National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Uterine Neoplasms

V.1.2010

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NCCN Guidelines Panel Disclosures

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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 changes in the 1.2010 version of the Uterine Neoplasms Guidelines from the 2.2009 version include:

Endometrial Carcinoma:

(ENDO-4)

- **Footnote "g": Potential adverse risk factors include the following: > 60 y...," changed to "Potential adverse risk factors include the following: Age..."**

(ENDO-B) Systemic Therapy for Recurrent, Metastatic or High-Risk Disease

- **Chemotherapy Regimens: "Ixabepilone may be used as a single agent for second line treatment of patients (category 2B)" was added.**

Uterine Sarcoma:

(UTSARC-A)

- **Chemotherapy Regimens:**
  - **First bullet: After "doxorubicin" the following phrase was removed "(most active single agent for LMS)".**
  - **Third bullet: The panel clarified all of the single agent options as category 2B.**

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Uterine Neoplasms

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
- Consider genetic counseling for patients with a significant family history

→ Pathology review

INITIAL CLINICAL FINDINGS

Epithelial carcinoma

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

Stromal/mesenchymal tumors

- Low-grade endometrial stromal sarcoma (ESS)
- 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)

[a] Staged aggressively, should be treated as a high-grade endometrial cancer.

[b] 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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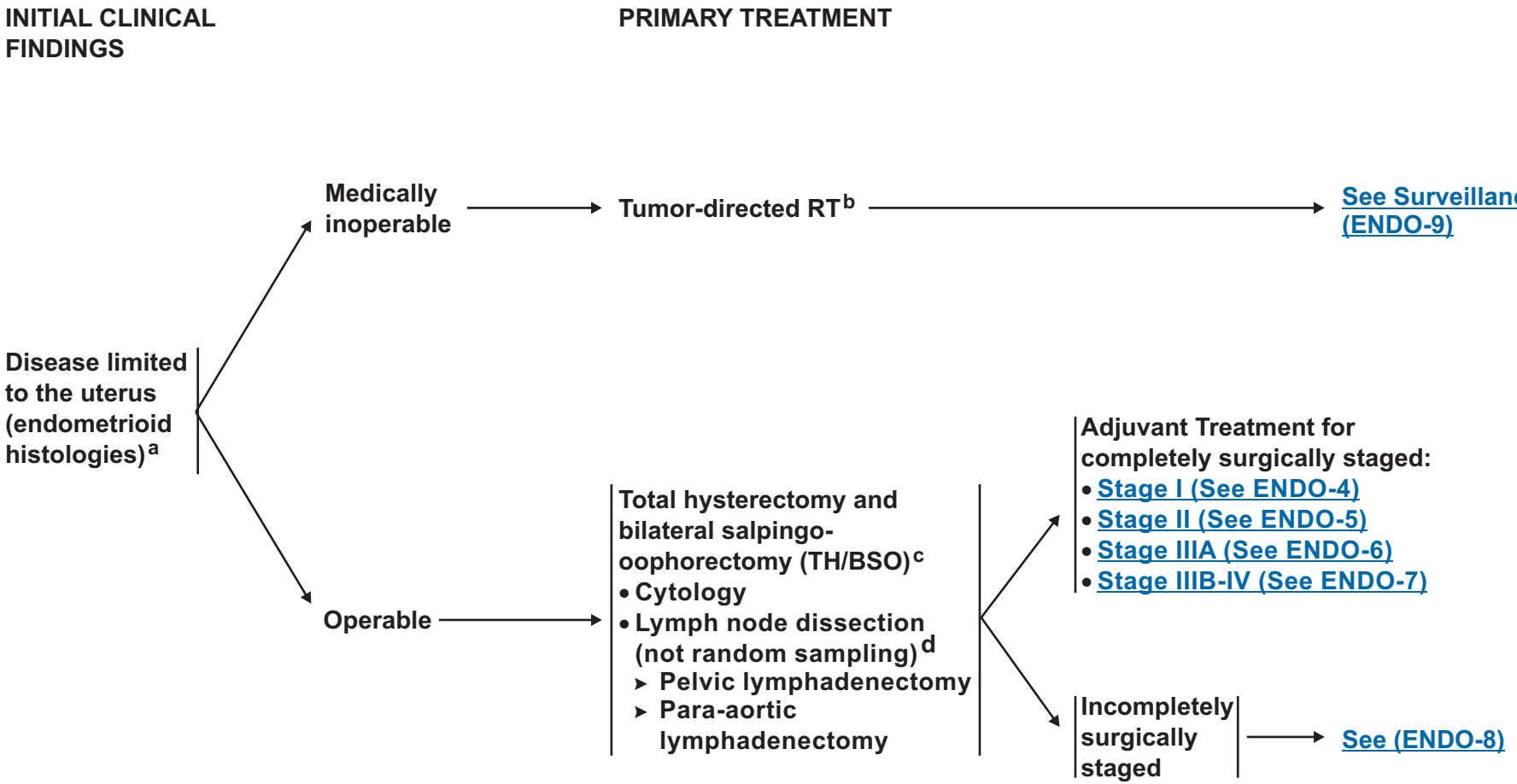
Endometrial Carcinoma



[a] See (UN-1) for clarification of uterine neoplasms.
[b] See Principles of Radiation Therapy (UN-A).
[c] See Hysterectomy (ENDO-A).
[d] American College of Obstetricians and Gynecologists practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstet Gynecol 2005 Aug;106:413-425.

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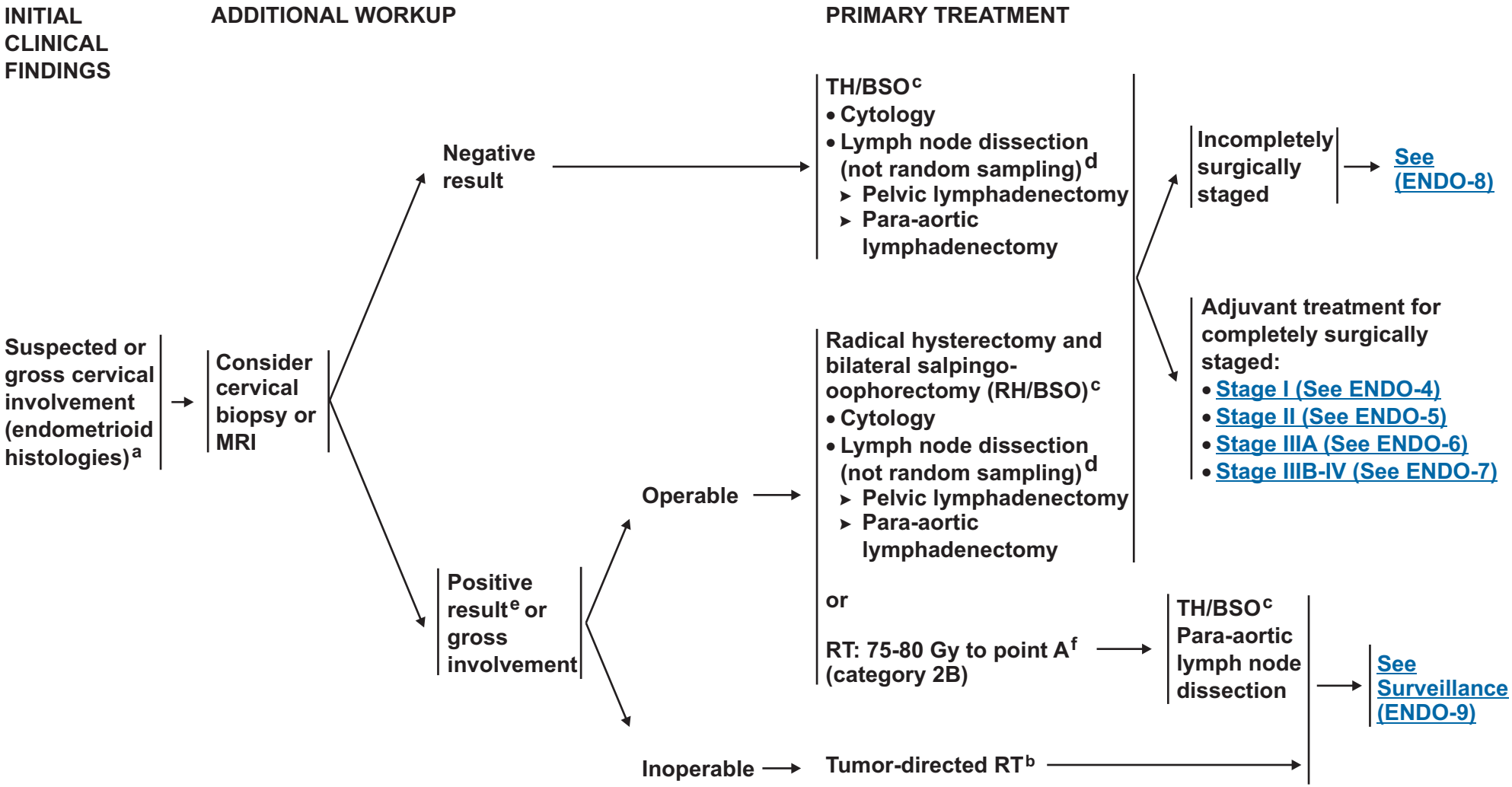

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[d] American College of Obstetricians and Gynecologists practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstet Gynecol 2005 Aug;106:413-425.
[e] Clear demonstration of cervical stromal involvement.
[f] Based on summation of conventional external-beam fractionation and low-dose-rate brachytherapy equivalent.

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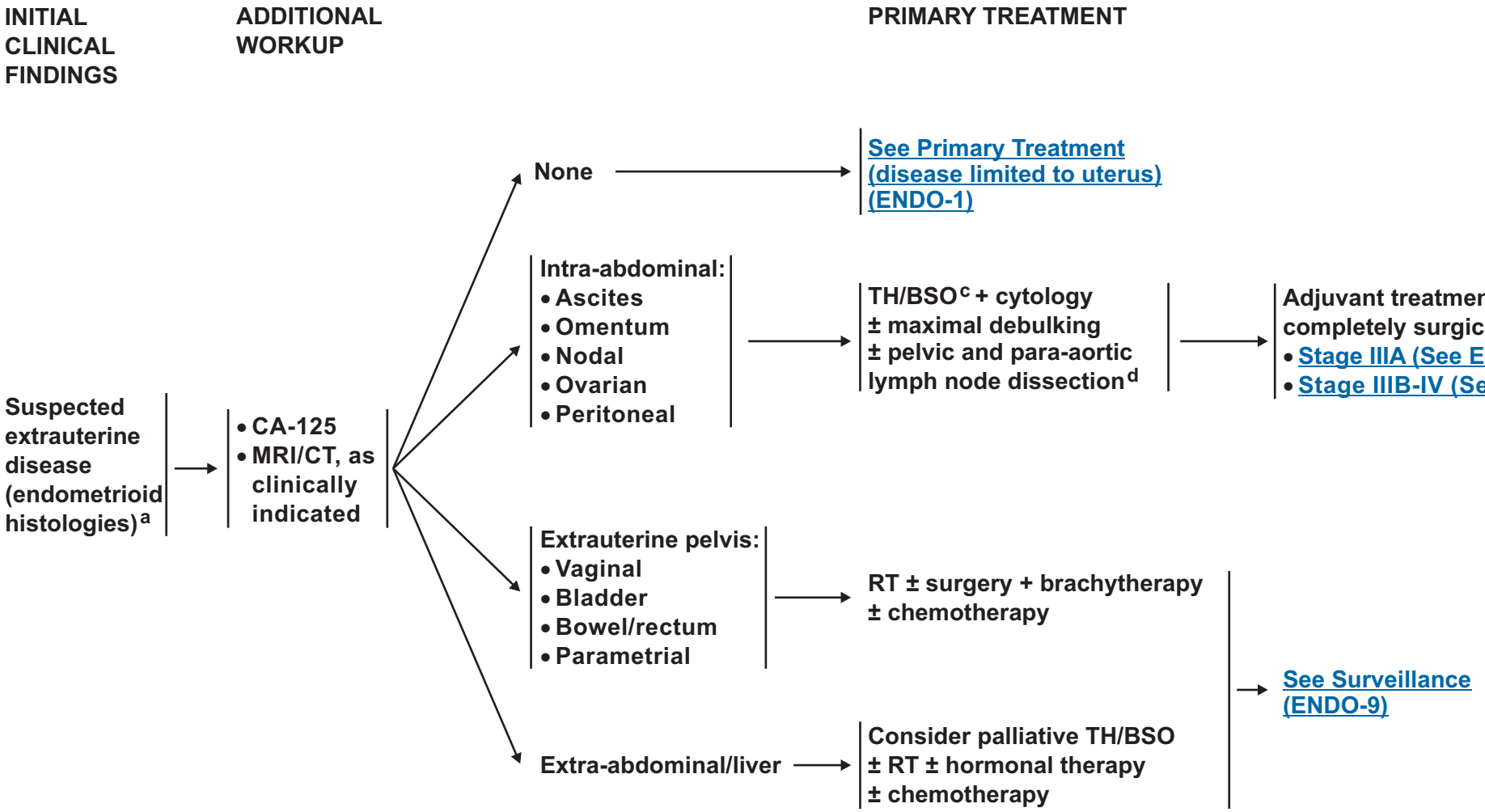
Endometrial Carcinoma



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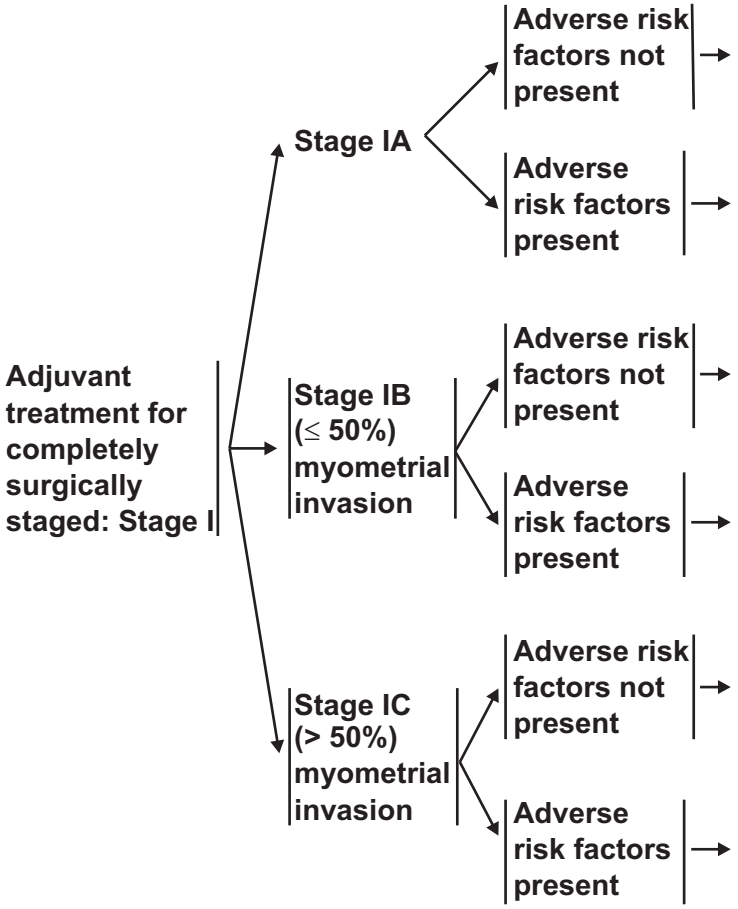

HISTOLOGIC GRADE/ADJUVANT TREATMENT[b,h,i,j]		
G1	G2	G3[i,j]
Observe	Observe	Observe or Vaginal brachytherapy
Observe	Observe	Observe or Vaginal brachytherapy and/or Pelvic RT
Observe	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy
Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or pelvic RT (category 2B for all options)	Observe or Vaginal brachytherapy and/or Pelvic RT
Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or Pelvic RT
Observe or Vaginal brachytherapy and/or Pelvic RT	Observe or Vaginal brachytherapy and/or Pelvic RT	Observe or Pelvic RT and/or Vaginal brachytherapy ± chemotherapy (category 2B for chemotherapy)

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

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

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

[i] The 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).

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

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See Surveillance (ENDO-9)

Endometrial Carcinoma

CLINICAL FINDINGS

HISTOLOGIC GRADE/ADJUVANT TREATMENT[b,h,i,j]

Adjuvant treatment for completely surgically staged: Stage II[k]

Stage IIA → **Optional vaginal brachytherapy for all patients; for recommendations based on findings in the uterine fundus (See ENDO-4)**

Stage IIB →

G1	G2	G3[i,j]
Pelvic RT + vaginal brachytherapy	Pelvic RT + vaginal brachytherapy	Pelvic RT + vaginal brachytherapy ± chemotherapy (category 2B for chemotherapy)

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

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

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

[k] Observation or vaginal brachytherapy is an option for patients with Stage II 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[b,h,i,j]

CLINICAL FINDINGS	G1	G2	G3
Adjuvant treatment for completely surgically staged: Stage IIIA — Positive cytology only, no other extrauterine disease	Observe[l]	Observe[l]	Observe[l] or Vaginal brachytherapy or Pelvic RT ± vaginal brachytherapy ± chemotherapy (category 2B)
Adjuvant treatment for completely surgically staged: Stage IIIA — All other IIIA	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy

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

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

[i] The 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).

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

[l] Intrauterine risk factors may be treated following the guidelines on (ENDO-4) and (ENDO-5).

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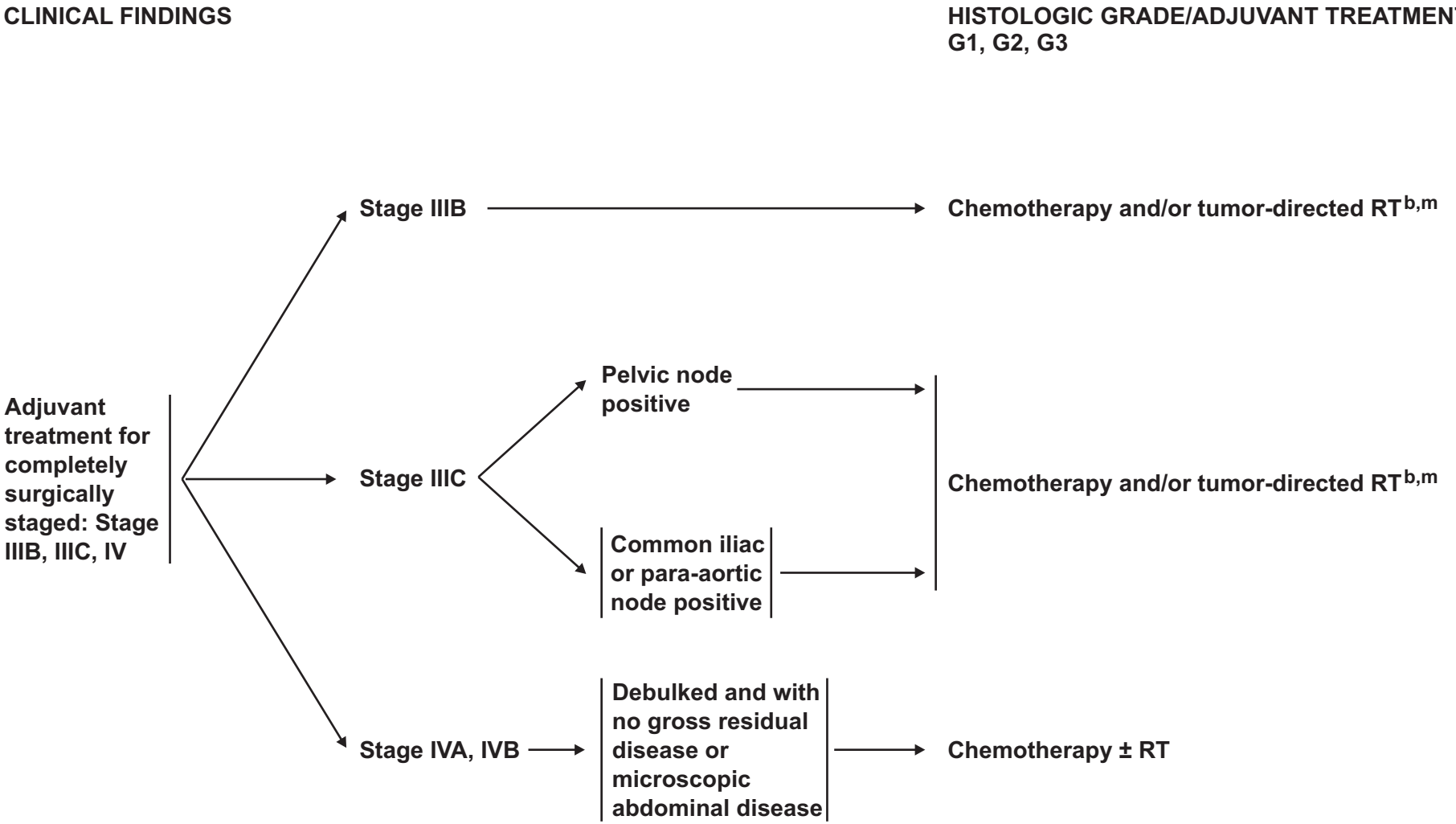
Endometrial Carcinoma



[b] See Principles of Radiation Therapy (UN-A).
[h] Adjuvant therapy determinations are made on the basis of pathologic findings.
[j] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-B).
[m] Pelvic ± para-aortic lymph node RT based on surgical/pathologic findings.

See Surveillance (ENDO-9)

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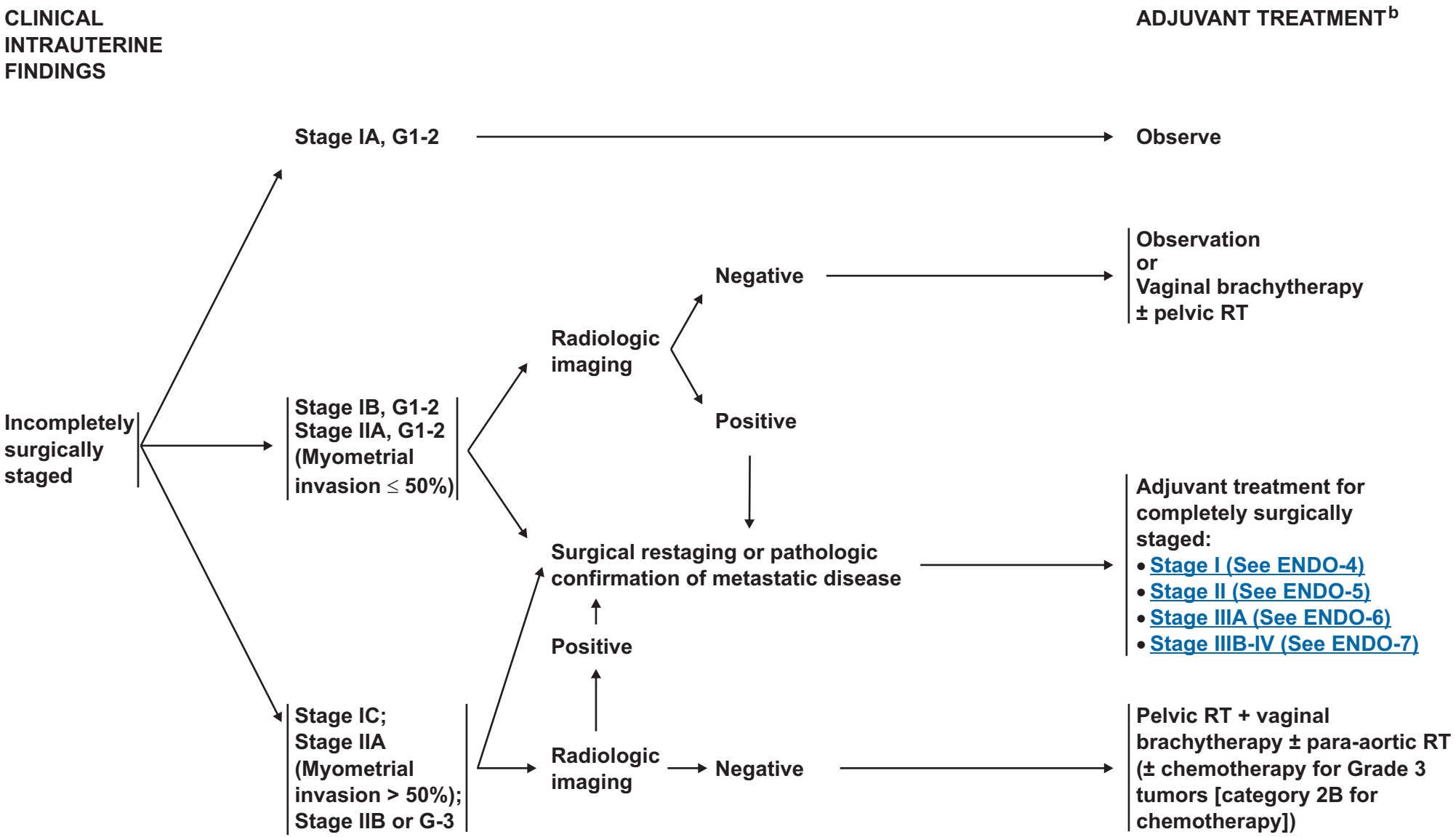
Endometrial Carcinoma



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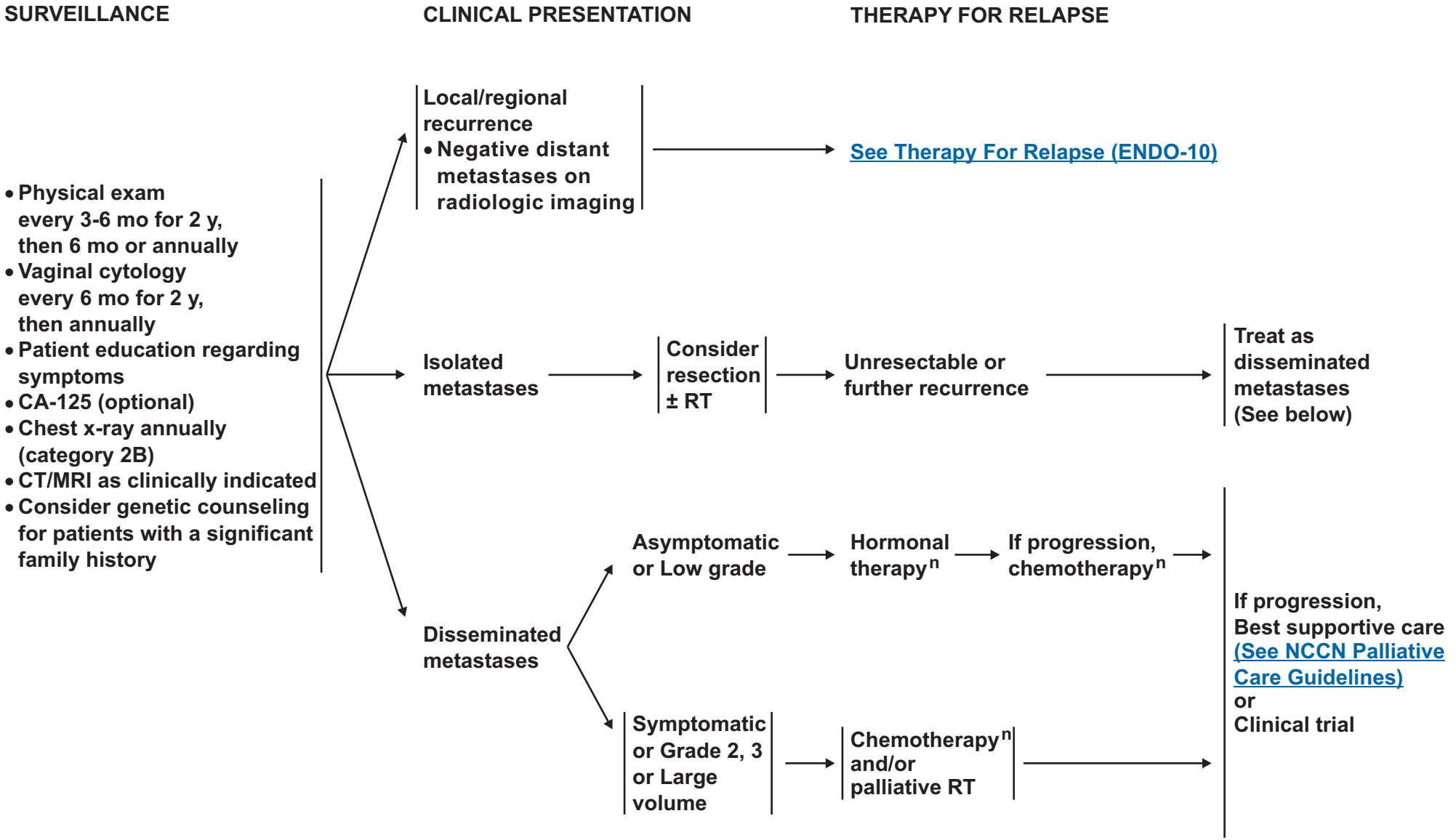

[n] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-B).

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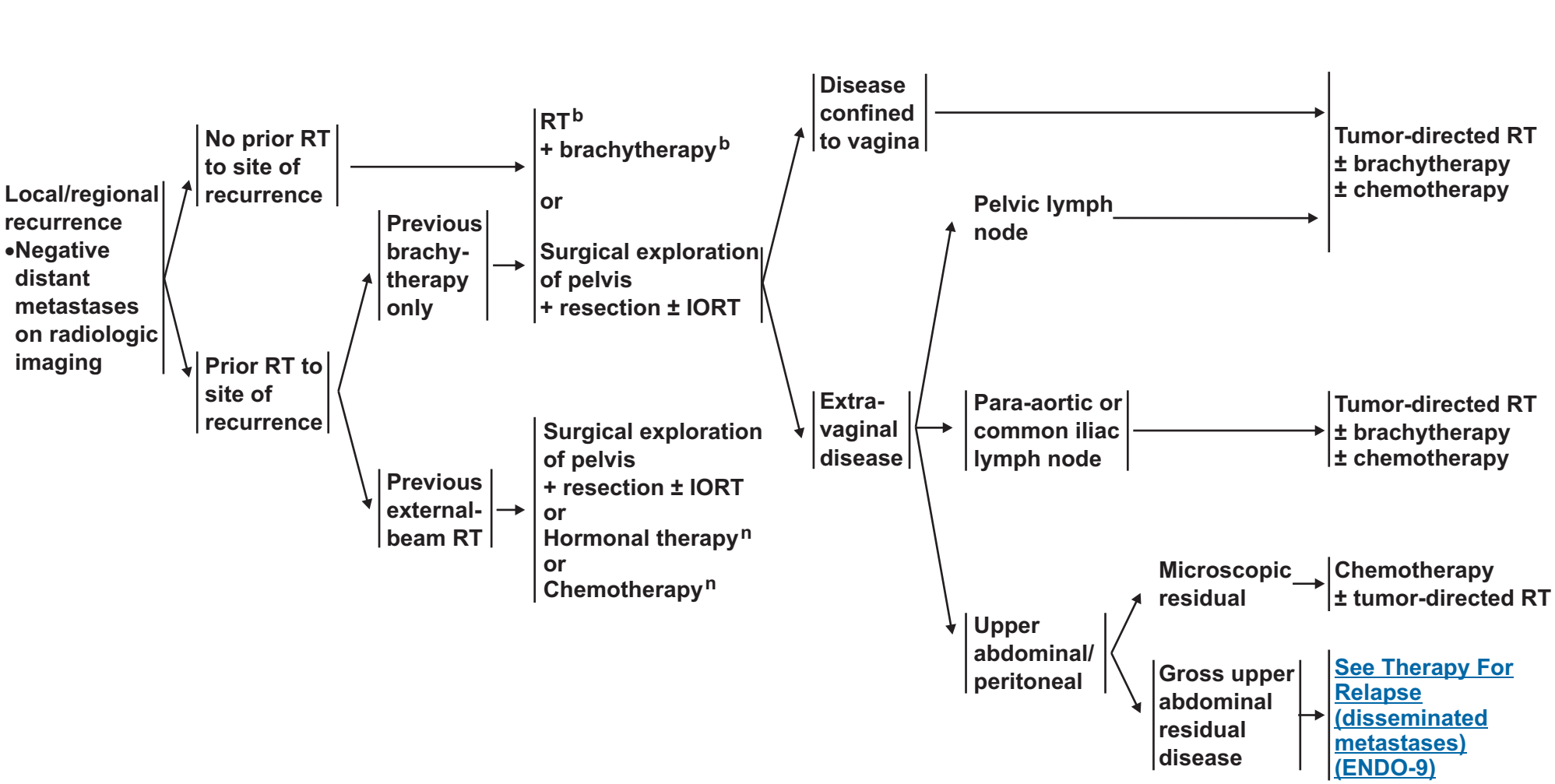
Endometrial Carcinoma



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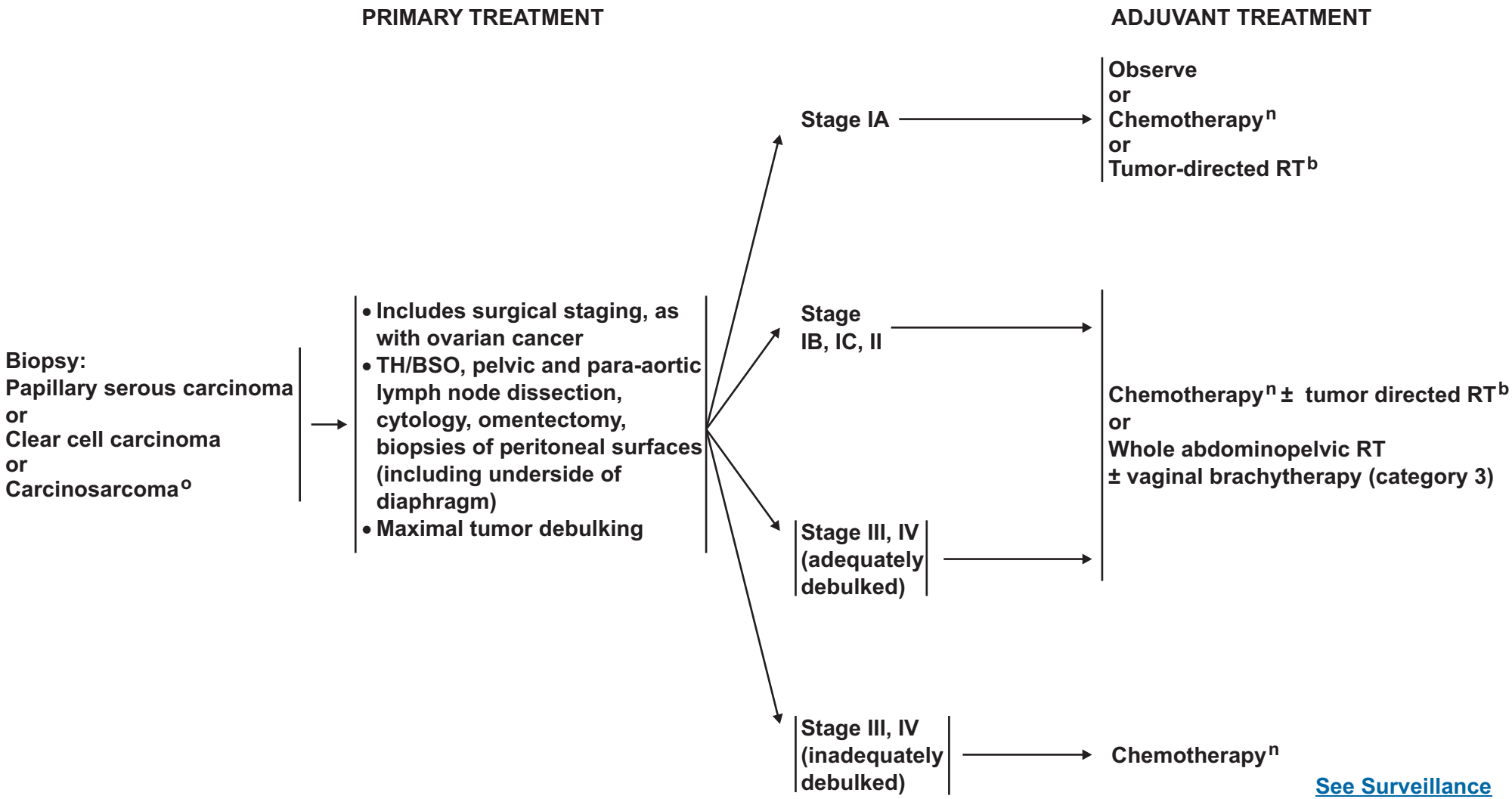
Endometrial Carcinoma

PAPILLARY SEROUS OR CLEAR CELL CARCINOMA OF THE ENDOMETRIUM OR CARCINOSARCOMA[o]



See Surveillance (ENDO-9)

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

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

[o] 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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Endometrial Carcinoma

HYSTERECTOMY

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

Pathologic assessment to include:

- **Nodes**
  - **Level of nodal involvement (pelvic, common iliac, para-aortic)**
- **Peritoneal cytology**
- **Uterus**
  - **Ratio of depth of myometrial/stromal invasion to myometrial thickness**
  - **Cervical stromal or glandular involvement**
  - **Tumor size**
  - **Tumor location (fundus vs lower uterine segment/cervix)**
  - **Histologic subtype with grade**
  - **Lymphovascular space invasion**
  - **Consider mismatch repair analysis to identify genetic problems**
- **Fallopian tubes/ovaries**

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Endometrial Carcinoma

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

HORMONAL THERAPY[1]

- **Aromatase inhibitors**
- **Progestational agents**
- **Tamoxifen**

CHEMOTHERAPY REGIMENS[2]

(Multi-agent chemotherapy regimens preferred, if tolerated)

- **Cisplatin/doxorubicin (category 1)**
- **Cisplatin/doxorubicin/paclitaxel(category 1)**
- **Ifosfamide plus paclitaxel (category 1 for carcinosarcoma)**
- **Carboplatin/paclitaxel**
- **Cisplatin**
- **Carboplatin**
- **Doxorubicin**
- **Paclitaxel**
- **Cisplatin/ifosfamide (for carcinosarcoma)**
- **Ifosfamide (for carcinosarcoma)**
- **Ixabepilone may be used as a single agent for second line treatment of patients (category 2B)**

[1] Hormonal therapy is for endometrioid histologies only (ie, not for papillary serous carcinoma, clear cell carcinoma, or carcinosarcoma).
[2] Chemotherapy regimens are for endometrioid histologies, papillary serous carcinoma, or clear cell carcinoma. A few of the agents can also be used for carcinosarcoma, as indicated.

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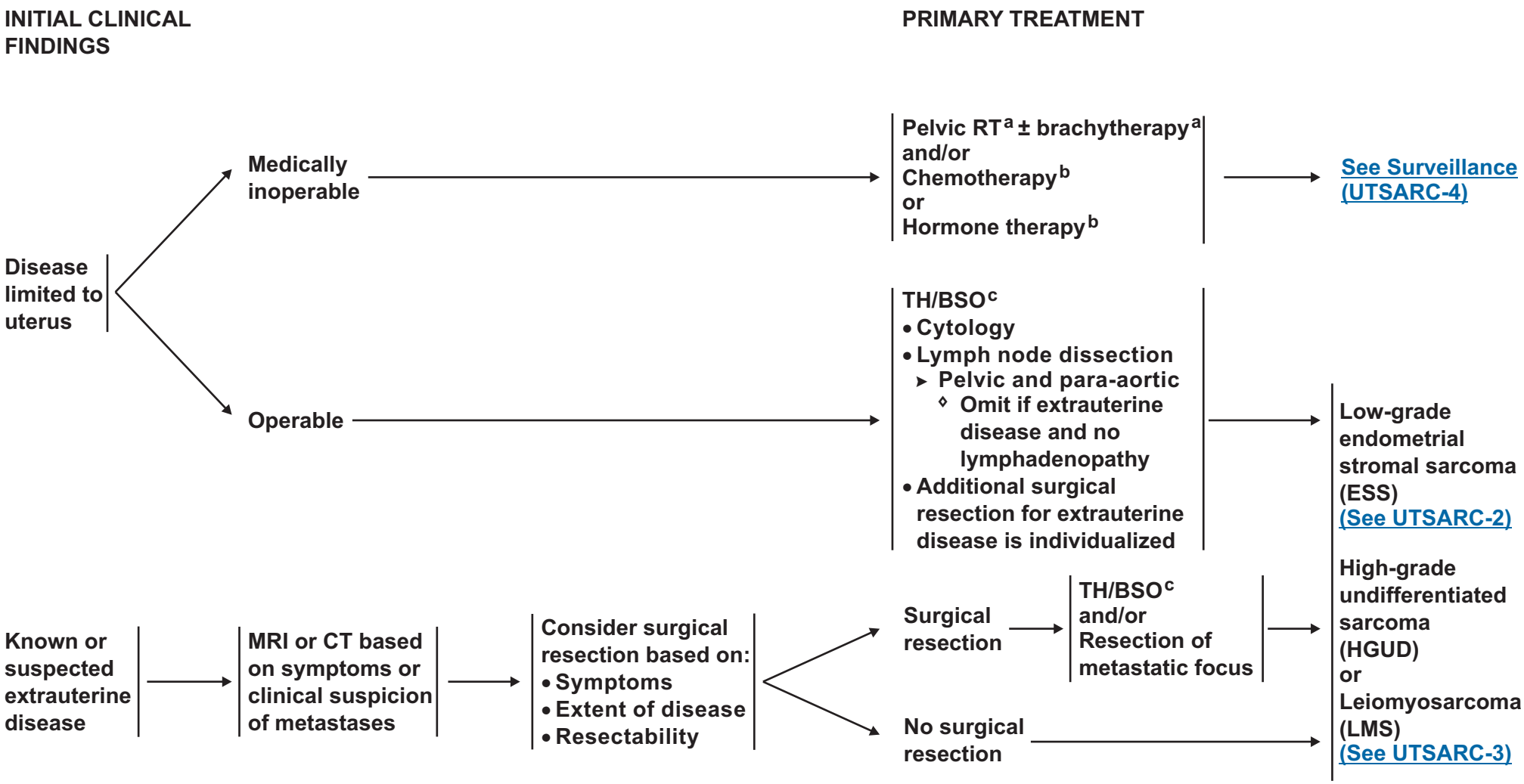
Uterine Sarcoma



[a] See Principles of Radiation Therapy (UN-A).
[b] See Systemic Therapy for Uterine Sarcoma (UTSARC-A).
[c] Oophorectomy/LND individualized for reproductive age patients. Fertility consultation as appropriate.

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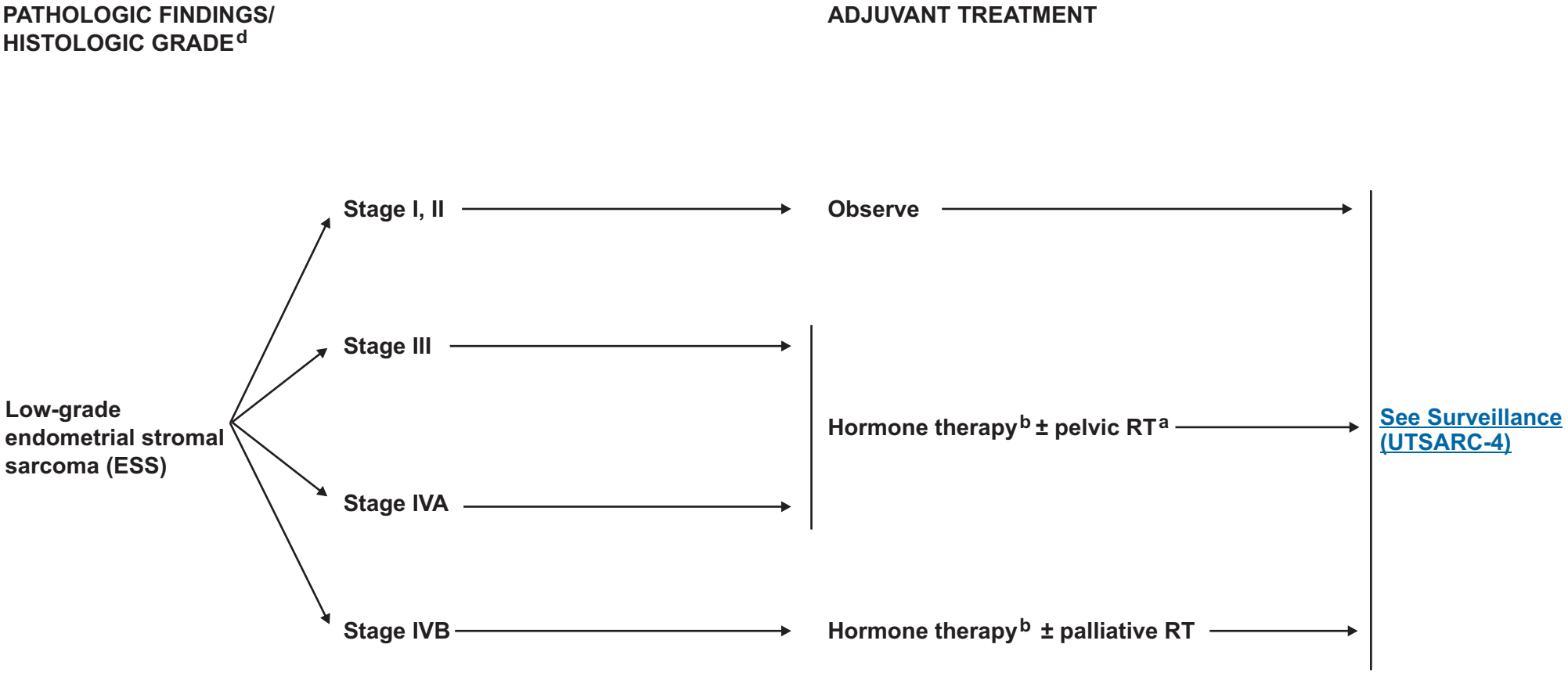
Uterine Sarcoma



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

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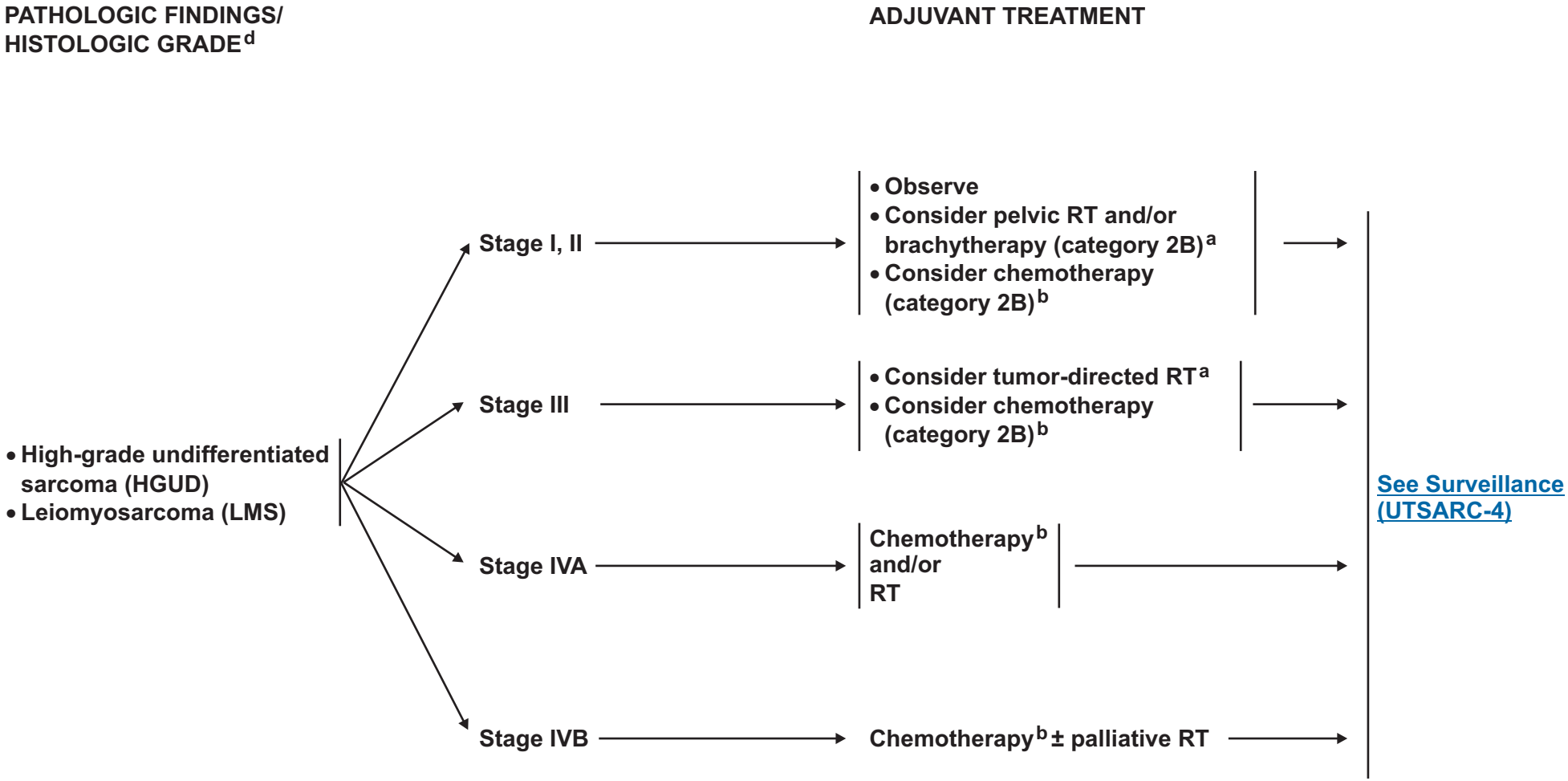
Uterine Sarcoma



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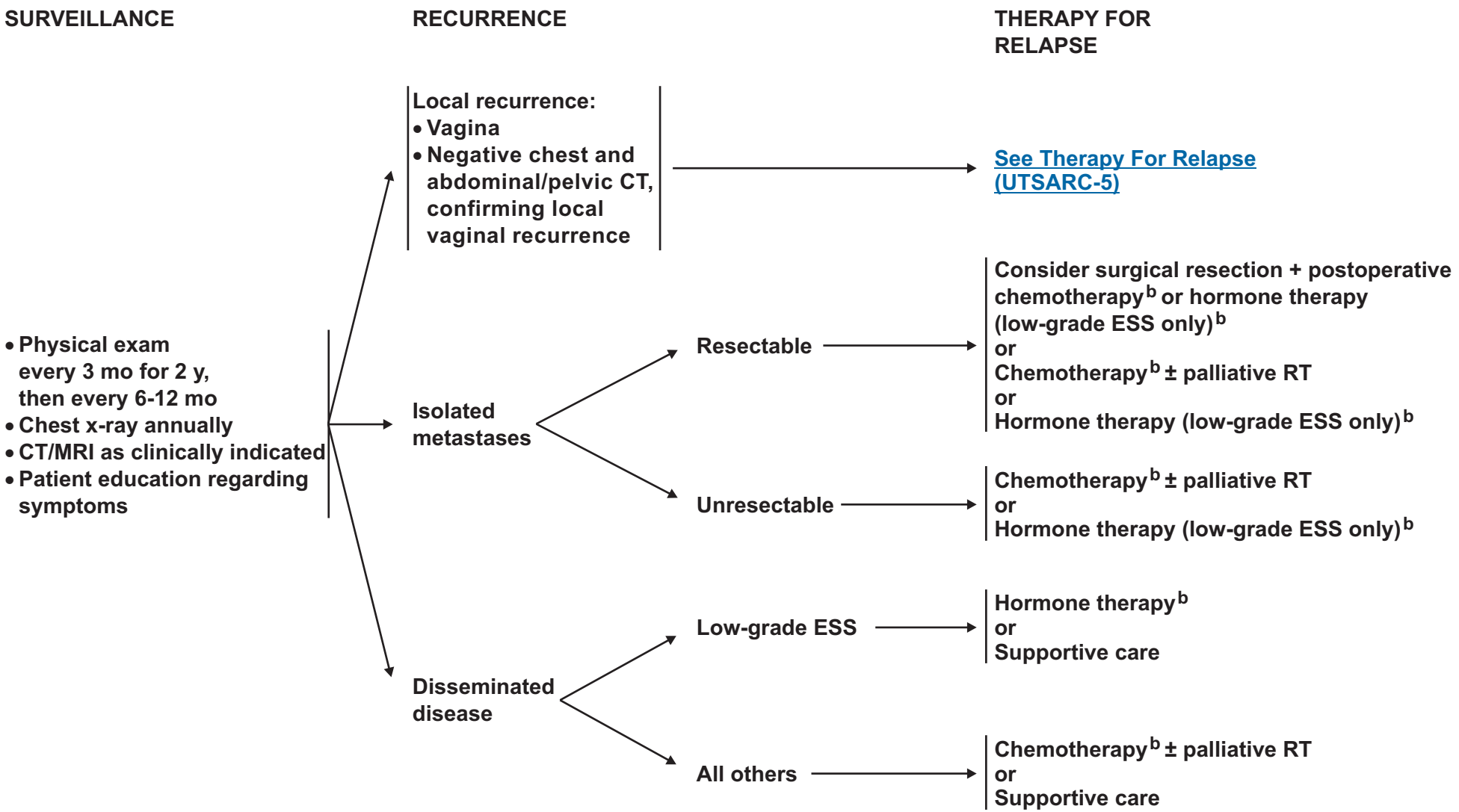

[b] See Systemic Therapy for Uterine Sarcoma (UTSARC-A).

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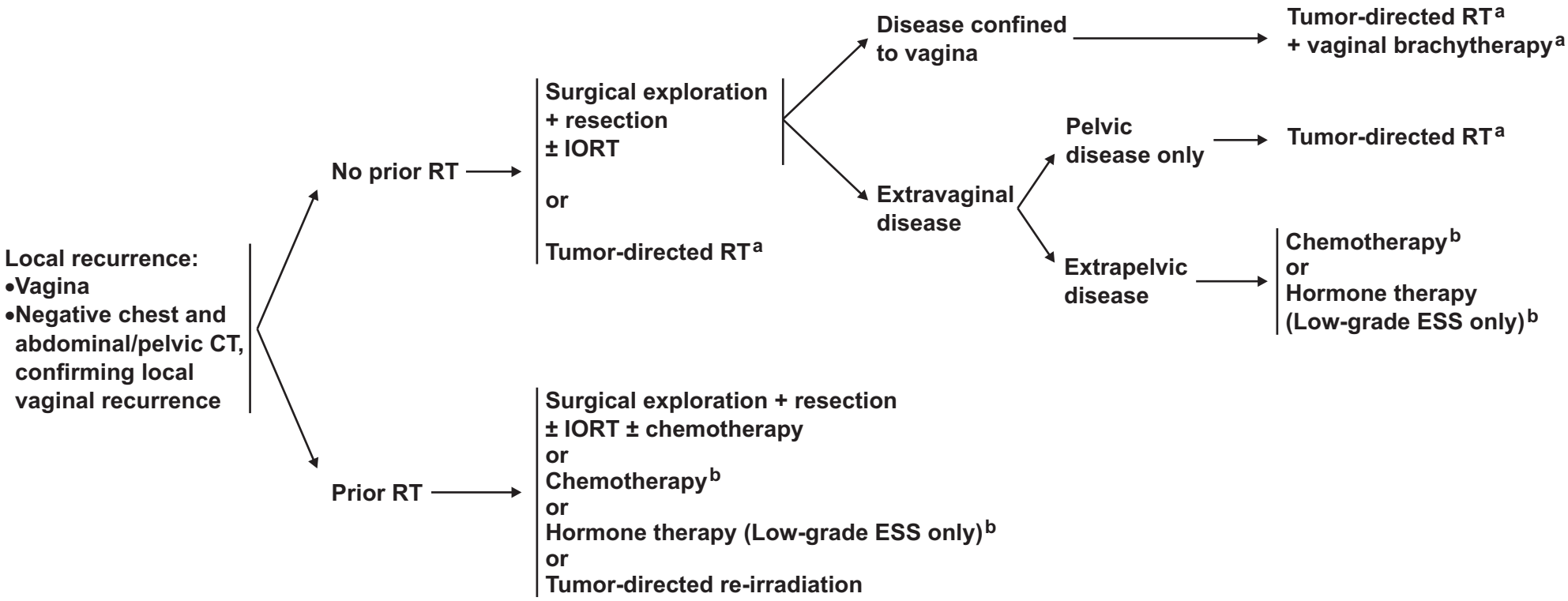
Uterine Sarcoma

RECURRENCE

THERAPY FOR RELAPSE



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

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

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SYSTEMIC THERAPY FOR UTERINE SARCOMA

CHEMOTHERAPY REGIMENS
(Clinical trials strongly recommended)

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

- **Doxorubicin**
- **Gemcitabine/docetaxel**
- **Other single agent options (category 2B): Dacarbazine, docetaxel, epirubicin, gemcitabine, ifosfamide, liposomal doxorubicin, and paclitaxel could also be considered**

HORMONE THERAPY (Low-grade ESS only)

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

Back to Recurrence (UTSARC-4)

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Uterine Sarcoma

UTERINE SARCOMA CLASSIFICATION

- Endometrial stromal sarcoma[1]
- Undifferentiated sarcoma (high-grade undifferentiated sarcoma (HGUD))[2] or pure heterologous sarcoma[3]
- Leiomyosarcoma[4]

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

[2] High-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.

[3] Rare 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.

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

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Endometrial Carcinoma

PRINCIPLES OF RADIATION THERAPY

- Tumor-directed RT refers to RT directed at sites of known or suspected tumor involvement, and may include external beam and/or brachytherapy. In general, tumor-directed external-beam RT (EBRT) is directed to the pelvis with or without the para-aortic region. Brachytherapy can be delivered: 1) to an intact uterus, either preoperatively or definitively; or 2) more commonly, to the vagina after hysterectomy. For the purposes of these guidelines, whole abdominal radiotherapy is not considered to be tumor-directed RT.

- Pelvic radiotherapy should target the gross disease (if present), the lower common iliacs, external iliacs, internal iliacs, parametrium, upper vagina, and presacral lymph nodes (in patients with cervical involvement). Extended-field radiotherapy should include the pelvic volume and also target the entire common iliac chain and para-aortic lymph node region. The upper border of the extended field depends on the clinical situation but should at least be to the level of the renal vessels. External-beam doses for microscopic disease should be 45-50 Gy. Multiple conformal fields based on CT-treatment planning should be utilized.

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

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

Staging

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.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 02/16/09

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Adenocarcinoma of the endometrium is the most common malignancy of the female genital tract in the United States. It is estimated that 40,100 new uterine cancer cases will be diagnosed in 2008, with 7,470 deaths resulting from the disease.[1] Uterine sarcomas are uncommon malignancies accounting for approximately 1 in 12 of all uterine cancers.[2] This NCCN guideline on uterine neoplasms describes epithelial carcinomas and uterine sarcomas; each of these major categories contains specific histologic groups that require different management.

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.

For patients with suspected uterine neoplasms, the initial preoperative evaluation includes a history and physical examination, endometrial biopsy, chest x-ray, a complete blood count, and platelet count. A pathology review will determine whether patients have either (1) epithelial carcinoma (such as, pure endometrioid cancer, papillary serous carcinoma, clear cell carcinoma, or carcinosarcoma, which is also known as malignant mixed Müllerian tumor [MMMT]); or (2) stromal/mesenchymal tumors (such as, low-grade endometrial stromal sarcoma [ESS], high-grade undifferentiated sarcoma [HGUD], or leiomyosarcoma [LMS]). If cervical involvement is suspected, cervical biopsy or magnetic resonance imaging (MRI) should be considered. Cervical cytology should be assessed using the NCCN Cervical Cancer Screening Guidelines.

Given the typical age group at risk for uterine neoplasms and the presence of comorbid illnesses, it is prudent in selected patients to also measure blood chemistry profile and renal & liver function.

Endometrial Cancer

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 the early symptoms of irregular vaginal bleeding (in this predominantly postmenopausal patient population) often trigger patients to seek care when the disease is at an early and treatable stage. Thus, endometrial cancer is often localized, yielding a generally high survival rate. However, data show that the mortality rate for uterine cancer has increased more rapidly than the incidence rate, which has remained stable over the last 20 years.[3] This increased mortality may be related to an increased rate of advanced-stage cancers and high-risk histologies (such as, serous tumors). In addition, many women did not receive adequate staging. To further improve on outcome for patients

with this disease, physicians need to identify high-risk patients and tailor treatment appropriately to provide the best long-term survival.

Diagnosis and Workup

Most patients (90%) with endometrial carcinoma have abnormal vaginal bleeding, most commonly in the postmenopausal period. The workup was previously described (see Overview). Diagnosis can usually be made by an office endometrial biopsy.

Other ancillary tests (such as, computed tomography, MRI) are 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.[4,5] However, serum CA 125 levels may be falsely increased in women who have peritoneal inflammation/infection or radiation injury, normal in women with isolated vaginal metastases, and may not predict recurrence in the absence of other clinical findings.[6-8]

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 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.[9]

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, diagnostic fractional dilation and curettage). Many patients at that time were not treated with primary surgery because of obesity or various other medical problems. Thus, the 1970 staging system is only 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.[10-12] This reported under-staging 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 surgico-pathologic assessment of data, such as histologic grade, myometrial invasion, and the extent and location of extrauterine spread (including retroperitoneal lymph node metastases) (see Table 1).[13]

Primary Treatment

A pathology review will provide clinical findings of various endometrioid histologies, papillary serous carcinoma, clear cell carcinoma, or carcinosarcoma. These NCCN guidelines divide pure endometrioid cancer into three categories for delineating treatment: (1) disease limited to the uterus, (2) suspected or gross cervical involvement, and (3) suspected extrauterine disease. The pathologic assessment of the uterus should include (1) ratio of depth of myometrial/stromal invasion to myometrial thickness; (2) cervical stromal or glandular involvement; (3) tumor size; (4) tumor location (fundus versus lower uterine segment/cervix); (5) histologic subtype with grade; (6) lymphovascular space invasion; and (7) consideration of mismatch repair analysis to identify genetic problems. The pathologic assessment of the nodes should include peritoneal cytology and level of nodal involvement (that is, pelvic, common iliac, and para-aortic). The pathologic assessment should also include the fallopian tubes and the ovaries. The College of American Pathologists (CAP) protocol for endometrial carcinoma is a

useful guide (http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2005/endometrium05_ckw.pdf).

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 endometrioid histologies 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.[14] 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 selection of adjuvant therapy. Pelvic and para-aortic lymphadenectomy and pathologic assessment of nodes are recommended for all patients even those with disease confined to the uterus and for suspected or gross cervical involvement.[15-17] There is very recent data questioning the role of routine pelvic lymphadenectomy in early-stage endometrial carcinoma;[18,19] these findings remain a point of contention and are not currently reflected in North American practice.[14] For patients with surgical stage I (any grade) endometrial cancer, the 5-year overall survival rate is 88%.[20]

For medically inoperable patients, exclusive tumor-directed 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.[21]

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.[22] As the grade of the tumor increases, the accuracy of intraoperative evaluation of myometrial invasion decreases (that is, 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.[23] 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.[24,25]

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, and 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, tumor-directed RT can provide long-term local control and cancer-specific survival rates (see "Radiotherapy Guidelines").[21]

Suspected Extrauterine Disease

If extrauterine 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, selective pelvic and para-aortic lymph node dissection, and maximal debulking. Patients with extrauterine pelvic disease (such as, vaginal, bladder, bowel/rectal, or parametrial involvement) are treated with RT and brachytherapy with or without surgery and chemotherapy. For extra-abdominal disease

(such as, liver involvement), palliative TH/BSO with or without RT, hormonal therapy, or chemotherapy can be considered.

Adjuvant Therapy

There is a lack of definitive data regarding the effectiveness of adjuvant therapy in patients with uterine-confined disease The basic concept underlying the NCCN 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 previously published trials have evaluated the role of pelvic RT in patients with endometrial carcinoma. In 2 of these trials, the patients were not formally staged;[26,27] however, patients were formally staged in the third trial.[28] The PORTEC-1 (Postoperative Radiation Therapy in Endometrial Carcinoma) trial was interpreted to show therapeutic benefit in selected patients with uterine-confined disease.[26,29] Although RT significantly decreased locoregional recurrence, it did not increase overall survival.[30] The Aalders' randomized trial found that RT reduced vaginal recurrences but did not reduce distant metastases or improve survival.[27] The Keys' trial (Gynecologic Oncology Group [GOG] 99) also showed improvement in locoregional control, without overall survival benefit, for adjuvant pelvic RT. 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.[28,31] To further assess the relative benefits of whole pelvic RT versus brachytherapy alone in uterine-confined disease, PORTEC-2 randomly assigned patients to these 2 modalities. PORTEC-2 showed excellent vaginal and pelvic control rates with both adjuvant radiation approaches, with no difference in overall survival. Given that vaginal brachytherapy is associated with significantly less toxicity than pelvic RT, it has been suggested that vaginal brachytherapy alone is a reasonable choice for most patients with uterine-confined endometrial cancer who are deemed candidates for adjuvant radiotherapy.[32] It should be noted that both PORTEC-1 and PORTEC-2 specifically excluded stage 1C grade 3 patients. A recent pooled randomized trial (ASTEC/EN.5) found that adjuvant pelvic RT alone did not improve survival in patients with intermediate-risk or high-risk early-stage endometrial cancer.[33]

A retrospective analysis of 21,249 women with endometrial cancer found that adjuvant pelvic RT only improved overall and relative survival in those with stage IC disease.[34] A meta-analysis of 5 randomized trials found that adjuvant pelvic RT for stage I disease was associated with a slight survival advantage in high-risk patients but not in lower risk patients.[35,36] The relative applications of brachytherapy and/or whole pelvic RT should be carefully tailored to a patient's pathologic findings.

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.[37] Whether adjuvant chemotherapy is beneficial in invasive high-grade uterine confined disease is the subject of current studies (for example, PORTEC-3). The Nordic trial closed early because of poor accrual; no overall survival benefit was demonstrated between the chemotherapy/RT versus RT groups.[38] The Nordic trial has several limitations: 1) nodal staging of patients was optional, 2) serous and clear cell patients were enrolled, 3) the RT dose was lower (44 Gy) than currently recommended, and 4) chemotherapy could be given either before or after RT.[38] 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.[39,40] 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.

Radiotherapy Principles

Tumor-directed RT refers to RT directed at sites of known or suspected tumor involvement and may include external-beam RT and/or brachytherapy. In general, tumor-directed external-beam RT (EBRT) is directed to the pelvis with or without the para-aortic region. Brachytherapy can be delivered: 1) to an intact uterus, either preoperatively or definitively; or 2) more commonly, to the vagina after hysterectomy. For the purposes of these guidelines, whole abdominal radiotherapy is not considered to be tumor-directed RT.

Pelvic radiotherapy should target the gross disease (if present), the lower common iliacs, external iliacs, internal iliacs, parametrium, upper vagina, and presacral lymph nodes (in patients with cervical involvement). Extended-field radiotherapy should include the pelvic volume and also the entire common iliac chain and para-aortic lymph node region. The upper border of the extended field depends on the clinical situation but should at least be to the level of the renal vessels. External-beam doses for microscopic disease should be 45-50 Gy. Multiple conformal fields based on CT-treatment planning should be used.

Brachytherapy doses for definitive therapy are individualized based on the clinical situation. For preoperative therapy in patients with gross stage IIB disease or in those with medically inoperable tumors, in general, intrauterine brachytherapy boost following external-beam RT to a cumulative total dose of 75-80 Gy low-dose rate equivalent to the tumor volume (uterus) is recommended. For patients who have undergone primary hysterectomy, vaginal brachytherapy, if used, 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 is often limited to the upper vagina. For high-dose rate brachytherapy, when used as a boost after EBRT, doses of 5-6 Gy × 2 fractions prescribed to the vaginal mucosa are commonly used. For high-dose rate vaginal brachytherapy alone, commonly used regimens include 7 Gy × 3 prescribed at a depth of 0.5 cm from the vaginal surface, or 6 Gy × 5 fractions prescribed to the vaginal surface.

Patients who receive radiation 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 2-4 weeks after RT is completed and can be done indefinitely (http://www.owenmumford.com/en/download.asp?id=59).

Completely Surgically Staged Patients

The imprecision of preoperative and intraoperative assessment of grade and myometrial invasion and 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 total laparoscopic hysterectomy has been proposed as an alternative surgical approach; however, 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 assessed patients with clinical stage I-IIA disease

(GOG-LAP2); this trial is now closed.[41] Preliminary results from LAP2 indicate that positive cytology results, positive nodes, and FIGO staging results were similar between groups and that 24% of patients needed conversion to laparotomy. Retrospective reviews of patients having either laparoscopic hysterectomy or total abdominal hysterectomy found that morbidity rates were lower with laparoscopy and that survival and recurrence rates were similar.[42,43] Robotic surgery is being evaluated for treatment of endometrial cancer patients.[44,45]

To assess the role of adjuvant radiation in surgically staged endometrial cancer patients without extrauterine disease, the GOG completed a multicenter trial (99) 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.[28] 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 the increased use of adjuvant vaginal brachytherapy alone for patients with tumors that are histologically confined to the uterus, despite the existence of other intrauterine risk features.[31,46-48] 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 with surgery alone, 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 stage I endometrial cancer who are completely surgically staged are stratified by adverse risk factors (such as, advanced age, lymphovascular invasion, tumor size, depth of invasion, and involvement of lower uterine segment). Observation is recommended for all stage IA, G1-2 patients. However, vaginal brachytherapy is also recommended for stage IA, G3 disease if no adverse risk factors are present; observation or vaginal brachytherapy and/or pelvic RT is recommended for patients with adverse risk factors. Stage IB, G2-3 patients without adverse risk factors can be observed or treated with vaginal brachytherapy; observation only is recommended for stage 1B, G1. If adverse factors are present, observation or vaginal brachytherapy is recommended for stage IB, G1 patients; however, options for stage 1B, G2 tumors include observation or vaginal brachytherapy with or without pelvic RT (category 2B for all options). For stage IB, G3 tumors with adverse risk factors, observation or vaginal brachytherapy and/or pelvic RT is recommended. For stage IC,G3 patients with adverse risk factors, observation or pelvic RT and/or vaginal brachytherapy with or without chemotherapy is recommended (category 2B for chemotherapy). For stage IC, G1-2 patients with adverse risk factors, observation or vaginal brachytherapy and/or pelvic RT is recommended. Otherwise, if no adverse risk factors are present, observation or vaginal brachytherapy is recommended for IC, G1-2 patients; however, observation or vaginal brachytherapy and/or pelvic RT is recommended for IC, G3 patients.

Based on a prospective evaluation of surgico-pathologic patterns of spread in endometrial cancer by the 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.[12,49] Given the wider acceptance of formal surgico-pathologic 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%.[39] The practice of surgical staging has led to a decrease in the use of adjuvant therapy for stage I endometrial carcinoma.[50,51]

For stage IIA patients, optional vaginal brachytherapy is recommended for all patients; for recommendations based on findings in the uterine fundus, refer to ENDO-4. The recommended treatment option for stage IIB, G1-2 patients is pelvic RT and vaginal brachytherapy. For stage IIB, G3 patients, chemotherapy may be added (category 2B for chemotherapy). Observation or vaginal brachytherapy is also an option for patients with stage II disease who have had a radical hysterectomy with negative surgical margins and no evidence of extrauterine disease.

Patients with extrauterine disease confined to the lymph nodes or the adnexa may be adequately treated with pelvic or extended-field RT.[52] Observation is recommended for noninvasive stage IIIA tumors confined to fundus or those with only positive cytology; G3 tumors can also be managed with (1) vaginal brachytherapy or (2) with pelvic RT with or without vaginal brachytherapy or chemotherapy. For all other stage IIIA tumors, the recommended options include (1) tumor-directed RT with or without chemotherapy; (2) chemotherapy with or without RT; or (3) pelvic RT with or without vaginal brachytherapy. A recent randomized phase III in patients with intermediate- and high-risk endometrial cancer (stages IC,G3 to IIIA) compared cisplatin-based chemotherapy with pelvic radiation.[53-55] The study suggested similar outcomes with either modality but was hampered by insufficient power to detect a small but clinically significant difference.

Despite the histologic grade, patients with completely resected stage IIIB and IIIC are treated with chemotherapy and/or tumor-directed RT After tumor debulking, chemotherapy with or without RT is recommended for stage IVA or IVB tumors with no gross residual disease or microscopic abdominal disease.

For patients deemed at risk of peritoneal failure, whole abdominal RT in carefully selected cases appears to have provided therapeutic benefit in retrospective studies.[56,57] 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/m^2) and cisplatin (50 mg/m^2) treatment, with an additional cycle of cisplatin (AP). This study revealed that AP chemotherapy improved progression-free survival and overall survival when compared with whole abdominopelvic RT; however, acute toxicity was greater in the AP chemotherapy arm.[58] This study has established the role of adjuvant multiagent systemic chemotherapy in curative-intent patients with extra-uterine disease spread. Recurrences were frequent, occurring in the pelvis and abdomen in both treatment arms. Approximately 52% of patients with advanced endometrial carcinoma had recurrences, indicating the need for further therapeutic improvement in this high-risk patient population.[58]

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 to either pelvis or

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.[59]

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 or pathologic confirmation of metastatic disease. For patients with stage IB or IIA disease with myometrial invasion of 50% or less and with 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. Options for stage IB or IIA tumors with positive radiologic findings include surgical restaging or pathologic confirmation of metastatic disease, followed by adjuvant treatment (for completely surgically staged patients). Patients with more aggressive tumors (such as, stage IC, stage IIA with myometrial invasion greater than 50%, stage IIB, or G3 tumors) are managed with radiologic imaging followed by either (1) surgical restaging or pathologic confirmation of metastatic disease followed by adjuvant treatment (for completely surgically staged) as indicated; or (2) pelvic RT and vaginal brachytherapy with or without para-aortic RT and/or with or without chemotherapy for grade 3 tumors [category 2B for chemotherapy] for negative radiologic findings.

Two randomized trials have addressed the role of adjuvant pelvic RT in patients with non-formally staged uterine-confined endometrial cancer; both the older Aalders' trial and the more recent PORTEC-1 analysis showed improvement in pelvic control with adjuvant RT, but without a significant effect on overall survival.[26,27,29,30]

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,[60,61] 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.[62-64] 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.[14,65,66]

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; patient education regarding symptoms of relapse is also recommended (see third paragraph in this section). Vaginal cytology is recommended every 6 months for 2 years, then annually. CA 125 levels are optional. Chest x-ray may be done annually (category 2B). Genetic counseling can be considered for a discussion of significant family history. These recommendations recognize that the value of intensive surveillance has not been demonstrated in this disease, and ancillary testing is therefore not recommended.[67-70]

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;[71] 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 includes 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, the NCCN panel believes that the algorithm represents a reasonable surveillance scheme.

Treatment of Relapsed or Metastatic Disease

Patients with local or regional recurrences after surgical therapy can be evaluated for surgical exploration of the pelvis and resection and/or RT. 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 at the recurrence site, recommended therapy for relapse includes 1) surgical exploration of the pelvis and resection with or without intraoperative radiotherapy (IORT), 2) hormonal therapy, or 3) chemotherapy. Radical surgery (such as, pelvic exenteration) has been performed with reported survival rates approximating 20%.[72] However, these patients may not require pelvic exenteration; a more limited partial vaginectomy with or without IORT may be adequate.[73,74] For patients without prior RT at the site of recurrence or with previous brachytherapy only, surgical exploration of the pelvis and abdominal resection may be performed with or without IORT; RT with brachytherapy is another treatment option for these patients.

For the recurrence confined to the vagina or with pelvic lymph node invasion, additional therapy is recommended such as tumor-directed RT with or without brachytherapy or chemotherapy. Vaginal recurrences treated with RT have reported survival rates of 40%-50%, with significantly worse results if there is extravaginal extension or

pelvic lymph node involvement.[75] Para-aortic or common iliac lymph node invasion is treated with tumor-directed RT with or without vaginal brachytherapy or chemotherapy. For upper abdominal or peritoneal recurrences, chemotherapy with or without tumor-directed RT is recommended for microscopic residual disease. However, for gross upper abdominal residual disease, more aggressive treatment for relapse is recommended, 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 Palliative Care Guidelines) as discussed in the following section.

Hormonal Therapy

Hormonal therapy is for endometrioid histologies only (that is, not for papillary serous carcinoma, clear cell carcinoma, or carcinosarcoma). Hormone therapy for metastatic disease involves mainly the use of progestational agents; tamoxifen and 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.[76,77] Tamoxifen has a 20% response rate in those who do not respond to standard progesterone therapy.[78,79] In a single institution study, arzoxifene (a SERM) showed a response rate of about 28% in metastatic endometrial cancer;[80] a phase II trial is ongoing to further assess the efficacy of arzoxifene. Other hormonal modalities have not been well studied, and adjuvant therapy with hormonal agents in the treatment of endometrial cancer remains unproved.[81] If disease progression is observed after hormonal therapy, cytotoxic chemotherapy can 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.

Therapy for relapse (such as, chemotherapy and/or palliative RT) is recommended to relieve symptoms in patients with symptomatic, grade 2-3, or large-volume disseminated metastases. If 2 chemotherapy regimens fail, patients can receive best supportive care or be enrolled in an appropriate clinical trial.

Chemotherapy for Metastatic 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%.

A phase III randomized trial (GOG 177) compared 2 combination chemotherapy regimens that have been previously shown to have significant activity. The 273 women with advanced/metastatic or recurrent endometrial carcinoma were randomly assigned to 1) cisplatin and doxorubicin versus 2) cisplatin, doxorubicin, and paclitaxel. The 3-drug regimen was associated with a slight improvement in survival (15 versus 12 months) but with significantly increased toxicity.[82] 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.[83,84]

Carboplatin and paclitaxel is an increasingly used regimen for advanced/metastatic or recurrent endometrial cancer based on ovarian studies; the response rate is about 40%, and overall survival is about 13 months.[85] Weekly low-dose paclitaxel and carboplatin also seems

useful.[86] A phase III study (GOG 209) is currently assessing 1) carboplatin and paclitaxel versus 2) cisplatin, doxorubicin, paclitaxel, and filgrastim (granulocyte-colony stimulating factor [G-CSF]). Given the data to date, multiagent chemotherapy regimens are preferred for metastatic/recurrent disease if tolerated. Biologic and molecular therapies remain unproven at this time in the treatment of recurrent or metastatic endometrial carcinoma.

Papillary Serous Carcinomas, Clear Cell Carcinomas, and Carcinosarcomas

Uterine papillary serous carcinomas, clear cell carcinomas, and carcinosarcomas are considered more aggressive histologic variants epithelial carcinoma, with a higher incidence of extrauterine disease at presentation.[87-89] Patterns of failure mimic those of ovarian cancer. Primary treatment includes TH/BSO with dissection of pelvic and para-aortic lymph nodes, peritoneal lavage for cytology, and maximal tumor debulking. 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 and appropriate biopsies. Adjuvant therapy is highly individualized.[90-94]

Adjuvant therapy recommendations for stage IA include (1) observation and/or chemotherapy, or (2) tumor-directed RT.[95] Recommendations for stage 1B-II include (1) chemotherapy with or without tumor-directed RT, or (2) whole abdominopelvic RT with or without vaginal brachytherapy (category 3); patients with adequately debulked stage III or IV disease can also receive these options. There was major disagreement among panel members about whether whole abdominal RT is appropriate.[96-99] Chemotherapy is recommended for patients with inadequately debulked stage III or IV disease. As previously mentioned, *tumor-directed RT* refers to RT directed at sites of known or suspected tumor involvement and may include external-beam RT and/or brachytherapy. In general, tumor-directed external-beam RT is directed to the pelvis with or without the para-aortic region. For the purposes of these guidelines, whole abdominal radiotherapy is not considered to be tumor-directed RT.

Note that the NCCN panel recently moved carcinosarcomas (also known as MMMTs) to the epithelial carcinoma guideline, because pathologists now believe they are metaplastic carcinomas.[89] Ifosfamide is the most active single agent for carcinosarcoma.[100,101] Cisplatin and ifosfamide is an active combination regimen that has been previously widely used. A recent phrase III trial showed that the combination of ifosfamide and paclitaxel was active for advanced carcinosarcoma with less toxicity than the cisplatin/ifosfamide regimen.[100]

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.[102-107] This local control improvement in some series correlates with an improvement in survival, although other data show that lymphadenectomy confers greater benefit.[106-109] A phase III randomized GOG trial (150) in patients with carcinosarcoma of the uterus assessed whole abdominal RT versus cisplatin and ifosfamide, but there was no difference in survival between the groups.[110]

Uterine Sarcomas

Overview

Uterine sarcomas are generally categorized into low-grade ESS, HGUD, and LMS. Consistent pathological definitions of the various histologies continue to be refined. Stromal/mesenchymal tumors are subdivided into ESS (which are low-grade sarcomas) and HGUD (previously considered high-grade ESS).

Evaluation and Primary Therapy

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. Decisions regarding lymph node dissection should be individualized based on clinical scenarios and intraoperative findings. For medically inoperable sarcomas, options include 1) pelvic RT (with or without brachytherapy) and chemotherapy; 2) chemotherapy; or 3) hormone therapy (but only for low-grade ESS).

Low-Grade Endometrial Stromal Sarcoma

Hormone therapy is recommended for stages III-IV low-grade ESS (such as, megestrol acetate, medroxyprogesterone, tamoxifen, gonadotropin-releasing hormone [GnRH] analogs, aromatase inhibitors [category 2B for last 3 agents]).[111] High-grade ESS is currently referred to as HGUD (see next section). Observation is recommended for stages I-II ESS. Hormone therapy is also recommended for ESS that have recurred or are unresectable.[111] Series of low-grade ESS suggest long disease-free intervals in the absence of specific therapy and offer less support for the use of adjuvant RT.[112] Adjuvant radiotherapy in ESS has been demonstrated to reduce local recurrence rates but again with limited effect on survival.[113,114] Because of concerns about radiation exposure, frequent routine asymptomatic surveillance imaging is no longer recommended for young women after primary therapy for ESS.[115]

Leiomyosarcoma and High-Grade Undifferentiated Sarcoma

The diagnosis of LMS is often made after surgery. Currently, neither the AJCC nor the FIGO staging systems are ideal for staging LMS; patients are often upstaged when using the AJCC staging system.[116]

The role of adjuvant radiotherapy in nonmetastatic disease is controversial. Most available data are retrospective in nature, except for a recent phase III randomized trial.[102] Most retrospective studies suggest an improvement in local pelvic control but no appreciable nor consistent improvement in overall survival, given the propensity of metastatic extrapelvic disease as a site of first or eventual recurrence.[117,118] In many series, the patients treated with adjuvant radiation were presumably felt to have higher risk factors (for example, larger tumors, deeper myometrial invasion), thus, biasing the data against radiotherapy. However, a recent phase III randomized trial in stage I and II uterine sarcomas reported that postoperative pelvic radiotherapy did not improve overall survival for LMS when compared with observation.[102] Thus, the use of adjuvant RT for local pelvic control is controversial. If used, adjuvant RT needs to be individualized and based on careful analysis of surgical pathologic findings.

The role of chemotherapy is even more poorly defined for patients with uterine-confined disease but has been considered because of the high risk of systemic relapse. For stage I and II LMS and HGUD that are completely resected, options for adjuvant therapy include 1) observation; 2) consider pelvic RT and/or brachytherapy (category 2B); or 3) consider chemotherapy (category 2B).

Doxorubicin is the most active single agent for LMS.[119] Combination regimens—such as, gemcitabine and docetaxel—have also been used.[120,121] Single-agent dacarbazine, docetaxel, liposomal doxorubicin, epirubicin, gemcitabine, ifosfamide, and paclitaxel can also be considered for advanced or metastatic disease (category 2B).[122-125] Enrollment in clinical trials is strongly recommended.

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