



National
Comprehensive
Cancer
Network®

NCCN Clinical Practice Guidelines in Oncology™

Uterine Neoplasms

V.1.2008

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These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations nor warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2007.

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This manuscript is being updated to correspond with the newly updated algorithm.

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

To find clinical trials online at NCCN member institutions, [click here:](#)
nccn.org/clinical_trials/physician.html

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

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

Summary of the Guidelines updates

Summary of the changes in the 1.2008 version of the Uterine Neoplasms Guidelines from the 1.2007 version include:

- “Carcinosarcoma” replaced “Malignant mixed Müllerian tumor” throughout the guideline.
- “Therapy for relapse” replaced “Salvage Therapy” throughout the guideline.

Endometrial Carcinoma:

(ENDO-1)

- Under Initial Clinical Findings: The panel included the phrase “Endometrioid histologies” with footnote “a” that refers readers of the guidelines to the UN-1 histology page.

(Also for ENDO-2 and ENDO-3)

(ENDO-4)

- Added new footnote “i” that states, “The role of adjuvant chemotherapy in invasive high grade uterine confined disease is the subject of current studies”. (Also for ENDO-5 and ENDO-6)

(ENDO-6)

- The “Adjuvant treatment for completely surgically staged: Stage IIIA” pathway and “Histologic Grade/Adjuvant Treatment” box on ENDO-5 were moved to page ENDO-6.

- Added new footnote “k” to the “Observe” recommendations that states, “Intrauterine risk factors may be treated following the guidelines on ENDO-4 and ENDO-5”.

(ENDO-7)

- First and Second Row under “Histologic Grade/Adjuvant Treatment”: “Tumor-directed RT + chemotherapy” was changed to “Chemotherapy + tumor-directed RT”.

(ENDO-8)

- Second column, Top row: The panel removed “with no adverse risk factors” after the phrase “Stage IA, G1-2”.
- Lower branch, after “Stage IC; Stage IIA (Myometrial invasion > 50%); Stage IIB or G-3” the panel added a new arrow pointing to “Surgical restaging”. This is to show that patients who were incompletely surgically staged, also have the option of surgical restaging or radiologic imaging.

(ENDO-10)

- Fourth column; Top pathway: The word “abdomen” was deleted from “Surgical exploration of pelvis + abdomen resection....” On this same point, the panel clarified that the “Disease confined to vagina” and “Extra-vaginal disease” pathways should only directly follow the “Surgical exploration....” recommendation and not the “RT + brachytherapy” recommendation.

- Extravaginal disease pathway; First and Second Row: After “vaginal brachytherapy” the panel added “± chemotherapy.

(ENDO-11)

- ▶ Top branch: The “Stage IA” pathway was changed to “Stage IA (confined to polyp)” with adjuvant treatment recommendations “Observe or vaginal brachytherapy”
- ▶ A new pathway entitled “Other Stage IA disease (not confined to polyp)” was created with adjuvant treatment recommendations of “Chemotherapy ± tumor directed RT”
- ▶ Under Stage IB, IC, II disease pathway:
 - ◊ Vaginal brachytherapy was removed as adjuvant therapy to clarify that this treatment option, as a sole adjuvant, is limited to Stage IA disease
 - ◊ “Chemotherapy ± vaginal brachytherapy” was changed to “Chemotherapy ± tumor directed RT”
 - ◊ The “Whole abdominopelvic RT ± vaginal brachytherapy” recommendation was changed from category 2B to category 3.

(ENDO-B)

- The page table is now entitled, “Systemic Therapy For Recurrent or Metastatic Disease” and the “Strongly encourage clinical trials” bullet was moved to the top and included as part of the page title. The panel wanted to emphasize the importance of patients participating in clinical trials.

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Summary of the Guidelines updates (continued)

Uterine Sarcoma:

(UTSARC-5)

- After “No prior RT”: The recommendation now reads “Surgical exploration + resection...” On this same point, the panel clarified that the “Disease confined to vagina” and “Extravaginal disease” pathways should only directly follow the “Surgical exploration...” recommendation and not the “Pelvic RT + brachytherapy” recommendation.
- Far Right, “Extrapelvic disease” pathway: “Whole abdominopelvic RT” was removed as a treatment option.

(UTSARC-A)

• Chemotherapy Regimens:

- ▶ **Bullet #1:** The recommendation for “Doxorubicin” was changed to “Doxorubicin or liposomal anthracycline...”
- ▶ **Bullet #2:** Gemcitabine and ifosfamide were added as “single-agents that have activity in other soft tissue sarcomas and could be considered”
- ▶ **Bullet #2:** Cisplatin and topotecan were removed as single-agents

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**INITIAL
EVALUATION**

- H&P
- CBC, platelets
- Endometrial biopsy
- Chest x-ray
- Current cervical cytology consistent with [NCCN Cervical Screening Guidelines](#)

- Optional:
- LFT/renal function tests/chemistry profile

Pathology review

Epithelial carcinoma

**INITIAL CLINICAL
FINDINGS**

Pure Endometrioid

Disease limited to uterus

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

Suspected or gross cervical involvement

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

Suspected extrauterine disease

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

Papillary serous or clear cell carcinoma

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

Carcinosarcoma^{a,b}

Stromal/mesenchymal tumors

- Endometrial stromal sarcoma (ESS)^c
- High-grade undifferentiated sarcoma (HGUD)
- Leiomyosarcoma (LMS)

Disease limited to uterus

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

Known or suspected extrauterine disease

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

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

^aStaged aggressively, should be treated as a high grade endometrial cancer.

^bAlso known as malignant mixed mesodermal tumor or malignant mixed Müllerian tumor and including those with either homologous or heterologous stromal elements.

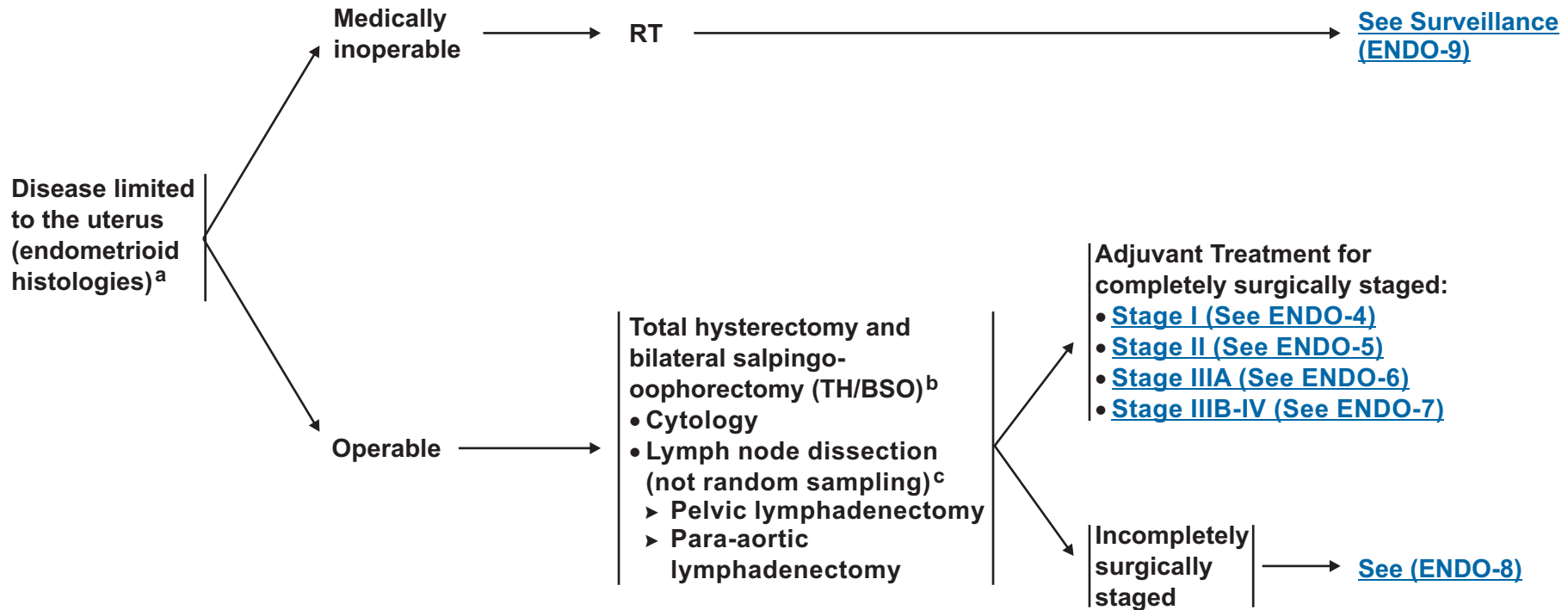
^cBy definition, ESS is a low-grade sarcoma.

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INITIAL CLINICAL FINDINGS

PRIMARY TREATMENT

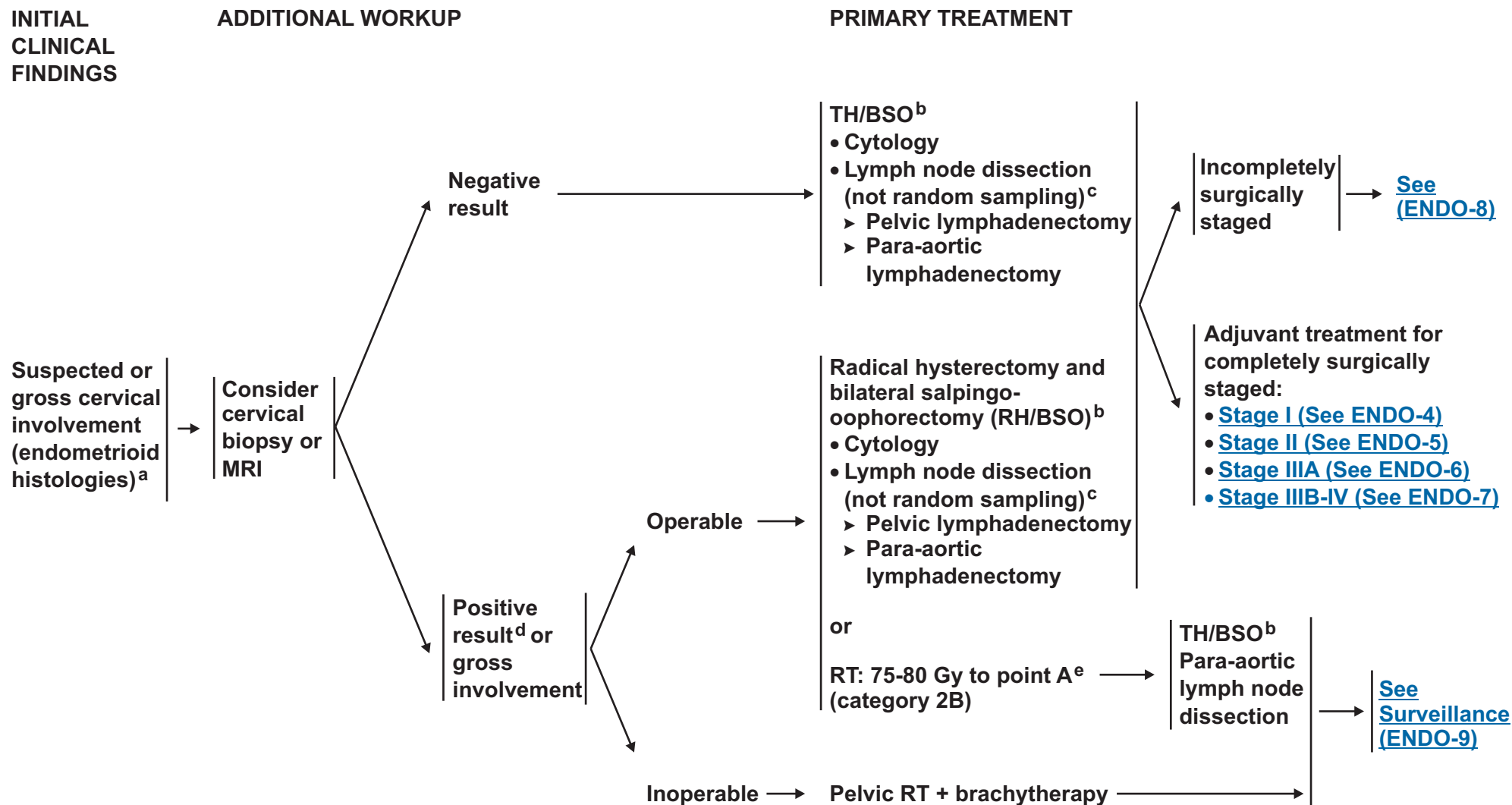


^aSee (UN-1) for clarification of uterine neoplasms.

^bSee Hysterectomy (ENDO-A).

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

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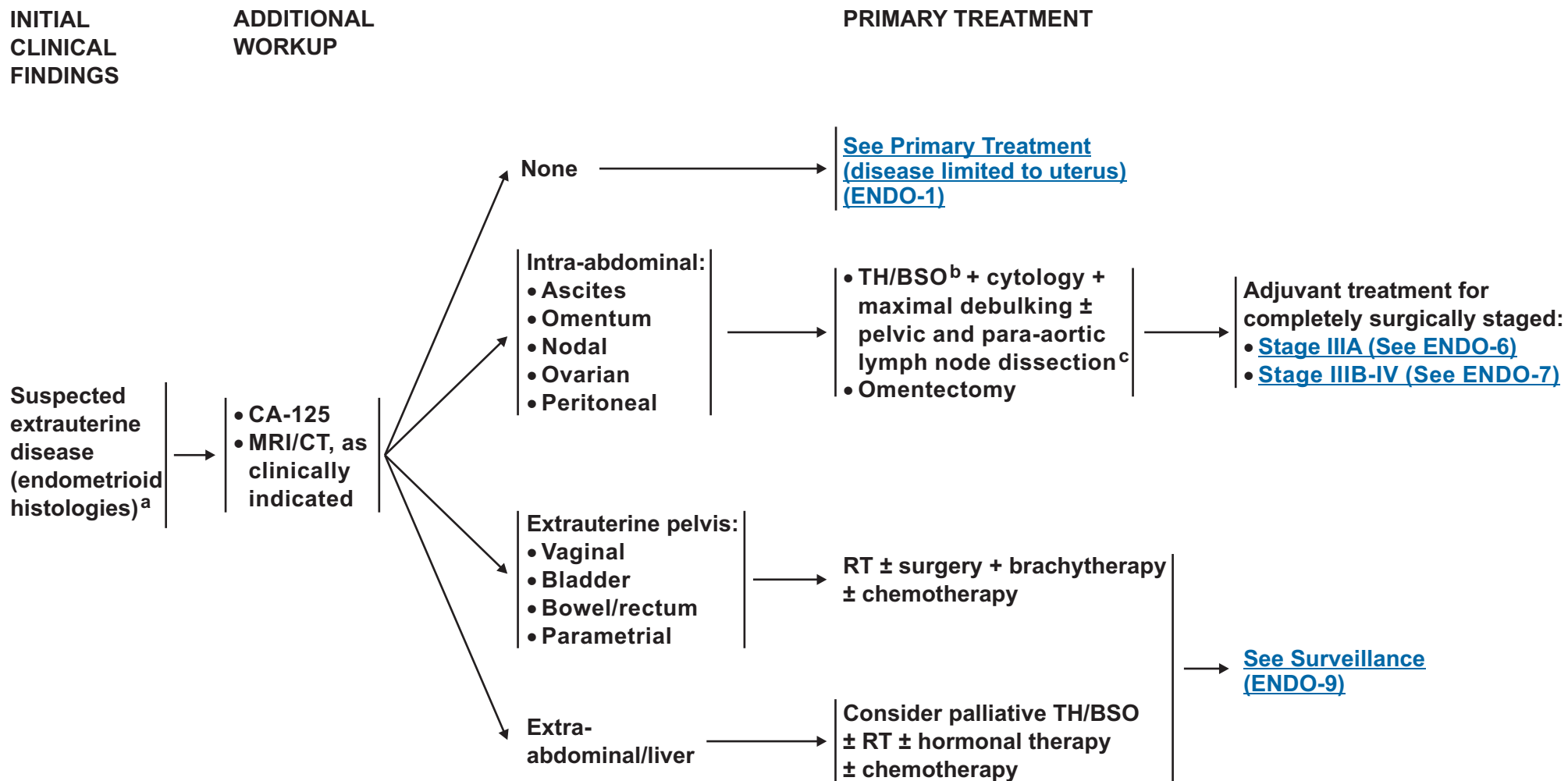
^cAmerican College of Obstetricians and Gynecologists practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. *Obstet Gynecol* 2005 Aug;106:413-425.

^dClear demonstration of cervical stromal involvement.

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

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^aSee [\(UN-1\)](#) for clarification of uterine neoplasms.

^bSee [Hysterectomy \(ENDO-A\)](#).

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

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CLINICAL FINDINGS

ADVERSE RISK FACTORS^f

HISTOLOGIC GRADE/ADJUVANT TREATMENT^{g,h,i}

		G1	G2	G3 ⁱ
<p>Adjuvant treatment for completely surgically staged: Stage I</p>	<p>Stage IA</p>	Adverse risk factors not present → Observe	Observe	Observe or Vaginal brachytherapy
		Adverse risk factors present → Observe	Observe	Observe or Vaginal brachytherapy ± Pelvic RT (category 2B for all options)
	<p>Stage IB (≤ 50%)</p>	Adverse risk factors not present → Observe	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy
		Adverse risk factors present → Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy ± pelvic RT (category 2B for all options)	Pelvic RT and/or vaginal brachytherapy (category 2B for all options)
	<p>Stage IC</p>	Adverse risk factors not present → Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy	Pelvic RT and/or vaginal brachytherapy (category 2B for all options)
		Adverse risk factors present → Pelvic RT and/or vaginal brachytherapy (category 2B for all options)	Pelvic RT and/or vaginal brachytherapy (category 2B for all options)	

^fPotential adverse risk factors include the following: > 60 y, positive lymphovascular invasion, tumor size, lower uterine involvement.

^gAdjuvant therapy determinations are made on the basis of pathologic findings.

^hAdjuvant pelvic RT: 45-50 Gy to clinical tumor volume (CTV).

ⁱThe role of adjuvant chemotherapy in invasive high grade uterine confined disease is the subject of current studies. (Creutzberg, CL Clinical Trial: Chemotherapy and Radiation Therapy Compared With Radiation Therapy Alone in Treating Patients With High-Risk Stage I, Stage II, or Stage III Endometrial Cancer; Clinical trial summary from the National Cancer Institute's PDQ® database. Study ID Numbers: CDR0000521447; CKTO-2006-04; ISRCTN14387080; CKTO-PORTEC-3; EU-20664--- <http://clinicaltrials.gov/ct/show/NCT00411138;jsessionid=2309E60C1051E921B4E2614F2BE708A4?order=9>. Hogberg T, Rosenberg P, Kristensen G, et al. A randomized phase-III study on adjuvant treatment with radiation (RT) ± chemotherapy (CT) in early-stage high-risk endometrial cancer (NSGO-EC-9501/EORTC 55991) [abstract]. J Clin Oncol 2007;25: 5503).

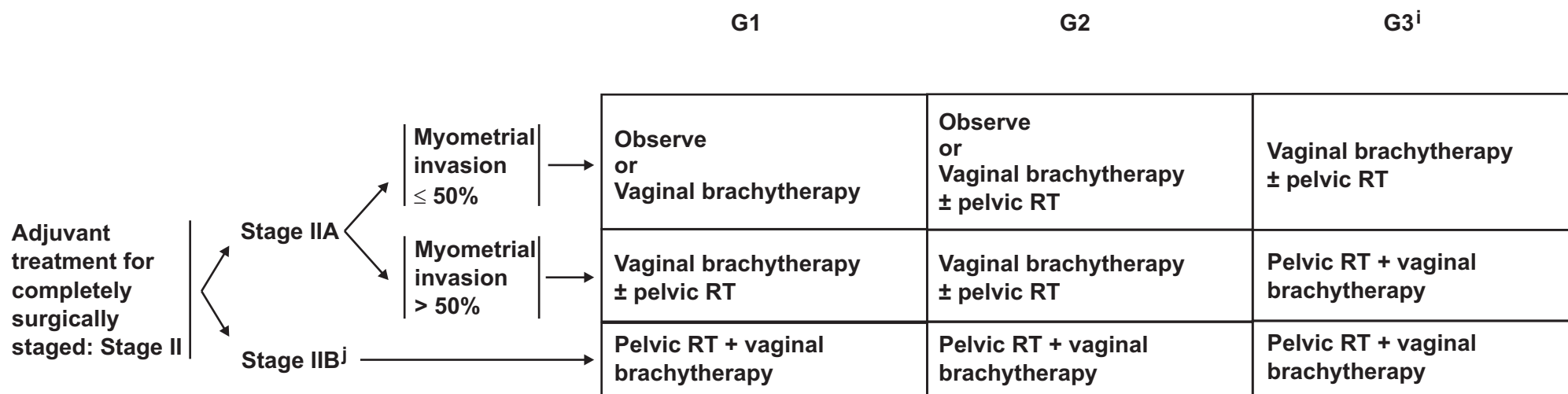
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[See Surveillance \(ENDO-9\)](#)

CLINICAL FINDINGS

HISTOLOGIC GRADE/ADJUVANT TREATMENT^{g,h,i}



^gAdjuvant therapy determinations are made on the basis of pathologic findings.

^hAdjuvant pelvic RT: 45-50 Gy to clinical tumor volume (CTV).

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^jObservation or vaginal brachytherapy is an option for patients with Stage IIB disease who are post primary radical hysterectomy, with negative surgical margins and no evidence of extrauterine disease.

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

CLINICAL FINDINGS

HISTOLOGIC GRADE/ADJUVANT TREATMENT^{g,h,i}

		G1	G2	G3 ⁱ
Adjuvant treatment for completely surgically staged: Stage IIIA	Positive cytology only, no other extrauterine disease	Observe ^k	Observe ^k	Observe ^k or Vaginal brachytherapy or Pelvic RT ± vaginal brachytherapy
	All other IIIA	Chemotherapy ± RT or Tumor-directed RT + chemotherapy or Pelvic RT ± vaginal brachytherapy or Whole abdominopelvic RT ± vaginal brachytherapy (category 2B for all options)	Chemotherapy ± RT or Tumor-directed RT + chemotherapy or Pelvic RT ± vaginal brachytherapy or Whole abdominopelvic RT ± vaginal brachytherapy (category 2B for all options)	Chemotherapy ± RT or Tumor-directed RT + chemotherapy or Pelvic RT ± vaginal brachytherapy or Whole abdominopelvic RT ± vaginal brachytherapy (category 2B for all options)

^gAdjuvant therapy determinations are made on the basis of pathologic findings.

^hAdjuvant pelvic RT: 45-50 Gy to clinical tumor volume (CTV).

ⁱThe role of adjuvant chemotherapy in invasive high grade uterine confined disease is the subject of current studies. (Creutzberg, CL Clinical Trial: Chemotherapy and Radiation Therapy Compared With Radiation Therapy Alone in Treating Patients With High-Risk Stage I, Stage II, or Stage III Endometrial Cancer; Clinical trial summary from the National Cancer Institute's PDQ® database. Study ID Numbers: CDR0000521447; CKTO-2006-04; ISRCTN14387080; CKTO-PORTEC-3; EU-20664--- <http://clinicaltrials.gov/ct/show/NCT00411138;jsessionid=2309E60C1051E921B4E2614F2BE708A4?order=9>.

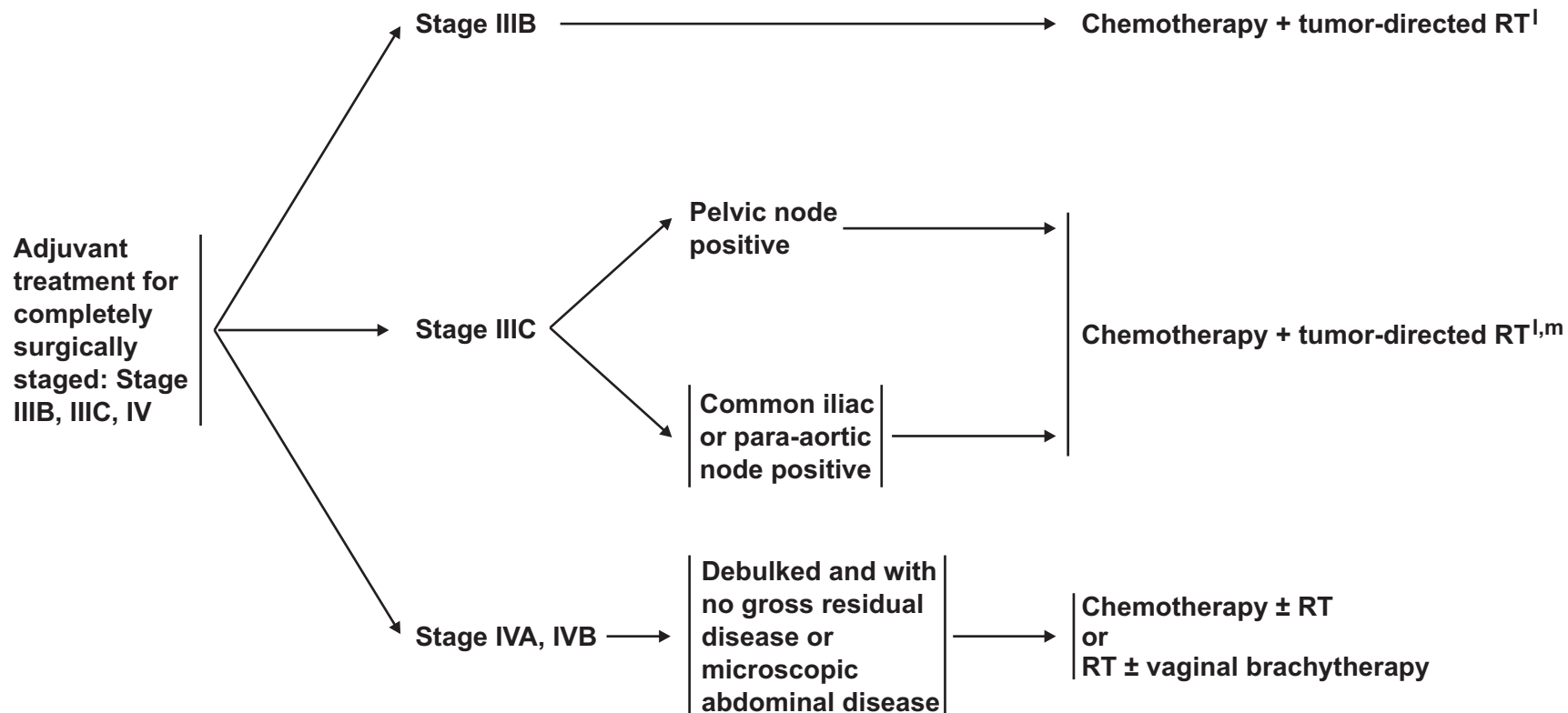
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^kIntrauterine risk factors may be treated following the guidelines on [\(ENDO-4\)](#) and [\(ENDO-5\)](#).

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CLINICAL FINDINGS

HISTOLOGIC GRADE/ADJUVANT TREATMENT⁹
G1, G2, G3



⁹Adjuvant therapy determinations are made on the basis of pathologic findings.

^lPelvic ± para-aortic lymph node RT based on surgical/pathologic findings.

^mRT to para-aortic nodes: 45-50 Gy to clinical tumor volume (CTV).

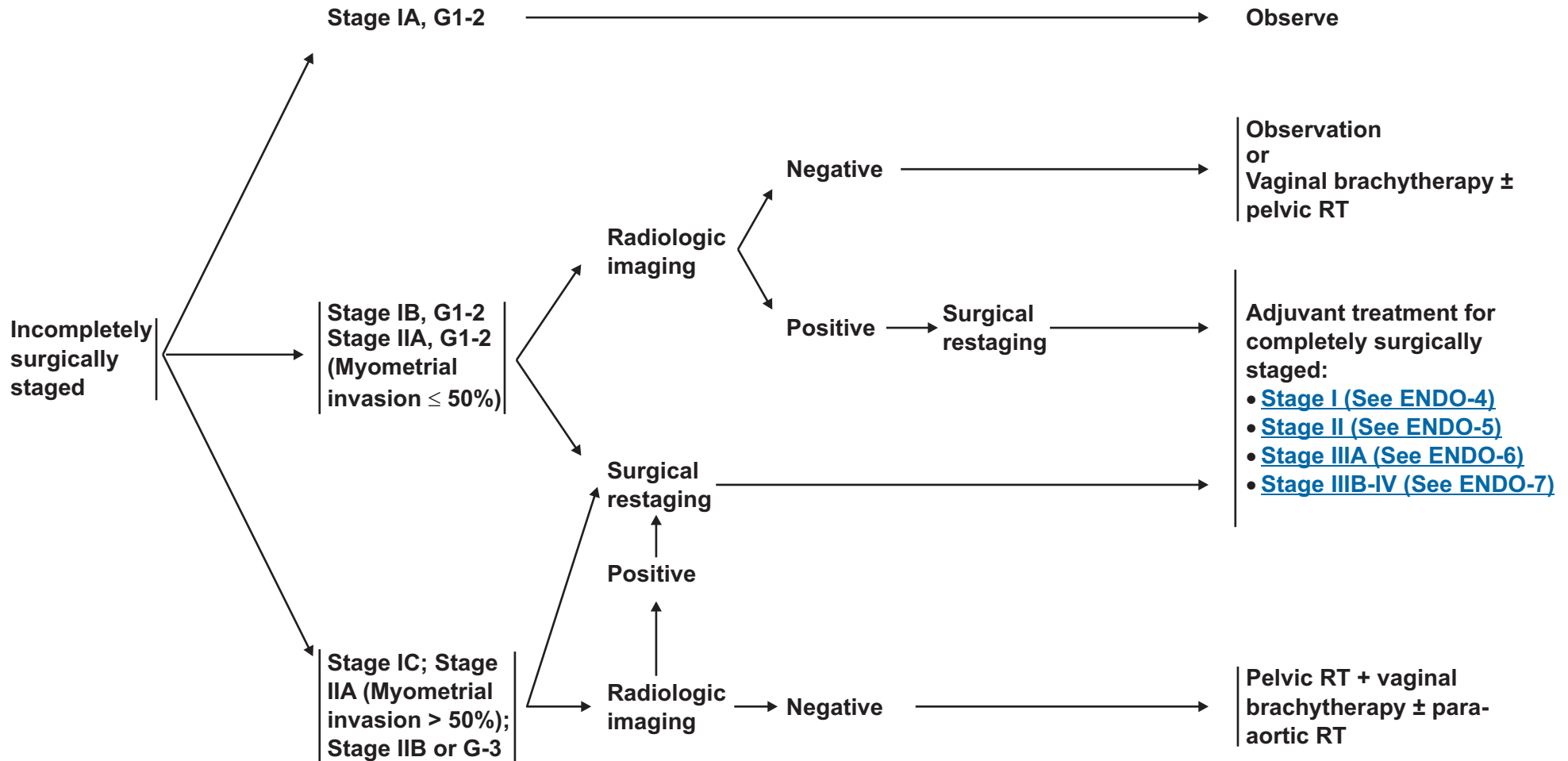
[See Surveillance \(ENDO-9\)](#)

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CLINICAL
INTRAUTERINE
FINDINGS

ADJUVANT TREATMENT



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SURVEILLANCE

- Physical exam every 3-6 mo for 2 y, then 6 mo or annually
- CA-125 (category 3)
- Chest x-ray annually (category 2B)
- Vaginal cytology every 6 mo for 2 y, then annually
- Patient education regarding symptoms

CLINICAL PRESENTATION

Local recurrence
• Vagina
• Negative metastases on radiologic imaging

Isolated metastases

Consider resection ± RT

Asymptomatic or Low grade

Disseminated metastases

Symptomatic or Grade 2, 3 or Large volume

THERAPY FOR RELAPSE

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

Unresectable or further recurrence

Hormonal therapyⁿ

If progression, chemotherapyⁿ

Chemotherapyⁿ and/or palliative RT

Treat as disseminated metastases (See below)

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

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

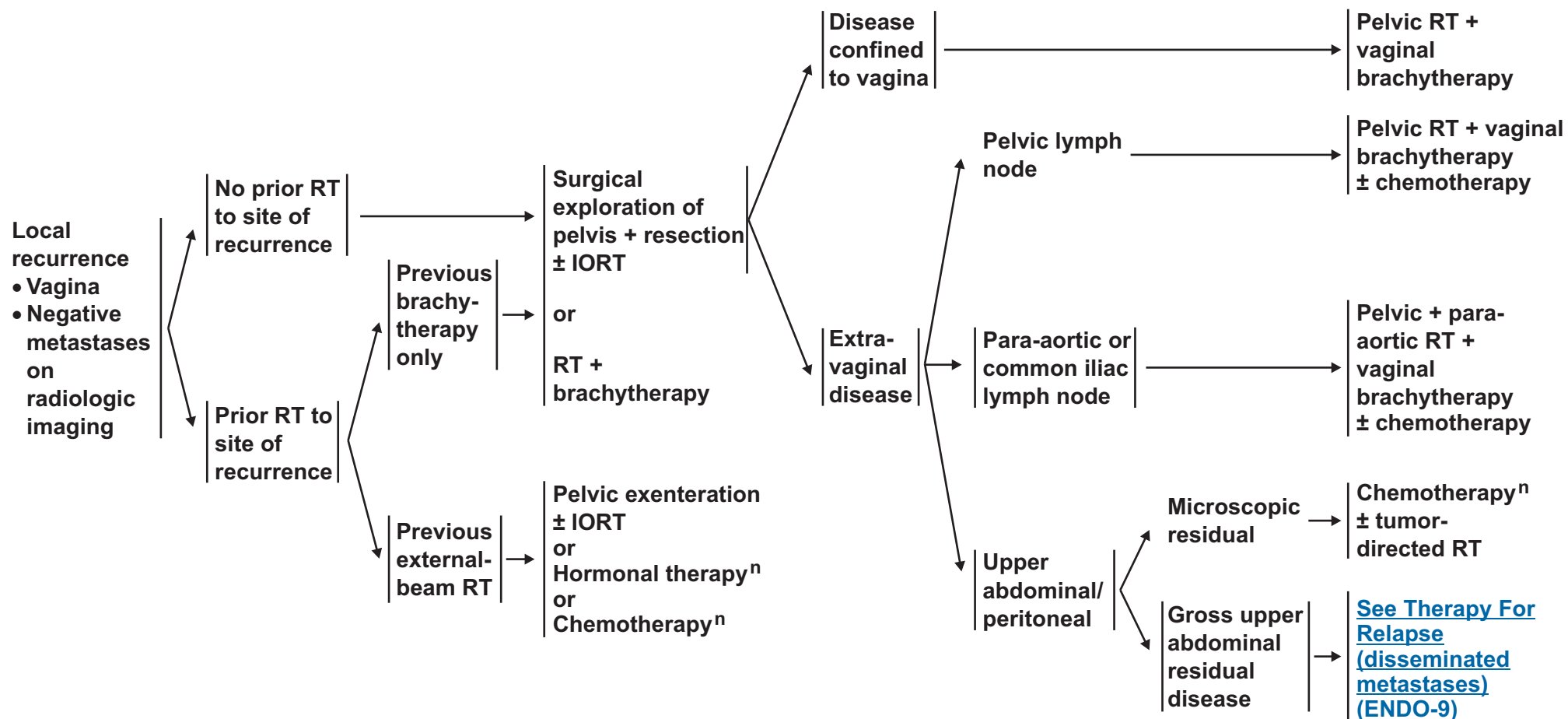
ⁿ[See Systemic Therapy for Recurrent or Metastatic Disease \(ENDO-B\).](#)

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CLINICAL PRESENTATION

THERAPY FOR RELAPSE

ADDITIONAL THERAPY



ⁿSee Systemic Therapy for Recurrent or Metastatic Disease (ENDO-B).

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PAPILLARY SEROUS OR CLEAR CELL CARCINOMA OF THE ENDOMETRIUM OR CARCINOSARCOMA^o

PRIMARY TREATMENT

ADJUVANT TREATMENT

Biopsy:
papillary serous
or clear cell
carcinoma
or
Carcinosarcoma^o

- Includes surgical staging, as with ovarian cancer
- TH/BSO, pelvic and para-aortic lymph node dissection, cytology, omentectomy, biopsies of peritoneal surfaces (including underside of diaphragm)
- Maximal tumor debulking

Stage IA
(confined to polyp)

Observe
or
vaginal brachytherapy

Other Stage IA disease
(not confined to polyp)

Chemotherapy + tumor directed RT

Stage
IB, IC, II

Chemotherapyⁿ ± tumor directed RT
or
Whole abdominopelvic RT ± vaginal
brachytherapy (category 3)

Stage III, IV
(adequately
debulked)

Stage III, IV
(inadequately
debulked)

Chemotherapyⁿ

ⁿSee [Systemic Therapy for Recurrent or Metastatic Disease \(ENDO-B\)](#).

^oAlso 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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HYSTERECTOMY

TH/BSO: Total hysterectomy + bilateral salpingo-oophorectomy

RH: Radical hysterectomy

Pathologic assessment to include:

- **Ratio of depth of myometrial invasion to myometrial thickness**
- **Tumor size**
- **Tumor location (fundus vs lower uterine segment/cervix)**
- **Histologic subtype with grade**
- **Lymphovascular space invasion**
- **Frozen section as indicated**

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**SYSTEMIC THERAPY FOR RECURRENT OR METASTATIC DISEASE
(STRONGLY ENCOURAGE PARTICIPATION IN CLINICAL TRIALS)****HORMONAL THERAPY**

- Progestational agents
- Tamoxifen
- Aromatase inhibitors

CHEMOTHERAPY REGIMENS

- Cisplatin
- Carboplatin
- Paclitaxel
- Doxorubicin
- Cisplatin/doxorubicin/paclitaxel
(category 1)
- Cisplatin/doxorubicin
(category 1)
- Carboplatin/paclitaxel
- Ifosfamide-based regimens for carcinosarcoma

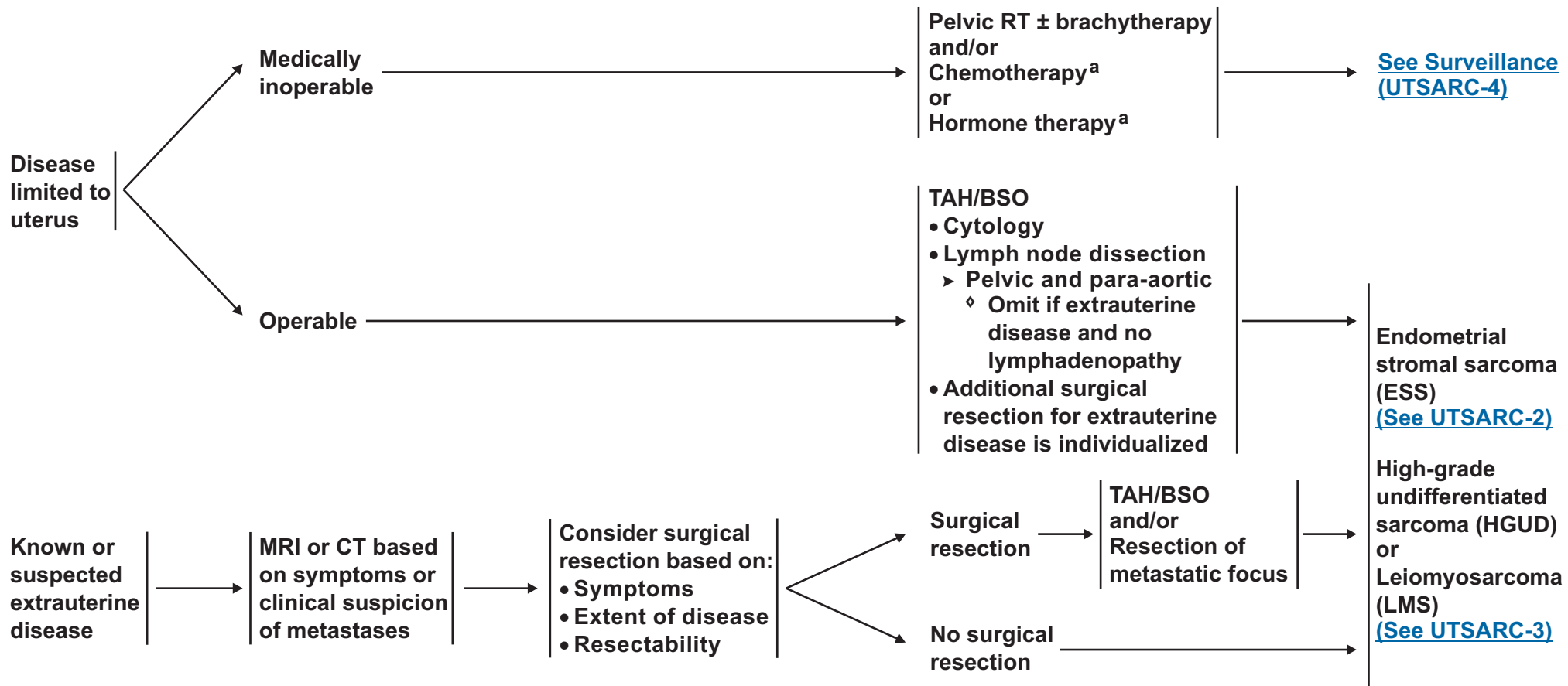
[Back to Therapy For
Relapse \(ENDO-9\)](#)

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INITIAL CLINICAL FINDINGS

PRIMARY TREATMENT

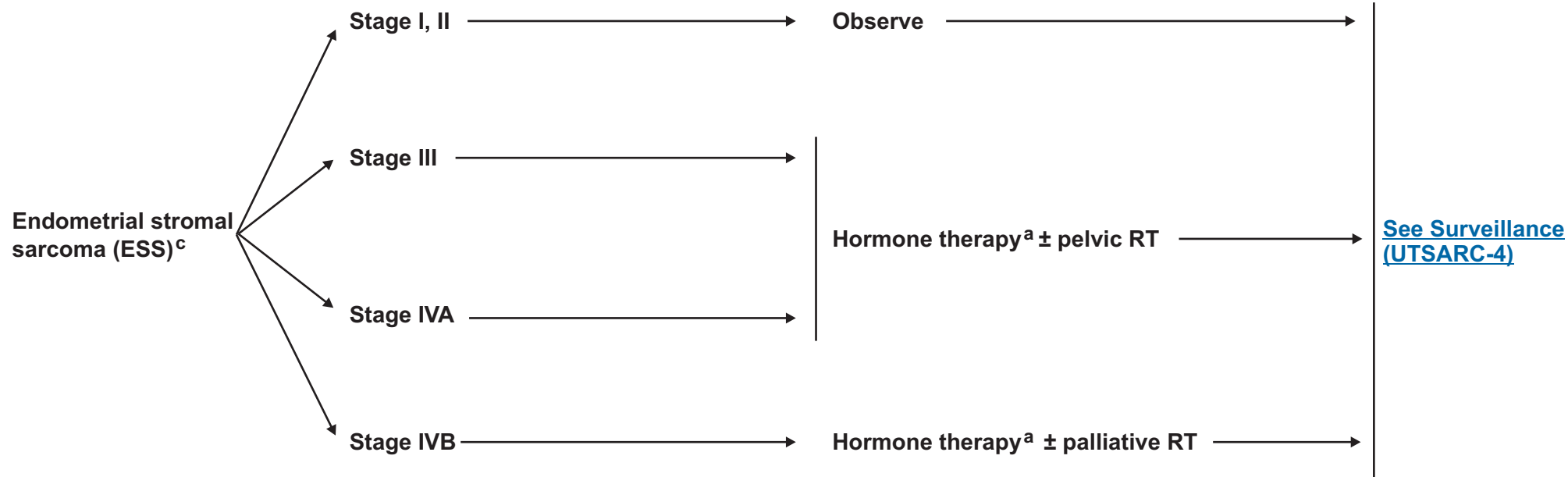


^a[See Systemic Therapy for Advanced or Metastatic Disease \(UTSARC-A\).](#)

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**PATHOLOGIC FINDINGS/
HISTOLOGIC GRADE^b**

ADJUVANT TREATMENT



^a[See Systemic Therapy for Advanced or Metastatic Disease \(UTSARC-A\).](#)

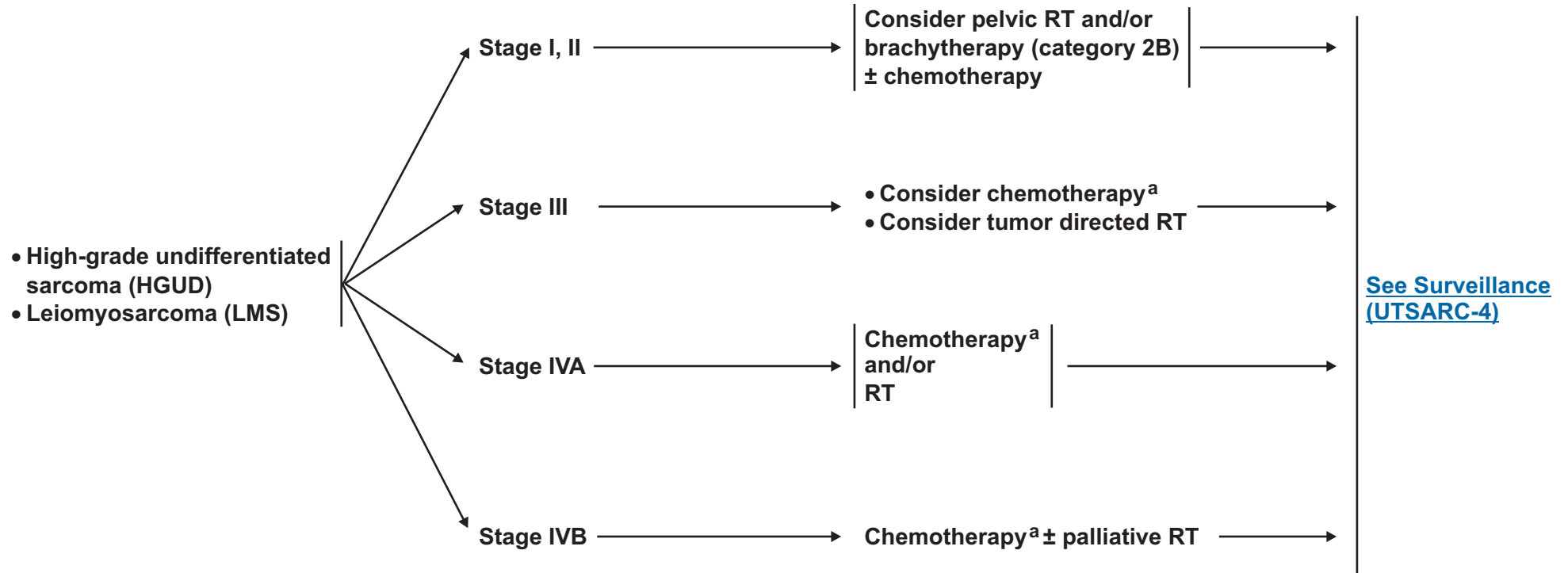
^b[See Uterine Sarcoma Classification \(UTSARC-B\).](#)

^cBy definition, ESS is a low-grade sarcoma.

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**PATHOLOGIC FINDINGS/
HISTOLOGIC GRADE^b**

ADJUVANT TREATMENT



^a[See Systemic Therapy for Advanced or Metastatic Disease \(UTSARC-A\).](#)

^b[See Uterine Sarcoma Classification \(UTSARC-B\).](#)

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SURVEILLANCE

- Physical exam every 3 mo for 2 y, then every 6-12 mo
- Chest/abdomen/pelvic imaging every 3-6 mo for 2 y, then annually
- CT/MRI as clinically indicated
- Patient education regarding symptoms

RECURRENCE

Local recurrence:
• Vagina
• Negative chest and abdominal/pelvic CT, confirming local vaginal recurrence

Isolated metastases

Disseminated disease

Resectable

Unresectable

ESS

All others

THERAPY FOR RELAPSE

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

Consider surgical resection + postoperative chemotherapy^a or hormone therapy (ESS only)^a
or
Chemotherapy^a ± palliative RT
or
Hormone therapy (ESS only)^a

Chemotherapy^a ± palliative RT
or
Hormone therapy (ESS only)^a

Hormone therapy^a
or
Supportive care

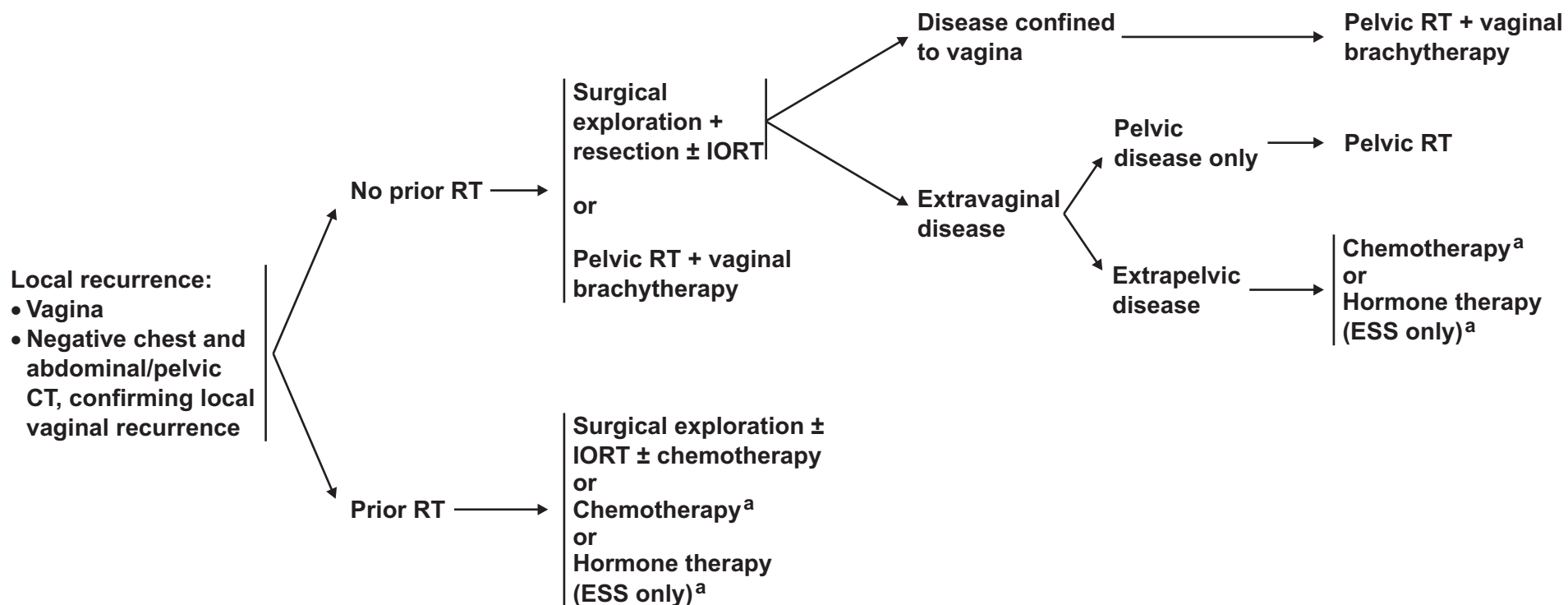
Chemotherapy^a ± palliative RT
or
Supportive care

^a[See Systemic Therapy for Advanced or Metastatic Disease \(UTSARC-A\).](#)

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

RECURRENCE

THERAPY FOR
RELAPSE



^aSee [Systemic Therapy for Advanced or Metastatic Disease \(UTSARC-A\)](#).

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

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE**CHEMOTHERAPY REGIMENS**

The following agents can be used as single agents or in combination, as clinically appropriate:

- Doxorubicin or liposomal anthracycline (most active single agent for LMS)
- Single-agent paclitaxel, docetaxel, epirubicin, gemcitabine, ifosfamide, and dacarbazine have activity in other soft tissue sarcomas, and could also be considered (category 2B).
- Gemcitabine/docetaxel (category 2B)
- Combination regimens such as MAID (mesna, adriamycin, ifosfamide, dacarbazine) (category 2B) or modification of combination regimens have been used

HORMONE THERAPY (ESS only)

- Megestrol acetate
- Medroxyprogesterone acetate
- Tamoxifen (category 2B)
- GnRH analogs (category 2B)
- Aromatase inhibitors (category 2B)

Clinical trials strongly recommended

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

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

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

UTERINE SARCOMA CLASSIFICATION

- Endometrial stromal sarcoma¹
- Undifferentiated sarcoma (high-grade endometrial stromal sarcoma)² or pure heterologous sarcoma³
- Leiomyosarcoma⁴

¹Endometrial stromal sarcomas displaying morphologic features of proliferative phase endometrial stroma and showing any mitotic index.

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

³Rare group of tumors including malignant fibrous histiocytoma, rhabdomyosarcoma, angiosarcoma, liposarcoma, chondrosarcoma, osteosarcoma, alveolar soft-part sarcoma, and other sarcomas with morphology comparable to extrauterine counterparts.

⁴Excludes smooth muscle tumors of uncertain malignant potential, epithelioid smooth muscle tumors, benign metastasizing leiomyomas, intravenous leiomyomatosis, diffuse leiomyomatosis; management in individual cases may be modified based on clinicopathologic prognostic factors, such as size (< or > 5 cm), mitotic activity (< or > 10 mf/10 hpf), age (< or > 50 years), and presence or absence of vascular invasion.

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

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

Staging

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

FIGO Stages†	Surgical-Pathologic Findings	TNM Categories Primary Tumor (T)
	Primary tumor cannot be assessed	TX
	No evidence of primary tumor	T0
0	Carcinoma in situ (preinvasive carcinoma)	Tis
I	Tumor confined to the corpus uteri	T1
IA	Tumor limited to endometrium	T1a
IB	Tumor invades one half or less of the myometrium	T1b
IC	Tumor invades more than one half of the myometrium	T1c
II	Tumor invades cervix but does not extend beyond uterus	T2
IIA	Endocervical glandular involvement only	T2a
IIB	Cervical stromal invasion	T2b
III	Local and/or regional spread as specified in IIIA, B, C	T3 and/or N1
IIIA	Tumor involves serosa and/or adnexa (direct extension or metastasis) and/or cancer cells in ascites or peritoneal washings	T3a
IIIB	Vaginal involvement (direct extension or metastasis)	T3b
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes	N1
IVA	Tumor invades bladder mucosa and/or bowel mucosa (the presence of bullous edema is not sufficient to classify tumor as T4)	T4
IVB	Distant metastasis (excluding metastasis to vagina, pelvic serosa, or adnexa; including metastasis to intra-abdominal lymph nodes other than para-aortic and/or inguinal lymph nodes)	M1

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

*Reprinted from: Benedet JL, Bender H, Jones H 3rd, et al. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet 2000;70:209-262. Copyright 2000, with permission from International Federation of Gynecology and Obstetrics

†All cases of FIGO stage I-IVA should be subclassified by histologic grade as follows: GX = grade cannot be assessed; G1 = well differentiated; G2 = moderately differentiated; G3 = poorly differentiated or undifferentiated.

Manuscript This manuscript is being updated to correspond with the newly **updated** algorithm. Last update 04/11/06

NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Endometrial Cancer

Overview

Adenocarcinoma of the endometrium is the most common malignancy of the female genital tract in the United States. It is estimated that 41,200 new uterine cancer cases will be diagnosed in 2006, with 7,350 deaths resulting from the disease.¹

In approximately 75% of patients with adenocarcinoma of the endometrium, the invasive neoplasm is confined to the uterus at diagnosis. Many physicians believe that adenocarcinoma of the endometrium is a relatively benign disease because of the early symptoms of irregular vaginal bleeding in this predominantly postmenopausal patient population, the often localized nature of the

disease, and the generally high survival rate. A critical evaluation of survival data, however, indicates that this belief is inaccurate.

Although the estimated incidence of endometrial cancer in the United States remained relatively constant from 1987 to 1998, the estimated number of deaths from endometrial cancer doubled from 2,900 in 1987 to 6,300 in 1998 and continues to increase.^{1,2} The reasons underlying this increase in the death rate are probably multifactorial, but they indicate the need for a critical reassessment of the guidelines for managing endometrial cancer. It is imperative that physicians identify high-risk patients and tailor treatment appropriately to provide the best opportunity for long-term survival.

By definition, the NCCN practice 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 members of the panel during the process of developing these guidelines.

Diagnosis and Workup

Most patients (90%) with endometrial carcinoma have abnormal vaginal bleeding, most commonly in the postmenopausal period. Initial preoperative evaluation for early-stage endometrial cancer should include a history and physical examination, chest x-ray, a complete blood count, and platelet count. Diagnosis can usually be made by an office endometrial biopsy. If cervical involvement is suspected, cervical biopsy or MRI should be considered. Cervical cytology should be assessed using the [NCCN Cervical Screening Guidelines](#).

Given the typical age group at risk for endometrial carcinoma and the presence of comorbid illnesses, it is prudent in selected patients to also include assessments of serum electrolytes, blood urea nitrogen, serum creatinine, serum glucose, and renal and liver function. Other

ancillary tests (such as cystoscopy, sigmoidoscopy, ultrasound, computed tomography, and magnetic resonance imaging [MRI]) should be reserved for evaluating extrauterine disease as indicated by clinical symptoms, physical findings, or abnormal laboratory findings. In patients with extrauterine disease, a serum CA 125 assay may be helpful in monitoring clinical response.^{3,4} However, serum CA 125 levels may be falsely increased in women who have severe radiation injury, normal in women with isolated vaginal metastases, and may not predict recurrence in the absence of other clinical findings.⁵⁻⁷

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 curettage under anesthesia. Hysteroscopy may be helpful in evaluating the endometrium for lesions, such as a polyp, if the patient has persistent or recurrent undiagnosed bleeding.⁸

Endometrial Cancer Staging

The FIGO (International Federation of Gynecology and Obstetrics) system is most commonly used for staging. The original 1970 criteria for staging endometrial cancer incorporated only information gained from presurgical evaluation, including physical examination as well as diagnostic fractional dilation and curettage. A substantial number of patients at that time were not treated with primary surgery because of obesity or various other medical problems. Thus, this staging system should only be used today in the rare instances when the patient is not a surgical candidate.

Several studies in the biomedical literature demonstrated that clinical staging was inaccurate and did not reflect actual disease

extent in 15% to 20% of patients.⁹⁻¹¹ 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 the Cancer Committee of FIGO modified its staging system to emphasize complete surgicopathologic assessment of data, such as histologic grade, myometrial invasion, as well as the extent and location of extrauterine spread, including retroperitoneal lymph node metastases (see [Table 1](#)).¹²

Primary Treatment

A pathology review will provide clinical findings of various endometrial histologies, or papillary serous or clear cell carcinoma. These NCCN guidelines divide endometrial cancer into three categories for delineating treatment: (1) disease limited to the uterus, (2) suspected or gross cervical involvement, and (3) suspected extrauterine disease. The pathologic assessment of the uterus should include (1) ratio of depth of myometrial invasion to myometrial thickness; (2) tumor size; (3) tumor location (fundus versus lower uterine segment/cervix); (4) histologic subtype with grade; (5) lymphovascular space invasion; and (6) frozen section as indicated.

Disease Limited to the Uterus. Most patients with endometrial cancer have stage I disease at presentation. If medically operable, the recommended surgical procedure for the staging of a patient with endometrial cancer clinically confined to the fundal portion of the uterus includes peritoneal lavage for cytology and total hysterectomy/bilateral salpingo-oophorectomy (TH/BSO) with dissection of pelvic and para-aortic lymph nodes via an abdominal approach.¹³ During surgery, the abdominal organs (including the diaphragm, liver, omentum, and pelvic and bowel peritoneal

surfaces) should be carefully inspected and palpated. The pathologic information obtained provides an optimal basis for the decision and design of adjuvant therapy. For medically inoperable patients, exclusive radiation therapy (RT) has been demonstrated as a well-tolerated and effective treatment that can provide some measure of pelvic control and long-term progression-free survival.¹⁴ Pelvic and aortic lymphadenectomy are recommended for all patients with disease confined to the uterus and for suspected or gross cervical involvement.

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.¹⁵ As the grade of the tumor increases, the accuracy of intraoperative evaluation of myometrial invasion by gross examination of fresh tissue decreases. 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.¹⁶ A further indication for complete surgical staging is suggested in reports demonstrating statistically improved survival in patients with complete node dissection versus no node dissection or limited node sampling, even after adjusting for other clinicopathologic variables.^{17,18}

Suspected or Gross Cervical Involvement. For patients with suspected or gross cervical involvement, cervical biopsy or MRI should be considered. If negative, patients are assumed to have disease that is limited to the uterus and are treated as previously described. For operable patients with cervical involvement, radical hysterectomy with bilateral salpingo-oophorectomy (RH/BSO), cytology, as well as dissection of pelvic and para-aortic lymph nodes are recommended. Alternatively, the patient may undergo RT (75-80 Gy to point A) (category 2B) followed by TH/BSO with para-aortic

lymph node dissection. For medically inoperable patients, pelvic RT with brachytherapy can provide long-term local control and cancer-specific survival rates.¹⁴

Suspected Extruterine Disease. If extruterine disease is suspected, laboratory tests of CA 125 level or imaging studies (such as MRI or CT) are recommended if clinically indicated. Patients with negative results are treated using the guidelines for disease limited to the uterus. Intra-abdominal disease (such as ascites, omental, nodal, ovarian, or peritoneal involvement) warrants surgical intervention using TH/BSO with cytology as well as selective pelvic and para-aortic lymph node dissection, omentectomy, and debulking. Patients with extruterine pelvic disease (such as vaginal, bladder, bowel/rectal, or parametrial involvement) are treated with RT and brachytherapy with or without surgery or chemotherapy. For extra-abdominal disease (such as liver involvement), palliative TH/BSO with or without RT, hormonal therapy, or chemotherapy is recommended.

Adjuvant Therapy

Given the lack of definitive data regarding the effectiveness of adjuvant therapy in patients with uterine-confined disease, the NCCN guidelines represent an evolving process. The basic concept underlying the recommendations is the trend toward selection of more aggressive adjuvant therapy for patients as tumor grade and myometrial and/or cervical invasion worsen. Other pathologic factors that may influence the decision regarding adjuvant therapy in surgical stage I and stage II endometrial cancer include patient age, lymphovascular space invasion, tumor volume, and involvement of the lower uterine segment.

Three trials have evaluated the role of pelvic RT in patients with endometrial carcinoma. In 2 of these trials, the patients were not

formally staged;^{19,20} however, patients were formally staged in the recent GOG trial.²¹ The PORTEC (Postoperative Radiation Therapy in Endometrial Carcinoma) trials showed that whole pelvic RT is not beneficial and that RT cannot overcome poor surgical treatment.^{19,22} The Aalders' randomized trial found that RT only prevents vaginal recurrences and that RT does not reduce distant metastases or improve survival.²⁰ The Keys' trial revealed that most of the initial recurrences were confined to the vagina, prompting the use of vaginal brachytherapy as adjunctive treatment.²¹ A recent retrospective analysis of 21,249 women with endometrial cancer found that adjuvant RT only improved overall and relative survival in those with stage IC disease.²³

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.²⁴ Treatment is often tailored to the surgically defined extent of disease. A point of historical controversy has been whether positive peritoneal cytology (stage IIIA) is an independent prognostic factor, after adjustment for other known risk factors.^{25,26} At present, there is general agreement that in the absence of other adverse pathologic features (high-grade tumors, deep myometrial invasion, papillary serous or clear cell histologies, or documented extrauterine disease), a positive peritoneal cytology may be a clinically inconsequential finding.

Completely Surgically Staged Patients. The imprecision of preoperative and intraoperative assessment of grade and myometrial invasion along with the potential therapeutic benefit of lymph node dissection make the concept of intraoperative decision-based lymph node dissection difficult to apply prospectively with accuracy. Therefore, complete surgical staging to gather full

pathologic and prognostic data on which to base decisions regarding adjuvant treatment should be advocated for all patients who do not have medical or technical contraindications to lymph node dissection.

Laparoscopic pelvic and para-aortic lymphadenectomy in association with laparoscopically assisted vaginal hysterectomy has been proposed as an alternative surgical approach; however, the panel recommends that this approach be used only in the context of a clinical trial and that patients should be followed over a long term to compare their outcomes with those of traditional laparotomy. A randomized phase III trial evaluating this potentially less invasive method is underway (GOG-LAP2).

To assess the role of adjuvant radiation in surgically staged endometrial cancer patients without extrauterine disease, the GOG completed a multicenter trial that randomly assigned patients with stage IB, stage IC, and occult stage II disease (any grade) to pelvic radiotherapy versus observation alone after primary surgery. Initial analysis of the study showed a significant decrease in overall recurrences and an improvement in the 2-year progression-free interval favoring the radiated cohort, but overall survival was not statistically different between the two groups.²¹ Patterns of failure analysis in the GOG trial revealed an intriguing finding: most of the initial pelvic recurrences in the observation group were limited to the vagina. This finding has prompted some clinicians to ask if vaginal brachytherapy is sufficient adjuvant treatment for patients with tumors that are histologically confined to the uterus, despite the existence of other intrauterine risk features.²⁷ The GOG randomized trial has also been criticized for including patients with a broad range of relapse risk, including many who probably have excellent prognoses, hence diluting the possibility of detecting a benefit to adjuvant therapy.

Adequate surgical staging provides important information to assist in selection of adjuvant therapy for endometrial tumors. Patients with completely surgically staged stage I endometrial cancer are stratified by adverse risk factors such as advanced age, lymphovascular invasion, tumor size, depth of invasion, and involvement of lower uterine segment. All stage IA, G1-3 patients should be observed. However, vaginal brachytherapy is also recommended for stage IA, G3 disease if no adverse risk factors are present.

Observation or vaginal brachytherapy with or without pelvic RT (category 2B for all options) is recommended for patients with adverse risk factors. Stage IB patients without adverse risk factors can be observed or treated with vaginal brachytherapy (G2-3). If adverse factors are present, stage IB, G1 patients should be observed or undergo vaginal brachytherapy; however, stage 1B, G2 tumors need observation or vaginal brachytherapy with or without pelvic RT (category 2B for all options). Stage IB, G3 tumors need pelvic RT and/or vaginal brachytherapy (category 2B for all options). For stage IC patients with adverse risk factors, pelvic RT and/or vaginal brachytherapy is recommended (category 2B for all options), regardless of their histologic grade. Otherwise, if no adverse risk factors are present, observation or vaginal brachytherapy is recommended for G1-2 patients; however, pelvic RT and/or vaginal brachytherapy (category 2B for all options) is recommended for G3 patients.

Based on a prospective evaluation of surgicopathologic patterns of spread in endometrial cancer by the Gynecologic Oncology Group (GOG) and others, it is now recognized that much of the adverse prognosis associated with intrauterine risk factors is mediated through nodal involvement. The incidence of pelvic nodal metastases is 5% or less for grade 1 and 2 tumors with inner one-third myometrial invasion. For patients with outer third infiltration,

nodal disease was found in 19% of grade 2 cancers and in 34% of grade 3 cancers.¹¹ Given the wider acceptance of formal surgicopathologic evaluation and the adoption of the 1988 FIGO staging classification (see [Table 1](#)), clinical stage I and stage II patients with adverse intrauterine features who were once deemed at risk for nodal metastases are now upstaged to stage III and stage IV when extrauterine disease is documented. The implications of this “stage migration” should be taken into account when evaluating historical data.

Significant controversy centers on appropriate adjuvant therapy in patients with surgical stage I and stage II endometrial cancer, regardless of intrauterine features, for whom extrauterine disease has been clearly ruled out. In a large prospective study, the GOG reported that the 5-year survival rate for surgical stage I patients with no adverse risk factors other than grade and myometrial invasion (ie, without extrauterine disease, isthmus/cervical involvement, or lymphovascular space invasion) was 92.7%.²⁵ The practice of surgical staging has led to a decrease in the use of adjuvant therapy for stage I endometrial carcinoma.²⁸

The benefit of external irradiation in pathologic stage I endometrial carcinoma with unfavorable prognostic factors was demonstrated by a prospective clinical study. Kucera and colleagues reported on a large series of 605 patients with stage I endometrial carcinoma initially treated with TH/BSO. Patients with low-grade and superficially invasive disease received vaginal brachytherapy only, whereas those with higher-grade disease and deeper myometrial infiltration underwent vaginal and external-beam radiation. The 5-year survival results showed that patients with poor prognostic factors who received external-beam radiation and vaginal brachytherapy did as well as the patients with a good prognosis who

were treated with vaginal radiation alone. This suggested that external radiation was able to compensate for the expected poorer outcome in patients with unfavorable risk factors.²⁹

For stage IIA patients with myometrial invasion less than 50%, observation or vaginal brachytherapy is recommended for G1 disease; observation or vaginal brachytherapy with or without pelvic RT is recommended for G2 tumors. Vaginal brachytherapy with or without pelvic RT is recommended for patients with G3 tumors. Patients with deeper myometrial invasion (more than 50%) who have G1-2 disease are treated with vaginal brachytherapy with or without pelvic RT; G3 disease is managed by pelvic RT and vaginal brachytherapy. The recommended treatment option for stage IIB patients is pelvic RT and vaginal brachytherapy. Observation or vaginal brachytherapy is also an option for patients with stage IIB disease who have had a radical hysterectomy with negative surgical margins and no evidence of extrauterine disease.

Patients with extrauterine disease confined to the lymph nodes or the adnexa may be adequately treated with pelvic or extended-field RT.³⁰ Noninvasive stage IIIA tumors confined to fundus or those with only positive cytology should be observed; G3 tumors can also be managed with vaginal brachytherapy or with pelvic RT with or without vaginal brachytherapy. For all other stage IIIA tumors, the recommended options (all are category 2B) include (1) tumor-directed RT and chemotherapy; (2) chemotherapy with or without RT; (3) pelvic RT with or without vaginal brachytherapy; or (4) whole abdominopelvic RT with or without vaginal brachytherapy.

Despite the histologic grade, patients with stage IIB are treated with tumor-directed RT with or without chemotherapy. Patients with stage IIC are treated with tumor-directed RT and chemotherapy. After tumor debulking, stage IVA or IVB tumors with no gross residual

disease or microscopic abdominal disease should be managed with either chemotherapy with or without RT, or RT with or without vaginal brachytherapy.

For patients deemed at risk of peritoneal failure, whole abdominal RT in carefully selected cases appears to provide therapeutic benefit.^{31,32} A randomized phase III GOG (122) trial assessed optimal adjuvant therapy for endometrial cancer with extrauterine disease. In this trial, patients with stage III and intra-abdominal stage IV disease who had minimal residual disease were randomly assigned to whole abdominopelvic RT versus 7 cycles of combined doxorubicin (60 mg/m²) and cisplatin (50 mg/m²) treatment, with an additional cycle of cisplatin (AP). Results of this study revealed that AP chemotherapy improved progression-free survival and overall survival when compared with whole abdominopelvic RT; however, acute toxicity is greater in the AP chemotherapy arm.³³ Recurrences were frequent, occurring in the pelvis and abdomen in both arms. Approximately 52% of patients with advanced endometrial carcinoma had recurrences.³³ Another phase III GOG trial in 273 women with advanced or recurrent endometrial carcinoma compared (1) doxorubicin and cisplatin versus (2) doxorubicin, cisplatin, and paclitaxel with filgrastim support. The addition of paclitaxel improved survival (15 versus 12 months); however, toxicity was increased.³⁴ Another GOG trial (209) is assessing (1) carboplatin plus paclitaxel versus (2) paclitaxel, doxorubicin, and cisplatin. The GOG 184 trial investigating combination chemotherapy with more limited radiation fields is closed and final results are not available yet.

Incompletely Surgically Staged Patients. For incompletely surgically staged patients, radiologic imaging is often required for stage IB, IC, IIA, and IIB tumors. Positive radiologic findings

necessitate surgical restaging. For patients with stage IB or IIA disease with myometrial invasion less than 50% and negative radiologic results, options include observation or vaginal brachytherapy with or without pelvic RT. It is recommended that stage IA, G1-2 tumors be observed. Stage IB or IIA tumors with positive radiologic findings need surgical restaging, followed by adjuvant treatment (for completely surgically staged). Patients with more aggressive tumors (such as stage IC, stage IIA with myometrial invasion of 50% or more, stage IIB, or G3 tumors) are managed with radiologic imaging followed by either (1) reoperative staging followed by adjuvant treatment (for completely surgically staged) as indicated; or (2) pelvic RT and vaginal brachytherapy with or without para-aortic RT.

In 384 nonsurgically staged patients with high-risk intrauterine features, selective adjuvant pelvic RT was beneficial.³⁵ An early prospective phase III study of stage I endometrial cancer (without lymph node sampling) randomly assigned patients to vaginal brachytherapy alone or in combination with external irradiation (40 Gy with central shielding after 20 Gy). Although there was no overall 5-year survival benefit from the addition of external-beam RT, there was some improvement in pelvic control.²⁰

Hormone Replacement Therapy for Endometrial Cancers

Hypoestrogenism is associated with hot flashes, mood lability, vaginal dryness, pelvic soft tissue atrophy, osteoporosis, and an increased risk of cardiovascular disease. Estrogen replacement therapy in postmenopausal women has been shown to reduce or reverse these signs and symptoms. Because endometrial adenocarcinoma has historically been considered an estrogen-linked malignancy,^{36,37} women who have been successfully treated for this cancer have usually been denied estrogen replacement

therapy for fear of inducing a higher relapse rate. However, estrogen replacement therapy for such patients remains controversial. It has never been proven that there is a higher relapse rate in endometrial cancer patients who receive estrogen replacement therapy after hysterectomy. Indeed, several retrospective trials of estrogen replacement after treatment of early-stage endometrial cancer have shown no increase in tumor recurrence or cancer-related deaths.³⁸⁻⁴⁰ However, estrogen replacement trials in postmenopausal females without a history of malignancy have demonstrated a significantly increased risk of breast cancer.

Panel members agree 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. If adjuvant treatment is carried out, there should be a 6- to 12-month waiting period before initiation of hormonal replacement therapy, and participation in clinical trials is strongly encouraged. Selective estrogen-receptor modulators (SERMs) may prove to be attractive options in hormone replacement therapy. For example, the SERM raloxifene does not exhibit a stimulatory effect on uterine or breast tissue but retains beneficial activity on bone and lipid metabolism. Unfortunately, raloxifene does not reduce vasomotor instability. Long-term comparisons between conjugated estrogens and SERMs for hormone replacement therapy are needed.

The primary treatment of endometrial cancer is usually hysterectomy. However, progesterone therapy has been used for (1) young women with either atypical endometrial hyperplasia or grade 1 endometrial hyperplasia who desire fertility preservation; or (2) women who are very poor surgical candidates.^{13,41,42}

Postoperative Surveillance

The panel recommends a postoperative surveillance protocol for endometrial cancer consisting of a clinic visit with a physical examination every 3 to 6 months for 2 years, and then at 6 month to 1 year intervals. Chest x-ray should be monitored annually (category 2B); vaginal cytology should be performed every 6 months for 2 years, then annually. The NCCN panel disagreed (category 3) about whether CA 125 levels were useful for surveillance. These recommendations recognize that the value of intensive surveillance has not been demonstrated in this disease, and ancillary testing is therefore not recommended.⁴³⁻⁴⁶

A review of the biomedical literature for routine intensive postoperative surveillance in patients with clinical stage I and stage II endometrial cancer showed an approximately 15% recurrence rate;⁴⁷ 58% of the patients had symptomatic recurrences. For most patients, disease recurred within 3 years of initial treatment.

All patients should receive verbal and written information 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.

In the absence of recurrence, post-treatment surveillance provides psychosocial reassurance and improves the quality of life for patients and their families. Health maintenance has been incorporated into the follow-up schedule and should include blood pressure determination, breast examination, mammography as clinically indicated, stool guaiac test, immunizations, and an opportunity to evaluate other health problems that often coexist in

patients with endometrial cancer. Given the lack of prospective studies regarding the optimal frequency of post-therapy follow-up, it was the NCCN panel's opinion that the algorithm represents a reasonable surveillance scheme.

Treatment of Relapsed or Metastatic Disease

Patients with recurrences confined to the pelvis after surgical therapy should be evaluated for surgical extirpation and/or RT. Vaginal recurrences treated with RT have reported survival rates of 40%, with significantly worse results if there is pelvic extension or pelvic lymph node involvement.⁴⁸ Patients with recurrences confined to the pelvis after RT are unusual. The management of such patients is still controversial.

For patients previously treated with external-beam RT to the recurrence site, recommended salvage therapy includes pelvic exenteration with or without intraoperative radiotherapy (IORT), hormonal therapy, or chemotherapy. Radical surgery, such as pelvic exenteration, has been performed with reported survival rates approximating 20%.⁴⁹ For patients without prior RT to the site of recurrence or with previous brachytherapy only, surgical exploration of the pelvis and abdominal resection should be performed with or without IORT. RT with brachytherapy is considered another treatment option for these patients.

For the recurrence confined to the vagina or with pelvic lymph node invasion, additional therapy is needed, such as pelvic RT with vaginal brachytherapy. Para-aortic or common iliac lymph node invasion is treated with pelvic and para-aortic RT with vaginal brachytherapy. For upper abdominal or peritoneal recurrences, chemotherapy with or without RT is recommended for microscopic residual disease. However, gross upper abdominal residual disease

needs more aggressive salvage treatment as outlined for disseminated metastases. For resectable isolated metastases, consider surgical resection with or without RT. Further recurrences or unresectable isolated metastases are treated as disseminated metastases. The management of systemic disease is usually palliative (see [NCCN's Palliative Care Guidelines](#)) as discussed in the following section.

Hormonal Therapy. The hormonal therapy of metastatic disease involves mainly the use of progestational agents; aromatase inhibitors are also being used. 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, 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 a good response for estrogen and progesterone receptor--positive patients.⁵⁰ Tamoxifen has a 20% response rate in those who do not respond to standard progesterone therapy.⁵¹ Other hormonal modalities have not been well studied, and adjuvant therapy with hormonal agents in the treatment of endometrial cancer remains unproved.⁵² If disease progression is observed after hormonal therapy, cytotoxic chemotherapy should be considered. However, clinical trials or best supportive care (see [NCCN Palliative Care Guidelines](#)) are appropriate for patients with disseminated metastatic recurrence who have a poor response to hormonal therapy and chemotherapy.

Salvage therapy (such as chemotherapy and/or RT) is recommended to relieve symptoms in patients with symptomatic, G2-3, or large-volume disseminated metastases. If 2 chemotherapy

regimens fail, patients should receive best supportive care or be enrolled in an appropriate clinical trial.

Chemotherapy for Advanced and Recurrent Disease.

Chemotherapy for endometrial cancer has been extensively studied. Single-agent therapy usually includes cisplatin, carboplatin, paclitaxel, and doxorubicin. Responses with these agents in advanced disease have ranged from 21% to 36%.

Two combination chemotherapy regimens that have been tested in phase III trials include (1) doxorubicin, cisplatin, and paclitaxel (GOG 177); and (2) cisplatin and doxorubicin (GOG 122). Regimen 1 is the most active but is also the most toxic.^{13,34} The response rates have ranged from 31% to 81% but with relatively short durations.

The median survival for patients in such trials remains approximately 1 year.^{53,54} Carboplatin and paclitaxel is an increasingly utilized regimen based on ovarian studies; a phase III study is currently assessing carboplatin and paclitaxel versus doxorubicin, cisplatin, paclitaxel, and filgrastim (G-CSF) (GOG 209).

Combination chemotherapy regimens in endometrial cancer should be undertaken judiciously with careful attention to toxicity, because there is no demonstrated improvement in quality of life and survival of patients. Biologic and molecular therapies have no proven role at this time in the treatment of recurrent or metastatic endometrial carcinoma.

Papillary Serous and Clear Cell Carcinomas

Uterine papillary serous and clear cell carcinomas are considered more aggressive histologies, with a higher incidence of extrauterine disease at presentation.^{55,56} Patterns of failure mimic those of ovarian cancer. Surgical staging for these tumor subtypes should

follow the procedures performed for ovarian cancer, which include detailed examination of the entire abdominopelvic cavity and retroperitoneal spaces as well as appropriate biopsies, with maximal tumor debulking as indicated. Adjuvant therapy is highly individualized.⁵⁷ Adjuvant therapy recommendations for stage IA-C or II include (1) vaginal brachytherapy, (2) chemotherapy with or without vaginal brachytherapy, or (3) whole abdominopelvic RT with or without vaginal brachytherapy (category 2B); patients with adequately debulked stage III or IV disease can also receive these options. Chemotherapy is recommended for patients with inadequately debulked stage III or IV disease.

Uterine Sarcomas

Overview

Uterine sarcomas are uncommon malignancies accounting for approximately 1 in 12 of all uterine cancers, yielding an annual incidence of 1.23/100,000 in the female population.⁵⁸ The tumors are generally categorized into three separate histologies: leiomyosarcomas (LMS), malignant mixed Müllerian tumors, or endometrial stromal sarcomas (low and high grade). Consistent pathological definitions of the various histologies continue to be refined. The NCCN Uterine Cancers Panel has elected to use the term *carcinosarcoma* instead of malignant mixed Müllerian sarcomas and to subdivide endometrial stromal sarcomas into endometrial stromal sarcomas (previously considered low-grade endometrial stromal sarcomas) and high-grade undifferentiated sarcomas (previously considered high-grade endometrial stromal sarcomas). Classification of uterine sarcomas is discussed in greater detail in the algorithm.

Treatment

After ruling out endometrial cancer, it is necessary to determine if the sarcoma is confined to the uterus or if there is extrauterine disease. If medically operable, then hysterectomy (TH/BSO), with or without lymph node dissection, is the initial treatment of choice for uterine sarcomas. For medically inoperable sarcomas, options include pelvic RT (with or without brachytherapy), chemotherapy, or hormone therapy.

The role of adjuvant radiotherapy in nonmetastatic disease is controversial. There are no category 1 data to define radiotherapy's role in uterine sarcomas; most available data are retrospective in nature. In many series, the patients treated with adjuvant radiotherapy are simply compared to patients treated with surgery alone. It is reasonable to assume that in a proportion of these cases, radiotherapy was delivered to patients thought to be at high risk of recurrence biasing the data against radiotherapy. Despite this obvious limitation, there is still substantial evidence that radiotherapy can play an important role in the curative therapy of uterine sarcomas. Thus, pelvic RT and/or brachytherapy (category 2B) with or without chemotherapy can be considered for stage I and II leiomyosarcomas, carcinosarcomas, and high-grade undifferentiated sarcomas.

Given the uncommon nature of the disease, a number of institutions have reported outcomes of all uterine sarcomas combined. Salazar and colleagues assessed their data and also reviewed more than 900 cases in the biomedical literature; they noted increased local control with the addition of radiotherapy and a trend towards improved survival.^{59,60} Several other studies have noted similar results,⁶¹⁻⁶³ with one also noting an improved survival with the addition of radiotherapy.⁶³

Data regarding carcinosarcoma seem to consistently suggest that adjuvant pelvic radiotherapy offers a statistically significant reduction in the rate of local recurrences when compared with surgery alone.⁶⁴⁻⁶⁹ This local control improvement in some series correlates with an improvement in survival.^{68,69} An improvement in local control with the addition of adjuvant radiotherapy is also seen in some series with leiomyosarcomas.^{70,71} Other series do suggest that RT has a limited effect on outcomes given the propensity for metastatic disease as a site of first recurrence.⁶⁵ Adjuvant radiotherapy in endometrial stromal sarcomas has also been demonstrated to reduce local recurrence rates; in a combined analysis of multiple series by Weitmann, there was also a suggestion of a survival advantage with the addition of pelvic radiotherapy.^{72,73} These studies included both low-grade endometrial stromal sarcomas (currently referred to as endometrial stromal sarcomas) and high-grade endometrial stromal sarcomas (currently referred to as high-grade undifferentiated sarcomas). Series that have looked at low-grade endometrial stromal sarcomas suggest long disease-free intervals in the absence of specific therapy and offer less support for the use of adjuvant radiotherapy.⁷⁴

Ifosfamide is the most active single agent for carcinosarcoma, whereas doxorubicin is the most active single agent for leiomyosarcoma.⁷⁵ Single-agent cisplatin, paclitaxel, docetaxel, epirubicin, topotecan, and dacarbazine can also be considered for advanced or metastatic disease, because these agents have activity in other soft tissue sarcomas (see [NCCN's Soft Tissue Sarcoma Guidelines](#)).⁷⁶ Combination regimens such as gemcitabine and

docetaxel,^{77,78} MAID (mesna, adriamycin, ifosfamide, dacarbazine), or a modification of combination regimens have also been used. Hormone therapy (such as megestrol acetate, medroxyprogesterone, tamoxifen, gonadotropin-releasing hormone [GnRH] analogs) has also been used for endometrial stromal sarcomas that have recurred or are unresectable. Enrollment in clinical trials is strongly recommended. An ongoing phase III randomized GOG trial (150) in patients with carcinosarcoma of the uterus is assessing whole abdominal RT versus cisplatin and ifosfamide.

Disclosures for the NCCN Uterine Cancers Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed the names of companies, foundations, and/or funding agencies from which they received research support; for which they participate in speakers' bureau, advisory boards; and/or in which they have equity interest or patents. Members of the panel indicated that they have received support from the following: Cardinal Health; CTI; Eli Lilly and Company; EMD Pharmaceuticals; Genentech, Inc; GlaxoSmithKline; Gynecologic Oncology Group; InterMune; Lilly Oncology; MedImmune; Merck & Co., Inc.; Novartis Pharmaceuticals; Ross Products; sanofi-aventis; Sanofi-Synthelabo, Inc.; Schering-Plough; Telik, Inc.; and Wyeth. Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.

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