National Comprehensive Cancer Network

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Uterine Neoplasms

Version 3.2012

NCCN.org

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NCCN Guidelines® Version 3.2012 Panel Members
Uterine Neoplasms

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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

NCCN Guidelines Version 3.2012 Updates
Uterine Neoplasms

Updates in Version 3.2012 of the NCCN Uterine Neoplasms Guidelines from Version 2.2012 include:

Global Changes:

MS-1

- The Discussion text was updated to correspond with the changes in the algorithm.

Uterine Neoplasms

UN-1

- Under Initial Evaluation, Optional: The second bullet was revised as follows, "Consider genetic counseling/testing for young patients (< 55 y) and those with a significant family history of endometrial and/or colorectal cancer."
- Footnote a: The second sentence was revised as follows, "In relatives with Lynch syndrome, but without endometrial cancer, a yearly endometrial biopsy is recommended until a hysterectomy and bilateral salpingo-oophorectomy (BSO) are performed."

Endometrial Carcinoma:

ENDO-3

- Third column, third pathway: The phrasing was changed to, "Initially unresectable extrauterine pelvic disease".

ENDO-4

- Stage IB; Adverse risk factors present pathway; Grade 3: The recommendation changed to "Pelvic RT and/or Vaginal brachytherapy ± chemotherapy (category 2B for chemotherapy) or Observe (category 2B)".

Updates in Version 2.2012 of the NCCN Uterine Neoplasms Guidelines from Version 1.2012 include:

ENDO-B

- The following systemic therapy agents were added as options for the treatment of recurrent, metastatic, or high-risk endometrial carcinoma:
  - Carboplatin/docetaxel with corresponding footnote 4 that states, "Docetaxel may be considered for patients in whom paclitaxel is contraindicated."
  - Docetaxel (category 2B) with corresponding footnote 4 noted above.
  - Bevacizumab (category 2B) with corresponding footnote 5 that states, "Bevacizumab may be considered for use in patients who have progressed on prior cytotoxic chemotherapy."

Updates in Version 1.2012 of the NCCN Uterine Neoplasms Guidelines from Version 2.2011 include:

Uterine Neoplasms

UN-1

Initial Evaluation:

- Optional;Second bullet: Changed to "Consider genetic counseling/testing for young patients (< 55 y) with a significant family history and/or selected pathologic risk features." The age range for young patients changed from "< 50 y" to "< 55 y".
- Footnote "a" stating, "Screening with immunohistochemistry (IHC) should be considered in all patients, but especially in patients younger than 55 years. Generally, if the patient is known to have Lynch syndrome, a yearly endometrial biopsy is recommended until a hysterectomy and bilateral salpingo-oophorectomy (BSO) are performed," is new to the algorithm.

Endometrial Carcinoma:

ENDO-1

Primary Treatment:

- For medically inoperable disease, "Consider hormone therapy in select patients" was added as an option. Corresponding footnote "c" was added that states, "Patients should be closely monitored. Consider endometrial biopsies every 3-6 months."

Continued

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Endometrial Carcinoma:

ENDO-1--continued

- **Primary Treatment**
  - **For Operable disease: The recommendation "Lymph node dissection (not random sampling)" with sub-bullets "Pelvic lymphadenectomy and Para-aortic lymphadenectomy" changed to "Pelvic and para-aortic lymph node dissection" with corresponding new footnote "i" which states, "Some patients may not be candidates for lymph node dissection." (Also for ENDO-2)**
- **Footnote "h": The statement "See Discussion for routine lymphadenectomy" was added. (Also for ENDO-2)**

ENDO-4

Histologic Grade/Adjuvant Treatment:

- **Stage IB; Adverse risk factors present pathway; Grade 3: The recommendation changed to "Observe or Pelvic RT and/or Vaginal brachytherapy ± chemotherapy (category 2B for observe; category 2B for chemotherapy)".**

ENDO-10

- **A new section for "Additional Workup" was added that includes "CA-125 (optional)" and "MRI/CT, as clinically indicated."**

Adjuvant Treatment

- **For Stage IA; Stage IB, II; and Stage III, IV: For clarification, the recommendation changed to "Whole abdominopelvic RT (category 3) ± vaginal brachytherapy (category 3)".**
- **Footnote "t": The following statement was added, "Most carcinosarcomas are treated the same as poorly differentiated adenocarcinomas".**

ENDO-A: Hysterectomy

- **Pathologic assessment; Uterus; Seventh arrow point: "Consider mismatch repair analysis to identify familial cancer syndromes, such as HNPCC/Lynch syndrome," changed to "Consider screening for inherited mismatch repair disease to identify familial cancer syndromes such as Lynch syndrome/HNPCC in young patients (< 55 y) with a significant family history and/or selected pathologic risk features..."**

Uterine Sarcoma:

UTSARC-3

Adjuvant treatment:

- **Stage I: The recommendation "Consider pelvic RT and/or brachytherapy" changed from category 2B to category 3.**
- **Stage II, III: The recommendation "Consider chemotherapy" changed from category 2B to category 2A.**

UTSARC-4

- **Surveillance: Second bullet: Changed to "Chest x-ray or CT imaging every 6-12 mo for 5 y".**

UTSARC-A Systemic Therapy for Uterine Sarcoma

- **Chemotherapy Regimens; Third bullet: Under Consider other single-agent options (all agents are category 2B): Temozolomide was added.**

Uterine Neoplasms

UN-A Principles of Radiation Therapy

- **Second bullet; First sentence: "upper vagina" changed to "upper vagina/para-vaginal tissue".**
- **Third bullet; Second arrow point: "...doses of 5-6 Gy X 2 fractions.." changed to "...doses of 4-6 Gy X 2-3 fractions..."**

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INITIAL EVALUATION

- H&P
- CBC (including platelets)
- Endometrial biopsy
- Chest x-ray
- Current cervical cytology consistent with NCCN Cervical Cancer Screening Guidelines

Optional:

- LFT/renal function tests/chemistry profile
- Consider genetic counseling/testing for young patients (< 55 y) and those with a significant family history of endometrial and/or colorectal cancer[a] (See Lynch syndrome/HNPCC in NCCN Colorectal Cancer Screening Guidelines)

→ 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-10)
  - Carcinosarcoma[b,c] → See Treatment for Papillary Serous or Clear Cell Carcinomas of the Endometrium or Carcinosarcoma (ENDO-10)
- Stromal/mesenchymal tumors
  - Endometrial stromal sarcoma (ESS)
  - Undifferentiated sarcoma
  - 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 updated 2010 FIGO staging. (See ST-1 and ST-2)

[a] Screening with immunohistochemistry (IHC) should be considered in all patients, but especially in patients younger than 55 years. In relatives with Lynch syndrome, but without endometrial cancer, a yearly endometrial biopsy is recommended until a hysterectomy and bilateral salpingo-oophorectomy (BSO) are performed.

[b] Staged as aggressive; should be treated as a high-grade endometrial cancer.

[c] 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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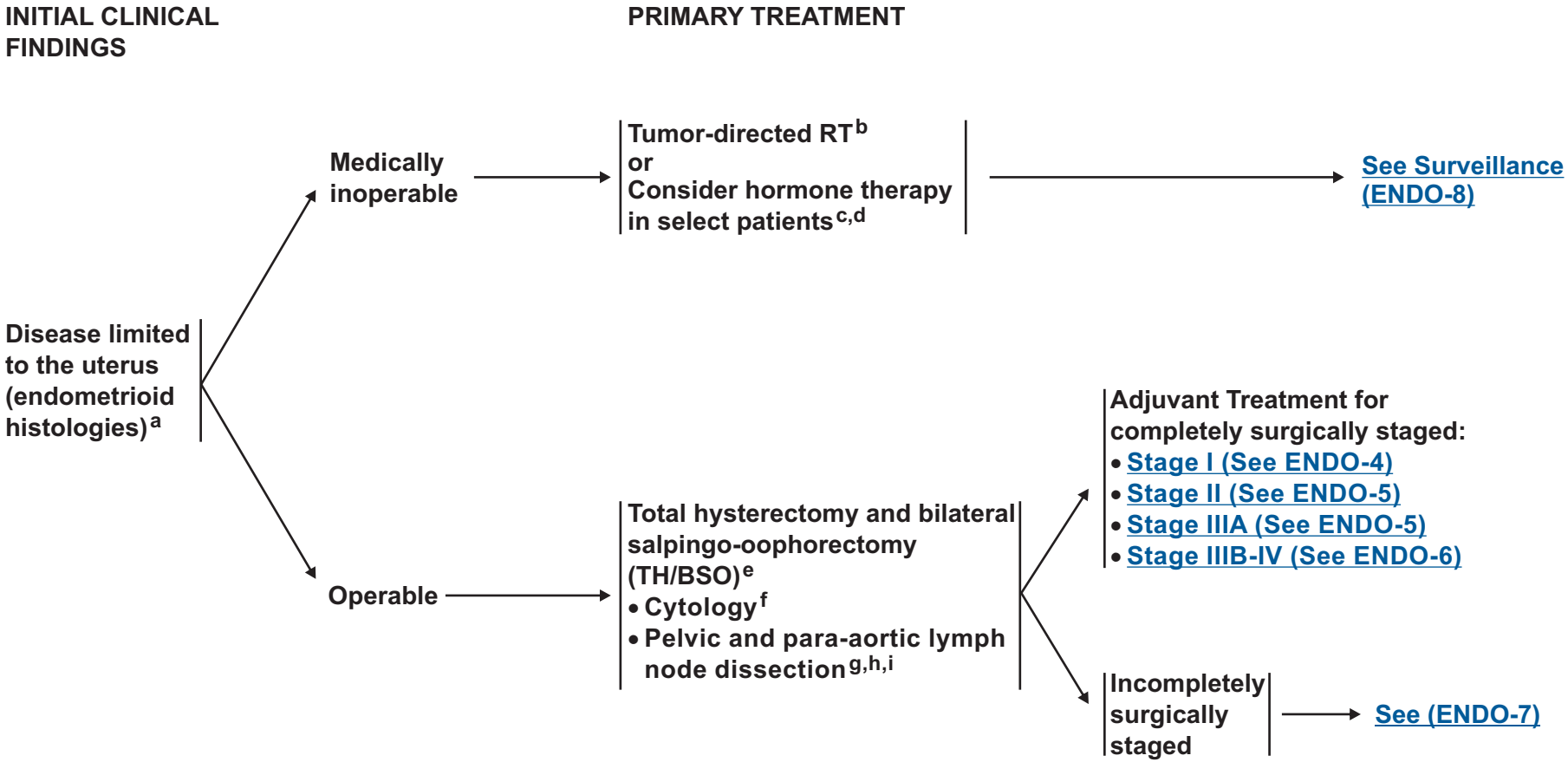
Endometrial Carcinoma



[a] See (UN-1) for clarification of uterine neoplasms.
[b] See Principles of Radiation Therapy (UN-A).
[c] Patients should be closely monitored. Consider endometrial biopsies every 3-6 months.
[d] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-B).
[e] See Hysterectomy (ENDO-A).
[f] Although peritoneal cytology by itself does not affect 2010 FIGO staging, cytology results should still be obtained and recorded.
[g] 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.
[h] A complete para-aortic lymphadenectomy would include nodes up to the renal vessel. See Discussion for routine lymphadenectomy.
[i] Some patients may not be candidates for lymph node dissection.

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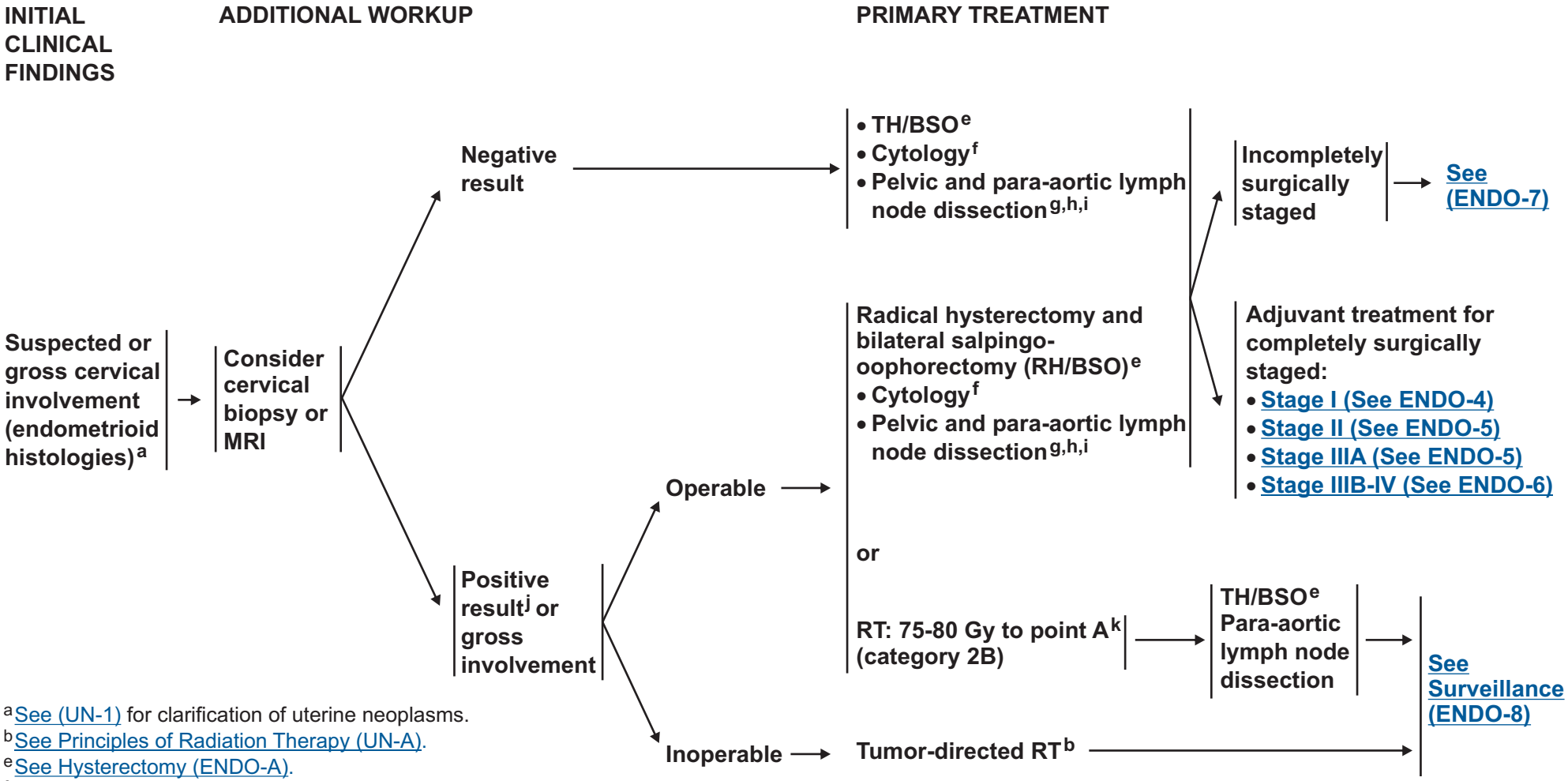

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[g] American College of Obstetricians and Gynecologists practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstet Gynecol 2005 Aug;106:413-425.
[h] A complete para-aortic lymphadenectomy would include nodes up to the renal vessel. See Discussion for routine lymphadenectomy.
[i] Some patients may not be candidates for lymph node dissection.
[j] Clear demonstration of cervical stromal involvement.
[k] Based on summation of conventional external-beam fractionation and low-dose-rate brachytherapy equivalent.

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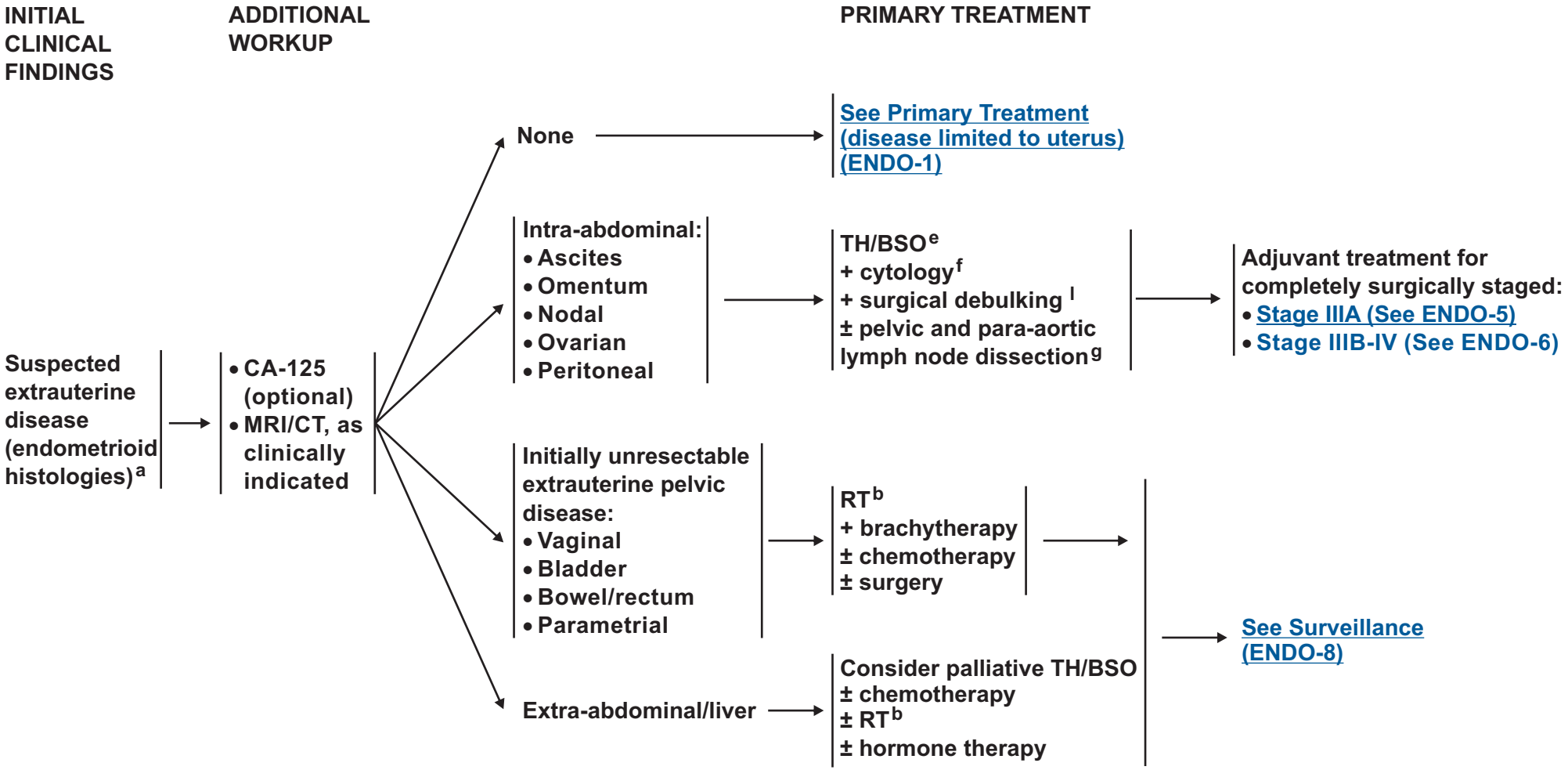

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[g] American College of Obstetricians and Gynecologists practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstet Gynecol 2005 Aug;106:413-425.
[l] The surgical goal is to have no measurable residual disease.

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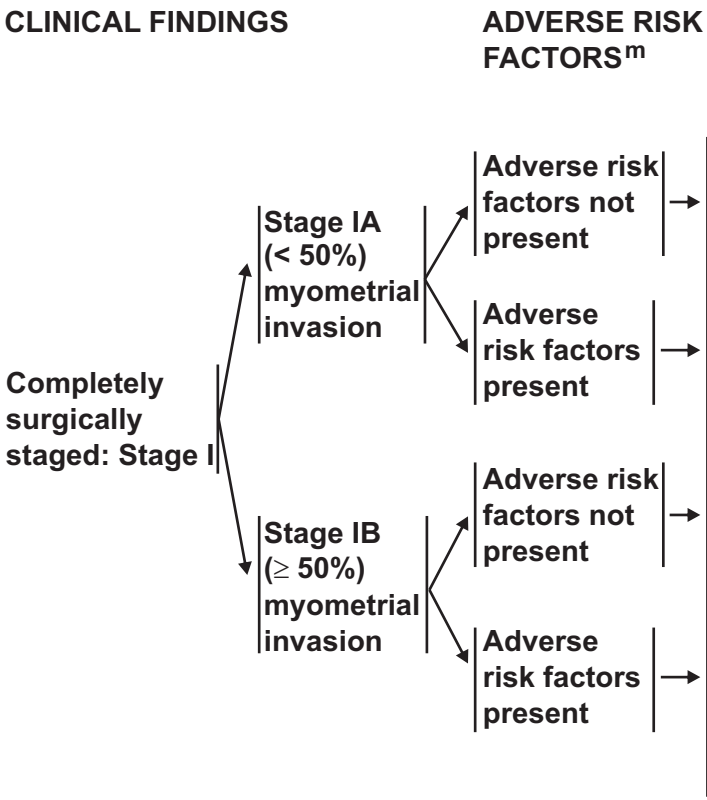
All staging in guideline is based on updated 2010 FIGO staging. (See ST-1)



HISTOLOGIC GRADE/ADJUVANT TREATMENT[b,n]		
G1	G2	G3
Observe	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy
Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or pelvic RT (category 2B for pelvic RT)	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	Pelvic RT and/or Vaginal brachytherapy ± chemotherapy[o,p] (category 2B for chemotherapy) or Observe (category 2B)

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

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

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

[o] 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, Signorelli M, de Oliveira CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur J Cancer 2010;46(13):2422-2431.)

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

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See Surveillance (ENDO-8)

All staging in guideline is based on updated 2010 FIGO staging. (See ST-1)

CLINICAL FINDINGS	HISTOLOGIC GRADE/ADJUVANT TREATMENT[b,n,p]		
	G1	G2	G3
Completely surgically staged: Stage II[q,r] →	Vaginal brachytherapy and/or pelvic RT	Pelvic RT + vaginal brachytherapy	Pelvic RT + vaginal brachytherapy ± chemotherapy[o,p] (category 2B for chemotherapy)
Completely surgically staged: Stage 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).

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

[o] 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, Signorelli M, de Oliveira CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur J Cancer 2010;46(13):2422-2431.)

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

[q] 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.

[r] The adverse fundal risk factors influencing therapy decisions for stage I disease (see ENDO-4) may also impact the choice of adjuvant therapy for stage II disease.

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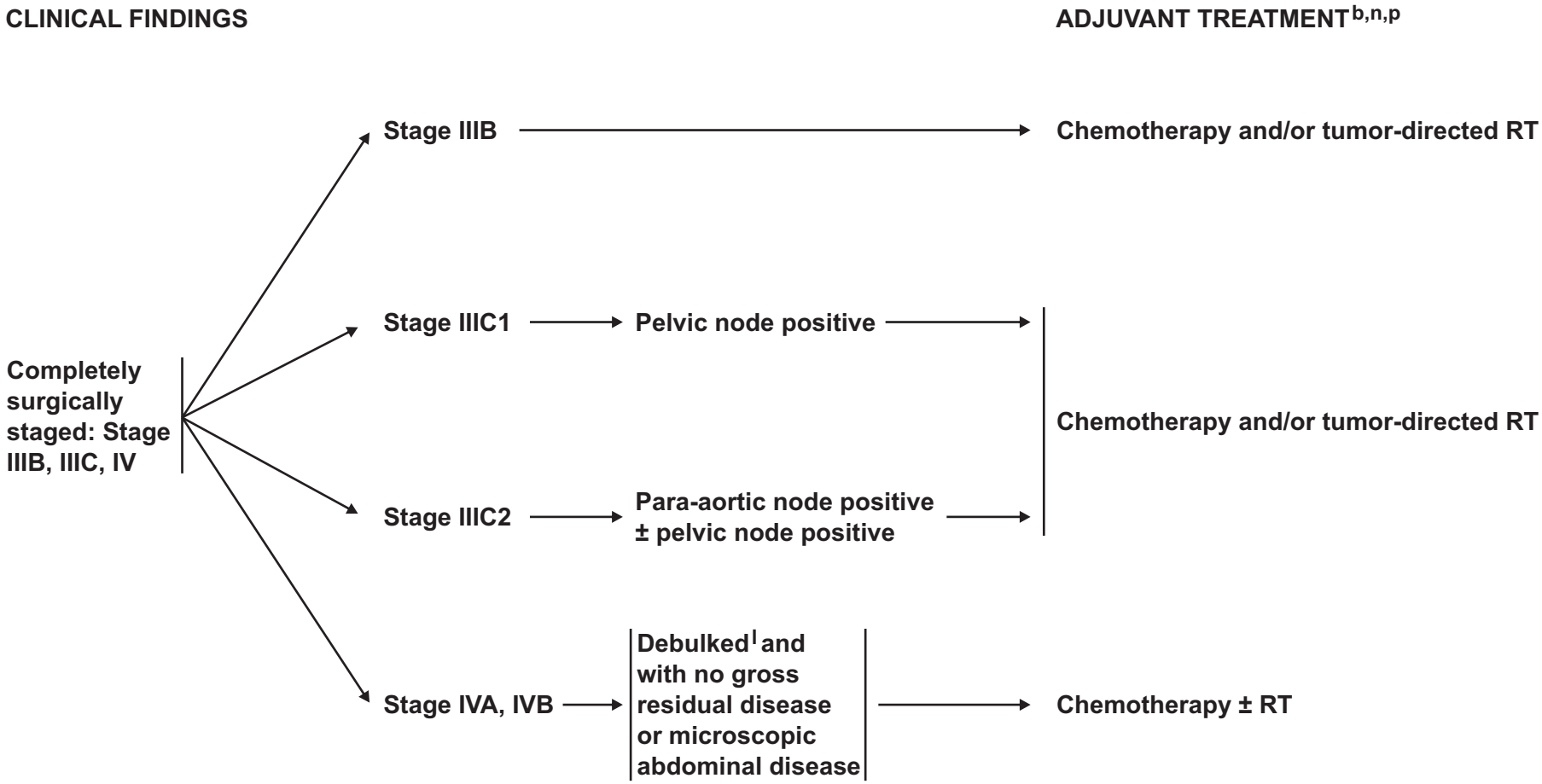

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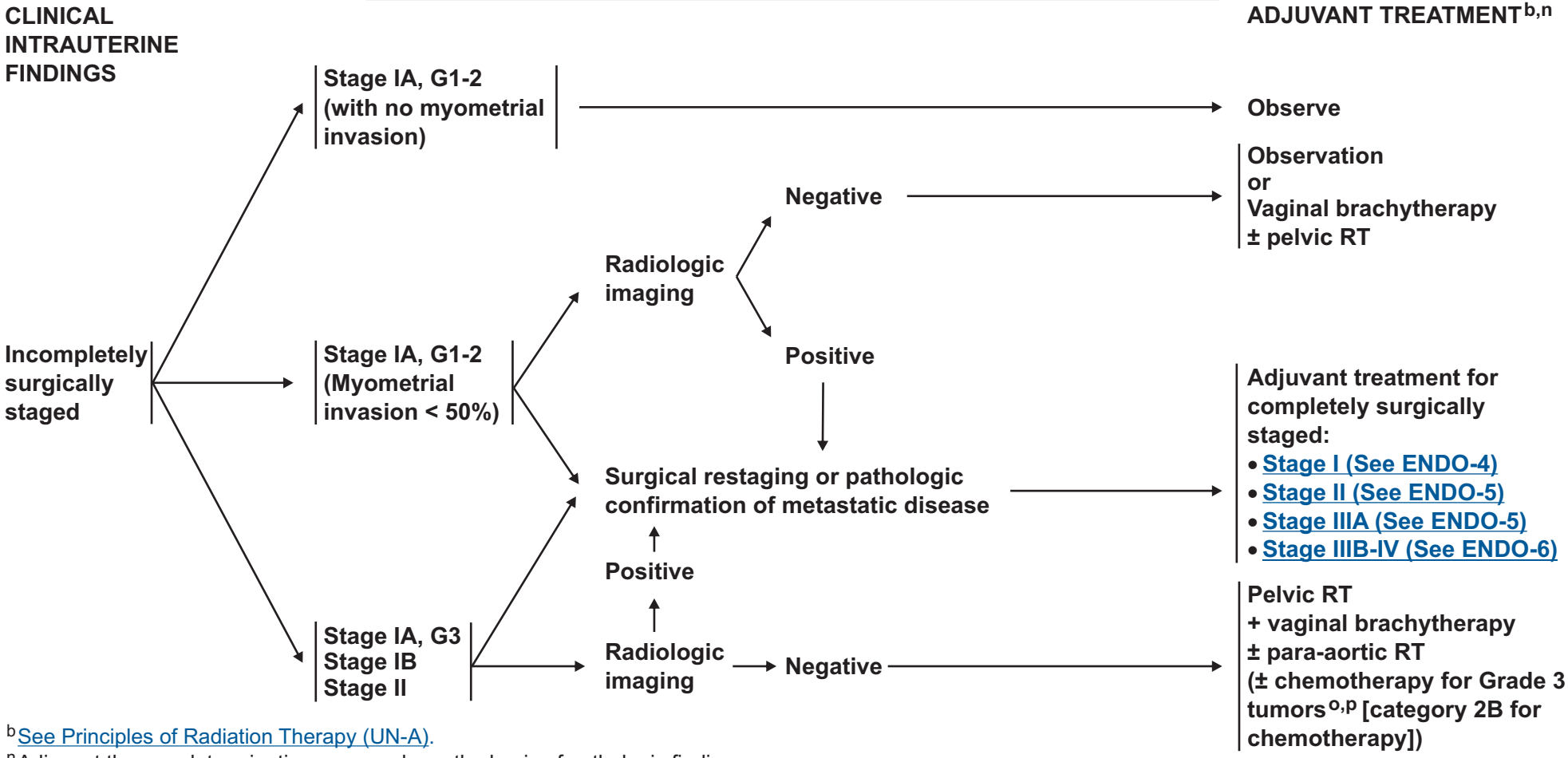

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SURVEILLANCE

- Physical exam every 3-6 mo for 2 y, then 6 mo or annually
- Vaginal cytology every 6 mo for 2 y, then annually (category 2B)
- Patient education regarding symptoms
- CA-125 (optional)
- Chest x-ray annually (category 2B)
- CT/MRI as clinically indicated
- Consider genetic counseling/testing for young patients (< 55y) with a significant family history and/or selected pathologic risk features[s] (See Lynch syndrome/HNPCC in NCCN Colorectal Cancer Screening Guidelines)

CLINICAL PRESENTATION

Local/regional recurrence
- Negative distant metastases on radiologic imaging

→ See Therapy For Relapse (ENDO-9)

Isolated metastases → **Consider resection ± RT[b]** → **Unresectable or further recurrence** → **Treat as disseminated metastases (See below)**

Disseminated metastases

- **Low grade or Asymptomatic** → **Hormone therapy[p]** → **If progression, chemotherapy[p]**
- **Symptomatic or Grade 2, 3 or Large volume** → **Chemotherapy[p] ± palliative RT[b]**

→ **If progression, Best supportive care (See NCCN Palliative Care Guidelines) or Clinical trial**

[b] See Principles of Radiation Therapy (UN-A).
[p] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-B).
[s] Screening with immunohistochemistry (IHC) should be considered in all patients, but especially in patients younger than 55 years.

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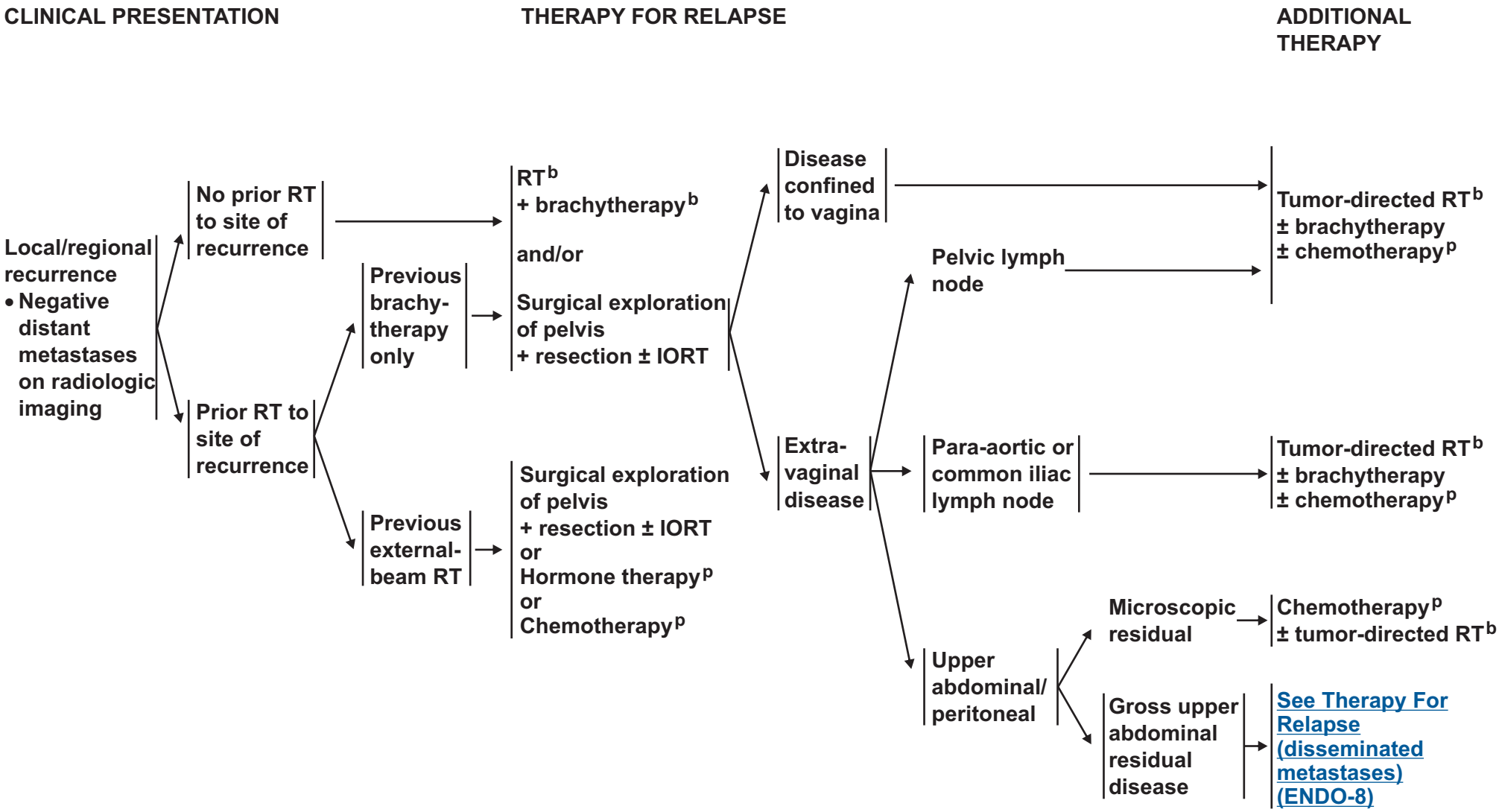

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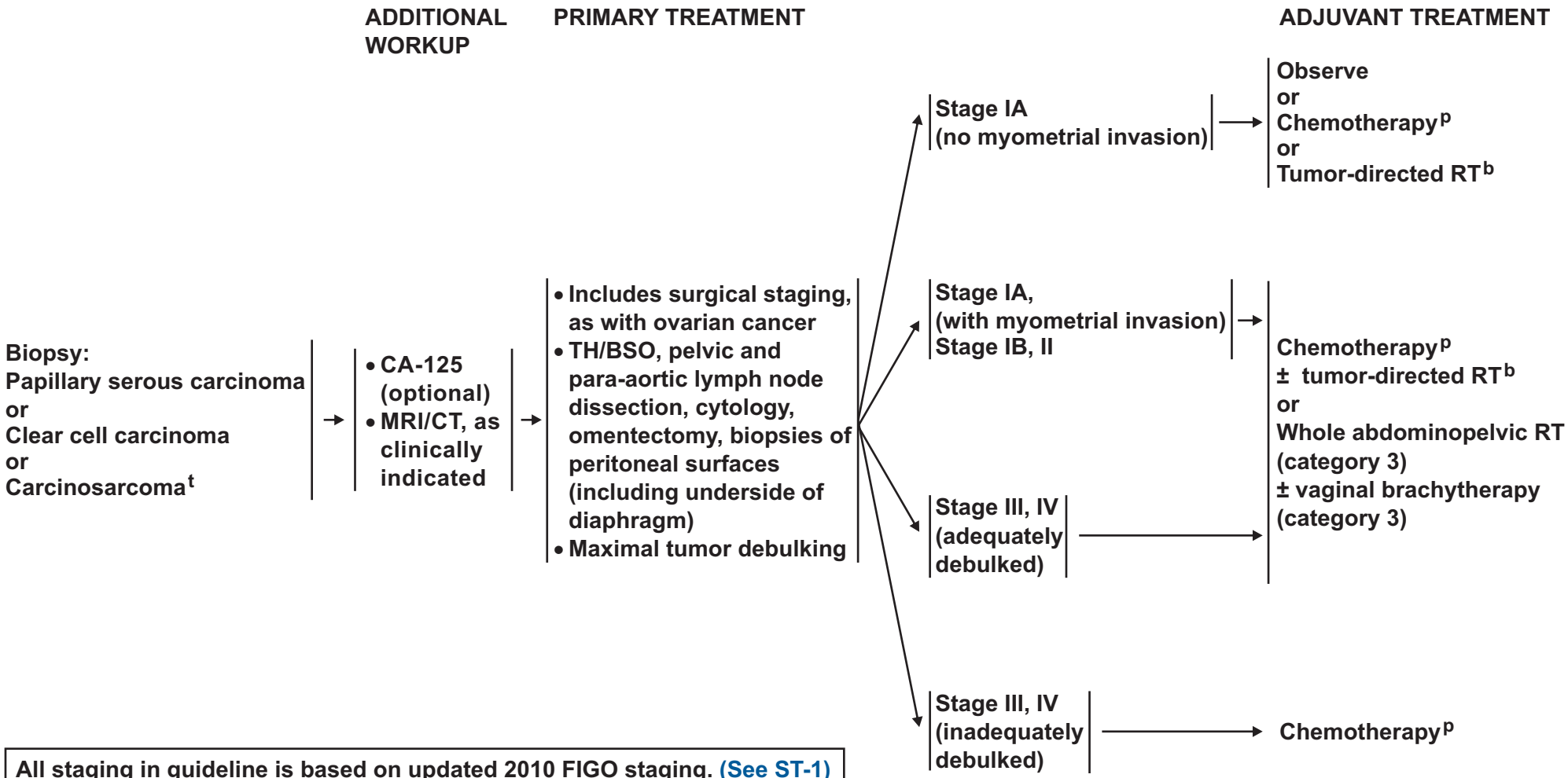
PAPILLARY SEROUS OR CLEAR CELL CARCINOMA OF THE ENDOMETRIUM OR CARCINOSARCOMA[t]



All staging in guideline is based on updated 2010 FIGO staging. (See ST-1)

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

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[t] Also known as malignant mixed mesodermal tumor or malignant mixed Müllerian tumor. Most carcinosarcomas are treated the same as poorly differentiated adenocarcinomas.

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See Surveillance (ENDO-8)

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HYSTERECTOMY[1]

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[2]**
- **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 screening for inherited mismatch repair disease to identify familial cancer syndromes, such as Lynch syndrome/HNPCC in young patients (< 55 y) with a significant family history and/or selected pathologic risk features (See NCCN Colorectal Cancer Screening Guidelines)**
- **Fallopian tubes/ovaries**

[1] 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.

[2] Although cytology by itself does not affect FIGO staging, cytology results should still be obtained because positive cytology is an adverse risk factor.

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

SYSTEMIC THERAPY FOR RECURRENT, METASTATIC OR HIGH-RISK DISEASE[1]
(STRONGLY ENCOURAGE PARTICIPATION IN CLINICAL TRIALS)

HORMONE THERAPY[2]
- **Progestational agents**
- **Tamoxifen**
- **Aromatase inhibitors**

CHEMOTHERAPY REGIMENS[3]
(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**
- **Carboplatin/docetaxel[4]**
- **Cisplatin**
- **Carboplatin**
- **Doxorubicin**
- **Liposomal doxorubicin**
- **Paclitaxel**
- **Docetaxel[4] (category 2B)**
- **Bevacizumab[5] (category 2B)**
- **Cisplatin/ifosfamide (for carcinosarcoma)**
- **Ifosfamide (for carcinosarcoma)**

[1] Cisplatin, carboplatin, liposomal doxorubicin, paclitaxel, and docetaxel may cause drug reactions (See NCCN Ovarian Cancer Guidelines--Management of Drug Reactions [OV-C])

[2] Hormonal therapy is for endometrioid histologies only (ie, not for papillary serous carcinoma, clear cell carcinoma, or carcinosarcoma).

[3] 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.

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

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

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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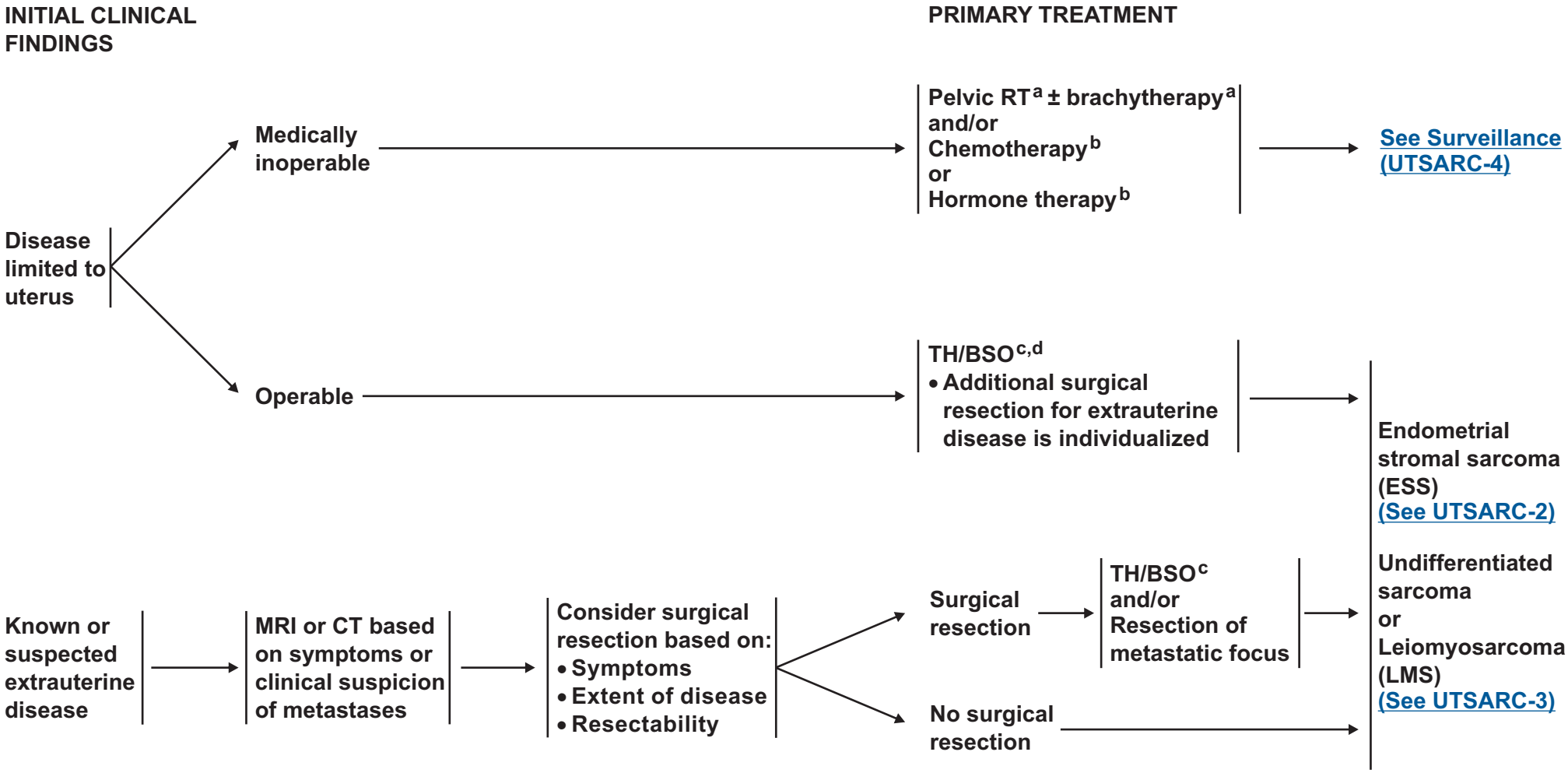
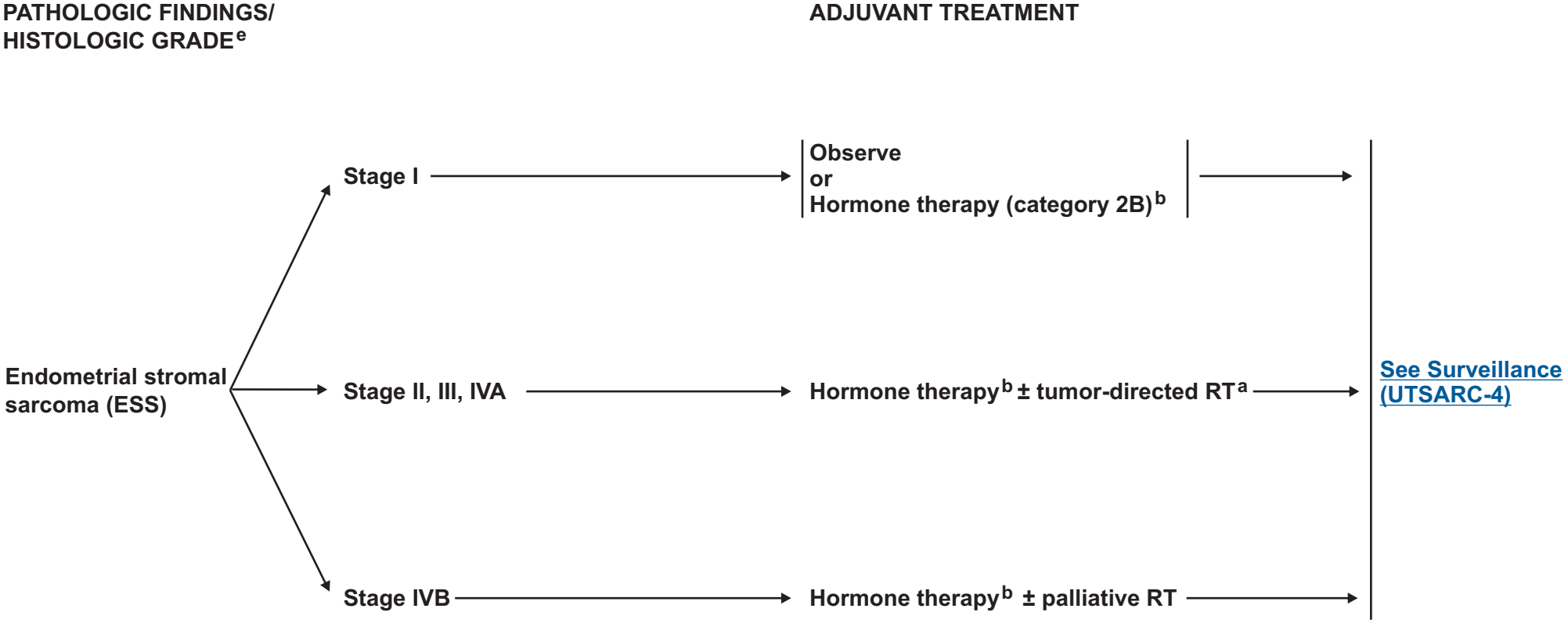


All staging in guideline is based on updated 2010 FIGO staging. (See ST-2)

[a] See Principles of Radiation Therapy (UN-A).
[b] See Systemic Therapy for Uterine Sarcoma (UTSARC-A).
[c] Oophorectomy individualized for reproductive age patients.
[d] For incidental finding of uterine sarcoma after TH/BSO: Recommend imaging and consider additional surgical resection on an individual basis.

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.

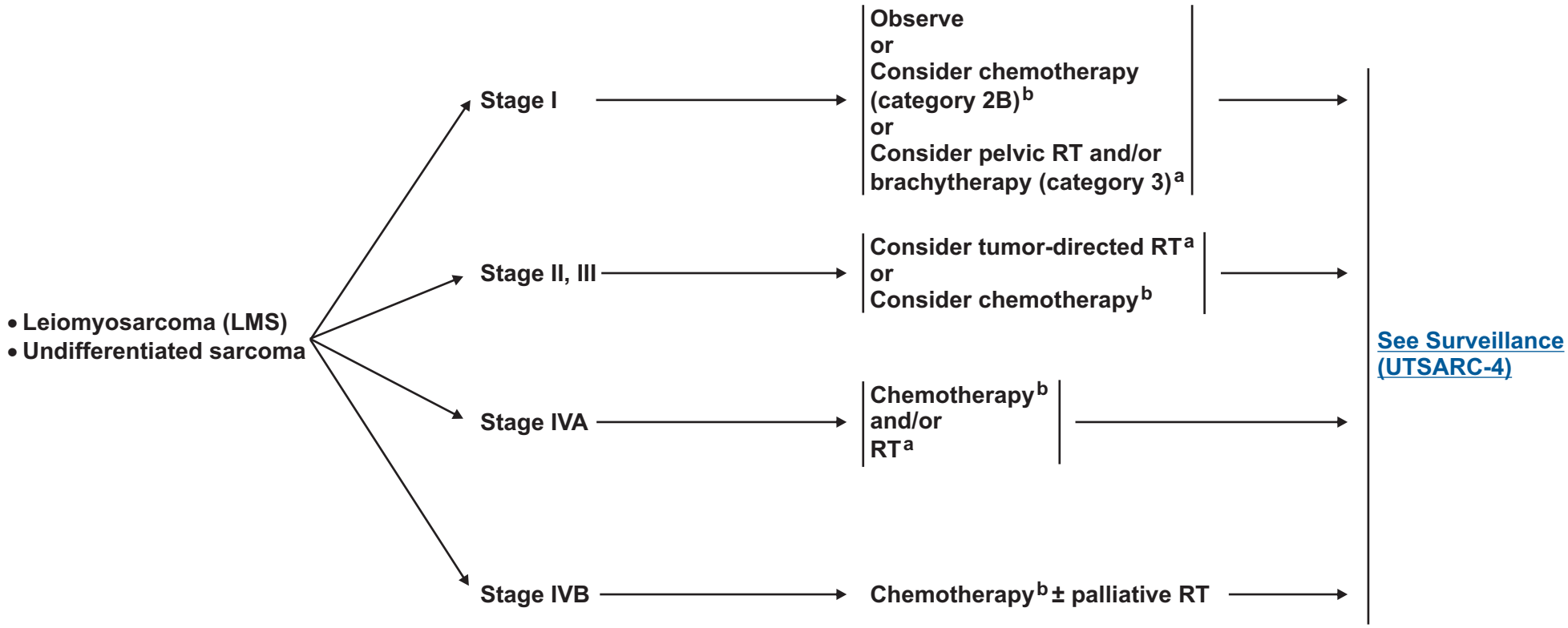


[a] See Principles of Radiation Therapy (UN-A).
[b] See Systemic Therapy for Uterine Sarcoma (UTSARC-A).
[e] See Uterine Sarcoma Classification (UTSARC-B).

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.

PATHOLOGIC FINDINGS/ HISTOLOGIC GRADE[e]

ADJUVANT TREATMENT



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

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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SURVEILLANCE

- Physical exam every 3 mo for 2 y, then every 6-12 mo
- Chest x-ray or CT imaging every 6-12 mo for 5 y
- CT/MRI as clinically indicated
- Other imaging as clinically indicated
- Patient education regarding symptoms

RECURRENCE

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

→ See Therapy For Relapse (UTSARC-5)

Isolated metastases

- Resectable → Consider surgical resection + postoperative chemotherapy[b] or hormone therapy (ESS only)[b] or Chemotherapy[b] ± palliative RT or Hormone therapy (ESS only)[b]
- Unresectable → Chemotherapy[b] ± palliative RT or Hormone therapy (ESS only)[b]

Disseminated disease

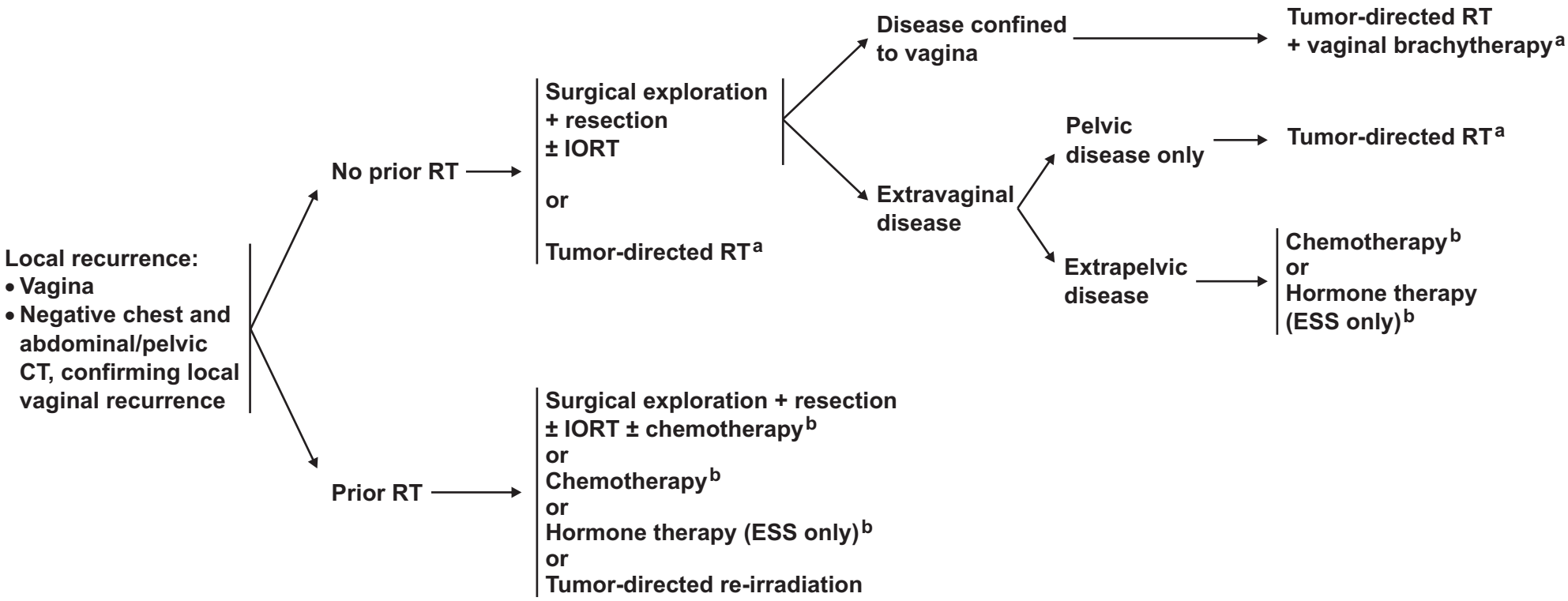
- ESS → Hormone therapy[b] or Supportive care
- All others → Chemotherapy[b] ± palliative RT or Supportive care

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

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

RECURRENCE

THERAPY FOR RELAPSE



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

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

SYSTEMIC THERAPY FOR UTERINE SARCOMA

CHEMOTHERAPY REGIMENS[1]
(Clinical trials strongly recommended)

- **Doxorubicin**
- **Gemcitabine/docetaxel**
- **Consider other single-agent options (all agents are category 2B):**
  - **Dacarbazine**
  - **Docetaxel**
  - **Epirubicin**
  - **Gemcitabine**
  - **Ifosfamide**
  - **Liposomal doxorubicin**
  - **Paclitaxel**
  - **Temozolomide**

HORMONE THERAPY (ESS only)

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

[1] Cisplatin, carboplatin, liposomal doxorubicin, docetaxel and paclitaxel may cause drug reactions (See NCCN Ovarian Cancer Guidelines--Management of Drug Reactions [OV-C])

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.

Back to Recurrence (UTSARC-4)

UTERINE SARCOMA CLASSIFICATION

- **Endometrial stromal sarcoma**[1]
- **Leiomyosarcoma**[2]
- **Undifferentiated sarcoma**[3]

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

[2] 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.

[3] High-grade sarcomas 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.

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.

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, parametria, upper vagina/para-vaginal tissue, and presacral lymph nodes (in patients with cervical involvement). Extended-field radiotherapy should include the pelvic volume and also target the entire common iliac chain and para-aortic lymph node region. The upper border of the extended field depends on the clinical situation but should at least be 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 4-6 Gy X 2-3 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-Endometrial Carcinoma

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

Primary Tumor (T)

TNM Categories	FIGO* Stages	Surgical-Pathologic Findings
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis**		Carcinoma in situ (preinvasive carcinoma)
T1	I	Tumor confined to the corpus uteri
T1a	IA	Tumor limited to endometrium or invades less than one-half of the myometrium
T1b	IB	Tumor invades one-half or more of the myometrium
T2	II	Tumor invades stromal connective tissue of the cervix but does not extend beyond uterus#
T3a	IIIA	Tumor involves serosa and/or adnexa (direct extension or metastasis)##
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement##
	IIIC	Metastases to pelvic and/or para-aortic lymph nodes##
	IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
T4	IVA	Tumor invades bladder mucosa and/or bowel (bullous edema is not sufficient to classify a tumor as T4)

*Either G1, G2, or G3
**Note: FIGO no longer includes Stage 0 (Tis).
#Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.
##Positive cytology has to be reported separately without changing the stage.

Regional Lymph Nodes (N)

TNM Categories	FIGO Stages	Surgical-Pathologic Findings
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC1	Regional lymph node metastasis to pelvic lymph nodes (positive pelvic nodes)
N2	IIIC2	Regional lymph node metastasis to para-aortic lymph nodes, with or without positive pelvic lymph nodes

Distant Metastasis (M)

TNM Categories	FIGO Stages	Surgical-Pathologic Findings
M0		No distant metastasis
M1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes intra-peritoneal disease, or lung, liver, or bone. It excludes metastasis to para-aortic lymph nodes, vagina, pelvic serosa, or adnexa)

Continued

Staging-Uterine Sarcoma

Table 2
AJCC Tumor-Node-Metastases (TNM) and International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging Systems for Uterine Sarcomas (includes Leiomyosarcoma and Endometrial Stromal Sarcoma)*

Leiomyosarcoma and Endometrial Stromal Sarcoma

Primary Tumor (T)

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

Note: Simultaneous tumors of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors.

*Carcinosarcomas should be staged as carcinomas of the endometrium (See ST-1).
**In this stage, lesions must infiltrate abdominal tissues and not just protrude into the abdominal cavity.

Regional Lymph Nodes (N)

TNM Categories	FIGO Stages	Definition
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC	Regional lymph node metastasis

Distant Metastasis (M)

TNM Categories	FIGO Stages	Definition
M0		No distant metastasis
M1	IVB	Distant metastasis (excluding adnexa, pelvic and abdominal tissues)

Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Adenocarcinoma of the endometrium (also known as endometrial cancer, or more broadly as uterine cancer or carcinoma of the uterine corpus) is the most common malignancy of the female genital tract in the United States. It is estimated that 47,100 new uterine cancer cases will occur in 2012, with 8,000 deaths resulting from the disease.[1] Uterine sarcomas are uncommon malignancies accounting for approximately 3% 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 (see UN-1 in the NCCN Uterine Neoplasms algorithm). Risk factors for uterine neoplasms include increased levels of estrogen (caused by obesity, diabetes, high-fat diet), early age at menarche, nulliparity, late age at menopause, Lynch syndrome, older age (55 years or older), and tamoxifen use.[3,4] Thus, the incidence of endometrial cancer is increasing because of increased life expectancy and obesity.

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 evaluation (i.e., workup) includes a history & physical examination, endometrial biopsy, and other studies (see UN-1).[5] A pathology review will determine whether a patient has either 1) an epithelial carcinoma (i.e., pure endometrioid cancer, uterine papillary serous carcinoma, clear cell carcinoma, or carcinosarcoma, which is also known as malignant mixed Müllerian tumor [MMMT]); or 2) a stromal/mesenchymal tumor (i.e., leiomyosarcoma, endometrial stromal sarcoma, or undifferentiated [endometrial] sarcoma). Given the typical age group at risk for uterine neoplasms (i.e., women 55 years or older) and the presence of comorbid illnesses in older patients, it is prudent in selected patients to also measure renal and liver function.

Most endometrial cancer is caused by sporadic mutations. However, genetic mutations cause endometrial cancer in about 5% of patients, which occurs 10-20 years before sporadic cancer.[6] Screening for genetic mutations (e.g., Lynch syndrome/Hereditary Non-Polyposis Colorectal Cancer [HNPCC]) should be considered in all patients but especially in those younger than 55 years.[6,7] Genetic testing and counseling should be considered for young (< 55 years) patients with endometrial cancer and those with a significant family history of endometrial and/or colorectal cancer.[8,9] If these patients have Lynch

syndrome, they are at greater risk for a second cancer (e.g., colorectal cancer, ovarian cancer).[4,10] In addition, their relatives may have Lynch syndrome.

Screening with immunohistochemistry should be considered to identify which patients should undergo mutation testing for Lynch syndrome (see the NCCN Colorectal Cancer Screening Guidelines).[6,7] Immunohistochemistry is used to assess for defective DNA mismatch repair (e.g., MSH2, MSH6), which is associated with Lynch syndrome.[6] The Society of Gynecologic Oncology (SGO) also has useful criteria for determining which patients should have mutation testing (e.g., diagnosis of multiple "Lynch syndrome" cancers in young patients, family members with similar cancers).[8,9]

Women with Lynch syndrome are at higher risk (60%) for endometrial cancer; thus, close monitoring is recommended.[7,11] In relatives with Lynch syndrome but without endometrial cancer, a yearly endometrial biopsy is recommended to assess for cancer.[9] This strategy also enables select women to defer surgery (and surgical menopause) and to preserve their fertility. Prophylactic hysterectomy/bilateral salpingo-oophorectomy can then be done after child bearing is complete or sooner, depending on patient preference.[12] In addition, interventions to decrease the risk from colorectal cancer may also be appropriate (e.g., annual colonoscopy).

Endometrial Cancer

In approximately 75% of patients with adenocarcinoma of the endometrium, the invasive neoplasm is confined to the uterus at diagnosis.[13] 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.[14] This increased mortality may be related to an increased rate of advanced-stage cancers and high-risk histologies (i.e., 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. A recent analysis of SEER (Surveillance, Epidemiology and End Results) data suggests that survival is increased in patients who are younger, have early stage disease, and lower grade disease.[15] It also suggested that gynecologic oncologists be involved in the primary management of patients with endometrial cancer.

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" in this Discussion). Diagnosis can usually be made by an office endometrial biopsy.[16,17] The histologic information from the endometrial biopsy (with or without endocervical curettage) should be sufficient for planning definitive treatment. Office endometrial biopsies have a false-negative rate of about 10%. Thus, a negative endometrial biopsy in a symptomatic patient must be followed by a fractional dilation and curettage (D&C) under anesthesia.[16,18] Hysteroscopy may be helpful in evaluating the endometrium for lesions, such as a polyp, if the patient has persistent or recurrent undiagnosed bleeding.[19]

Other ancillary tests (i.e., computed tomography, magnetic resonance imaging [MRI]) are reserved for evaluating extrauterine disease as indicated by clinical symptoms, physical findings, or abnormal laboratory findings.[20,21] In patients with extrauterine disease, a serum CA 125 assay may be helpful in monitoring clinical response.[22,23] 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.[24-26]

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 only used information gained from presurgical evaluation (including physical examination, diagnostic fractional D&C). At that time, many patients were not treated with primary surgery because of obesity or various other medical problems. Thus, the 1970 staging system is rarely used today (e.g., when the patient is not a surgical candidate).

However, several studies demonstrated that clinical staging was inaccurate and did not reflect actual disease extent in 15% to 20% of patients.[27-29] This reported understaging and, more importantly, the ability to identify multiple prognostic factors with a full pathologic review made possible with surgical staging, motivated a change in the staging classification. Therefore, in 1988, FIGO modified its staging system to emphasize 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).[30]

FIGO and the American Joint Committee on Cancer (AJCC) updated the staging for uterine neoplasms, which became effective in 2010.[31-34] There are now separate staging systems for epithelial carcinomas and uterine sarcomas (see Tables 1 and 2, respectively). The new staging has streamlined stages I and II endometrial carcinoma. These revisions were made because the survival rates for some of the previous stages were similar.[33] Stage IA is now less than 50% myometrial invasion, and stage IB is 50% or more myometrial invasion. Stage II only includes patients with cervical stromal invasion. Patients with endocervical glandular involvement without invasion are no longer upstaged.[33] However, stage IIIC is now subdivided into IIIC1 and IIIC2, because survival is worse with positive para-aortic nodes.[33] All the previously published studies discussed in this NCCN guideline are based on the older 1988 FIGO staging system but have been reinterpreted by the panel to reconcile with the new 2010 staging system.

Primary Treatment

A pathology review will determine the specific epithelial histology of the tumor (i.e., 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 and the nodes is described in detail in the algorithm; this assessment should also include the Fallopian tubes and the ovaries (see ENDO-A). Peritoneal cytology no longer affects FIGO staging, because it is not viewed as an independent risk factor.[34] However, peritoneal washings should still be obtained, because positive cytology may add to the effect of other risk factors and should continue to be reported.[35,36]

The College of American Pathologists (CAP) protocol for endometrial carcinoma is a useful guide (http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2011/Endometrium_11protocol.pdf). This CAP protocol was revised in February 2011 and reflects recent updates in the FIGO/AJCC staging (i.e., AJCC staging manual, 7th edition).

Disease Limited to the Uterus

Most patients with endometrial cancer have stage I disease at presentation, and surgery (with or without adjuvant therapy) is recommended for medically operable patients. For patients with surgical stage I (any grade) endometrial cancer, the 5-year overall survival rate is 88% after treatment.[13]

Medically Operable Patients

For the staging of a patient (if medically operable) with endometrioid histologies clinically confined to the fundal portion of the uterus, the recommended surgical procedure includes peritoneal lavage for cytology and total hysterectomy/ bilateral salpingo-oophorectomy (TH/BSO) with dissection of pelvic and para-aortic lymph nodes (see ENDO-1 and ENDO-A; see also “Minimally Invasive Surgery” in this Discussion).[37] Complete surgical staging is recommended by the NCCN panel—to gather full pathologic and prognostic data on which to base decisions regarding adjuvant treatment—for all patients who do not have medical or technical contraindications to lymph node dissection (see also comments on routine lymphadenectomy in this section).

During surgery, the abdominal organs (including the diaphragm, liver, omentum, and pelvic and bowel peritoneal surfaces) should be carefully inspected and palpated; suspicious areas should be biopsied. 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.[38-40] The para-aortic lymphadenectomy should be done up to the renal vessels.[34,38] 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.[41,42] In addition, a recent retrospective analysis reported that survival increased in patients with an intermediate or high risk of recurrence who had combined pelvic and para-aortic lymphadenectomy.[43]

Recent data have questioned the role of routine pelvic lymphadenectomy in early stage endometrial carcinoma;[44-46] however, these findings remain a point of contention and are not currently reflected in North American practice.[37,47,48] Two randomized clinical trials from Europe reported that lymph node dissection did not improve the outcome of endometrial cancer patients; however, lymphadenectomy did identify those with nodal disease.[45,46] To avoid over interpretation of these results, it is important to address the limitations of these randomized studies including selection of patients, extent of lymph node dissection, and standardization of postoperative therapy.[49,50] The other concerns regarding these trials include the lack of central pathology review, subspecialty of surgeons, and adequacy of statistical power.

Prior studies have shown that 10% to 35% of patients have para-aortic nodal metastases without disease in the pelvic nodes.[29,38,51] In addition, there was a high rate of lymphatic metastasis above the inferior mesenteric artery, suggesting a need for systematic pelvic and para-aortic lymphadenectomy. However, in these 2 European

randomized trials, para-aortic lymphadenectomy was performed at the discretion of the surgeon. Clearly, the standardization of surgical effort to include systematic para-aortic lymphadenectomy may be important to definitively prove the potential survival advantage associated with lymphadenectomy.

Another associated benefit of lymphadenectomy is the diagnosis of those with nodal metastases to guide appropriate adjuvant treatment to improve survival or decrease toxicity. However, one of the trials was not designed to address this question.[46] Therefore, there was no standardization of adjuvant treatment after staging surgery with lymphadenectomy. In fact, the use of lymphadenectomy did not translate into an increased use of adjuvant therapy. This may have contributed to the lack of difference in recurrence and survival in the two groups.

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.[52] As the grade of the tumor increases, the accuracy of intraoperative evaluation of myometrial invasion decreases (i.e., 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.[53]

In summary, systematic pelvic and para-aortic lymph node dissection identifies patients requiring adjuvant treatment with RT and/or chemotherapy.[54] A subset of patients may not benefit from lymphadenectomy; however, it is difficult to preoperatively identify these patients because of the uncontrollable variables of change in grade and depth of invasion on final pathology. At this point, pending further trials that seek to define the clinical benefit of lymphadenectomy, the NCCN panel recommends that pelvic and para-aortic lymphadenectomy should be part of the standard surgical procedure for all patients with endometrial cancer.

In premenopausal women with stage IA-B endometrial cancer, a recent study suggested that preserving an ovary is safe and not associated with an increased risk of cancer-related mortality; patients were followed for 16 years.[55]

Although the primary treatment of endometrial cancer is usually hysterectomy, initial hormonal therapy may be considered for highly selected patients. 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.[37,56-58] The NCCN panel recommends close monitoring of these patients (e.g., consider endometrial biopsies every 3-6 months). Although some young women who had subsequent negative endometrial biopsies after hormonal therapy were able to become pregnant, their ultimate recurrence rate was high (44%).[58,59]

Medically Inoperable Patients

For medically inoperable patients, tumor-directed radiation therapy (RT) is a well-tolerated and effective treatment that can provide some measure of pelvic control and long-term progression-free survival (see UN-A).[60-62]

Hormonal therapy may be considered in select patients (e.g., estrogen and progesterone receptor–positive patients), who are not candidates for RT or surgery, if they are closely monitored (e.g., consider endometrial biopsies every 3-6 months). Medroxyprogesterone acetate

can provide some benefit with low toxicity in patients with low-grade tumors.[63] Tamoxifen and aromatase inhibitors have also been used.

Suspected or Gross Cervical Involvement

For patients with suspected or gross cervical involvement (endometrioid histologies), cervical biopsy or MRI should be considered (see ENDO-2).[64,65] If negative, patients are assumed to have disease that is limited to the uterus and are treated as previously described (see ENDO-2). It may be difficult to distinguish primary cervical carcinoma from stage II endometrial carcinoma. Thus, for operable patients with cervical involvement, radical hysterectomy is recommended along with BSO, cytology (peritoneal lavage), and dissection of pelvic and para-aortic lymph nodes.[37] In these patients, radical hysterectomy may improve local control and survival when compared with total hysterectomy.[66,67] Alternatively, the patient may undergo RT (category 2B) followed by TH/BSO with para-aortic lymph node dissection. However, preoperative RT is a category 2B recommendation because the panel feels that upfront surgery is the preferred option for these patients. For medically inoperable patients, tumor-directed RT can provide long-term local control and cancer-specific survival rates (see UN-A).[60]

Suspected Extrauterine Disease

If extrauterine disease (endometrioid histologies) is suspected, imaging studies are recommended if clinically indicated (see ENDO-3). Patients with no extrauterine disease are treated using the guidelines for disease limited to the uterus. Intra-abdominal disease (i.e., ascites, omental, nodal, ovarian, or peritoneal involvement) warrants surgical intervention using TH/BSO with cytology (peritoneal lavage), pelvic and para-aortic lymph node dissection, and surgical debulking. The surgical goal is to have no measurable residual disease; several studies support debulking.[37,68-70] Patients with unresectable extrauterine pelvic disease (i.e., vaginal, bladder, bowel/rectal, or parametrial involvement) are typically treated with RT and brachytherapy with (or without) chemotherapy, followed by re-evaluation of tailored surgery.[71-73] For extra-abdominal disease (e.g., liver involvement), palliative TH/BSO with (or without) chemotherapy, RT, and/or hormonal therapy can be considered.

Adjuvant Therapy

Uterine-Confined Disease

Surgical Staging

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 (i.e., age, positive lymphovascular space invasion [LVSI], tumor size, and lower uterine [cervical/glandular] segment involvement). Recommended adjuvant treatment is shown in the algorithm (see ENDO-1). Note that the treatment algorithm was revised in 2010 based on the new FIGO/AJCC staging (7th edition).[31,33] However, by necessity, much of the discussion in this manuscript has been based on the older FIGO/AJCC staging system. Although adjuvant RT has been shown to decrease locoregional recurrence, it has not been shown to improve survival (see UN-A).

Based on a prospective evaluation of surgico-pathologic patterns of spread in endometrial cancer by the GOG and others, it is recognized that much of the adverse prognosis associated with intrauterine risk factors is mediated through nodal involvement.[29] For patients with greater than 50% myometrial invasion, nodal disease was found in 17% of grade 2 and in 28% of grade 3 tumors.[29,74] For patients with less than 50% myometrial invasion, the incidence of pelvic nodal metastases is 0% for grade 1 and 10% for grade 2 tumors.[74] However, patients with

grade 1-2 tumors, but without myometrial invasion, have minimal pelvic node metastases.[75] Given the wider acceptance of formal surgico-pathologic evaluation and the adoption of the 1988 and 2010 FIGO/AJCC staging classifications (see Table 1), clinical stage I and stage II patients with adverse intrauterine features who were once deemed at risk for nodal metastases are upstaged to stage III when extrauterine disease is documented. The implications of this "stage migration" should be taken into account when evaluating historical data.

Significant controversy centers on whether adjuvant therapy is necessary in patients with surgical stage I 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 (i.e., without extrauterine disease, isthmus/cervical involvement, or LVSI) was 92.7%.[76] The practice of surgical staging has led to a decrease in the use of adjuvant therapy for stage I endometrial carcinoma, which is reflected in the option of "observation" in the NCCN guidelines (see ENDO-4).[54,77-80]

Adjuvant RT

Several phase III trials have assessed adjuvant therapy in patients with uterine-confined disease. In summary, the use of adjuvant RT improves pelvic control in patients with selected risk factors (and in some patients, RT also improves progression-free survival), but RT did not improve overall survival in any of the trials. However, many of these trials had limitations because most of the patients were low risk (i.e., they had low-risk intrauterine pathologic risk factors). Thus, the trials were underpowered for patients with high-risk factors. It is recognized that in patients with uterine-confined disease, there is a spectrum of risk based on intrauterine pathologic findings. Adverse intrauterine pathologic risk factors include high-grade tumors, deep myometrial invasion (and consequently more advanced stage), LVSI, and papillary serous or clear cell histologies. More recently, studies have evaluated the role of chemotherapy in "highest risk" uterine-confined disease.[81]

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.[77] In surgical stage I and II endometrial cancer, other pathologic factors that may influence the decision regarding adjuvant therapy include patient age, tumor volume, and involvement of the lower uterine segment.

Four trials have evaluated the role of adjuvant pelvic RT in patients with endometrial carcinoma. In 2 of these trials, the patients were not formally staged (Postoperative Radiation Therapy in Endometrial Carcinoma [PORTEC-1], Aalders).[82,83] In the third trial (ASTEC/EN.5), only 50% of the patients were adequately staged as part of a companion surgical protocol.[45,84] However, formal surgical staging was mandated for all patients in the fourth trial (Gynecologic Oncology Group [GOG] 99).[85] Note that these trials used the older pre2010 staging system.

The PORTEC-1 trial suggested that RT provides a therapeutic benefit in selected patients with uterine-confined disease.[82,86] Although RT significantly decreased locoregional recurrence, it did not increase overall survival.[87] The Aalders' randomized trial found that RT reduced vaginal (i.e., locoregional) recurrences but did not reduce distant metastases or improve survival.[83] A recent pooled randomized trial (ASTEC/EN.5) suggested that adjuvant pelvic RT alone did not improve either relapse-free survival (i.e., progression-free survival) or overall survival in patients with intermediate-risk or high-risk early stage endometrial cancer, but there was a small improvement in pelvic

control.[84] However, the ASTEC/EN.5 study is very controversial; 51% of the patients in the ASTEC observation group received vaginal brachytherapy.[48,88] The Keys' trial (GOG 99) showed that adjuvant pelvic RT improved locoregional control and relapse-free interval (i.e., progression-free survival), without overall survival benefit.[85] 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.[85,89,90]

To further assess the relative benefits of whole pelvic RT versus vaginal brachytherapy alone in uterine-confined disease, PORTEC-2 randomly assigned patients to these 2 modalities. PORTEC-2 showed excellent and equivalent vaginal and pelvic control rates with both adjuvant radiation approaches, and no difference in overall survival.[91] Given that vaginal brachytherapy is associated with significantly less toxicity than pelvic RT, vaginal brachytherapy alone is a reasonable choice for most patients with uterine-confined endometrial cancer who are deemed candidates for adjuvant radiotherapy.[90-94] The relative applications of vaginal brachytherapy and/or whole pelvic RT should be carefully tailored to a patient's pathologic findings. It should be noted that both PORTEC-1 and PORTEC-2 specifically excluded patients with stage 1C, grade 3 endometrial carcinoma. Note that stage IC, grade 3 has been revised to stage IB, grade 3 in the new FIGO staging.[31,33]

The benefit of adjuvant external-beam RT in the highest risk spectrum of uterine-confined disease remains controversial. Most panel members feel that patients with deeply invasive grade 3 tumors should receive adjuvant treatment. However, given the lack of consistent absolute survival benefit, observation (category 2B) may be appropriate in select cases. Two large retrospective SEER analyses of women with endometrial cancer found that adjuvant RT improved overall survival in those with high-risk disease.[95,96] In a meta-analysis of randomized trials, a subset analysis found that adjuvant pelvic RT for stage I disease was associated with a trend towards a survival advantage in high-risk patients (e.g., pre2010 stage IC grade 3) but not in lower risk patients.[97,98]

Adjuvant Chemoradiation

Patients with historical stage IC, deeply invasive, grade 3, uterine-confined disease have a relatively poor prognosis (revised to stage IB, grade 3 with new 2010 staging). Despite adjuvant therapy with pelvic RT, a significant number of patients continue to have an appreciable risk of distant metastases.[85,86] Therefore, some clinicians suggested that adding chemotherapy to adjuvant RT may provide added therapeutic benefit (i.e., decrease distant metastases).[77,81] Progression-free survival is improved with adjuvant sequential chemoRT.[81] However, panel members feel that adjuvant chemotherapy is a category 2B recommendation in this setting because an overall survival advantage has not been shown yet.[81] The role of adjuvant chemotherapy in invasive high-grade, uterine-confined disease is being further studied (e.g., GOG 249, PORTEC-3).

The recommended adjuvant treatment options for completely surgically staged II patients are shown in the algorithm (see ENDO-5). The panel generally agrees on the role of adjuvant therapy for patients with invasive cervical disease. For patients with stage II disease who have had a radical hysterectomy with negative surgical margins, observation may also be an option.

Advanced Stage/Extrauterine Disease

There is a consensus that patients with documented extrauterine disease are at increased risk for recurrence and need adjuvant therapy; however, the optimal form of adjuvant therapy has yet to be

determined.[99,100] Patients with extrauterine disease confined to the lymph nodes or the adnexa may be treated with pelvic or extended-field RT alone.[101] However, chemotherapy is regarded as the foundation of adjuvant therapy for patients with extrauterine disease. For stage III tumors, the recommended options are shown in the algorithm (see ENDO-6).

Previously, whole abdominal RT was used for carefully selected patients deemed at risk for peritoneal failure, and RT appeared to have provided therapeutic benefit in retrospective studies.[102,103] A randomized phase III GOG (122) trial assessed optimal adjuvant therapy for patients with endometrial cancer who had extrauterine disease. In this trial, patients with stage III and intra-abdominal stage IV disease who had minimal residual disease were randomly assigned to whole abdominopelvic RT versus 7 cycles of combined doxorubicin (60 mg/m^2) and cisplatin (50 mg/m^2) treatment, with an additional cycle of cisplatin (AP). This GOG trial reported that AP chemotherapy improved progression-free survival and overall survival when compared with whole abdominopelvic RT; however, acute toxicity (e.g., peripheral neuropathy) was greater in the AP chemotherapy arm.[71]

The GOG 122 study established the role of adjuvant multiagent systemic chemotherapy for curative intent in patients with extrauterine disease. Thus, in the NCCN treatment algorithm, chemotherapy forms the established framework of adjuvant therapy for patients with stage III or IV disease. Whole abdominal RT as a single modality (as used in GOG 122) is considered inferior (and is no longer recommended) to chemotherapy. Multimodality therapy is now the basis of randomized trials evaluating therapy (e.g., GOG 258).

Recurrences were frequent in both treatment arms of GOG 122, occurring in the pelvis and abdomen. Approximately 52% of patients with advanced endometrial carcinoma had recurrences, indicating the need for further therapeutic improvement in this high-risk patient population.[71] A recent study found that sequential multimodality therapy (chemotherapy followed by RT and then further chemotherapy, which is termed “sandwich therapy”) improved survival when compared with other sequencing modalities (either chemotherapy followed by RT or vis versa).[73]

A follow-up study evaluated the role of chemotherapy ‘intensification’ for this patient population. The GOG 184 trial assessed combination chemotherapy (cisplatin and doxorubicin with or without paclitaxel) with more limited radiation fields (involved-field radiation either to the pelvis or to the pelvis plus para-aortic nodes). Results indicate that the 3-drug regimen did not improve survival when compared with the 2-drug regimen after 3 years of follow-up and that the more intensive chemotherapy resulted in greater toxicity (e.g., hematologic toxicity, sensory neuropathy, and myalgia).[72]

Radiotherapy Principles

RT has been a widely used modality in the treatment of patients with endometrial cancer; it clearly improves locoregional control. *Tumor-directed RT* refers to RT directed at sites of known or suspected tumor involvement and may include external-beam RT and/or brachytherapy. The “Principles of Radiotherapy” are described in detail in the algorithm, including target areas and doses for pelvic RT and brachytherapy (see UN-A).

Although adjuvant RT is typically not associated with high rates of severe morbidity,[104] recent studies have focused on subtle effects on quality of life (e.g., diarrhea, bowel symptoms) that deserve further investigation.[93] Patients treated with RT are prone to vaginal stenosis, which can impair sexual function. Women can use vaginal dilators to

prevent or treat vaginal stenosis. Dilator use can start 2-4 weeks after RT is completed and can be done indefinitely (http://www.ukons.org/storage/dilators_guidelines.pdf) and (http://www.mskcc.org/patient_education/_assets/downloads-english/571.pdf).

Surgical Staging

As previously mentioned, complete surgical staging—to gather full pathologic and prognostic data on which to base decisions regarding adjuvant treatment—is recommended by the NCCN panel for all patients who do not have medical or technical contraindications to lymph node dissection.

Minimally Invasive Procedures

Laparoscopic pelvic and para-aortic lymphadenectomy in association with total laparoscopic hysterectomy is being used in many practices.[105] However, patients having laparoscopy should be followed over a long term to compare their outcomes with those of traditional laparotomy.[106] A randomized phase III trial evaluated laparoscopy for comprehensive surgical staging; patients (n = 2616) with clinical stage I-IIA disease (GOG-LAP2) were assessed.[106,107] Patients were randomly allocated 2:1 to laparoscopy or laparotomy.

Results from LAP2 indicate that 26% of patients needed conversion to laparotomy because of poor visibility, metastatic cancer, bleeding, increased age, or increased body mass index. Detection of advanced cancer was not significantly different between the groups. However, there were significant differences in removal of pelvic and para-aortic nodes (8% not removed with laparoscopy versus 4% with laparotomy, $P < .0001$).[108,109] Significantly fewer postoperative adverse events and shorter hospitalization occurred with laparoscopy compared with laparotomy. Recurrence rates were 11.4% for laparoscopy versus 10.2% for laparotomy. The 5-year overall survival rate was 84.8% for both arms of LAP2.[107]

Another recent randomized trial (n = 283) comparing laparoscopy versus laparotomy reported shorter hospital stay, less pain, and faster resumption of daily activities with laparoscopy.[110] However, laparotomy may still be required for certain clinical situations (such as elderly patients, those with a very large uterus) or certain metastatic presentations.[106]

Robotic surgery is a new minimally invasive technology that has been advocated by some as being a feasible approach in the primary management of endometrial cancer.[105,111-115] Costs for equipment and maintenance remain high.[116] Given the recent introduction of robotic surgery, long-term outcomes are still pending.[117] However, due to its potential advantages over traditional laparoscopic approaches, it is rapidly becoming the preferred technique for minimally invasive surgery in endometrial cancer.

Incomplete Surgical Staging

For patients with incomplete surgical staging, radiologic imaging is often recommended, especially in patients with higher grade and more deeply invasive tumors.[64,65] Surgical restaging, including lymph node dissection, can also be done.[118] Based on the radiologic and/or surgical restaging results, recommended treatment options are provided in the algorithm (see ENDO-7).

Post-Treatment Surveillance

The recommended post-treatment surveillance protocol for endometrial cancer is shown in the algorithm (see ENDO-8). These recommendations recognize that the value of intensive surveillance has

not been demonstrated in this disease; therefore, ancillary testing is not recommended.[119]

Patients with clinical stage I and stage II endometrial cancer have a recurrence rate of approximately 15%;[119-121] 50%-70% of patients have symptomatic recurrences. For most patients, disease recurs within 3 years of initial treatment. Because most recurrences are symptomatic, all patients should receive verbal and written information regarding the symptoms of recurrent disease.[119] 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 (e.g., blood pressure determination, breast examination, mammography as clinically indicated, stool guaiac test, immunizations); other health problems that often coexist in patients with endometrial cancer can also be evaluated during follow-up. Given the lack of prospective studies regarding the optimal frequency of post-treatment follow-up, the NCCN panel believes that the algorithm represents a reasonable surveillance scheme. However, the use of vaginal cytology in asymptomatic patients is controversial, which is reflected by the category 2B recommendation.[119,121,122]

Hormone Replacement Therapy for Hypoestrogenism

After bilateral salpingo-oophorectomy, hypoestrogenism is associated with hot flashes, mood lability, vaginal dryness, pelvic soft tissue atrophy, osteoporosis, and an increased risk of cardiovascular disease. In postmenopausal women, estrogen replacement therapy was believed to reduce or reverse some of these signs and symptoms. However, women who have had bilateral salpingo-oophorectomy for endometrial adenocarcinoma have usually been denied estrogen replacement therapy for fear of inducing a higher relapse rate, because this cancer has historically been considered an estrogen-linked malignancy.[123,124] 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.[125-127] In women with stage I-II endometrial cancer who had hysterectomy, a randomized trial of estrogen replacement therapy versus placebo did not find an increased rate of recurrence or new malignancy; the median follow-up was 35.7 months.[128] However, estrogen replacement trials in postmenopausal females without a history of malignancy have demonstrated a significantly increased risk of breast cancer.[129]

Initially, the Women's Health Initiative (WHI) Estrogen-Alone Trial in women who had hysterectomy (n = 10,739) reported that the risk of breast cancer and cardiovascular disease (e.g., stroke) were increased and that estrogen replacement therapy was of concern; thus, the trial was stopped.[130] However, recent long-term follow-up data from this trial suggest that the risk from estrogen replacement therapy may not be as high in younger women (< 60 years) who have had hysterectomy.[131]

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.[132,133] If adjuvant treatment is carried out, there

should be a 6- to 12-month waiting period before initiation of hormone replacement therapy, and participation in clinical trials is strongly encouraged. Selective estrogen-receptor modulators (SERMs) may prove to be attractive options for hormone replacement therapy.[134,135] Long-term comparisons between conjugated estrogens and SERMs for hormone replacement therapy are needed. Non-hormonal therapy may be considered in patients who are deemed poor candidates for hormone replacement therapy (e.g., smokers, history of breast cancer, and history of multiple strokes).[136,137]

Treatment of Recurrent or Metastatic Disease

Patients with local or regional recurrences can be evaluated for further treatment (see ENDO-8). For recurrences confined to the vagina or the pelvis alone, second-line treatment (typically with RT and/or surgery or chemotherapy [or hormonal therapy]) can be effective. Isolated vaginal recurrences treated with RT have good local control and 5-year survival rates of 50%-70%,[138-140] although prognosis is worse if there is extravaginal extension or pelvic lymph node involvement.[139]

After RT, it is unusual for patients to have recurrences confined to the pelvis. 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) surgery with (or without) intraoperative radiotherapy (IORT), 2) hormonal therapy, or 3) chemotherapy. Radical surgery (i.e., pelvic exenteration) has been performed with reported 5-year survival rates approximating 20%.[141,142] However, these patients may not require pelvic exenteration; a more limited partial vaginectomy (with or without IORT) may be adequate.[143,144]

Treatment for para-aortic or common iliac lymph node invasion and for upper abdominal or peritoneal recurrences is shown in the algorithm (see ENDO-9). However, for gross upper abdominal residual disease, more aggressive treatment for relapse is recommended, as outlined for disseminated metastases (see ENDO-8). For resectable isolated metastases, consider surgical resection with or without RT. Further recurrences or unresectable isolated metastases are treated as disseminated metastases. Palliative care measures should also be considered in management of patients with systemic disease (see the NCCN Palliative Care Guidelines) (http://emedicine.medscape.com/article/270646-overview).

Hormonal Therapy for Recurrent or Metastatic Disease

The role of hormonal therapy in recurrent or metastatic cancer has been primarily evaluated in patients with endometrioid histologies only (i.e., not for papillary serous carcinoma, clear cell carcinoma, or carcinosarcoma). Hormonal therapy is also used for select patients with ESS (see section on “Uterine Sarcomas” in this Discussion). Progestational agents are mainly used for metastatic disease; however, 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 a small subset of estrogen and progesterone receptor–positive patients.[145-148] Tamoxifen has a 20% response rate in those who do not respond to standard progesterone therapy.[149,150] Tamoxifen has also been combined with progestational agents; however, a few patients had grade 4 thromboembolic events with this combination regimen.[151-153] In some patients, aromatase inhibitors (e.g., anastrozole, letrozole) may be substituted for progestational agents or tamoxifen.[147,148,154,155] Other

hormonal modalities have not been well studied, and adjuvant therapy with hormonal agents has not been compared with cytotoxic agents.[147,156]

If disease progression is observed after hormonal therapy, cytotoxic chemotherapy can be considered. However, clinical trials or best supportive care (see the NCCN Palliative Care Guidelines) are appropriate for patients with disseminated metastatic recurrence who have a poor response to hormonal therapy and chemotherapy.

Chemotherapy for Metastatic, Recurrent, or High-Risk Disease

Chemotherapy for endometrial cancer has been extensively studied.[157,158] Based on the current data, multiagent chemotherapy regimens are preferred for metastatic, recurrent, or high-risk disease, if tolerated. Single-agent therapy can also be used (see ENDO-B).

A phase III randomized trial (GOG 177) compared 2 combination chemotherapy regimens in women with advanced/metastatic or recurrent endometrial carcinoma. The 273 women were randomly assigned to either 1) cisplatin, doxorubicin, and paclitaxel, or 2) cisplatin and doxorubicin. The 3-drug regimen was associated with improved survival (15 versus 12 months, $P < .04$) but with significantly increased toxicity (i.e., peripheral neuropathy).[159] Based on this study, both regimens are category 1 in the NCCN guidelines (see ENDO-B). 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.[157,158]

Carboplatin and paclitaxel is an increasingly used regimen for advanced/metastatic or recurrent endometrial cancer based on ovarian cancer studies; the response rate is about 40%-62%, and overall survival is about 13-29 months.[160-162] Weekly low-dose paclitaxel and carboplatin also seems useful.[163] 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]). Carboplatin/paclitaxel is being used because it is less toxic than cisplatin regimens. For patients in whom paclitaxel is contraindicated, docetaxel can be considered in combination with carboplatin.[164]

If multiagent chemotherapy regimens are contraindicated, then single-agent therapy options include cisplatin, carboplatin, paclitaxel, doxorubicin, liposomal doxorubicin, and docetaxel (category 2B for docetaxel) (see ENDO-B).[147] When single agents are used as first-line treatment, responses range from 21% to 36%.[148,165] When single agents are used as second-line treatment, responses range from 4% to 27%; paclitaxel is the most active in this setting.[165] Some oncologists have used liposomal doxorubicin, because it is less toxic than doxorubicin; the response rate of liposomal doxorubicin is 9.5%.[166] Docetaxel is recommended (category 2B) for use as a single agent; however, it is a category 2B recommendation because some panel members would not use docetaxel as it is less active (7.7% response rate) than other agents.[63,167]

New biologic and molecular therapies for the treatment of recurrent or metastatic endometrial carcinoma are being assessed in clinical trials.[63] Recently, bevacizumab was shown to have a 13.5% response rate and overall survival rate of 10.5 months in a phase II trial for persistent or recurrent endometrial cancer.[168] The panel recommends bevacizumab (category 2B) as single-agent therapy for patients who have progressed on previous cytotoxic chemotherapy. However, it is a category 2B recommendation because some panel members would not use bevacizumab as it is less active and more toxic than other agents.[168]

Drug Reactions

Virtually all drugs have the potential to cause adverse hypersensitivity reactions, either during or after the infusion.[169] In gynecologic oncology treatment, drugs that more commonly cause adverse reactions include carboplatin, cisplatin, docetaxel, liposomal doxorubicin, and paclitaxel. Most of these drug reactions are mild infusion reactions (i.e., skin reactions, cardiovascular reactions, respiratory or throat tightness), but more severe allergic reactions (i.e., life-threatening anaphylaxis) can occur.[170-172] In addition, patients can have mild allergic reactions or severe infusion reactions. Infusion reactions are more common with paclitaxel.[173] Allergic reactions (i.e., true drug allergies) are more common with platinum agents (i.e., carboplatin, cisplatin).[173,174]

Management of drug reactions is discussed in the NCCN Ovarian Cancer guideline.[173] It is important to note that patients who have had severe life-threatening reactions should not receive the implicated agent again unless under the care of an allergist or expert in managing drug reactions. If a mild allergic reaction has previously occurred and it is appropriate to administer the drug again, a desensitization regimen should be used even if the symptoms have resolved; various desensitization regimens have been published and should be followed.[175-177] Patients must be desensitized with each infusion if they previously had a reaction. Almost all patients can be desensitized (about 90%).[169] To maximize safety; it is prudent to desensitize patients in the intensive care unit.[169]

Uterine Papillary Serous Carcinomas, Clear Cell Carcinomas, and Carcinosarcomas

Overview

Uterine papillary serous carcinomas (i.e., serous adenocarcinomas), clear cell carcinomas (i.e., clear cell adenocarcinomas), and carcinosarcomas are considered more aggressive histologic variants of epithelial carcinoma, with a higher incidence of extrauterine disease at presentation.[178-185] Even patients with apparent early stage disease may have distant metastases. Patients may present with pelvic masses, abnormal cervical cytology, or ascites in addition to postmenopausal bleeding. Both the NCCN panel and the SGO recommend that CA 125 and MRI/CT may be useful before surgery to assess if extrauterine disease is present.[178]

Papillary serous carcinomas, clear cell carcinomas, and carcinosarcomas are all considered high-risk tumors (i.e., grade 3), although they are staged using the same FIGO/AJCC staging system (i.e., 7th edition) as endometrial cancers (see Table 1).[31] Patterns of failure often mimic those of ovarian cancer.

Multimodality therapy is recommended for these tumors. Primary treatment includes TH/BSO with dissection of pelvic and para-aortic lymph nodes, peritoneal lavage for cytology, and maximal tumor debulking.[186] Comprehensive 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 along with appropriate biopsies (see the NCCN Ovarian Cancer algorithm).

Adjuvant therapy is highly individualized.[187-194] For patients with stage IA without myometrial invasion, options include 1) observation; 2) chemotherapy; or 3) tumor-directed RT.[195] For all other patients with more advanced disease, chemotherapy with (or without) tumor-directed RT is the preferred option.[180,188,192,196] Adjuvant platinum/taxane-based therapy appears to improve survival in patients with uterine papillary serous carcinoma and clear cell carcinoma, whereas ifosfamide/paclitaxel is recommended for carcinosarcomas.[178-180,197,198]

Whole abdominopelvic RT (category 3) with (or without) vaginal brachytherapy has had reported efficacy in highly selected patients.[71,193,199]

There was major disagreement among panel members about whether whole abdominal RT is appropriate, which is reflected in the category 3 recommendation.[71,196] Chemotherapy with (or without RT) appears to be more effective than RT alone.[188] Data are conflicting regarding the rate of abdominal recurrence in these patients.[196,200-204] For the purposes of these guidelines, whole abdominal radiotherapy is not considered to be tumor-directed RT (see UN-A). 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.

Carcinosarcomas (MMMTs)

Carcinosarcomas are aggressive tumors that are staged as high-grade endometrial cancer (see Table 1). Pathologists now believe that carcinosarcomas (also known as MMMTs) are metaplastic carcinomas and not uterine sarcomas; therefore, the NCCN panel recently moved carcinosarcomas to the epithelial carcinoma guideline.[182,185,205]

Ifosfamide was historically considered the most active single agent for carcinosarcoma.[198,206] A phrase III trial for advanced carcinosarcoma showed that the combination of ifosfamide and paclitaxel increased survival and was less toxic than the previously used cisplatin/ifosfamide regimen.[198,207] Overall survival was 13.5 months with ifosfamide/paclitaxel versus 8.4 months with ifosfamide alone. Therefore, ifosfamide/paclitaxel is category 1 in the NCCN guidelines (see ENDO-B).[198] A recent phase II trial suggests that paclitaxel/carboplatin is also a useful regimen for carcinosarcoma (response rate, 54%).[208]

Data regarding carcinosarcoma suggest that adjuvant pelvic radiotherapy decreases the rate of local recurrences when compared with surgery alone.[209-214] This local control improvement in some series correlates with an improvement in survival, although other data show that lymphadenectomy confers greater benefit.[213-216] A phase III randomized trial (GOG 150) in patients with carcinosarcoma of the uterus assessed whole abdominal RT versus cisplatin/ifosfamide, but there was no difference in survival between the groups.[204]

Uterine Sarcomas

Overview

Uterine sarcomas are uncommon tumors (about 3% of all uterine neoplasms). They are stromal/mesenchymal tumors that are generally categorized into leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), and undifferentiated [endometrial] sarcoma (see UTSARC-B). Most uterine sarcomas are LMS; ESS and undifferentiated sarcomas are rare. Pathological definitions of the various histologies have been revised. ESS were previously termed low-grade sarcomas, and undifferentiated sarcomas were previously termed high-grade undifferentiated sarcomas (HGUD).[2]

Evaluation and Primary Therapy

The diagnosis of ESS and LMS is often made after surgery. The previous FIGO/AJCC staging systems for endometrial cancer were not appropriate for staging ESS and LMS; patients were often upstaged when using the older AJCC staging system.[217] A new staging system for ESS and LMS from FIGO/AJCC took effect in 2010 (see Table

2).[31,218] This new staging accounts for the fact that uterine sarcomas are different from endometrial cancers.

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) is the initial treatment of choice for uterine sarcomas (see UTSARC-1). Additional surgical resection should be individualized based on clinical scenarios and intraoperative findings. Lymphadenectomy is controversial.[2] Uterine sarcomas tend to show hematogenous metastases to the lungs; lymph node metastases are uncommon. For medically inoperable sarcomas, options include 1) RT and chemotherapy; 2) chemotherapy alone; or 3) hormone therapy (but only for ESS).

Leiomyosarcoma and Undifferentiated Sarcoma

The role of adjuvant radiotherapy in nonmetastatic disease is controversial. Most available data are retrospective, except for a phase III randomized trial.[209] Most retrospective studies of adjuvant RT 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.[219-222] In many series, the patients treated with adjuvant radiation presumably had higher risk factors (e.g., larger tumors, deeper myometrial invasion), thus, biasing the data against radiotherapy. However, a phase III randomized trial in stage I and II uterine sarcomas reported that postoperative pelvic radiotherapy did not improve overall survival for LMS when compared with observation.[209] Therefore, most NCCN panel members feel that postoperative RT is not routinely recommended for stage I patients with leiomyosarcoma, which is reflected in the category 3 recommendation. If used, adjuvant RT needs to be individualized and based on careful analysis of surgical pathologic findings.

The role of adjuvant chemotherapy is also poorly defined; however, adjuvant chemotherapy has been utilized because of the high risk of systemic relapse. Given the uncertainties regarding any adjuvant treatment for stage I LMS and undifferentiated [endometrial] sarcoma, options following complete resection include 1) observation; 2) chemotherapy (category 2B); or 3) RT (category 3). Because of the increased risk profile in patients with completely resected stage II and III LMS and undifferentiated [endometrial] sarcoma, the panel believes that it is appropriate to consider adjuvant therapy (see UTSARC-3). In patients with incompletely resected or metastatic disease, chemotherapy with (or without) RT is generally recommended.

Doxorubicin is an active single agent for LMS and is less toxic than combination regimens.[223,224] Combination regimens—such as, gemcitabine and docetaxel—have also been used.[225-227] Single-agent options (category 2B for all) can also be considered for advanced or metastatic disease including dacarbazine, docetaxel, liposomal doxorubicin, epirubicin, gemcitabine, ifosfamide, paclitaxel, and temozolomide.[228-236] Recent data indicate that trabectedin may be useful in patients who have exhausted standard chemotherapy; overall survival was 13.9 months.[237-239] Enrollment in clinical trials is strongly recommended.

Because the recurrence rate is high in leiomyosarcomas (50%-70%),[2] RT is recommended for local recurrence. Chemotherapy with (or without) palliative RT is recommended for metastatic disease; surgery may be appropriate for select patients (see UTSARC-5).[232]

Endometrial Stromal Sarcoma

Observation is recommended for postoperative stage I ESS (see UTSARC-2). Postoperative hormone therapy (with or without RT) is recommended for stages II-IV ESS; it is also an option for stage I

(category 2B for stage I only). Typical hormone therapy includes megestrol acetate or medroxyprogesterone; other options (category 2B) include tamoxifen, gonadotropin-releasing hormone [GnRH] analogs, or aromatase inhibitors.[223,240] Hormone therapy is also recommended for ESS that have recurred or are unresectable (see UTSARC-5).[240]

Series of ESS suggest long disease-free intervals in the absence of specific therapy and offer less support for the use of adjuvant RT.[241] Adjuvant radiotherapy in ESS has been demonstrated to reduce local recurrence rates but again with limited effect on survival.[242,243] Because of concerns about radiation exposure, frequent routine asymptomatic surveillance imaging is no longer recommended for young women after primary therapy for ESS.[244]

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