomas, clear cell carcinomas, carcinosarcomas, and undifferentiated/dedifferentiated carcinomas are considered more aggressive histologic variants of malignant epithelial tumors, with a higher incidence of extrauterine disease at presentation.[269-276] Carcinosarcomas are aggressive tumors that are staged as high-grade endometrial cancer.[277,278] Carcinosarcomas (also known as MMMTs) are metaplastic carcinomas and not uterine sarcomas; therefore, carcinosarcomas are included as part of the high-risk malignant epithelial tumors.[273,276,279,280] 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. Serous carcinomas, clear cell carcinomas, carcinosarcomas, and undifferentiated/dedifferentiated carcinomas are all considered high-risk histologies and high grade by default, although they are staged using the same FIGO/AJCC staging system as endometrial cancers.[63]Patients with uterine serous carcinoma, clear cell carcinoma, carcinosarcoma, or undifferentiated/dedifferentiated carcinomas may present with pelvic masses, abnormal cervical cytology, or ascites in addition to postmenopausal bleeding. Both the NCCN Panel and the SGO recommend that CA-125 and MRI or chest/abdominal/pelvic CT may be useful before surgery to assess if extrauterine disease is present; PET may also be useful.[269] Patterns of failure often mimic those of ovarian cancer.

Primary Treatment

Suitable for Primary Surgery

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).[281] Minimally invasive surgery is the preferred approach when technically feasible.[282-286]

Additional treatment options are highly individualized and are based on the histology and stage of the tumor.[287-294] For patients with clear cell or serous carcinomas with no residual disease in the hysterectomy specimen, observation is the recommended option. For stage IA disease without myometrial invasion with negative peritoneal washings, options include vaginal brachytherapy with (or without) systemic therapy (category 2B for systemic therapy) or observation. If the washings are positive, both systemic therapy and vaginal brachytherapy are recommended. [295,296] For patients with invasive stage IA, IB, or II, options include systemic therapy with (or without) EBRT with (or without) vaginal brachytherapy; or EBRT with (or without) vaginal brachytherapy. For patients with clear cell or serous carcinoma at a more advanced stage (ie, stage III or IV), or with undifferentiated/dedifferentiated histology, systemic therapy with (or

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without) EBRT with (or without) vaginal brachytherapy is recommended.[271,288,292,297]

For the patients with carcinosarcoma histology at stage IA, systemic therapy and vaginal brachytherapy are recommended with an option for EBRT, if it has high-grade epithelial components and is sarcoma dominant (>50% of sarcoma component in uterine tumor).[298] The panel notes that the initiation of chemotherapy within 3 to 6 weeks postoperatively should be considered and vaginal brachytherapy can be integrated with chemotherapy.

For patients with advanced histologies, whole abdominopelvic RT with (or without) vaginal brachytherapy is no longer recommended as a primary treatment option.[205,297,299 288] Multimodality therapy including systemic therapy, EBRT, and vaginal brachytherapy appears to be more effective. Data are conflicting regarding the rate of abdominal recurrence in these patients.[297,300-304] Whole abdominal radiotherapy is not considered to be tumor-directed RT (see *Principles of Radiation Therapy* in the NCCN Guidelines for Uterine Neoplasms). As previously mentioned, *tumor-directed RT* refers to RT directed at sites of known or suspected tumor involvement and may include EBRT with (or without) vaginal brachytherapy. In general, tumor-directed EBRT is directed to the pelvis with (or without) the para-aortic region.

Not Suitable for Primary Surgery
For patients with disease that is not amenable to resection, or is not suitable for surgery due to comorbidities, the primary treatment option is EBRT with (or without) brachytherapy with (or without) systemic therapy and then re-evaluation for surgery. Alternatively, systemic therapy could be given first, and then patients can be re-evaluated for surgery before giving RT based on the tumor response. For patients with carcinosarcoma histology with unresectable tumor that has metastasized, the panel recommends systemic therapy with (or without) EBRT or best supportive care.

Treatment of Recurrent or Metastatic Disease

Locoregional Recurrence
Patients with local or regional recurrences (negative for distance metastases on radiologic imaging) can be evaluated for further treatment (see *Clinical Presentation* in the NCCN Guidelines for Endometrial Carcinoma). For recurrences confined to the vagina or the pelvis alone, second-line treatment (typically with RT and/or surgery or systemic therapy) can be effective and selection depends on prior therapy. For patients with no prior RT exposure at the recurrence site, the panel recommends EBRT with (or without) brachytherapy and systemic therapy, or surgery with (or without) intraoperative RT (IORT) and systemic therapy. For patients previously treated with brachytherapy only at the recurrence site, surgery with (or without) IORT is recommended (category 3 for IORT).

For patients previously treated with EBRT at the recurrence site, recommended therapy for isolated relapse includes surgery with (or without) IORT (category 3 for IORT) plus or minus systemic therapy. Use of RT in the context of recurrence depends on the site of recurrence (inside or outside the prior radiation field), and dose of prior therapy. Re-irradiation is used only in the context of limited disease for palliation and lack of other options. In selected patients, radical surgery (ie, pelvic exenteration) has been performed with reported 5-year survival rates approximating 20%.[305-308]

Isolated vaginal recurrences treated with RT have good local control and 5-year survival rates of 50% to 70%.[309-311] Prognosis is worse if there is extravaginal extension or pelvic lymph node involvement.[310] After RT, it is

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unusual for patients to have recurrences confined to the pelvis. The management of such patients remains controversial.

Additional therapy options for disease confined to vagina or paravaginal soft tissues include EBRT with (or without) brachytherapy with (or without) systemic therapy. EBRT and systemic therapy are also included as options for the additional treatment of pelvic lymph node recurrence, para-aortic or common iliac lymph node invasion, and upper abdominal or peritoneal recurrences as shown in the algorithm (see *Additional Therapy* in the NCCN Guidelines for Endometrial Carcinoma).

Distant Metastases

For gross upper abdominal residual disease, more aggressive treatment for relapse is recommended, as outlined for disseminated metastases in *Therapy for Relapse* in the NCCN Guidelines for Endometrial Carcinoma. For resectable isolated metastases, consider surgical resection and/or EBRT, or ablative therapy. Ablative RT can be considered for 1 to 5 metastatic lesions if the primary cancer has been controlled (category 2B).[198] Providers can also consider systemic therapy (category 2B). Further recurrences or disease not amenable to local therapy are treated as disseminated metastases. Treatment options for disseminated metastases are systemic therapy with (or without) palliative EBRT. For persistent progression of disseminated metastases, best supportive care is recommended (see the NCCN Guidelines for Palliative Care available at https://www.nccn.org/professionals/physician_gls/pdf/palliative.pdf and http://emedicine.medscape.com/article/270646-overview).

Hormonal Therapy

The role of hormonal therapy in recurrent or metastatic cancer has been primarily evaluated in patients with endometrioid histologies only. Hormonal therapy is typically used for lower-grade endometrioid histologies, preferably in patients with small tumor volume or an indolent growth pace. Hormonal agents for treating metastatic disease include megestrol acetate with alternating tamoxifen, everolimus/letrozole combination, progestational agents (such as medroxyprogesterone acetate and megestrol acetate), aromatase inhibitors, tamoxifen alone, or fulvestrant.[312-317] 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.[318-321] Tamoxifen has a 20% response rate in disease that does not respond to standard progesterone therapy.[322,323] Tamoxifen has also been combined with progestational agents; however, a few patients had grade 4 thromboembolic events with this combination regimen.[314,315,324] In some patients, aromatase inhibitors (eg, anastrozole, letrozole) may be substituted for progestational agents or tamoxifen.[320,321,325,326]

Everolimus combined with letrozole is recommended for recurrent disease of endometrioid histology. In the phase 2 trial, in patients with progressive or recurrent endometrial cancer who had received up to two prior therapies, the clinical benefit rate and objective response rate among 35 evaluable patients was 40% and 32%, respectively.[327] In a following phase 2 study, patients (with or without prior chemotherapy) were treated either with the everolimus/letrozole combination or medroxyprogesterone acetate/tamoxifen regimen. Twenty-two percent of patients responded to the everolimus/letrozole therapy, while 25% showed a response with the medroxyprogesterone acetate/tamoxifen regimen.[328] Median PFS was 6 months for the everolimus/letrozole arm and 4 months for the hormonal therapy arm. Median OS was 31 months and 17 months for the everolimus/letrozole and medroxyprogesterone acetate/tamoxifen arms,

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respectively. Higher PFS was observed in both arms for patients who had not received any prior chemotherapy.

Other hormonal modalities have not been well-studied, and adjuvant therapy with hormonal agents has not been compared with cytotoxic agents.[320,329] 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 available at https://www.nccn.org/professionals/physician_gls/pdf/palliative.pdf) are appropriate for patients with disseminated metastatic recurrence who have a poor response to hormonal therapy and chemotherapy.

Systemic Therapy

Based on the current data, multiagent regimens are preferred for advanced disease, if tolerated. The NCCN Guidelines for Endometrial Carcinoma has updated the systemic therapy recommendation by including immunotherapy and chemotherapy-based combination regimens as preferred, first-line options for recurrent disease. The NRG-GY018, randomized, phase III trial evaluated the benefits of pembrolizumab/carboplatin/paclitaxel regimen over the carboplatin/paclitaxel regimen in 816 patients with stage III or IVA endometrial carcinoma with measurable disease, or stage IVB or recurrent disease of any histologic subtype, except for carcinosarcoma.[254] The patients who had received adjuvant therapy at least 12 months before were included. The patients were stratified based on the dMMR or MMR-proficient (pMMR) status of the tumors. The PFS was 74% versus 38% in the dMMR cohort for the triplet regimen versus the chemotherapy arm, respectively (HR, 0.30; 95% CI, 0.19–0.48; $P < .001$). In pMMR tumors, the median PFS was 13.1 months in pembrolizumab arm versus 8.7 months in the chemotherapy arm (HR, 0.54; 95% CI, 0.41–0.71; $P < .001$). Another phase III, randomized trial (RUBY) showed benefits of adding dostarlimab to the carboplatin/paclitaxel regimen in 494 patients with stage III or IV or recurrent disease, including all histologies.[253] At 24 months, PFS was 36.1% versus 18.1% (HR, 0.64; 95% CI, 0.51–0.80; $P < .001$) and OS was 71.3% versus 56% (HR, 0.64; 95% CI, 0.46–0.87) in the dostarlimab-based arm versus the chemotherapy arm, respectively. Significantly more benefits were observed in patient with dMMR/MSI-H tumors with PFS of 61.4% versus 15.7% (HR, 0.28; 95% CI, 0.16–0.50; $P < .001$) in the triplet versus the doublet therapy arms, respectively.

Based on the results from the NRG-GY018 and RUBY trials, the NCCN Panel has added pembrolizumab/carboplatin/paclitaxel (except for carcinosarcoma histology) and dostarlimab/ carboplatin/paclitaxel as Category 1, preferred, first-line therapy options for recurrent endometrial carcinoma.

Chemotherapy for endometrial cancer has been extensively studied.[330,331] Other multiagent regimens such as carboplatin/paclitaxel, carboplatin/docetaxel, and carboplatin/paclitaxel/bevacizumab are included as first-line therapy options for the recurrent disease setting.

Carboplatin and paclitaxel is an increasingly used regimen for advanced/metastatic or recurrent endometrial cancer; the response rate is about 40% to 62%, and OS is about 13 to 29 months.[332-335] A phase III trial (GOG 209) compared carboplatin and paclitaxel versus cisplatin, doxorubicin, paclitaxel, and filgrastim (granulocyte colony-stimulating factor).[332] Trial data show that oncologic outcomes are similar, but the toxicity and tolerability profile favor carboplatin/paclitaxel.[336] Thus, the carboplatin/paclitaxel regimen is a preferred, first-line option in the NCCN Guidelines. For patients in whom paclitaxel is contraindicated, docetaxel can be considered in combination with carboplatin.[337,338]

A phase II trial initially examined the addition of bevacizumab to carboplatin and paclitaxel among 15 patients with advanced or recurrent endometrial carcinoma.[339] Although this study was closed early due to the

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initiation of a national trial, a retrospective analysis was performed to include data from an additional 27 patients who had received carboplatin/paclitaxel/bevacizumab for advanced or recurrent disease.[340] Collective median PFS was 20 months with a median OS of 56 months. An overall response rate (ORR) of 82.8% was noted, with an 87.5% response rate among the subset of 8 patients who received this triplet regimen as second-line therapy after carboplatin/paclitaxel.[340] Another phase 2 randomized study showed that the carboplatin/paclitaxel/bevacizumab combination improved OS from 29.7 months to 40 months compared to the doublet regimen.[341] Another meta-analysis of three studies also concluded similar results where the triplet combination increased the OS and PFS at >12 months with an ORR of 76%.[342]

Other combination therapies such as cisplatin/doxorubicin, cisplatin/doxorubicin/paclitaxel, ifosfamide/paclitaxel (for carcinosarcoma), and cisplatin/ifosfamide (for carcinosarcoma) are added as subsequent-therapy options. A phase III randomized trial (GOG 177) compared 2 combination chemotherapy regimens in females with advanced/metastatic or recurrent endometrial carcinoma. The 273 participants were randomly assigned to 1) cisplatin/doxorubicin/paclitaxel; or 2) cisplatin/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.[343-345] These regimens are recommended as subsequent therapy options in the NCCN Guidelines, because most panel members feel that carboplatin/paclitaxel is a less toxic and preferred first-line option. The response rates with other multiagent chemotherapies have ranged from 31% to 81%, but with relatively short durations. The median survival for patients in such trials remains approximately 1 year.[330,331]

If multiagent chemotherapy regimens are contraindicated, then single-agent therapy options for recurrent disease include cisplatin, carboplatin, doxorubicin, liposomal doxorubicin, paclitaxel, albumin-bound paclitaxel, topotecan, temsirolimus, cabozantinib, and docetaxel (category 2B for docetaxel).[320,346-348321,349] When single agents are used as second-line treatment, responses range from 4% to 27%; paclitaxel is the most active in this setting.[349] Some oncologists have used liposomal doxorubicin, because it is less toxic than doxorubicin; the response rate of liposomal doxorubicin is 9.5%.[350] Docetaxel is recommended for use as a single agent; however, it is a category 2B recommendation because it is less active (7.7% response rate) than other agents.[351,352] Bevacizumab was shown to have a 13.5% response rate and OS rate of 10.5 months in a phase II trial for persistent or recurrent endometrial cancer.[353] Based on these studies, the NCCN Panel considers bevacizumab as appropriate single-agent biologic therapy for patients who have progressed on previous cytotoxic chemotherapy.[353-356]

Useful in Certain Circumstances, Biomarker-Directed Therapies

In the advanced endometrial cancer cohort (n = 24) of the phase Ib KEYNOTE-028 trial, durable antitumor responses were noted in a small subset of patients with programmed death ligand 1 (PD-L1)–positive tumors (3 partial response, 3 stable disease).[357] Studies have also indicated that dMMR tumors are sensitive to programmed death receptor-1 (PD-1) blockade.[358-360] Results were published from a study of patients with dMMR tumors of various disease sites. Among patients with dMMR endometrial carcinoma who received pembrolizumab (n = 15), the objective response rate was 52% and the disease control rate was 73% (3 complete response, 5 partial response, and 3 stable disease).[358] The phase 2 Keynote-158 trial further demonstrated robust antitumor activity of pembrolizumab with encouraging survival outcomes in patients with previously treated MSI-H/dMMR endometrial cancer and manageable adverse events.[361] Pembrolizumab is included as a treatment option for

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patients with recurrent endometrial cancer with MSI-H/dMMR disease that has progressed on or following prior treatment with a platinum-containing regimen in any setting including neoadjuvant or adjuvant therapy. The panel recommends that recurrent endometrial tumors be tested for MSI-H or dMMR if not done previously. The panel also recommends TMB-H testing if not previously done and has included the pembrolizumab option for patients with TMB-H tumors (>10 mut/Mb), as determined by a validated and/or FDA-approved test, who have progressed following prior treatment and who have no satisfactory alternative treatment options.[362]

Further studies have indicated that pembrolizumab monotherapy is less active in patients with microsatellite-stable or pMMR disease versus MSI-H/dMMR disease. Only 16% to 31% of endometrial cancers are MSI-H/dMMR.[357,363,364] The Keynote-146 phase 1/2 trial showed that the combination of pembrolizumab/lenvatinib had a promising antitumor response in patients with advanced endometrial cancer regardless of their tumor MSI status.[365] The Keynote-775 phase 3 trial randomly assigned 827 patients with pMMR (MSI-stable), previously treated advanced endometrial cancer to receive pembrolizumab/lenvatinib combination or chemotherapy (doxorubicin or paclitaxel).[366] The median PFS for the pembrolizumab/lenvatinib arm was 7.2 months versus 3.8 months for the chemotherapy arm (HR, 0.56; 95% CI, 0.47–0.66; $P < .001$). The median OS was also longer for the pembrolizumab/lenvatinib arm than for the chemotherapy arm (18.3 vs. 11.4 months; HR, 0.62; 95% CI, 0.51–0.75; $P < .001$). Based on these data, the NCCN Guidelines for Endometrial Carcinoma include lenvatinib/pembrolizumab as a category 1 option for pMMR tumors for patients who have received prior platinum-based therapy in any setting, including neoadjuvant and adjuvant therapy.

Other anti-PD-1 inhibitors, such as dostarlimab and nivolumab, have also shown antitumor activity against MSI-H tumors. Dostarlimab is being evaluated in the ongoing GARNET phase 1 trial for patients with advanced endometrial cancer with dMMR/MSI-H disease. The ORR after 16.3 months was 43.5% with a manageable safety profile. The NCCN Panel recommends dostarlimab for the treatment of patients with recurrent dMMR/MSI-H endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen in any setting including neoadjuvant or adjuvant therapy.

Nivolumab monotherapy has also demonstrated promising activity in endometrial carcinoma with dMMR tumors.[367] The PD-L1 inhibitor, avelumab, has shown an ORR of 26.7% in advanced endometrial cancer with dMMR tumor as monotherapy. Nivolumab and avelumab are included as biomarker-directed subsequent therapy options for recurrent dMMR/MSI-H endometrial tumors. The NCCN Panel also recommends larotrectinib or entrectinib for *NTRK* gene fusion-positive endometrial tumors as a category 2B subsequent therapy option.

Systemic Therapy Options for High-Risk Endometrial Histologies

The NCCN Panel notes that the systemic therapy options recommended in the NCCN Guidelines can be used for all carcinoma histologies. Among these, carboplatin/paclitaxel is included as a category 1, preferred option for patients with carcinosarcoma histology. A randomized phase II study examined the addition of trastuzumab to carboplatin/paclitaxel for patients with advanced or recurrent HER2/neu-positive uterine serous carcinoma.[368] Among patients with stage III/IV disease undergoing primary treatment (n = 41), median PFS was 17.9 months versus 9.3 months for the experimental and control arms, respectively ($P = .013$). PFS for patients with recurrent disease (n = 17) was 9.2 months versus 6.0 months ($P = .003$). The addition of trastuzumab appeared to improve PFS without increasing overall toxicity. The safety and tolerability of the trastuzumab combination was further evaluated in 61 patients in a recent phase 2 trial with PFS as the primary endpoint.[369] The triplet therapy regimen carboplatin/paclitaxel/trastuzumab is recommended by the NCCN

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Panel as a preferred option for HER2-positive uterine serous carcinoma or HER2-positive carcinosarcoma as: 1) primary therapy for stage III/IV disease; or 2) a first-line option for recurrent disease. The NCCN Panel has designated the regimen a category 2B option for HER2-positive carcinosarcoma in both disease settings. This triplet regimen is recommended for patients who have not received any prior trastuzumab therapy. In subsequent therapy, the NCCN Panel has included ifosfamide, ifosfamide/paclitaxel, and ifosfamide/cisplatin as options for carcinosarcoma treatment only. For treating carcinosarcoma, ifosfamide was historically considered the most active single agent.[370-372] A phase III trial for advanced carcinosarcoma showed that the combination of ifosfamide and paclitaxel increased survival and was less toxic than the previously used cisplatin/ifosfamide regimen.[370,373] OS was 13.5 months with ifosfamide/paclitaxel versus 8.4 months with ifosfamide alone.[299,370]

Radiotherapy Principles

RT has been a widely used modality in the treatment of patients with endometrial cancer; it clearly improves locoregional control. *Tumor-directed RT* refers to RT directed at sites of known or suspected tumor involvement and may include EBRT and/or vaginal brachytherapy.[211] Imaging is required to assess locoregional extent and to rule out distant metastases before administration of RT. In general, EBRT is directed to the pelvis with or without the para-aortic region. Brachytherapy can be delivered: 1) to an intact uterus, either preoperatively or definitely; 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. The panel notes that chemoradiation can be given concurrently or sequentially. 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,[374] studies have focused on subtle effects on quality of life (eg, diarrhea, bowel symptoms) that deserve further investigation.[229,231,375] In the PORTEC-2 trial, vaginal brachytherapy was associated with better quality of life when compared with EBRT without a significant detriment to outcome.[229] 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. Individuals assigned female at birth can use vaginal dilators to prevent or treat vaginal stenosis. Dilator use can start 2 to 4 weeks after RT is completed and can be used indefinitely (https://www.mskcc.org/cancer-care/patient-education/vaginal-health).

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).[43,49] These recommendations recognize that the value of intensive surveillance has not been demonstrated in this disease; therefore, ancillary testing is not recommended.[376,377]

Patients with clinical stage I and stage II endometrial cancer have a recurrence rate of approximately 15%;[377-380] 50% to 70% of these patients are symptomatic. For most patients, disease recurs within 3 years of initial treatment. Because most recurrences are symptomatic, all patients should receive verbal and written information regarding the symptoms of potential recurrence.[377] 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.

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History and physical exam is recommended every 3 to 6 months for the first 2 to 3 years, and then every 6 to 12 months thereafter for up to the fifth year, then annually. For non-fertility sparing treatment, imaging should be guided by patient symptoms, risk assessment, and clinical concern for recurrent or metastatic disease. The indications of metastatic disease may include abnormal physical exam finding, bulky uterine tumor, vaginal or extrauterine involvement, delay in presentation or treatment, and abdominal or pulmonary symptoms. For fertility-sparing treatment, the panel recommends repeat pelvic MRI (preferred) for patients with persistent endometrial carcinoma after 6 to 9 months of failed medical therapy, especially if considering further fertility-sparing approaches. Abdominal/pelvic MRI and/or chest CT is recommended based on symptoms or physical exam findings. Whole body FDG-PET/CT and/or abdomen/pelvis MRI can be considered in select patients as clinically indicated.

In the absence of recurrence, post-treatment surveillance provides psychosocial reassurance and improves quality of life for patients and their families. Health maintenance has been incorporated into the follow-up schedule (eg, blood pressure determination, breast examination, mammography as clinically indicated, stool guaiac test, immunizations). Patients should receive counseling and education regarding lifestyle, obesity, exercise, smoking cessation, sexual health, nutrition, and potential late or long-term effects of treatment (see the NCCN Guidelines for Survivorship (available at https://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf), the NCCN Guidelines for Smoking Cessation (available at https://www.nccn.org/professionals/physician_gls/pdf/smoking.pdf), and http://www.cancer.org/treatment/survivorshipduringandaftertreatment/index).[375,381-383] Other health problems that often coexist in patients with endometrial cancer can also be evaluated during follow-up.

Given the lack of prospective studies regarding the optimal frequency of post-treatment follow-up, the NCCN Panel believes that the algorithm represents a reasonable surveillance scheme. The use of vaginal cytology is no longer recommended for patients who are asymptomatic consistent with the SGO guidelines.[376,377,380,384] 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.[376,385] A multi-institutional review examined the utility of various surveillance methods in 254 patients with high-grade disease, revealing that symptoms led to the detection of the most recurrences (56%), followed by physical exam (18%), surveillance CT (15%), CA-125 (10%), and vaginal cytology (1%).[386]

Hormone 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 patients who are postmenopausal, estrogen therapy was believed to reduce or reverse some of these signs and symptoms. However, patients who have had BSO for endometrial adenocarcinoma have usually been denied estrogen therapy for fear of inducing a higher relapse rate, because this cancer has historically been considered an estrogen-linked malignancy.[387,388] As such, estrogen therapy for such patients remains controversial.

However, it has never been proven that relapse rates are higher in patients with endometrial cancer who receive estrogen therapy after hysterectomy. Several retrospective trials of estrogen therapy after treatment of early-stage endometrial cancer have shown no increase in tumor recurrence or cancer-related deaths.[389-391] In females with stage I to II endometrial cancer who had hysterectomy, a randomized trial of estrogen therapy versus placebo did not find an increased rate of

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recurrence or new malignancy; the median follow-up was 35.7 months.[392] However, estrogen trials in postmenopausal females without a history of malignancy have demonstrated a significantly increased risk for breast cancer.[393]

Initially, the Women's Health Initiative (WHI) Estrogen-Alone Trial in females who had hysterectomy (n = 10,739) reported that the risk of breast cancer and cardiovascular disease (eg, stroke) were increased and that estrogen therapy was of concern; thus, the trial was stopped.[394] 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 patients (<60 years) who have had hysterectomy.[395]

The NCCN Panel agrees that estrogen 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.[396,397] If adjuvant treatment is carried out, there should be a 6- to 12-month waiting period before initiation of hormone therapy, and participation in clinical trials is strongly encouraged. Selective estrogen-receptor modulators (SERMs) may prove to be attractive options for hormone therapy.[398,399] Long-term comparisons between conjugated estrogens and SERMs for hormone therapy are needed. Non-hormonal therapy may be considered in patients who are deemed poor candidates for hormone therapy (eg, people who smoke, those with a history of breast cancer, those with a history of multiple strokes).[400,401]

Uterine Sarcomas

Overview

Uterine sarcomas are uncommon malignant mesenchymal tumors, accounting for approximately 3% of all uterine cancers, and include high or low-grade ESS, UUS, uLMS, and others such as PEComas (see *Initial Clinical Findings* in the NCCN Guidelines for Uterine Sarcoma).[402] According to a 2012 systematic review of data from 1970 to 2011, uLMS was the most common subtype (63%), followed by ESS (21%) and less common subtypes such as UUS.[403] Even rarer subtypes of malignant mesenchymal tumors that can occur in the uterus include adenosarcoma, rhabdomyosarcoma (RMS), and PEComa.[404] Carcinosarcomas were previously categorized and included in the sarcoma treatment algorithms until the mid-2000s, but are now considered and treated as high-grade epithelial tumors (carcinomas).[273] Screening for Lynch syndrome is not usually done for patients with malignant mesenchymal tumors.

Pathology and Molecular Analysis

Expert gynecologic pathology review is recommended for the assessment and histologic differentiation of uterine sarcomas including uLMS, UUS, ESS, and adenosarcoma.[83] The pathologic assessment of the uterus should include hysterectomy type, specimen integrity (intact, opened, morcellated, or other), tumor size, myometrial invasion (for adenosarcoma only), histologic type, grade (for adenosarcoma only), and LVSI. The assessment should also include other tissues/organ involvement (fallopian tubes, ovaries, vagina, parametrium, omentum, or other). Peritoneal/ascitic fluid cytology should also be done. If the lymph nodes are resected, the level of nodal involvement and the number of lymph nodes with metastasis should be determined. Routine node dissection is not required in the absence of clinical suspicion of nodal involvement.

Recent advances have expanded our understanding of the molecular features of these tumors, leading to the identification of genetic signatures that characterize some of the uterine sarcoma subtypes. Historically, mesenchymal tumors were primarily diagnosed using histopathologic criteria, and the results of molecular studies were not used in routine pathologic evaluation. However, given the overlap in histopathologic features of these tumors, molecular analysis (eg, identification of

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characteristic translocations) can help classify difficult cases and provide future therapeutic targets. The panel notes that comprehensive genomic profiling in the setting of metastatic disease with a validated and/or FDA-approved assay is informative for predicting rare pan-tumor–targeted therapy opportunities. The panel recommends testing of at least NTRK, MSI, and TMB proteins. Since the molecular profiling is informative in many mesenchymal malignancies for accurate classification,[405] the NCCN Guidelines for Uterine Neoplasms include a table containing information on histologic and molecular findings, specific biomarkers, relevant confirmatory molecular tests, prognostic features, and other clinically useful information to help clinicians differentiate between and classify uterine sarcoma subtypes. This information is intended to complement histopathologic testing to improve differential diagnosis of relatively rare uterine sarcoma subtypes and provide safer, more effective care for patients with the disease. The panel notes that this information is not exhaustive and intends to update these recommendations as more data becomes available.

Low-Grade and High-Grade Endometrial Stromal Sarcoma (ESS)

ESSs are the second most common mesenchymal tumors of the uterus. ESSs are composed of cells resembling the endometrial stroma in the proliferative phase.[404,406] LGESSs have distinct fingerlike patterns of myometrial invasion, and LVSI is usually present. ESS displays a heterogenous mix of morphologic and genetic features. A significant proportion of these tumors (ie, up to half) harbor *JAZF1*, *PHF1*, or *EPC1* gene fusions and present as earlier-stage tumors.[407-410] The panel notes that diagnosis of low-grade ESS can be confirmed by identifying any low-grade ESS-associated gene fusion by using FISH and/or targeted RNA sequencing, though the lack of rearrangement or fusion does not exclude the diagnosis. It is worth noting that in rare instances, low-grade ESS can transform into high-grade ESS (either at the time of primary diagnosis or recurrence), which will require histopathologic and molecular (eg, *JAZF1* or *PHF1* translocation) confirmation.

A higher-grade and more aggressively behaving ESS variant with a unique genetic rearrangement *YWHAE*::*FAM22A/B*, also known as *YWHAE*::*NUTM2A/B*, has been identified.[411,412] This subtype is known as high-grade ESS. Another subtype of high-grade ESS harboring *BCOR* is either in the form of a ZC3H7B::*BCOR* fusion or an internal tandem duplication. Both *ZC3H7B*::*BCOR* fusion-positive and *BCOR* internal tandem duplication high-grade ESS have spindle and/or round cells embedded in myxoid matrix, and demonstrate strong and diffuse positivity for cyclin D1 and variable positivity for CD10, ER, and PR.[413] IHC testing for CD10, cyclin D1, and *BCOR* and, in some cases, molecular analysis of *BCOR* alterations, may help differentiate between *BCOR*-altered high-grade ESS and myxoid uterine leiomyosarcoma (myxoid ULMS) due to overlapping morphologic features. It is currently unclear whether specific types of high-grade ESS (ie, *YWHAE*-altered or *BCOR*-altered) differ in prognosis and/or response to chemotherapy.

These findings provided support for subdividing ESS into distinct low- and high-grade entities based on histopathology, clinical behavior, and patient outcomes. The updated 2014 edition of the WHO *Classification of Tumors of Female Reproductive Organs* recognizes low-grade ESS and high-grade ESS as distinct histopathologic entities.[414] The 5th edition on *Female Genital Tumors* in 2020 also recognizes BCOR-altered sarcomas as a distinct subtype of high-grade ESS.[415]

Undifferentiated Uterine Sarcoma (UUS)

UUSs are a group of high-grade/aggressive sarcomas characterized by infiltrative sheets of epithelioid and/or spindle cells that may be uniform or pleomorphic. As a class, it is a heterogenous group of high-grade mesenchymal neoplasms of the uterus that fail to meet the diagnostic

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threshold for other characterized uterine mesenchymal neoplasms. As such, UUS is usually reserved as a diagnosis of exclusion, after other defined uterine mesenchymal neoplasms have been excluded using a multiprong approach that often requires a combination of extensive IHC panel and next-generation sequencing (NGS) molecular analysis. For example, high-grade ESS is often misdiagnosed as UUS due to a shared lack of smooth muscle differentiation.[416] The panel notes that molecular testing for *BCOR* alterations, which can occur in high-grade ESS as noted above, is useful to exclude a high-grade ESS diagnosis before rendering a diagnosis of UUS.

A subset of UUSs called SMARCA4-deficient uterine sarcomas (SDUSs) have distinctive morphology (eg, phyllodiform architecture) along with biallelic inactivation of *SMARCA4* that results in loss of *SMARCA4*/*BRG1* expression. These tumors occur in younger patients and may be associated with very aggressive clinical behavior.[417] The panel recommends analysis of *SMARCA4*/*BRG1* by IHC and/or *SMARCA4* by DNA sequencing to confirm a diagnosis of SDUS with otherwise appropriate morphologic and immunophenotypic features. However, loss of *SMARCA4*/*BRG1* alone does not constitute a diagnosis of SDUS, and other aggressive malignancies such as undifferentiated endometrial carcinoma may show loss of expression of this protein.

Uterine Leiomyosarcoma (uLMS)

uLMS are usually of the spindle cell (conventional) type, but less common variants with myxoid or epithelioid morphology also exist. Although morphology differs between subtypes, all express varying degrees of the smooth muscle markers, including desmin, smooth muscle actin (SMA), and caldesmon. The panel recommends an IHC panel including desmin and SMA to support a uLMS diagnosis, particularly if myxoid or epithelioid uLMS is suspected.

Myxoid uLMSs may appear histologically similar to *BCOR*-altered HGESSs or inflammatory myofibroblastic tumor (IMT). The panel recommends cyclin D1 and/or *BCOR* IHC to help exclude an HGESS diagnosis, as the latter is often overexpressed in HGESS. A subset (25%) of myxoid ULMSs also harbor *PLAG1* fusions. Therefore, a myxoid ULMS diagnosis may be supported by positive desmin and SMA IHC along with *PLAG1* rearrangement by FISH assay or RNA sequencing. One differential diagnosis that must be considered for epithelioid uLMS is PEComa, given the observed similarities in morphology and IHC for smooth muscle markers. IHC testing for HMB45 and melanA may be performed if a diagnosis of PEComa is being considered, with HMB45 being fairly sensitive and melanA being specific for PEComa compared with uLMS. However, it is recognized that uterine mesenchymal tumors with myomelanocytic differentiation can still be challenging to classify solely by IHC. A study examining this specific group of diagnostically challenging tumors supported the use of genomic profiling to aid in their classification.[418]

Uterine Tumor Resembling Ovarian Sex Cord Tumor (UTROSCT)

UTROSCTs are very rare tumors with sex cord-like differentiation, but without a stromal component as observed in ESSs. Most of these tumors harbor either *ESR1* or *GREB1* fusions.[419,420] The panel recommends an IHC panel that includes sex cord markers (eg, inhibin, calretinin, SF1, FOXL2); UTROSCTs are often positive for a broad range of biomarkers. In some cases, FISH or RNA sequencing for *ESR1* or *GREB1* fusions may be helpful to confirm the diagnosis. Approximately 25% of these tumors are malignant; the panel notes that the presence of necrosis, high mitotic index, and *GREB1* fusions may be associated with malignant behavior.

Rhabdomyosarcoma

Uterine RMSs are an aggressive, heterogeneous group of tumors that are extremely rare in adult patients. Subtypes include alveolar, embryonal,

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and pleiomorphic; all express myogenic biomarkers (eg, myogenin and MyoD1).[421] Therefore, the panel notes that diffuse expression of myogenic biomarkers by IHC can help confirm a uterine RMS diagnosis. Prognosis differs between subtypes, with embryonal RMS having the best prognosis of the 3 subtypes. Molecular alterations also differ between subtypes. *FOXO1* fusions are found in alveolar RMS, whereas *PIK3CA* and *TP53* mutations are found in pleomorphic RMS. *DICER1* mutations are present in up to 95% of embryonal RMS. The embryonal subtype also is known to harbor *FGFR4/RAS/AKT* pathway mutations.[422] The panel notes that extensive sampling should be performed to exclude epithelial components and diagnoses of carcinosarcoma and adenosarcoma with heterologous rhabdomyosarcomatous differentiation. The panel recommends FISH and/or RNA sequencing for *FOXO1* to help confirm cases of suspected uterine alveolar RMS.

Staging and Treatment

When evaluating suspected uterine sarcomas, biopsy may be helpful but is less sensitive than for endometrial cancers. The diagnosis of ESS and uLMS is often made after hysterectomy. The previous FIGO/AJCC staging systems for endometrial cancer were not appropriate for staging ESS and uLMS; patients were often upstaged when using the older AJCC staging system.[423] A new staging system for ESS and uLMS from FIGO/AJCC took effect in 2009 accounting for the differences between uterine sarcomas and endometrial cancers.[63,424]

Confirmation of the type of mesenchymal malignancy by expert pathology review is critical. In addition, initial evaluation should include imaging of the chest/abdomen/pelvis by CT or combination MRI/CT. It is important to determine if the sarcoma is confined to the uterus or if extrauterine disease is present. Pelvic MRI can be used to evaluate local tumor extension or residual abnormality in cases where the uterus or adnexa were not resected or incompletely resected (ie, supracervical hysterectomy, myomectomy, possible tumor fragmentation, intraperitoneal morcellation). Neck/chest/abdomen/pelvis/groin FDG-PET/CT may be used to clarify ambiguous findings. If medically operable, then hysterectomy with (or without) BSO and en bloc resection of tumor is the initial treatment of choice for uterine sarcomas (see *Primary Treatment* in the NCCN Guidelines for Uterine Sarcoma).[425]

The panel recommends ER/PR testing for LMS, ESS, and adenosarcoma to guide decisions regarding management of the ovaries, particularly in young patients who are premenopausal. In general, BSO is favored for low-grade ESS or tumors expressing ER/PR, although management of the ovaries may be individualized in patients of reproductive-age.[426] A systemic review and meta-analysis of 786 patients reported 46.8% of tumor recurrence rate in ovarian preservation group versus 24.2% recurrence in the BSO group.[427] In another multicenter retrospective study, the PFS for patients who underwent BSO versus ovarian preservation as 38 versus 11 months (P = .071).[428]

Uterine sarcoma should be removed en bloc to optimize outcomes; intraperitoneal morcellation is contraindicated.[171,174] For incidental diagnoses of uterine sarcoma after hysterectomy, or in the case of a fragmented specimen, imaging is recommended and re-exploration for surgical resection can be considered. The ovaries may be preserved in selected patients with early-stage uLMS who wish to retain hormonal function.[429] Additional surgical resection should be individualized based on clinical scenarios and intraoperative findings. Lymphadenectomy is controversial.[2,404,429-432] High-grade uterine sarcomas tend to show hematogenous metastases to the lungs; lymph node metastases are uncommon.

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

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Low-Grade Endometrial Stromal Sarcoma

Recommended adjuvant therapy options for stage I ESS include BSO or observation (if menopausal or prior BSO). BSO with (or without) anti-estrogen hormone therapy is recommended for stages II to IV ESS. Adjuvant EBRT may be added for stage II, III, or IVA (category 2B). Palliative EBRT may be added for patients with stage IVB disease.[404,433,434] Anti-estrogen hormone therapy is also recommended for ESSs that have recurred or are unresectable (see *Therapy for Relapse* in the NCCN Guidelines for Uterine Sarcoma).[435] Given the histologic similarities between low-grade ESS and uterine adenosarcoma, the panel recommends similar adjuvant therapy options for adenosarcoma as provided for low-grade ESS. For patients with uterine adenosarcoma with sarcomatous overgrowth (SO) in advanced stages, the panel recommends BSO with a consideration of systemic therapy and EBRT. EBRT is palliative for stage IVB disease.

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.[436] Adjuvant radiotherapy in ESS has been demonstrated to reduce local recurrence rates but again with limited effect on survival.[437,438] Because of concerns about radiation exposure, frequent routine surveillance imaging is no longer recommended for patients who are young and asymptomatic after primary therapy for ESS.[439]

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

Typical hormone therapy for low-grade ESS or adenosarcoma without SO or ER/PR-positive uterine sarcoma includes aromatase inhibitors[440] (preferred for low-grade ESS or adenosarcoma without SO), fulvestrant, megestrol acetate (category 2B for ER/PR-positive uterine sarcoma), or medroxyprogesterone acetate (category 2B for ER/PR-positive uterine sarcoma). Gonadotropin-releasing hormone [GnRH] analogs are also included as a category 2B option.[404,429,435] For ER/PR-positive uterine sarcomas, the anti-estrogen hormone therapy should preferably be considered for patients with small tumor volume or an indolent growth pace.

High-Grade Endometrial Stromal Sarcoma, Leiomyosarcoma, Undifferentiated Uterine Sarcoma, and PEComa

The role of adjuvant radiotherapy in nonmetastatic disease is controversial. Most available data are retrospective except for a phase III randomized trial.[441] Most retrospective studies of adjuvant RT suggest an improvement in local pelvic control but no appreciable or consistent improvement in OS, given the propensity of metastatic extrapelvic disease as a site of first or eventual recurrence.[442-445] In many series, the patients treated with adjuvant radiation presumably had higher-risk factors (eg, larger tumors, deeper myometrial invasion), thus biasing the data against radiotherapy. However, a phase III randomized trial in stage I and II uterine sarcomas reported that postoperative pelvic radiotherapy did not improve OS for uLMS when compared with observation.[441] Therefore, routine postoperative RT is not recommended for stage I patients with uLMS and UUS.[433] If used in more advanced stages, adjuvant RT needs to be individualized and based on careful analysis of surgical pathologic findings.

The role of adjuvant systemic therapy is also poorly defined; however, adjuvant systemic therapy has been used because of the high risk of systemic relapse. Given the uncertainties regarding any adjuvant treatment for stage I high-grade ESS, uLMS, USS, and other sarcomas (such as PEComa) after complete resection, observation is the only option. A systemic review and meta-analysis concluded that adjuvant

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chemotherapy in early-stage uLMS was not beneficial in reducing locoregional and distant recurrences over observation.[446] Because of the increased risk profile in patients with completely resected stage II and III tumors, the panel believes that it is appropriate to consider adjuvant systemic therapy and/or EBRT. Observation can be considered for patients with completely resected tumors with negative margins. (see *Additional Therapy* in the NCCN Guidelines for Uterine Sarcoma).[447] In patients with stage IV incompletely resected or metastatic disease, systemic therapy and/or EBRT is generally recommended. For stage IVB disease, systemic therapy with an option of palliative EBRT is recommended.

Treatment of Recurrent or Metastatic Disease

The recurrence rate is high in uLMS (50%–70%).[2] The guidelines provide recommendations based on tumor resectability and patients' prior RT exposure (see *Therapy for Relapse* in the NCCN Guidelines for Uterine Sarcoma). Treatment recommendations are made according to the site and nature of the recurrence.

Local recurrences are classified as recurrence in the vagina/pelvis with imaging that is negative for distant metastatic disease. Surgical and RT treatment pathways are provided. The surgical pathway for treating local recurrence in patients without prior RT exposure includes the option of IORT (category 3 for IORT). Preoperative EBRT with (or without) systemic therapy are also options to consider. For residual disease following surgery in patients without preoperative RT, EBRT with (or without) brachytherapy with (or without) systemic therapy can be considered. Primary RT offers an alternative pathway for treating localized recurrence in patients without prior exposure. EBRT should be given along with the option of brachytherapy and systemic therapy. For both the surgical and RT treatment pathways, further adjuvant systemic therapy should be considered after initial treatment.

Patients with local recurrence who have had prior RT exposure can be treated with: 1) surgery with the option of IORT with (or without) systemic therapy (category 3 for IORT); 2) systemic therapy; or 3) selected reirradiation with EBRT and/or brachytherapy. A retrospective analysis of patients with ESS suggested that cytoreductive resection improved OS in patients with recurrent lesions. [448]

Systemic therapy with (or without) palliative EBRT or best supportive care is recommended for metastatic disease.[449] For patients with isolated metastases that is resectable, surgical resection or other ablative therapy (eg, radiofrequency ablation, SBRT) may be appropriate. Patients with uLMS who experience longer time to recurrence may have improved survival outcomes following metastasectomy.[450] Pre- or postoperative EBRT and/or systemic therapy can be considered. Observation may be an option in select, completely resected cases with no evidence of disease on postoperative imaging. Systemic therapy and/or local therapy (tumor-directed EBRT or local ablative therapy) are reasonable options for patients with unresectable isolated metastases (see *Therapy for Relapse* in the NCCN Guidelines for Uterine Sarcoma).[451-454] For recurrent low-grade ESS, the first choice of systemic therapy is anti-estrogen hormone therapy.

Systemic Therapy for Advanced, Metastatic/Recurrent or Inoperable Disease

If systemic therapy is used for treating high-grade uterine sarcoma, preferred first-line therapy options include single-agent doxorubicin, gemcitabine/docetaxel,[455-460] doxorubicin/ifosfamide, and doxorubicin/dacarbazine (see *Systemic Therapy* in the NCCN Guidelines for Uterine Sarcoma).[404,406,449] Doxorubicin is an active single agent for uLMS and is less toxic than combination regimens.[404,449]

The LMS-04 phase 3 randomized trial with 150 patients (67 with uLMS and 83 with soft-tissue LMS) tested the benefits of doxorubicin/trabectedin

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versus doxorubicin alone as first-line therapy. Median PFS for the combination arm was longer than for the doxorubicin arm (12.2 months vs. 6.2 months, respectively; HR, 0.41; 95% CI, 0.29–0.58; $P < .0001$). Based on these findings, the panel recommends doxorubicin/trabectedin for patients with LMS.

For second-line or subsequent therapy, trabectedin is included as a preferred option for unresectable or metastatic uLMS that has been treated with a prior anthracycline-containing regimen. Data indicate that trabectedin may be useful in patients who have exhausted standard chemotherapy.[461-464] The phase III data revealed a 2.7-month PFS benefit versus dacarbazine in metastatic liposarcoma or leiomyosarcoma that progressed after anthracycline-based therapy.[465] Follow-up subgroup analysis of patients with uLMS (n = 232) revealed PFS of 4.0 months for trabectedin versus 1.5 months for dacarbazine (HR, 0.57; 95% CI, 0.41–0.81; $P = .0012$).[466] However, OS did not differ significantly between the treatment arms (13.4 months for trabectedin vs. 12.9 months for dacarbazine; HR, 0.89; 95% CI, 0.65–1.24; $P = .51$). Other recommended regimens include gemcitabine/dacarbazine, gemcitabine/vinorelbine, dacarbazine, gemcitabine, epirubicin, ifosfamide, liposomal doxorubicin, pazopanib, temozolomide, and eribulin (category 2B).[372,452,455,456,467-483]

Eribulin is included based on results from a phase III trial comparing the survival benefit of eribulin and dacarbazine in 452 patients with advanced leiomyosarcoma or adipocytic sarcoma.[484] Median OS was 13.5 and 11.5 months for eribulin and dacarbazine, respectively (HR, 0.77; 95% CI, 0.62–0.95; $P = .017$). Eribulin was designated as category 2B upon panel review of the mature trial data.

For first-line biomarker-directed therapies, the panel recently added crizotinib, ceritinib, brigatinib, lorlatinib, and alectinib for anaplastic lymphoma kinase (ALK) fusion-positive IMTs for uterine sarcomas based on the literature evidence derived from non-small cell lung cancer.[485-488]

The panel also recommends larotrectinib or entrectinib for *NTRK* gene fusion-positive tumors. For PEComa, albumin-bound sirolimus is recommended as a first-line therapy option and sirolimus, everolimus, temsirolimus are recommended as second-line or subsequent therapy options. Pembrolizumab has been added for the treatment of patients with unresectable or metastatic TMB-H tumors that have progressed following prior treatment and have no satisfactory alternative treatment options. Olaparib, rucaparib, and niraparib are included as second-line/subsequent therapy options for *BRCA2*-altered uLMS.[489]

Post-Treatment Surveillance

The recommended post-treatment surveillance protocol for uterine sarcoma is depicted in the algorithm (see *Surveillance* in the NCCN Guidelines for Uterine Sarcoma). History and physical exam is recommended every 3 to 4 months for the first 2 to 3 years, and then every 6 to 12 months thereafter. Imaging surveillance should include chest/abdominal/pelvic CT every 3 to 6 months for the first 3 years and then every 6 to 12 months for the next 2 years. Depending on histology, grade, and initial stage, annual to biannual imaging can be considered for an additional 5 years. Follow-up imaging may be as frequent as every 3 months or change based on histology grade and/or stage of tumor. Abdominal/pelvic MRI and chest CT without contrast is optional. Neck/chest/abdomen/pelvis/groin FDG-PET/CT can be considered if metastasis is suspected in select patients. Additional imaging should be based on symptomatology and clinical concern for metastatic disease.

Patients should receive education regarding the symptoms of recurrent disease. Patients with bleeding (vaginal, bladder, or rectal), decreased appetite, weight loss, pain (in the pelvis, abdomen, hip, or back), cough, shortness of breath, and swelling (in the abdomen or legs) should seek prompt evaluation and not delay until the next scheduled appointment. Imaging may be helpful in the detection of recurrence. Patients should be

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educated regarding healthy lifestyle choices, obesity, exercise, smoking cessation, nutrition, and potential long-term and late effects of treatment. See *Principles of Gynecologic Survivorship* within the NCCN Guidelines for Uterine Neoplasms (also see the NCCN Guidelines for Survivorship, NCCN Guidelines for Smoking Cessation, and http://www.cancer.org/treatment/survivorshipduringandaftertreatment/index).[381-383] The panel also recommends patient education regarding sexual health, vaginal dilator use, and vaginal lubricants or moisturizers.

Drug Reactions

Virtually all drugs have the potential to cause adverse hypersensitivity reactions, either during or after the infusion.[490] 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.[491-493] In addition, patients can have mild allergic reactions or severe infusion reactions. Infusion reactions are more common with paclitaxel.[494] Allergic reactions (ie, true drug allergies) are more common with platinum agents (ie, carboplatin, cisplatin).[494,495]

Management of drug reactions is discussed in the NCCN Guidelines for Ovarian Cancer.[494] 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.[496-498] Patients must be desensitized with each infusion if they previously had a reaction. Almost all patients can be desensitized (about 90%).[490] To maximize safety, it is prudent to desensitize patients in the intensive care unit.[490]

Gynecologic Survivorship

Treatment for gynecologic cancer typically involves surgery, chemotherapy, hormone therapy, RT, and/or immunotherapy, which may cause acute, short-term, and long-term toxicities. Surgical approaches may be extensive and cause adhesions to form, which in turn may cause pain and contribute to the development of small bowel obstruction, urinary or gastrointestinal complications (eg, incontinence, diarrhea), pelvic floor dysfunction (manifested by a variety of urinary, bowel, and/or sexual effects), and lymphedema. Chemotherapy agents vary, though commonly used regimens may pose a significant risk of neurotoxicity, cardiac toxicity, cognitive dysfunction, and the development of hematologic cancers. Long-term estrogen deprivation may cause symptoms such as hot flashes, vaginal dryness, and bone loss. RT may cause long-term complications (eg, fibrosis, stenosis, vulvovaginal atrophy) and may predispose patients to subsequent cancers of the skin, subcutaneous tissue, and/or underlying organs that are proximal to the radiation field. Use of immunotherapy agents in gynecologic cancers is emerging, and to date, long-term effects of these treatments are unknown.

Following completion of treatment, all gynecologic cancer survivors should receive regular general medical care that focuses on managing chronic diseases (eg, depression, diabetes, hypertension), monitoring cardiovascular risk factors, receiving recommended vaccinations, and encouraging adoption of a healthy lifestyle (eg, promoting exercise, smoking cessation). In order to assess the late and long-term effects of gynecologic cancers, clinicians should comprehensively document the patient's history, including prior treatment history, and conduct a thorough physical examination followed by necessary imaging and/or laboratory testing. As most treatments for gynecologic cancers will cause sexual

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dysfunction, early menopause, and infertility, special attention to the resultant medical and psychosocial implications is needed. All patients, whether sexually active or not, should be asked about genitourinary symptoms, including vulvovaginal dryness. Post-radiation use of vaginal dilators and moisturizers is recommended. Psychosocial effects may include psychological (eg, depression, anxiety, fear of recurrence, altered body image), financial (eg, return to work, insurance concerns), and interpersonal (eg, relationships, sexuality, intimacy). Patients should be referred to appropriate specialty providers (eg, physical therapy, pelvic floor therapy, sexual therapy, psychotherapy) as needed, based on prior treatment history and assessed risk of developing late effects and/or existing concerns. Communication and coordination with all clinicians involved in the care of survivors, including primary care clinicians, is critical. Providing survivors with a summary of their treatment and recommendations for follow-up is also recommended. To this end, the SGO has developed templates for gynecologic cancer-specific Survivorship Care Plans to aid survivors and their clinicians in summarizing cancer history, treatments received, possible side effects, and recommended follow-up.

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