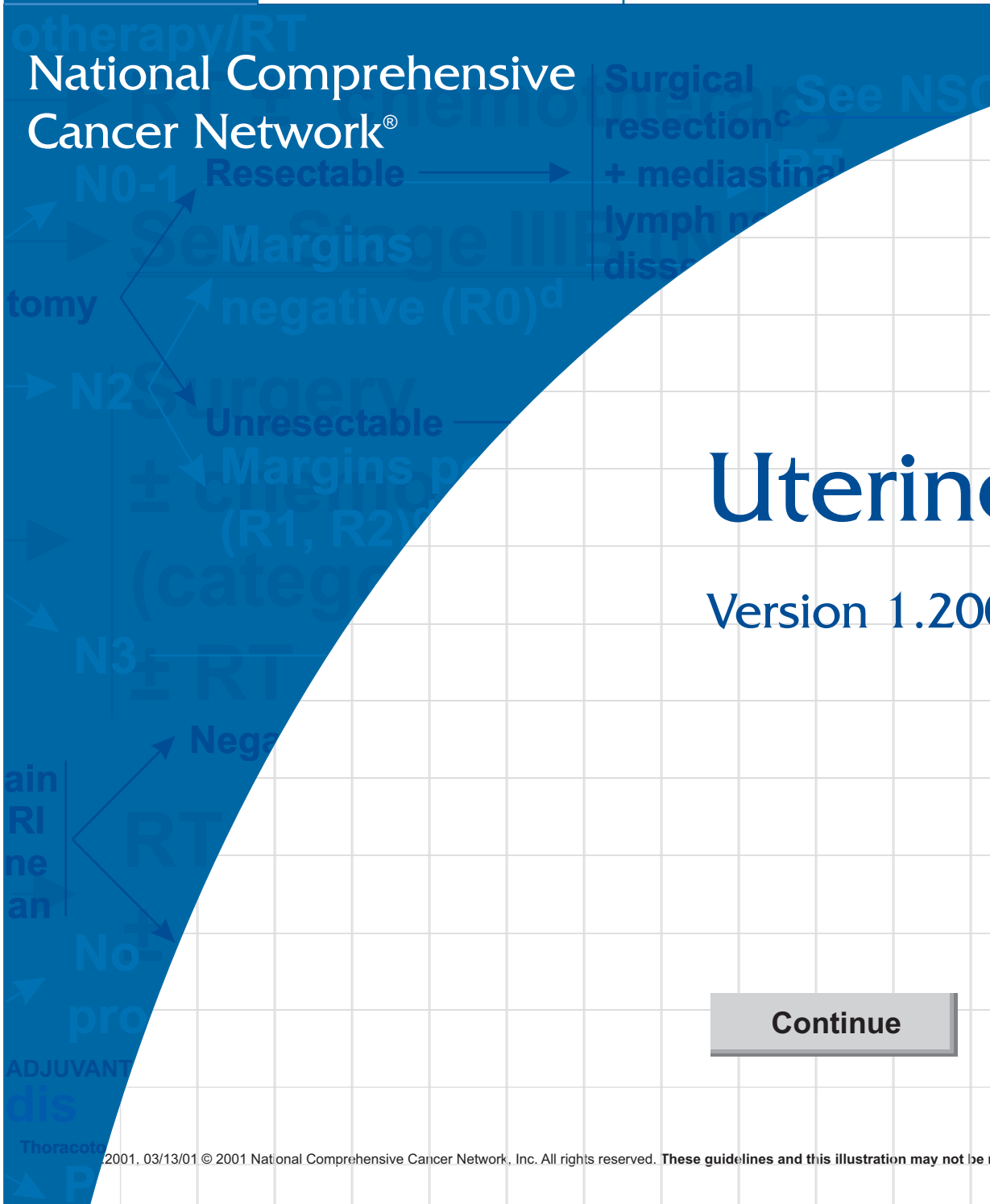
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Uterine Cancers

Version 1.2001

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NCCN Endometrial Cancer and Uterine Sarcoma Panel Members

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References

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.

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

See NCCN Categories of Consensus

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. ©2001.

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Endometrial Cancer

INITIAL EVALUATION

- H&P
- CBC, platelets
- Endometrial biopsy
- Chest x-ray

Optional:

- LFT/renal function tests/ chemistry profile

→ Pathology review

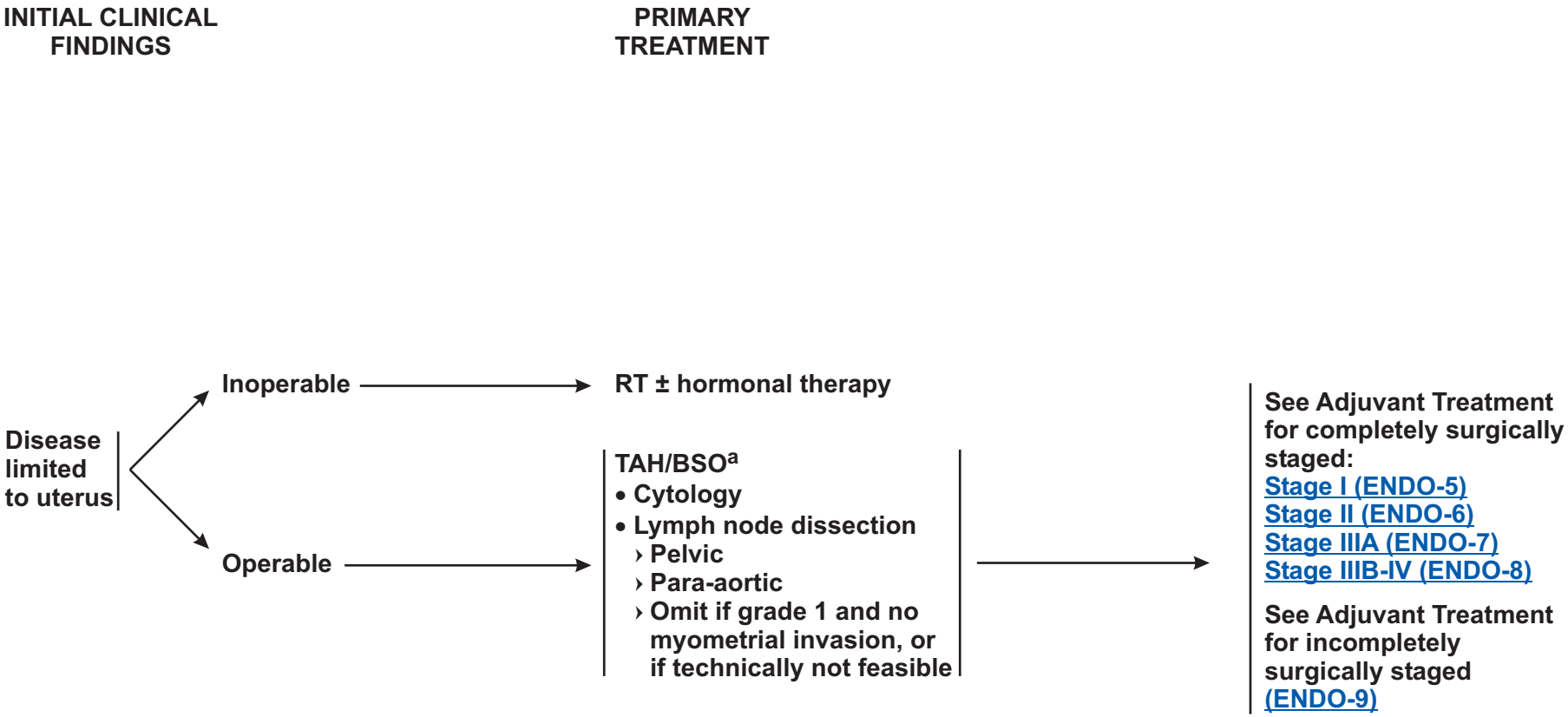
INITIAL CLINICAL FINDINGS

- Other endometrial cancer histologies
  - Disease limited to uterus → See Primary Treatment (ENDO-2)
  - Suspected or gross cervical involvement → See Primary Treatment (ENDO-3)
  - Suspected extrauterine disease → See Primary Treatment (ENDO-4)
- Papillary serous or clear cell carcinoma → See Papillary Serous or Clear-Cell Carcinomas of the Endometrium (ENDO-A)

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Endometrial Cancer



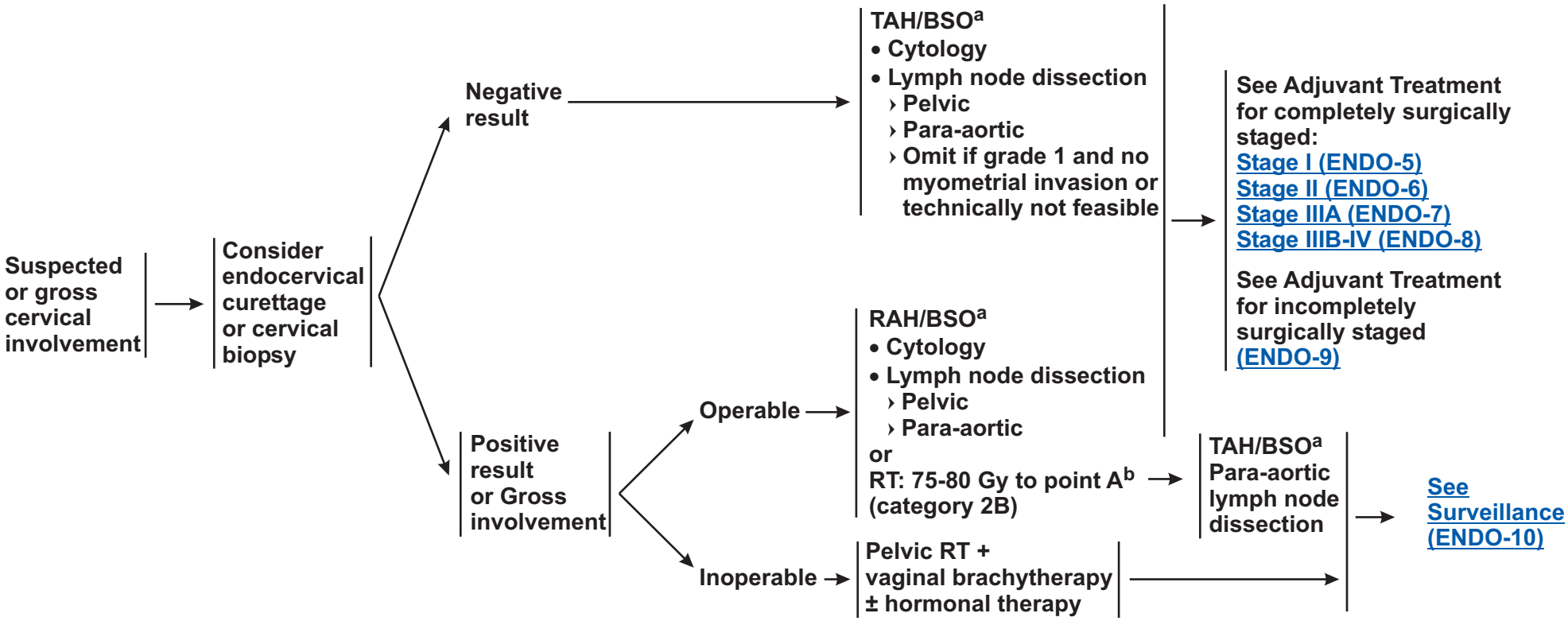
[a]See Hysterectomy (ENDO-B).

See Surveillance (ENDO-10)

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Endometrial Cancer

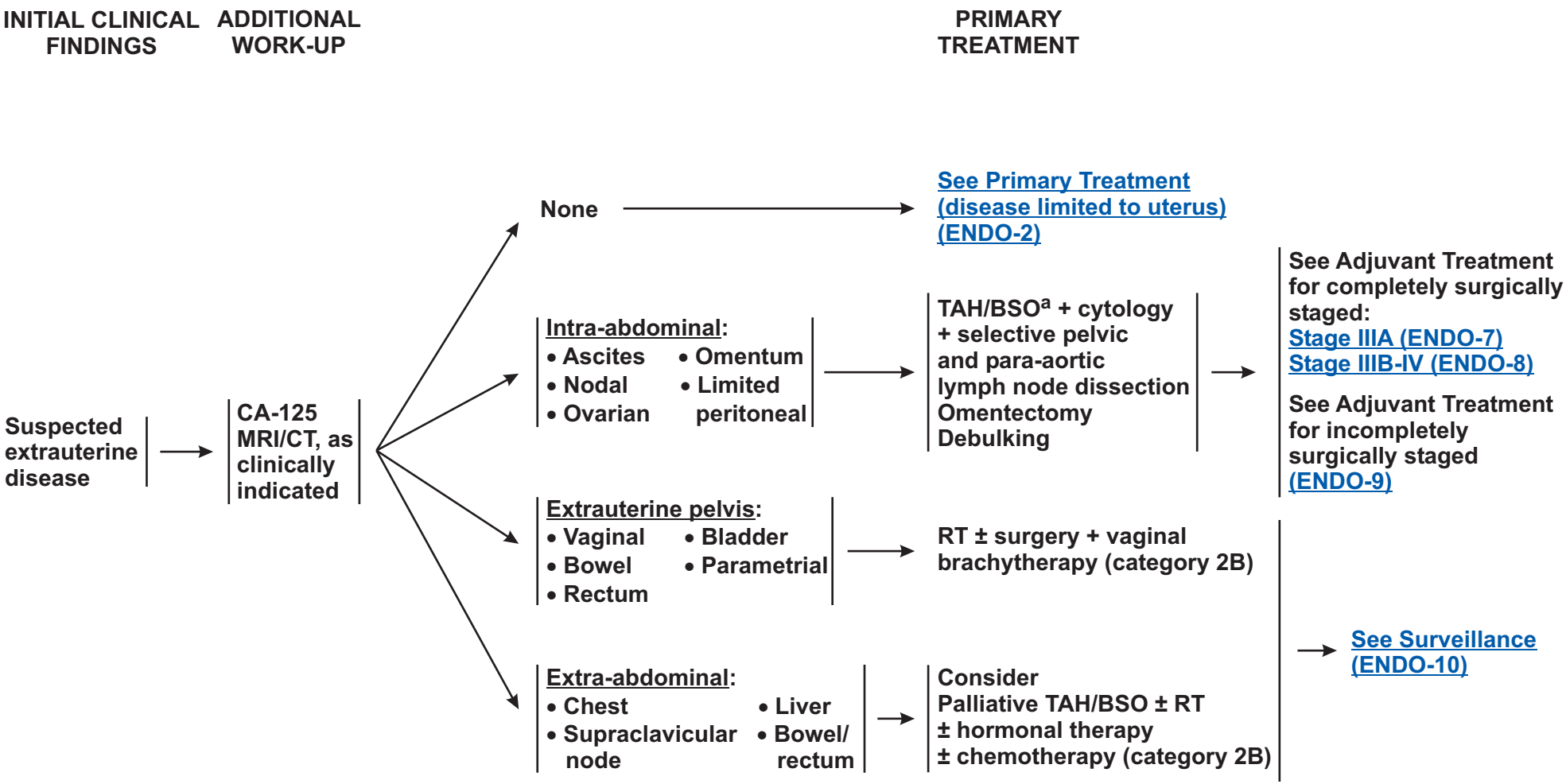


[a] See Hysterectomy (ENDO-B).
[b] Based on summation of conventional external-beam fractionation and low-dose-rate brachytherapy equivalent.

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Endometrial Cancer



[a]See Hysterectomy (ENDO-B).

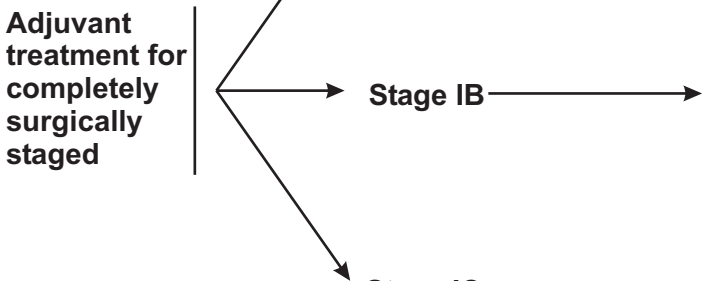
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Endometrial Cancer

CLINICAL FINDINGS

HISTOLOGIC GRADE/ADJUVANT TREATMENT[c,d,e]



	G1	G2	G3
Stage IA	Observe	Observe	Observe or Vaginal brachytherapy or Pelvic RT ± vaginal brachytherapy
Stage IB	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy or Pelvic RT ± vaginal brachytherapy	Observe or Vaginal brachytherapy or Pelvic RT ± vaginal brachytherapy
Stage IC	Observe or Vaginal brachytherapy or Pelvic RT ± vaginal brachytherapy	Observe or Vaginal brachytherapy or Pelvic RT ± vaginal brachytherapy	Pelvic RT ± vaginal brachytherapy

[c]Adjuvant therapy determinations are made on the basis of pathologic findings.
[d]Adjuvant pelvic RT: 45-50 Gy.
[e]The role of adjuvant RT may be further defined following the publishing of the results of GOG protocol #99 in the near future.

See Surveillance (ENDO-10)

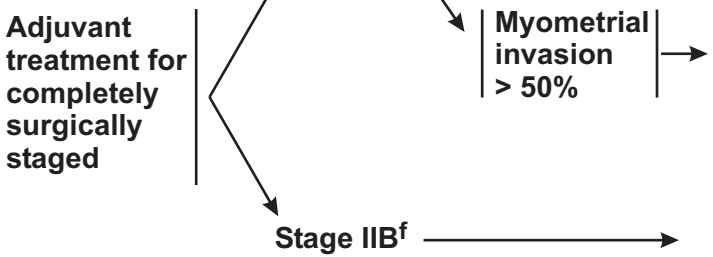
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Endometrial Cancer

CLINICAL FINDINGS

HISTOLOGIC GRADE/ADJUVANT TREATMENT[c,d,e]



	G1	G2	G3
Stage IIA, Myometrial invasion < 50%	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy or Pelvic RT ± vaginal brachytherapy	Pelvic RT + vaginal brachytherapy
Stage IIA, Myometrial invasion > 50%	Pelvic RT + vaginal brachytherapy	Pelvic RT + vaginal brachytherapy	Pelvic RT + vaginal brachytherapy
Stage IIB[f]	Pelvic RT + vaginal brachytherapy	Pelvic RT + vaginal brachytherapy	Pelvic RT + vaginal brachytherapy

[c]Adjuvant therapy determinations are made on the basis of pathologic findings.
[d]Adjuvant pelvic RT: 45-50 Gy.
[e]The role of adjuvant RT may be further defined following the publishing of the results of GOG protocol #99 in the near future.
[f]Observation or vaginal brachytherapy is an option only for patients with Stage IIB disease who are postprimary radical hysterectomy, with negative surgical margins and no evidence of extrauterine disease.

See Surveillance (ENDO-10)

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Endometrial Cancer

CLINICAL FINDINGS

HISTOLOGIC GRADE/ADJUVANT TREATMENT[c,d,e]

Stage IIIA

	G1	G2	G3
Positive cytology only, noninvasive tumor confined to fundus	Observe	Observe	Observe or Vaginal brachytherapy or Pelvic RT ± vaginal brachytherapy
All other IIIA	Pelvic RT or Whole abdominopelvic RT ± vaginal brachytherapy or Chemotherapy ± RT on protocol only (category 3 for protocol vs conventional therapy)	Pelvic RT or Whole abdominopelvic RT ± vaginal brachytherapy or Chemotherapy ± RT on protocol only (category 3 for protocol vs conventional therapy)	Pelvic RT or Whole abdominopelvic RT ± vaginal brachytherapy or Chemotherapy ± RT on protocol only (category 3 for protocol vs conventional therapy)

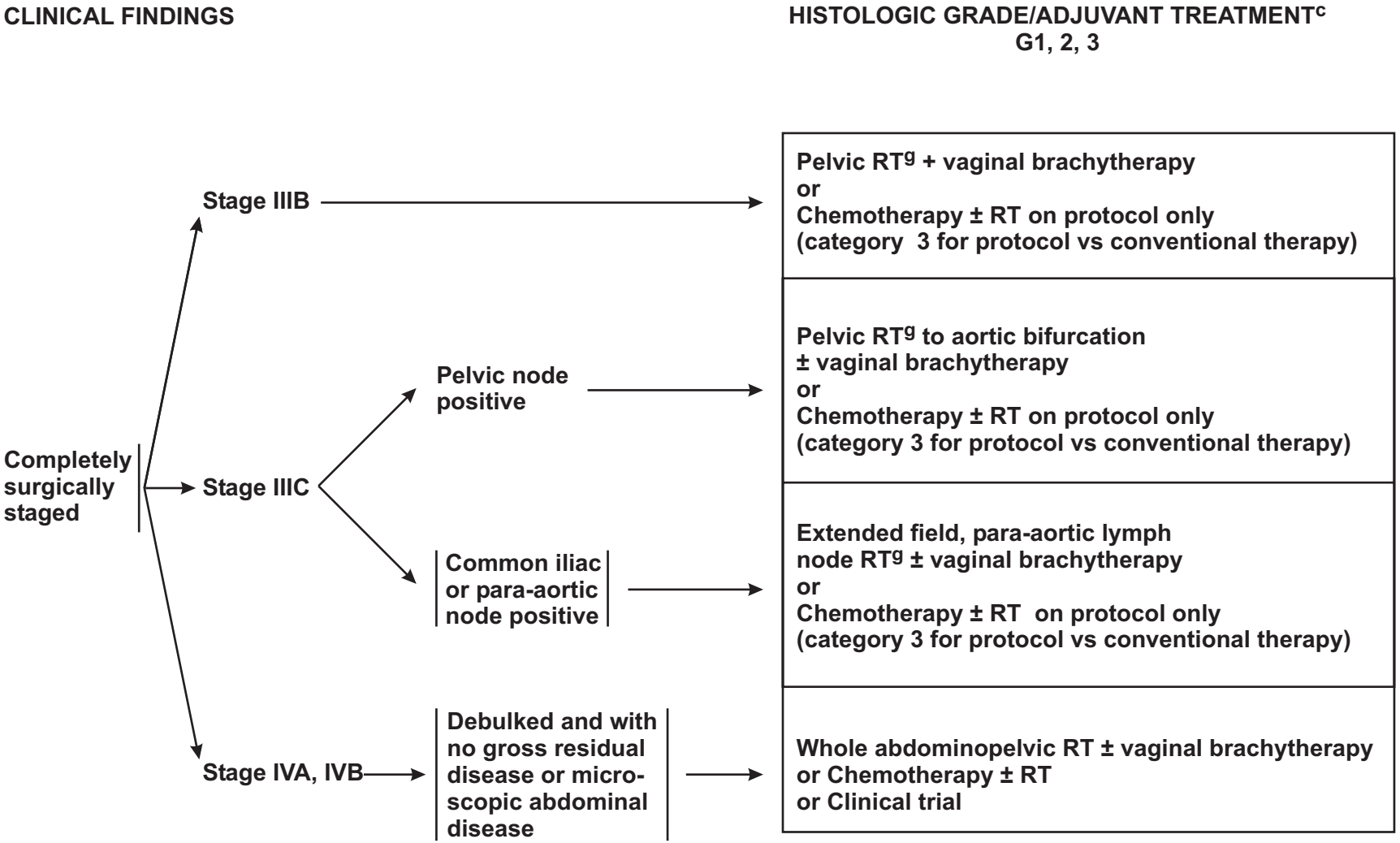
[c]Adjuvant therapy determinations are made on the basis of pathologic findings.
[d]Adjuvant pelvic RT: 45-50 Gy.
[e]The role of adjuvant RT may be further defined following the publishing of the results of GOG protocol #99 in the near future.

See Surveillance (ENDO-10)

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Endometrial Cancer



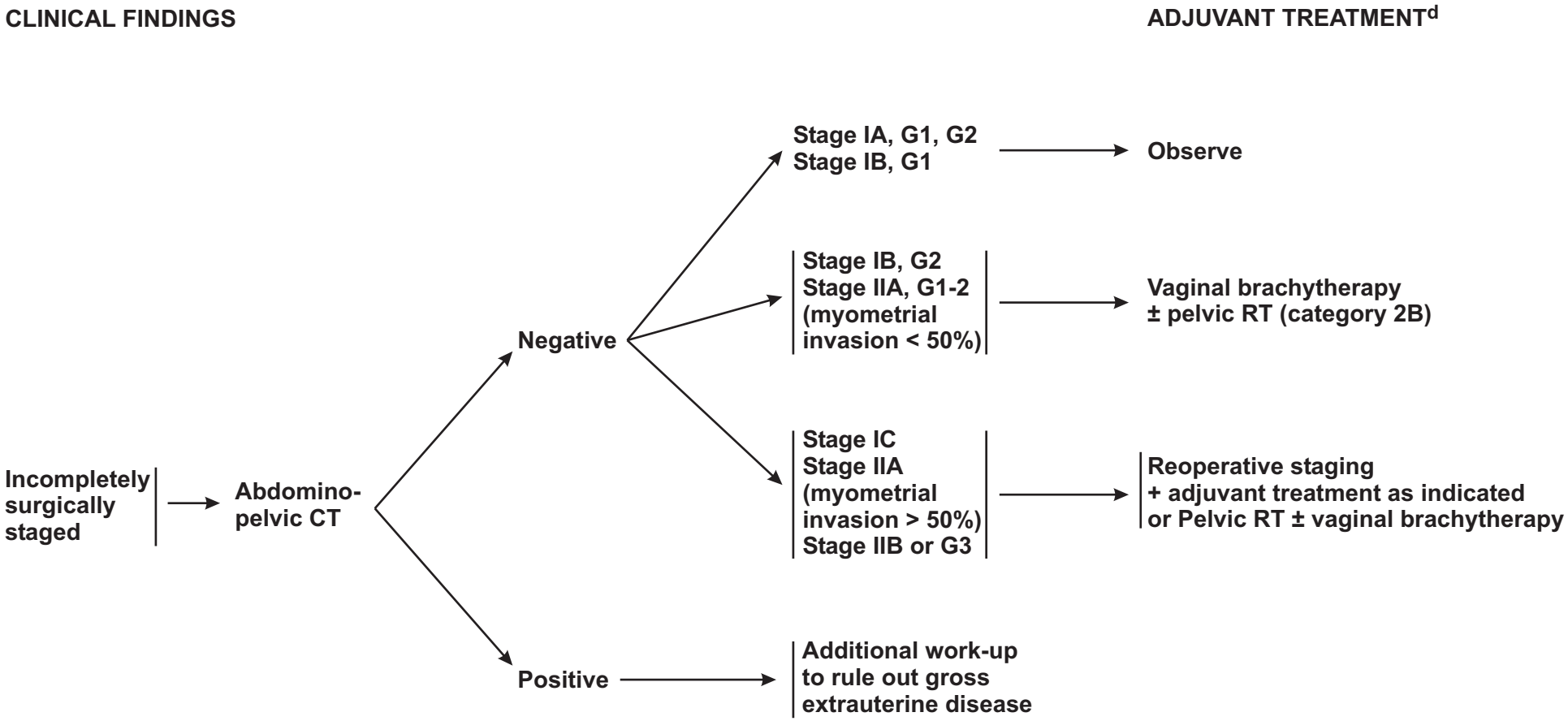
[c]Adjuvant therapy determinations are made on the basis of pathologic findings.
[g]Optional whole abdominopelvic RT for adnexa involvement and/or positive cytology.

See Surveillance (ENDO-10)

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Endometrial Cancer



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

See Surveillance (ENDO-10)

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Endometrial Cancer

SURVEILLANCE

- Physical exam every 3-6 mo for 2 yr, then annually
- CA-125 if initially elevated, then at each visit
- Vaginal cytology every 6 mo for 2 yr, then annually
- If low risk, surgery alone:
  - Consider immediate hormone replacement therapy[h]
  - If adjuvant treatment, wait 6-12 mo, then hormone replacement therapy
- Patient education regarding symptoms

CLINICAL PRESENTATION

Local recurrence
- Vagina
- Negative chest x-ray
- Negative chest, abdominal CT

→ See Salvage Therapy (ENDO-11)

Isolated metastases → See Salvage Therapy (ENDO-13)

Disseminated metastases → See Salvage Therapy (ENDO-13)

[h]Hormone replacement therapy following treatment for endometrial cancer should be limited to clinical trial participation because of the lack of literature documentation regarding its safety.

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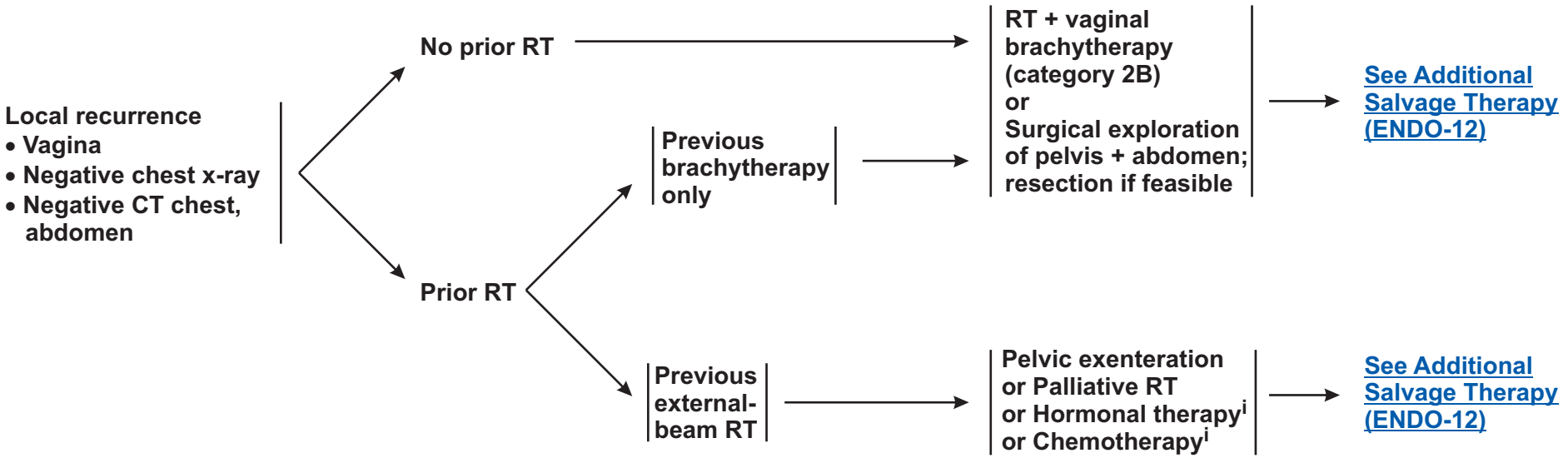
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Endometrial Cancer

CLINICAL PRESENTATION

SALVAGE THERAPY



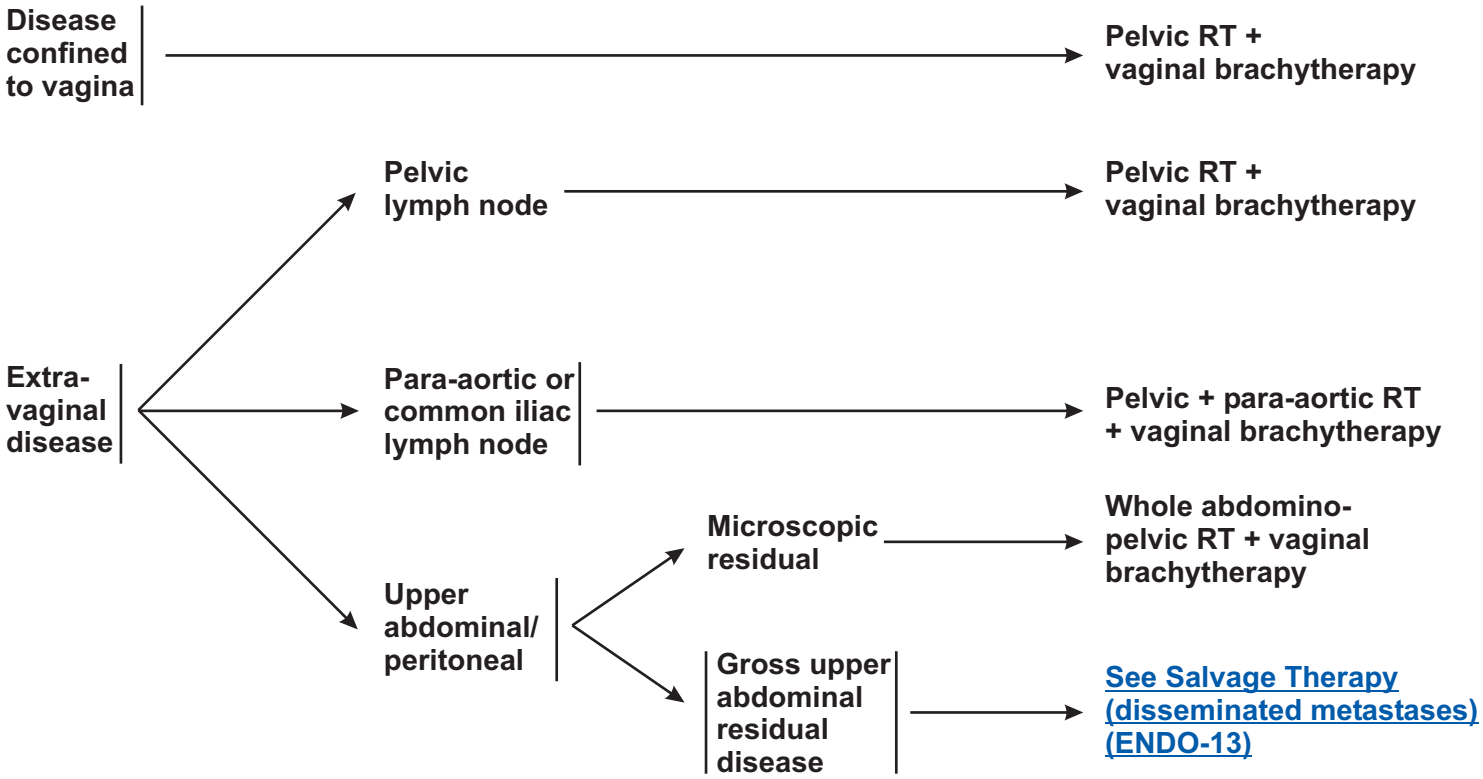
[i] For hormonal therapy and chemotherapy regimens, see Salvage Therapy (ENDO-C).

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Endometrial Cancer

ADDITIONAL SALVAGE THERAPY

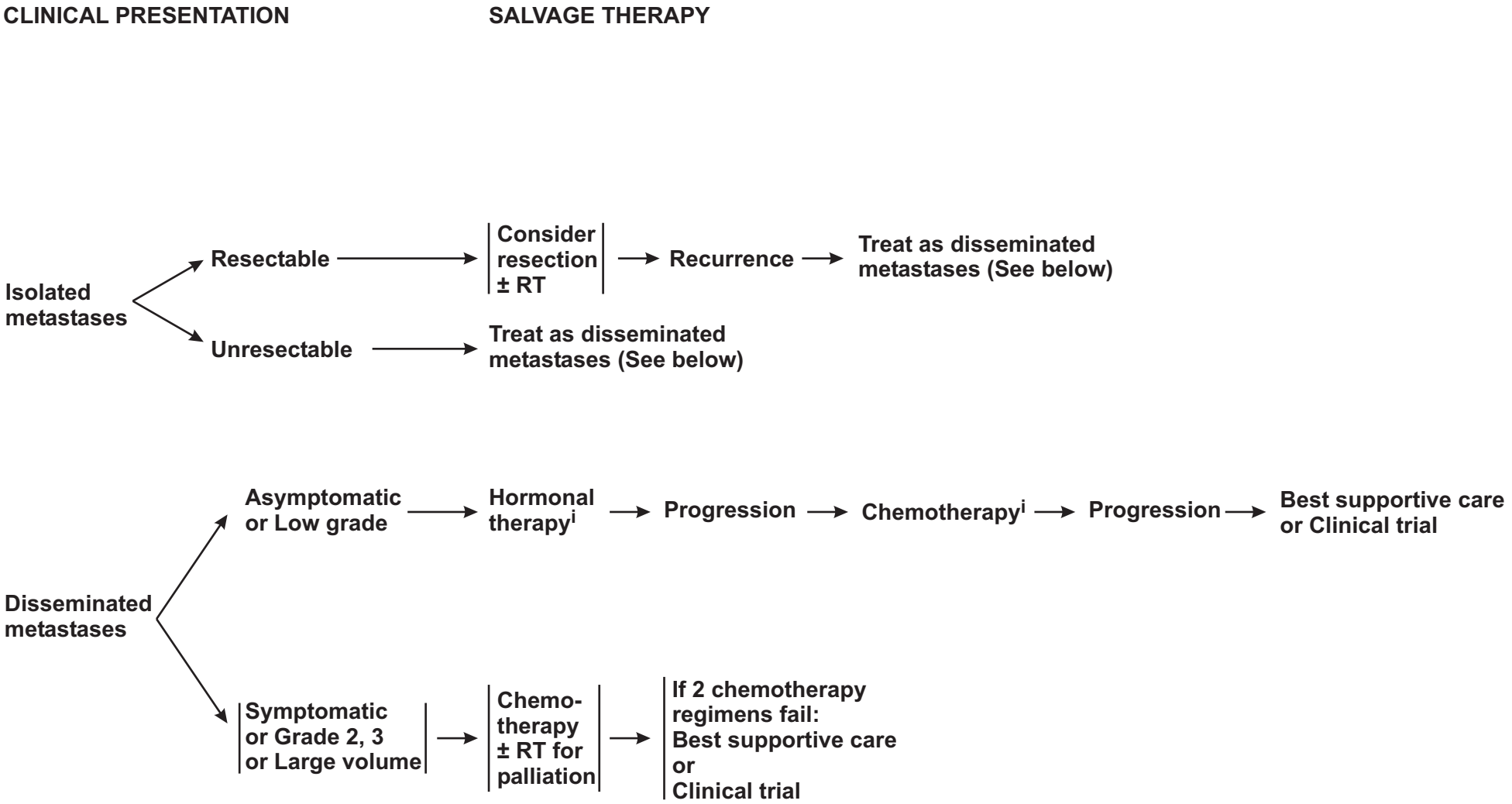


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Endometrial Cancer



[i]For hormonal therapy and chemotherapy regimens, see Salvage Therapy (ENDO-C).

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Endometrial Cancer

PAPILLARY SEROUS OR CLEAR CELL CARCINOMAS OF THE ENDOMETRIUM

Primary treatment:

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

Adjuvant treatment:

- Stage IA:
  Observation
  or Vaginal brachytherapy
  or Pelvic RT ± vaginal brachytherapy (category 2B)
- Stage IB, IC, II:
  Pelvic RT
  or Whole abdominopelvic RT
  ± vaginal brachytherapy (category 2B)
- Stage III, IV (adequately debulked):
  Whole abdominopelvic RT
  ± vaginal brachytherapy (category 2B)
  or Chemotherapy
  or Clinical trial

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Endometrial Cancer

HYSTERECTOMY

1. Laparoscopy-assisted vaginal hysterectomy should be performed in the context of a clinical trial

2. Operative assessment to include:
   a. Depth of myometrial invasion
   b. Tumor size
   c. Tumor location (fundus vs lower uterine segment/cervix)
   d. Frozen section as indicated
   e. TAH/BSO: Total abdominal hysterectomy + bilateral salpingo-oophorectomy
      RAH: Radical abdominal hysterectomy

Back to Initial Evaluation (ENDO-1)

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Endometrial Cancer

SALVAGE THERAPY

HORMONAL THERAPY

- Progestational agents
- Tamoxifen

CHEMOTHERAPY REGIMENS

- Doxorubicin
- Cisplatin
- Cisplatin/doxorubicin ± cyclophosphamide
- Carboplatin
- Paclitaxel
- Strongly encourage clinical trials

Back to Salvage Therapy (ENDO-10)

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Uterine Sarcoma

INITIAL EVALUATION

- H&P
- Endometrial biopsy or Dilatation and curettage
- Chest x-ray
- CBC, LFT/renal function tests

→ Pathology review

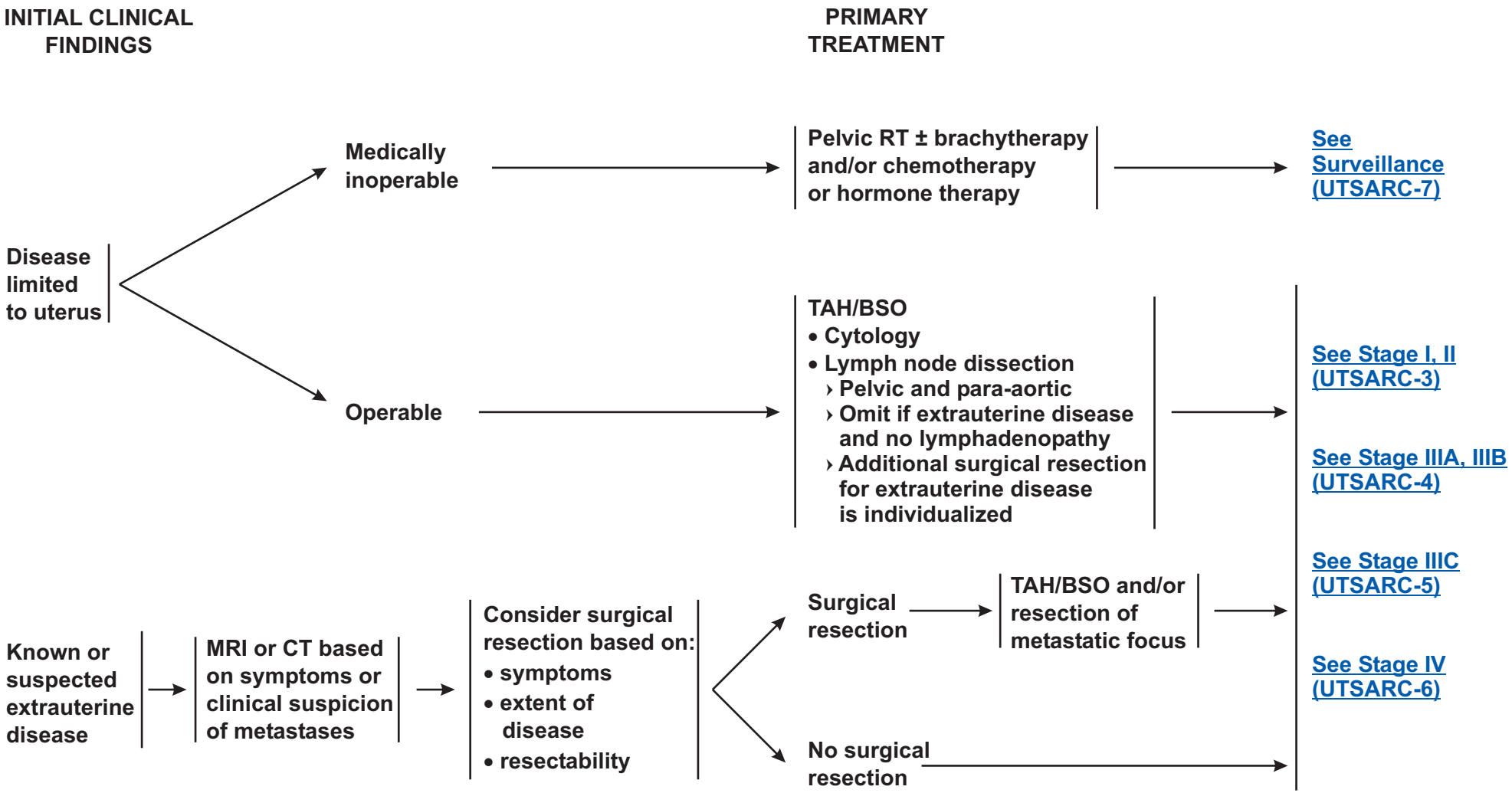
INITIAL CLINICAL FINDINGS

- Endometrial cancer → See NCCN Endometrial Cancer Guidelines (Uterine Cancers Table of Contents)
- Uterine sarcoma
  - Disease limited to uterus → See Primary Treatment (UTSARC-2)
  - Known or suspected extrauterine disease → See Primary Treatment (UTSARC-2)

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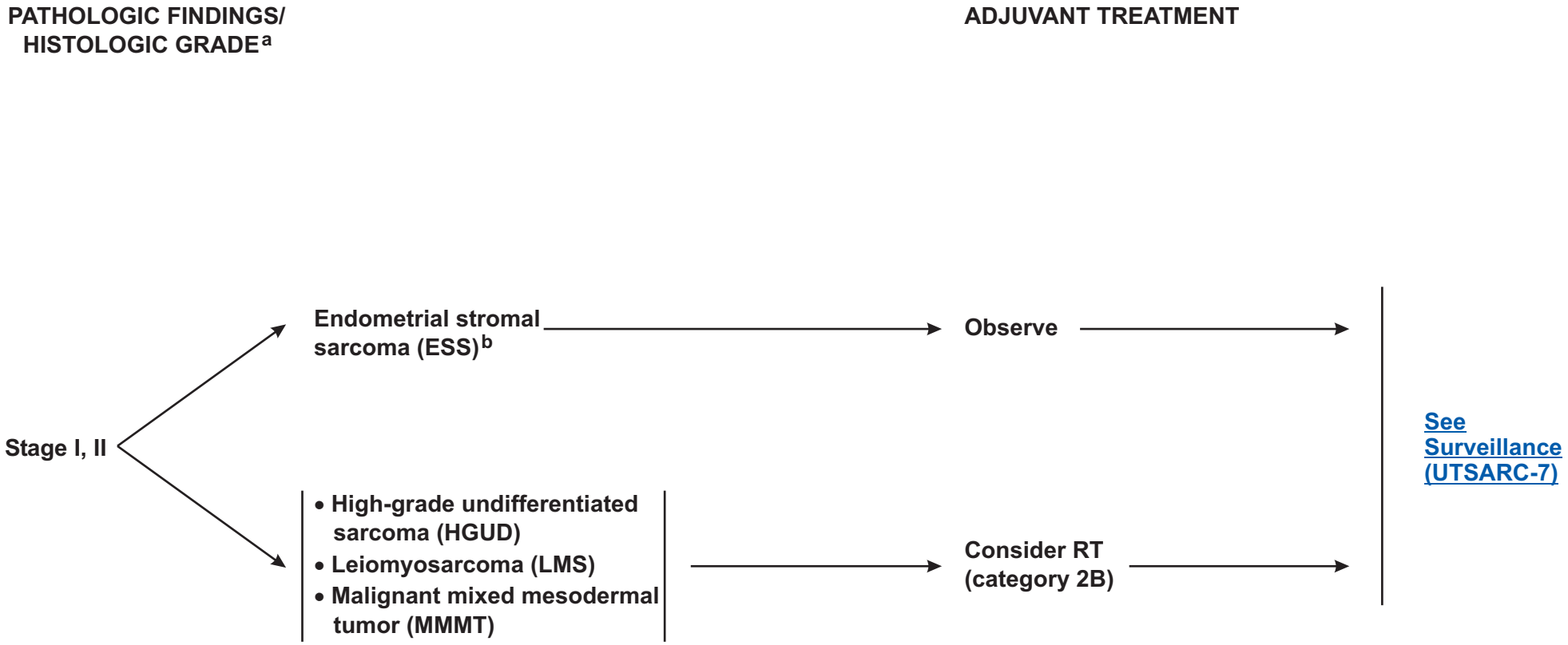
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Uterine Sarcoma

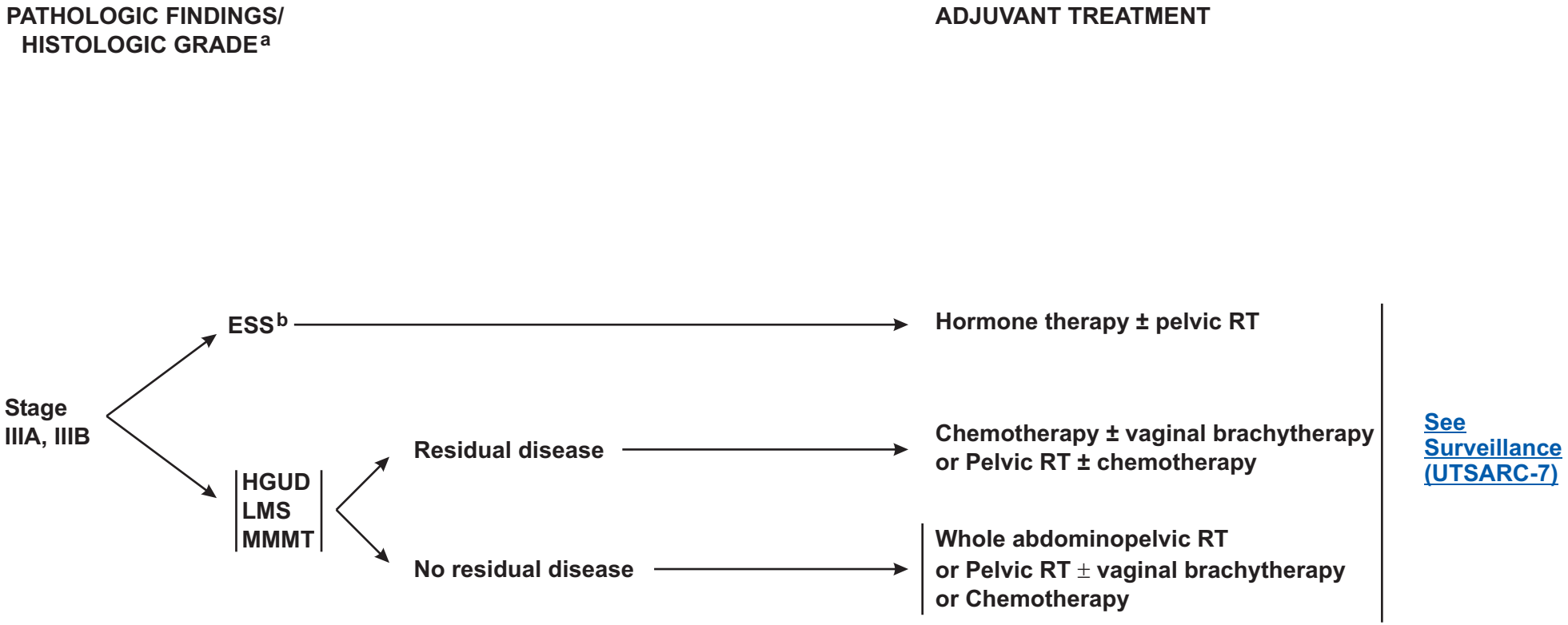


[a] See Uterine Sarcoma Classification (UTSARC-A).
[b] By definition, ESS is a low-grade sarcoma.

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

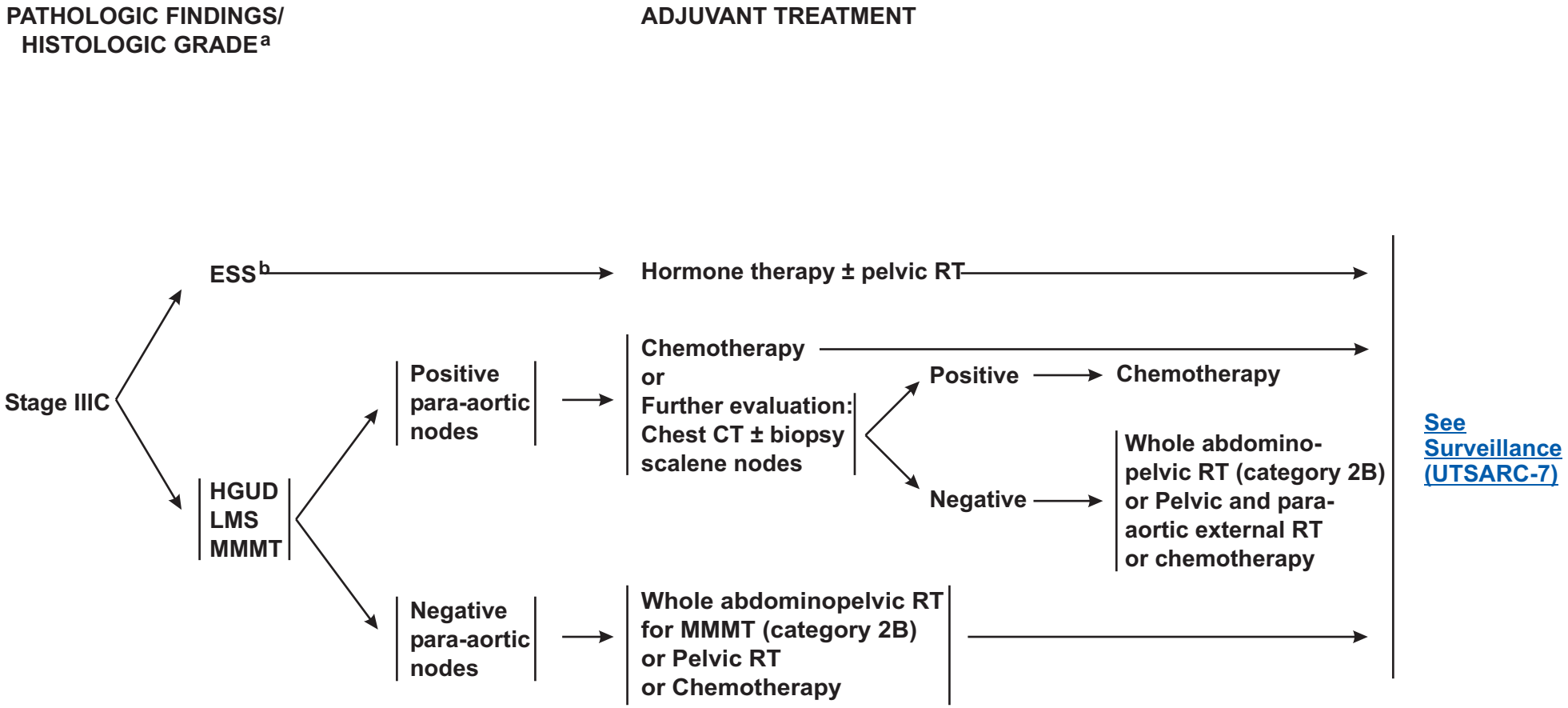


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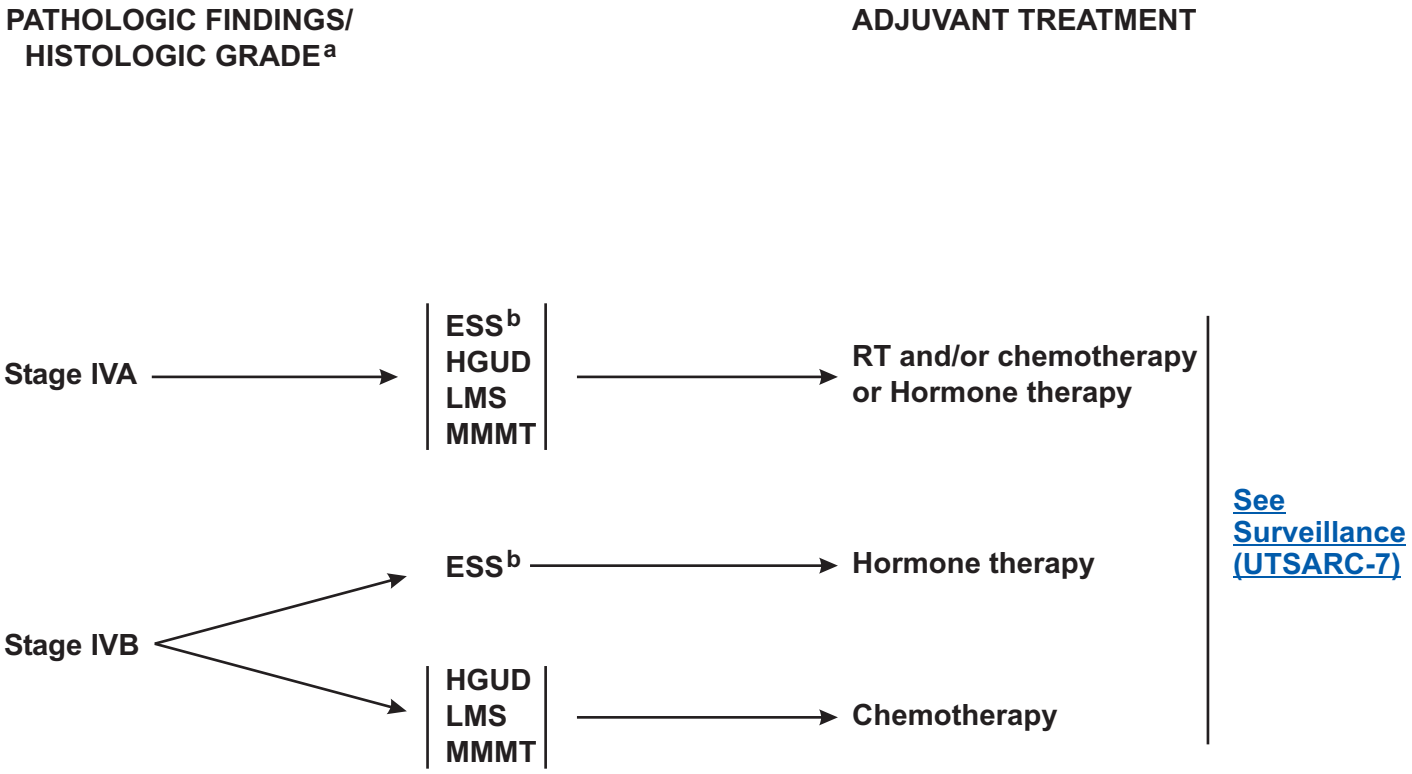


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Uterine Sarcoma

SURVEILLANCE

- Physical exam every 3 mo for 2 yr, then every 6 mo
- Chest x-ray every 6-12 mo for 2 yr
- CT/MRI as clinically indicated
- Patient education regarding symptoms

RECURRENCE

Local recurrence:
- vagina
- negative chest and abdominopelvic CT, confirming local vaginal recurrence

→ See Salvage Therapy (UTSARC-8)

Isolated metastases → See Salvage Therapy (UTSARC-9)

Disseminated disease → See Salvage Therapy (UTSARC-9)

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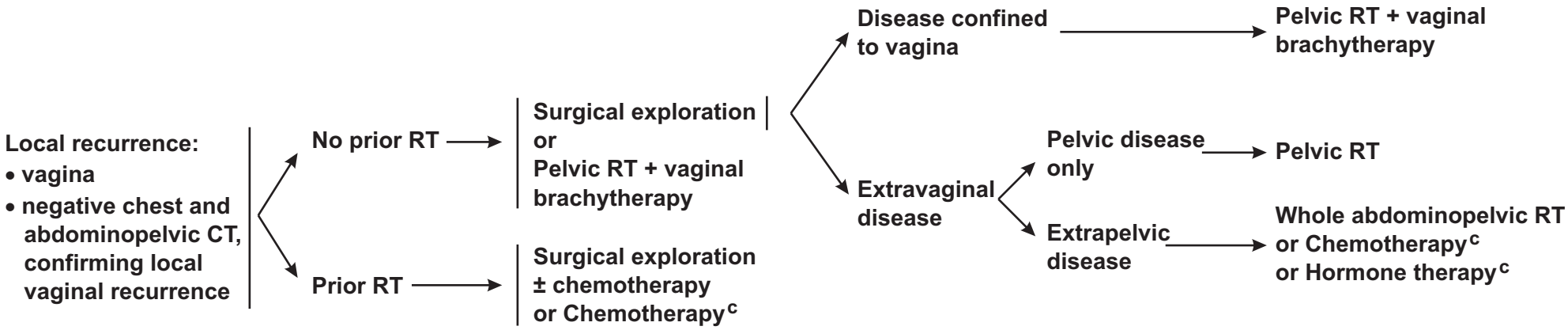
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Uterine Sarcoma

RECURRENCE

SALVAGE THERAPY



See Salvage Therapy (isolated metastases and disseminated disease) (UTSARC-9)

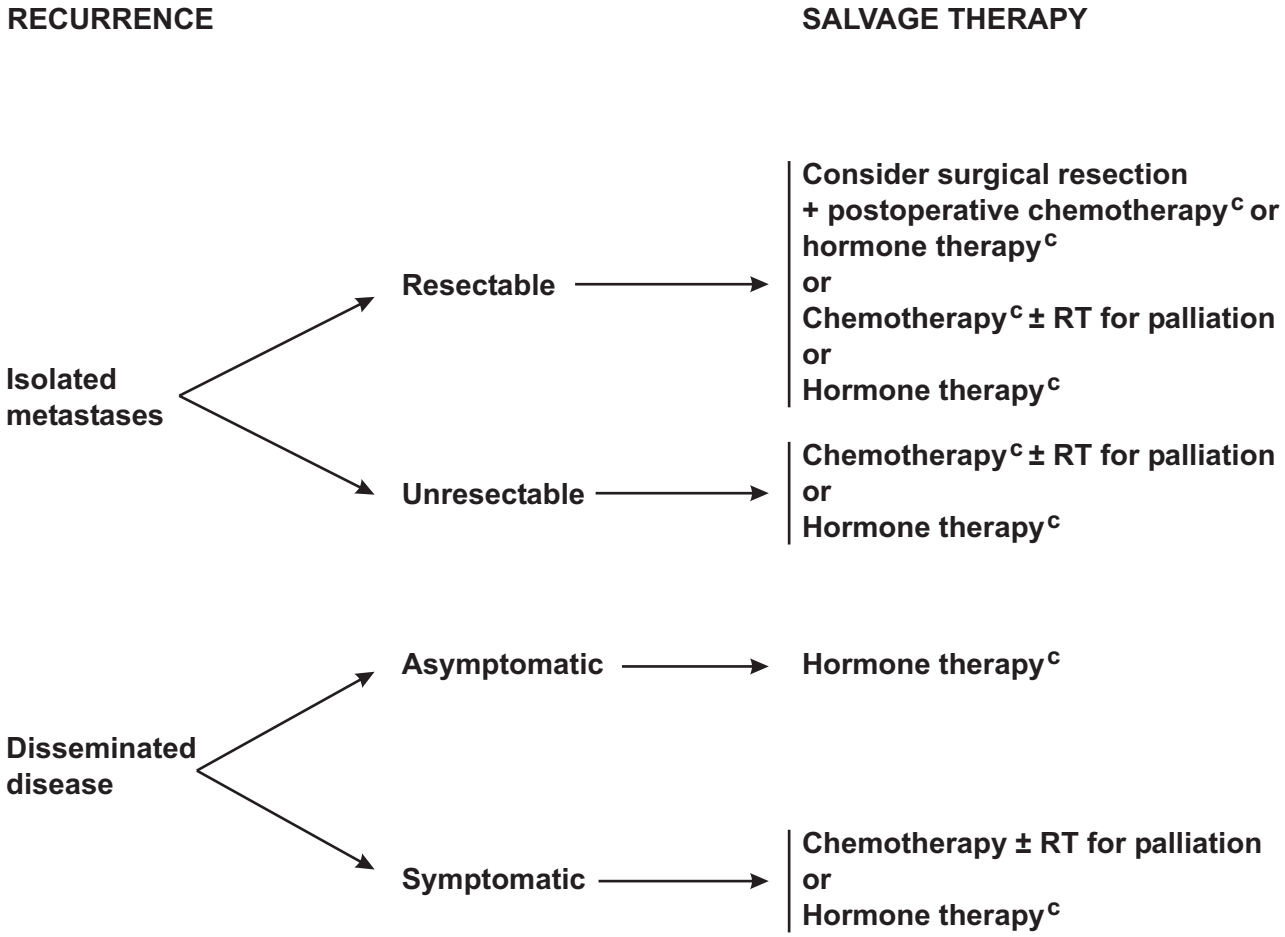
[c] For hormone therapy and chemotherapy regimens, see Salvage Therapy (UTSARC-B).

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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.

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Uterine Sarcoma



[c] For hormone therapy and chemotherapy regimens, see Salvage Therapy (UTSARC-B).

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Uterine Sarcoma

UTERINE SARCOMA CLASSIFICATION

Pure Uterine Sarcoma:

- **Endometrial stromal sarcoma[d]**
- **Undifferentiated sarcoma (high-grade endometrial stromal sarcoma)[e] or pure heterologous sarcoma[f]**
- **Leiomyosarcoma[g]**

Mixed Epithelial-Nonepithelial Malignant Tumors:

- **Malignant mixed mesodermal tumor[h]**
- **Adenosarcoma[i]**

[d] Endometrial stromal sarcomas displaying morphologic features of proliferative phase endometrial stroma and showing any mitotic index.
[e] 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.
[f] 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.
[g] 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 prgnostic 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.
[h] Also known as carcinosarcomas or malignant mixed Müllerian tumors and including those with either homologous or heterologous stromal elements.
[i] Rare tumors for which management is individualized based on pathologic prognostic factors such as grade of sarcomatous component, presence or absence of stromal overgrowth.

Back to Primary Treatment (UTSARC-2)

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Uterine Sarcoma

SALVAGE THERAPY

CHEMOTHERAPY REGIMENS

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

- **Ifosfamide (most active single agent for MMMT)**
- **Doxorubicin (most active single agent for LMS)**
- **Single-agent cisplatin, paclitaxel, and DTIC have been shown to have activity**

HORMONE THERAPY

- **Megestrol acetate**
- **Medroxyprogesterone acetate**
- **Tamoxifen**
- **GnRH analogs**

Clinical trials strongly recommended

Back to Recurrence (UTSARC-7)

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Staging

Table 1

FIGOa Staging for Endometrial Cancer: 1988

Stage IA	G1, G2, G3	Tumor limited to endometrium
Stage IB	G1, G2, G3	Invasion to less than one half of the myometrium
Stage IC	G1, G2, G3	Invasion to more than one half of the myometrium
Stage IIA	G1, G2, G3	Endocervical glandular involvement only
Stage IIB	G1, G2, G3	Cervical stromal invasion
Stage IIIA	G1, G2, G3	Tumor invades serosa and/or adnexa, and/or positive peritoneal cytology
Stage IIIB	G1, G2, G3	Vaginal metastases
Stage IIIC	G1, G2, G3	Metastases to pelvic and/or paraaortic lymph nodes
Stage IVA	G2, G3	Tumor invasion of bladder and/or bowel mucosa
Stage IVB		Distant metastases including intra-abdominal and/or inguinal lymph nodes

Histopathology - Degree of Differentiation

Cases of carcinoma of the corpus should be classified (or graded) according to the degree of histologic differentiation, as follows:
G1 = 5% or less of a nonsquamous or nonmorular solid growth pattern

G2 = 6% to 50% of a nonsquamous or nonmorular solid growth pattern
G3 = more than 50% of a nonsquamous or nonmorular solid growth pattern

Notes on Pathologic Grading:

1 Notable nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade 1 or grade 2 tumor by 1.
2. In serous adenocarcinomas, clear-cell adenocarcinomas, and squamous cell carcinomas, nuclear grading takes precedence.
3. Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.

Rules Related to Staging:

1. Because corpus cancer is now staged surgically, procedures previously used for determination of stages are no longer applicable, such as the findings from fractional dilation and curettage to differentiate between stage I and II.
2. It is appreciated that there may be a small number of patients with corpus cancer who will be treated primarily with radiation therapy. If that is the case, the clinical staging adopted by FIGO in 1971 should still apply, but designation of that staging system would be noted.
3. Ideally, width of the myometrium should be measured along with the width of tumor invasion.

[a]Federation Internationale de Gynecogie et d'Obstetrique
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Manuscript

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.

Overview

Adenocarcinoma of the endometrium is the most common malignancy of the female genital tract in the United States. It is estimated that 38,300 new cases will be diagnosed in 2001, with 6,600 deaths resulting from the disease (Greenlee et al, 2001).

In approximately 75% of patients with adenocarcinoma of the endometrium, the invasive neoplasm is confined to the uterus at diagnosis. Because of 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, many physicians have the attitude that adenocarcinoma of the endometrium is a relatively benign disease. A critical evaluation of survival data, however, indicates that this concept is erroneous. Although the estimated incidence of endometrial cancer in the United States has remained relatively constant over the past decade, the estimated number of deaths from this disease has more than doubled from 2,900 in 1987 to 6,300 in 1998 (Podratz et al, 1998).

The reasons underlying this increase in deaths 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.

Diagnosis and Work-up

Most patients (90%) with endometrial carcinoma have abnormal vaginal bleeding, most commonly in the postmenopausal period. Diagnosis can usually be made by an office endometrial biopsy. If cervical involvement is suspected, endocervical curettage or cervical biopsy should be performed.

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 (Gimpelson and Rappold, 1998). Minimal preoperative evaluation for early-stage endometrial cancer should include a chest x-ray, a complete blood count, and platelet count.

Given the typical age group at risk and the presence of other comorbid illnesses, it is prudent in selected patients to also include

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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 should be reserved for evaluating extrauterine disease as indicated by clinical symptoms, physical findings, or abnormal laboratory findings. In patients with extrauterine disease or papillary serous or clear cell histology, a serum CA 125 assay can be helpful in monitoring clinical response (Duk et al, 1986).

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 and diagnostic fractional dilation and curettage. A significant number of patients at that time were not treated with primary surgery because of obesity or various other medical problems. Thus, that staging system should be used if the patient is not a surgical candidate.

Over the past 20 years, several studies in the literature demonstrated that clinical staging was inaccurate and did not reflect actual disease extent in 15% to 20% of patients (Boronow et al, 1984; Cowles et al, 1985; Creasman et al, 1987). This reported understaging--and more importantly, the ability to identify multiple prognostic factors with 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 (Cancer Committee to the General Assembly of FIGO, 1989) to emphasize complete surgicopathologic assessment of data, such as histologic grade, myometrial invasion, and the extent and location of extrauterine spread, including retroperitoneal lymph node metastases (Staging).

Primary Treatment

The majority of patients with endometrial cancer have stage I disease at presentation. The 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, total abdominal hysterectomy/bilateral salpingo-oophorectomy (TAH/BSO), and dissection of pelvic and aortic nodes via an abdominal approach. 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.

Recently, laparoscopic pelvic and para-aortic lymphadenectomy in association with laparoscopically assisted vaginal hysterectomy (category 2B) has been proposed as an alternative surgical approach (ENDO-B). Trials evaluating this new potentially less invasive method are underway (Childers et al, 1993). This approach, however, should be applied judiciously by experienced practitioners, and patients should be followed over a long term to compare their outcomes with those of traditional laparotomy.

Lymph Node Dissection

The most controversial component of surgical staging is pelvic and aortic lymphadenectomy and whether it should be required for all patients with disease confined to the uterus. Among issues to be considered are the need for the operating surgeon to be familiar with gynecological cancer surgery, the required extent of lymphadenectomy, the contention of some physicians that low-grade

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and noninvasive endometrial cancers do not justify routine lymphadenectomy, and the reality that some obese patients are not technically suitable for nodal dissection. The incidence of pelvic and aortic node metastasis is related to the grade of tumor and the depth of myometrial invasion.

Based upon retrospective analysis of patients who have undergone full surgicopathologic correlation, it has been suggested that patients with grade 1 tumors and invasion of less than one third of the myometrium may be spared the risks associated with lymph node dissection, whereas nodal sampling is recommended for all patients with grade 2 to 3 tumors, deep myometrial invasion, cervical involvement, or suspect nodes at surgery.

Other intraoperative and postoperative considerations must be factored into the decision of whether or not to perform lymphadenectomy. 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 (Daniel and Peters, 1988). In addition, the intraoperative evaluation of myometrial invasion by gross examination of fresh tissue becomes increasingly inaccurate as the grade of tumor increases. 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 (Goff and Rice, 1990). A further indication for complete surgical staging is suggested in a recent report 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 (Kilgore et al, 1995).

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. The exception would be those with grade 1 noninvasive disease. Ideally, the grade and lack of invasive disease in such patients should be confirmed by frozen section.

Medically Inoperable Patients

In patients with medically inoperable early-stage disease, definitive radiotherapy (external-beam radiation and/or brachytherapy) alone can provide long-term local control and cancer-specific survival (Fishman et al, 1996). Radiation therapy can be given with or without hormonal therapy. In patients in whom radiation therapy is precluded, hormonal therapy may be used alone.

Advanced Carcinomas

Stage III and IV endometrial carcinomas require individualized treatment planning. These later-stage carcinomas may be diagnosed preoperatively or at the time of exploratory surgery. Even in advanced cases, surgery is often indicated for control of bleeding, relief of obstructive symptoms, and tumor debulking.

Papillary Serous and Clear Cell Carcinomas

Uterine papillary serous and clear cell carcinomas (ENDO-A) are considered more aggressive histologies, with a higher incidence of extrauterine disease at presentation (Goff et al, 1994; Hendrickson et al, 1994). Patterns of failure mimic those of ovarian cancer. Surgical staging for these tumor subtypes should follow the

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procedures performed for ovarian cancer, which include detailed examination of the entire abdominopelvic cavity and retroperitoneal spaces and appropriate biopsies, with maximal tumor debulking as indicated. Adjuvant therapy is highly individualized (Grice et al, 1998).

Adjuvant Therapy

Before the widespread use of full surgicopathologic staging, it was appreciated that various intrauterine risk factors, most notably grade and depth of myometrial invasion, correlated with prognosis in endometrial cancer. This knowledge formed an early basis for selection of adjuvant therapy, which typically consisted of external-beam pelvic radiation with or without brachytherapy.

Kucera and colleagues reported on a large series of 605 patients treated with TAH/BSO for endometrial carcinoma, only 10% of whom underwent pelvic and para-aortic node dissection. 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 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 (Kucera et al, 1990).

The potential benefit of selective adjuvant pelvic radiation in nonsurgically staged patients with high-risk intrauterine features was echoed in another report on 384 patients (Carey et al, 1995). An early prospective phase III study of stage I endometrial cancer (without lymph node sampling) randomized 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 radiotherapy, there was some improvement in pelvic control (Aalders et al, 1980).

Nodal Involvement

Based upon 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 34% of grade 3 cancers (Creasman et al, 1987). 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 considered 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. Indeed, 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,

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isthmus/cervical involvement, or lymphovascular space invasion) was 92.7% (Morrow et al, 1991). The practice of surgical staging has led to a decrease in the use of adjuvant therapy for stage I endometrial carcinoma (Gretz et al, 1996).

Role of Radiation Therapy

To assess the role of adjuvant radiation in surgically staged endometrial cancer patients without extrauterine disease, the GOG completed a multicenter trial that randomized patients with stage IB, stage IC, and occult stage II disease (any grade) to pelvic radiotherapy versus observation alone following 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 (Roberts et al, 1998).

Patterns of failure analysis in the GOG trial revealed an intriguing finding: the majority of 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 (Chadha et al, 1999). The GOG randomized trial has also been criticized for including patients with a broad range of relapse risk, including many who are often considered to have excellent prognoses, hence diluting the possibility of detecting a benefit to adjuvant therapy.

Risk of Relapse

An assessment of relapse risk in patients with surgically staged endometrial carcinoma histologically confined to the uterus (stage I and II) was performed by Kadar and colleagues (Kadar et al, 1992a). Although all patients in this series had surgicopathologically excluded extrauterine disease, the authors noted that patients with two or more of four primary risk features (grade 3, invasion of one third or more of the myometrium, invasion of the vascular space, or involvement of the cervical stroma) had significantly reduced survival rates (Kadar et al, 1992a). These factors were incorporated into a GOG trial (GOG 156) of “high-risk” stage I and stage II endometrial carcinomas. Patients were randomized to receive adjuvant pelvic radiation or six cycles of doxorubicin plus cisplatin. This trial was unfortunately closed due to lack of accrual.

Rationale for Adjunctive Radiotherapy

Given the lack of definitive data regarding the effectiveness of adjuvant therapy, in patients with uterine-confined disease the guidelines represent an evolving process with expected variances of opinion. 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 advances. Other pathologic factors that may influence the decision regarding adjuvant therapy in surgical stage I and stage II endometrial cancer include lymphovascular space invasion, tumor volume, and involvement of the lower uterine segment.

Unlike patients with uterine-confined tumors, there is a consensus that patients with documented extrauterine disease are at increased risk for recurrence and need adjuvant therapy. The optimal form of adjuvant therapy has yet to be determined. 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 (Morrow et al, 1991; Kadar et al, 1992b). At

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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.

Patients with extrauterine disease confined to the lymph nodes or the adnexa may be adequately treated with pelvic or extended-field radiotherapy (Greven et al, 1993). For patients deemed at risk of peritoneal failure, whole abdominal radiation in carefully selected cases appears to provide therapeutic benefit (Gibbons et al, 1991; Greer and Hamberger, 1983). An ongoing GOG study (GOG 122) seeks to elucidate optimal adjuvant therapy for endometrial cancer with extrauterine disease. In this trial, patients with stage III and intra-abdominal stage IV disease with minimal residual disease are randomized to whole abdominopelvic radiotherapy versus eight cycles of combined doxorubicin-cisplatin treatment. Results of this study should become available in 2002.

Adjuvant Chemotherapy

Adjuvant chemotherapy for stage III disease is under active investigation and most members of the panel felt that chemotherapy should only be used within the context of a clinical trial, since there is no definitive evidence supporting its use in this disease. Other panel members felt that since the use of adjuvant radiation therapy in advanced disease was not based on high-level evidence and this modality was still listed as an option, it was reasonable to give adjuvant chemotherapy, with or without radiation therapy, off protocol in this setting.

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, then annually. If CA 125 is elevated initially it should be repeated at each surveillance visit. These recommendations recognize that the value of intensive surveillance has not been demonstrated in this disease, and ancillary testing is therefore not recommended (Podczaski et al, 1992; Shumsky et al, 1994; Berchuck et al, 1995; Reddoch et al, 1995). A 1992 survey confirmed that, with some variations, these follow-up guidelines were widely practiced (Barnhill et al, 1992).

A recent review of the literature for routine intensive postoperative surveillance in patients with clinical stage I and stage II endometrial cancer showed approximately a 15% recurrence rate (Greer et al, 1997). Fifty-eight percent 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, posttreatment 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 posttherapy follow-up, it

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was the panel's opinion that the guidelines given in the algorithm represented a reasonable surveillance scheme.

Hormone Replacement Therapy

Hypoestrogenism is associated with hot flashes, mood liability, 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 consequences.

Because endometrial adenocarcinoma has historically been considered an estrogen-linked malignancy (Smith et al, 1975; Ziel and Finkle, 1975), women who have been successfully treated for this cancer have usually been denied estrogen replacement therapy for fear of inducing a higher relapse rate.

Estrogen replacement therapy for such patients remains controversial. A higher relapse rate in endometrial cancer patients who receive estrogen replacement therapy following hysterectomy has never been proven. Indeed, several retrospective trials of estrogen replacement following treatment of early-stage endometrial cancer have shown no increase in tumor recurrence or cancer-related deaths (Creasman et al, 1986; Lee et al, 1990; Chapman et al, 1996).

The issue of hormone replacement therapy is currently being investigated in a prospective phase III intergroup study. Eligible patients who have undergone hysterectomy for surgical stage I and occult stage II endometrial adenocarcinoma (regardless of grade or cell type) are randomized to 3 years of estrogen replacement therapy or placebo (GOG 137/ECOG #GO137). Enrollment in this randomized clinical trial was strongly supported by members of the panel.

Panel members agreed 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 wait before initiation of hormonal replacement therapy. Participation in clinical trials is strongly encouraged to definitively answer this question.

Recently developed 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.

Treatment of Relapsed or Metastatic Disease

Patients with recurrences confined to the pelvis following surgical therapy should be evaluated for surgical extirpation and/or radiation therapy. Vaginal recurrences treated with radiation have reported survival rates of 40%, with a significant decrease if there is pelvic extension or pelvic lymph node involvement (Poulsen and Roberts, 1988). Patients with recurrences confined to the pelvis following radiation are unusual. The management of such patients is controversial. Radical surgery, such as pelvic exenteration, has been performed with reported survival rates approximating 20% (Barakat et al, 1996).

The management of systemic disease is usually palliative. The principles of therapy include the amelioration of symptomatic metastatic sites with radiotherapy, appropriate use of consultants in

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pain management, and the involvement of support organizations, such as hospice care. The hormonal therapy of metastatic disease involves mainly the use of progestational agents. 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.

The presence of estrogen and progesterone receptors does not appear superior to the classic clinical criteria of predicting a hormonal response in the disease. The response rates to progestins in several published studies have ranged from approximately 10% to 60%. These studies have included patients with different grades, tumor locations, and disease-free intervals. The combination of progestational agents with chemotherapy has been studied, and there is no convincing evidence of superiority of either modality alone.

Tamoxifen has also been reported to achieve response rates of approximately 20%. Patients with prior responses to hormonal therapy and better-differentiated tumors are more likely to respond. Other hormonal modalities have not been well studied, and adjuvant therapy with hormonal agents in the treatment of endometrial cancer remains unproved (Quin, 1999).

Chemotherapy for Advanced and Recurrent Disease

Chemotherapy in endometrial cancer has been extensively studied. Single-agent therapy usually includes cisplatin, carboplatin, doxorubicin, epirubicin, and paclitaxel. Responses with these agents in advanced disease have ranged from 21% to 36%. Single-agent therapy has not been proven to improve quality of life or prolong survival.

Combination chemotherapy regimens have also been studied extensively. Response rates generally have improved with the combinations of doxorubicin and cisplatin/carboplatin, with or without concomitant cyclophosphamide. The response rates have ranged from 31% to 81%, but with relatively short durations. The median survival in such trials remains approximately 1 year (Muss, 1994; Reddy et al, 1996). The combination of cisplatin and paclitaxel is undergoing study.

Combination chemotherapy regimens in endometrial cancer should be undertaken judiciously with careful attention to toxicity, as, again, 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.

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