National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Uterine Neoplasms

Version 1.2022 — November 4, 2021

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Uterine Neoplasms

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

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 1.2022 of the NCCN Guidelines for Uterine Neoplasms from Version 4.2021 include:

General

- Separate pathways were created for the following high-risk endometrial carcinoma histologies: Serous carcinoma (ENDO-11), Clear cell carcinoma (ENDO-12), or Undifferentiated/dedifferentiated carcinoma (ENDO-13) and Carcinosarcoma (ENDO-14). Previously these histologies were on the same page and treated similarly.
- The Uterine Sarcoma algorithms were extensively revised to include recommendations and new pathways for the treatment of adenosarcoma ± sarcomatous overgrowth (SO). (UN-1, UTSARC-1 through UTSARC-6)
- The AJCC Staging tables were updated to include staging for adenosarcoma (ST-4)

Uterine Neoplasms

UN-1

- Initial evaluation; 5th bullet revised: ~~Consider genetic evaluation~~ *Recommend genetic evaluation of tumor and evaluation for inherited cancer risk*.
- New pathway was added for "High-risk endometrial carcinoma histology".
- Under "Malignant mesenchymal (sarcoma)" first bullet revised: Low-grade endometrial stromal sarcoma (ESS) *or adenosarcoma*
- Footnote b revised: "... If there is suspicion of ~~malignant mesenchymal sarcoma,~~ *malignancy*, fragmentation/morcellation should be avoided."

Endometrial Carcinoma

ENDO-1 Disease limited to the uterus

- Not suitable for primary surgery; Primary Treatment: Revised, Consider hormone therapy *(including progestin IUD)* in select patients.

ENDO-4 Surgically staged: Stage I

- Adjuvant Treatment
  - FIGO Stage IA; G3: Consider EBRT if ~~high-intermediate risk (HIR)~~ *either age ≥70 y or LVSI* (category 2B)
  - FIGO Stage IB; G1: Consider observation if *age <60 y and* no *LVSI* ~~other adverse risk factors~~
  - FIGO Stage IB, G2:
    - ◊ Consider EBRT if ~~HIR~~ ≥60 y and/or LVSI
    - ◊ Consider observation if *age <60 y and* no *LVSI* ~~no other adverse risk factors~~

ENDO-4 Surgically staged: Stage I (continued)

- The following footnotes were removed:
  - If HIR per GOG 249: age 50–69 y with two risk factors or age <50 y with three risk factors, or age ≥70 y with one risk factor. Risk factors include grade 2 or 3, depth of invasion to outer half, and LVSI.
  - Potential adverse risk factors: age ≥60 y, depth of invasion, and/or LVSI. See Discussion for additional information on adverse risk factors.
  - Risk factors that would lead to EBRT ± systemic therapy are: age, LVSI, and depth of myoinvasion. Risk factors are continuous variables. Risk of recurrence is higher with older age (especially >60 y), extensive LVSI, and deeper myoinvasion (>50%). Also, when there are more risk factors present, the risk of recurrence is higher. See Systemic Therapy for Endometrial Carcinoma (ENDO-D).

Continued
UPDATES

Endometrial Carcinoma–continued

ENDO-8 Criteria For Fertility-Sparing Options For Management of Endometrial Carcinoma

- Second column; 2nd bullet revised: ~~Genetic counseling/testing in selected patients~~ *Recommend genetic evaluation of tumor and evaluation for inherited cancer risk* (See UN-1)
- Primary treatment; 1st bullet; 3rd arrow sub-bullet revised: ~~Levonorgestrel~~ *Progestin* IUD
- Surveillance
  - Complete response by 6 mo pathway: New recommendation added, *Ovarian preservation may be considered in select premenopausal patients.*
  - Endometrial cancer present at 6–12 mo pathway: New recommendation added, *Ovarian preservation may be considered in select patients.*

ENDO- 9

- Footnote w revised: "Consider ablative radiation therapy for 1–5 metastatic lesions if the primary *cancer* has..."

ENDO-A Principles of Pathology and Molecular Analysis
Page 1 of 4

- Pathologic assessment for carcinoma
  - 6th bullet revised: "...recommended for possible treatment of advanced-stage or recurrent serous endometrial carcinoma *or carcinosarcoma*."
  - New bullet added: Consider HER2 IHC testing in *TP53*-aberrant endometrial carcinoma regardless of histotyping.

Page 2 of 4

- New bullet added: Consider comprehensive genomic profiling via a validated and/or FDA-approved assay in the initial evaluation of uterine neoplasms.
- Fourth bullet revised: Universal testing of endometrial carcinomas for MMR proteins~~/MSI~~ is recommended *(MSI testing if results equivocal)*.
  - 2nd arrow sub-bullet revised: "...promoter methylation to assess *an* epigenetic ~~process~~ *mechanism*.

ENDO-A (continued)
Page 3 of 4

- Figure 1 title revised: 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)*
- Endometrioid carcinoma and serous carcinoma language was removed from the figure.
- Footnote g revised: Diagnostic algorithm for integrated genomic-pathologic classification of endometrial carcinomas. ~~(blue represents histotype; red represents TCGA genomic class).~~
- The following footnotes were removed
  - *POLE* sequencing made by mutational analysis may not be available at all institutions.
  - May also apply to clear cell carcinomas
  - This algorithm does not distinguish between high-grade tumors that cannot otherwise be classified (ie, high-grade carcinoma, serous carcinoma, clear cell carcinoma).

Page 4 of 4

- References were updated.

ENDO-B Principles of Imaging

- Initial Workup; Non–Fertility-Sparing Treatment
  - 4th arrow sub-bullet revised: For high-grade carcinoma, consider chest/abdomen/pelvis CT *(preferred)* to evaluate for metastatic disease.
  - 5th arrow sub-bullet revised: For patients who underwent TH with incidental finding of endometrial cancer or *whose cancer was* incompletely staged..."

ENDO-C Principles of Evaluation and Surgical Staging
Page 1 of 6

- 7th bullet revised: SLN mapping ~~may be considered~~ *is preferred*.
- Last bullet revised: For stage II patients, *TH/BSO is the standard procedure.* ~~extrafascial or radical hysterectomy should be based on preoperative workup with the goal of achieving negative margins.~~ *Radical hysterectomy should only be performed if needed to obtain negative margins*.

Continued

UPDATES

ENDO-C Continued
Page 2 of 6 Principles of Evaluation and Surgical Staging When SLN Mapping is Used
- 5th bullet revised: Injection into the uterine cervix provides excellent dye penetration to ~~the region of~~ the uterine..."
- New bullet added: *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.*

Page 3 of 6
- 2nd bullet revised: "...likely to harbor metastasis ~~coupled~~ *combined* with enhanced pathology protocols,..."

ENDO-D Systemic Therapy for Endometrial Carcinoma
Page 1 of 4
- Systemic Therapy Table
  - Table Titles revised
    - ◊ *Primary or* Adjuvant Treatment When Used for Uterine-Confined *High-Risk* Disease
    - ◊ Recurrent~~,~~ *or* Metastatic~~, Or High-Risk~~ Disease
  - Biomarker-directed systemic therapy for second-line treatment; Preferred regimens: Clarified as, Lenvatinib/pembrolizumab (category 1) for non–MSI-high [MSI-H]/*non*–MMR-deficient [dMMR] tumors

Page 2 of 4
- Hormone Therapy Table Title revised: ~~Recurrent, Metastatic, or High-Risk Disease~~ *Hormone Therapy.*

Page 3 of 4
- Footnote l revised: "...as determined by ~~an~~ *a validated and/or* FDA-approved test,..."

Uterine Sarcoma
UTSARC-1
- Additional Evaluation; Last bullet revised for both pathways: *Consider* ER/PR testing *for LMS, ESS, and adenosarcoma*
- After "Tumor initially fragmented or Residual cervix," revised: Consider *re-exploration/*reresection.
- Last column revised to: High-grade ESS or UUS or uLMS *or Other sarcomas*

UTSARC-4
- Additional therapy; Stage II, III: *Consider observation if completely resected with negative margins* added as an option.
- Footnote removed: Observation may be an option in select, completely resected cases with no evidence of disease on postoperative imaging.

UTSARC-5
- 2nd bullet revised: Imaging *as clinically indicated*

UTSARC-6
- Footnote m revised: For low-grade ESS *or adenosarcoma without SO*, the first choice of systemic therapy

UTSARC-A Principles of Pathology and Molecular Analysis
Page 2 of 8 through Page 7 of 8
- Table 1 (Uterine Sarcoma Classifications)
  - The table was extensively revised.
  - Table title revised: Uterine Sarcoma~~: Mesenchymal Tumors & Mixed Epithelial and Mesenchymal Tumors~~

Page 8 of 8
- References were updated.

Continued

UPDATES

Uterine Sarcoma (continued)
UTSARC-C Systemic Therapy for Uterine Sarcoma
Page 1 of 2

- **Systemic therapies; Preferred regimens: Docetaxel/gemcitabine moved from Other Recommended Regimens to the list of Preferred Regimens.**
- **Biomarker-Directed Systemic Therapy for Second-Line Treatment; Useful in Certain Circumstances: Consider PARP inhibitors for *BRCA2*-altered uLMs was listed as an option. The following PARP inhibitors were listed:**
  - **Olaparib**
  - **Rucaparib**
  - **Niraparib**
- **Footnote d revised: "...as determined by ~~an~~ *a validated and/or* FDA-approved test,..."**

Page 2 of 2

- **First column header revised: Anti-Estrogen Hormone Therapy for Low-Grade ESS *or Adenosarcoma Without SO* or Hormone Receptor-Positive (ER/PR) ~~uLMS~~ *Uterine Sarcomas***
- **Preferred regimens: Aromatase inhibitors for low-grade ESS *or adenosarcoma without SO***
- **Other recommended regimens; The following changes were made:**
  - **Aromatase inhibitors (for ER/PR-positive ~~uLMS~~ *uterine sarcomas*)**
  - **Megestrol acetate (category 2B for ER/PR-positive ~~uLMS~~ *uterine sarcomas*)**
  - **Medroxyprogesterone acetate (category 2B for ER/PR-positive ~~uLMS~~ *uterine sarcomas*)**
  - **GnRH analogs (category 2B for low-grade ESS*, adenosarcoma without SO,* and ER/PR-positive ~~uLMS~~ *uterine sarcomas*)**
- **Footnote e revised: "These hormonal therapies may be considered for patients with ~~uLMS~~ *uterine sarcomas* that are ER/PR-positive..."**

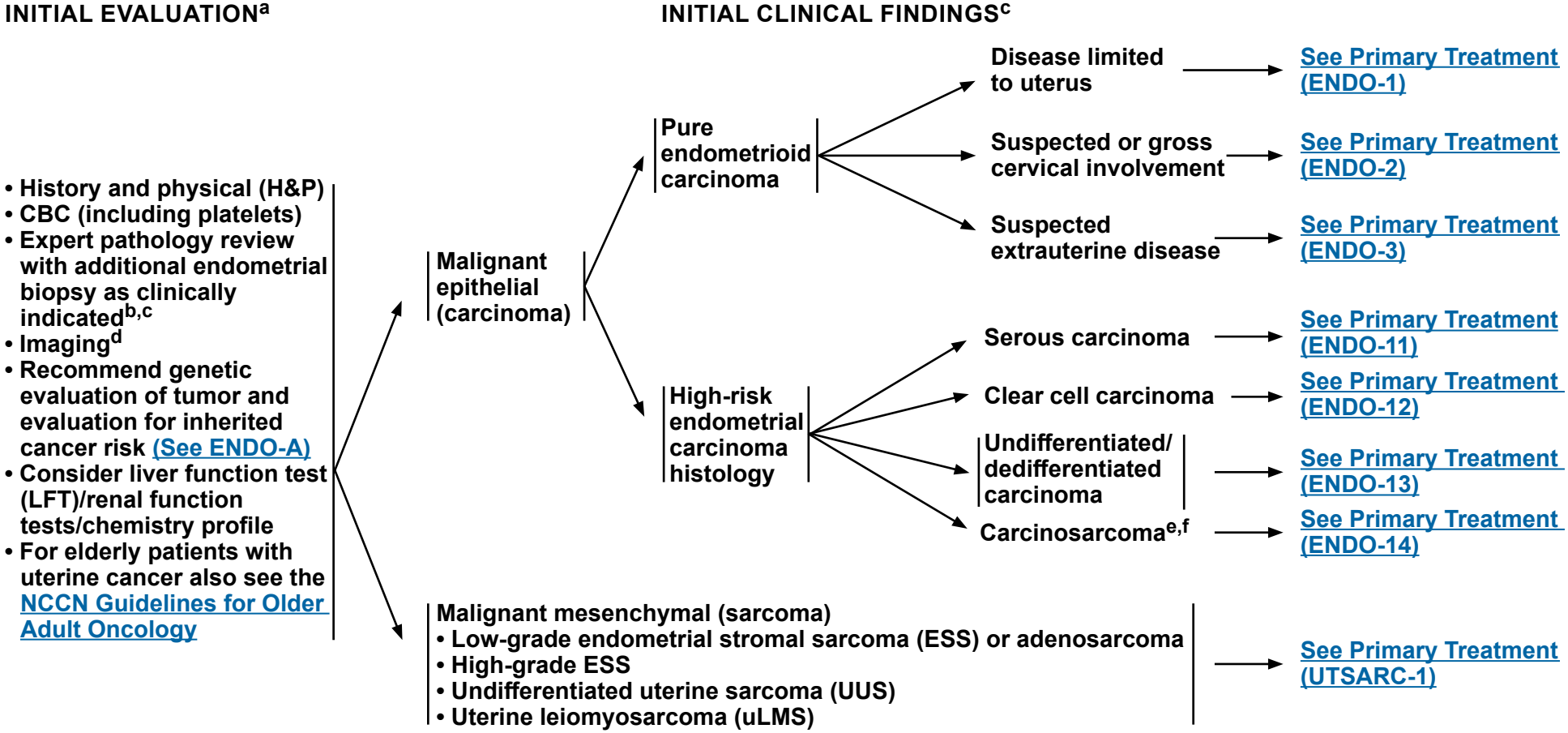
Uterine Neoplasms
UN-A Principles of Radiation Therapy for Uterine Neoplasms

- **General Principles–Uterine Neoplasms: New bullet added, Chemoradiation can be given concurrently or sequentially**

UN-B Principles of Gynecologic Survivorship

- **Psychosocial effects revised: Psychosocial effects after cancer may ~~include~~ *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) ~~effects~~ *in nature*.**
- **Clinical approach**
  - **1st bullet: "...focuses on *managing* chronic disease ~~management~~, monitoring ~~of~~ cardiovascular risk factors, *providing* recommended vaccinations..."**
  - **2nd bullet: "...physical examination, and ~~conduct~~ *provide any* necessary imaging and/or laboratory testing. All ~~women~~ *patients*, whether sexually active or not, should be asked about genitourinary symptoms, including vulvovaginal dryness..."**
  - **New bullet added: For premenopausal patients, hormone replacement therapy should be considered.**

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



[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] Should be treated as a high-grade endometrial cancer.
[f] 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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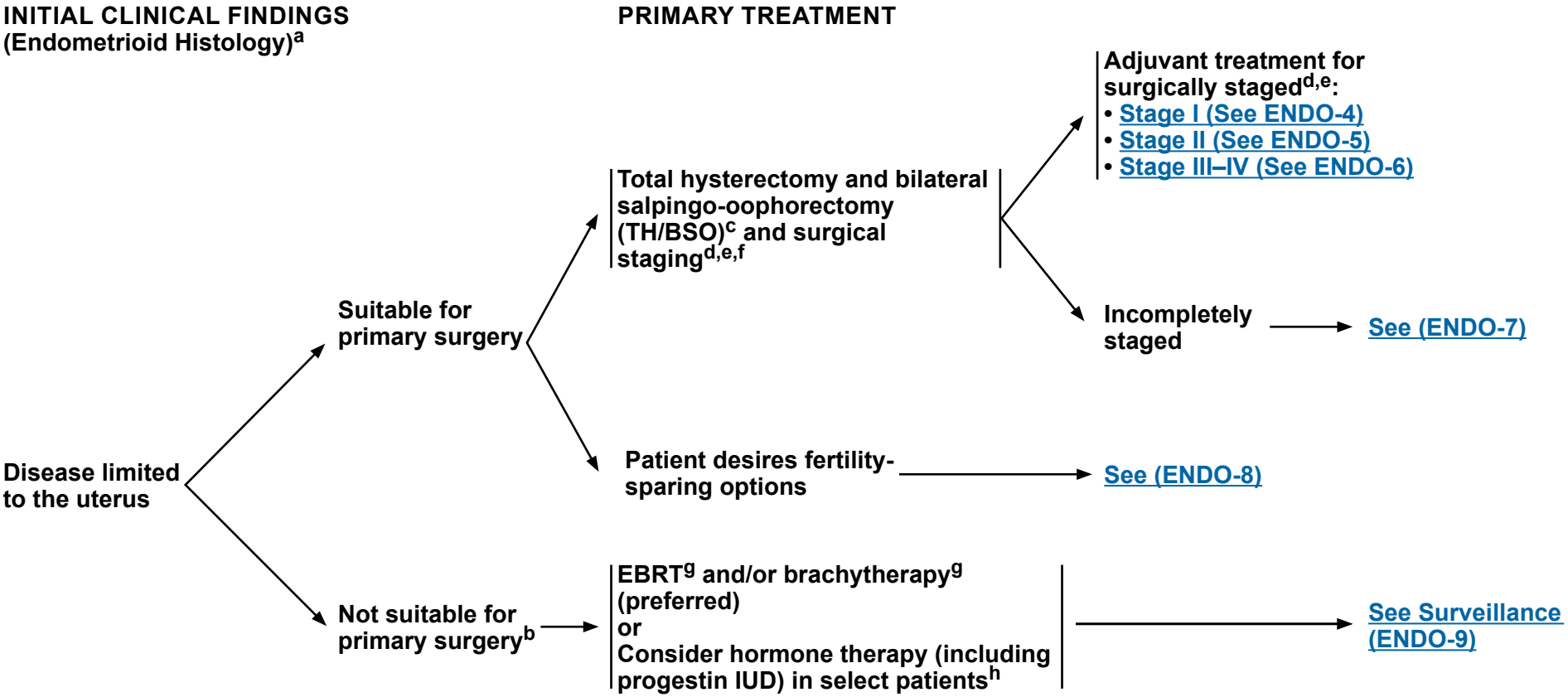

[a] See (UN-1) for classification of uterine neoplasms.
[b] Patient declines surgery or is not suitable for surgery based on comorbidities.
[c] See Principles of Pathology and Molecular Analysis (ENDO-A).
[d] Minimally invasive surgery (MIS) is the preferred approach when technically feasible. See Principles 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 premenopausal patients with early-stage endometrioid cancer, normal-appearing ovaries, and no family history of breast/ovarian cancer or Lynch syndrome. Salpingectomy is recommended.
[g] See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] See Systemic Therapy for Endometrial Carcinoma (ENDO-D).

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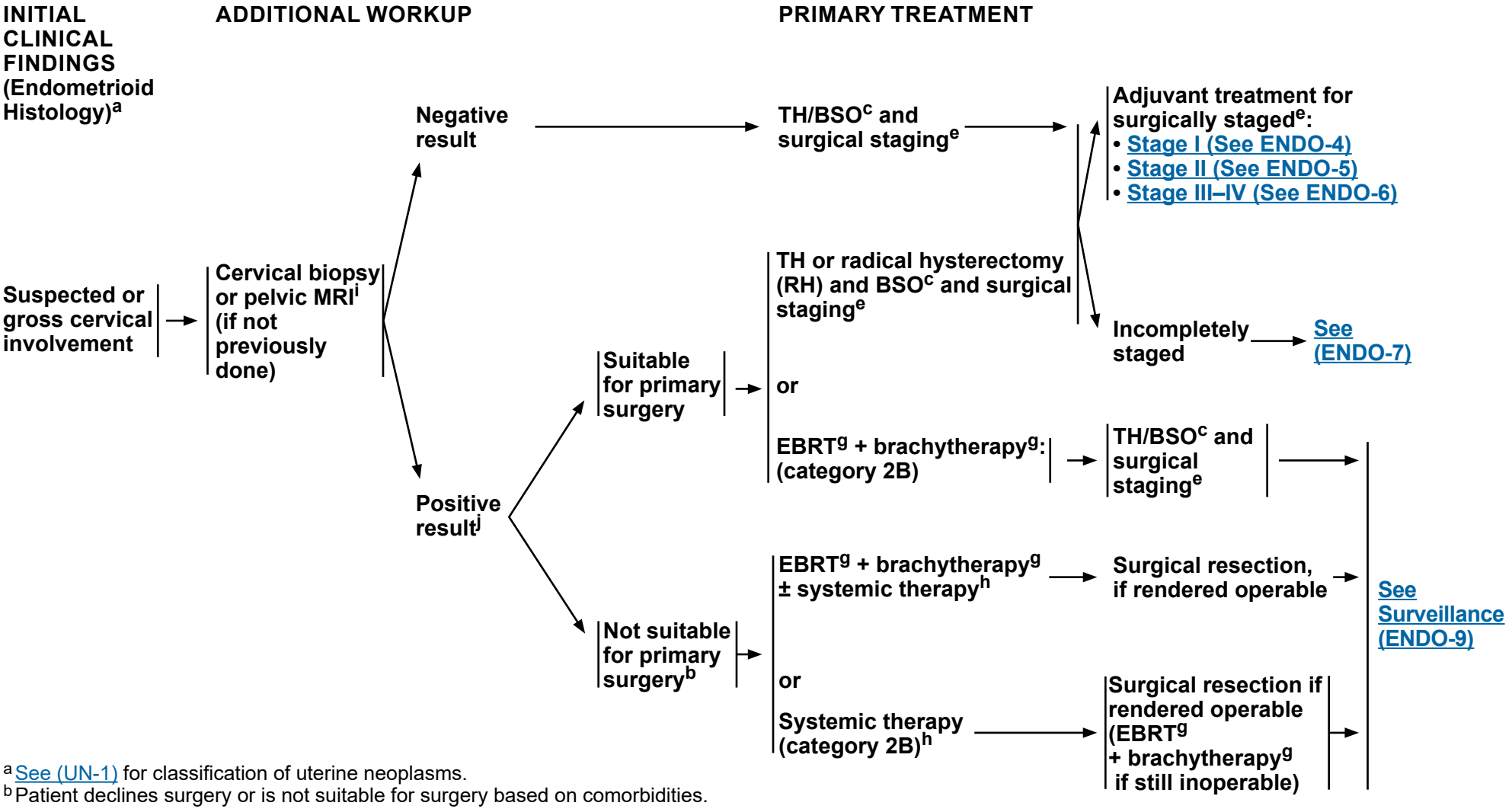

[a] See (UN-1) for classification of uterine neoplasms.
[b] Patient declines surgery or is not suitable for surgery based on comorbidities.
[c] See Principles of Pathology and Molecular Analysis (ENDO-A).
[e] The degree of surgical staging to assess disease status depends on preoperative and intraoperative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

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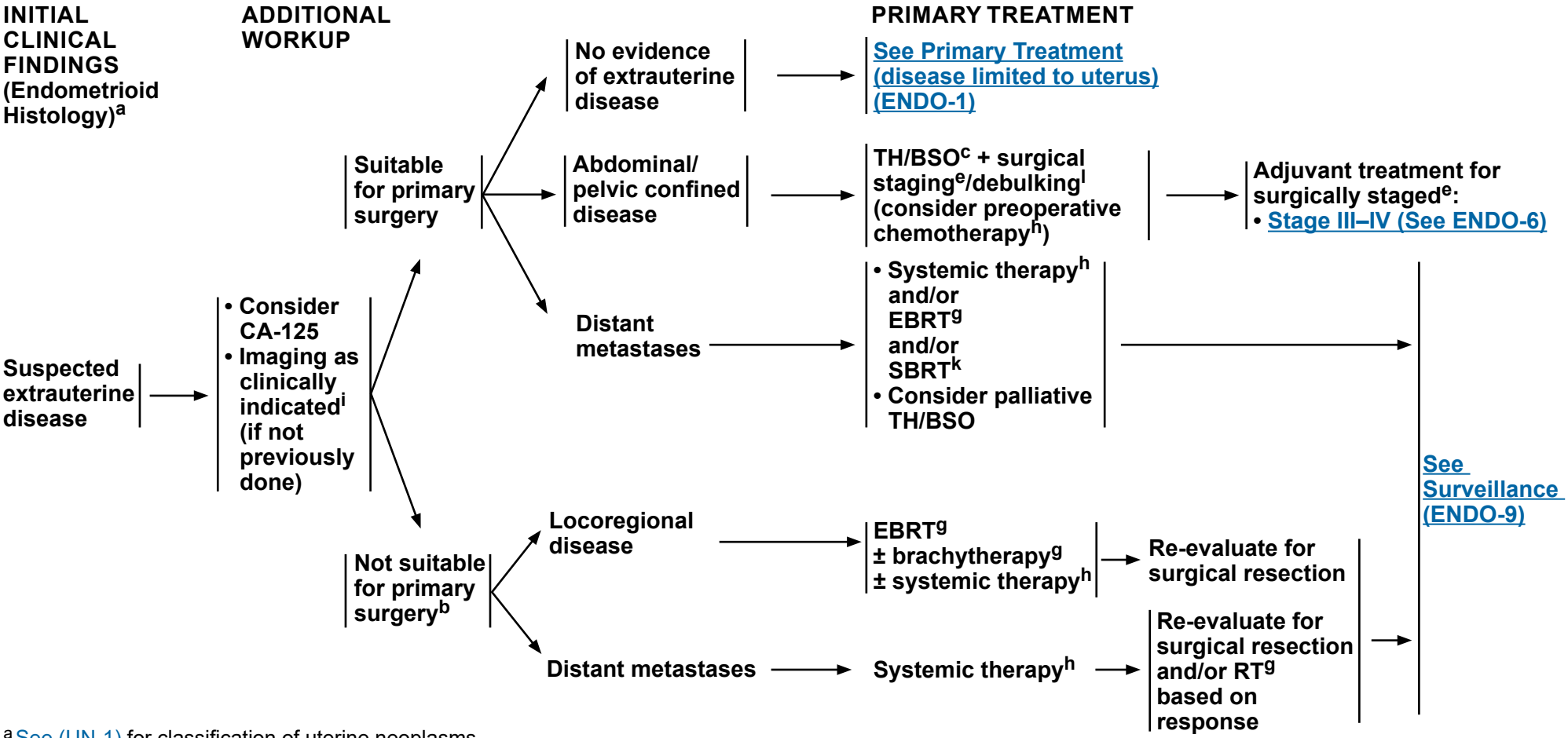

[a] See (UN-1) for classification of uterine neoplasms.
[b] Patient declines surgery or is not suitable for surgery based on comorbidities.
[c] See Principles of Pathology and Molecular Analysis (ENDO-A).
[e] The degree of surgical staging to assess disease status depends on preoperative and intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).
[g] See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] See Systemic Therapy for Endometrial Carcinoma (ENDO-D).
[i] See Principles of Imaging (ENDO-B).
[k] Consider ablative radiation therapy 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. (See 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] See (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] See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] See 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 strongly suggested if two risk factors 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)

See Surveillance (ENDO-9)

[a] See (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] See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] See 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 (See 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.

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CLINICAL FINDINGS
(Endometrioid Histology)[a]

ADJUVANT TREATMENT[g,h]

Surgically staged[e]:
Stage III, IV[r] → **Systemic therapy**
± EBRT
± vaginal brachytherapy[s]

[a] See (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] See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] See 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. Combination therapy is preferred for stage III disease.

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See Surveillance (ENDO-9)

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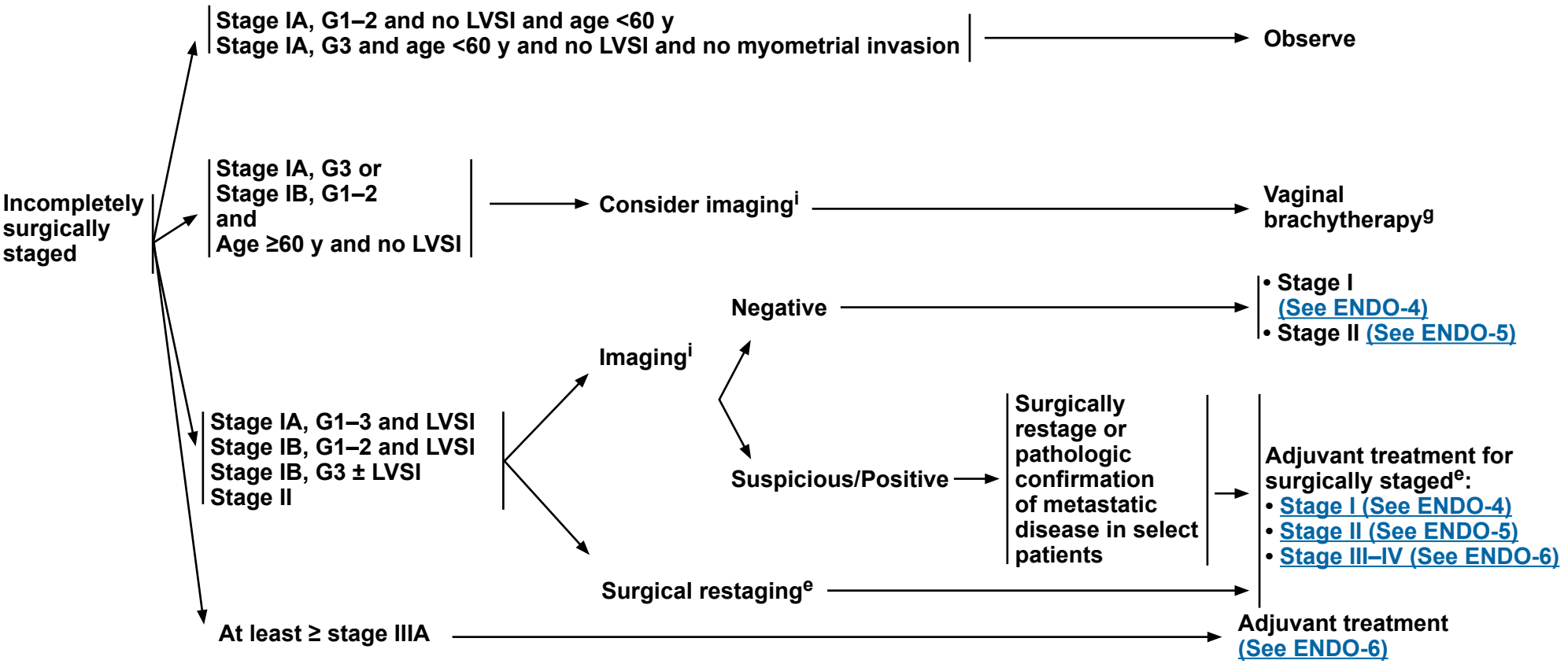
CLINICAL INTRAUTERINE FINDINGS (Endometrioid Histology)[a]

ADJUVANT TREATMENT



[a] See (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] See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[i] See Principles of Imaging (ENDO-B).

See Surveillance (ENDO-9)

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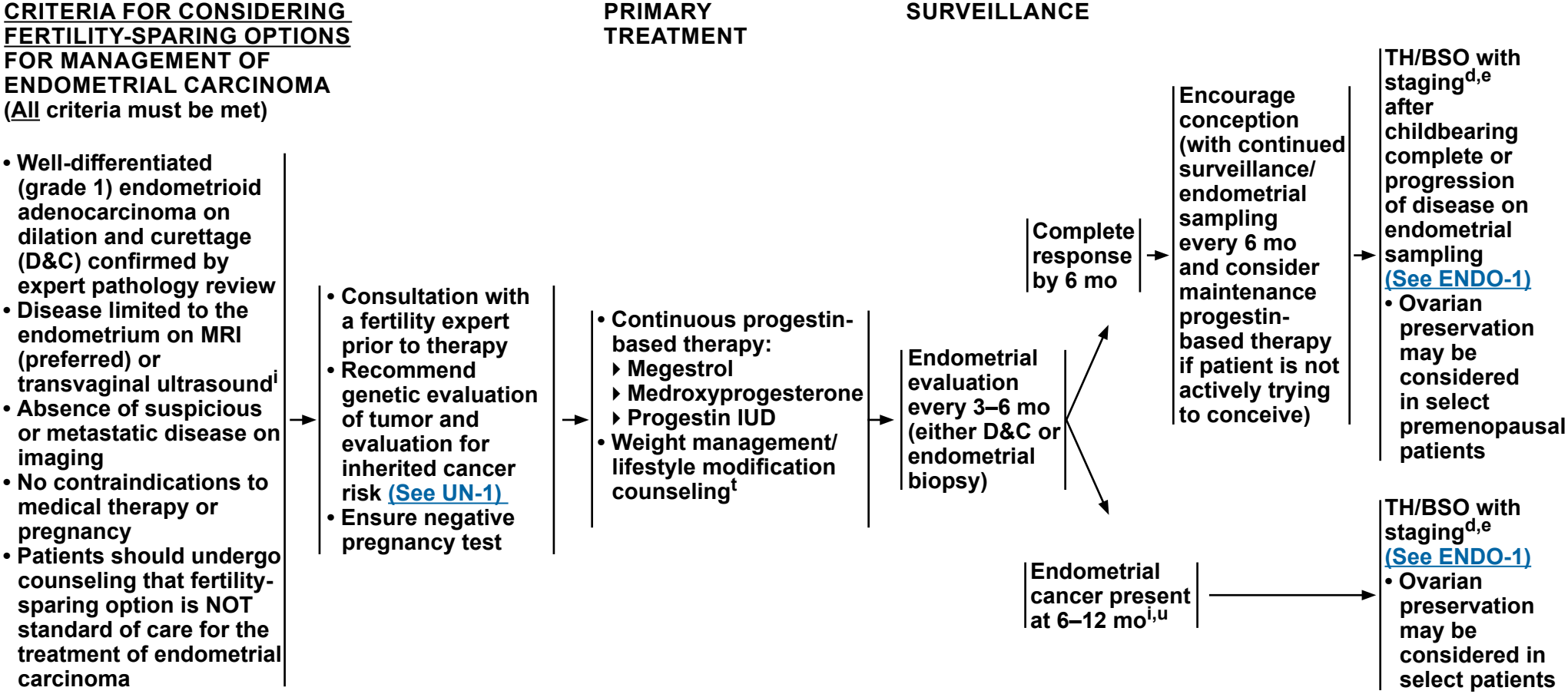

[d] MIS is the preferred approach when technically feasible. See Principles of Evaluation and Surgical Staging (ENDO-C).
[e] The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).
[i] See 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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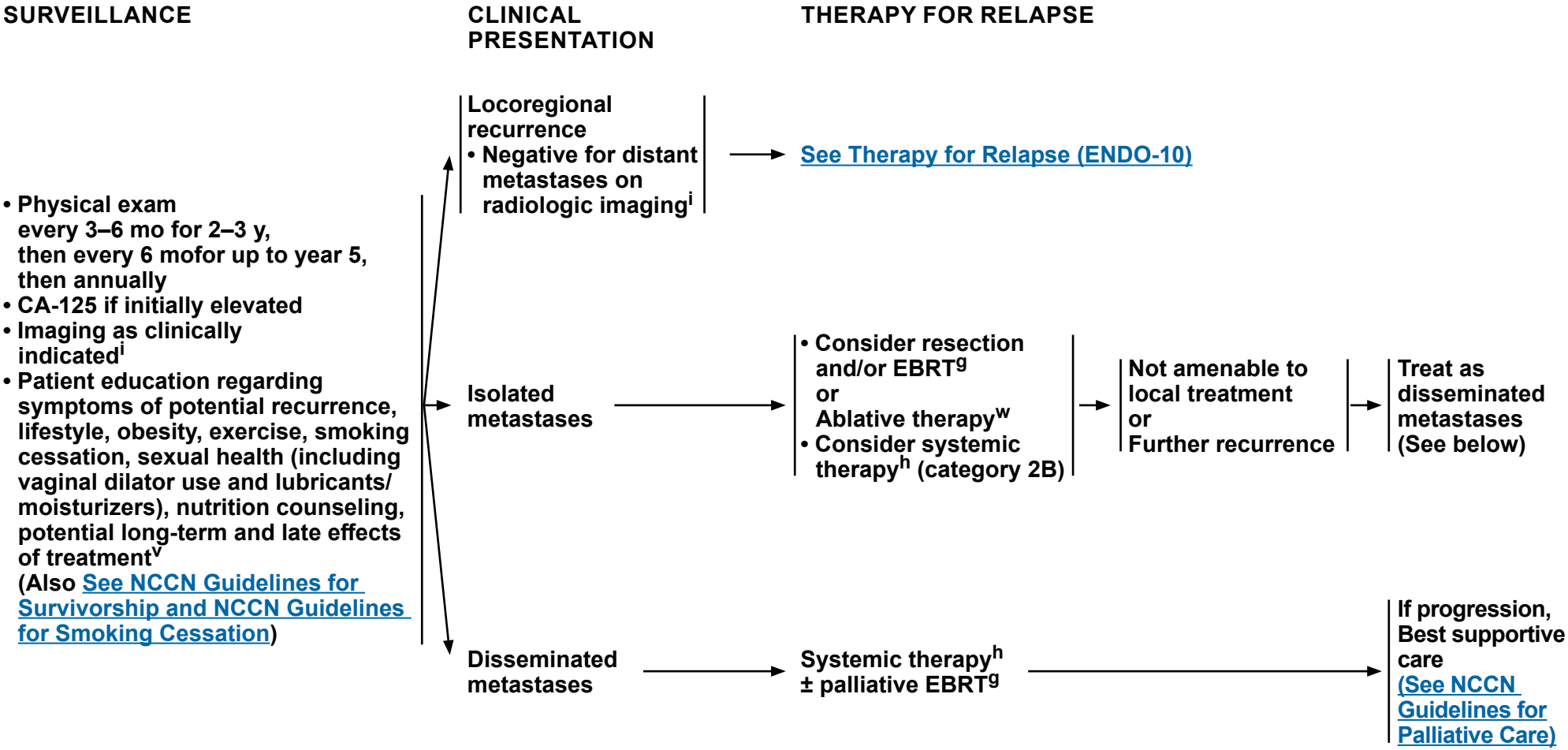

[g] See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] See Systemic Therapy for Endometrial Carcinoma (ENDO-D).
[i] See Principles of Imaging (ENDO-B).
[v] See Principles of Gynecologic Survivorship (UN-B).
[w] Consider ablative radiation therapy for 1–5 metastatic lesions if the primary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

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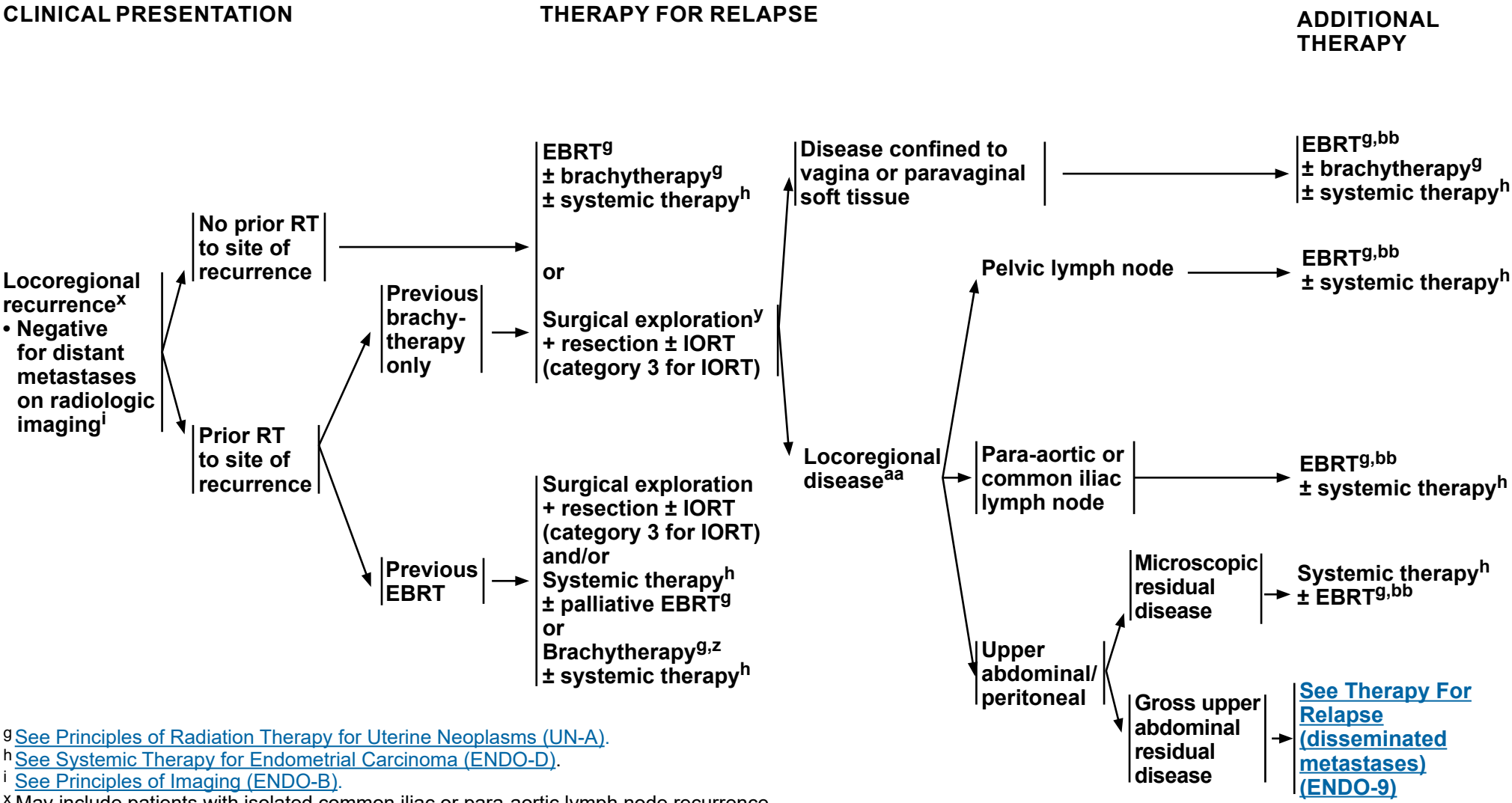

[g] See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] See Systemic Therapy for Endometrial Carcinoma (ENDO-D).
[i] See Principles of Imaging (ENDO-B).
[x] May include patients with isolated common iliac or para-aortic lymph node recurrence.
[y] Consider preoperative EBRT in select 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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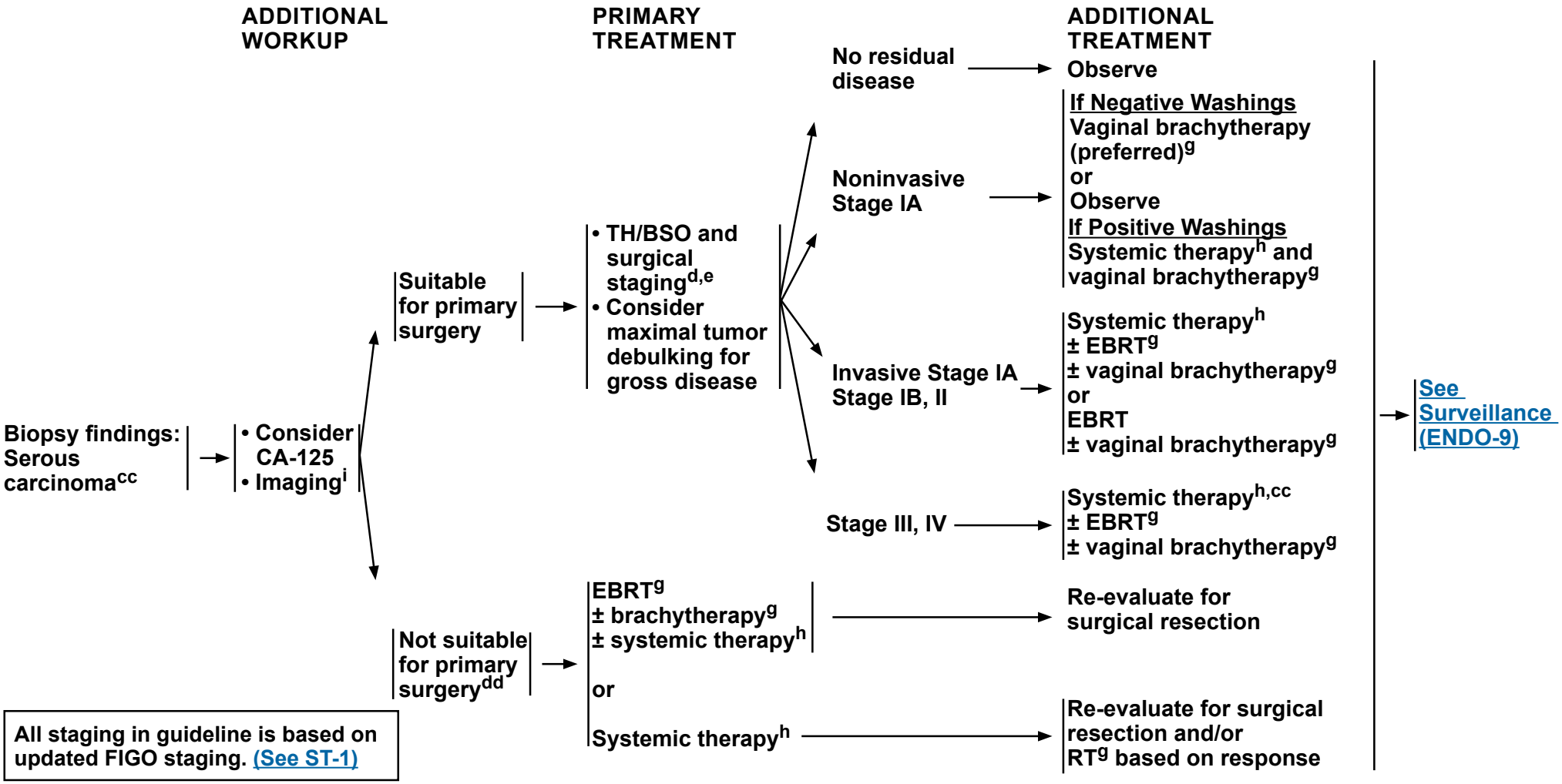

All staging in guideline is based on updated FIGO staging. (See ST-1)

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

[h] See Systemic Therapy for Endometrial Carcinoma (ENDO-D).

[i] See Principles of Imaging (ENDO-B).

[cc] HER2 testing is recommended for advanced or metastatic disease.

[dd] Disease is not amenable to resection, patient declines surgery, or patient is not suitable for surgery based on comorbidities.

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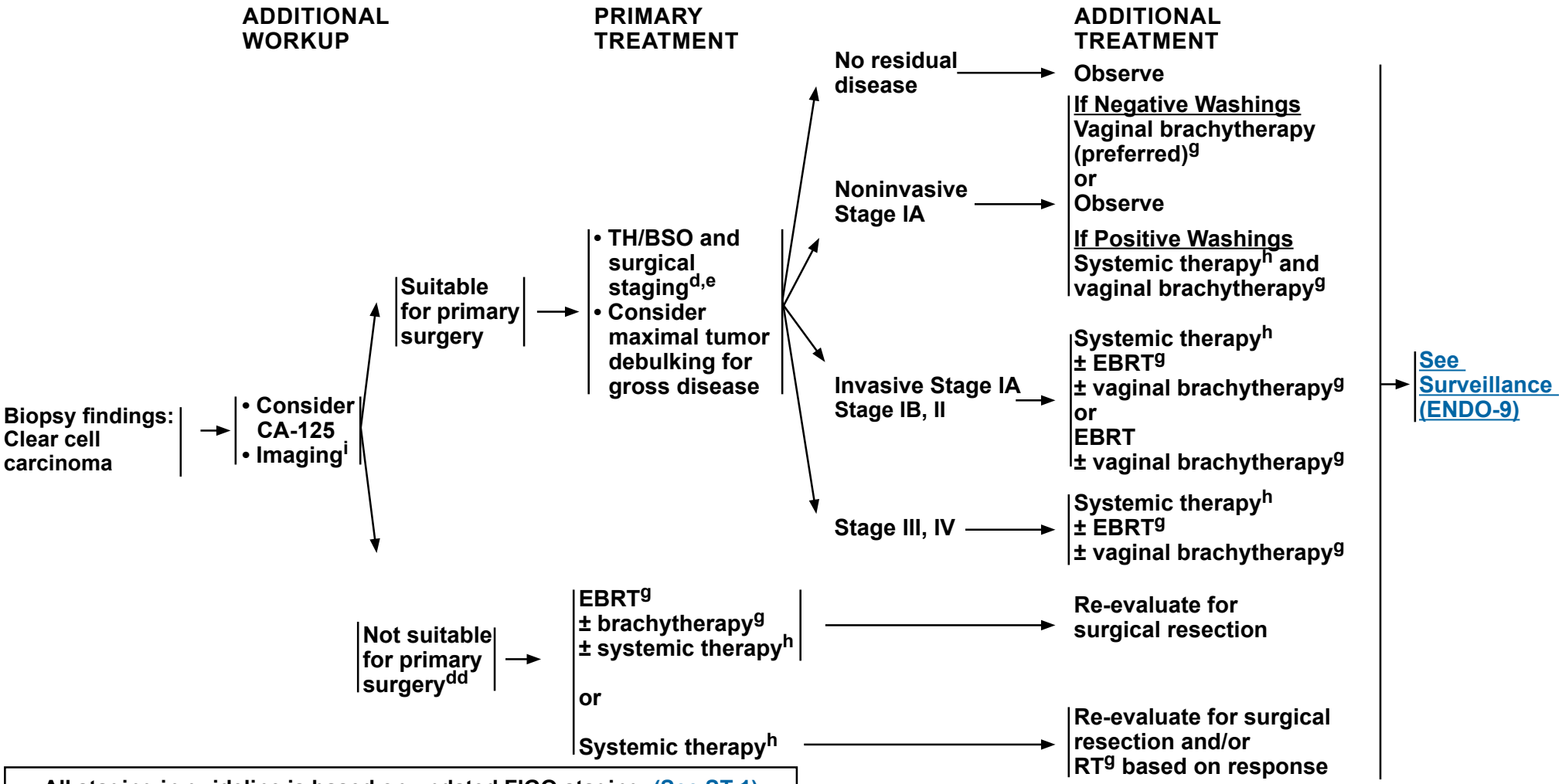

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[h] See Systemic Therapy for Endometrial Carcinoma (ENDO-D).

[i] See Principles of Imaging (ENDO-B).

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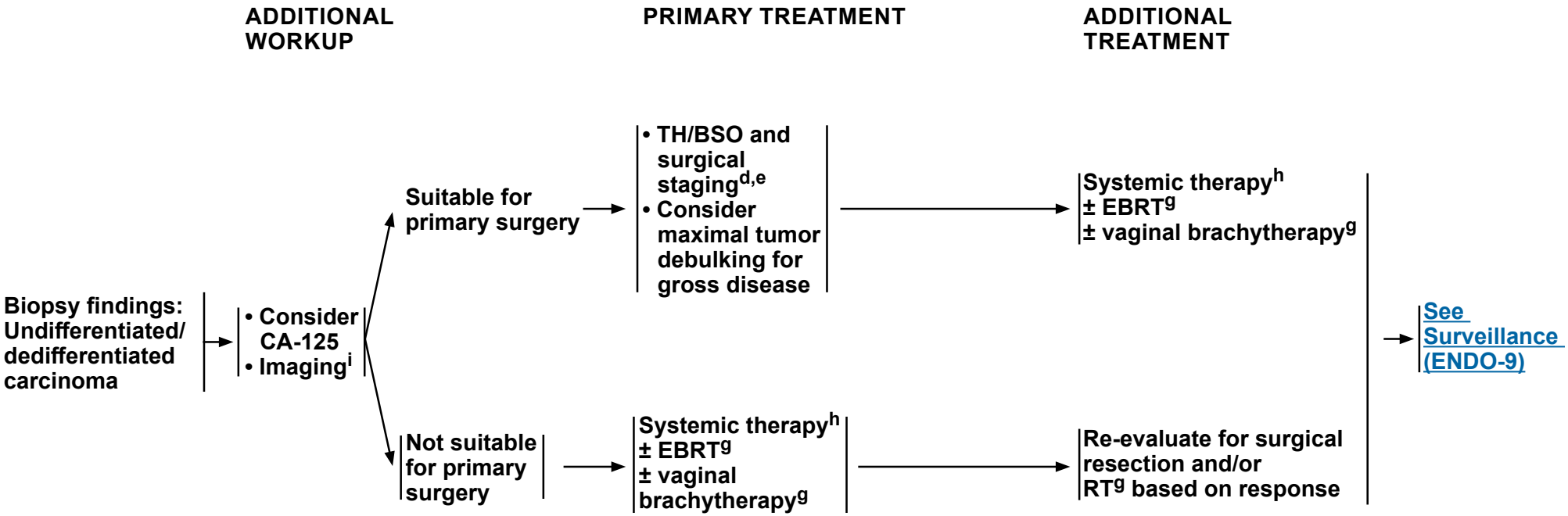

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[e] The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-C).
[g] See Principles of Radiation Therapy for Uterine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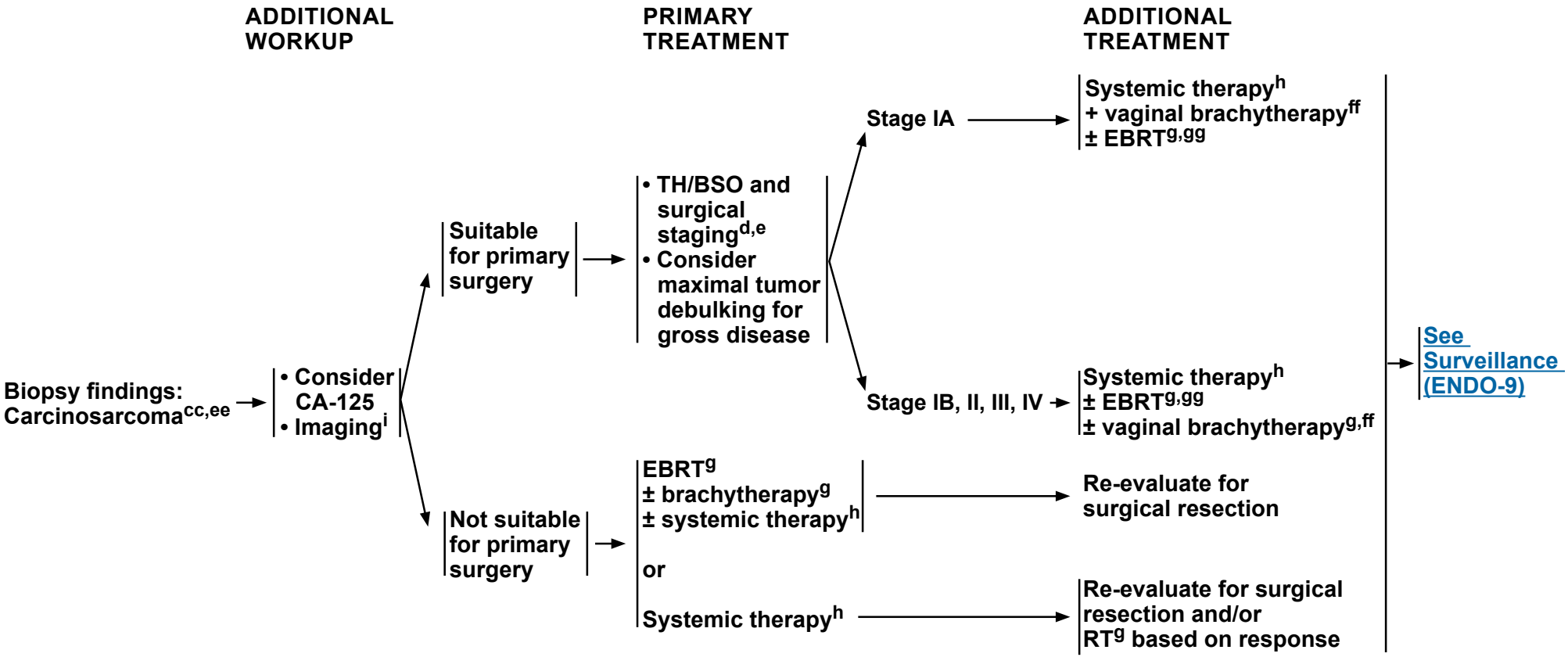

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[g] See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] See Systemic Therapy for Endometrial Carcinoma (ENDO-D).
[i] See Principles of Imaging (ENDO-B).

[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 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.**
- **Estrogen receptor (ER) testing is recommended in the settings of stage III, stage IV, and recurrent disease.**
- **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 serous endometrial carcinoma or carcinosarcoma.[4-7]**
- **Consider HER2 IHC testing in *TP53*-aberrant endometrial carcinoma regarless of histotyping.**
- **Morphologic evaluation of endometrial carcinoma to determine histologic type—especially in high-grade cancers—is challenging and issues exist regarding diagnostic reproducibility.[8,9]**

[a] See 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. In patients from the PORTEC trial with clinical stage I endometrial carcinoma, substantial LVSI was an independent prognostic factor for pelvic regional recurrence, distant metastasis, and overall survival.[10] Bosse et al[11] utilized a previously described three-tiered scoring system, including: none (no LVSI), mild (a focus of LVSI recognized around a tumor), or substantial (diffuse or multifocal LVSI recognized around a tumor). Note that mild LVSI may involve more than one vessel. A panel of six gynecologic pathologists demonstrated substantial reproducibility for grading LVSI using this three-tiered system.[12]
[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 hematoxylin and eosin (H&E)-stained sections with or without cytokeratin immunohistochemistry for all blocks of SLN. There is no standard protocol for lymph node ultrastaging.

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References
Continued

PRINCIPLES OF MOLECULAR ANALYSIS

- **Molecular analysis of endometrial carcinoma has identified four clinically significant molecular subgroups with differing clinical prognoses: *POLE* mutations, microsatellite instability-high (MSI-H), copy number low, and copy number high.[13]**
- **Consider comprehensive genomic profiling via a validated and/or FDA-approved assay in the initial evaluation of uterine neoplasms.**
- **Ancillary studies for *POLE* mutations, mismatch repair (MMR)/MSI, and aberrant p53 expression are encouraged to complement morphologic assessment of histologic tumor type.[14] See Figure 1: Pathology and Genomics in Endometrial Carcinoma (ENDO-A 3 of 4).**
- **Universal testing of endometrial carcinomas for MMR proteins is recommended (MSI testing if results equivocal).**
  - **Testing may be performed on the initial biopsy or D&C material or the final hysterectomy specimen.**
  - **MLH1 loss should be further evaluated for promoter methylation to assess an epigenetic mechanism.**
  - **Genetic counseling, molecular analysis, and testing for all other MMR abnormalities is recommended.**
  - **For those who are MMR-intact/MSI-stable or those who have not been screened, but who have a strong family history of endometrial and/or colorectal cancer, genetic counseling and testing is recommended. (See Lynch Syndrome/HNPCC 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 a validated and/or FDA-approved assay.[15]**

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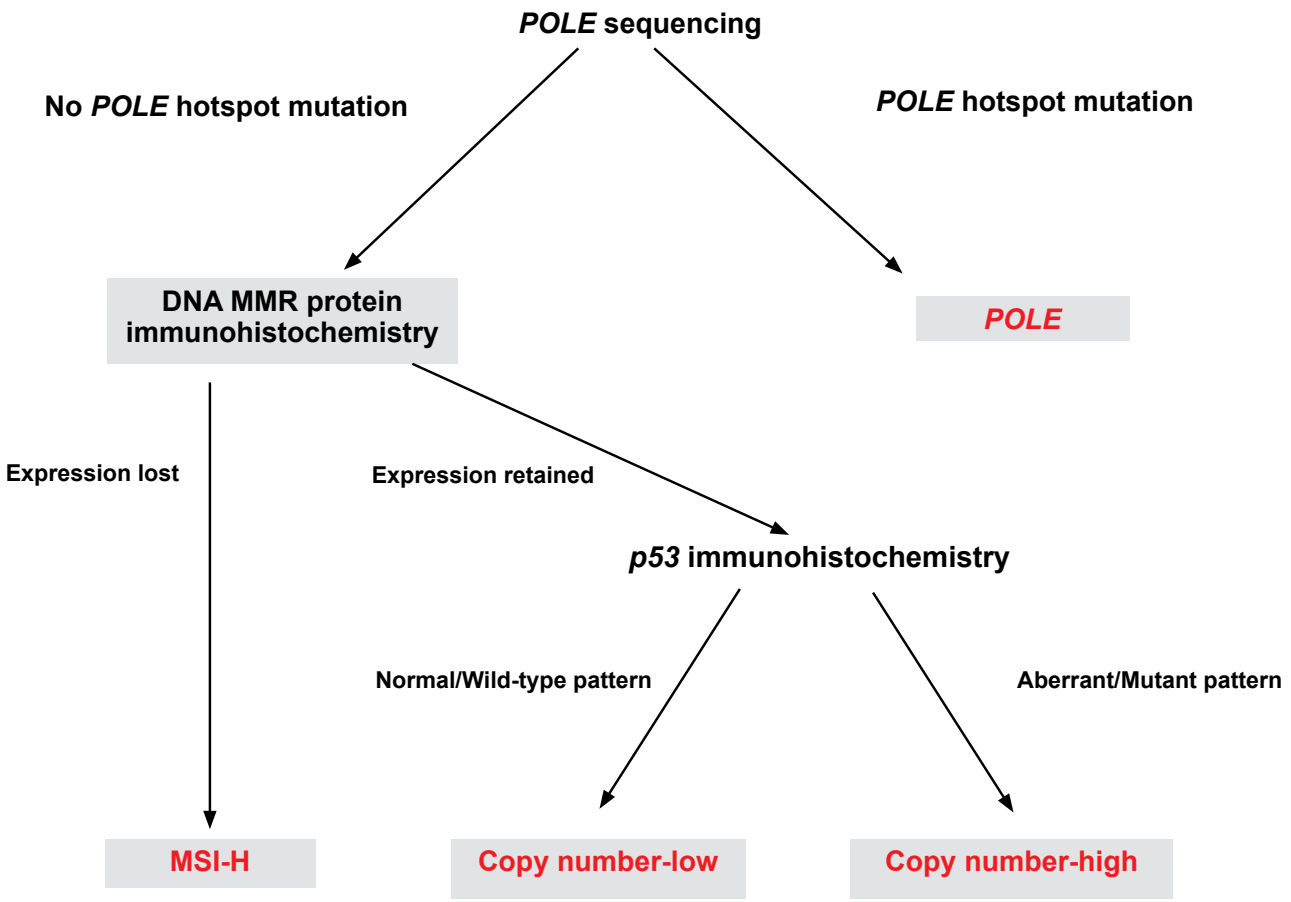
References
Continued

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.
[g] Diagnostic algorithm for integrated genomic-pathologic classification of endometrial carcinomas.

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PRINCIPLES OF PATHOLOGY AND MOLECULAR ANALYSIS
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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 (See ENDO-7) with uterine risk factors,[c] consider chest/abdomen/pelvis CT to evaluate for metastatic disease.
  - Consider neck/chest/abdomen/pelvis/groin 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.
  - 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 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 failed medical therapy, 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 and/or chest CT is recommended based on symptoms or physical exam findings.[e]**
- **Consider whole body PET/CT and/or abdomen/pelvis MRI in select patients as clinically indicated.**

[a] MRI and CT are performed with contrast throughout the guidelines 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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References

PRINCIPLES OF IMAGING
References

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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 (See ENDO-8).[1-3] Select patients with metastatic endometrial carcinoma are also candidates for hysterectomy. (See 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.
- Omental biopsy is commonly performed in those with serous carcinoma, clear cell carcinoma, or carcinosarcoma histologies.
- For stage II patients, TH/BSO is the standard procedure. Radical hysterectomy 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 (^{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 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, intraoperative pathologic assessment of primary tumor specimen may be used to determine need for additional lymphadenectomy and to guide treatment.
- 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.

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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]**

Continued

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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]

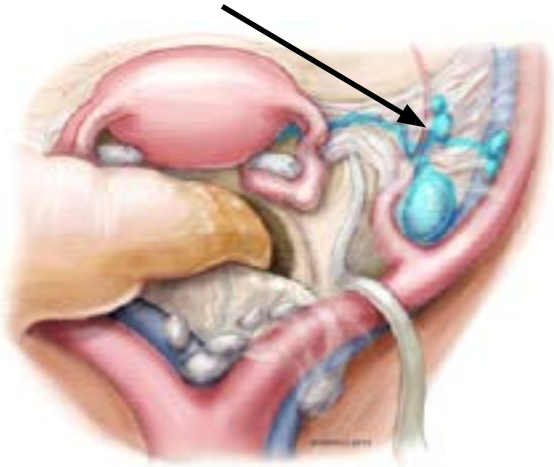
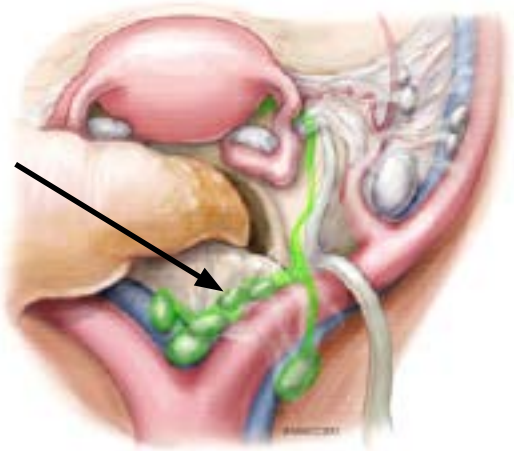


Figure 3: Less common location of SLNs (green, arrow) usually seen when lymphatic trunks are not crossing over the umbilical ligament but following the mesoureter cephalad to common iliac and presacral region[a]



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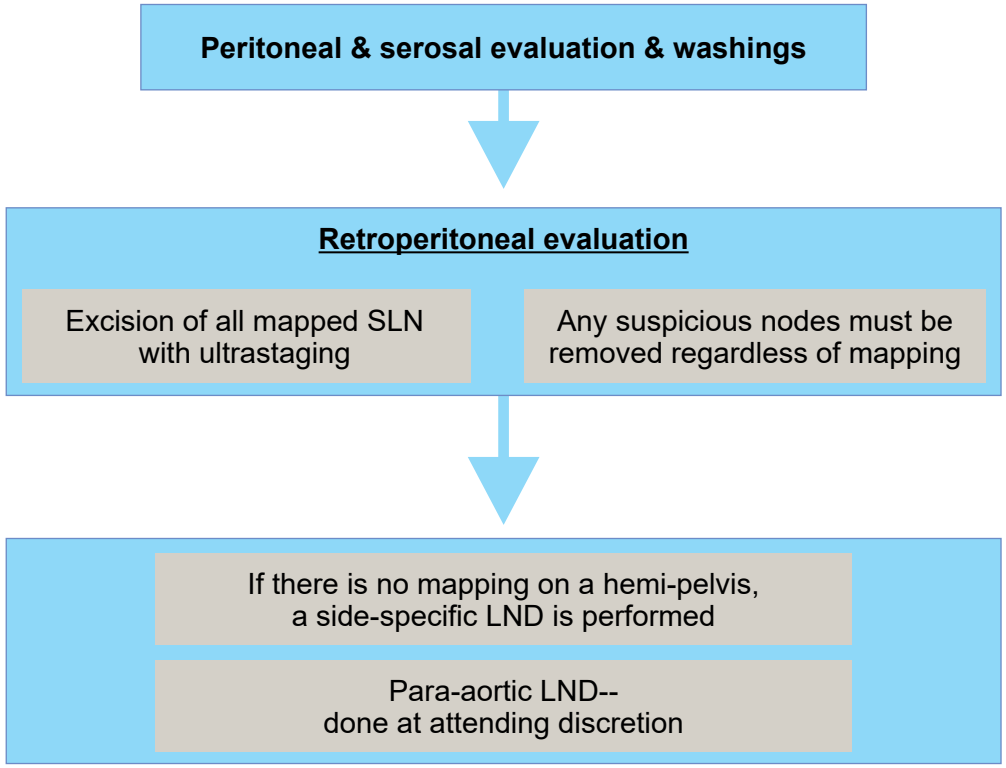
PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

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



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

Continued

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF EVALUATION AND SURGICAL STAGING
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SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Primary or Adjuvant Treatment When Used for Uterine-Confined High-Risk Disease
Preferred Regimens • Carboplatin/paclitaxel

Recurrent or Metastatic Disease[a,b]		
	Preferred Regimens	**Other Recommended Regimens**
Systemic therapies[a,b]	• Carboplatin/paclitaxel (category 1 for carcinosarcoma)[1] • Carboplatin/paclitaxel/trastuzumab[c] (for stage III/IV or recurrent HER2-positive uterine serous carcinoma)[2]	• Carboplatin/docetaxel[d] • Cisplatin/doxorubicin[3] • Cisplatin/doxorubicin/paclitaxel[e,f,3] • Carboplatin/paclitaxel/bevacizumab[e,g,4] • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel[5] • Albumin-bound paclitaxel[h] • Topotecan • Bevacizumab[g,i,6] • Temsirolimus[7] • Docetaxel[d] (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma)[8] • Cisplatin/ifosfamide (for carcinosarcoma)
Biomarker-directed systemic therapy for second-line treatment	• Lenvatinib/pembrolizumab (category 1) for non–MSI-high [MSI-H]/non–MMR-deficient [dMMR] tumors[j,9] • Pembrolizumab[k] for TMB-H[10] or MSI-H/dMMR tumors[l,11]	• Nivolumab for dMMR/MSI-H tumors[12] • Dostarlimab-gxly for dMMR/MSI-H tumors[m,13] • Larotrectinib or entrectinib for *NTRK* gene fusion-positive tumors (category 2B)[e] • Avelumab for dMMR/MSI-H tumors • Cabozantinib

Footnotes on page ENDO-D 3 OF 4

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References Continued

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Hormone Therapy[n]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**

• Medroxyprogesterone acetate/tamoxifen (alternating)
• Megestrol acetate/tamoxifen (alternating)
• Progestational agents
  ▸ Medroxyprogesterone acetate
  ▸ Megestrol acetate
  ▸ Levonorgestrel intrauterine device (IUD) (for select fertility-sparing cases)
• Aromatase inhibitors
• Tamoxifen
• Fulvestrant
	• Everolimus/letrozole (for endometrioid histology)	N/A

Footnotes on page ENDO-D 3 OF 4

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Continued

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA
FOOTNOTES

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

[b] Chemotherapy regimens can be used for all carcinoma histologies. Carcinosarcomas are now considered and treated as high-grade carcinomas.

[c] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

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

[e] For advanced and recurrent disease only.

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

[g] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

[h] 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 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.

[i] Bevacizumab may be considered for use in patients who have progressed on prior cytotoxic chemotherapy.

[j] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

[k] For recurrent endometrial cancer, NCCN recommends MSI-H or dMMR testing if not previously done.

[l] 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, who have progressed following prior treatment and who have no satisfactory alternative treatment options.

[m] Dostarlimab-gxly is indicated for patients with dMMR/MSI-H recurrent or advanced endometrial carcinoma that has progressed on or following prior treatment with a platinum-containing regimen.

[n] 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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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Uterine Sarcoma

NCCN Guidelines Index
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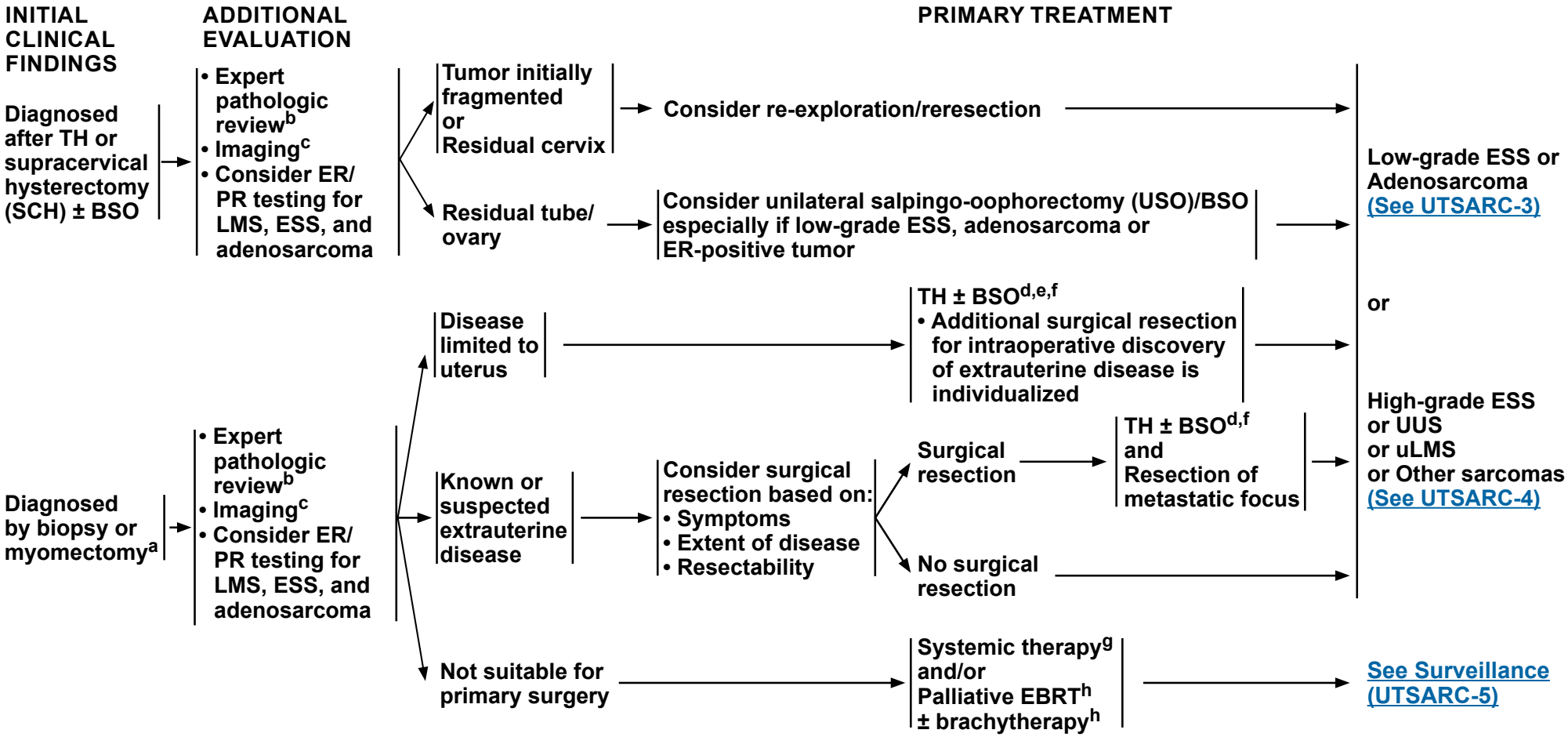
Discussion



[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] See Principles of Pathology and Molecular Analysis (UTSARC-A).
[c] See Principles of Imaging (UTSARC-B).
[d] Oophorectomy individualized for reproductive-age patients. Favor BSO if ER/PR positive.
[e] For incidental finding of uterine sarcoma after TH/BSO or fragmented specimen: recommend imaging and consider additional surgical resection on an individual basis.
[f] Uterine sarcoma should be removed en bloc to optimize outcomes; morcellation should be avoided.
[g] See Systemic Therapy (UTSARC-C).
[h] See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).

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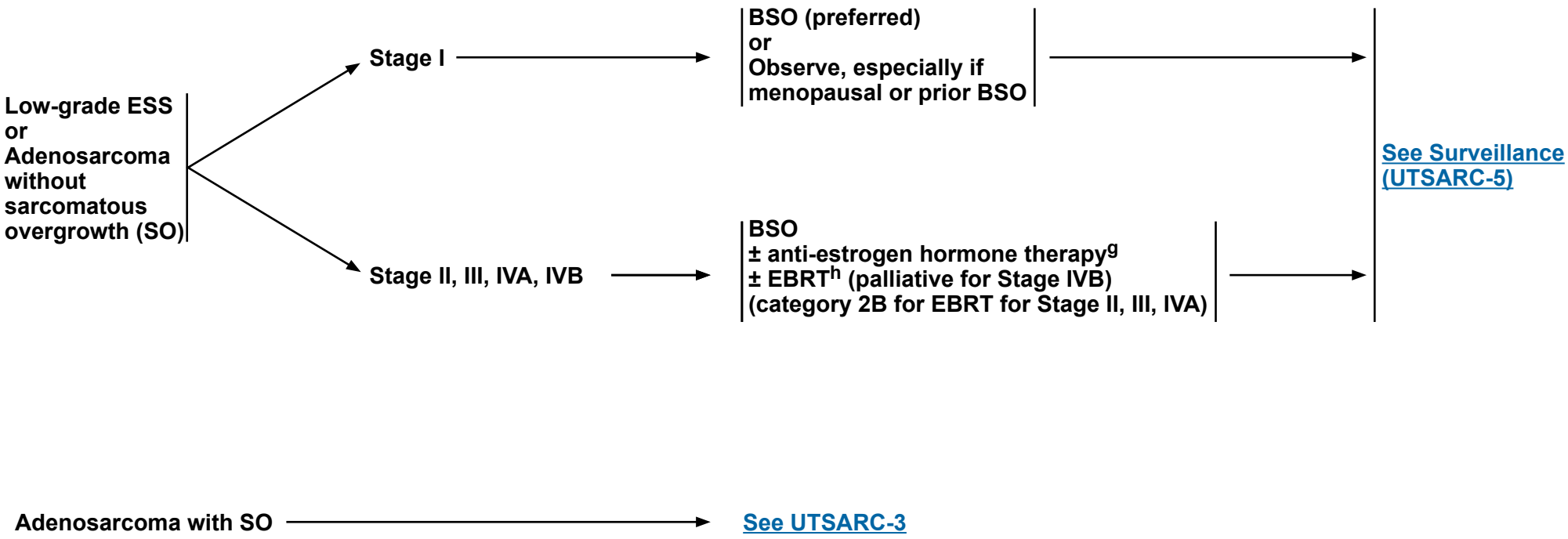

g. See Systemic Therapy (UTSARC-C).
h See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
i See Principles of Pathology and Molecular Analysis (UTSARC-A 2 of 8).

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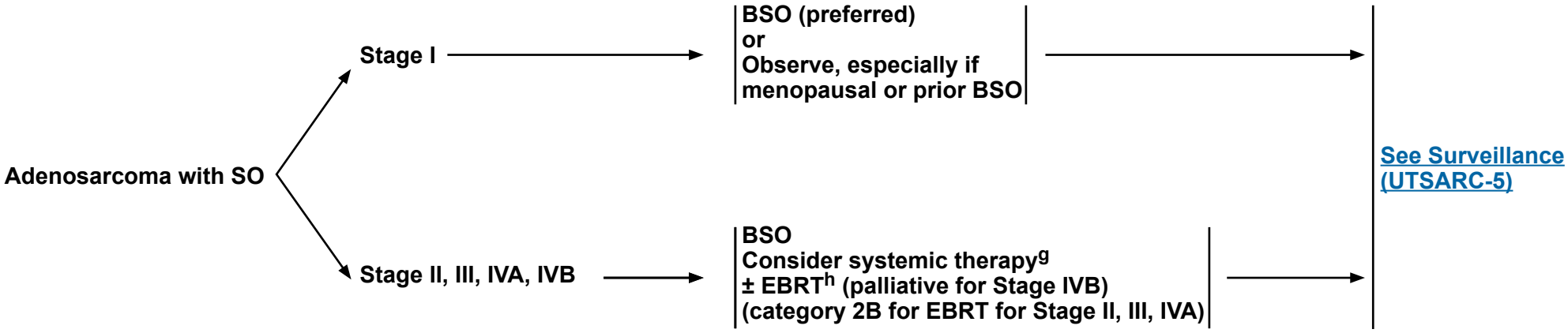

[g] See Systemic Therapy (UTSARC-C).
[h] See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[i] See Principles of Pathology and Molecular Analysis (UTSARC-A 2 of 8).

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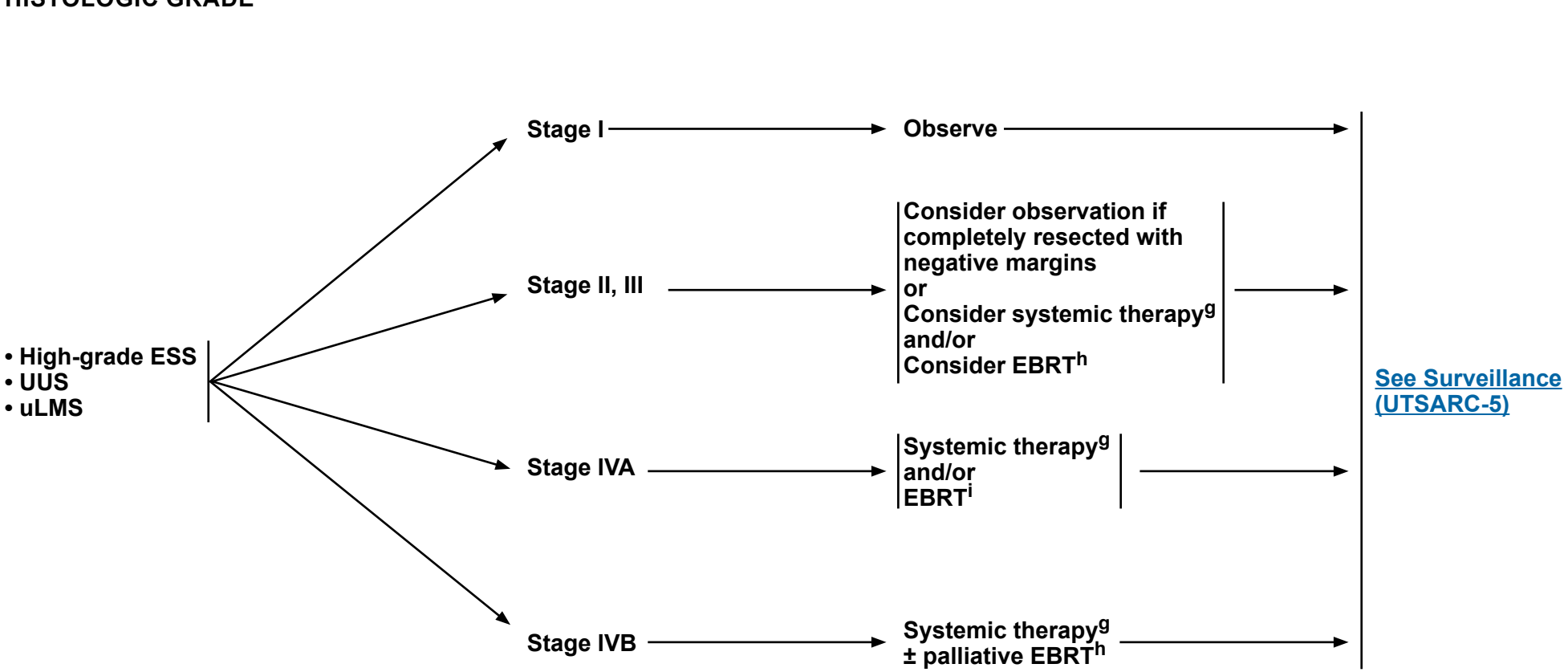

[g] See Systemic Therapy (UTSARC-C).
[h] See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[i] See Principles of Pathology and Molecular Analysis (UTSARC-A 2 of 8).

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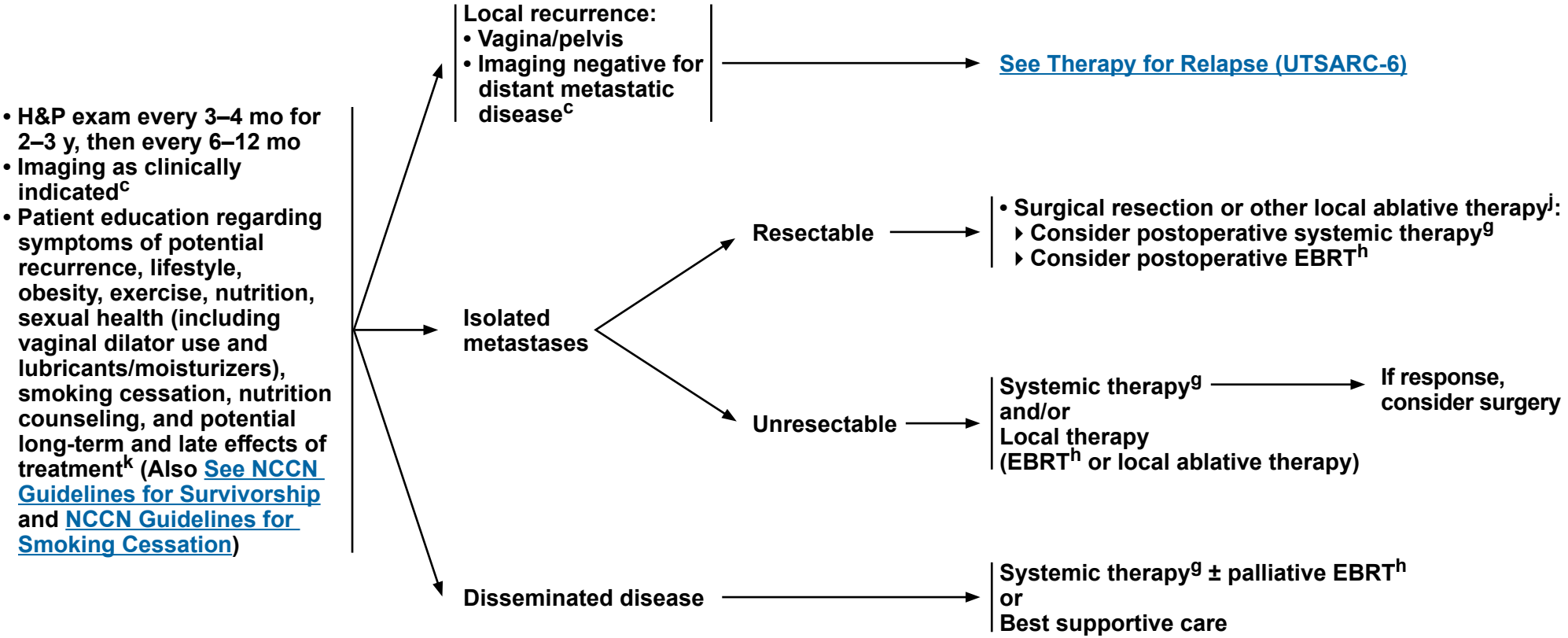

[c] See Principles of Imaging (UTSARC-B).
[g] See Systemic Therapy (UTSARC-C).
[h] See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[j] Observation may be an option in select, completely resected cases with no evidence of disease on postoperative imaging.
[k] See Principles of Gynecologic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

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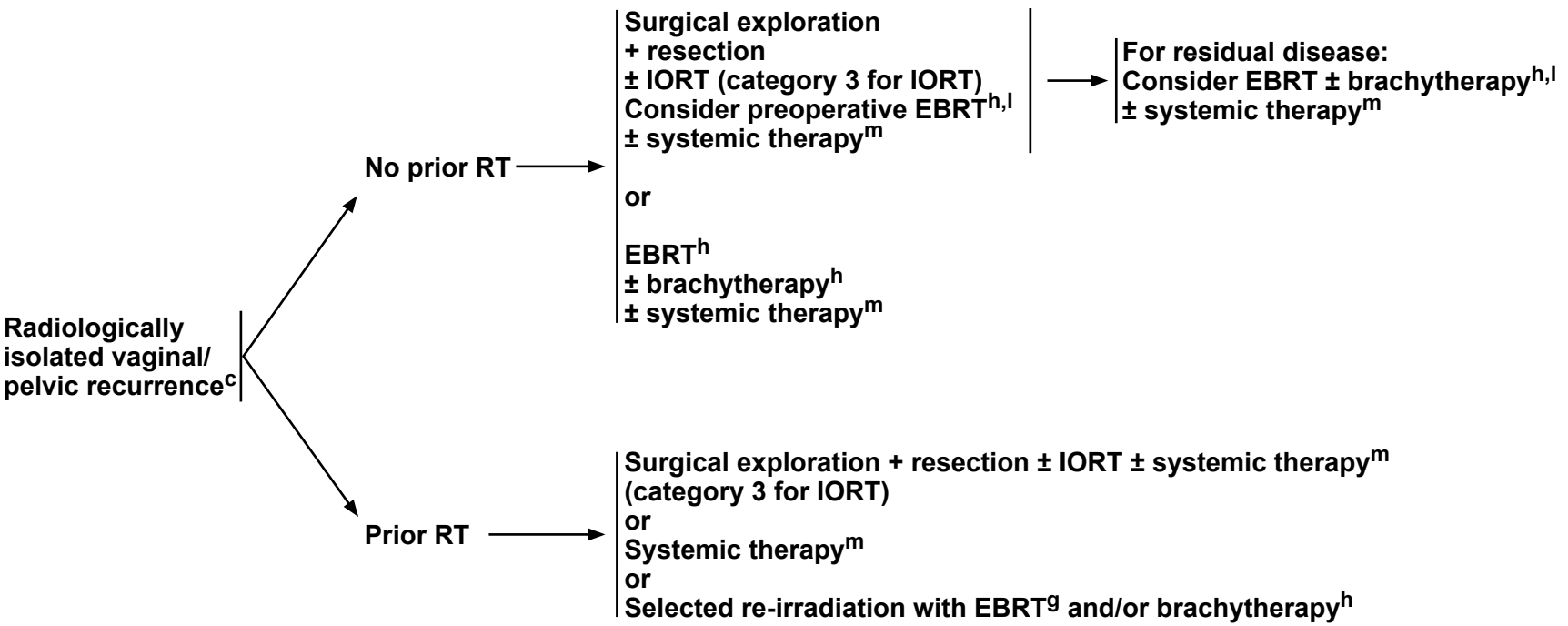
RECURRENCE

THERAPY FOR RELAPSE



[c] See Principles of Imaging (UTSARC-B).
[h] See Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[l] The use of preoperative EBRT would preclude postoperative EBRT.
[m] 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**
- **RH: Radical hysterectomy**

Pathologic assessment for sarcoma (including leiomyosarcoma, adenosarcoma, endometrial stromal sarcoma, and undifferentiated sarcoma):
- **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[b]**
- **Lymph nodes (when resected)**
  - **Level of nodal involvement (ie, pelvic, common iliac, para-aortic)**
  - **Number of lymph nodes with metastasis**

Molecular analysis for sarcoma
- **Molecular profiling is informative in many mesenchymal malignancies for accurate classification[3]**
  (See Uterine Sarcoma: Mesenchymal Tumors & Mixed Epithelial and Mesenchymal Tumors [UTSARC-A 2 of 8])
- **Comprehensive genomic profiling with a validated and/or FDA-approved assay 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] Although cytology by itself does not affect FIGO staging, cytology results should still be obtained because positive cytology is an adverse risk factor.

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Continued

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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*, and *PTEN*.	Immunoexpression of smooth muscle markers 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 prog-nostic 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 perivascular epithelioid cell neoplasms (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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References Continued

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**	**Other**
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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References
Continued

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**
Low-Grade Endometrial Stromal Sarcoma (LGESS)[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 an LGESS-associated fusion by FISH and/or targeted RNA sequencing is confirmatory.	Stage is the most important prognostic factor.	
High-Grade Endometrial Stromal Sarcoma (HGESS)[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 HGESS 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* internal tandem duplication.	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 *YWHAE*-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 LGESS.	
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/mm2 is associated with decreased survival.	

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References
Continued

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**
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 benign, uncertain malignant potential, and malignant as outlined below. Benign (<5 cm, no evidence of infiltrative growth, LVSI, or high nuclear grade, and ≤1 mitosis/50 mm^2). Uncertain malignant potential (general criteria: >5 cm or presence of nuclear pleomorphism/ multinucleated giant cells; modified gynecology specific criteria: <3 of the following (≥5 cm, high nuclear grade, >1 mitosis/50 mm^2, necrosis, or vascular invasion). Malignant if ≥2 of the following are present per general criteria and ≥3 features per modified criteria (>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 tumors.	Immunoexpression of cathepsin K, and 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 the three proposed algorithms and tumor stratification into the benign, uncertain malignant potential, and malignant subgroups. Treatment with mTOR inhibitors may be considered.	
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 cases. 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 cases 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. Tumors with *ALK* rearrangement may respond to tyrosine kinase inhibitors.	

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References
Continued

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). Immunohistochemistry 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 tyrosine kinase receptors has shown clinical benefit.	More commonly occurs in the uterine cervix.

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References
Continued

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)[16-18]	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 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)[19-21]	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 sarcomatous overgrowth. 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)[22-25]	Biphasic tumor with benign often metaplastic epithelium associated with an atypical usually low-grade spindle cell proliferation exhibiting phyllodes growth and periglandular stromal condensation. Sarcomatous overgrowth 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 sarcomatous overgrowth are poor prognostic factors. High-grade cytologic features may also portend a worse prognosis.	

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Continued

PRINCIPLES OF PATHOLOGY AND MOLECULAR ANALYSIS
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PRINCIPLES OF IMAGING[a,1-9]

Initial Workup

- **Chest/abdomen/pelvic CT**
- **For patients who underwent TH with incidental finding of uterine sarcoma or incompletely resected uterus/adnexa (ie, 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 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 annual to biannual imaging 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 annual to biannual imaging thereafter up to an additional 5 years.[c]**
- **Consider neck/chest/abdomen/pelvis/groin 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 and CT are performed with contrast throughout the guidelines 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.

Continued

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

	Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Systemic Therapies	• Doxorubicin • Docetaxel/ gemcitabine	• Doxorubicin/ifosfamide • Doxorubicin/dacarbazine • Gemcitabine/dacarbazine • Gemcitabine/vinorelbine • Dacarbazine • Gemcitabine • Epirubicin • Ifosfamide • Liposomal doxorubicin • Pazopanib[b] • Temozolomide[b] • Trabectedin[c] • Eribulin (category 2B)[b]	N/A
Biomarker-Directed Systemic Therapy for Second-Line Treatment	N/A	N/A	• Pembrolizumab for TMB-H tumors[d] • Larotrectinib or entrectinib for *NTRK* gene fusion-positive tumors[b] (category 2B) • Consider PARP inhibitors for *BRCA2*-altered uLMS[1] ▸ Olaparib[2] ▸ Rucaparib ▸ Niraparib

Footnotes

[a] See NCCN Guidelines for Ovarian Cancer--Management of Drug Reactions (OV-D).

[b] Pazopanib, temozolomide, eribulin, and larotrectinib or entrectinib may be considered for use in patients with recurrent or metastatic disease that has progressed on prior cytotoxic chemotherapy.

[c] For uLMS that has been treated with a prior anthracycline-containing regimen.

[d] For the treatment of patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors, as determined by a validated and/or FDA-approved test, that have progressed following prior treatment and have no satisfactory alternative treatment options.

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SYSTEMIC 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[e]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Aromatase inhibitors for low-grade ESS or adenosarcoma without SO	• Aromatase inhibitors (for ER/PR-positive uterine sarcomas) • Fulvestrant • 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)	N/A

[a] See NCCN Guidelines for Ovarian Cancer--Management of Drug Reactions (OV-D).
[e] 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.

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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 integrated 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.

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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. Multiple conformal fields based on CT treatment planning should be utilized, and consideration for IMRT for normal tissue sparing may be considered, with appropriate attention to quality assurance (QA) and tissue interfraction mobility. 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 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 cases.
    - ◊ 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 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.

- • **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.

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PRINCIPLES OF GYNECOLOGIC SURVIVORSHIP

Physical Effects

- Gynecologic cancer treatment typically involves surgery, chemotherapy, hormone therapy, radiation therapy, 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.
- Radiation therapy 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.
- 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 premenopausal patients, hormone replacement 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

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

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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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise 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.

NCCN Guidelines Version 1.2022
Uterine Neoplasms

Discussion

This discussion corresponds to the NCCN Guidelines for Uterine Neoplasms. Last updated: February 8, 2019.

Table of Contents

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 63,230 new uterine cancer cases will occur in 2018, with 11,350 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, older age (≥55 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). By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the NCCN panel during the process of developing these guidelines.

For patients with known or suspected uterine neoplasms, the initial preoperative evaluation/workup for known or suspected malignancy includes a history and physical examination, expert pathology review with additional endometrial biopsy as indicated, imaging, consideration of genetic evaluation, and other studies (see *Initial Evaluation* and *Principles of Imaging* in the NCCN Guidelines for Uterine Neoplasms).[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, 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 in older patients, it is prudent in selected patients to also measure renal and liver function.

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

Screening of the tumor for defective DNA mismatch repair (MMR) using immunohistochemistry and/or microsatellite instability (MSI) is used to

identify which patients should undergo mutation testing for Lynch syndrome (see *Lynch Syndrome* in the NCCN Guidelines for Colorectal Cancer Screening).[9,10,16-20] Universal testing of endometrial tumors for defects in DNA MMR is recommended (eg, *MLH1*, *MSH2*, *MSH6*). *MLH1* loss should be further evaluated for promoter methylation to assess for an epigenetic process rather than a germline mutation.[18] Genetic counseling and testing is recommended for patients with all other MMR abnormalities and for patients without MMR defects but who have a significant family history of endometrial and/or colorectal cancer (See *Lynch Syndrome [Hereditary Non-Polyposis Colorectal Cancer]* in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal).

Women with Lynch syndrome are at higher lifetime risk (up to 60%) for endometrial cancer; thus, close monitoring and discussion of risk-reducing strategies is recommended.[10,21,22] In relatives with Lynch syndrome but without endometrial cancer, a yearly endometrial biopsy is recommended to assess for cancer.[13,23] This strategy also enables select women to defer surgery (and surgical menopause) and to preserve their fertility. Prophylactic hysterectomy/bilateral salpingo-oophorectomy (BSO) can then be done after childbearing is complete or sooner, depending on patient preference.[24,25] In addition, interventions to decrease the risk from colorectal cancer may also be appropriate (eg, annual colonoscopy).

Literature Search Criteria and Guidelines Update Methodology

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 cervical cancer published since the previous Guidelines update, using the following search terms: uterine or endometrial and sarcoma or carcinoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only 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 during the Guidelines update 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.

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

Endometrial Cancer

In 2017, 67% of patients with adenocarcinoma of the endometrium were diagnosed with disease confined to the uterus at diagnosis.[26] Regional and distant disease comprised 21% and 8% of cases, respectively.

Many physicians believe that adenocarcinoma of the endometrium is a more treatable malignancy because the early symptoms of irregular vaginal bleeding (in this predominantly postmenopausal patient population) often trigger patients to seek care when the disease is at an early and treatable stage. However, data show that the mortality rate for uterine cancer has increased more rapidly than the incidence rate.[27] This increased mortality may be related to an increased rate of advanced-stage cancers, high-risk histologies (eg, serous carcinomas), and patients being diagnosed at an older age. Analysis of SEER data suggests that survival is increased in patients who are younger, have early-stage disease, and have lower-grade disease.[28] In addition to grade and depth of myometrial invasion, other risk factors associated with poor prognosis include age,

lymph node status, tumor size, lymphovascular space invasion (LVSI), and tumor involvement of the lower uterine segment.[29,30] To further improve outcome for patients with this disease, physicians need to identify high-risk patients and to tailor treatment appropriately to provide the best long-term survival. The panel suggests that gynecologic oncologists be involved in the primary management of all patients with endometrial cancer.

Diagnosis and Workup

About 90% of patients with endometrial carcinoma have abnormal vaginal bleeding, most commonly in the postmenopausal period. The workup was previously described (see *Overview* in this Discussion). Diagnosis can usually be made by an office endometrial biopsy.[31,32] The histologic information from the endometrial biopsy (with or without endocervical curettage) should be sufficient for planning definitive treatment. Office endometrial biopsies have a false-negative rate of about 10%. Thus, a negative endometrial biopsy in a symptomatic patient must be followed by a fractional dilation and curettage (D&C) under anesthesia.[31,33] Hysteroscopy may be helpful in evaluating the endometrium for lesions, such as a polyp, if the patient has persistent or recurrent undiagnosed bleeding.[34] Endometrial biopsy may not be accurate for diagnosing malignancies of the uterine wall such as mesenchymal tumors.

For detailed imaging recommendations by stage and planned treatment approach, see *Principles of Imaging* in the NCCN Guidelines for Uterine Neoplasms. Consideration of chest imaging (chest x-ray) is recommended. Other imaging tests such as CT, MRI, and/or PET/CT may be used to assess disease extent and to evaluate for metastatic disease as indicated based on clinical symptoms, physical findings, or abnormal laboratory findings.[35-40] In patients with extrauterine disease, a serum CA-125 assay may be helpful in monitoring clinical response.[41,42] However, serum CA-125 levels can be falsely increased in women who have peritoneal inflammation/infection or radiation injury, may be normal in women with isolated vaginal metastases, and may not predict recurrence in the absence of other clinical findings.[43-45] Currently, there is no validated screening test for endometrial carcinoma.[46,47]

Disease Staging

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

Several studies demonstrated that clinical staging was inaccurate and did not reflect actual disease extent in 15% to 20% of patients.[48-50] 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).[51] FIGO updated and refined the surgical/pathologic staging criteria for uterine neoplasms in 2009.[52-55] 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 updated (to take effect January 2018).[56]

The 2009 FIGO staging system streamlined stages I and II endometrial carcinoma. These revisions were made because the survival rates for some of the previous sub-stages were similar.[54] Stage IA is now less than

50% myometrial invasion, and stage IB is 50% or more myometrial invasion. Stage II only includes patients with cervical stromal invasion. Patients with uterine-confined disease and endocervical glandular involvement (mucosal involvement) without cervical stromal invasion are no longer considered stage II.[54] Stage IIIC is now subdivided into IIIC1 and IIIC2, because survival is worse with positive para-aortic nodes.[54] While most of the previously published studies discussed in these NCCN Guidelines used the older 1988 FIGO staging system, these have been reinterpreted by the NCCN panel to reconcile with the 2009 staging system.

Peritoneal cytology no longer affects the 2009 FIGO staging, because it is not viewed by some authors as an independent risk factor.[55] However, FIGO and AJCC continue to recommend that peritoneal washings be obtained and results recorded, because positive cytology may add to the effect of other risk factors (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).[57,58]

Principles of Evaluation and Surgical Staging for Endometrial Carcinoma

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

Pathology

An expert pathology review will determine the specific epithelial histology of the tumor (ie, various endometrioid histologies, serous carcinoma, clear cell carcinoma, carcinosarcoma, undifferentiated carcinoma). The pathologic assessment of the uterus and the nodes is described in the algorithm; this assessment should also include the Fallopian tubes, ovaries, and peritoneal cytology. If nodal resection was performed, the level of nodal involvement and size of metastasis should be determined. See *Hysterectomy and Pathologic Evaluation* in the NCCN Guidelines for Endometrial Carcinoma. The *Protocol for 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). Estrogen receptor testing is recommended in the setting of stage III, IV, or recurrent endometrioid carcinoma.

As the grade of the tumor increases, the accuracy of intraoperative evaluation of myometrial invasion decreases (ie, assessment by gross examination of fresh tissue). In one study, the depth of invasion was accurately determined by gross examinations in 87.3% of grade 1 lesions, 64.9% of grade 2 lesions, and 30.8% of grade 3 lesions.[59] 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.[60]

Lymphadenectomy

Previously, a full standard lymphadenectomy (ie, dissection and assessment of both pelvic and para-aortic nodes) was recommended for all patients; however, a more selective and tailored lymphadenectomy approach that may include the SLN algorithm is now recommended by the NCCN Panel to avoid systematic overtreatment.[61] No randomized trial data support routine full lymphadenectomy,[62] although some retrospective

studies have suggested that it is beneficial.[63-65] Two randomized clinical trials from Europe reported that routine lymph node dissection did not improve the outcome of endometrial cancer patients, but lymphadenectomy did identify those with nodal disease.[66,67] However, these findings remain a point of contention.[68-70] 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.[71,72] The other concerns include the lack of central pathology review, subspecialty of surgeons, and adequacy of statistical power.

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

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

The question of whether to add para-aortic lymphadenectomy to pelvic node dissection has been debated. Prior studies have shown conflicting information regarding the risk of para-aortic nodal metastases in patients without disease in the pelvic nodes.[50,73,75,76] There was a high rate of lymphatic metastasis above the inferior mesenteric artery, suggesting a need for systematic pelvic and para-aortic lymphadenectomy. Hence, para-aortic lymphadenectomy up to the renal vessels may be considered for selective high-risk situations, including those with pelvic lymphadenectomy or high-risk histologic features. Many surgeons do not do a full lymphadenectomy in patients with grade 1 early-stage endometrial cancer.[61]

In summary, lymph node dissection identifies patients requiring adjuvant treatment with RT and/or systemic therapy.[77] A subset of patients may not benefit from lymphadenectomy; however, it is difficult to preoperatively identify these patients because of the uncontrollable variables of change in grade and depth of invasion on final pathology. The NCCN panel recommends that lymphadenectomy should be done for selected patients with endometrial cancer with para-aortic lymphadenectomy done as indicated for high-risk patients (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).[6] Lymphadenectomy is contraindicated for patients with uterine sarcoma. SLN mapping can be considered as an alternative to full lymphadenectomy in the setting of apparent uterine-confined disease. The SLN surgical algorithm is described below.

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 with apparent uterine-confined endometrial cancer to assess whether they have metastatic pelvic lymph nodes.[78-82] In SLN mapping, dye is injected into the cervix, which travels to the sentinel nodes (see Figures 1–3 in *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).

A surgical SLN algorithm is proposed to decrease the false-negative rate (see Figure 4 in *Principles of Evaluation and Surgical Staging* in the NCCN

Guidelines for Endometrial Carcinoma).[78,83] 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.[84,85] Because SLNs identify the primary lymphatic pathway, this increases the yield of finding metastatic disease during the mapping process. If SLN mapping fails, a reflex side-specific nodal dissection should be performed.[78,86] 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.[82,85-91] Recent findings also suggest that indocyanine green may be preferable to blue dyes.[91-95] Attention to detail and experience are critical to ensure optimal outcomes.

An updated literature review and consensus recommendations for SLN mapping in endometrial cancer were recently released by the Society of Gynecologic Oncology (SGO).[82] 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. Additionally, results were recently published from the FIRES trial, which compared SLN mapping to lymphadenectomy for endometrial cancer in the largest multicenter prospective study to date (n = 385).[91] 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).

Until recently, much of the data to support SLN mapping was based on single-institution studies. 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.[96] Another recent systematic review and meta-analysis of 55 studies with n > 10 patients (n = 4915) generated an overall detection rate of 81% with a 50% bilateral pelvic node detection rate and 17% paraaortic detection rate.[95]

SLN mapping should be done in institutions with expertise in this procedure. If patients have apparent metastatic disease (based on imaging and surgical exploration), removal of nodes for staging purposes is not necessary because it will not change management.[35] The main contraindication for SLN mapping is uterine sarcoma. Historically, SLN mapping was controversial in patients with high-risk histology (eg, serous carcinoma, clear cell carcinoma, carcinosarcoma).[61,97] However, recently, 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 lymphadenectomy.[86,98]

SLN Ultrastaging

Recent data highlight the potential significance and impact of SLN ultrastaging (ie, serial sectioning and immunohistochemistry) to improve the accuracy of detecting micrometastases. Ultrastaging of SLNs can reveal lymph node metastases undetected through conventional histology, and studies suggest that SLN ultrastaging leads to upstaging in 5% to 15% of patients.[81,84,88,90,96]

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.[99] Long-term follow-up was reported from a prospective multicenter study in 125 patients with early-stage endometrial carcinoma who underwent SLN biopsy. Patients with a positive SLN underwent external beam radiation therapy (EBRT) and chemotherapy at a higher rate than those with a negative SLN. In patients with a detected

SLN, recurrence-free survival at 50 months was 84.7%, and no difference was detected between patients with and without a positive SLN (P = .5).[100]

In a cohort of 508 patients who underwent SLN mapping, ultrastaging detected 23 additional cases of micrometastasis that would have been missed by conventional hematoxylin and eosin staining.[101] A multicenter study of 304 women 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.[102]

Although these findings do not appear to be an artifact of uterine manipulation,[103] the implications and appropriate management of micrometastases or isolated tumor cells (ITCs) detected via SLN ultrastaging are not yet clear.[82,84,90,104-106] The prognostic significance of ITCs has been studied in breast cancer[107] where nodes containing ITCs are excluded from the positive node count per AJCC staging. Studies have recently begun to investigate the significance of ITCs discovered during SLN mapping in early-stage endometrial cancer.

A retrospective review examined 844 patients with endometrial cancer that underwent SLN mapping.[108] The majority of patients with ITCs, micrometastasis, and macrometastasis received adjuvant chemotherapy (83%, 81%, and 89%, respectively). Recurrence-free survival 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 recurrence-free survival (71%, P < .001).

A recent prospective observational study of 519 patients compared outcomes for patients with SLN macrometastasis, micrometastasis, and ITCs, taking into account adjuvant treatment.[109] 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. Future evaluation of prognosis/outcome may need to prospectively examine the threshold for and impact of adjuvant therapy for patients with scattered ITCs.

Minimally Invasive Procedures

Over the past decade, practice has trended towards minimally invasive approaches to total hysterectomy (TH)/BSO and lymph node assessment in patients with early-stage endometrial cancer.[110] Although these procedures may be performed by any surgical route (eg, laparoscopic, robotic, vaginal, abdominal), the standard in those with apparent uterine-confined disease is to perform the procedure via a minimally invasive approach. Randomized trials, a Cochrane Database Systematic Review, and population-based surgical studies support that minimally invasive techniques are preferred in this setting due to a lower rate of surgical site infection, transfusion, venous thromboembolism, decreased hospital stay, and lower cost of care, without compromise in oncologic outcome.[110-116] 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.[112,116]

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.[115,117] 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, $P < .0001$).[118,119] 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.[117] Laparoscopic staging was associated with improved postoperative quality of life across several parameters.[114]

Results were recently published from the LACE trial, which compared outcomes of patients with stage I endometrial carcinoma (n = 760) who were randomized to undergo TAH or total laparoscopic hysterectomy.[111] 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.[120] However, laparotomy may still be required for certain clinical situations (eg, elderly patients, those with a very large uterus) or certain metastatic presentations.[115,121,122]

Robotic surgery is a minimally invasive technology that has been increasingly used in the surgical staging of early-stage endometrial carcinoma due to its potential advantages over laparotomy, especially for obese patients.[123-127] Prospective cohort and retrospective studies suggest that robotic approaches perform similarly to laparoscopy and result in comparable or improved perioperative outcomes.[127-130] Oncologic outcomes appear to be comparable to other surgical approaches, although longer-term outcomes are still being investigated.[131-133] In heavier patients, robotic surgery may result in less frequent conversion to laparotomy when compared with laparoscopic approaches and also appears to be safe and feasible in patients at higher anesthesiologic risk.[127,128,134]

Costs for robotic equipment and maintenance remain high.[135 123,124,131-133,136] 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.[137-139] For recent reviews on the robotic-assisted surgery for gynecologic malignancies and associated cost issues, see Sinno and Fader and Gala et al.[140,141]

Primary Treatment

These NCCN Guidelines divide pure endometrioid cancer into three categories for delineating treatment: 1) disease limited to the uterus; 2) suspected or gross cervical involvement; and 3) suspected extrauterine disease. Most patients with endometrial cancer have stage I disease at presentation, and surgery (with or without adjuvant therapy) is recommended for medically operable patients. As a general principle, endometrial carcinoma should be removed en bloc to optimize outcomes; intraperitoneal morcellation should be avoided.[142-145]

Disease Limited to the Uterus

To stage medically operable patients with endometrioid histologies clinically confined to the fundal portion of the uterus, the recommended surgical procedure includes TH/BSO with surgical staging and lymph node assessment (see *Hysterectomy and Pathologic Evaluation,* and *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma and in this Discussion).[68] When indicated, surgical staging is recommended to gather full pathologic and prognostic data on which to base decisions regarding adjuvant treatment for select patients who do not have medical or technical contraindications to lymph node dissection (see *Lymphadenectomy* and *Sentinel Lymph Node Mapping* in

this Discussion). Ovarian preservation may be safe in select premenopausal women with stage I endometrioid cancer.[146-148] 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; www.facs.org/quality-programs/cancer/ncdb/qualitymeasures).

During surgery, the intraperitoneal structures should be carefully evaluated, and suspicious areas should be biopsied. While not specifically affecting staging, FIGO recommends that peritoneal cytology should be collected and results should be recorded. Enlarged or suspicious lymph nodes should be excised to confirm or rule out metastatic disease. Retroperitoneal node dissection with pathologic evaluation—in the absence of clinically apparent lymphadenectomy—is useful when using the 2009 FIGO staging criteria, but its routine use has been questioned (see *Lymphadenectomy* in this Discussion).

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

Incomplete Surgical Staging

For patients with incomplete (ie, not thorough) surgical staging and high-risk intrauterine features, imaging is often recommended, especially in patients with higher grade and more deeply invasive tumors.[149,150] Surgical restaging, including lymph node dissection, can also be done.[73] Based on the imaging and/or surgical restaging results, recommended adjuvant treatment options are provided in the algorithm (see Adjuvant Treatment for *Incompletely Surgically Staged* in the NCCN Guidelines for Endometrial Carcinoma).

Fertility-Sparing Therapy

Although the primary treatment of endometrial cancer is usually hysterectomy, continuous progestin-based therapy may be considered for highly selected patients with Grade 1, stage IA (noninvasive) disease who wish to preserve their fertility.[151-155] 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. When considering fertility-sparing therapy, all of the criteria must be met as outlined in the algorithm (eg, no metastatic disease). Selected patients may require genetic counseling and testing. Patients should also receive counseling that fertility-sparing therapy is not the standard of care for the treatment of endometrial carcinoma. TH/BSO with surgical staging is recommended after childbearing is complete, if therapy is not effective, or if progression occurs. Fertility-sparing therapy is not recommended for high-risk patients (eg, those with high-grade endometrioid adenocarcinomas, uterine serous carcinoma, clear cell carcinoma, carcinosarcoma, and uLMS).

Continuous progestin-based therapy may include megestrol acetate, medroxyprogesterone, or an intrauterine device containing levonorgestrel.[151,152,156] A durable complete response occurs in about 50% of patients.[151] The use of progestin-based therapy should be carefully considered in the context of other patient-specific factors, including contraindications such as breast cancer, stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis, and smoking.

In patients receiving progestin-based therapies, the NCCN panel recommends close monitoring with endometrial sampling (biopsies or

D&C) every 3 to 6 months. TH/BSO with staging is recommended: 1) after childbearing is complete; 2) if patients have documented progression on the biopsies; or 3) if endometrial cancer is still present after 6 to 12 months of progestin-based therapy.[155,157] Although some young women who had subsequent negative endometrial biopsies after hormonal therapy were able to become pregnant (35%), their ultimate recurrence rate was high (35%).[151,154,158-160] In patients with persistent endometrial carcinoma after 6 months of failed hormonal therapy, the panel recommends pelvic MRI as to exclude myoinvasion and nodal/ovarian metastasis before continuing on fertility sparing therapy.

In premenopausal women with stage IA to B endometrial cancer, data suggest that ovarian preservation is safe and not associated with an increased risk of cancer-related mortality; patients were followed for 16 years.[146] Other studies also suggest that ovarian preservation may be safe in women with early-stage endometrial cancer.[147,148]

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).[149,150] If negative, patients are assumed to have disease that is limited to the uterus and are treated as previously described (see *Primary Treatment* in the NCCN Guidelines for Endometrial Carcinoma). It may be difficult to distinguish primary cervical carcinoma from stage II endometrial carcinoma. Thus, for operable patients with cervical involvement, TH or radical hysterectomy is recommended along with BSO, cytology (peritoneal lavage), and dissection of lymph nodes if indicated (see *Principles of Evaluation and Surgical Staging* and *Hysterectomy and Pathologic Evaluation* in the NCCN Guidelines for Endometrial Carcinoma).[68] In these patients, radical or modified radical hysterectomy may improve local control and survival when compared with TH.[161,162] Alternatively, the patient may undergo EBRT and brachytherapy (category 2B) followed by TH/BSO and surgical staging. However, preoperative RT is a category 2B recommendation because the NCCN panel feels that upfront surgery is the preferred option for these patients.

Patients Not Suited for Primary Surgery

For uterine-confined disease not suitable for primary surgery, EBRT and/or brachytherapy is the preferred treatment approach. Initial systemic therapy can also be considered for selected patients with uterine-confined tumors of endometrioid histology (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).[46,163] Progesterone-based therapy has been shown to provide some benefit with low toxicity in patients with low-grade tumors.[164] Tamoxifen with alternating megestrol[165] and aromatase inhibitors have also been used.[166-169]

For suspected gross cervical involvement in patients who are not suited for primary surgery, EBRT and brachytherapy is an effective treatment that can provide some measure of pelvic control and long-term PFS (see *Principles of Radiation Therapy* in the NCCN Guidelines for Uterine Neoplasms).[170-173] EBRT and brachytherapy should be administered with (or without) systemic therapy. If rendered operable, local treatment should follow. Systemic therapy alone is also a primary treatment option (category 2B), but should be followed by local treatment consisting of surgery if feasible (EBRT + brachytherapy if inoperable).

Suspected Extrauterine Disease

If extrauterine disease (endometrioid histologies) is suspected, imaging studies are recommended if clinically indicated (see *Additional Workup* in the NCCN Guidelines for Endometrial Carcinoma) and CA-125 testing can be considered. Estrogen receptor 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. Ascites or disease with involvement of the omentum, nodes (including inguinal nodes), ovaries, or peritoneum warrants surgical intervention using TH/BSO with cytology (peritoneal lavage), pelvic and para-aortic lymph node dissection if indicated, and surgical debulking. Consider preoperative systemic therapy. The surgical goal is to have no measurable residual disease; several studies support debulking.[68,174-176]

Patients with unresectable extrauterine pelvic disease (ie, vaginal, bladder, bowel/rectal, nodal, or parametrial involvement) are typically treated with EBRT with (or without) brachytherapy and/or systemic therapy, followed by re-evaluation of tailored surgery.[177-180] Systemic therapy alone can also be considered. Based on treatment response, patients should be re-evaluated for surgical resection and/or RT. For distant visceral metastasis (eg, liver involvement), recommended options include systemic therapy and/or EBRT and/or hormone therapy. Palliative TH/BSO may be considered.

Adjuvant Therapy

Uterine-Confined Disease

Thorough surgical staging provides important information to assist in selection of adjuvant therapy for endometrial tumors (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma). Patients with stage I endometrial cancer who have thorough surgical staging are stratified by adverse risk factors (ie, age, positive LVSI, tumor size, and lower uterine segment or surface glandular involvement).[181,182] Recommended adjuvant treatment is shown in the algorithm (see the NCCN Guidelines for Endometrial Carcinoma). Note that the treatment algorithm was revised in 2010 based on the updated FIGO staging.[54] However, by necessity, much of the discussion in this manuscript has been based on data from patients staged using the older FIGO/AJCC staging system. The implications of *stage migration* should be taken into account when evaluating historical data.

The basic concept underlying the recommendations in the NCCN Guidelines is the trend toward selection of more aggressive adjuvant therapy for patients as tumor grade and myometrial and/or cervical invasion worsen, because risk exists on a continuum.[183-185] In surgical stage I and II endometrial cancer, other pathologic factors that may influence the decision regarding adjuvant therapy include LVSI, patient age, tumor volume, depth of invasion, and lower uterine segment or surface cervical glandular involvement. When administering adjuvant RT, it should be initiated as soon as the vaginal cuff has healed, no later than 12 weeks after surgery.

Significant controversy centers on how much adjuvant therapy is necessary in patients with surgical stage I endometrial cancer, regardless of intrauterine features, if extrauterine disease has been clearly ruled out. In a large prospective study, the Gynecologic Oncology Group (GOG) reported that the 5-year survival rate for surgical stage I patients with no adverse risk factors other than grade and myometrial invasion (ie, without extrauterine disease, isthmus/cervical involvement, or LVSI) was 92.7%.[186] The practice of surgical staging has led to a decrease in the use of adjuvant therapy for stage I endometrial carcinoma, which is reflected in the option of *observation* in the NCCN Guidelines (see section on adjuvant treatment in the NCCN Guidelines for Endometrial Carcinoma).[77,182,183,187-189] The NCCN panel recommends observation only for select patients with no residual disease in the hysterectomy specimen.

The recommended postoperative (ie, adjuvant) treatment options for surgical stage II patients (using thorough surgical staging) are shown in the algorithm (see *Adjuvant Treatment for Stage II* in the NCCN Guidelines for Endometrial Carcinoma). The NCCN panel generally agrees on the role of adjuvant therapy for patients with an invasive

cervical component if extrafascial hysterectomy is performed. However, for patients with stage II disease who have had a radical hysterectomy with negative surgical margins and no evidence of extrauterine disease, observation or vaginal brachytherapy are options. As with stage I disease, the presence of adverse risk factors should be considered when selecting adjuvant therapy.[190]

In 2017, the panel removed observation as a recommended option in the adjuvant setting for patients with stage IA, grade 3 disease with additional risk factors and stage IB grade 3 disease without adverse risk factors. For patients with stage IA/IB, grade 3 disease (IA with adverse risk factors and IB without), systemic therapy was added as a category 2B option when performed along with the primary recommendation of vaginal brachytherapy and/or EBRT. For stage IB, grade 3 disease with adverse risk factors, the option of systemic therapy (in addition to EBRT and/or vaginal brachytherapy) was upgraded to a category 2A option.

Adjuvant RT

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

Four trials have evaluated the role of adjuvant external-beam pelvic RT in patients with endometrial carcinoma. In 2 of these trials, the patients were not formally staged (Postoperative Radiation Therapy in Endometrial Carcinoma [PORTEC-1], Aalders).[191,192] In the third trial (ASTEC/EN.5), only 50% of the patients were thoroughly staged as part of a companion surgical protocol.[66,193] However, formal surgical staging was mandated for all patients in the fourth trial (GOG 99).[194] Note that these trials used the older staging system (ie, before 2009).

The PORTEC-1 trial suggested that external-beam pelvic RT provides a therapeutic benefit in selected patients with uterine-confined disease.[191,195] Although RT significantly decreased locoregional recurrence, it did not increase OS.[196] The Aalders' randomized trial found that RT reduced vaginal (ie, locoregional) recurrences but did not reduce distant metastases or improve survival.[192] A recent pooled randomized trial (ASTEC/EN.5) suggested that adjuvant pelvic RT alone did not improve either relapse-free survival (ie, PFS) or OS in patients with intermediate-risk or high-risk early-stage endometrial cancer, but there was a small improvement in pelvic control.[193] However, the ASTEC/EN.5 study is very controversial; 51% of the patients in the ASTEC observation group received vaginal brachytherapy.[70,197] The Keys' trial (GOG 99) showed that adjuvant pelvic RT improved locoregional control and relapse-free interval (ie, PFS), without OS benefit.[194] Both the GOG 99 and PORTEC-1 trials revealed that most of the initial recurrences for patients with initial uterine-confined tumors were limited to the vagina, prompting the increasing use of vaginal brachytherapy alone as adjunctive treatment.[194,198,199]

To help select a patient population who may benefit from adjuvant RT, the GOG 99 and PORTEC trials defined risk factors for women at high-intermediate risk (HIR) for recurrence.[191,194] These risk factors include age, in addition to deep myometrial invasion, grade, and LVSI. In GOG 99, women younger than 50 years had to have all 3 histologic risk factors to be considered HIR.[194] If they were 50 to 70 years, they were considered

HIR if they had 2 histologic risk factors. Women 70 years or older were defined as HIR if they also had one risk factor. In PORTEC-1, women had to have 2 of 3 risk factors (ie, age >60 years, deep myometrial invasion, grade 3 histology) to be considered at HIR for recurrence.[191,198]

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.[200] Given that vaginal brachytherapy is associated with significantly less toxicity than pelvic RT, vaginal brachytherapy alone is a reasonable choice for most patients with uterine-confined endometrial cancer who are deemed candidates for adjuvant radiotherapy.[198-207] The use of vaginal brachytherapy and/or whole pelvic RT should be carefully tailored to a patient's pathologic findings. Both PORTEC-1 and PORTEC-2 specifically excluded patients with 1998 FIGO stage 1C and grade 3 endometrial carcinoma (2009 FIGO stage IB, grade 3);[54] thus, the use of adjuvant brachytherapy alone in the highest risk subset remains undetermined.

A recent trial (GOG 249) examined vaginal cuff brachytherapy and carboplatin/paclitaxel therapy (brachy+chemo) versus pelvic EBRT only in patients with high-risk, uterine-confined endometrial carcinoma (n= 601). Unlike PORTEC-2, GOG 249 reported significantly increased rates of nodal recurrence (primarily pelvic) in the brachy+chemo arm versus 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 brachy+chemo arm. At a median follow-up of 53 months, 3-year recurrence-free survival was 82% for both treatment arms; 3-year OS was 88% for the brachy+chemo 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.[208]

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 versus vaginal brachytherapy) was predictive for LRR and DFS.[181] The benefit of adjuvant EBRT in the highest risk spectrum of uterine-confined disease remains controversial. Most NCCN Panel Members feel that patients with deeply invasive grade 3 tumors should receive adjuvant treatment. Two large retrospective SEER analyses of women with endometrial cancer found that adjuvant RT improved OS in those with high-risk disease.[209,210] 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.[202,211-215]

Recently, results were published from a long-term follow-up study (median 20.5 years) of 568 patients with early-stage endometrial carcinoma who were enrolled in the Aalders trial. The study compared long-term outcomes in women who received vaginal brachytherapy plus EBRT versus vaginal brachytherapy alone. The findings suggested no statistical difference in OS between the study groups, and in this cohort, patients younger than 60 years of age who received EBRT had increased incidence of secondary cancers and subsequent higher mortality rates.[202]

Adjuvant Systemic Therapy

Patients with deeply invasive, grade 3, uterine-confined disease (2009 FIGO stage IB, grade 3 [formerly 1988 FIGO stage IC, grade 3]) have a relatively poor prognosis. Despite adjuvant therapy with pelvic RT, a

significant number of patients continue to have an appreciable risk of distant metastases.[194,195] Therefore, some clinicians suggested that adding systemic therapy to adjuvant RT may provide added therapeutic benefit (ie, decrease in distant metastases).[183,216] Studies have evaluated the role of systemic therapy in highest risk uterine-confined disease.[216,217] PFS is improved with adjuvant sequential chemotherapy/RT.[216] 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.[216] We await final results from GOG 249.

Carboplatin/paclitaxel is the preferred regimen in the adjuvant setting for high-risk uterine confined disease.[218-220]

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.[221-223] Patients with extrauterine disease confined to the lymph nodes or the adnexa may be treated with pelvic or extended-field RT alone.[224] However, systemic therapy is regarded as the foundation of adjuvant therapy for patients with extrauterine disease.

For stage IIIA to IIIC disease, the recommended treatment options are systemic therapy and/or EBRT with (or without) vaginal brachytherapy. For stage IVA/IVB disease systemic therapy forms the mainstay of treatment and can be combined with EBRT and/or vaginal brachytherapy.

Previously, whole abdominal RT was used for carefully selected patients deemed at risk for peritoneal failure, and RT appeared to have provided therapeutic benefit in retrospective studies.[225,226] 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.[178]

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 no longer recommended. For the purposes of these guidelines, whole abdominal radiotherapy is not considered to be tumor-directed RT (see *Principles of Radiation Therapy* in the NCCN Guidelines for Uterine Neoplasms). Multimodality therapy is now the basis of randomized trials evaluating therapy (eg, GOG 258, PORTEC-3).

Recurrences were frequent in both treatment arms of GOG 122, occurring in the pelvis and abdomen. Approximately 52% of patients with advanced endometrial carcinoma had recurrences, indicating the need for further therapeutic improvement in this high-risk patient population.[178] A study found that combined modality adjuvant therapy (using chemotherapy and tumor-directed RT) may provide a therapeutic benefit when compared with other sequencing modalities (chemotherapy followed by RT or vice versa).[180,227,228]

A follow-up study evaluated the role of chemotherapy “intensification” for this patient population. The GOG 184 trial assessed combination chemotherapy (cisplatin and doxorubicin with [or without] paclitaxel) with more limited radiation fields (involved-field radiation either to the pelvis or to the pelvis plus para-aortic nodes). Results indicate that the 3-drug

regimen did not improve survival when compared with the 2-drug regimen after 3 years of follow-up and that the more intensive chemotherapy resulted in greater toxicity (eg, hematologic toxicity, sensory neuropathy, myalgia).[179]

Adjuvant therapy options were compared in a multicenter retrospective analysis of 265 patients with optimally resected stage IIIC endometrial carcinoma. Compared with patients receiving adjuvant RT or adjuvant RT plus chemotherapy, patients who received adjuvant chemotherapy had a 2.2 fold increased risk of recurrence and a 4.0 fold increased risk of death.[223] 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 that received RT had similar OS compared with those who did not.[229] In a multicenter retrospective review of 73 patients with stage IIIA endometrial carcinoma, surgery followed by both chemotherapy and radiation therapy provided the highest 5-year OS.[230] 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%.[231] The role of adjuvant RT with systemic therapy for treating high-risk endometrial carcinoma remains an area of active investigation (eg, GOG 258, PORTEC-3).

Radiotherapy Principles

RT has been a widely used modality in the treatment of patients with endometrial cancer; it clearly improves locoregional control. *Tumor-directed RT* refers to RT directed at sites of known or suspected tumor involvement and may include EBRT and/or vaginal brachytherapy.[184] 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,[232] studies have focused on subtle effects on quality of life (eg, diarrhea, bowel symptoms) that deserve further investigation.[203,205,233] In the PORTEC-2 trial, vaginal brachytherapy was associated with better quality of life when compared with EBRT without a significant detriment to outcome.[203] Therefore, many patients who were previously treated with adjuvant EBRT are now appropriately treated with vaginal brachytherapy; this recommendation is reflected in the NCCN Guidelines. Patients treated with RT are prone to vaginal stenosis, which can impair sexual function. Women can use vaginal dilators to prevent or treat vaginal stenosis. Dilator use can start 2 to 4 weeks after RT is completed and can be used indefinitely (http://www.mskcc.org/cancer-care/patient-education/resources/improving-your-vaginal-health-after-radiation-therapy).

Post-Treatment Surveillance

The recommended post-treatment surveillance protocol for endometrial cancer is shown in the algorithm (see *Surveillance* in the NCCN Guidelines for Endometrial Carcinoma).[35] These recommendations recognize that the value of intensive surveillance has not been demonstrated in this disease; therefore, ancillary testing is not recommended.[234,235]

Patients with clinical stage I and stage II endometrial cancer have a recurrence rate of approximately 15%;[235-238] 50% to 70% of these patients are symptomatic. For most patients, disease recurs within 3 years of initial treatment. Because most recurrences are symptomatic, all patients should receive verbal and written information regarding the symptoms of recurrent disease.[235] Patients with bleeding (vaginal, bladder, or rectal), decreased

appetite, weight loss, pain (in the pelvis, abdomen, hip, or back), cough, shortness of breath, and swelling (in the abdomen or legs) should seek prompt evaluation and not delay until the next scheduled appointment.

As clinically indicated, imaging may be helpful in the detection of recurrence. The panel recommends imaging based on symptomatology and clinical concern for metastatic disease. In patients with treated stage III/IV disease, chest/abdominal/pelvic CT is an optional recommendation every 6 months during the first 3 years of surveillance, and every 6 to 12 months for an 2 additional years.

For suspected recurrence or metastasis, several imaging recommendations were added in 2017. Abdominal/pelvic CT and/or chest CT is recommended based on symptoms or physical exam findings suspicious for recurrence or metastasis. Additional imaging considerations include whole body PET/CT in select patients who may be candidates for surgery/locoregional therapy and/or pelvic MRI for patients who retain their uterus.

In the absence of recurrence, post-treatment surveillance provides psychosocial reassurance and improves quality of life for patients and their families. Health maintenance has been incorporated into the follow-up schedule (eg, blood pressure determination, breast examination, mammography as clinically indicated, stool guaiac test, immunizations). Patients should receive counseling and education regarding lifestyle, obesity, exercise, smoking cessation, sexual health, nutrition, and potential late or long-term effects of treatment (see the NCCN Guidelines for Survivorship, the NCCN Guidelines for Smoking Cessation, and http://www.cancer.org/treatment/survivorshipduringandaftertreatment/index).[233,239-241] Other health problems that often coexist in patients with endometrial cancer can also be evaluated during follow-up.

Given the lack of prospective studies regarding the optimal frequency of post-treatment follow-up, the NCCN Panel believes that the algorithm represents a reasonable surveillance scheme. The use of vaginal cytology is no longer recommended for asymptomatic patients consistent with the SGO guidelines.[234,235,238,242] 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.[234,243] A recent multi-institutional review examined the utility of various surveillance methods in 254 patients with high-grade disease, revealing that symptoms led to the detection of the most recurrences (56%), followed by physical exam (18%), surveillance CT (15%), CA-125 (10%), and vaginal cytology (1%).[244]

Hormone Replacement Therapy for Hypoestrogenism

After BSO, hypoestrogenism is associated with hot flashes, mood lability, vaginal dryness, pelvic soft tissue atrophy, osteoporosis, and an increased risk of cardiovascular disease. In postmenopausal women, estrogen replacement therapy was believed to reduce or reverse some of these signs and symptoms. However, women who have had BSO for endometrial adenocarcinoma have usually been denied estrogen replacement therapy for fear of inducing a higher relapse rate, because this cancer has historically been considered an estrogen-linked malignancy.[245,246] As such, estrogen replacement therapy for such patients remains controversial.

However, it has never been proven that relapse rates are higher in endometrial cancer patients who receive estrogen replacement therapy after hysterectomy. Several retrospective trials of estrogen replacement after treatment of early-stage endometrial cancer have shown no increase in tumor recurrence or cancer-related deaths.[247-249] In women with stage I to II endometrial cancer who had hysterectomy, a randomized trial of

estrogen replacement therapy versus placebo did not find an increased rate of recurrence or new malignancy; the median follow-up was 35.7 months.[250] However, estrogen replacement trials in postmenopausal females without a history of malignancy have demonstrated a significantly increased risk for breast cancer.[251]

Initially, the Women's Health Initiative (WHI) Estrogen-Alone Trial in women who had hysterectomy (n = 10,739) reported that the risk of breast cancer and cardiovascular disease (eg, stroke) were increased and that estrogen replacement therapy was of concern; thus, the trial was stopped.[252] However, recent long-term follow-up data from this trial suggest that the risk from estrogen-alone replacement therapy (without progesterone) may not be as high in younger women (<60 years) who have had hysterectomy.[253]

The NCCN panel agrees that estrogen replacement therapy is a reasonable option for patients who are at low risk for tumor recurrence, but initiating such therapy should be individualized and discussed in detail with the patient.[254,255] If adjuvant treatment is carried out, there should be a 6- to 12-month waiting period before initiation of hormone replacement therapy, and participation in clinical trials is strongly encouraged. Selective estrogen-receptor modulators (SERMs) may prove to be attractive options for hormone replacement therapy.[256,257] Long-term comparisons between conjugated estrogens and SERMs for hormone replacement therapy are needed. Non-hormonal therapy may be considered in patients who are deemed poor candidates for hormone replacement therapy (eg, smokers, history of breast cancer, history of multiple strokes).[258,259]

Treatment of Recurrent or Metastatic Disease

Localized Disease

Patients with local or regional recurrences can be evaluated for further treatment (see *Clinical Presentation* in the NCCN Guidelines for Endometrial Carcinoma). For recurrences confined to the vagina or the pelvis alone, second-line treatment (typically with RT and/or surgery or systemic therapy) can be effective. For patients with no prior RT exposure at the recurrence site or previous brachytherapy only, the panel recommends RT plus brachytherapy, or surgery. Isolated vaginal recurrences treated with RT have good local control and 5-year survival rates of 50% to 70%.[260-262] Prognosis is worse if there is extravaginal extension or pelvic lymph node involvement.[261] After RT, it is unusual for patients to have recurrences confined to the pelvis. The management of such patients remains controversial. For patients previously treated with brachytherapy only at the recurrence site, surgery with (or without) intraoperative RT (IORT) is recommended (category 3 for IORT). For patients previously treated with EBRT at the recurrence site, recommended therapy for isolated relapse includes: 1) surgery with (or without) IORT (category 3 for IORT); and/or 2) systemic therapy with (or without) palliative RT. In selected patients, radical surgery (ie, pelvic exenteration) has been performed with reported 5-year survival rates approximating 20%.[263-266]

Treatment for para-aortic or common iliac lymph node invasion and for upper abdominal or peritoneal recurrences is shown in the algorithm (see *Additional Therapy* in the NCCN Guidelines for Endometrial Carcinoma). However, for gross upper abdominal residual disease, more aggressive treatment for relapse is recommended, as outlined for disseminated metastases in *Therapy for Relapse* in the NCCN Guidelines for Endometrial Carcinoma. For resectable isolated metastases, consider surgical resection and/or RT, or ablative therapy. Providers can also consider systemic therapy (category 2B). Further recurrences or disease not amenable to local therapy are treated as disseminated metastases. Palliative care measures should also be considered in management of patients with systemic disease (see the NCCN Guidelines for Palliative Care and http://emedicine.medscape.com/article/270646-overview).

Systemic Disease

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

Hormonal Therapy

The role of hormonal therapy in recurrent or metastatic cancer has been primarily evaluated in patients with endometrioid histologies only. Hormonal therapy is also used for selected patients with ESS (see section on *Uterine Sarcomas* in this Discussion). Hormonal agents for treating metastatic disease include megestrol with alternating tamoxifen, progestational agents alone, aromatase inhibitors, tamoxifen alone, or fulvestrant.[165-167,267-269] 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.[169,270-272] Tamoxifen has a 20% response rate in disease that does not respond to standard progesterone therapy.[273,274] Tamoxifen has also been combined with progestational agents; however, a few patients had grade 4 thromboembolic events with this combination regimen.[165,267,275] In some patients, aromatase inhibitors (eg, anastrozole, letrozole) may be substituted for progestational agents or tamoxifen.[168,169,272,276]

Other hormonal modalities have not been well-studied, and adjuvant therapy with hormonal agents has not been compared with cytotoxic agents.[169,277] If disease progression is observed after hormonal therapy, cytotoxic chemotherapy can be considered. However, clinical trials or best supportive care (see the NCCN Guidelines for Palliative Care) are appropriate for patients with disseminated metastatic recurrence who have a poor response to hormonal therapy and chemotherapy.

Systemic Therapy

Chemotherapy for endometrial cancer has been extensively studied.[278,279] Based on the current data, multiagent chemotherapy regimens are preferred for metastatic, recurrent, or high-risk disease, if tolerated. Single-agent therapy can also be used (see *Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease* in the NCCN Guidelines for Endometrial Carcinoma). Recommended multiagent chemotherapy regimens include carboplatin/paclitaxel, cisplatin/doxorubicin, cisplatin/doxorubicin/paclitaxel, carboplatin/docetaxel, carboplatin/paclitaxel/bevacizumab, ifosfamide/paclitaxel (for carcinosarcoma, category 1), cisplatin/ifosfamide (for carcinosarcoma), carboplatin/paclitaxel/trastuzumab (for HER2-positive serous carcinoma), and everolimus/letrozole (for endometrioid histologies). See *Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease* in the NCCN Guidelines for Endometrial Carcinoma.

A phase III randomized trial (GOG 177) compared 2 combination chemotherapy regimens in women with advanced/metastatic or recurrent endometrial carcinoma. The 273 women were randomly assigned to 1) cisplatin, doxorubicin, and paclitaxel; or 2) cisplatin and doxorubicin. The 3-drug regimen was associated with improved survival (15 vs. 12 months, $P < .04$) but with significantly increased toxicity (ie, peripheral neuropathy); therefore, it is not widely used.[280,281] These regimens are now category 2A in the NCCN Guidelines, because most panel members feel that

carboplatin/paclitaxel is a less toxic regimen (see *Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease* in the NCCN Guidelines for Endometrial Carcinoma). The response rates with other multiagent chemotherapy have ranged from 31% to 81% but with relatively short durations. The median survival for patients in such trials remains approximately 1 year.[278,279]

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.[282-285] A phase III trial (GOG 209) compared carboplatin and paclitaxel versus cisplatin, doxorubicin, paclitaxel, and filgrastim (granulocyte-colony stimulating factor).[282] Trial data presented at a national meeting show that oncologic outcomes are similar, but the toxicity and tolerability profile favor carboplatin/paclitaxel. Thus, the carboplatin/paclitaxel regimen is now the preferred approach for many patients. For patients in whom paclitaxel is contraindicated, docetaxel can be considered in combination with carboplatin.[286]

A phase II trial initially examined the addition of bevacizumab to carboplatin and paclitaxel among 15 patients with advanced or recurrent endometrial carcinoma.[287] Although this study was closed early due to the 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.[288] Collective median PFS was 20 months with a median OS of 56 months. An overall response rate of 82.8% was noted, with an 87.5% response rate among the subset of 8 patients who received this triplet as second-line therapy after carboplatin/paclitaxel.[288]

Everolimus combined with letrozole is under investigation for recurrent disease with positive preliminary findings in disease of endometrioid histology. In the preliminary results, the clinical benefit rate and objective response rate among 35 evaluable patients was 40% and 32%, respectively.[289]

If multiagent chemotherapy regimens are contraindicated, then single-agent therapy options include paclitaxel, albumin-bound paclitaxel, cisplatin, carboplatin, doxorubicin, liposomal doxorubicin, topotecan, and docetaxel (category 2B for docetaxel) (see *Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease* in the NCCN Guidelines for Endometrial Carcinoma).[169,290-292] When single agents are used as first-line treatment, responses range from 21% to 36%.[272,293] When single agents are used as second-line treatment, responses range from 4% to 27%; paclitaxel is the most active in this setting.[293] Some oncologists have used liposomal doxorubicin, because it is less toxic than doxorubicin; the response rate of liposomal doxorubicin is 9.5%.[294] Docetaxel is recommended for use as a single agent; however, it is a category 2B recommendation because some panel members would not use docetaxel because it is less active (7.7% response rate) than other agents.[164,295]

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).[296] Studies have also indicated that MMR-deficient (dMMR) tumors are sensitive to programmed death receptor-1 (PD-1) blockade.[297-299] Results were recently 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).[297] The FDA expanded pembrolizumab approval in 2017 to include treatment of unresectable or metastatic, MSI-high (MSI-H), or dMMR solid tumors that have progressed following prior treatment and that have no satisfactory alternative treatment options.[299] The panel voted

to include pembrolizumab as a treatment option for MSI-H/dMMR endometrial tumors and recommends that recurrent endometrial tumors be tested for MSI-H or dMMR if not done previously.

New biologic and molecular therapies for the treatment of recurrent or metastatic endometrial carcinoma are being assessed in clinical trials.[164,300] 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.[301] Temsirolimus has been used as first-line or second-line therapy for recurrent or metastatic endometrial cancer and has a partial response rate of 4% in second-line therapy.[302] Based on these studies, the NCCN panel considers bevacizumab or temsirolimus as appropriate single-agent biologic therapy for patients who have progressed on previous cytotoxic chemotherapy.[300-303]

Uterine Serous Carcinomas, Clear Cell Carcinomas, and Carcinosarcomas

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.[304-311] Carcinosarcomas are aggressive tumors that are staged as high-grade endometrial cancer.[312,313] 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 (see Table 1).[56]

Pathologists now believe that carcinosarcomas (also known as MMMTs) are metaplastic carcinomas and not uterine sarcomas; therefore, carcinosarcomas are included in the high-risk malignant epithelial tumors section of the NCCN Guidelines (see *Serous Carcinoma, Clear Cell Carcinoma, or Carcinosarcoma* in the NCCN Guidelines for Endometrial Carcinoma).[308,311,314,315] Even patients with apparent early-stage disease may have distant metastases. Thus, fertility-sparing therapy is not recommended for these aggressive tumors. If done, SLN mapping should proceed with particular caution.

Patients with uterine serous carcinoma, clear cell carcinoma, 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.[304] Patterns of failure often mimic those of ovarian cancer.

Treatment

Multimodality therapy is typically recommended for these histologically aggressive tumors. Primary treatment includes TH/BSO with surgical staging, peritoneal lavage for cytology, omental and peritoneal biopsies, and consideration of maximal tumor debulking for gross disease (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).[316] Minimally invasive surgery is the preferred approach when technically feasible.[317-321]

Adjuvant therapy is highly individualized.[322-329] For patients with stage IA without myometrial invasion, options include: 1) chemotherapy with (or without) vaginal brachytherapy (preferred approach); 2) observation if no residual serous or clear cell carcinoma in hysterectomy specimen; or 3) EBRT with (or without) vaginal brachytherapy.[330,331] For all other patients with more advanced disease, systemic therapy with (or without) tumor-directed RT is the preferred option.[306,323,327,332] Adjuvant

platinum/taxane-based therapy appears to improve survival in patients with uterine serous carcinoma and clear cell carcinoma, whereas ifosfamide/paclitaxel (category 1) is recommended for carcinosarcomas (see *Uterine Serous Carcinomas, Clear Cell Carcinomas, and Carcinosarcomas* in this Discussion and *Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease* in the NCCN Guidelines for Endometrial Carcinoma).[304-306,333-335]

Whole abdominopelvic RT with (or without) vaginal brachytherapy is no longer recommended as a primary treatment option for patients with advanced disease, because the NCCN panel no longer feels that routine use of whole abdominal RT is appropriate.[178,332,336] Chemotherapy with (or without) RT appears to be more effective than RT alone.[323] Data are conflicting regarding the rate of abdominal recurrence in these patients.[332,337-341] Whole abdominal radiotherapy is not considered to be tumor-directed RT (see *Principles of Radiation Therapy* in the NCCN Guidelines for Uterine Neoplasms). As previously mentioned, *tumor-directed RT* refers to RT directed at sites of known or suspected tumor involvement and may include EBRT with (or without) vaginal brachytherapy. In general, tumor-directed EBRT is directed to the pelvis with (or without) the para-aortic region.

Several studies have examined treatment paradigms for uterine serous or clear cell carcinoma. A recent phase II trial in patients with papillary serous carcinoma suggested favorable outcomes with concurrent pelvic RT and paclitaxel followed by additional rounds of adjuvant paclitaxel,[342] indicating the potential benefits of combined modality therapy. Retrospective data were reviewed from 279 patients with serous or clear cell carcinoma who were treated at high-volume cancer centers. Adjuvant treatment (RT, systemic therapy, or chemoradiation) was associated with improved OS in stages IB-II disease but not stage IA disease (HR, 0.14; 95% CI, 0.02–0.78; *P* = .026).[317] Additionally, survival outcomes did not differ based upon surgical approach (robotic laparoscopy versus laparotomy).

Two multi-institutional retrospective reviews examined the impact of adjuvant therapy (vaginal brachytherapy, n = 103; adjuvant pelvic radiation or chemotherapy, n = 115) in patients with stage 1A uterine papillary serous carcinoma. In both cohorts, patients undergoing surgical staging/lymphadenectomy had greater PFS and OS than unstaged patients.[343,344] Vaginal brachytherapy reduced the vaginal recurrence rate but did not impact PFS or OS.[343] In unstaged patients, chemotherapy or pelvic RT were associated with greater PFS and OS, but no survival benefits were observed for adjuvant treatment in surgically staged patients.[344]

A recent randomized phase II study examined the addition of trastuzumab to carboplatin/paclitaxel for patients with advanced or recurrent human epidermal growth factor receptor 2 (HER2)/neu–positive uterine serous carcinoma.[345] 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* = 0.013). PFS for patients with recurrent disease (n = 17) was 9.2 months versus 6.0 months (*P* = 0.003). The addition of trastuzumab appeared to improve PFS without increasing overall toxicity.

For treating carcinosarcoma, ifosfamide was historically considered the most active single agent.[334,346,347] 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.[334,348] OS was 13.5 months with ifosfamide/paclitaxel versus 8.4 months with ifosfamide alone. Therefore, ifosfamide/paclitaxel is a category 1 recommendation in the NCCN Guidelines (see *Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease* in the NCCN Guidelines for Endometrial Carcinoma).[334,336]

However, the toxicity of ifosfamide has led to investigation of better-tolerated regimens. A phase II trial suggests that paclitaxel/carboplatin is also a useful regimen for carcinosarcoma (response rate, 54%).[349] A GOG trial is currently assessing ifosfamide/paclitaxel versus carboplatin/paclitaxel.[312] The panel now considers carboplatin/paclitaxel the preferred adjuvant therapy regimen for uterine-confined endometrial cancers, including carcinosarcoma.

Data regarding carcinosarcoma suggest that adjuvant pelvic radiotherapy decreases the rate of local recurrences when compared with surgery alone.[350-355] This local control improvement in some series correlates with an improvement in survival, although other data show that lymphadenectomy confers greater benefit.[354-357] A phase III randomized trial (GOG 150) in patients with carcinosarcoma of the uterus showed a trend towards a decreased mortality rate for patients receiving cisplatin/ifosfamide vs. whole-abdominal RT (*P* = .085), although these did not reach statistical significance in this underpowered trial.[336,341] A recent cohort study in women with early-stage MMMT suggests that postoperative chemotherapy improves PFS compared to RT or observation.[312]

Uterine Sarcomas

Overview

In 2017, an estimated 4910 cases of uterine sarcomas are anticipated.[358] Uterine sarcomas are malignant mesenchymal tumors that include ESS, UUS, and uLMS (see *Uterine Sarcoma Classification* in the NCCN Guidelines for Uterine Sarcoma). According to 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.[359] Even rarer subtypes of malignant mesenchymal tumors that can occur in the uterus include adenosarcoma, rhabdomyosarcoma (RMS), and PEComa.[360] 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).[308]Screening for Lynch syndrome is not usually done for patients with malignant mesenchymal tumors.

ESSs are composed of cells resembling the endometrial stroma in the proliferative phase.[360,361] ESS displays a heterogenous mix of morphologic and genetic features. A significant proportion of these tumors (ie, up to half) harbor a *JAZF1-SUZ12* (formerly *JAZF1-JJAZ1*) gene fusion and present as lower grade, earlier stage tumors.[362-365] More recently, a higher-grade and more aggressively behaving ESS variant with a unique genetic rearrangement *YWHAE-FAM22A/B*, also known as *YWHAE-NUTM2A/B,* was identified.[366,367] These findings provided support for subdividing ESS into distinct low- and high-grade entities based on histopathology, clinical behavior, and patient outcomes. In light of new information, WHO released an updated (4th) edition of the *WHO Classification of Tumours of Female Reproductive Organs*. The updated 2014 edition recognizes low-grade ESS and high-grade ESS as distinct histopathologic entities.[368]

Recent advances have expanded our understanding of the molecular features of these tumors, leading to the identification of genetic signatures that characterize some of the uterine sarcoma subtypes. At present, mesenchymal tumors are primarily diagnosed using histopathologic criteria, and the results of molecular studies are not used in routine pathologic evaluation. However, molecular analysis (eg, identification of characteristic translocations) can help classify difficult cases and provide future therapeutic targets.

Staging and Treatment

When evaluating suspected uterine sarcomas, biopsy may be helpful but is less sensitive than for endometrial cancers. The diagnosis of ESS and uLMS is often made after hysterectomy. The previous FIGO/AJCC staging

systems for endometrial cancer were not appropriate for staging ESS and uLMS; patients were often upstaged when using the older AJCC staging system.[369] 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.[56,370]

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). Whole-body PET/CT may be used to clarify ambiguous findings. If medically operable, then hysterectomy with (or without) BSO is the initial treatment of choice for uterine sarcomas (see *Primary Treatment* in the NCCN Guidelines for Uterine Sarcoma).[371]

The panel recommends ER/PR testing to guide decisions regarding management of the ovaries, particularly in young premenopausal patients. In general, BSO is favored for low-grade ESS or tumors expressing ER/PR, although management of the ovaries may be individualized in reproductive-age patients.

Uterine sarcoma should be removed en bloc to optimize outcomes; intraperitoneal morcellation is contraindicated.[142-145] For incidental diagnoses of uterine sarcoma after hysterectomy, or in the case of a fragmented specimen, imaging is recommended and re-exploration can be considered. The ovaries may be preserved in selected patients with early-stage uLMS who wish to retain hormonal function.[372] Additional surgical resection should be individualized based on clinical scenarios and intraoperative findings. Lymphadenectomy is controversial.[2,360,372-375]

High-grade uterine sarcomas tend to show hematogenous metastases to the lungs; lymph node metastases are uncommon.

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

Low-Grade Endometrial Stromal Sarcoma

If there is no evidence of disease after primary surgery (TH/BSO) for stage I ESS, then observation can be considered (see *Additional Therapy* in the NCCN Guidelines for Uterine Sarcoma).[373,374] Recommended adjuvant therapy options for stage I ESS include observation (especially if menopause or prior BSO) or estrogen blockade (category 2B). Postoperative estrogen blockade is recommended for stages II to IV ESS. Adjuvant EBRT may be added for stage II-IVA (category 2B). Palliative RT may be added to estrogen blockade for patients with stage IVB disease.[360,376,377] Typical hormone therapy includes aromatase inhibitors (preferred), megestrol acetate, or medroxyprogesterone acetate. Gonadotropin-releasing hormone [GnRH] analogs (category 2B) are also an option.[360,372,378] In 2014, tamoxifen was removed from the NCCN Guidelines for ESS because it is contraindicated in women diagnosed with ESS or ER/PR-positive uLMS.[372,377-379] Estrogen blockade is also recommended for ESSs that have recurred or are unresectable (see *Therapy for Relapse* in the NCCN Guidelines for Uterine Sarcoma).[378]

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.[380] Adjuvant radiotherapy in ESS has been demonstrated to reduce local recurrence rates but again with limited effect on survival.[381,382] Because of concerns about radiation exposure, frequent routine surveillance imaging is no longer recommended for asymptomatic young women after primary therapy for ESS.[383]

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

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

The role of adjuvant radiotherapy in nonmetastatic disease is controversial. Most available data are retrospective except for a phase III randomized trial.[350] 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.[384-387] 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.[350] Therefore, routine postoperative RT is not recommended for stage I patients with uLMS and high-grade (undifferentiated) endometrial sarcoma.[376] If used in more advanced stages, adjuvant RT needs to be individualized and based on careful analysis of surgical pathologic findings.

The role of adjuvant systemic therapy is also poorly defined; however, adjuvant systemic therapy has been used because of the high risk of systemic relapse. Given the uncertainties regarding any adjuvant treatment for stage I uLMS and high-grade (undifferentiated) endometrial sarcoma, after complete resection options include: 1) observation; 2) systemic therapy (category 2B); or 3) estrogen blockade if ER positive may be considered. Because of the increased risk profile in patients with completely resected stage II and III uLMS and high-grade (undifferentiated) endometrial sarcoma, the panel believes that it is appropriate to consider adjuvant systemic therapy and/or EBRT (see *Additional Therapy* in the NCCN Guidelines for Uterine Sarcoma).[388] In patients with incompletely resected or metastatic disease, systemic therapy with (or without) palliative EBRT is generally recommended.

An ongoing phase III randomized trial (GOG 277) is assessing the role of postoperative adjuvant chemotherapy (ie, gemcitabine/docetaxel followed by doxorubicin) versus observation in patients with high-grade stage I and II uLMS.[389]

If systemic therapy is used for treating high-grade uterine sarcoma, preferred therapies include single-agent doxorubicin, and gemcitabine/docetaxel[389-394] combination therapy (see *Systemic Therapy* in the NCCN Guidelines for Uterine Sarcoma).[360,361,395] Doxorubicin is an active single agent for uLMS and is less toxic than combination regimens.[360,395]

Other recommended combination regimens include doxorubicin/ifosfamide, doxorubicin/dacarbazine, gemcitabine/dacarbazine, and gemcitabine/vinorelbine.[347,391,396-398] Other single-agent options (category 2A unless otherwise noted) can also be considered for advanced or metastatic disease, including dacarbazine, gemcitabine, epirubicin, ifosfamide, liposomal doxorubicin, pazopanib, temozolomide, trabectedin (for uLMS treated with a prior anthracycline-containing regimen), eribulin (category 2B), vinorelbine (category 2B), and docetaxel (category 3).[360,361,390,396,397,399-415] Aromatase inhibitors can be considered for ER/PR-expressing uLMS.[416] Dacarbazine was elevated to a category 2A recommendation (from a category 2B) in 2014 because this agent was used as the standard arm in several phase II trials.[396] In 2016, trabectedin and eribulin were both included in the guidelines.

Data indicate that trabectedin may be useful in patients who have exhausted standard chemotherapy.[417-420] Preliminary phase III data revealed a 2.7-month PFS benefit versus dacarbazine in metastatic liposarcoma or leiomyosarcoma that progressed after anthracycline-based therapy.[421] 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).[422] 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). Following its October 2015 FDA approval, trabectedin was added to the guidelines as an option for unresectable or metastatic uLMS previously treated with an anthracycline-containing regimen.

Eribulin was included based on results from a phase III trial comparing the survival benefit of eribulin and dacarbazine in 452 patients with advanced leiomyosarcoma or adipocytic sarcoma.[423] 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.

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. Abdominal/pelvic MRI and chest CT can also be considered, with PET/CT or other imaging as needed to clarify findings or upon clinical concern for metastasis.

Patients should receive education regarding the symptoms of recurrent disease. Patients with bleeding (vaginal, bladder, or rectal), decreased appetite, weight loss, pain (in the pelvis, abdomen, hip, or back), cough, shortness of breath, and swelling (in the abdomen or legs) should seek prompt evaluation and not delay until the next scheduled appointment. As clinically indicated, imaging may be helpful in the detection of recurrence. Patients should be educated regarding healthy lifestyle, obesity, exercise, smoking cessation, nutrition, and potential long-term and late effects of treatment (see the NCCN Guidelines for Survivorship, NCCN Guidelines for Smoking Cessation, and http://www.cancer.org/treatment/survivorshipduringandaftertreatment/index).[239-241] The panel also recommends patient education regarding sexual health, vaginal dilator use, and vaginal lubricants or moisturizers.

Treatment of Recurrent or Metastatic Disease

The recurrence rate is high in uLMS (50%–70%).[2] The guidelines provide recommendations based on tumor resectability and patients' prior RT exposure (see *Therapy for Relapse* in the NCCN Guidelines for Uterine Sarcoma). 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 and/or systemic therapy are also options to consider. For residual disease following surgery in patients without preoperative RT, EBRT with (or without) brachytherapy and/or 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 and/or systemic therapy (category 3 for IORT); 2) systemic therapy; or 3) selected reirradiation with EBRT and/or brachytherapy. A recent retrospective analysis of patients with ESS suggested that cytoreductive resection improved OS in patients with recurrent lesions. [424]

Systemic therapy with (or without) palliative EBRT or best supportive care is recommended for metastatic disease.[395] For patients with isolated metastases, surgical resection or other ablative therapy (eg, radiofrequency ablation, stereotactic body RT) may be appropriate. Patients with uLMS who experience longer time to recurrence may have improved survival outcomes following metastasectomy.[425] Postoperative EBRT and/or systemic therapy can be considered. Systemic therapy and/or local therapy (tumor-directed EBRT or local ablative therapy) are reasonable options for patients with unresectable isolated metastases (see *Therapy for Relapse* in the NCCN Guidelines for Uterine Sarcoma).[411,426-428] For recurrent low-grade ESS, the first choice of systemic therapy is estrogen blockade.

Drug Reactions

Virtually all drugs have the potential to cause adverse hypersensitivity reactions, either during or after the infusion.[429] 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.[430-432] In addition, patients can have mild allergic reactions or severe infusion reactions. Infusion reactions are more common with paclitaxel.[433] Allergic reactions (ie, true drug allergies) are more common with platinum agents (ie, carboplatin, cisplatin).[433,434]

Management of drug reactions is discussed in the NCCN Guidelines for Ovarian Cancer.[433] 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.[435-437] Patients must be desensitized with each infusion if they previously had a reaction. Almost all patients can be desensitized (about 90%).[429] To maximize safety, it is prudent to desensitize patients in the intensive care unit.[429]

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