NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Uterine Neoplasms

Version 2.2016

NCCN.org

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NCCN Guidelines Version 2.2016 Panel Members
Uterine Neoplasms

*Wui-Jin Koh, MD/Co-Chair §
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

*Benjamin E. Greer, MD/Co-Chair Ω
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

Nadeem R. Abu-Rustum, MD Ω
Memorial Sloan-Kettering Cancer Center

Sachin M. Apte, MD, MS Ω
Moffitt Cancer Center

Susana M. Campos, MD, MPH, MS †
Dana-Farber/Brigham and Women's Cancer Center

*Kathleen R. Cho, MD ≠
University of Michigan Comprehensive Cancer Center

Christina Chu, MD Ω
Fox Chase Cancer Center

David Cohn, MD Ω
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Marta Ann Crispens, MD Ω
Vanderbilt-Ingram Cancer Center

NCCN
Fay Ferkle, PharmD
Nicole McMillian, MS
Jillian Scavone, PhD

Don S. Dizon, MD †
Massachusetts General Hospital Cancer Center

Oliver Dorigo, MD, PhD Ω
Stanford Cancer Institute

Patricia J. Eifel, MD §
The University of Texas MD Anderson Cancer Center

Christine M. Fisher, MD, MPH §
University of Colorado Cancer Center

Peter Frederick, MD Ω
Roswell Park Cancer Institute

David K. Gaffney, MD, PhD §
Huntsman Cancer Institute at the University of Utah

Suzanne George, MD/Liaison †
Dana-Farber/Brigham and Women's Cancer Center

Ernest Han, MD, PhD Ω
City of Hope Comprehensive Cancer Center

Susan Higgins, MD
Yale Cancer Center/Smilow Cancer Hospital

Warner K. Huh, MD Ω
University of Alabama at Birmingham Comprehensive Cancer Center

John R. Lurain, III, MD Ω
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Andrea Mariani, MD Ω
Mayo Clinic Cancer Center

David Mutch, MD Ω
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Amanda Nickles Fader, MD Ω
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Steven W. Remmenga, MD Ω
Fred & Pamela Buffet Cancer Center at The Nebraska Medical Center

R. Kevin Reynolds, MD Ω
University of Michigan Comprehensive Cancer Center

Todd Tillmanns, MD Ω
St. Jude Children's Research Hospital/ University of Tennessee Health Science Center

Fidel A. Valea, MD Ω
Duke Cancer Institute

Catheryn M. Yashar, MD §
UC San Diego Moores Cancer Center

Ω Gynecologic oncology
† Medical oncology
‡ Hematology
§ Radiation oncology
≠ Pathology
* Writing committee member

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NCCN Guidelines Panel Disclosures

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Clinical Trials: 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 2.2016 Updates Uterine Neoplasms

Updates in Version 2.2016 of the NCCN Guidelines for Uterine Neoplasms from Version 1.2016 include:

- **The Discussion section has been updated to reflect the changes in the endometrial carcinoma and uterine sarcoma algorithms. (MS-1)**

Endometrial Carcinoma:

ENDO-2

- **New footnote "h" added: "*MRI performed with contrast unless contraindicated*."**

ENDO-3

- **New footnote "k" added: "*CT and MRI performed with contrast throughout the guidelines unless contraindicated. Contrast not required for screening chest CT*."**

Uterine Sarcoma

UTSARC-1

- **New footnote "b" added: "*CT and MRI performed with contrast throughout the guidelines unless contraindicated. Contrast not required for screening chest CT*."**

UTSARC-A Systemic Therapy for Uterine Sarcoma

- **Trabectedin added as a single-agent option with corresponding footnote "3" that states, "*For uLMS that has been treated with a prior anthracycline-containing regimen*."**

Updates in Version 1.2016 of the NCCN Guidelines for Uterine Neoplasms from Version 2.2015 include:

Global changes

- **"Serous adenocarcinoma" changed to "Serous *carcinoma*".**
- **"Clear cell adenocarcinoma changed to "Clear cell *carcinoma*".**
- **"Stromal mesenchymal tumors" changed to "*Malignant* mesenchymal *(sarcoma)*".**
- **"Endometrial stromal sarcoma (ESS)" was divided into "*Low-grade endometrial stromal sarcoma*" and "*High-grade endometrial stromal sarcoma*".**
- **"High-grade (undifferentiated) endometrial sarcoma" changed to "*Undifferentiated uterine sarcoma (UUS)*".**

Uterine Neoplasms

UN-1

- **Footnote "a" revised: "~~Endometrial biopsy is typically not useful in diagnosing malignancies of the uterine wall such as stromal/mesenchymal tumors~~. *Preoperative imaging and biopsy may help to identify uterine sarcomas although biopsy sensitivity is less than for endometrial cancer. If there is suspicion of malignant mesenchymal sarcoma, fragmentation should be avoided.*"**

Footnote "b" revised: "... An infrastructure needs to be in place to handle the screening results. IHC and/or MSI screening is usually performed on epithelial tumors ~~and not stromal/mesenchymal endometrial tumors~~."

- **The following footnote was removed: "By definition, ESS has low-grade cytologic features. High-grade subtypes of endometrial sarcomas (undifferentiated endometrial sarcomas in WHO classification) are still being defined."**

Continued

Endometrial Carcinoma:

ENDO-1

- **Second column pathway decision points revised "*Medically* operable" and "~~Medically inoperable~~ *Not suitable for primary surgery*". (Also for ENDO-2)**

ENDO-2

- **"Medically operable" pathway; Primary Treatment: Recommendation revised, "RT: 75–80 Gy to point A/*paracervical dose* (category 2B)".**
- **"Not suitable for primary surgery" pathway; Primary Treatment:**
  - **Recommendation revised "Tumor-directed RT ± *chemotherapy*". The subsequent recommendation was also revised, "~~Re-evaluate for~~ Surgical resection, *if rendered operable*."**
  - **For patients with suspected or gross cervical involvement, a new neoadjuvant "*Chemotherapy (category 2B)*" pathway was added, followed by re-evaluation for local therapy.**

ENDO-3

- **Intra-abdominal; Primary Treatment:**
  - **Revised: "TH/BSO ~~and~~ + surgical staging*/debulking* ~~+ surgical debulking~~ (may consider preoperative chemotherapy)."**
- **Initially unresectable extrauterine pelvic disease; Primary Treatment:**
  - **Revised: "RT + brachytherapy ± chemotherapy ~~± surgery~~"**
  - **"*Chemotherapy*" was added as an option, followed by "*Re-evaluate for surgical resection and/or RT based on response*".**
- **Extra-abdominal/liver; Primary Treatment:**
  - **"Consider palliative TH/BSO ± chemotherapy ± RT ± hormone therapy" changed to "*Chemotherapy and/or RT and/or Hormone therapy*".**
  - **"*May consider palliative TH/BSO"* was listed as a separate option."**

ENDO-4

- **In the table, "Pelvic RT" changed to "*External beam radiation therapy (EBRT)*". (Also for ENDO-5)**
- **Footnote "k" revised: "~~Potential adverse risk factors include the following: age, positive lymphovascular invasion, tumor size, and lower uterine segment or surface cervical glandular involvement.~~ *See Discussion for information on adverse risk factors.*"**
- **Footnote "n": New sentenced added, "*Hormonal therapy is not used for high-grade disease.*"**

ENDO-5

- **Surgically staged: Stage II, Histologic Grade 2; Adjuvant Treatment: "Pelvic RT + vaginal brachytherapy" removed as an option and "*Vaginal brachytherapy and/or EBRT*" was added.**
- **Stage II, Histologic Grade 3; Adjuvant Treatment:"Pelvic RT + vaginal brachytherapy ± chemotherapy..." changed to "*EBRT* ± vaginal brachytherapy ± chemotherapy".**

ENDO-7

- **Second column pathway decision points revised: "Intrauterine Stage IA, G1-2 (~~with no~~ < *50%* myometrial invasion, *no lymphovascular space invasion (LVSI), and <2 cm tumor*)" and "Intrauterine Stage IA, G1-2 (myometrial invasion > 50% *LVSI, or ≥2cm*); Stage IA G3, Stage IB, Stage II."**

Continued

Endometrial Carcinoma--continued

ENDO-9

- **Surveillance: Fifth bullet regarding patient education revised to include smoking cessation and a link to the NCCN Guidelines for Smoking Cessation.**
- **Footnote "s" revised to include new histologic classification language of "*malignant mesenchymal (sarcoma)*."**

ENDO-10

- **Therapy for Relapse: Recommendation revised, "Surgical exploration ~~of pelvis~~ + resection ...".**
- **Additional Therapy for Extravaginal disease; Para-aortic or common iliac lymph node: Recommendation revised, "Tumor-directed RT ~~± brachytherapy~~ ± chemotherapy".**
- **Footnote "t" is new: "*May include patients with isolated common iliac or para-aortic lymph node recurrence.*"**
- **Footnote "u" is new: "*Consider preoperative EBRT in select patients.*"**
- **Footnote "v" is new: "*Post-resection consolidation RT can be considered in patients who were not previously radiated or who are deemed to have additional tolerance for radiation.*"**

ENDO-11

- **After Primary Treatment: "Stage IA" treatment decisions are no longer divided by myometrial invasion. Previously, "Stage IA (with myometrial invasion)" received "Chemotherapy ± tumor-directed RT".**

ENDO-A

- **Footnote "3" revised to include new histologic classification language of "*malignant mesenchymal (sarcoma)*."**

ENDO-C--Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease

- **Footnote "1" revised: "Hormonal therapy *may be used for lower grade* endometrioid histologies only (ie, not for *G3 endometrioid,* serous ~~adeno~~carcinoma, clear cell ~~adeno~~carcinoma, or carcinosarcoma) *preferably in patients with small tumor volume or an indolent growth pace*."**

Continued

Uterine Sarcoma

UTSARC-1

- Top pathway; "Diagnosed after TH or supracervical hysterectomy ± BSO" pathway: Recommendation revised, "Consider reresection especially if *low-grade* ESS".
- Bottom pathway; Third column pathway decision point revised "~~Medically inoperable~~ *Not suitable for primary surgery*".
- "Primary Treatment" for patients not suitable for primary surgery: Recommendation revised, "Pelvic RT ± brachytherapy and/or ~~Chemotherapy or Hormone~~ *Systemic* therapy".
- Footnote "a" revised: "~~Endometrial biopsy is typically not useful in diagnosing malignancies of the uterine wall such as stromal/mesenchymal tumors~~. *Preoperative imaging and biopsy may help to identify uterine sarcomas although biopsy sensitivity is less than for endometrial cancer. If there is suspicion of malignant mesenchymal sarcoma, fragmentation should be avoided.*"
- Footnote removed: "By definition, ESS has low-grade cytologic features. High-grade subtypes of endometrial sarcomas (undifferentiated endometrial sarcomas in WHO classification) are still being defined."

UTSARC-2

- Under "Pathologic Findings/Histologic Grade": "ESS" clarified as "*Low-grade* ESS"

UTSARC-3

- "*High grade ESS*" was added to the list of Pathologic Findings/Histologic Grades and is treated the same as UUS and uLMs.

UTSARC-4

- Surveillance
  - Second bullet revised: "~~Consider~~ CT imaging chest/abdomen/pelvis) every 3–6 mo for 2–3 y, then every 6 mo for next 2 y, then annually *for high-grade sarcomas*."
  - Fourth bullet revised to include smoking cessation and a link to the NCCN Guidelines for Smoking Cessation.
- Recurrence; Local recurrence:
  - First bullet revised: " Vagina/*pelvis*"
  - Second bullet revised: "~~Negative~~ Chest and abdominal/pelvic CT *negative for metastatic disease*~~, confirming local vaginal recurrence~~."
- Isolated metastases, Therapy for Relapse:
  - Resectable pathway: Recommendation revised "Consider postoperative *systemic therapy* ~~chemotherapyor hormone therapy (hormone therapy for ESS only)~~
  - Unresectable pathway: Recommendations revised, "*Systemic therapy and/or Local therapy (tumor directed RT or local ablative therapy).*"
- Disseminated disease; Therapy for Relapse: This pathway and its treatment recommendations were revised.

UTSARC-5

- First column under "Recurrence" revised to "*Radiologically isolated vaginal/pelvic recurrence*".
- Therapy for Relapse:
  - No prior RT:
    - Recommendation revised, "Tumor-directed RT ± *systemic therapy* ~~chemotherapy or hormone therapy~~ ~~(hormone therapy for ESS only)~~."
    - Extrapelvic disease pathway revised, "*Systemic therapy* ~~Chemotherapy or Hormone therapy (ESS only)~~."
  - Prior RT: Recommendations revised, "Surgical exploration + resection ± IORT ± ~~chemotherapy~~ *systemic therapy* (category 3 for IORT) or ~~Chemotherapy or Hormone therapy (ESS only)~~ *Systemic therapy*..."

Continued

UTSARC-A Systemic Therapy for Uterine Sarcoma

- **Eribulin was added as a single agent option.**
- **Hormone Therapy: Title revised, "Hormone Therapy ~~(ESS only)~~ *(For Low-grade ESS or Hormone Receptor Positive (ER/PR) uLMS).*"**
  - **The categories of evidence and consensus for the following hormone therapies were revised:**
    - ◊ **Medroxyprogesterone acetate *(category 2B for ER/PR positive uLMS)***
    - ◊ **Megestrol acetate *(category 2B for ER/PR positive uLMS)***
    - ◊ **GnRH analogs (category 2B *for low-grade ESS and ER/PR positive uLMS*)**
- **Footnote "1" revised: ~~Liposomal doxorubicin and docetaxel may cause drug reactions~~ See NCCN Guidelines for Ovarian Cancer--Management of Drug Reactions [OV-C].**
- **Footnote removed: "Aromatase inhibitors for uLMS that are ER/PR positive."**
- **Footnote "2" is new: "*These hormonal therapies may be considered for patients with uLMS that is ER/PR positive, preferably with small tumor volume or an indolent growth pace.*"**

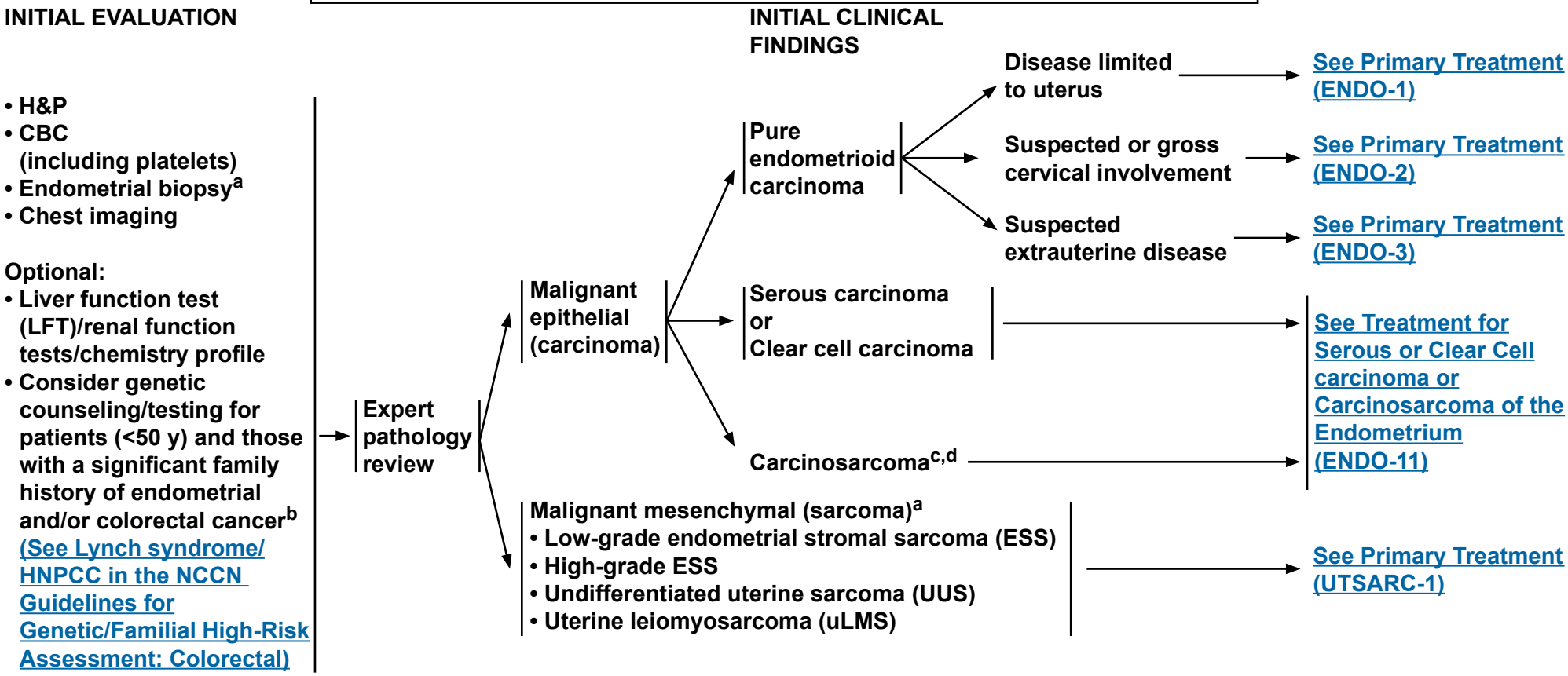
UTSARC-B--Uterine Sarcoma Classification

- **The following uterine sarcoma classifications were revised:**
  - ***Low-grade* endometrial stromal sarcoma (ESS)**
  - ***High-grade ESS***
  - ***~~High-grade (undifferentiated) endometrial sarcoma~~ Undifferentiated uterine sarcoma (UUS)***
- **A section listing "*Other Rare Uterine Mesenchymal Sarcoma Subtypes*" was added.**
- **The following footnotes were added:**
  - ***Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO Classification of Tumours of the Female Reproductive Organs, Volume 6, 2014***
  - ***Endometrial stromal sarcomas (LGESS) are characterized by small cells with low-grade cytology and features resembling stromal cells in proliferative endometrium. Mitotic activity is usually low (<5 MF per 10 HPF).***
  - ***High-grade endometrial stromal sarcomas (HGESS) are characterized by small cells with high-grade cytology, frequent necrosis, and brisk mitotic activity (>10 MF per 10 HPF). HGESS can contain areas of conventional LGESS.***
  - ***Undifferentiated uterine sarcomas (UUS) are characterized by cells with high-grade cytologic features lacking any resemblance to the stromal cells in proliferative endometrium or any other specific type of differentiation.***
- **The following footnotes were removed:**
  - **Endometrial stromal sarcomas displaying morphologic features of proliferative phase endometrial stroma and showing any mitotic index. By definition, ESS is low-grade histology.**
  - **High-grade sarcomas showing pleomorphism or anaplasia greater than that seen in proliferative phase endometrial stroma or completely lacking recognizable stromal differentiation; mitotic index is almost always >10 mf/10 hpf.**

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

- **Third bullet; First sub-bullet revised: "The target for vaginal brachytherapy after hysterectomy should be limited to the upper *two-thirds of the* vagina.**
- **New bullet added: "*Palliative RT should be individualized to disease extent and patient performance status. Various dose/fractionation schemes can be considered. A common approach is 30 Gy in 10 fractions.*"**

All staging in guideline is based on updated 2010 FIGO staging. (See ST-1 and ST-2)



[a]Preoperative imaging and biopsy may help to identify uterine sarcomas although biopsy sensitivity is less than for endometrial cancer. If there is suspicion of malignant mesenchymal sarcoma, fragmentation should be avoided.
[b]Recently, immunohistochemistry (IHC) and/or microsatellite instability (MSI) screening of all colorectal and endometrial cancers, regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for Lynch syndrome (LS). An infrastructure needs to be in place to handle the screening results. IHC and/or MSI screening is usually performed on epithelial tumors.
[c]Staged as aggressive; should be treated as a high-grade endometrial cancer.
[d]Also known as malignant mixed mesodermal tumor or malignant mixed Müllerian tumor and including those with either homologous or heterologous stromal elements.

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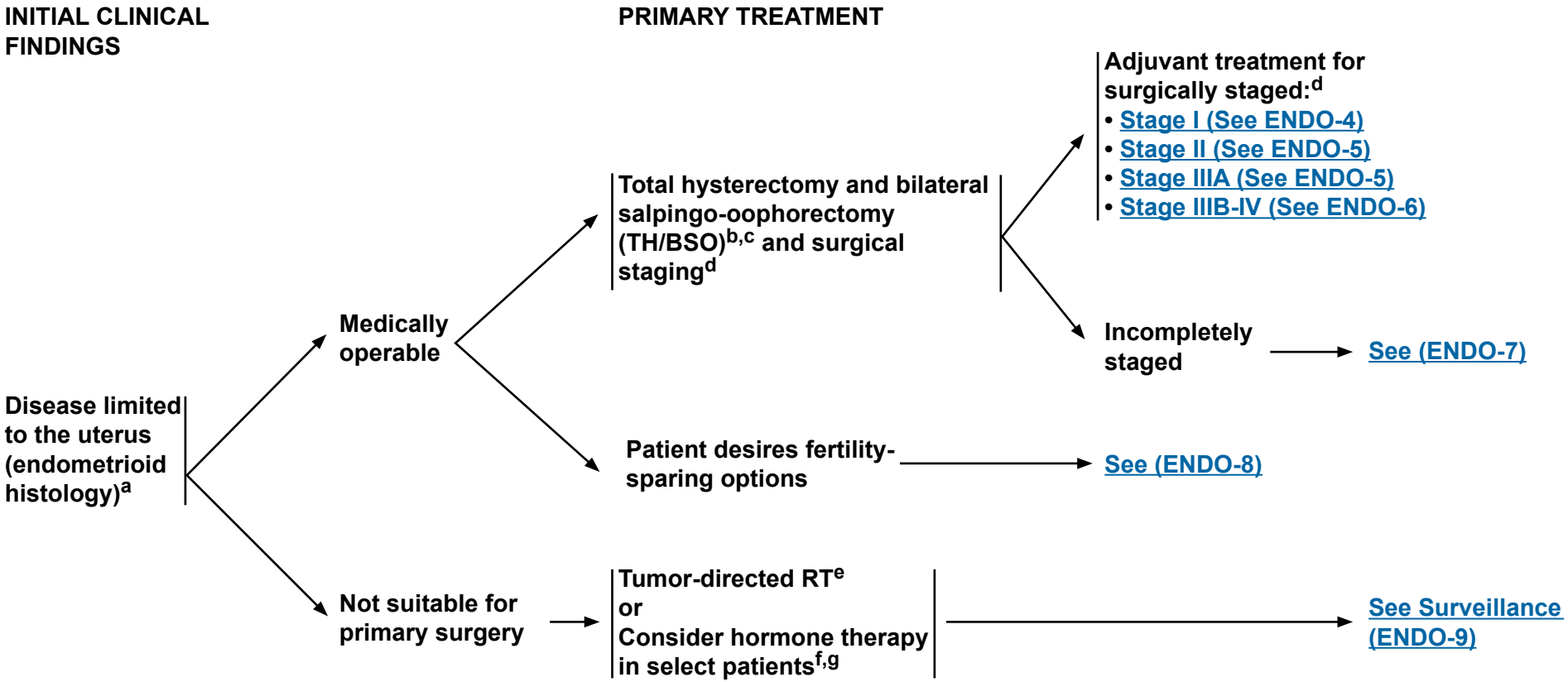

[a]See (UN-1) for clarification of uterine neoplasms.
[b]See Hysterectomy and Pathologic Evaluation (ENDO-A).
[c]Endometrial carcinoma should be removed *en bloc* to optimize outcomes; morcellation should be avoided.
[d]The degree of surgical staging to assess disease status depends on preoperative and intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-B).
[e]See Principles of Radiation Therapy (UN-A).
[f]Patients should be closely monitored. Consider endometrial biopsies every 3 to 6 months.
[g]See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-C).

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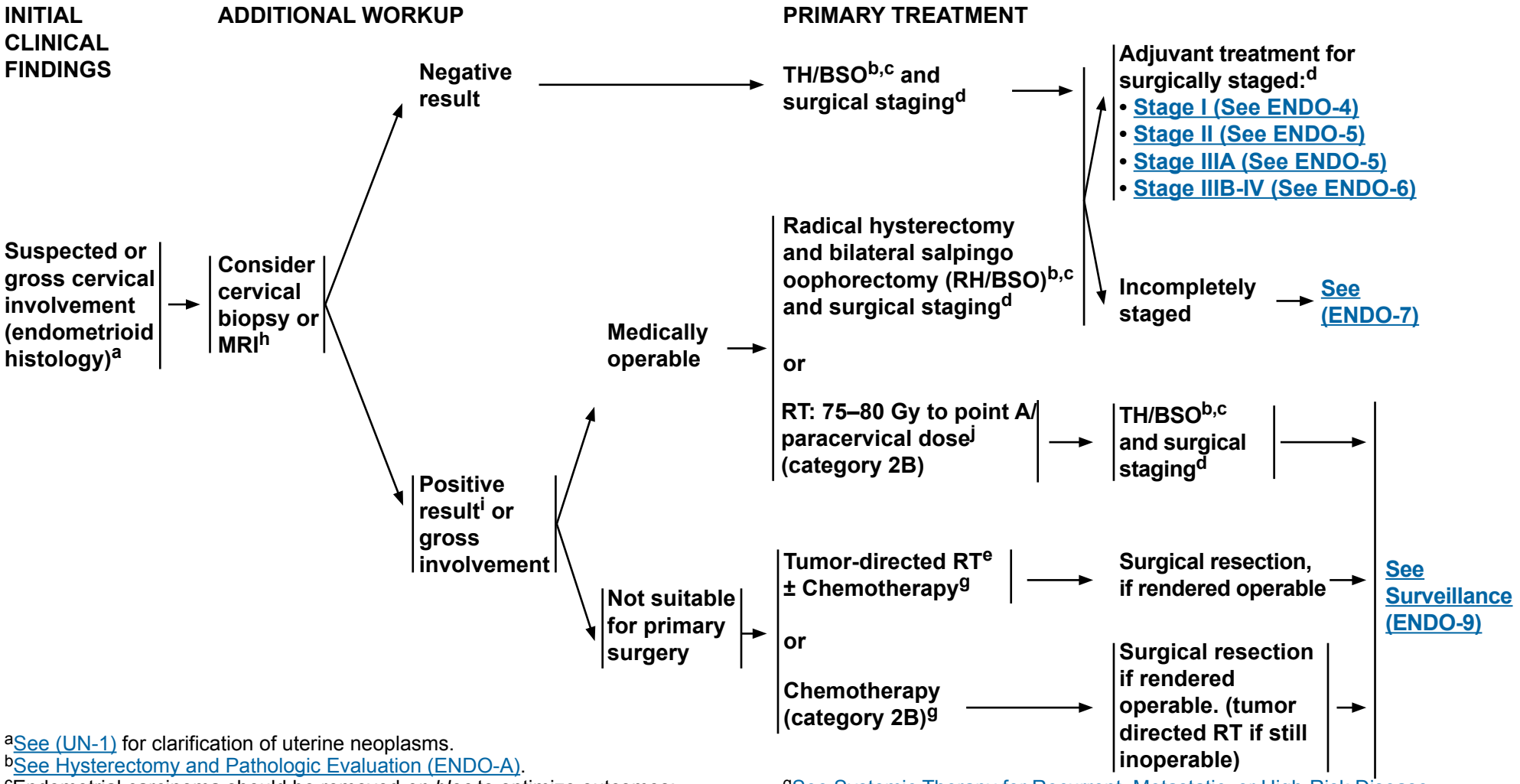

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[d]The degree of surgical staging to assess disease status depends on preoperative and intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-B).
[e]See Principles of Radiation Therapy (UN-A).
[g]See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-C).
[h]MRI performed with contrast unless contraindicated.
[i]Clear demonstration of cervical stromal involvement.
[j]Based on summation of conventional external-beam fractionation and low-dose-rate brachytherapy equivalent.

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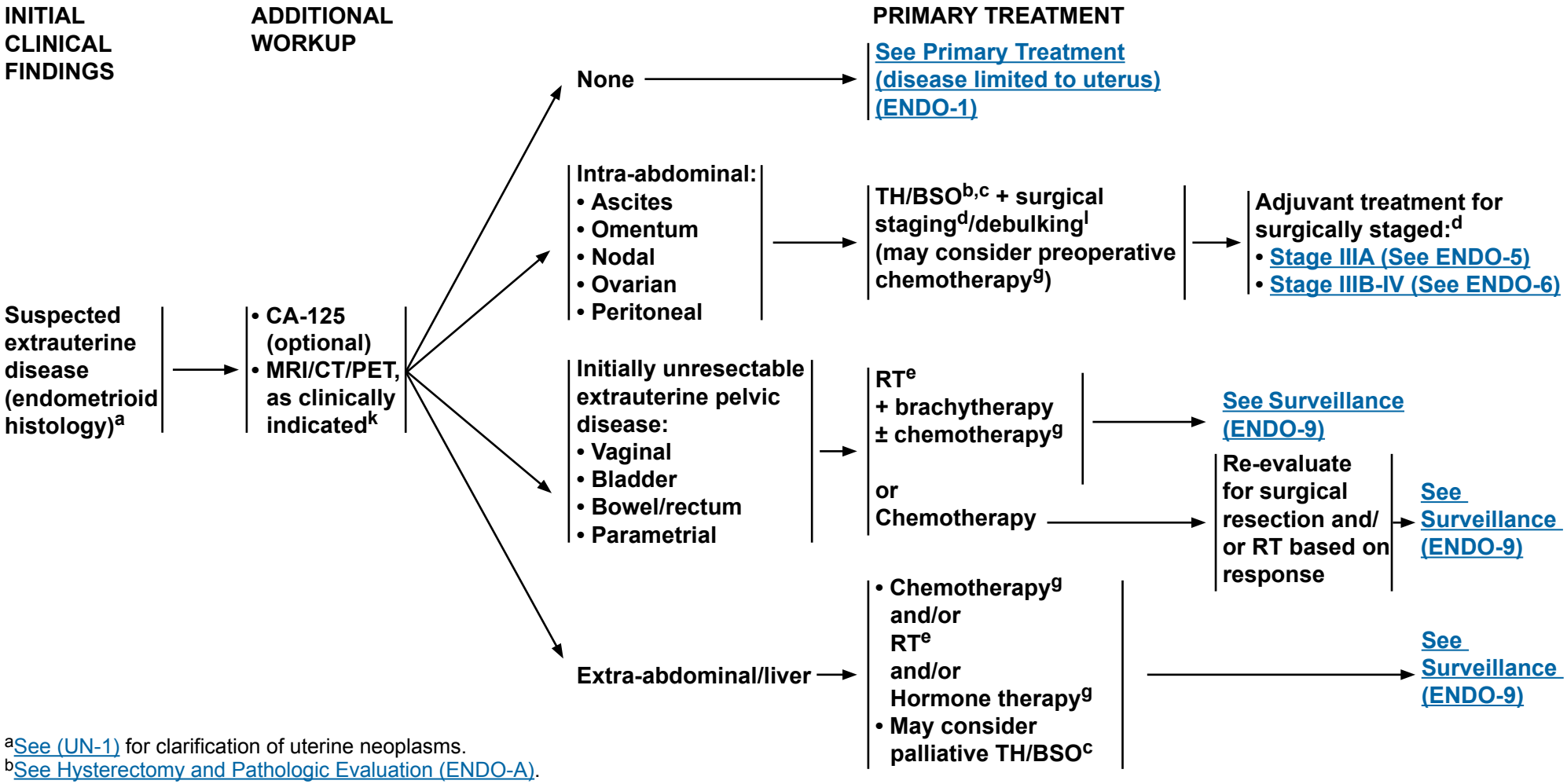

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[b]See Hysterectomy and Pathologic Evaluation (ENDO-A).
[c]Endometrial carcinoma should be removed *en bloc* to optimize outcomes; morcellation should be avoided.
[d]The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-B).
[e]See Principles of Radiation Therapy (UN-A).
[g]See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-C).
[k]CT and MRI performed with contrast throughout the guidelines unless contraindicated. Contrast not required for screening chest CT.
[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)

CLINICAL FINDINGS		ADVERSE RISK FACTORS[m]	HISTOLOGIC GRADE/ADJUVANT TREATMENT[e,n,o] G1	G2	G3
Surgically staged:Stage I[d]	Stage IA (<50% myometrial invasion)	Adverse risk factors not present	Observe	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy
		Adverse risk factors present	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or EBRT (category 2B for EBRT)	Observe or Vaginal brachytherapy and/or EBRT
	Stage IB (≥50% myometrial invasion)	Adverse risk factors not present	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy	Vaginal brachytherapy and/or EBRT or Observe (category 2B for observation)
		Adverse risk factors present	Observe or Vaginal brachytherapy and/or external beam radiation therapy (EBRT)	Observe or Vaginal brachytherapy and/or EBRT	EBRT and/or Vaginal brachytherapy ± chemotherapy[g,p] (category 2B for chemotherapy)

[d]The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-B).
[e]See Principles of Radiation Therapy (UN-A).
[g]See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-C).
[m]See Discussion for information on adverse risk factors.
[n]Adjuvant therapy determinations are made on the basis of pathologic findings.
[o]Initiate RT as soon as the vaginal cuff is healed, preferably no later than 12 weeks after surgery.
[p]The role of adjuvant chemotherapy in invasive, high-grade, uterine-confined disease is the subject of current studies. (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;46:2422-2431.) Hormonal therapy is not used for high grade disease.

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See Surveillance (ENDO-9)

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CLINICAL FINDINGS	HISTOLOGIC GRADE/ADJUVANT TREATMENT[e,g,n,o]		
	G1	G2	G3
Surgically staged:[d] Stage II[q,r] →	Vaginal brachytherapy and/or EBRT	Vaginal brachytherapy and/or EBRT	EBRT ± vaginal brachytherapy ± chemotherapy[p] (category 2B for chemotherapy)
Surgically staged:[d] Stage IIIA →	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or EBRT ± vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or EBRT ± vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or EBRT ± vaginal brachytherapy

[d]The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-B).
[e]See Principles of Radiation Therapy (UN-A).
[g]See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-C).
[n]Adjuvant therapy determinations are made on the basis of pathologic findings.
[o]Initiate RT as soon as the vaginal cuff is healed, no later than 12 weeks after surgery.
[p]The role of adjuvant chemotherapy in invasive high-grade uterine confined disease is the subject of current studies. (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;46:2422-2431.) Hormonal therapy is not used for high grade disease.
[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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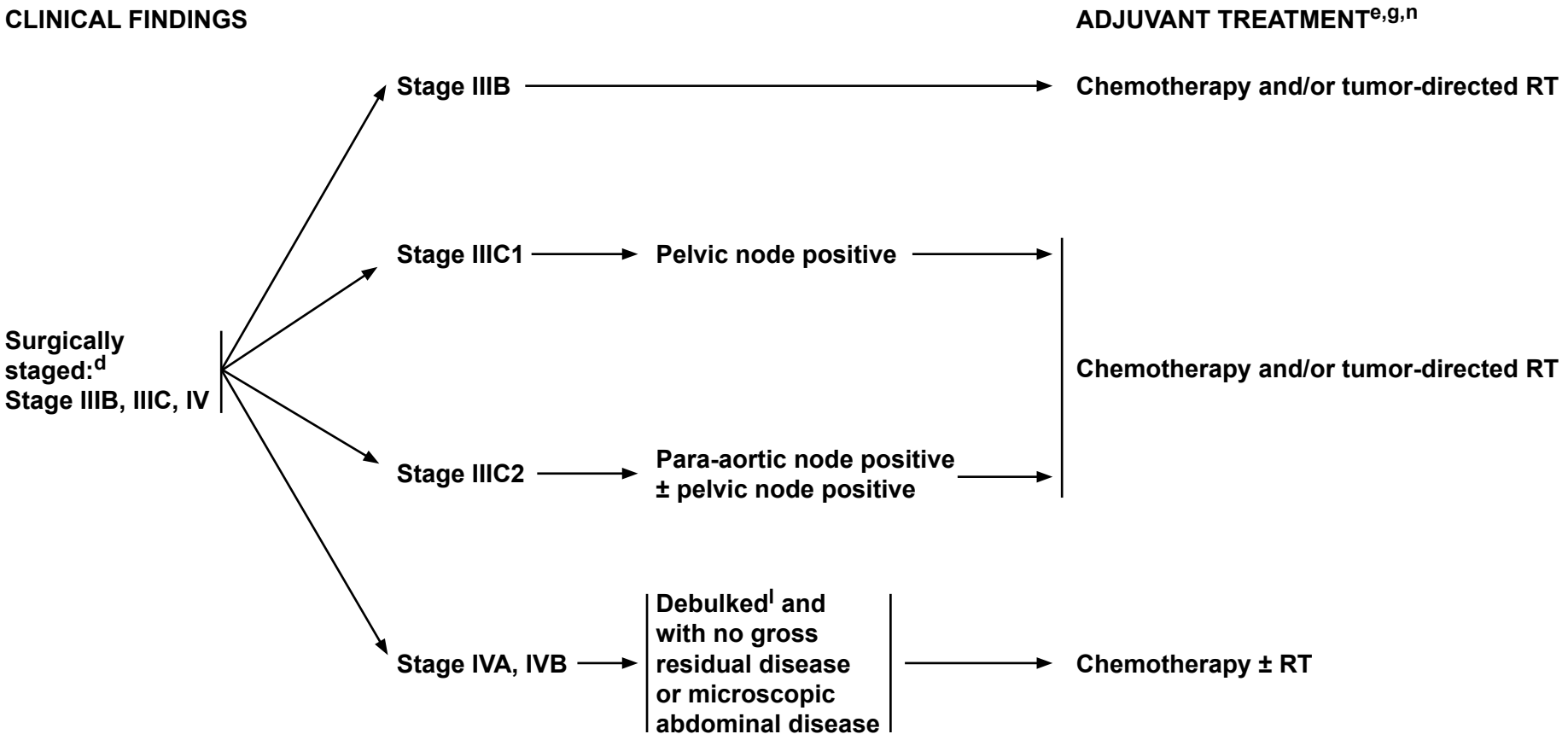

[d]The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-B).
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[l]The surgical goal is to have no measurable residual disease.
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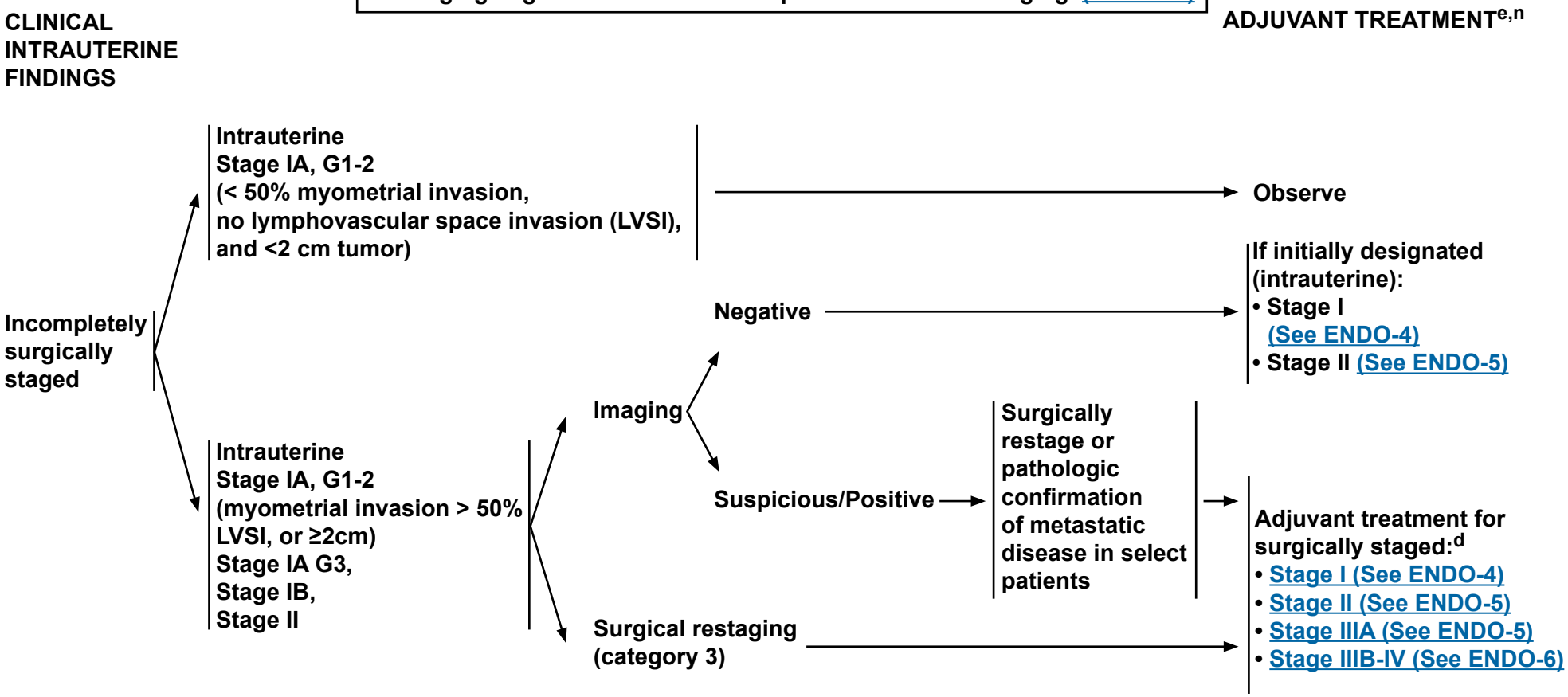

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See Surveillance (ENDO-9)

CRITERIA FOR CONSIDERING FERTILITY-SPARING OPTIONS FOR MANAGEMENT OF ENDOMETRIAL CARCINOMA (All criteria must be met)

- Well-differentiated (grade 1) endometrioid adenocarcinoma on dilation and curettage (D&C) confirmed by expert pathology review
- Disease limited to the endometrium on MRI (preferred) or transvaginal ultrasound
- Absence of suspicious or metastatic disease on imaging
- No contraindications to medical therapy or pregnancy
- Patients should undergo counseling that fertility-sparing option is NOT standard of care for the treatment of endometrial carcinoma

→

PRIMARY TREATMENT

- Consultation with a fertility expert prior to therapy
- Genetic counseling/testing in selected patients (See UN-1)

→ Continuous progestin-based therapy:
- Megestrol
- Medroxyprogesterone
- Levonorgestrel IUD

→ Endometrial sampling every 3–6 mo (either D&C or endometrial biopsy)

SURVEILLANCE

→ Complete response by 6 mo → Encourage conception[t] (with continued surveillance every 3–6 mo) → TH/BSO[c] with staging[d] after childbearing complete or progression of disease on endometrial sampling (see ENDO-1)

→ Endometrial cancer present at 6–9 months[s] → TH/BSO[c] with staging[d] (see ENDO-1)

[c]Endometrial carcinoma should be removed *en bloc* to optimize outcomes; morcellation should be avoided.
[d]The degree of surgical staging to assess disease status depends on preoperative and intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-B).
[s]Gunderson CC, Fader AN, Carson KA, Bristow RE. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. 2012 Gynecologic Oncology;125:477-482 and Hubbs JL, Saig RM, Abaid LN, et al. Systemic and local hormone therapy for endometrial hyperplasia and early adenocarcinoma. Obstet Gynecol 2013;121:1172-1180.
[t]Endometrial sampling every 3 to 6 months and progestin-based therapy are recommended if patient is not in the active process of trying to conceive.

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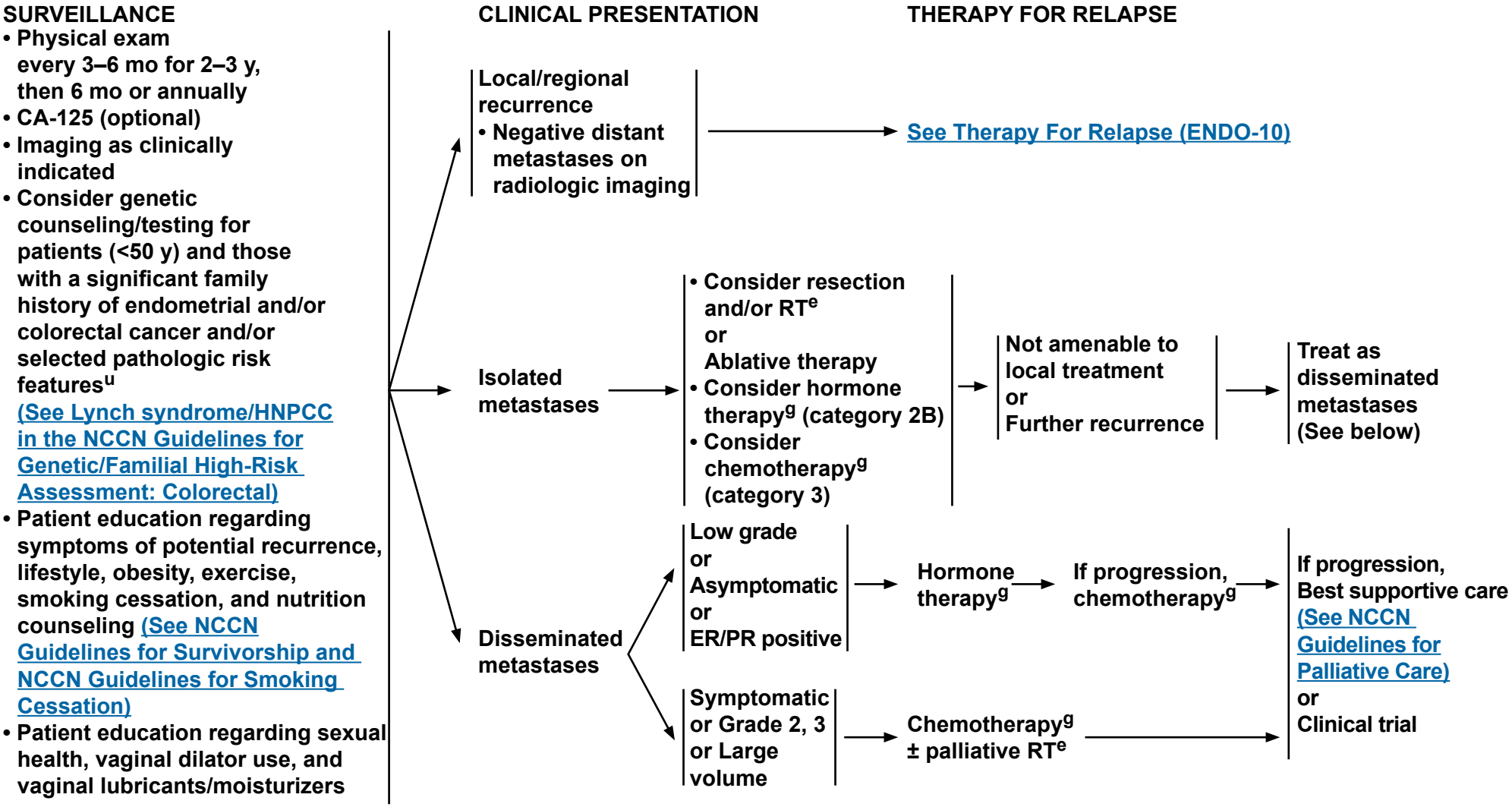

[e]See Principles of Radiation Therapy (UN-A).
[g]See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-C).
[u]Recently, immunohistochemistry (IHC) and/or microsatellite instability (MSI) screening of all colorectal and endometrial cancers, regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for Lynch syndrome (LS). An infrastructure needs to be in place to handle the screening results. IHC and/or MSI screening is usually performed on epithelial tumors and not malignant mesenchymal (sarcoma).

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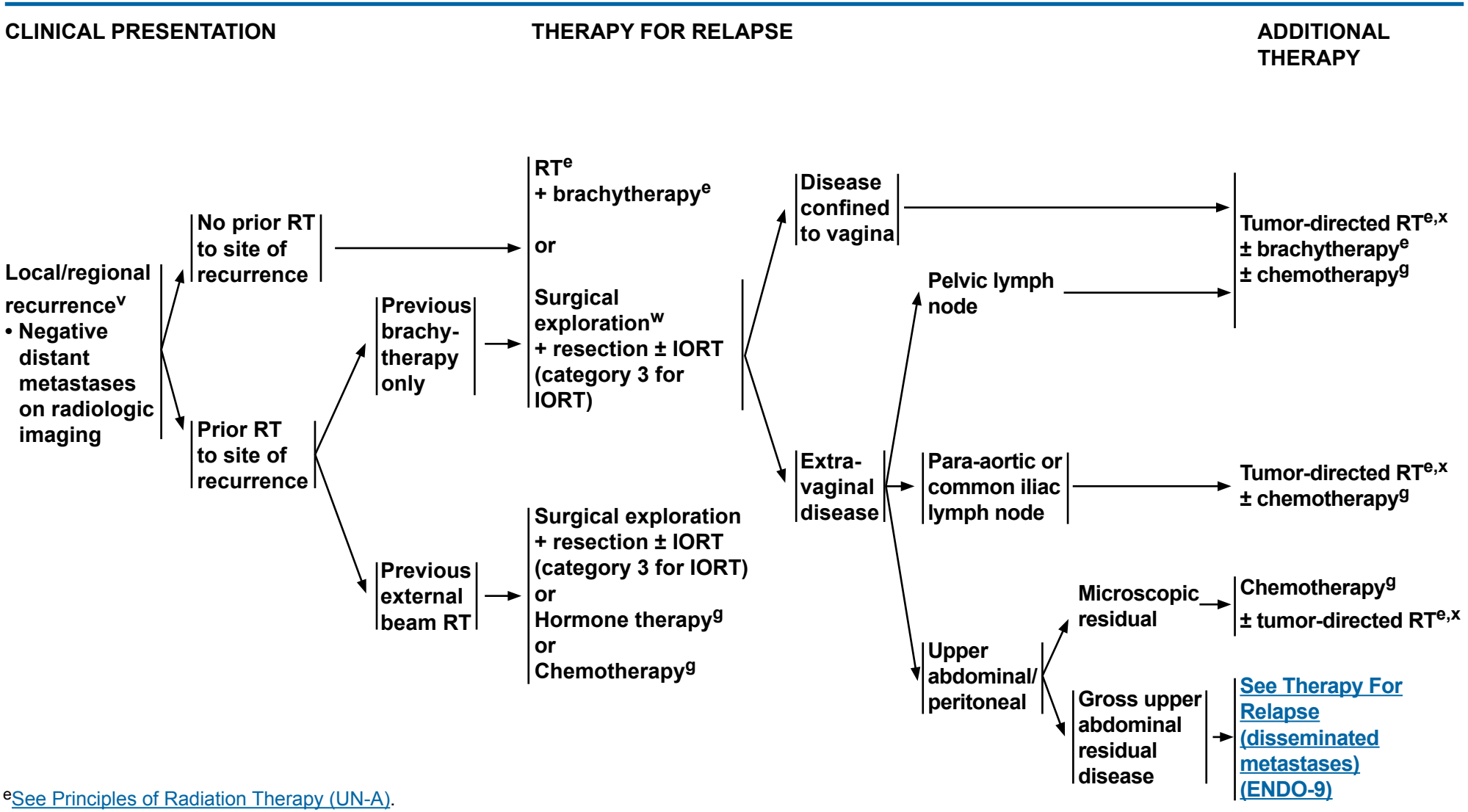

[e]See Principles of Radiation Therapy (UN-A).
[g]See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-C).
[v]May include patients with isolated common iliac or para-aortic lymph node recurrence.
[w]Consider preoperative EBRT in select patients.
[x]Post-resection consolidation RT can be considered in patients who were not previously radiated or who are deemed to have additional tolerance for radiation.

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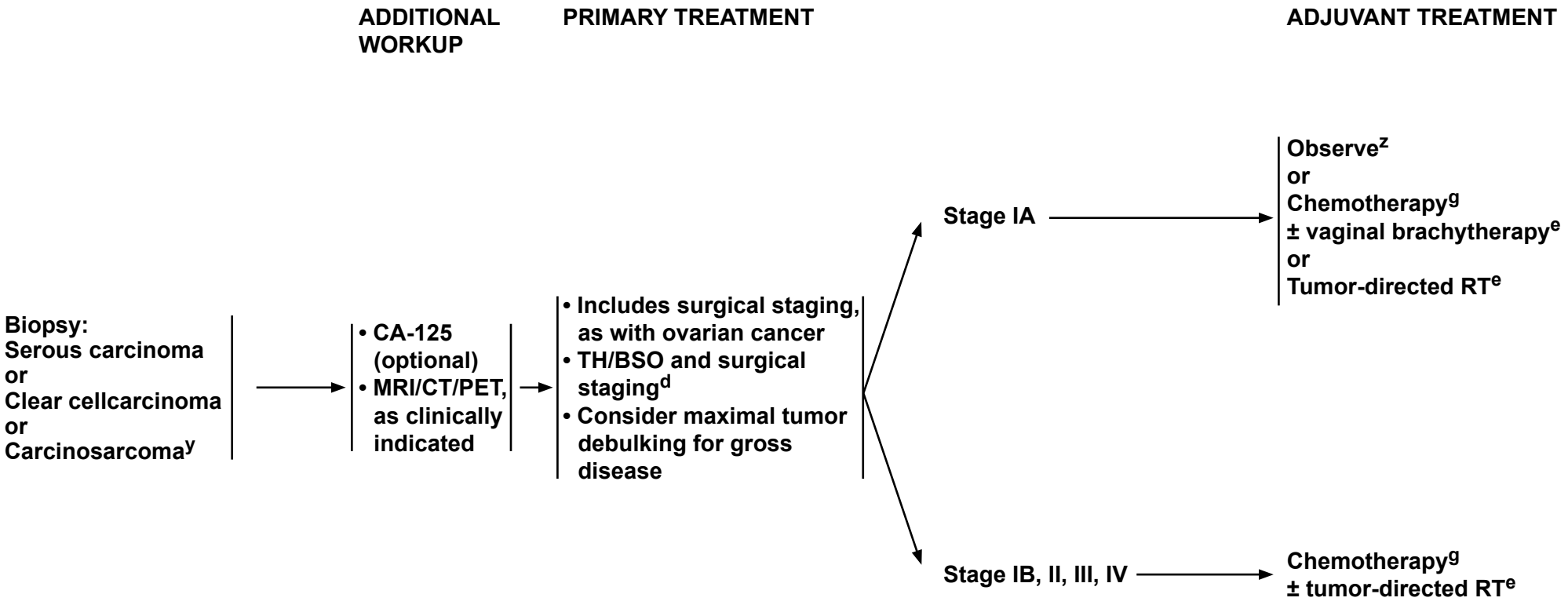
SEROUS OR CLEAR CELL CARCINOMA OR CARCINOSARCOMA OF THE ENDOMETRIUM[y]



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

[d]The degree of surgical staging to assess disease status depends on intraoperative findings. Multidisciplinary expertise is recommended. See Principles of Evaluation and Surgical Staging (ENDO-B).
[e]See Principles of Radiation Therapy (UN-A).
[g]See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-C).
[y]Also known as malignant mixed mesodermal tumor or malignant mixed Müllerian tumor. Carcinosarcomas are treated the same as poorly differentiated adenocarcinomas.
[z]Observation only for select patients with no residual disease in the hysterectomy specimen.

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See Surveillance (ENDO-9)

HYSTERECTOMY AND PATHOLOGIC EVALUATION[1,2]

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

Pathologic assessment to include:

- **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 with IHC and MSI for inherited mismatch repair gene mutations in patients <50 y and those with a significant family history of endometrial and/or colorectal cancer and/or selected pathologic risk features to identify familial cancer syndromes, such as Lynch syndrome/HNPCC[3]**
    (See Lynch syndrome/HNPCC in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal)
- **Fallopian tubes/ovaries**
- **Peritoneal cytology[4]**
- **Nodes (when resected)**
  - **Level of nodal involvement (ie, pelvic, common iliac, para-aortic)**

[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;106:413-425.
[2]See Principles of Evaluation and Surgical Staging (ENDO-B).
[3]Recently, immunohistochemistry (IHC) and/or microsatellite instability (MSI) screening of all colorectal and endometrial cancers, regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for Lynch syndrome (LS). An infrastructure needs to be in place to handle the screening results. IHC and/or MSI screening is usually performed on epithelial tumors and not malignant mesenchymal (sarcoma).
[4]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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PRINCIPLES OF EVALUATION AND SURGICAL STAGING

Principles of Surgical Staging for Endometrial Cancer[1-3]

- **Total hysterectomy and bilateral salpingo-oophorectomy (TH/BSO) is the main treatment of apparent uterine-confined endometrial cancer, unless patients are interested in and are candidates for fertility-sparing options (See ENDO-8). Many patients with locally advanced endometrial carcinoma are also candidates for TH/BSO. (See Hysterectomy and Pathologic Evaluation [ENDO-A])**
- **The hysterectomy and adnexectomy may be performed through laparotomy, vaginally, or via minimally invasive techniques such as laparoscopy or robotic surgery.**
- **Visual evaluation of the peritoneal, diaphragmatic, and serosal surfaces with biopsy of any suspicious lesions is important to exclude extrauterine disease.**
- **While peritoneal cytology does not affect staging, FIGO and AJCC continue to recommend that it be obtained and reported.**
- **Omental biopsy is commonly performed in tumors with serous carcinoma, clear cell carcinoma, or carcinosarcoma histology.**
- **Excision of suspicious or enlarged lymph nodes in the pelvic or paraaortic regions is important to exclude nodal metastasis.**
- **Pelvic nodal dissection with pathologic evaluation continues to be an important part of the surgical staging for selected uterine-confined endometrial cancer as it can identify important prognostic information that may alter treatment decisions.**
- **Pelvic lymph nodes from the external iliac, internal iliac, obturator, and common iliac nodes are frequently removed for staging purposes.**
- **Para-aortic nodal evaluation from the inframesenteric and infrarenal regions may also be utilized for staging of select high-risk tumors such as deeply invasive lesions, high-grade histology, and tumors of serous carcinoma, clear cell carcinoma, or carcinosarcoma features.**
- **Sentinel lymph node (SLN) mapping may be considered (category 3) in selected patients. (See pages 2-4 of ENDO-B)**
- **Some patients may not be candidates for lymph node dissection.**

Continued

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PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Principles of Sentinel Lymph Node (SLN) Mapping for Endometrial Cancer Staging-----

- **The role of SLN mapping is currently being evaluated. No prospective randomized trials have been reported that evaluate this technique in endometrial cancer. If SLN mapping is considered, the expertise of the surgeon and attention to technical detail is critical. The use of SLN mapping in high-risk histologies (serous carcinoma, clear cell carcinoma, or carcinosarcomas) should be undertaken with particular caution.**
- **SLN mapping can be considered (category 3) for the surgical staging of apparent uterine-confined malignancy when there is no metastasis demonstrated by imaging studies or no obvious extrauterine disease at exploration.**
- **A cervical injection with dye has emerged as a useful and validated technique for identification of lymph nodes that are at high risk for metastases (ie, SLN in patients with early-stage endometrial cancer[4-6]).**
- **The combination of a superficial (1–3 mm) and deep (1–2 cm) cervical injection leads to dye delivery to the main layers of lymphatic channel origins in the cervix and corpus, namely the superficial subserosal, intermediate stromal, and deep submucosal lymphatic sites of origin (Figure 1 on ENDO-B 3 of 5).**
- **Injection into the uterine cervix provides excellent dye penetration to the region of the uterine vessels and main uterine lymphatic trunks that condense in the parametria and appear in the broad ligament leading to pelvic and occasionally paraaortic sentinel nodes.**
- **The uterine body lymphatic trunks commonly cross over the obliterated umbilical artery with the most common location of pelvic SLN being medial to the external iliac, ventral to the hypogastric, or in the superior part of the obturator region (Figure 2 on ENDO-B 3 of 5).**
- **A less common location is usually seen when the lymphatic trunks do not cross over the obliterated umbilical and move cephalad following the mesoureter; in these cases, the SLN is usually seen in the common iliac presacral region (Figure 3 on ENDO-B 3 of 5).**
- **The radiolabeled colloid most commonly injected into the cervix is technetium-99m (^{99m}Tc); colored dyes are available in a variety of forms (Isosulfan Blue 1% and Methylene Blue 1%, Patent Blue 2.5% sodium).**
- **Indocyanine green (ICG) recently emerged as a useful imaging dye that requires near-infrared camera for localization, provides a very high SLN detection rate, and is commonly used in many practices at the present time.**
- **Low-volume nodal metastasis to SLN detected only by enhanced pathologic ultrastaging is another potential value to staging with SLN.[7-9]**
- **Key points to a successful SLN mapping is the adherence to the SLN algorithm, which requires the performance of a side-specific nodal dissection in cases of failed mapping and removal of any suspicious or grossly enlarged nodes regardless of mapping (Figure 4 on ENDO-B 4 of 5).[10-12]**

Continued

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PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Figure 1: Common cervical injection sites for mapping uterine cancer†

Figure 2: Most common location of SLNs (blue, arrow) following a cervical injection†

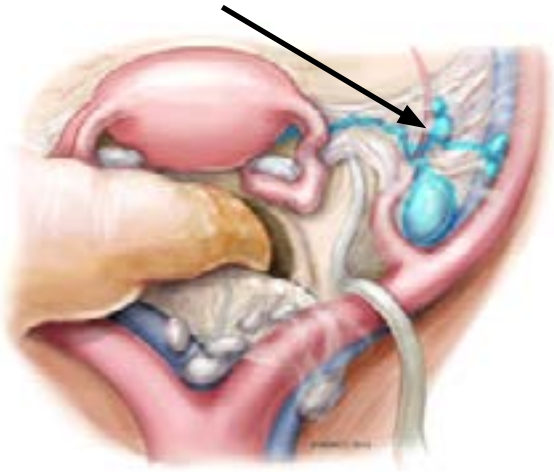
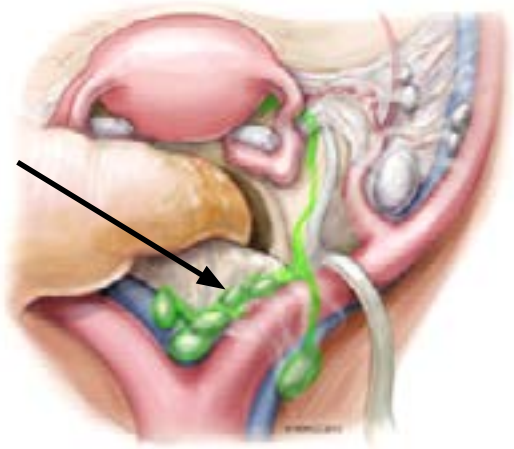


Figure 3: Less common location of SLNs (green, arrow) usually seen when lymphatic trunks are not crossing over the umbilical ligament but following the mesoureter cephalad to common iliac and presacral region†



†Figures 1, 2, and 3 are reproduced with permission from Memorial Sloan Kettering Cancer Center. © 2013, Memorial Sloan Kettering Cancer Center.

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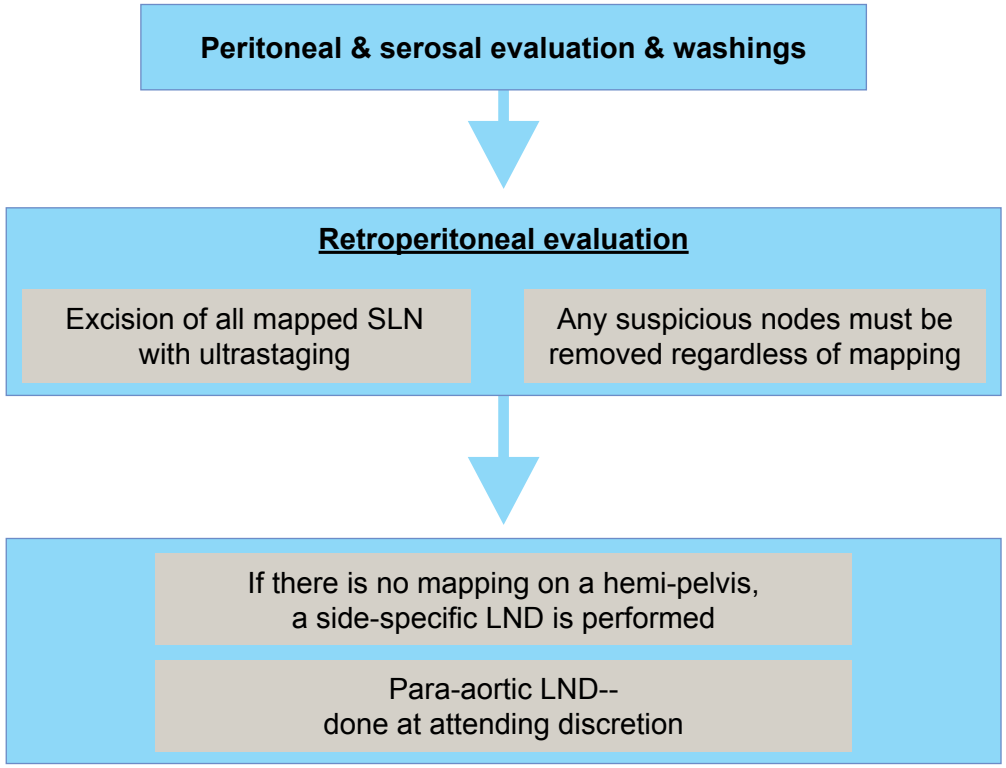
PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Figure 4: The SLN algorithm for surgical staging of endometrial cancer*



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

Continued

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PRINCIPLES OF EVALUATION AND SURGICAL STAGING

[1]American College of Obstetricians and Gynecologists. ACOG practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstet Gynecol 2005;106:413-425.
[2]Bakkum-Gamez JN, Gonzalez-Bosquet J, Laack NN, et al. Current issues in the management of endometrial cancer. Mayo Clin Proc. 2008 Jan;83:97-112.
[3]Edge SB, Byrd DR, Compton CC. AJCC Cancer Staging Manual, 7th edition. New York: Springer; 2010.
[4]Abu-Rustum NR, Khoury-Collado F, Pandit-Taskar N, et al. Sentinel lymph node mapping for grade 1 endometrial cancer: is it the answer to the surgical staging dilemma? Gynecol Oncol 2009;113:163-169.
[5]Khoury-Collado F, Glaser GE, Zivanovic O, et al. Improving sentinel lymph node detection rates in endometrial cancer: how many cases are needed? Gynecol Oncol 2009;115:453-455.
[6]Khoury-Collado F, Murray MP, Hensley ML, et al. Sentinel lymph node mapping for endometrial cancer improves the detection of metastatic disease to regional lymph nodes. Gynecol Oncol 2011;122:251-254.
[7]Frimer M, Khoury-Collado F, Murray MP, et al. Micrometastasis of endometrial cancer to sentinel lymph nodes: is it an artifact of uterine manipulation? Gynecol Oncol 2010;119:496-499.
[8]Leitao MM Jr, Khoury-Collado F, Gardner G, et al. Impact of incorporating an algorithm that utilizes sentinel lymph node mapping during minimally invasive procedures on the detection of stage IIIC endometrial cancer. Gynecol Oncol 2013;129:38-41.
[9]Kim CH, Soslow RA, Park KJ, et al. Pathologic ultrastaging improves micrometastasis detection in sentinel lymph nodes during endometrial cancer staging. Int J Gynecol Cancer 2013;23:964-970.
[10]Barlin JN, Khoury-Collado F, Kim CH, et al. The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: Beyond removal of blue nodes. Gynecol Oncol 2012;125:531-535.
[11]Vidal F, Leguevaque P, Motton S, Det al. Evaluation of the sentinel lymph node algorithm with blue dye labeling for early-stage endometrial cancer in a multicentric setting. Int J Gynecol Cancer 2013; 23:1327-1243.
[12]Abu-Rustum NR. The Increasing credibility of sentinel lymph node mapping in endometrial cancer. Ann Surg Oncol 2013;20:353-354.

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

HORMONE THERAPY[1]
- **Megestrol/tamoxifen (alternating)**
- **Progestational agents**
- **Aromatase inhibitors**
- **Tamoxifen**

CHEMOTHERAPY REGIMENS[2,3]
- **Multi-agent chemotherapy regimens preferred, if tolerated**
  - **Carboplatin/paclitaxel**[4]
  - **Cisplatin/doxorubicin**[5]
  - **Cisplatin/doxorubicin/paclitaxel**[5,6]
  - **Carboplatin/docetaxel**[7]
  - **Ifosfamide/paclitaxel (category 1 for carcinosarcoma)**[8]
  - **Cisplatin/ifosfamide (for carcinosarcoma)**
- **Single agents**
  - **Cisplatin**
  - **Carboplatin**
  - **Doxorubicin**
  - **Liposomal doxorubicin**
  - **Paclitaxel**
  - **Topotecan**
  - **Bevacizumab**[9]
  - **Temsirolimus**[10]
  - **Docetaxel**[7] **(category 2B)**
  - **Ifosfamide (for carcinosarcoma)**

[1]Hormonal therapy may be used for lower grade endometrioid histologies only (ie, not for G3 endometrioid, serous carcinoma, clear cell carcinoma, or carcinosarcoma) preferably in patients with small tumor volume or an indolent growth pace.
[2]Cisplatin, carboplatin, liposomal doxorubicin, paclitaxel, and docetaxel may cause drug reactions.
(See NCCN Guidelines for Ovarian Cancer--Management of Drug Reactions [OV-C])
[3]Chemotherapy regimens can be used for all carcinoma histologies. Carcinosarcomas are now considered and treated as high-grade carcinomas. However, ifosfamide-based regimens were previously used for carcinosarcomas.
[4]Miller D, Filiaci V, Fleming G, et al. Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: a Gynecologic Oncology Group study [abstract]. Gynecol Oncol 2012;125:771.
[5]Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A Gynecologic Oncology Group study. Gynecol Oncol 2009;112:543-552.
[6]The cisplatin/doxorubicin/paclitaxel regimen is not widely used because of concerns about toxicity.
[7]Docetaxel may be considered for patients in whom paclitaxel is contraindicated.
[8]Homesley HD, Filiaci V, Markman M, et al. Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:526-531.
[9]Bevacizumab may be considered for use in patients who have progressed on prior cytotoxic chemotherapy. (Aghajanian C, Sill MW, Darcy KM, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. J Clin Oncol 2011;29:2259-2265.)
[10]Oza AM, Elit L, Tsao MS, et al. Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trials Group. J Clin Oncol 2011;29:3278-3285.

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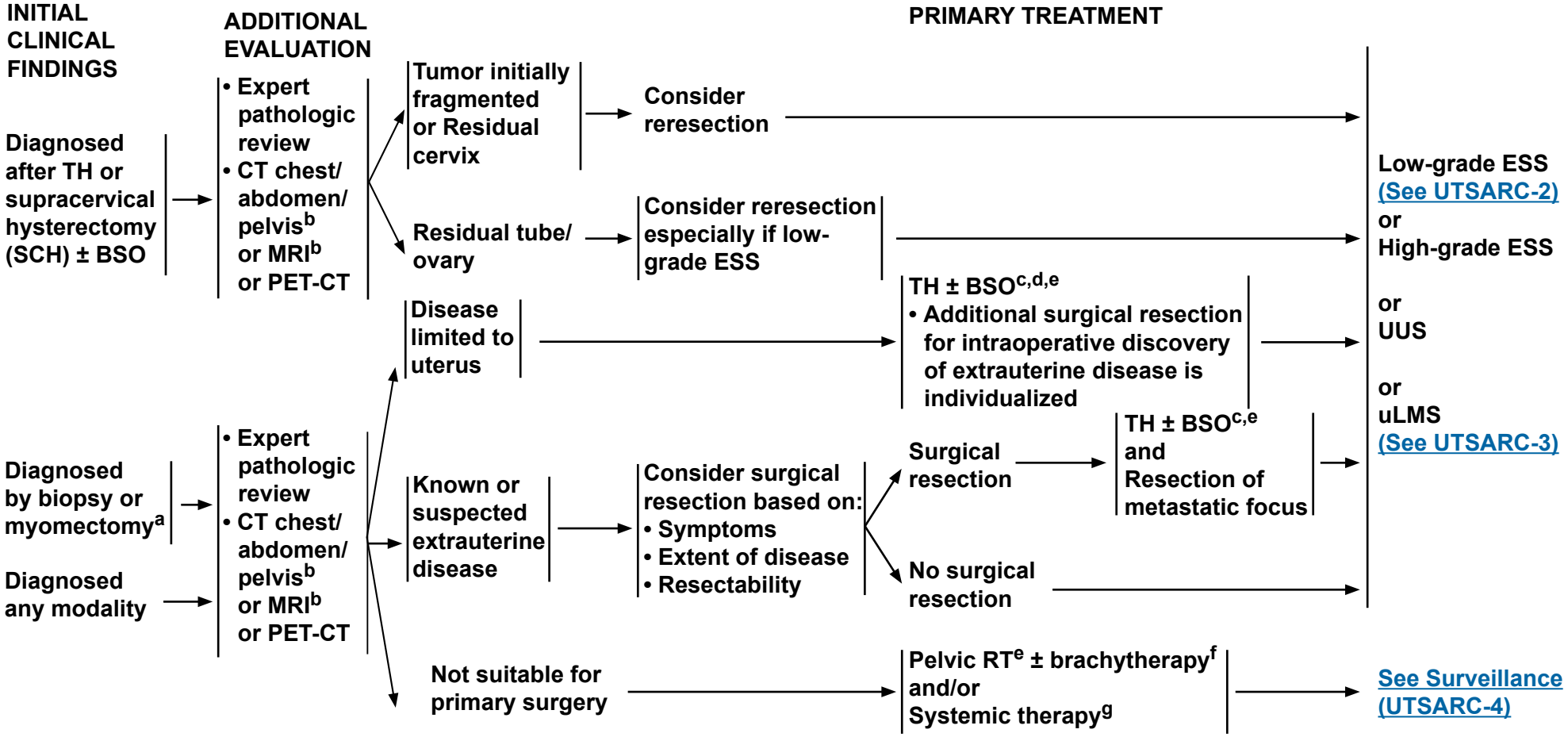

[a]Preoperative imaging and biopsy may help to identify uterine sarcomas although biopsy sensitivity is less than for endometrial cancer. If there is suspicion of malignant mesenchymal sarcoma, fragmentation should be avoided.
[b]CT and MRI performed with contrast throughout the guidelines unless contraindicated. Contrast not required for screening chest CT.
[c]Oophorectomy individualized for reproductive-age patients.
[d]For incidental finding of uterine sarcoma after TH/BSO or fragmented specimen: Recommend imaging and consider additional surgical resection on an individual basis.
[e]Uterine sarcoma should be removed *en bloc* to optimize outcomes; morcellation should be avoided.
[f]See Principles of Radiation Therapy (UN-A).
[g]See Systemic Therapy for Uterine Sarcoma (UTSARC-A).

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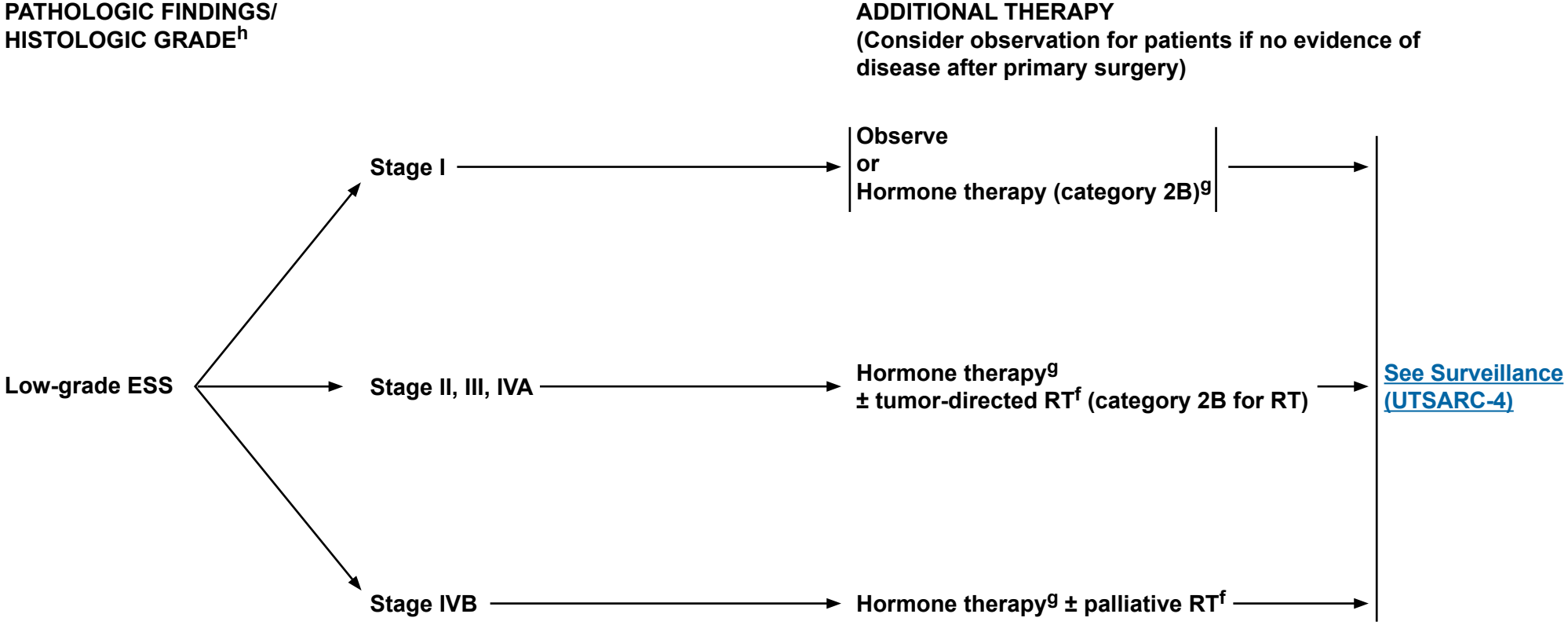

[f]See Principles of Radiation Therapy (UN-A).
[g]See Systemic Therapy for Uterine Sarcoma (UTSARC-A).
[h]See Uterine Sarcoma Classification (UTSARC-B).

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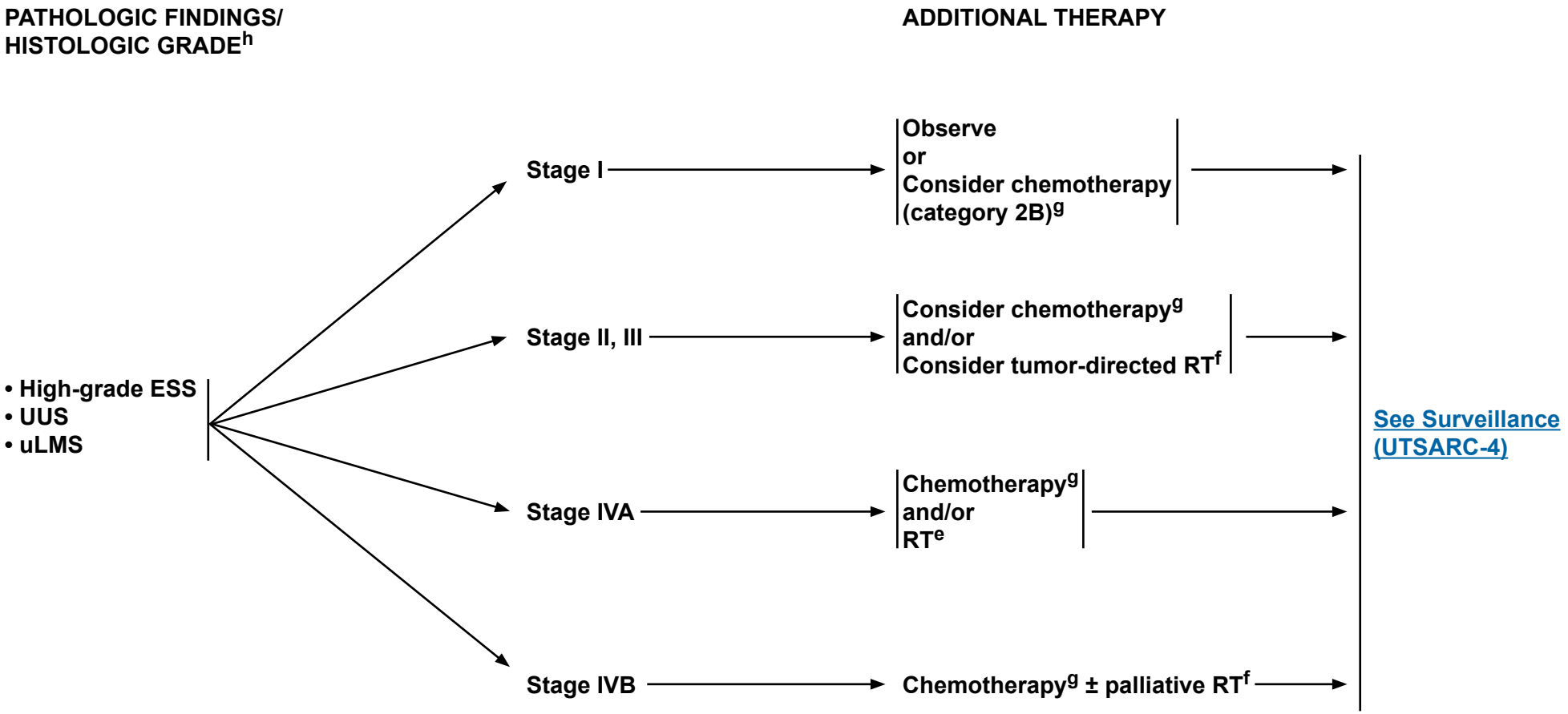

[f]See Principles of Radiation Therapy (UN-A).
[g]See Systemic Therapy for Uterine Sarcoma (UTSARC-A).
[h]See Uterine Sarcoma Classification (UTSARC-B).

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SURVEILLANCE

- History and physical exam every 3 mo for 2 y, then every 6–12 mo
- CT imaging (chest/abdomen/pelvis) every 3–6 mo for 2–3 y, then every 6 mo for next 2 y, then annually for high-grade sarcomas
- Consider other imaging (MRI/PET) as clinically indicated
- Patient education regarding symptoms of potential recurrence, lifestyle, obesity, exercise, nutrition, and smoking cessation counseling (See NCCN Guidelines for Survivorship and NCCN Guidelines for Smoking Cessation)
- Patient education regarding sexual health, vaginal dilator use, and vaginal lubricants/moisturizers

RECURRENCE

Local recurrence:
- Vagina/pelvis
- Chest and abdominal/pelvic CT negative for metastatic disease

→ See Therapy For Relapse (UTSARC-5)

Isolated metastases

→ Resectable →
- Surgical resection or other local ablative therapy:
  - Consider postoperative systemic therapy[g]
  - Consider postoperative RT[f]

→ Unresectable →
- Systemic therapy[g] → If response, consider surgery
- and/or
- Local therapy (tumor directed RT[f] or local ablative therapy)

Disseminated disease

→
- Systemic therapy[g] ± palliative RT[f]
- or
- Supportive care

THERAPY FOR RELAPSE

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

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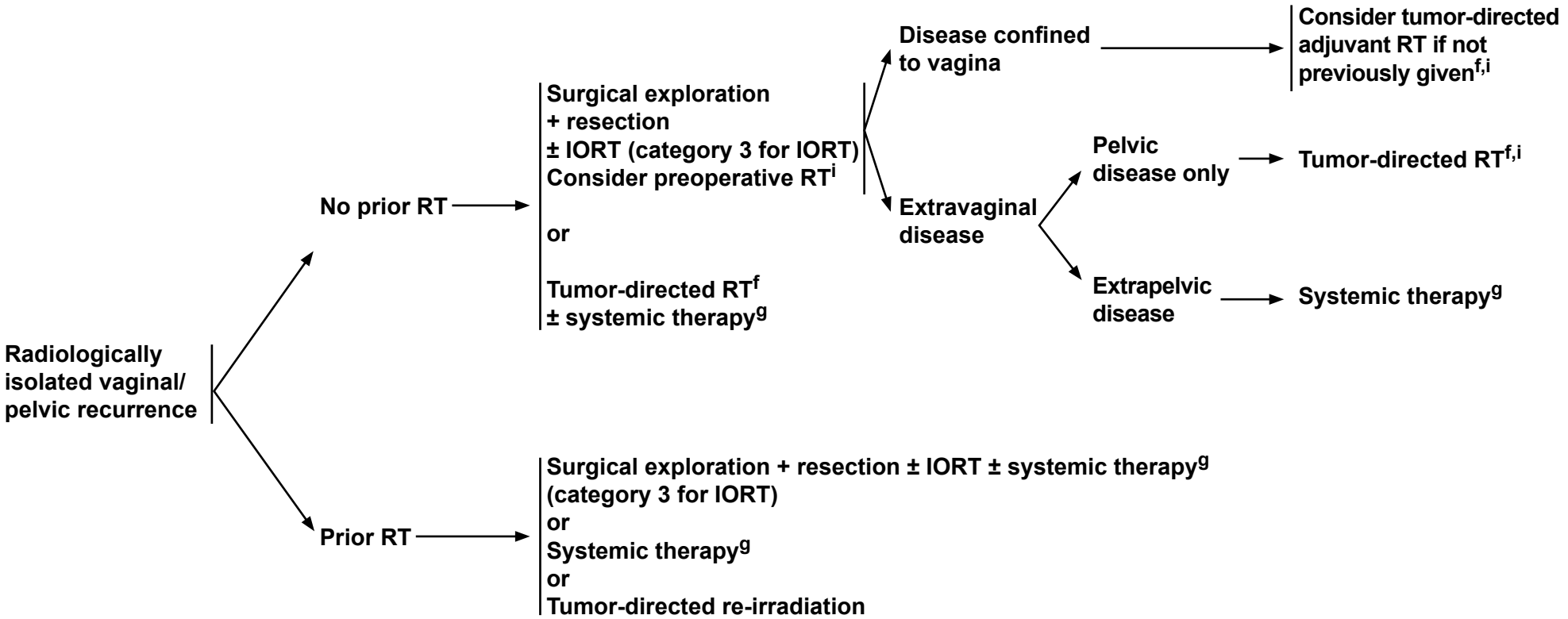
RECURRENCE

THERAPY FOR RELAPSE



[f]See Principles of Radiation Therapy (UN-A).
[g]See Systemic Therapy for Uterine Sarcoma (UTSARC-A).
[i]The use of preoperative RT would preclude postoperative RT.

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SYSTEMIC THERAPY FOR UTERINE SARCOMA[1]
(Clinical trials strongly recommended)

Combination regimens:
- Docetaxel/gemcitabine (preferred for leiomyosarcoma)
- Doxorubicin/ifosfamide
- Doxorubicin/dacarbazine
- Gemcitabine/dacarbazine
- Gemcitabine/vinorelbine

Single-agent options:
- Dacarbazine
- Doxorubicin
- Epirubicin
- Eribulin
- Gemcitabine
- Ifosfamide
- Liposomal doxorubicin
- Pazopanib
- Temozolomide
- Trabectedin[3]
- Vinorelbine (category 2B)
- Docetaxel (category 3)

HORMONE THERAPY (For Low-grade ESS or Hormone Receptor Positive (ER/PR) uLMS[2]):
- Medroxyprogesterone acetate (category 2B for ER/PR positive uLMS)
- Megestrol acetate (category 2B for ER/PR positive uLMS)
- Aromatase inhibitors
- GnRH analogs (category 2B for low-grade ESS and ER/PR positive uLMS)

[1]See NCCN Guidelines for Ovarian Cancer--Management of Drug Reactions [OV-C].
[2]These hormonal therapies may be considered for patients with uLMS that is ER/PR positive, preferably with small tumor volume or an indolent growth pace.
[3]For uLMS that has been treated with a prior anthracyline-containing regimen.

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Back to Recurrence (UTSARC-4)

UTERINE SARCOMA CLASSIFICATION[1]

- **Low-grade endometrial stromal sarcoma (ESS)[2]**
- **High-grade ESS[3]**
- **Undifferentiated uterine sarcoma (UUS)[4]**
- **Uterine leiomyosarcoma (uLMS)[5]**

Other Rare Uterine Mesenchymal Sarcoma Subtypes:
(see the NCCN Guidelines for Soft Tissue Sarcoma)

- **Adenosarcomas**
- **PEComas**
- **Rhabdomyosarcoma**

[1]Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO Classification of Tumours of the Female Reproductive Organs, Volume 6, 2014.
[2]Low-grade endometrial stromal sarcomas (LGESS) are characterized by small cells with low-grade cytology and features resembling stromal cells in proliferative endometrium. Mitotic activity is usually low (<5 MF per 10 HPF)
[3]High-grade endometrial stromal sarcomas (HGESS) are characterized by small cells with high-grade cytology, frequent necrosis, and brisk mitotic activity (>10 MF per 10 HPF). HGESS can contain areas of conventional LGESS.
[4]Undifferentiated uterine sarcomas (UUS) are characterized by cells with high-grade cytologic features lacking any resemblance to the stromal cells in proliferative endometrium or any other specific type of differentiation.
[5]Excludes smooth muscle tumors of uncertain malignant potential, epithelioid smooth muscle tumors, benign metastasizing leiomyomas, intravenous leiomyomatosis, diffuse leiomyomatosis; management in individual cases may be modified based on clinicopathologic prognostic factors, such as size (< or > 5 cm), mitotic activity (< or > 10 mf/10 hpf), age (< or > 50 years), and presence or absence of vascular invasion.

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PRINCIPLES OF RADIATION THERAPY FOR UTERINE NEOPLASMS

- **Tumor-directed RT refers to RT directed at sites of known or suspected tumor involvement, and may include external beam RT (EBRT) and/or brachytherapy. Diagnostic imaging is often used to assess locoregional extent and to rule out distant metastases before administration of RT. In general, tumor-directed 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 to 50 Gy. Multiple conformal fields based on CT-treatment planning should be utilized.**
- **Initiate brachytherapy as soon as the vaginal cuff is healed, preferably no later than 12 weeks after surgery. 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 to 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 two-thirds of the vagina.**
  - **For high-dose rate brachytherapy, when used as a boost to EBRT, doses of 4 to 6 Gy x 2 to 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.**
- **Evidence supports the use of combined modality radiation and chemotherapy as adjuvant treatment for patients with extrauterine disease.[1]**
- **Palliative RT should be individualized to disease extent and patient performance status. Various dose/fractionation schemes can be considered. A common approach is 30 Gy in 10 fractions.**

[1]Klopp A, Smith BD, Alektiar K, et al. The role of postoperative radiation therapy for endometrial cancer: executive summary of an american society for radiation oncology evidence-based guideline. Pract Radiat Oncol. 2014;4:137-144.

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)

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and
Reprinted from: Pecorelli S, Denny L, Ngan H, et al. Revised FIGO staging for carcinoma of the vulva, cervix and endometrium. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet 2009;105:103-104. Copyright 2009, with permission from International Federation of Gynecology and Obstetrics.

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)

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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.

Table of Contents

Overview

Adenocarcinoma of the endometrium (also known as endometrial cancer, or more broadly as uterine cancer or carcinoma of the uterine corpus) is the most common malignancy of the female genital tract in the United States. It is estimated that 54,870 new uterine cancer cases will occur in 2015, with 10,170 deaths resulting from the disease.[1] Uterine sarcomas are uncommon malignancies accounting for approximately 3% of all uterine cancers.[1,2] The NCCN Guidelines for Uterine Neoplasms describe malignant epithelial tumors and uterine sarcomas; each of these major categories contains specific histologic groups that require different management (see *Initial Clinical Findings* in the NCCN Guidelines for Uterine Neoplasms).

Risk factors for uterine neoplasms include increased levels of estrogen (caused by obesity, diabetes, and high-fat diet), early age at menarche, nulliparity, late age at menopause, Lynch syndrome, older age (≥55 years), and tamoxifen use.[3-6] Thus, the incidence of endometrial cancer is increasing because of increased life expectancy and obesity. The *Summary of the Guidelines Updates* describes the most recent revisions to the algorithms, which have been incorporated into this revised Discussion text (see the NCCN Guidelines for Uterine Neoplasms). By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the NCCN Panel during the process of developing these guidelines.

For patients with suspected uterine neoplasms, the initial evaluation/workup includes a history and physical examination, endometrial biopsy, and other studies (see *Initial Evaluation* in the NCCN Guidelines for Uterine Neoplasms).[7] Preoperative imaging and biopsy may help to identify uterine sarcomas although biopsy sensitivity is less than that for endometrial cancer. An expert pathology review will determine whether a patient has a malignant epithelial tumor or a stromal/malignant mesenchymal tumor. Epithelial tumor types include pure endometrioid cancer, uterine serous carcinoma, clear cell carcinoma, and carcinosarcoma (also known as malignant mixed Müllerian tumor [MMMT]). Stromal tumor types include uterine leiomyosarcoma (uLMS), endometrial stromal sarcoma (ESS), and undifferentiated uterine (previously called high-grade undifferentiated endometrial sarcoma). Given the typical age group at risk for uterine neoplasms (ie, ≥55 years) and the presence of comorbid illnesses in older patients, it is prudent in selected patients to also measure renal and liver function.

Most endometrial cancer is caused by sporadic mutations. However, genetic mutations cause endometrial cancer in about 5% of patients, which occurs 10 to 20 years before sporadic cancer.[8] Screening for genetic mutations (eg, Lynch syndrome/hereditary non-polyposis colorectal cancer) should be considered in all patients with endometrial (and colorectal) cancer but especially in those younger than 50 years of age.[6,8-10] Genetic testing and counseling should be considered for patients younger than 50 years of age with endometrial cancer and those with a significant family history of endometrial and/or colorectal cancer.[11-13] If these patients have Lynch syndrome, they are at greater risk for a second cancer (eg, colorectal cancer, ovarian cancer).[4,10,14] In addition, their relatives may have Lynch syndrome.

Screening of the tumor for defective DNA mismatch repair using immunohistochemistry and/or microsatellite instability (MSI) should be considered to identify which patients should undergo mutation testing for Lynch syndrome (see *Lynch Syndrome* in the NCCN Guidelines for Colorectal Cancer Screening).[8,9,15,16] Immunohistochemistry and/or MSI is used to assess for defective DNA mismatch repair (eg, MLH1, MSH2,

MSH6), which is associated with Lynch syndrome.[8] The Society of Gynecologic Oncology (SGO) also has useful criteria for determining which patients should have mutation testing (eg, diagnosis of multiple Lynch syndrome cancers in young patients, family members with similar cancers).[11,12] Some centers do immunohistochemistry and/or MSI screening in all patients with colorectal and endometrial cancer to identify those at risk for Lynch syndrome, regardless of age at diagnosis or family history.[15,16] However, this screening is usually done in patients with epithelial tumors and not those with mesenchymal endometrial tumors.

Women with Lynch syndrome are at higher risk (60%) for endometrial cancer; thus, close monitoring is recommended.[9,17,18] In relatives with Lynch syndrome but without endometrial cancer, a yearly endometrial biopsy is recommended to assess for cancer.[12,19] This strategy also enables select women to defer surgery (and surgical menopause) and to preserve their fertility. Prophylactic hysterectomy/bilateral salpingo-oophorectomy (BSO) can then be done after childbearing is complete or sooner, depending on patient preference.[20,21] In addition, interventions to decrease the risk from colorectal cancer may also be appropriate (eg, annual colonoscopy).

Endometrial Cancer

In approximately 70% of patients with adenocarcinoma of the endometrium, the invasive neoplasm is confined to the uterus at diagnosis.[22] 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.[23]

However, data show that the mortality rate for uterine cancer has increased more rapidly than the incidence rate.[24] This increased mortality may be related to an increased rate of advanced-stage cancers, high-risk histologies (eg, serous carcinomas), and patients being diagnosed at an older age. Analysis of SEER data suggests that survival is increased in patients who are younger, have early-stage disease, and have lower-grade disease.[25] In addition to grade and depth of myometrial invasion, other risk factors associated with poor prognosis include age, tumor size, lymphovascular space invasion (LVSI), and tumor involvement of the lower uterine segment.[26,27] To further improve outcome for patients with this disease, physicians need to identify high-risk patients and to tailor treatment appropriately to provide the best long-term survival. The panel suggests that gynecologic oncologists be involved in the primary management of patients with endometrial cancer.

Diagnosis and Workup

About 90% of patients with endometrial carcinoma have abnormal vaginal bleeding, most commonly in the postmenopausal period. The workup was previously described (see *Overview* in this Discussion). Diagnosis can usually be made by an office endometrial biopsy.[28,29] 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.[28,30] Hysteroscopy may be helpful in evaluating the endometrium for lesions, such as a polyp, if the patient has persistent or recurrent undiagnosed bleeding.[31] Endometrial biopsy may not be accurate for diagnosing malignancies of the uterine wall such as mesenchymal tumors.

Other ancillary tests (ie, CT, MRI, PET) are reserved for evaluating extrauterine disease as indicated by clinical symptoms, physical findings, or abnormal laboratory findings.[32-36] In patients with extrauterine disease, a serum CA-125 assay may be helpful in monitoring clinical response.[37,38] However, serum CA-125 levels may be falsely increased in women who have peritoneal inflammation/infection or radiation injury, may be normal in women with isolated vaginal metastases, and may not predict recurrence in the absence of other clinical findings.[39-41] Currently, there is no validated screening test for endometrial carcinoma.[42,43]

Disease Staging

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

Several studies demonstrated that clinical staging was inaccurate and did not reflect actual disease extent in 15% to 20% of patients.[44-46] This reported understaging and, more importantly, the ability to identify multiple prognostic factors with a full pathologic review made possible with surgical staging, motivated a change in the staging classification. Therefore, in 1988, FIGO modified its staging system to emphasize thorough surgico-pathologic assessment of data, such as histologic grade, myometrial invasion, and the extent and location of extrauterine spread (including retroperitoneal lymph node metastases).[47] FIGO and the AJCC updated and refined the surgical/pathologic staging criteria for uterine neoplasms in 2009.[48-52] Separate staging systems for malignant epithelial tumors and uterine sarcomas are now available (see Tables 1 and 2, respectively).

The 2009 staging system streamlined stages I and II endometrial carcinoma. These revisions were made because the survival rates for some of the previous stages were similar.[51] 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.[51] Stage IIIC is now subdivided into IIIC1 and IIIC2, because survival is worse with positive para-aortic nodes.[51] While most of the previously published studies discussed in these NCCN Guidelines used the older 1988 FIGO staging system, these have been reinterpreted by the NCCN Panel to reconcile with the 2009 staging system.

Peritoneal cytology no longer affects the 2009 FIGO staging, because it is not viewed as an independent risk factor.[52] However, FIGO and AJCC continue to recommend that peritoneal washings be obtained and results recorded, because positive cytology may add to the effect of other risk factors (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).[53,54]

Principles of Evaluation and Surgical Staging for Endometrial Carcinoma

Staging should be done by a team with expertise in imaging, pathology, and surgery. The amount of surgical staging that is necessary to determine disease status depends on preoperative and intraoperative assessment of findings by experienced surgeons. For the 2014 update, the NCCN Panel added a new section on surgical staging (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines

for Endometrial Carcinoma). However, this surgical staging section only applies to malignant epithelial tumors and not to uterine sarcomas.

Pathology

An expert pathology review will determine the specific epithelial histology of the tumor (ie, various endometrioid histologies, serous carcinoma, clear cell carcinoma, carcinosarcoma). The pathologic assessment of the uterus and the nodes is described in the algorithm; this assessment should also include the Fallopian tubes and the ovaries (see *Hysterectomy and Pathologic Evaluation* in the NCCN Guidelines for Endometrial Carcinoma). The *Protocol for Examination of Specimens from Patients With Carcinoma of the Endometrium* from the College of American Pathologists (CAP) is a useful guide (http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2013/Endometrium_13protocol_3200.pdf) This CAP protocol was revised in October 2013 and reflects the updated FIGO/AJCC 2009 staging (ie, AJCC Cancer Staging Manual, 7th edition).

As the grade of the tumor increases, the accuracy of intraoperative evaluation of myometrial invasion decreases (ie, assessment by gross examination of fresh tissue). In one study, the depth of invasion was accurately determined by gross examinations in 87.3% of grade 1 lesions, 64.9% of grade 2 lesions, and 30.8% of grade 3 lesions.[55] 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.[56]

Additionally, recent data highlight the potential importance of ultrastaging (ie, serial sectioning and immunohistochemistry) to improve the accuracy of detecting micrometastases. In a cohort of 508 patients who underwent sentinel lymph node (SLN) mapping, ultrastaging detected 23 additional cases of micrometastasis that would have been missed by conventional hematoxylin and eosin staining.[57] A multicenter study of 304 women with presumed low- or intermediate-risk disease showed that SLN biopsy and ultrastaging detected metastatic SLNs in 3-fold greater number of patients than standard lymphadenectomy.[58]

Finally, SLN ultrastaging led to upstaging in a subset of the cohort of 89 patients with presumed low- or intermediate-risk endometrial cancer, including patients whose positive SLNs went undiagnosed by conventional histology.[59] Ultrastaging of SLNs led to modifications to planned adjuvant therapy in about half of this cohort.

Lymphadenectomy

Previously, a full standard lymphadenectomy (ie, dissection and assessment of both pelvic and para-aortic nodes) was recommended for all patients; however, a more selective and tailored lymphadenectomy approach is now recommended by the NCCN Panel to avoid systematic over-treatment.[60] No randomized trial data support routine full lymphadenectomy,[61] although some retrospective studies have suggested that it is beneficial.[62-64] Two randomized clinical trials from Europe reported that routine lymph node dissection did not improve the outcome of endometrial cancer patients, but lymphadenectomy did identify those with nodal disease.[65,66] However, these findings remain a point of contention.[67-69] 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.[70,71] The other concerns include the lack of central pathology review, subspecialty of surgeons, and adequacy of statistical power.

Decisions about whether to perform lymphadenectomy, and, if done, to what extent (eg, pelvic nodes only or both pelvic and para-aortic nodes), can be made based on preoperative and intraoperative findings. Criteria

have been suggested as indicative of low-risk for nodal metastases: 1) less than 50% myometrial invasion; 2) tumor less than 2 cm; and 3) well or moderately differentiated histology.[72,73] However, this may be difficult to accurately determine before final pathology results are available.

Another associated benefit of lymphadenectomy is the diagnosis of those with nodal metastases to guide appropriate adjuvant treatment to improve survival or decrease toxicity. However, one of the trials was not designed to address this question.[66] Therefore, there was no standardization of adjuvant treatment after staging surgery with lymphadenectomy. In fact, the use of lymphadenectomy did not translate into an increased use of adjuvant therapy. This may have contributed to the lack of difference in recurrence and survival in the two groups.

The question of whether to add periaortic lymphadenectomy to pelvic node dissection has been debated. Prior studies have shown conflicting information regarding the risk of para-aortic nodal metastases in patients without disease in the pelvic nodes.[46,72,74,75] There was a high rate of lymphatic metastasis above the inferior mesenteric artery, suggesting a need for systematic pelvic and para-aortic lymphadenectomy. Hence, periaortic lymphadenectomy up to the renal vessels may be considered for selective high-risk situations including those with pelvic lymphadenectomy or high-risk histologic features. Many surgeons do not do a full lymphadenectomy in patients with grade 1 early-stage endometrial cancer.[60]

In summary, lymph node dissection identifies patients requiring adjuvant treatment with RT and/or chemotherapy.[76] 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 lymphadenectomy should be done for selected patients with endometrial cancer with para-aortic lymphadenectomy done as indicated for high-risk patients (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).[5] Lymphadenectomy is contraindicated for patients with uterine sarcoma.

Sentinel Lymph Node Mapping

The new section on surgical staging (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma) includes recommendations about SLN mapping. SLN mapping may be considered (category 3) for patients with apparent uterine-confined endometrial cancer to assess whether they have metastatic pelvic lymph nodes.[77-80] In SLN mapping, dye is injected into the cervix, which travels to the sentinel nodes (see Figures 1–3 in *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma). A surgical SLN algorithm is proposed to decrease the false-negative rate (see Figure 4 in *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).[77,81] For example, suspicious or grossly enlarged nodes should be removed regardless of SLN mapping results. If mapping fails, a side-specific nodal dissection should be done.[77]

Because many NCCN Member Institutions do not routinely use SLN, it is a category 3 recommendation. In SLN mapping, the surgeon's expertise and attention to technical detail are critical. Patients may be able to avoid the morbidity of a standard lymphadenectomy with SLN mapping.[82,83] Because SLNs identify the primary lymphatic pathway, this increases the yield of finding metastatic disease during the mapping process.

SLN mapping may be most appropriate for those at low to intermediate risk for metastases and/or for those who may not tolerate a standard lymphadenectomy.[83-87] It is important to note that system-wide long-term outcomes data are not yet available for SLN mapping in endometrial cancer.[88,89]

Much of the data to support SLN mapping are based on single institution studies. Meta-analyses of the SLN mapping data in patients with endometrial cancer report a broad range in SLN detection rates and false negative rates.[90-92] A recent systematic review of seventeen studies with n >30 patients revealed detection rates of 60% to 100%; detection rates for studies with larger cohorts (n>100) were at least 80%. Retrospective application of a surgical algorithm generated 95% sensitivity, 99% predictive value, and a 5% false negative rate.[93]

Ultrastaging of SLNs can reveal lymph node metastases undetected through conventional histology, and studies suggest that SLN ultrastaging leads to upstaging in 5%-15% of patients.[80,82,85,87,93] However, the implications and appropriate management of micrometastases or isolated tumor cells (ITC) detected via SLN ultrastaging are not yet clear.[82,87,92,94,95] Future evaluation of prognosis may need to separately examine patients with scattered ITCs versus patients with aggregated micrometastasis.

Long-term follow-up was reported from a prospective multicenter study in 125 patients with early-stage endometrial carcinoma who underwent SLN biopsy. Patients with a positive SLN underwent EBRT and chemotherapy at a higher rate than those with a negative SLN. In patients with a detected SLN, recurrence-free survival at 50 months was 84.7%, and no difference was detected between patients with and without a positive SLN (P= .5).[96]

SLN mapping should be done in institutions with expertise in this procedure. If patients have apparent metastatic disease (based on imaging and surgical exploration), removal of nodes for staging purposes is not necessary because it will not change management.[32] The main contraindication for SLN mapping is uterine sarcoma. Additionally, SLN mapping should be done with particular caution in patients with high-risk histology (eg, serous carcinoma, clear cell carcinoma, carcinosarcoma).[60,97]

Minimally Invasive Procedures

Laparoscopic pelvic and para-aortic lymphadenectomy in association with total laparoscopic hysterectomy is being used in many practices.[60,98,99] However, patients having laparoscopy should be followed over a long term to compare their outcomes with those of traditional laparotomy.[100]

A randomized phase III trial evaluated laparoscopy for comprehensive surgical staging; patients (n = 2616) with clinical stage I to IIA disease (GOG-LAP2) were assessed.[100,101] Patients were randomly allocated 2:1 to laparoscopy or laparotomy. Results from LAP2 indicate that 26% of patients needed conversion to laparotomy because of poor visibility, metastatic cancer, bleeding, increased age, or increased body mass index. Detection of advanced cancer was not significantly different between the groups. However, significant differences were noted in removal of pelvic and para-aortic nodes (8% not removed with laparoscopy vs. 4% with laparotomy, $P < .0001$).[102,103] 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.[101]

Another randomized trial (n = 283) comparing laparoscopy versus laparotomy reported shorter hospital stay, less pain, and faster resumption of daily activities with laparoscopy.[104] However, laparotomy may still be required for certain clinical situations (eg, elderly patients, those with a very large uterus) or certain metastatic presentations.[100] Recent meta-analyses of the data from studies comparing hysterectomy via laparoscopy versus laparotomy report reduced surgical complication rates and hospital stays for laparoscopic procedures.[105,106] Survival outcomes were generally found to be comparable between both approaches in these analyses.

Robotic surgery is a minimally invasive technology that has been advocated by some as being a feasible approach in the primary management of endometrial cancer.[98,99,107-114] Costs for equipment and maintenance remain high.[115] Given the recent introduction of robotic surgery, long-term outcomes are still pending.[116-119] However, due to its potential advantages over traditional laparoscopic approaches, providers may elect to use this technique for minimally invasive surgery in endometrial cancer, especially for obese patients.[98,120] The SGO, American Association of Gynecologic Laparoscopists (AAGL), and American Congress of Obstetricians and Gynecologists (ACOG) have recently published guidelines or position statements about robotic surgery.[121-123] For recent reviews on the robotic-assisted surgery for gynecologic malignancies and associated cost issues, see Sinno and Fader and Gala et al.[124,125]

Primary Treatment

These NCCN Guidelines divide pure endometrioid cancer into three categories for delineating treatment: 1) disease limited to the uterus; 2) suspected or gross cervical involvement; and 3) suspected extrauterine disease. Most patients with endometrial cancer have stage I disease at presentation, and surgery (with or without adjuvant therapy) is recommended for medically operable patients. As a general principle, endometrial carcinoma should be removed en bloc to optimize outcomes; morcellation should be avoided.[126-128]

Disease Limited to the Uterus

To stage medically operable patients with endometrioid histologies clinically confined to the fundal portion of the uterus, the recommended surgical procedure includes total hysterectomy (TH)/BSO with selective surgical staging (see *Hysterectomy and Pathologic Evaluation,* and *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma and in this Discussion).[67] When indicated, surgical staging is recommended to gather full pathologic and prognostic data on which to base decisions regarding adjuvant treatment for select patients who do not have medical or technical contraindications to lymph node dissection (see *Lymphadenectomy* and *Sentinel Lymph Node Mapping* in this Discussion).

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

Selected patients with apparent uterine-confined endometrial carcinoma may be candidates for sentinel node mapping (category 3), which assesses the pelvic nodes and is less morbid than standard

lymphadenectomy (see *Sentinel Lymph Node Mapping* in this Discussion).

Incomplete Surgical Staging
For patients with incomplete (ie, not thorough) surgical staging and high-risk intrauterine features, imaging is often recommended, especially in patients with higher grade and more deeply invasive tumors.[129,130] Surgical restaging, including lymph node dissection, can also be done.[72] Based on the imaging and/or surgical restaging results, recommended adjuvant treatment options are provided in the algorithm (see Adjuvant Treatment for *Incompletely Surgically Staged* in the NCCN Guidelines for Endometrial Carcinoma).

Fertility-Sparing Therapy
Although the primary treatment of endometrial cancer is usually hysterectomy, continuous progestin-based therapy may be considered for highly selected patients with stage IA disease who wish to preserve their fertility.[131-135] Likewise, it may also be selectively used for young patients with endometrial hyperplasia who desire fertility preservation. The guidelines include an algorithm for fertility-sparing therapy in selected patients with biopsy-proven grade 1, stage IA endometrioid adenocarcinoma (see *Criteria for Considering Fertility-Sparing Options* in the NCCN Guidelines for Endometrial Cancer). The panel recommends consultation with a fertility expert. When considering fertility-sparing therapy, all of the criteria must be met as outlined in the algorithm (eg, no metastatic disease). Selected patients may require genetic counseling and testing. Patients should also receive counseling that fertility-sparing therapy is not the standard of care for the treatment of endometrial carcinoma. TH/BSO with surgical staging is recommended after childbearing is complete, if therapy is not effective, or if progression occurs. Fertility-sparing therapy is not recommended for high-risk patients (eg, those with high-grade endometrioid adenocarcinomas, uterine serous carcinoma, clear cell carcinoma, carcinosarcoma, and uLMS).

Continuous progestin-based therapy may include megestrol acetate, medroxyprogesterone, or an intrauterine device containing levonorgestrel.[131,132,136] A durable complete response occurs in about 50% of patients.[131] The use of progestin-based therapy should be carefully considered in the context of other patient-specific factors including contraindications such as breast cancer, stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis, and smoking.

In patients receiving progestin-based therapies, the NCCN Panel recommends close monitoring with endometrial sampling (biopsies or D&C) every 3 to 6 months. TH/BSO with staging is recommended: 1) after childbearing is complete; 2) if patients have documented progression on the biopsies; or 3) if endometrial cancer is still present after 6 to 9 months of progestin-based therapy.[135,137] Although some young women who had subsequent negative endometrial biopsies after hormonal therapy were able to become pregnant (35%), their ultimate recurrence rate was high (35%).[131,134,138-140]

In premenopausal women with stage IA to B endometrial cancer, data suggest that ovarian preservation is safe and not associated with an increased risk of cancer-related mortality; patients were followed for 16 years.[141] Other studies also suggest that ovarian preservation may be safe in women with early-stage endometrial cancer.[142,143]

Suspected or Gross Cervical Involvement
For patients with suspected or gross cervical involvement (endometrioid histologies), cervical biopsy or MRI should be considered (see *Additional Workup* in the NCCN Guidelines for Endometrial Carcinoma).[129,130] If negative, patients are assumed to have disease that

is limited to the uterus and are treated as previously described (see *Primary Treatment* in the NCCN Guidelines for Endometrial Carcinoma). It may be difficult to distinguish primary cervical carcinoma from stage II endometrial carcinoma. Thus, for operable patients with cervical involvement, radical hysterectomy is recommended along with BSO, cytology (peritoneal lavage), and dissection of lymph nodes if indicated (see *Principles of Evaluation and Surgical Staging* and *Hysterectomy and Pathologic Evaluation* in the NCCN Guidelines for Endometrial Carcinoma).[67] In these patients, radical or modified radical hysterectomy may improve local control and survival when compared with TH.[144,145] Alternatively, the patient may undergo RT (category 2B) followed by TH/BSO. However, preoperative RT is a category 2B recommendation because the NCCN Panel feels that upfront surgery is the preferred option for these patients.

Patients Not Suited for Primary Surgery

Tumor-directed radiation therapy (RT) with (or without) chemotherapy is an effective treatment that can provide some measure of pelvic control and long-term progression-free survival (PFS) (see *Principles of Radiation Therapy* in the NCCN Guidelines for Uterine Neoplasms).[146-148] If rendered operable, surgical resection should follow. Initial chemotherapy alone can also be considered (category 2B). Following chemotherapy, local treatment should still be utilized (ie, surgery if feasible, or RT).

Hormonal therapy may be considered in selected patients with endometrioid histology (eg, estrogen and progesterone receptor–positive [ER/PR-positive] patients), who are not candidates for RT or surgery, if they are closely monitored (eg, consider endometrial biopsies every 3–6 months).[42,149] Progesterone-based therapy can provide some benefit with low toxicity in patients with low-grade tumors.[150] Tamoxifen with alternating megestrol may be used.[151] Aromatase inhibitors have also been used.[152-155]

Suspected Extrauterine Disease

If extrauterine disease (endometrioid histologies) is suspected, imaging studies are recommended if clinically indicated (see *Additional Workup* in the NCCN Guidelines for Endometrial Carcinoma). Patients with no extrauterine disease are treated using the guidelines for disease limited to the uterus. Intra-abdominal disease (ie, ascites; omental, nodal, ovarian, or peritoneal involvement) warrants surgical intervention using TH/BSO with cytology (peritoneal lavage), pelvic and para-aortic lymph node dissection if indicated, and surgical debulking. Preoperative chemotherapy can be considered.

The surgical goal is to have no measurable residual disease; several studies support debulking.[67,156-158] Patients with unresectable extrauterine pelvic disease (ie, 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.[159-162] Chemotherapy alone can also be considered. Based on treatment response, patients should be re-evaluated for surgical resection and/or RT. For extra-abdominal disease (eg, liver involvement), recommended options include chemotherapy and/or RT and/or hormone therapy. Palliative TH/BSO may be considered.

Adjuvant Therapy

Uterine-Confined Disease

Thorough surgical staging provides important information to assist in selection of adjuvant therapy for endometrial tumors (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma). Patients with stage I endometrial cancer, who have thorough surgical staging, are stratified by adverse risk factors (ie,

age, positive LVSI, tumor size, depth of invasion, lower uterine [cervical/glandular] segment involvement).[163,164] Recommended adjuvant treatment is shown in the algorithm (see the NCCN Guidelines for Endometrial Carcinoma). Note that the treatment algorithm was revised in 2010 based on the updated FIGO/AJCC staging (7th edition).[49,51] However, by necessity, much of the discussion in this manuscript has been based on data from patients staged using the older FIGO/AJCC staging system. The implications of *stage migration* should be taken into account when evaluating historical data (see Table 1).

The basic concept underlying the recommendations in the NCCN Guidelines is the trend toward selection of more aggressive adjuvant therapy for patients as tumor grade and myometrial and/or cervical invasion worsen, because risk exists on a continuum.[165,166] In surgical stage I and II endometrial cancer, other pathologic factors that may influence the decision regarding adjuvant therapy include LVSI, patient age, tumor volume, depth of invasion, and lower uterine segment or surface cervical glandular involvement. When administering adjuvant RT, it should be initiated as soon as the vaginal cuff has healed, no later than 12 weeks after surgery.

Significant controversy centers on how much adjuvant therapy is necessary in patients with surgical stage I endometrial cancer, regardless of intrauterine features, if extrauterine disease has been clearly ruled out. In a large prospective study, the GOG reported that the 5-year survival rate for surgical stage I patients with no adverse risk factors other than grade and myometrial invasion (ie, without extrauterine disease, isthmus/cervical involvement, or LVSI) was 92.7%.[167] The practice of surgical staging has led to a decrease in the use of adjuvant therapy for stage I endometrial carcinoma, which is reflected in the option of *observation* in the NCCN Guidelines (see section on adjuvant treatment on ENDO-4 in the NCCN Guidelines for Endometrial Carcinoma).[76,164,165,168-170]

The recommended postoperative (ie, adjuvant) treatment options for surgical stage II patients (using thorough surgical staging) are shown in the algorithm (see *Adjuvant Treatment for Stage II* in the NCCN Guidelines for Endometrial Carcinoma). The NCCN Panel generally agrees on the role of adjuvant therapy for patients with an invasive cervical component if extrafascial hysterectomy is performed. However, for patients with stage II disease who have had a radical hysterectomy with negative surgical margins and no evidence of extrauterine disease, observation or vaginal brachytherapy are options. As with stage I disease, the presence of adverse risk factors should be considered when selecting adjuvant therapy.[171]

In 2015, the panel removed observation as a recommended option in the adjuvant setting for patients with Stage IB, grade 3 disease with additional risk factors. Observation was changed from a category 2A recommendation to category 2B for patients with Stage IB, grade 3 disease with no additional risk factors. For the 2016 update of the guidelines, recommendations for Stage II, grades 2 and 3 disease were amended. For stage II, grade 2 disease, the revised recommendations are vaginal brachytherapy and/or EBRT [formerly pelvic RT and vaginal brachytherapy]. For stage II, grade 3 disease, revised recommendations are EBRT with (or without) vaginal brachytherapy, with (or without) chemotherapy [formerly pelvic RT *and* vaginal brachytherapy, with (or without) chemotherapy].

Adjuvant RT

Several phase III trials have assessed adjuvant therapy in patients with uterine-confined disease. In summary, the use of adjuvant RT improves pelvic control in patients with selected risk factors (and may improve

PFS), but RT did not improve overall survival in any of the trials. However, many of these trials had limitations because most of the patients were low risk (ie, they had low-risk intrauterine pathologic risk factors). Thus, the trials were underpowered for patients with high-risk factors. It is recognized that in patients with uterine-confined disease, there is a spectrum of risk based on intrauterine pathologic findings. Adverse intrauterine pathologic risk factors include high-grade tumors, deep myometrial invasion (and consequently more advanced stage), LVSI, and serous or clear cell carcinoma histologies.

Four trials have evaluated the role of adjuvant external-beam pelvic RT in patients with endometrial carcinoma. In 2 of these trials, the patients were not formally staged (Postoperative Radiation Therapy in Endometrial Carcinoma [PORTEC-1], Aalders).[172,173] In the third trial (ASTEC/EN.5), only 50% of the patients were thoroughly staged as part of a companion surgical protocol.[65,174] However, formal surgical staging was mandated for all patients in the fourth trial (Gynecologic Oncology Group [GOG] 99).[175] Note that these trials used the older staging system (ie, before 2009).

The PORTEC-1 trial suggested that external-beam pelvic RT provides a therapeutic benefit in selected patients with uterine-confined disease.[172,176] Although RT significantly decreased locoregional recurrence, it did not increase overall survival.[177] The Aalders' randomized trial found that RT reduced vaginal (ie, locoregional) recurrences but did not reduce distant metastases or improve survival.[173] A recent pooled randomized trial (ASTEC/EN.5) suggested that adjuvant pelvic RT alone did not improve either relapse-free survival (ie, PFS) or overall survival in patients with intermediate-risk or high-risk early-stage endometrial cancer, but there was a small improvement in pelvic control.[174] However, the ASTEC/EN.5 study is very controversial; 51% of the patients in the ASTEC observation group received vaginal brachytherapy.[69,178] The Keys' trial (GOG 99) showed that adjuvant pelvic RT improved locoregional control and relapse-free interval (ie, PFS), without overall survival benefit.[175] 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.[175,179,180]

To help select a patient population who may benefit from adjuvant RT, the GOG 99 and PORTEC trials defined risk factors for women at high-intermediate risk (HIR) for recurrence.[172,175] These risk factors include age, in addition to deep myometrial invasion, grade, and LVSI. In GOG 99, women younger than 50 years had to have all 3 histologic risk factors to be considered HIR.[175] If they were 50 to 70 years, they were considered HIR if they had 2 histologic risk factors. Women 70 years or older were defined as HIR if they also had one risk factor. In PORTEC-1, women had to have 2 of 3 risk factors (ie, age >60 years, deep myometrial invasion, grade 3 histology) to be considered at HIR for recurrence.[172,179]

Due to concerns about potential toxicity of external-beam pelvic RT, the role of vaginal brachytherapy alone in uterine-confined disease has been evaluated. PORTEC-2 randomly assigned patients to external-beam pelvic RT versus vaginal brachytherapy alone in uterine-confined disease. PORTEC-2 showed excellent and equivalent vaginal and pelvic control rates with both adjuvant radiation approaches and no difference in overall survival.[181] 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.[179-188] The use of vaginal brachytherapy and/or whole pelvic RT should be carefully tailored to a patient's pathologic

findings. Both PORTEC-1 and PORTEC-2 specifically excluded patients with 1998 FIGO stage 1C and grade 3 endometrial carcinoma (2009 FIGO stage IB, grade 3);[49,51] thus, the use of adjuvant brachytherapy alone in the highest risk subset remains undetermined. A recent trial (GOG 249) examined vaginal cuff brachytherapy followed by carboplatin/paclitaxel therapy versus EBRT only in patients with high-risk, uterine-confined endometrial carcinoma. Preliminary data suggest no significant difference in survival outcomes between the groups, although the brachytherapy/chemotherapy group experienced more acute toxicity.[189]

Analysis of pooled data from PORTEC-1 and PORTEC-2 ranked the predictive power of multiple variables on patient outcomes examined in these trials. Patient age, tumor grade, and LVSI were highly predictive for locoregional relapse (LRR), distant relapse (DR), overall survival (OS), and disease-free survival (DFS), and treatment given (EBRT versus vaginal brachytherapy) were predictive for LRR and DFS.[163] The benefit of adjuvant external-beam RT (EBRT) in the highest risk spectrum of uterine-confined disease remains controversial. Most NCCN Panel Members feel that patients with deeply invasive grade 3 tumors should receive adjuvant treatment. Two large retrospective SEER analyses of women with endometrial cancer found that adjuvant RT improved overall survival in those with high-risk disease.[190,191] In a meta-analysis of randomized trials, a subset analysis found that adjuvant pelvic RT for stage I disease was associated with a trend towards a survival advantage in the highest-risk spectrum (eg, those with 1988 FIGO stage IC grade 3) but not in lower risk patients; however, other reviews have shown conflicting results.[183,192-196]

Recently, results were published from a long-term follow-up study (median 20.5 years) of 568 patients with early-stage endometrial carcinoma who were enrolled in the Aalders trial. The study compared long-term outcomes in women who received vaginal brachytherapy plus EBRT versus vaginal brachytherapy alone. The findings suggested no statistical difference in overall survival between the study groups, and in this cohort, patients younger than 60 years of age who received EBRT had increased incidence of secondary cancers and subsequent higher mortality rates.[183]

Adjuvant Chemotherapy

Patients with deeply invasive, grade 3, uterine-confined disease (2009 FIGO stage IB, grade 3 [formerly 1988 FIGO stage IC, grade 3]) have a relatively poor prognosis. Despite adjuvant therapy with pelvic RT, a significant number of patients continue to have an appreciable risk of distant metastases.[175,176] Therefore, some clinicians suggested that adding chemotherapy to adjuvant RT may provide added therapeutic benefit (ie, decrease distant metastases).[165,197] Studies have evaluated the role of chemotherapy in highest risk uterine-confined disease.[197,198] PFS is improved with adjuvant sequential chemotherapy/RT.[197] However, the NCCN Panel feels that adjuvant chemotherapy is a category 2B recommendation in this setting because an overall survival advantage has not been shown.[197] We await final results from GOG 249.

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.[199-201] Patients with extrauterine disease confined to the lymph nodes or the adnexa may be treated with pelvic or extended-field RT alone.[202] 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 *Adjuvant Treatment for Stage III* in the NCCN Guidelines for

Endometrial Carcinoma) and include chemotherapy and/or tumor-directed RT.

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.[203,204] A randomized phase III GOG (122) trial assessed optimal adjuvant therapy for patients with endometrial cancer who had extrauterine disease. In this trial, patients with stage III and intra-abdominal stage IV disease who had minimal residual disease were randomly assigned to whole abdominopelvic RT versus 7 cycles of combined doxorubicin (60 mg/m^2) and cisplatin (50 mg/m^2) treatment, with an additional cycle of cisplatin (AP). This GOG trial reported that AP chemotherapy improved PFS and overall survival when compared with whole abdominopelvic RT; however, acute toxicity (eg, peripheral neuropathy) was greater in the AP chemotherapy arm.[160]

The GOG 122 study established the role of adjuvant multiagent systemic chemotherapy for curative intent in patients with extrauterine disease. Thus, in the NCCN Guidelines, 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 to chemotherapy and is no longer recommended. For the purposes of these guidelines, whole abdominal radiotherapy is not considered to be tumor-directed RT (see *Principles of Radiation Therapy* in the NCCN Guidelines for Uterine Neoplasms). Multimodality therapy is now the basis of randomized trials evaluating therapy (eg, GOG 258, PORTEC-3).

Recurrences were frequent in both treatment arms of GOG 122, occurring in the pelvis and abdomen. Approximately 52% of patients with advanced endometrial carcinoma had recurrences, indicating the need for further therapeutic improvement in this high-risk patient population.[160] A study found that combined modality adjuvant therapy (using chemotherapy and tumor-directed RT) may provide a therapeutic benefit when compared with other sequencing modalities (chemotherapy followed by RT or vice versa).[162,205,206]

A follow-up study evaluated the role of chemotherapy “intensification” for this patient population. The GOG 184 trial assessed combination chemotherapy (cisplatin and doxorubicin with [or without] paclitaxel) with more limited radiation fields (involved-field radiation either to the pelvis or to the pelvis plus para-aortic nodes). Results indicate that the 3-drug regimen did not improve survival when compared with the 2-drug regimen after 3 years of follow-up and that the more intensive chemotherapy resulted in greater toxicity (eg, hematologic toxicity, sensory neuropathy, myalgia).[161]

Adjuvant therapy options were compared in a multicenter retrospective analysis of 265 patients with optimally resected stage IIIC endometrial carcinoma. Compared with patients receiving adjuvant RT or adjuvant RT plus chemotherapy, patients who received adjuvant chemotherapy had a 2.2 fold increased risk of recurrence and a 4.0 fold increased risk of death.[201] In a retrospective review of 116 patients with stage IIIC endometrial cancer, adjuvant RT significantly improved overall survival in patients with endometriod histology, high-grade tumors, and positive para-aortic lymph nodes. Conversely, patients with low-grade tumors and non-endometrioid histology that received RT had similar overall survival compared with those who did not. [207] In a multicenter retrospective review of 73 patients with stage IIIA endometrial carcinoma, surgery followed by both chemotherapy and radiation therapy provided the highest 5-year OS.[208]The role of adjuvant RT with chemotherapy for treating high-risk endometrial carcinoma remains an area of active investigation (eg, GOG 258, PORTEC-3).

Radiotherapy Principles

RT has been a widely used modality in the treatment of patients with endometrial cancer; it clearly improves locoregional control. *Tumor-directed RT* refers to RT directed at sites of known or suspected tumor involvement and may include EBRT and/or brachytherapy.[166] RT is described in detail in the algorithm, including target areas and doses for pelvic RT and brachytherapy (see *Principles of Radiation Therapy* in the NCCN Guidelines for Uterine Neoplasms).

Although adjuvant RT is typically not associated with high rates of severe morbidity,[209] studies have focused on subtle effects on quality of life (eg, diarrhea, bowel symptoms) that deserve further investigation.[184,186] In the PORTEC-2 trial, vaginal brachytherapy was associated with better quality of life when compared with EBRT without a significant detriment to outcome.[184] Therefore, many patients who were previously treated with adjuvant EBRT are now appropriately treated with vaginal brachytherapy; this recommendation is reflected in the NCCN Guidelines. Patients treated with RT are prone to vaginal stenosis, which can impair sexual function. Women can use vaginal dilators to prevent or treat vaginal stenosis. Dilator use can start 2 to 4 weeks after RT is completed and can be used indefinitely (http://www.mskcc.org/cancer-care/patient-education/resources/improving-your-vaginal-health-after-radiation-therapy).

Post-Treatment Surveillance

The recommended post-treatment surveillance protocol for endometrial cancer is shown in the algorithm (see *Surveillance* in the NCCN Guidelines for Endometrial Carcinoma).[32] These recommendations recognize that the value of intensive surveillance has not been demonstrated in this disease; therefore, ancillary testing is not recommended.[210,211]

Patients with clinical stage I and stage II endometrial cancer have a recurrence rate of approximately 15%;[23,211-213] 50% to 70% of these patients are symptomatic. For most patients, disease recurs within 3 years of initial treatment. Because most recurrences are symptomatic, all patients should receive verbal and written information regarding the symptoms of recurrent disease.[211] Patients with bleeding (vaginal, bladder, or rectal), decreased appetite, weight loss, pain (in the pelvis, abdomen, hip, or back), cough, shortness of breath, and swelling (in the abdomen or legs) should seek prompt evaluation and not delay until the next scheduled appointment. As clinically indicated, imaging may be helpful in the detection of recurrence.

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 (eg, blood pressure determination, breast examination, mammography as clinically indicated, stool guaiac test, immunizations), including lifestyle, obesity, exercise, smoking cessation and nutrition counseling (see the NCCN Guidelines for Survivorship, the NCCN guidelines for Smoking Cessation, and http://www.cancer.org/treatment/survivorshipduringandaftertreatment/index).[214-216] Patients should be educated regarding sexual health, vaginal dilator use, and vaginal lubricants or moisturizers. Other health problems that often coexist in patients with endometrial cancer can also be evaluated during follow-up.

Given the lack of prospective studies regarding the optimal frequency of post-treatment follow-up, the NCCN Panel believes that the algorithm represents a reasonable surveillance scheme. The use of vaginal

cytology is no longer recommended for asymptomatic patients consistent with the SGO guidelines.[210,211,213,217] Patients with stage I endometrial cancer have a low risk of asymptomatic vaginal recurrence (2.6%), especially after adjuvant brachytherapy, and vaginal cytology is not independently useful for detecting recurrences in this group of patients.[218] A recent multi-institutional review examined the utility of various surveillance methods in 254 patients with high-grade disease, revealing that symptoms led to the detection of the most recurrences (56%), followed by physical exam (18%), surveillance CT (15%), CA-125 (10%), and vaginal cytology (1%).[219]

Hormone Replacement Therapy for Hypoestrogenism

After BSO, hypoestrogenism is associated with hot flashes, mood lability, vaginal dryness, pelvic soft tissue atrophy, osteoporosis, and an increased risk of cardiovascular disease. In postmenopausal women, estrogen replacement therapy was believed to reduce or reverse some of these signs and symptoms. However, women who have had BSO for endometrial adenocarcinoma have usually been denied estrogen replacement therapy for fear of inducing a higher relapse rate, because this cancer has historically been considered an estrogen-linked malignancy.[220,221] As such, estrogen replacement therapy for such patients remains controversial.

However, it has never been proven that relapse rates are higher in endometrial cancer patients who receive estrogen replacement therapy after hysterectomy. Several retrospective trials of estrogen replacement after treatment of early-stage endometrial cancer have shown no increase in tumor recurrence or cancer-related deaths.[222-224] In women with stage I to II endometrial cancer who had hysterectomy, a randomized trial of estrogen replacement therapy versus placebo did not find an increased rate of recurrence or new malignancy; the median follow-up was 35.7 months.[225] However, estrogen replacement trials in postmenopausal females without a history of malignancy have demonstrated a significantly increased risk of breast cancer.[226]

Initially, the Women's Health Initiative (WHI) Estrogen-Alone Trial in women who had hysterectomy (n = 10,739) reported that the risk of breast cancer and cardiovascular disease (eg, stroke) were increased and that estrogen replacement therapy was of concern; thus, the trial was stopped.[227] However, recent long-term follow-up data from this trial suggest that the risk from estrogen-alone replacement therapy (without progesterone) may not be as high in younger women (<60 years) who have had hysterectomy.[228]

The NCCN Panel agrees that estrogen replacement therapy is a reasonable option for patients who are at low risk for tumor recurrence, but initiating such therapy should be individualized and discussed in detail with the patient.[229,230] 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.[231,232] Long-term comparisons between conjugated estrogens and SERMs for hormone replacement therapy are needed. Non-hormonal therapy may be considered in patients who are deemed poor candidates for hormone replacement therapy (eg, smokers, history of breast cancer, history of multiple strokes).[233,234]

Treatment of Recurrent or Metastatic Disease

Localized Disease

Patients with local or regional recurrences can be evaluated for further treatment (see *Clinical Presentation* in the NCCN Guidelines for Endometrial Carcinoma). For recurrences confined to the vagina or the

pelvis alone, second-line treatment (typically with RT and/or surgery or chemotherapy [or hormonal therapy]) can be effective. For patients with no prior RT exposure at the recurrence site or previous brachytherapy only, the panel recommends RT plus brachytherapy, or surgery. Isolated vaginal recurrences treated with RT have good local control and 5-year survival rates of 50% to 70%[235-237]. Prognosis is worse if there is extravaginal extension or pelvic lymph node involvement.[236]

After RT, it is unusual for patients to have recurrences confined to the pelvis. The management of such patients remains controversial. For patients previously treated with EBRT at the recurrence site, recommended therapy for isolated relapse includes: 1) surgery with (or without) intraoperative RT (IORT) (category 3 for IORT); 2) hormonal therapy; or 3) chemotherapy. In selected patients, radical surgery (ie, pelvic exenteration) has been performed with reported 5-year survival rates approximating 20%.[238-241]

Treatment for para-aortic or common iliac lymph node invasion and for upper abdominal or peritoneal recurrences is shown in the algorithm (see *Additional Therapy* in the NCCN Guidelines for Endometrial Carcinoma). However, for gross upper abdominal residual disease, more aggressive treatment for relapse is recommended, as outlined for disseminated metastases in *Therapy for Relapse* in the NCCN *Guidelines for Endometrial Carcinoma*. For resectable isolated metastases, consider surgical resection with or without RT or ablative therapy. Providers can also consider hormone therapy (category 2B) or chemotherapy (category 3). Further recurrences or disease not amenable to local therapy are treated as disseminated metastases. Palliative care measures should also be considered in management of patients with systemic disease (see the NCCN Guidelines for Palliative Care and http://emedicine.medscape.com/article/270646-overview).

Systemic Disease

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

Hormonal Therapy

The role of hormonal therapy in recurrent or metastatic cancer has been primarily evaluated in patients with endometrioid histologies only. Hormone therapy should only be considered for lower grade endometrioid histologies (ie, not for patients with grade 3 endometrioid, serous, or clear cell carcinomas, or carcinosarcoma), and in patients with small tumor volume or indolent growth rate. Hormonal therapy is also used for selected patients with ESS (see section on *Uterine Sarcomas* in this Discussion). Hormonal agents for treating metastatic disease include megestrol with alternating tamoxifen, progestational agents alone, aromatase inhibitors, or tamoxifen alone.[151-153,242-244] No particular drug, dose, or schedule has been found to be superior. The main predictors of response in the treatment of metastatic disease are well-differentiated tumors, expression of ER/PR receptors, a long disease-free interval, and the location and extent of extrapelvic (particularly pulmonary) metastases.

For asymptomatic or low-grade disseminated metastases, hormonal therapy with progestational agents has shown good responses, particularly in patients with ER/PR-positive disease.[155,245-247] Tamoxifen has a 20% response rate in those who do not respond to standard progesterone therapy.[248,249] Tamoxifen has also been combined with progestational agents; however, a few patients had grade 4

thromboembolic events with this combination regimen.[151,242,250] In some patients, aromatase inhibitors (eg, anastrozole, letrozole) may be substituted for progestational agents or tamoxifen.[154,155,247,251]

Other hormonal modalities have not been well studied, and adjuvant therapy with hormonal agents has not been compared with cytotoxic agents.[155,252] If disease progression is observed after hormonal therapy, cytotoxic chemotherapy can be considered. However, clinical trials or best supportive care (see the NCCN Guidelines for Palliative Care) are appropriate for patients with disseminated metastatic recurrence who have a poor response to hormonal therapy and chemotherapy.

Chemotherapy

Chemotherapy for endometrial cancer has been extensively studied.[253,254] Based on the current data, multiagent chemotherapy regimens are preferred for metastatic, recurrent, or high-risk disease, if tolerated. Single-agent therapy can also be used (see *Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease* in the NCCN Guidelines for Endometrial Carcinoma).

A phase III randomized trial (GOG 177) compared 2 combination chemotherapy regimens in women with advanced/metastatic or recurrent endometrial carcinoma. The 273 women were randomly assigned to 1) cisplatin, doxorubicin, and paclitaxel; or 2) cisplatin and doxorubicin. The 3-drug regimen was associated with improved survival (15 vs. 12 months, $P < .04$) but with significantly increased toxicity (ie, peripheral neuropathy); therefore, it is not widely used.[255,256] These regimens are now category 2A in the NCCN Guidelines, because most panel members feel that carboplatin/paclitaxel is a less toxic regimen (see *Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease* in the NCCN Guidelines for Endometrial Carcinoma). The response rates with other multiagent chemotherapy have ranged from 31% to 81% but with relatively short durations. The median survival for patients in such trials remains approximately 1 year.[253,254]

Carboplatin and paclitaxel is an increasingly used regimen for advanced/metastatic or recurrent endometrial cancer; the response rate is about 40% to 62%, and overall survival is about 13 to 29 months.[257-260] A phase III trial (GOG 209) compared carboplatin and paclitaxel versus cisplatin, doxorubicin, paclitaxel, and filgrastim (granulocyte-colony stimulating factor).[257] Trial data presented at a national meeting show that oncologic outcomes are similar, but the toxicity and tolerability profile favor carboplatin/paclitaxel. Thus, the carboplatin/paclitaxel regimen is now the preferred approach for many patients. For patients in whom paclitaxel is contraindicated, docetaxel can be considered in combination with carboplatin.[261]

If multiagent chemotherapy regimens are contraindicated, then single-agent therapy options include paclitaxel, cisplatin, carboplatin, doxorubicin, liposomal doxorubicin, topotecan, and docetaxel (category 2B for docetaxel) (see *Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease* in the NCCN Guidelines for Endometrial Carcinoma).[155,262-264] When single agents are used as first-line treatment, responses range from 21% to 36%.[247,265] When single agents are used as second-line treatment, responses range from 4% to 27%; paclitaxel is the most active in this setting.[265] Some oncologists have used liposomal doxorubicin, because it is less toxic than doxorubicin; the response rate of liposomal doxorubicin is 9.5%.[266] 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 because it is less active (7.7% response rate) than other agents.[150,267]

New biologic and molecular therapies for the treatment of recurrent or metastatic endometrial carcinoma are being assessed in clinical trials.[150,268] 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.[269] Temsirolimus has been used as first-line or second-line therapy for recurrent or metastatic endometrial cancer and has a partial response rate of 4% in second-line therapy.[270] Based on these studies, the NCCN Panel considers bevacizumab or temsirolimus as appropriate single-agent biologic therapy for patients who have progressed on previous cytotoxic chemotherapy.[268-271] Everolimus combined with letrozole is also under investigation for recurrent disease with positive preliminary findings.[272]

Uterine Serous Carcinomas, Clear Cell Carcinomas, and Carcinosarcomas

Overview

Uterine serous carcinomas, clear cell carcinomas, and carcinosarcomas are considered more aggressive histologic variants of malignant epithelial tumors, with a higher incidence of extrauterine disease at presentation.[273-280] Carcinosarcomas are aggressive tumors that are staged as high-grade endometrial cancer (see Table 1).[281,282] Serous carcinomas, clear cell carcinomas, and carcinosarcomas are all considered high-risk histologies and high-grade by default, although they are staged using the same FIGO/AJCC staging system (ie, 7th edition) as endometrial cancers (see Table 1).[49]

Pathologists now believe that carcinosarcomas (also known as MMMTs) are metaplastic carcinomas and not uterine sarcomas; therefore, carcinosarcomas are included in the high-risk malignant epithelial tumors section of the NCCN Guidelines (see *Serous Carcinoma, Clear Cell Carcinoma, or Carcinosarcoma* in the NCCN Guidelines for Endometrial Carcinoma).[277,280,283,284] Even patients with apparent early-stage disease may have distant metastases. Thus, fertility-sparing therapy is not recommended for these aggressive tumors. If done, SLN mapping should proceed with particular caution.

Patients with uterine serous carcinoma, clear cell carcinoma, or carcinosarcoma 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; PET may also be useful.[273] Patterns of failure often mimic those of ovarian cancer.

Treatment

Multimodality therapy is typically recommended for these histologically aggressive tumors. Primary treatment includes TH/BSO with surgical staging, peritoneal lavage for cytology, omental and peritoneal biopsies, and consideration of maximal tumor debulking for gross disease (see *Principles of Evaluation and Surgical Staging* in the NCCN Guidelines for Endometrial Carcinoma).[285]

Adjuvant therapy is highly individualized.[286-293] For patients with stage IA without myometrial invasion, options include: 1) observation (if no residual disease in hysterectomy specimen); 2) chemotherapy with (or without) vaginal brachytherapy; or 3) tumor-directed RT.[294] For all other patients with more advanced disease, chemotherapy with (or without) tumor-directed RT is the preferred option.[275,287,291,295] Adjuvant platinum/taxane-based therapy appears to improve survival in patients with uterine serous carcinoma and clear cell carcinoma, whereas ifosfamide/paclitaxel (category 1) is recommended for carcinosarcomas (see *Uterine Serous Carcinomas, Clear Cell Carcinomas, and Carcinosarcomas* in this Discussion and *Systemic Therapy for*

Recurrent, Metastatic, or High-Risk Disease in the NCCN Guidelines for Endometrial Carcinoma).[273-275,296-298]

Whole abdominopelvic RT with (or without) vaginal brachytherapy is no longer recommended as a primary treatment option for patients with advanced disease, because the NCCN Panel no longer feels that routine use of whole abdominal RT is appropriate.[160,295,299] Chemotherapy with (or without RT) appears to be more effective than RT alone.[287] Data are conflicting regarding the rate of abdominal recurrence in these patients.[295,300-304] Whole abdominal radiotherapy is not considered to be tumor-directed RT (see *Principles of Radiation Therapy* in the NCCN Guidelines for Uterine Neoplasms). As previously mentioned, *tumor-directed RT* refers to RT directed at sites of known or suspected tumor involvement and may include EBRT and/or brachytherapy. In general, tumor-directed EBRT is directed to the pelvis with (or without) the para-aortic region.

Several studies have examined treatment paradigms for uterine serous or clear cell carcinoma. A recent phase II trial in patients with papillary serous carcinoma suggested favorable outcomes with concurrent pelvic RT and paclitaxel followed by additional rounds of adjuvant paclitaxel,[305] indicating the potential benefits of combined modality therapy. Retrospective data was reviewed from 279 patients with serous or clear cell carcinoma who were treated at high-volume cancer centers. Adjuvant treatment (RT, chemotherapy, or chemoradiation) was associated with improved OS in stages IB-II disease but not stage IA disease (HR, 0.14; 95% CI, 0.02 to 0.78; p=0.026) disease.[306] Additionally, survival outcomes did not differ based upon surgical approach (robotic laparoscopy versus laparotomy).

Two multi-institutional retrospective reviews examined the impact of adjuvant therapy (vaginal brachytherapy, n=103; adjuvant pelvic radiation or chemotherapy, n=115) in patients with stage 1A uterine papillary serous carcinoma. In both cohorts, patients undergoing surgical staging/lymphadenectomy had greater PFS and OS than unstaged patients.[307,308] Vaginal brachytherapy reduced the vaginal recurrence rate but did not impact PFS or OS.[307] In unstaged patients, chemotherapy or pelvic RT were associated with greater PFS and OS, but no survival benefits were observed for adjuvant treatment in surgically staged patients.[308]

For treating carcinosarcoma, ifosfamide was historically considered the most active single agent.[297,309,310] A phase III trial for advanced carcinosarcoma showed that the combination of ifosfamide and paclitaxel increased survival and was less toxic than the previously used cisplatin/ifosfamide regimen.[297,311] 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 *Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease* in the NCCN Guidelines for Endometrial Carcinoma).[297,299] However, the toxicity of ifosfamide has led to investigation of better-tolerated regimens. A phase II trial suggests that paclitaxel/carboplatin is also a useful regimen for carcinosarcoma (response rate, 54%).[312] A GOG trial is currently assessing ifosfamide/paclitaxel versus carboplatin/paclitaxel.[281]

Data regarding carcinosarcoma suggest that adjuvant pelvic radiotherapy decreases the rate of local recurrences when compared with surgery alone.[313-318] This local control improvement in some series correlates with an improvement in survival, although other data show that lymphadenectomy confers greater benefit.[317-320] A phase III randomized trial (GOG 150) in patients with carcinosarcoma of the uterus showed a trend towards a decreased mortality rate for patients receiving cisplatin/ifosfamide vs. whole-abdominal RT (P = .085),

although these did not reach statistical significance in this underpowered trial.[299,304] A recent cohort study in women with early-stage MMMT suggests that postoperative chemotherapy improves PFS compared to RT or observation.[281]

Uterine Sarcomas

Overview

In 2015, an estimated 1600 cases of uterine sarcomas are anticipated (about 3% of all uterine neoplasms).[1,2] Uterine sarcomas are malignant mesenchymal tumors that include endometrial stromal sarcoma (ESS), undifferentiated uterine sarcoma (UUS), and uterine leiomyosarcoma (uLMS) (see *Uterine Sarcoma Classification* in the NCCN Guidelines for Uterine Sarcoma). According to 2012 systematic review of data from 1970 to 2011, uLMS was the most common subtype (63%), followed by ESS (21%) and less common subtypes such as UUS.[321] Even rarer subtypes of malignant mesenchymal tumors that can occur in the uterus include adenosarcoma, rhabdomyosarcoma (RMS), and perivascular epithelioid cell neoplasm (PEComa).[322] Carcinosarcomas were previously categorized and included in the sarcoma treatment algorithms until the mid-2000's, but are now considered and treated as high-grade epithelial tumors (carcinomas).[277]Screening for Lynch syndrome is not usually done for patients with malignant mesenchymal tumors.

Endometrial stromal sarcomas are composed of cells resembling the endometrial stroma in the proliferative phase.[322,323] ESS displays a heterogenous mix of morphologic and genetic features. A significant proportion of these tumors (ie, up to half) harbor a *JAZF1-SUZ12* (formerly *JAZF1-JJAZ1*) gene fusion and present as lower grade, earlier stage tumors.[324-327] More recently, a higher-grade and more aggressively-behaving ESS variant with a unique genetic rearrangement *YWHAE-FAM22A/B*, also known as *YWHAE-NUTM2A/B,* was identified.[328,329] These findings provided support for subdividing ESS into distinct low- and high-grade entities based on histopathology, clinical behavior, and patient outcomes. In light of new information, the World Health Organization (WHO) released an updated (4th) edition of the *WHO Classification of Tumours of Female Reproductive Organs*. The updated 2014 edition recognizes low-grade ESS and high-grade ESS as distinct histopathological entities.[330]

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

Staging and Treatment

When evaluating suspected uterine sarcomas, biopsy may be helpful but is less sensitive than for endometrial cancers. The diagnosis of ESS and uLMS is often made after hysterectomy. The previous FIGO/AJCC staging systems for endometrial cancer were not appropriate for staging ESS and uLMS; patients were often upstaged when using the older AJCC staging system.[331] A new staging system for ESS and uLMS from FIGO/AJCC took effect in 2009 (see Table 2).[49,332] This updated staging system accounts for the differences between uterine sarcomas and endometrial cancers.

Evaluation should include expert pathologic review and imaging (ie, CT scan of the chest, abdomen, and pelvis; or MRI; or PET-CT). It is important to determine if the sarcoma is confined to the uterus or if

extrauterine disease is present. If medically operable, then hysterectomy with (or without) BSO is the initial treatment of choice for uterine sarcomas (see *Primary Treatment* in the NCCN Guidelines for Uterine Sarcoma).[333]

Uterine sarcoma should be removed en bloc to optimize outcomes; morcellation is contraindicated.[126-128] For incidental diagnoses of uterine sarcoma after hysterectomy, or in the case of a fragmented specimen, imaging is recommended and re-exploration can be considered. The ovaries may be preserved in selected patients with early-stage uLMS who wish to retain hormonal function.[334] Additional surgical resection should be individualized based on clinical scenarios and intraoperative findings. Lymphadenectomy is controversial.[2,322,334-337] High-grade uterine sarcomas tend to show hematogenous metastases to the lungs; lymph node metastases are uncommon.

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

Low-Grade Endometrial Stromal Sarcoma

If there is no evidence of disease after primary surgery for ESS, then observation can be considered (see *Additional Therapy* in the NCCN Guidelines for Uterine Sarcoma).[335,336] Postoperative hormone therapy is recommended for stages I to IV ESS (category 2A for stages II-IV; category 2B for stage I). Adjuvant tumor-directed RT may be added for stage II-IVA (category 2B); palliative RT may be added for stage IVB.[322,338,339] Typical hormone therapy includes megestrol, medroxyprogesterone, or aromatase inhibitors; gonadotropin-releasing hormone [GnRH] analogs (category 2B) are also an option.[322,334,340] In 2014, tamoxifen was deleted from the NCCN Guidelines for ESS because it is contraindicated in women diagnosed with ESS or ER/PR-positive uLMS.[334,339-341] Hormone therapy is also recommended for ESS that have recurred or are unresectable (see *Therapy for Relapse* in the NCCN Guidelines for Uterine Sarcoma).[340]

Case series of patients with ESS suggest long disease-free intervals in the absence of specific therapy and raise questions about the use of adjuvant RT.[342] Adjuvant radiotherapy in ESS has been demonstrated to reduce local recurrence rates but again with limited effect on survival.[343,344] Because of concerns about radiation exposure, frequent routine surveillance imaging is no longer recommended for asymptomatic young women after primary therapy for ESS.[345]

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

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

The role of adjuvant radiotherapy in nonmetastatic disease is controversial. Most available data are retrospective except for a phase III randomized trial.[313] Most retrospective studies of adjuvant RT suggest an improvement in local pelvic control but no appreciable or consistent improvement in overall survival, given the propensity of metastatic extrapelvic disease as a site of first or eventual recurrence.[346-349] In many series, the patients treated with adjuvant radiation presumably had higher-risk factors (eg, larger tumors, deeper myometrial invasion), thus biasing the data against radiotherapy. However, a phase III randomized trial in stage I and II uterine sarcomas reported that postoperative pelvic radiotherapy did not improve overall survival for uLMS when compared with observation.[313] Therefore,

routine postoperative RT is not recommended for stage I patients with uLMS and high-grade (undifferentiated) endometrial sarcoma.[338] If used in more advanced stages, adjuvant RT needs to be individualized and based on careful analysis of surgical pathologic findings.

The role of adjuvant chemotherapy is also poorly defined; however, adjuvant chemotherapy has been used because of the high risk of systemic relapse. Given the uncertainties regarding any adjuvant treatment for stage I uLMS and high-grade (undifferentiated) endometrial sarcoma, after complete resection options include: 1) observation; or 2) chemotherapy (category 2B). Because of the increased risk profile in patients with completely resected stage II and III uLMS and high-grade (undifferentiated) endometrial sarcoma, the panel believes that it is appropriate to consider adjuvant chemotherapy and/or RT (see *Additional Therapy* in the NCCN Guidelines for Uterine Sarcoma).[350] In patients with incompletely resected or metastatic disease, chemotherapy with (or without) palliative RT is generally recommended.

An ongoing phase III randomized trial (GOG 277) is assessing the role of postoperative adjuvant chemotherapy (ie, gemcitabine/docetaxel followed by doxorubicin) versus observation in patients with high-grade stage I and II uLMS.[351]

If chemotherapy is used, gemcitabine/docetaxel (preferred for uLMS) is recommended for uterine sarcoma (see *Systemic Therapy* in the NCCN Guidelines for Uterine Sarcoma).[323,352-356] Other combination regimens include doxorubicin/ifosfamide, doxorubicin/dacarbazine, gemcitabine/dacarbazine, and gemcitabine/vinorelbine.[310,357-359]

Doxorubicin is an active single agent for uLMS and is less toxic than combination regimens.[322,360] Other single-agent options (category 2A unless otherwise noted) can also be considered for advanced or metastatic disease including dacarbazine, doxorubicin, epirubicin, gemcitabine, ifosfamide, liposomal doxorubicin, pazopanib, temozolomide, vinorelbine (category 2B), and docetaxel (category 3).[322,323,352,357,358,361-377] Aromatase inhibitors can be considered for ER/PR-expressing uLMS.[378]

In 2014, dacarbazine was changed to a category 2A recommendation (from a category 2B) because dacarbazine has been used as the standard arm in several phase II trials.[357]

In 2016, eribulin and trabectedin were both included in the guidelines as category 2A recommendations for systemic therapy. Eribulin was included based on results from a phase III trial comparing the survival benefit of eribulin and dacarbazine in 452 patients with advanced leiomyosarcoma or adipocytic sarcoma.[379] Median overall survival was 13.5 and 11.5 months for eribulin and dacarbazine, respectively (HR = 0.77, 95% CI 0.62–0.95; *P*= 0.017). Data have also indicated that trabectedin may be useful in patients who have exhausted standard chemotherapy.[380-383] Recent phase III data revealed a 2.7 month PFS benefit versus dacarbazine in metastatic liposarcoma or leiomyosarcoma that progressed after anthracycline-based therapy; the study is ongoing to determine OS.[384] Following its October 2015 FDA approval, trabectedin was added to the guidelines as an option for unresectable or metastatic uterine leiomyosarcoma previously treated with an anthracycline-containing regimen.

Post-Treatment Surveillance

The recommended post-treatment surveillance protocol for uterine sarcoma is depicted in the algorithm (see *Surveillance* in the NCCN Guidelines for Uterine Sarcoma). Patients should receive education regarding the symptoms of recurrent disease. Patients with bleeding

(vaginal, bladder, or rectal), decreased appetite, weight loss, pain (in the pelvis, abdomen, hip, or back), cough, shortness of breath, and swelling (in the abdomen or legs) should seek prompt evaluation and not delay until the next scheduled appointment. As clinically indicated, imaging may be helpful in the detection of recurrence. Patients should be educated regarding healthy lifestyle, obesity, exercise, smoking cessation, and nutrition counseling (see the NCCN Guidelines for Survivorship, NCCN Guidelines for Smoking Cessation, and http://www.cancer.org/treatment/survivorshipduringandaftertreatment/index).[214-216] The panel also recommends patient education regarding sexual health, vaginal dilator use, and vaginal lubricants or moisturizers.

Treatment of Recurrent or Metastatic Disease

The recurrence rate is high in uLMS (50%–70%).[2] The guidelines provide recommendations based on tumor resectability and patients' prior RT exposure (see *Therapy for Relapse* in the NCCN Guidelines for Uterine Sarcoma). For treating local recurrence in patients without prior RT exposure, options include surgery with the option of IORT (category 3 for IORT) or tumor-directed RT with (or without) systemic therapy. Hormone therapy is an option for patients with ESS. Preoperative RT can be considered. Patients with local recurrence who have had prior RT exposure can be treated with: 1) surgery with the option of IORT and/or systemic therapy (category 3 for IORT); 2) systemic therapy; or 3) tumor-directed reirradiation. A recent retrospective analysis of patients with ESS suggested that cytoreductive resection improved OS in patients with recurrent lesions.[385] Systemic therapy with (or without) palliative RT or supportive care is recommended for metastatic disease.[360] For patients with isolated metastases, surgical resection or other ablative therapy (eg, radiofrequency ablation, stereotactic body RT) may be appropriate. Postoperative RT and/or systemic therapy can be considered. Systemic therapy and/or local ablative therapy are reasonable options for patients with unresectable isolated metastases (see *Therapy for Relapse* in the NCCN Guidelines for Uterine Sarcoma).[373,386-388]

Drug Reactions

Virtually all drugs have the potential to cause adverse hypersensitivity reactions, either during or after the infusion.[389] In gynecologic oncology treatment, drugs that more commonly cause adverse reactions include carboplatin, cisplatin, docetaxel, liposomal doxorubicin, and paclitaxel. Most of these drug reactions are mild infusion reactions (ie, skin reactions, cardiovascular reactions, respiratory or throat tightness), but more severe allergic reactions (ie, life-threatening anaphylaxis) can occur.[390-392] In addition, patients can have mild allergic reactions or severe infusion reactions. Infusion reactions are more common with paclitaxel.[393] Allergic reactions (ie, true drug allergies) are more common with platinum agents (ie, carboplatin, cisplatin).[393,394]

Management of drug reactions is discussed in the NCCN Guidelines for Ovarian Cancer.[393] 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.[395-397] Patients must be desensitized with each infusion if they previously had a reaction. Almost all patients can be desensitized (about 90%).[389] To maximize safety, it is prudent to desensitize patients in the intensive care unit.[389]

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25559415.

2. D'Angelo E, Prat J. Uterine sarcomas: a review. Gynecol Oncol 2010;116:131-139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19853898.

3. Van den Bosch T, Coosemans A, Morina M, et al. Screening for uterine tumours. Best Pract Res Clin Obstet Gynaecol 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22078749.

4. Kitchener HC, Trimble EL. Endometrial cancer state of the science meeting. Int J Gynecol Cancer 2009;19:134-140. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19258955.

5. Dinkelspiel HE, Wright JD, Lewin SN, Herzog TJ. Contemporary clinical management of endometrial cancer. Obstet Gynecol Int 2013;2013:583891. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23864861.

6. Obermair A, Youlden DR, Young JP, et al. Risk of endometrial cancer for women diagnosed with HNPCC-related colorectal carcinoma. Int J Cancer 2010;127:2678-2684. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20533284.

7. Katz VL. Diagnostic procedures. Imaging, endometrial sampling, endoscopy: indications and contraindications, complications. In: Katz VL, Lentz GM, Lobo RA, Gershenson DM, eds. Comprehensive Gynecology. 5th ed. Philadelphia, Pa: Mosby; 2007:chap 11.

8. Resnick KE, Hampel H, Fishel R, Cohn DE. Current and emerging trends in Lynch syndrome identification in women with endometrial cancer. Gynecol Oncol 2009;114:128-134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19375789.

9. Kwon JS, Scott JL, Gilks CB, et al. Testing women with endometrial cancer to detect Lynch syndrome. J Clin Oncol 2011;29:2247-2252. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21537049.

10. Win AK, Lindor NM, Winship I, et al. Risks of colorectal and other cancers after endometrial cancer for women with Lynch syndrome. J Natl Cancer Inst 2013;105:274-279. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23385444.

11. Lancaster JM, Powell CB, Kauff ND, et al. Society of Gynecologic Oncologists Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol Oncol 2007;107:159-162. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17950381.

12. Meyer LA, Broaddus RR, Lu KH. Endometrial cancer and Lynch syndrome: clinical and pathologic considerations. Cancer Control 2009;16:14-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19078925.

13. Bonnet D, Selves J, Toulas C, et al. Simplified identification of Lynch syndrome: a prospective, multicenter study. Dig Liver Dis 2012;44:515-522. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22480969.

14. Walsh CS, Blum A, Walts A, et al. Lynch syndrome among gynecologic oncology patients meeting Bethesda guidelines for screening. Gynecol Oncol 2010;116:516-521. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20034658.

15. Clarke BA, Cooper K. Identifying Lynch syndrome in patients with endometrial carcinoma: shortcomings of morphologic and clinical schemas. Adv Anat Pathol 2012;19:231-238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22692286.

16. Evaluation of Genomic Applications in P, Prevention Working G. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed

at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med 2009;11:35-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19125126.

17. Smith RA, Cokkinides V, Brawley OW. Cancer screening in the United States, 2012: A review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin 2012. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22261986.

18. Crispens MA. Endometrial and ovarian cancer in lynch syndrome. Clin Colon Rectal Surg 2012;25:97-102. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23730224.

19. Manchanda R, Saridogan E, Abdelraheim A, et al. Annual outpatient hysteroscopy and endometrial sampling (OHES) in HNPCC/Lynch syndrome (LS). Arch Gynecol Obstet 2012;286:1555-1562. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22865035.

20. Jarvinen HJ, Renkonen-Sinisalo L, Aktan-Collan K, et al. Ten years after mutation testing for Lynch syndrome: cancer incidence and outcome in mutation-positive and mutation-negative family members. J Clin Oncol 2009;27:4793-4797. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19720893.

21. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med 2006;354:261-269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16421367.

22. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24399786.

23. Lajer H, Elnegaard S, Christensen RD, et al. Survival after stage IA endometrial cancer; can follow-up be altered? A prospective nationwide Danish survey. Acta Obstet Gynecol Scand 2012;91:976-982. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22548255.

24. Ueda SM, Kapp DS, Cheung MK, et al. Trends in demographic and clinical characteristics in women diagnosed with corpus cancer and their potential impact on the increasing number of deaths. Am J Obstet Gynecol 2008;198:218 e211-216. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18226630.

25. Chan JK, Sherman AE, Kapp DS, et al. Influence of gynecologic oncologists on the survival of patients with endometrial cancer. J Clin Oncol 2011;29:832-838. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21263082.

26. Benedetti Panici P, Basile S, Salerno MG, et al. Secondary analyses from a randomized clinical trial: age as the key prognostic factor in endometrial carcinoma. Am J Obstet Gynecol 2014;210:363 e361-363 e310. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24361787.

27. Doll KM, Tseng J, Denslow SA, et al. High-grade endometrial cancer: revisiting the impact of tumor size and location on outcomes. Gynecol Oncol 2014;132:44-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24183734.

28. McCluggage WG. My approach to the interpretation of endometrial biopsies and curettings. J Clin Pathol 2006;59:801-812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16873562.

29. McKenney JK, Longacre TA. Low-grade endometrial adenocarcinoma: a diagnostic algorithm for distinguishing atypical endometrial hyperplasia and other benign (and malignant) mimics. Adv Anat Pathol 2009;16:1-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19098463.

30. Leitao MM, Jr., Kehoe S, Barakat RR, et al. Comparison of D&C and office endometrial biopsy accuracy in patients with FIGO grade 1 endometrial adenocarcinoma. Gynecol Oncol 2009;113:105-108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19167049.

31. Gimpelson RJ, Rappold HO. A comparative study between panoramic hysteroscopy with directed biopsies and dilatation and curettage. A review of 276 cases. Am J Obstet Gynecol 1988;158:489-492. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3348309.

32. Lee JH, Dubinsky T, Andreotti RF, et al. ACR appropriateness Criteria(R) pretreatment evaluation and follow-up of endometrial cancer of the uterus. Ultrasound Q 2011;27:139-145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21606818.

33. Ortashi O, Jain S, Emannuel O, et al. Evaluation of the sensitivity, specificity, positive and negative predictive values of preoperative magnetic resonance imaging for staging endometrial cancer. A prospective study of 100 cases at the Dorset Cancer Centre. Eur J Obstet Gynecol Reprod Biol 2008;137:232-235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17537566.

34. Crivellaro C, Signorelli M, Guerra L, et al. Tailoring systematic lymphadenectomy in high-risk clinical early stage endometrial cancer: the role of 18F-FDG PET/CT. Gynecol Oncol 2013;130:306-311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23707673.

35. Kitajima K, Suzuki K, Senda M, et al. Preoperative nodal staging of uterine cancer: is contrast-enhanced PET/CT more accurate than non-enhanced PET/CT or enhanced CT alone? Ann Nucl Med 2011;25:511-519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21670955.

36. Antonsen SL, Jensen LN, Loft A, et al. MRI, PET/CT and ultrasound in the preoperative staging of endometrial cancer - a multicenter prospective comparative study. Gynecol Oncol 2013;128:300-308. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23200916.

37. Duk JM, Aalders JG, Fleuren GJ, de Bruijn HW. CA 125: a useful marker in endometrial carcinoma. Am J Obstet Gynecol 1986;155:1097-1102. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3465243.

38. Duk JM, Aalders JG, Fleuren GJ, et al. Tumor markers CA 125, squamous cell carcinoma antigen, and carcinoembryonic antigen in patients with adenocarcinoma of the uterine cervix. Obstet Gynecol 1989;73:661-668. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2648225.

39. Patsner B, Orr JW, Jr., Mann WJ, Jr. Use of serum CA 125 measurement in posttreatment surveillance of early-stage endometrial carcinoma. Am J Obstet Gynecol 1990;162:427-429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2309825.

40. Rose PG, Sommers RM, Reale FR, et al. Serial serum CA 125 measurements for evaluation of recurrence in patients with endometrial carcinoma. Obstet Gynecol 1994;84:12-16. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8008305.

41. Price FV, Chambers SK, Carcangiu ML, et al. CA 125 may not reflect disease status in patients with uterine serous carcinoma. Cancer 1998;82:1720-1725. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9576294.

42. Leslie KK, Thiel KW, Goodheart MJ, et al. Endometrial cancer. Obstet Gynecol Clin North Am 2012;39:255-268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22640714.

43. Smith RA, Brooks D, Cokkinides V, et al. Cancer screening in the United States, 2013: a review of current American Cancer Society guidelines, current issues in cancer screening, and new guidance on cervical cancer screening and lung cancer screening. CA Cancer J Clin 2013;63:88-105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23378235.

44. Boronow RC, Morrow CP, Creasman WT, et al. Surgical staging in endometrial cancer: clinical-pathologic findings of a prospective study. Obstet Gynecol 1984;63:825-832. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6728365.

45. Cowles TA, Magrina JF, Masterson BJ, Capen CV. Comparison of clinical and surgical-staging in patients with endometrial carcinoma.

Obstet Gynecol 1985;66:413-416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/4022500.

46. Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer 1987;60:2035-2041. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3652025.

47. Benedet JL, Bender H, Jones H, et al. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet 2000;70:209-262. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11041682.

48. Wright JD, Barrena Medel NI, Sehouli J, et al. Contemporary management of endometrial cancer. Lancet 2012;379:1352-1360. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22444602.

49. Edge SB, Byrd DR, Compton CC. AJCC Cancer Staging Manual, 7th edition. New York: Springer; 2010.

50. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 2009;105:103-104. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19367689.

51. Creasman W. Revised FIGO staging for carcinoma of the endometrium. Int J Gynaecol Obstet 2009;105:109. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19345353.

52. Mariani A, Dowdy SC, Podratz KC. New surgical staging of endometrial cancer: 20 years later. Int J Gynaecol Obstet 2009;105:110-111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19285672.

53. Wethington SL, Barrena Medel NI, Wright JD, Herzog TJ. Prognostic significance and treatment implications of positive peritoneal cytology in endometrial adenocarcinoma: Unraveling a mystery. Gynecol Oncol 2009;115:18-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19632708.

54. Takeshima N, Nishida H, Tabata T, et al. Positive peritoneal cytology in endometrial cancer: enhancement of other prognostic indicators. Gynecol Oncol 2001;82:470-473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11520142.

55. Goff BA, Rice LW. Assessment of depth of myometrial invasion in endometrial adenocarcinoma. Gynecol Oncol 1990;38:46-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2354826.

56. Daniel AG, Peters WA, 3rd. Accuracy of office and operating room curettage in the grading of endometrial carcinoma. Obstet Gynecol 1988;71:612-614. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3353053.

57. Kim CH, Soslow RA, Park KJ, et al. Pathologic ultrastaging improves micrometastasis detection in sentinel lymph nodes during endometrial cancer staging. Int J Gynecol Cancer 2013;23:964-970. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23694985.

58. Raimond E, Ballester M, Hudry D, et al. Impact of sentinel lymph node biopsy on the therapeutic management of early-stage endometrial cancer: Results of a retrospective multicenter study. Gynecol Oncol 2014;133:506-511. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24642092.

59. Ballester M, Naoura I, Chereau E, et al. Sentinel node biopsy upstages patients with presumed low- and intermediate-risk endometrial cancer: results of a multicenter study. Ann Surg Oncol 2013;20:407-412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23054119.

60. Soliman PT, Frumovitz M, Spannuth W, et al. Lymphadenectomy during endometrial cancer staging: practice patterns among gynecologic oncologists. Gynecol Oncol 2010;119:291-294. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20708226.

61. Kumar S, Mariani A, Bakkum-Gamez JN, et al. Risk factors that mitigate the role of paraaortic lymphadenectomy in uterine endometrioid cancer. Gynecol Oncol 2013;130:441-445. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23747331.

62. Kilgore LC, Partridge EE, Alvarez RD, et al. Adenocarcinoma of the endometrium: survival comparisons of patients with and without pelvic node sampling. Gynecol Oncol 1995;56:29-33. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7821843.

63. Havrilesky LJ, Cragun JM, Calingaert B, et al. Resection of lymph node metastases influences survival in stage IIIC endometrial cancer. Gynecol Oncol 2005;99:689-695. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16126261.

64. Todo Y, Kato H, Kaneuchi M, et al. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet 2010;375:1165-1172. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20188410.

65. Kitchener H, Swart AM, Qian Q, et al. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 2009;373:125-136. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19070889.

66. Benedetti Panici P, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 2008;100:1707-1716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19033573.

67. ACOG practice bulletin, clinical management guidelines for obstetrician-gynecologists, number 65, August 2005: management of endometrial cancer. Obstet Gynecol 2005;106:413-425. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16055605.

68. Seamon LG, Fowler JM, Cohn DE. Lymphadenectomy for endometrial cancer: the controversy. Gynecol Oncol 2010;117:6-8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20110120.

69. Creasman WT, Mutch DE, Herzog TJ. ASTEC lymphadenectomy and radiation therapy studies: are conclusions valid? Gynecol Oncol 2010;116:293-294. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19897230.

70. Uccella S, Podratz KC, Aletti GD, Mariani A. Lymphadenectomy in endometrial cancer. Lancet 2009;373:1170; author reply 1170-1171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19345823.

71. Uccella S, Podratz KC, Aletti GD, Mariani A. Re: Systematic pelvic lymphadenectomy vs no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 2009;101:897-898; author reply 898-899. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19509367.

72. Milam MR, Java J, Walker JL, et al. Nodal metastasis risk in endometrioid endometrial cancer. Obstet Gynecol 2012;119:286-292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22270280.

73. Neubauer NL, Lurain JR. The role of lymphadenectomy in surgical staging of endometrial cancer. Int J Surg Oncol 2011;2011:814649. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22312525.

74. Mariani A, Dowdy SC, Cliby WA, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecol Oncol 2008;109:11-18. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18304622.

75. Hirahatake K, Hareyama H, Sakuragi N, et al. A clinical and pathologic study on para-aortic lymph node metastasis in endometrial carcinoma. J Surg Oncol 1997;65:82-87. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9209518.

76. Frederick PJ, Straughn JM, Jr. The role of comprehensive surgical staging in patients with endometrial cancer. Cancer Control 2009;16:23-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19078926.

77. Barlin JN, Khoury-Collado F, Kim CH, et al. The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: beyond removal of blue nodes. Gynecol Oncol 2012;125:531-535. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22366409.

78. Ballester M, Koskas M, Coutant C, et al. Does the use of the 2009 FIGO classification of endometrial cancer impact on indications of the sentinel node biopsy? BMC Cancer 2010;10:465. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20804553.

79. How J, Lau S, Press J, et al. Accuracy of sentinel lymph node detection following intra-operative cervical injection for endometrial cancer: a prospective study. Gynecol Oncol 2012;127:332-337. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22910695.

80. Khoury-Collado F, Murray MP, Hensley ML, et al. Sentinel lymph node mapping for endometrial cancer improves the detection of metastatic disease to regional lymph nodes. Gynecol Oncol 2011;122:251-254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21570109.

81. Vidal F, Leguevaque P, Motton S, et al. Evaluation of the sentinel lymph node algorithm with blue dye labeling for early-stage endometrial cancer in a multicentric setting. Int J Gynecol Cancer 2013;23:1237-1243. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23839245.

82. Kim CH, Khoury-Collado F, Barber EL, et al. Sentinel lymph node mapping with pathologic ultrastaging: A valuable tool for assessing nodal metastasis in low-grade endometrial cancer with superficial myoinvasion. Gynecol Oncol 2013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24099838.

83. Group SGOCPECW, Burke WM, Orr J, et al. Endometrial cancer: a review and current management strategies: part I. Gynecol Oncol 2014;134:385-392. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24905773.

84. Abu-Rustum NR, Khoury-Collado F, Pandit-Taskar N, et al. Sentinel lymph node mapping for grade 1 endometrial cancer: is it the answer to the surgical staging dilemma? Gynecol Oncol 2009;113:163-169. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19232699.

85. Ballester M, Dubernard G, Lecuru F, et al. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). Lancet Oncol 2011;12:469-476. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21489874.

86. Press JZ, Gotlieb WH. Controversies in the treatment of early stage endometrial carcinoma. Obstet Gynecol Int 2012;2012:578490. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22685466.

87. Touhami O, Trinh XB, Gregoire J, et al. Predictors of non-sentinel lymph node (non-SLN) metastasis in patients with sentinel lymph node (SLN) metastasis in endometrial cancer. Gynecol Oncol 2015;138:41-45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25891803.

88. Levenback CF, van der Zee AG, Rob L, et al. Sentinel lymph node biopsy in patients with gynecologic cancers Expert panel statement from the International Sentinel Node Society Meeting, February 21, 2008. Gynecol Oncol 2009;114:151-156. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19457548.

89. Frumovitz M, Levenback CF. Is lymphatic mapping in uterine cancer feasible? Ann Surg Oncol 2008;15:1815-1817. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18473144.

90. Ansari M, Rad MA, Hassanzadeh M, et al. Sentinel node biopsy in endometrial cancer: systematic review and meta-analysis of the literature. Eur J Gynaecol Oncol 2013;34:387-401. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24475571.

91. Levinson KL, Escobar PF. Is sentinel lymph node dissection an appropriate standard of care for low-stage endometrial cancers? A

review of the literature. Gynecol Obstet Invest 2013;76:139-150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23942330.

92. Touboul C, Bentivegna E, Uzan C, et al. Sentinel lymph node in endometrial cancer: a review. Curr Oncol Rep 2013;15:559-565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24190831.

93. Cormier B, Rozenholc AT, Gotlieb W, et al. Sentinel lymph node procedure in endometrial cancer: A systematic review and proposal for standardization of future research. Gynecol Oncol 2015;138:478-485. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26047592.

94. Amezcua CA, MacDonald HR, Lum CA, et al. Endometrial cancer patients have a significant risk of harboring isolated tumor cells in histologically negative lymph nodes. Int J Gynecol Cancer 2006;16:1336-1341. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16803526.

95. Todo Y, Kato H, Okamoto K, et al. Isolated tumor cells and micrometastases in regional lymph nodes in FIGO stage I to II endometrial cancer. J Gynecol Oncol 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25925293.

96. Darai E, Dubernard G, Bats AS, et al. Sentinel node biopsy for the management of early stage endometrial cancer: long-term results of the SENTI-ENDO study. Gynecol Oncol 2015;136:54-59. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25450151.

97. Naoura I, Canlorbe G, Bendifallah S, et al. Relevance of sentinel lymph node procedure for patients with high-risk endometrial cancer. Gynecol Oncol 2015;136:60-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25449312.

98. Mori KM, Neubauer NL. Minimally invasive surgery in gynecologic oncology. ISRN Obstet Gynecol 2013;2013:312982. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23997959.

99. Mabrouk M, Frumovitz M, Greer M, et al. Trends in laparoscopic and robotic surgery among gynecologic oncologists: A survey update. Gynecol Oncol 2009;112:501-505. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19138793.

100. Walker JL, Piedmonte MR, Spirtos NM, et al. Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2. J Clin Oncol 2009;27:5331-5336. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19805679.

101. Walker JL, Piedmonte MR, Spirtos NM, et al. Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group LAP2 Study. J Clin Oncol 2012;30:695-700. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22291074.

102. King LP, Miller DS. Recent progress: gynecologic oncology group trials in uterine corpus tumors. Rev Recent Clin Trials 2009;4:70-74. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19463102.

103. Vergote I, Amant F, Neven P. Is it safe to treat endometrial carcinoma endoscopically? J Clin Oncol 2009;27:5305-5307. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19805666.

104. Mourits MJ, Bijen CB, Arts HJ, et al. Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: a randomised trial. Lancet Oncol 2010;11:763-771. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20638901.

105. He H, Zeng D, Ou H, et al. Laparoscopic treatment of endometrial cancer: systematic review. J Minim Invasive Gynecol 2013;20:413-423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23506718.

106. Wang HL, Ren YF, Yang J, et al. Total laparoscopic hysterectomy versus total abdominal hysterectomy for endometrial cancer: a meta-analysis. Asian Pac J Cancer Prev 2013;14:2515-2519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23725166.

107. Cho JE, Shamshirsaz AH, Nezhat C, Nezhat F. New technologies for reproductive medicine: laparoscopy, endoscopy, robotic surgery and gynecology. A review of the literature. Minerva Ginecol 2010;62:137-167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20502426.

108. Seamon LG, Cohn DE, Henretta MS, et al. Minimally invasive comprehensive surgical staging for endometrial cancer: Robotics or laparoscopy? Gynecol Oncol 2009;113:36-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19168206.

109. Boggess JF, Gehrig PA, Cantrell L, et al. A comparative study of 3 surgical methods for hysterectomy with staging for endometrial cancer: robotic assistance, laparoscopy, laparotomy. Am J Obstet Gynecol 2008;199:360 e361-369. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18928974.

110. Bandera CA, Magrina JF. Robotic surgery in gynecologic oncology. Curr Opin Obstet Gynecol 2009;21:25-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19125000.

111. Bell MC, Torgerson J, Seshadri-Kreaden U, et al. Comparison of outcomes and cost for endometrial cancer staging via traditional laparotomy, standard laparoscopy and robotic techniques. Gynecol Oncol 2008;111:407-411. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18829091.

112. ElSahwi KS, Hooper C, De Leon MC, et al. Comparison between 155 cases of robotic vs. 150 cases of open surgical staging for endometrial cancer. Gynecol Oncol 2012;124:260-264. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22036203.

113. Siesto G, Ornaghi S, Ieda N, Vitobello D. Robotic surgical staging for endometrial and cervical cancers in medically ill patients. Gynecol Oncol 2013;129:593-597. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23454499.

114. Jernigan AM, Auer M, Fader AN, Escobar PF. Minimally invasive surgery in gynecologic oncology: a review of modalities and the literature. Womens Health (Lond Engl) 2012;8:239-250. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22554172.

115. van Dam P, Hauspy J, Verkinderen L, et al. Are costs of robot-assisted surgery warranted for gynecological procedures? Obstet Gynecol Int 2011;2011:973830. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21941556.

116. Brudie LA, Backes FJ, Ahmad S, et al. Analysis of disease recurrence and survival for women with uterine malignancies undergoing robotic surgery. Gynecol Oncol 2013;128:309-315. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23153590.

117. Backes FJ, Brudie LA, Farrell MR, et al. Short- and long-term morbidity and outcomes after robotic surgery for comprehensive endometrial cancer staging. Gynecol Oncol 2012;125:546-551. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22387522.

118. Fleming ND, Ramirez PT. Robotic surgery in gynecologic oncology. Curr Opin Oncol 2012;24:547-553. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22581356.

119. Weinberg L, Rao S, Escobar PF. Robotic surgery in gynecology: an updated systematic review. Obstet Gynecol Int 2011;2011:852061. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22190948.

120. Krill LS, Bristow RE. Robotic surgery: gynecologic oncology. Cancer J 2013;19:167-176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23528726.

121. Ramirez PT, Adams S, Boggess JF, et al. Robotic-assisted surgery in gynecologic oncology: a Society of Gynecologic Oncology consensus statement. Developed by the Society of Gynecologic Oncology's Clinical Practice Robotics Task Force. Gynecol Oncol 2012;124:180-184. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22079679.

122. AAGL. Guidelines for privileging for robotic-assisted gynecologic laparoscopy. J Minim Invasive Gynecol 2014;21:157-167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24509290.

123. American Congress of Obstetricians and Gynecologists. Statement on Robotic Surgery by ACOG President James T. Breeden. 2013. Available at: http://www.acog.org/About-ACOG/News-Room/News-Releases/2013/Statement-on-Robotic-Surgery. Accessed

124. Sinno AK, Fader AN. Robotic-assisted surgery in gynecologic oncology. Fertil Steril 2014;102:922-932. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25274485.

125. Gala RB, Margulies R, Steinberg A, et al. Systematic review of robotic surgery in gynecology: robotic techniques compared with laparoscopy and laparotomy. J Minim Invasive Gynecol 2014;21:353-361. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24295923.

126. SGO Position Statement: Morcellation. Society of Gynecologic Oncology; 2013. Available at: https://www.sgo.org/newsroom/position-statements-2/morcellation/. Accessed September 30, 2014.

127. Power Morcellation and Occult Malignancy in Gynecologic Surgery. The American College of Obstetrics and Gynecologists; 2014. Available at: http://www.acog.org/Resources-And-Publications/Task-Force-and-Work-Group-Reports/Power-Morcellation-and-Occult-Malignancy-in-Gynecologic-Surgery. Accessed September 30, 2014.

128. U.S. Department of Health and Human Services. FDA discourages use of laparoscopic power morcellation for removal of uterus or uterine fibroids Food and Drug Administration; 2014. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm393689.htm. Accessed September 30, 2014.

129. Manfredi R, Mirk P, Maresca G, et al. Local-regional staging of endometrial carcinoma: role of MR imaging in surgical planning. Radiology 2004;231:372-378. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15031434.

130. Akin O, Mironov S, Pandit-Taskar N, Hann LE. Imaging of uterine cancer. Radiol Clin North Am 2007;45:167-182. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17157628.

131. Gunderson CC, Fader AN, Carson KA, Bristow RE. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. Gynecol Oncol 2012;125:477-482. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22245711.

132. Baker J, Obermair A, Gebski V, Janda M. Efficacy of oral or intrauterine device-delivered progestin in patients with complex endometrial hyperplasia with atypia or early endometrial adenocarcinoma: a meta-analysis and systematic review of the literature. Gynecol Oncol 2012;125:263-270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22196499.

133. Gracia CR, Jeruss JS. Lives in the balance: women with cancer and the right to fertility care. J Clin Oncol 2013;31:668-669. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23341520.

134. Ushijima K, Yahata H, Yoshikawa H, et al. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. J Clin Oncol 2007;25:2798-2803. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17602085.

135. Hubbs JL, Saig RM, Abaid LN, et al. Systemic and local hormone therapy for endometrial hyperplasia and early adenocarcinoma. Obstet Gynecol 2013;121:1172-1180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23812449.

136. Trimble CL, Method M, Leitao M, et al. Management of endometrial precancers. Obstet Gynecol 2012;120:1160-1175. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23090535.

137. Mehasseb MK, Latimer JA. Controversies in the management of endometrial carcinoma: an update. Obstet Gynecol Int

2012;2012:676032. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22518164.

138. Hahn HS, Yoon SG, Hong JS, et al. Conservative treatment with progestin and pregnancy outcomes in endometrial cancer. Int J Gynecol Cancer 2009;19:1068-1073. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19820370.

139. Park JY, Kim DY, Kim JH, et al. Long-term oncologic outcomes after fertility-sparing management using oral progestin for young women with endometrial cancer (KGOG 2002). Eur J Cancer 2013;49:868-874. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23072814.

140. Park JY, Seong SJ, Kim TJ, et al. Pregnancy outcomes after fertility-sparing management in young women with early endometrial cancer. Obstet Gynecol 2013;121:136-142. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23262938.

141. Wright JD, Buck AM, Shah M, et al. Safety of ovarian preservation in premenopausal women with endometrial cancer. J Clin Oncol 2009;27:1214-1219. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19171707.

142. Koskas M, Bendifallah S, Luton D, et al. Safety of uterine and/or ovarian preservation in young women with grade 1 intramucous endometrial adenocarcinoma: a comparison of survival according to the extent of surgery. Fertil Steril 2012;98:1229-1235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22959452.

143. Lee TS, Lee JY, Kim JW, et al. Outcomes of ovarian preservation in a cohort of premenopausal women with early-stage endometrial cancer: A Korean Gynecologic Oncology Group study. Gynecol Oncol 2013;131:289-293. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23994534.

144. Boente MP, Yordan EL, Jr., McIntosh DG, et al. Prognostic factors and long-term survival in endometrial adenocarcinoma with cervical involvement. Gynecol Oncol 1993;51:316-322. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8112639.

145. Sartori E, Gadducci A, Landoni F, et al. Clinical behavior of 203 stage II endometrial cancer cases: the impact of primary surgical approach and of adjuvant radiation therapy. Int J Gynecol Cancer 2001;11:430-437. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11906545.

146. Fishman DA, Roberts KB, Chambers JT, et al. Radiation therapy as exclusive treatment for medically inoperable patients with stage I and II endometrioid carcinoma with endometrium. Gynecol Oncol 1996;61:189-196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8626131.

147. Coon D, Beriwal S, Heron DE, et al. High-dose-rate Rotte "Y" applicator brachytherapy for definitive treatment of medically inoperable endometrial cancer: 10-year results. Int J Radiat Oncol Biol Phys 2008;71:779-783. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18258388.

148. Niazi TM, Souhami L, Portelance L, et al. Long-term results of high-dose-rate brachytherapy in the primary treatment of medically inoperable stage I-II endometrial carcinoma. Int J Radiat Oncol Biol Phys 2005;63:1108-1113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16099598.

149. Gadducci A, Cosio S, Genazzani AR. Old and new perspectives in the pharmacological treatment of advanced or recurrent endometrial cancer: Hormonal therapy, chemotherapy and molecularly targeted therapies. Crit Rev Oncol Hematol 2006;58:242-256. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16436330.

150. Mountzios G, Pectasides D, Bournakis E, et al. Developments in the systemic treatment of endometrial cancer. Crit Rev Oncol Hematol 2011;79:278-292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20833559.

151. Fiorica JV, Brunetto VL, Hanjani P, et al. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92:10-14. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14751131.

152. Altman AD, Thompson J, Nelson G, et al. Use of aromatase inhibitors as first- and second-line medical therapy in patients with endometrial adenocarcinoma: a retrospective study. J Obstet Gynaecol Can 2012;34:664-672. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22742486.

153. Barker LC, Brand IR, Crawford SM. Sustained effect of the aromatase inhibitors anastrozole and letrozole on endometrial thickness in patients with endometrial hyperplasia and endometrial carcinoma. Curr Med Res Opin 2009;25:1105-1109. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19301987.

154. Rose PG, Brunetto VL, VanLe L, et al. A phase II trial of anastrozole in advanced recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2000;78:212-216. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10926805.

155. Decruze SB, Green JA. Hormone therapy in advanced and recurrent endometrial cancer: a systematic review. Int J Gynecol Cancer 2007;17:964-978. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17442022.

156. Barlin JN, Puri I, Bristow RE. Cytoreductive surgery for advanced or recurrent endometrial cancer: a meta-analysis. Gynecol Oncol 2010;118:14-18. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20434198.

157. Landrum LM, Moore KN, Myers TK, et al. Stage IVB endometrial cancer: does applying an ovarian cancer treatment paradigm result in similar outcomes? A case-control analysis. Gynecol Oncol 2009;112:337-341. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19041126.

158. Lambrou NC, Gomez-Marin O, Mirhashemi R, et al. Optimal surgical cytoreduction in patients with Stage III and Stage IV endometrial carcinoma: a study of morbidity and survival. Gynecol Oncol 2004;93:653-658. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15196860.

159. Smith SC, Koh WJ. Palliative radiation therapy for gynaecological malignancies. Best Pract Res Clin Obstet Gynaecol 2001;15:265-278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11358401.

160. Randall ME, Filiaci VL, Muss H, et al. Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol 2006;24:36-44. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16330675.

161. Homesley HD, Filiaci V, Gibbons SK, et al. A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A Gynecologic Oncology Group study. Gynecol Oncol 2009;112:543-552. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19108877.

162. Secord AA, Havrilesky LJ, O'Malley DM, et al. A multicenter evaluation of sequential multimodality therapy and clinical outcome for the treatment of advanced endometrial cancer. Gynecol Oncol 2009;114:442-447. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19560193.

163. Creutzberg CL, van Stiphout RG, Nout RA, et al. Nomograms for prediction of outcome with or without adjuvant radiation therapy for patients with endometrial cancer: a pooled analysis of PORTEC-1 and PORTEC-2 trials. Int J Radiat Oncol Biol Phys 2015;91:530-539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25680597.

164. Group SGOCPECW, Burke WM, Orr J, et al. Endometrial cancer: a review and current management strategies: part II. Gynecol Oncol 2014;134:393-402. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24929052.

165. Creutzberg CL, Nout RA. The role of radiotherapy in endometrial cancer: current evidence and trends. Curr Oncol Rep 2011;13:472-478. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21845420.

166. Klopp A, Smith BD, Alektiar K, et al. The role of postoperative radiation therapy for endometrial cancer: Executive summary of an American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol 2014;4:137-144. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24766678.

167. Morrow CP, Bundy BN, Kurman RJ, et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol 1991;40:55-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1989916.

168. Neubauer NL, Havrilesky LJ, Calingaert B, et al. The role of lymphadenectomy in the management of preoperative grade 1 endometrial carcinoma. Gynecol Oncol 2009;112:511-516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19144394.

169. Gretz HFr, Economos K, Husain A, et al. The practice of surgical staging and its impact on adjuvant treatment recommendations in patients with stage I endometrial carcinoma. Gynecol Oncol 1996;61:409-415. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8641624.

170. Ben-Shachar I, Pavelka J, Cohn DE, et al. Surgical staging for patients presenting with grade 1 endometrial carcinoma. Obstet Gynecol 2005;105:487-493. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15738013.

171. Elshaikh MA, Al-Wahab Z, Mahdi H, et al. Recurrence patterns and survival endpoints in women with stage II uterine endometrioid carcinoma: a multi-institution study. Gynecol Oncol 2015;136:235-239. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25511158.

172. Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000;355:1404-1411. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10791524.

173. Aalders J, Abeler V, Kolstad P, Onsrud M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol 1980;56:419-427. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6999399.

174. Blake P, Swart AM, Orton J, et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet 2009;373:137-146. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19070891.

175. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92:744-751. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14984936.

176. Creutzberg CL, van Putten WLJ, Wárlám-Rodenhuis CC, et al. Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the Postoperative Radiation Therapy in Endometrial Carcinoma Trial. J Clin Oncol 2004;22:1234-1241. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15051771.

177. Scholten AN, van Putten WLJ, Beerman H, et al. Postoperative radiotherapy for stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int J Radiat Oncol Biol Phys 2005;63:834-838. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15927414.

178. Hockel M, Dornhofer N. Treatment of early endometrial carcinoma: is less more? Lancet 2009;373:97-99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19070890.

179. Creutzberg CL, Nout RA, Lybeert ML, et al. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. Int J Radiat Oncol Biol Phys 2011;81:e631-638. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21640520.

180. Alektiar KM, Venkatraman E, Chi DS, Barakat RR. Intravaginal brachytherapy alone for intermediate-risk endometrial cancer. Int J Radiat Oncol Biol Phys 2005;62:111-117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15850910.

181. Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet 2010;375:816-823. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20206777.

182. Small W, Jr., Beriwal S, Demanes DJ, et al. American Brachytherapy Society consensus guidelines for adjuvant vaginal cuff brachytherapy after hysterectomy. Brachytherapy 2012;11:58-67. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22265439.

183. Onsrud M, Cvancarova M, Hellebust TP, et al. Long-term outcomes after pelvic radiation for early-stage endometrial cancer. J Clin Oncol 2013;31:3951-3956. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24019546.

184. Nout RA, Putter H, Jurgenliemk-Schulz IM, et al. Five-year quality of life of endometrial cancer patients treated in the randomised Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial and comparison with norm data. Eur J Cancer 2012;48:1638-1648. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22176868.

185. Roper B, Astner ST, Heydemann-Obradovic A, et al. Ten-year data on 138 patients with endometrial carcinoma and postoperative vaginal brachytherapy alone: no need for external-beam radiotherapy in low and intermediate risk patients. Gynecol Oncol 2007;107:541-548. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17884152.

186. Nout RA, Putter H, Jurgenliemk-Schulz IM, et al. Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. J Clin Oncol 2009;27:3547-3556. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19546404.

187. McCloskey SA, Tchabo NE, Malhotra HK, et al. Adjuvant vaginal brachytherapy alone for high risk localized endometrial cancer as defined by the three major randomized trials of adjuvant pelvic radiation. Gynecol Oncol 2010;116:404-407. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19944453.

188. Dunn EF, Geye H, Platta CS, et al. Predictive factors of recurrence following adjuvant vaginal cuff brachytherapy alone for stage I endometrial cancer. Gynecol Oncol 2014;133:494-498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24657301.

189. McMeekin DS, Filiaci V, Aghajanian C, et al. A randomized phase III trial of pelvic radiation therapy (PXRT) versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy (VCB/C) in patients with high risk (HR), early stage endometrial cancer (EC): a Gynecologic Oncology Group trial [abstract]. SGO Annual Meeting: Society for Gynecologic Oncology; 2014. Available at: https://www.sgo.org/wp-content/uploads/2014/05/LATE-BREAKING-ABSTRACTS-FINAL-03-15-14.pdf.

190. Chino JP, Jones E, Berchuck A, et al. The Influence of Radiation Modality and Lymph Node Dissection on Survival in Early-stage Endometrial Cancer. Int J Radiat Oncol Biol Phys 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21640502.

191. Lee CM, Szabo A, Shrieve DC, et al. Frequency and effect of adjuvant radiation therapy among women with stage I endometrial

adenocarcinoma. JAMA 2006;295:389-397. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16434629.

192. Johnson N, Cornes P. Survival and recurrent disease after postoperative radiotherapy for early endometrial cancer: systematic review and meta-analysis. BJOG 2007;114:1313-1320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17803718.

193. Kong A, Johnson N, Cornes P, et al. Adjuvant radiotherapy for stage I endometrial cancer. Cochrane Database Syst Rev 2007. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17443533.

194. Kong A, Johnson N, Kitchener HC, Lawrie TA. Adjuvant radiotherapy for stage I endometrial cancer: an updated Cochrane systematic review and meta-analysis. J Natl Cancer Inst 2012;104:1625-1634. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22962693.

195. Eifel PJ. The role of adjuvant radiation therapy for stage I endometrial cancer: does meta-analysis reveal the answer? J Natl Cancer Inst 2012;104:1615-1616. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23104209.

196. Park HJ, Nam EJ, Kim S, et al. The benefit of adjuvant chemotherapy combined with postoperative radiotherapy for endometrial cancer: a meta-analysis. Eur J Obstet Gynecol Reprod Biol 2013;170:39-44. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23810000.

197. 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;46:2422-2431. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20619634.

198. Johnson N, Bryant A, Miles T, et al. Adjuvant chemotherapy for endometrial cancer after hysterectomy. Cochrane Database Syst Rev 2011:CD003175. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21975736.

199. Hogberg T. Adjuvant chemotherapy in endometrial carcinoma: overview of randomised trials. Clin Oncol (R Coll Radiol) 2008;20:463-469. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18467080.

200. Koh WJ, Tran AB, Douglas JG, Stelzer KJ. Radiation therapy in endometrial cancer. Best Pract Res Clin Obstet Gynaecol 2001;15:417-432. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11476563.

201. Secord AA, Geller MA, Broadwater G, et al. A multicenter evaluation of adjuvant therapy in women with optimally resected stage IIIC endometrial cancer. Gynecol Oncol 2013;128:65-70. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23085460.

202. Greven KM, Lanciano RM, Corn B, et al. Pathologic stage III endometrial carcinoma. Prognostic factors and patterns of recurrence. Cancer 1993;71:3697-3702. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8490920.

203. Gibbons S, Martinez A, Schray M, et al. Adjuvant whole abdominopelvic irradiation for high risk endometrial carcinoma. Int J Radiat Oncol Biol Phys 1991;21:1019-1025. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1917597.

204. Greer BE, Hamberger AD. Treatment of intraperitoneal metastatic adenocarcinoma of the endometrium by the whole-abdomen moving-strip technique and pelvic boost irradiation. Gynecol Oncol 1983;16:365-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6654180.

205. Abaid LN, Rettenmaier MA, Brown JV, 3rd, et al. Sequential chemotherapy and radiotherapy as sandwich therapy for the treatment of high risk endometrial cancer. J Gynecol Oncol 2012;23:22-27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22355463.

206. Geller MA, Ivy JJ, Ghebre R, et al. A phase II trial of carboplatin and docetaxel followed by radiotherapy given in a "Sandwich" method for stage III, IV, and recurrent endometrial cancer. Gynecol Oncol

2011;121:112-117. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21239048.

207. Brown AP, Gaffney DK, Dodson MK, et al. Survival analysis of endometrial cancer patients with positive lymph nodes. Int J Gynecol Cancer 2013;23:861-868. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23598890.

208. Lum MM, Belnap TW, Frandsen J, et al. Survival Analysis of Cancer Patients With FIGO Stage IIIA Endometrial Cancer. Am J Clin Oncol 2015;38:283-288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23774072.

209. Le T, Menard C, Samant R, et al. Longitudinal assessments of quality of life in endometrial cancer patients: effect of surgical approach and adjuvant radiotherapy. Int J Radiat Oncol Biol Phys 2009;75:795-802. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19250764.

210. Salani R, Backes FJ, Fung MF, et al. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. Am J Obstet Gynecol 2011;204:466-478. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21752752.

211. Fung-Kee-Fung M, Dodge J, Elit L, et al. Follow-up after primary therapy for endometrial cancer: a systematic review. Gynecol Oncol 2006;101:520-529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16556457.

212. Greer BE, Goff BA, Koh WJ. Endometrial carcinoma. In: Johnson FE, Virgo KS, eds. Cancer Patient Follow-up. St. Louis: Mosby; 1997:357-377.

213. Bristow RE, Purinton SC, Santillan A, et al. Cost-effectiveness of routine vaginal cytology for endometrial cancer surveillance. Gynecol Oncol 2006;103:709-713. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16797686.

214. Cowens-Alvarado R, Sharpe K, Pratt-Chapman M, et al. Advancing survivorship care through the National Cancer Survivorship Resource Center: developing American Cancer Society guidelines for primary care providers. CA Cancer J Clin 2013;63:147-150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23512728.

215. McCabe MS, Bhatia S, Oeffinger KC, et al. American Society of Clinical Oncology statement: achieving high-quality cancer survivorship care. J Clin Oncol 2013;31:631-640. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23295805.

216. Smith WA, Nolan VG, Robison LL, et al. Physical activity among cancer survivors and those with no history of cancer- a report from the National Health and Nutrition Examination Survey 2003-2006. Am J Transl Res 2011;3:342-350. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21904654.

217. Cooper AL, Dornfeld-Finke JM, Banks HW, et al. Is cytologic screening an effective surveillance method for detection of vaginal recurrence of uterine cancer? Obstet Gynecol 2006;107:71-76. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16394042.

218. Salani R, Nagel CI, Drennen E, Bristow RE. Recurrence patterns and surveillance for patients with early stage endometrial cancer. Gynecol Oncol 2011;123:205-207. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21820709.

219. Hunn J, Tenney ME, Tergas AI, et al. Patterns and utility of routine surveillance in high grade endometrial cancer. Gynecol Oncol 2015;137:485-489. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25838164.

220. Smith DC, Prentice R, Thompson DJ, Herrmann WL. Association of exogenous estrogen and endometrial carcinoma. N Engl J Med 1975;293:1164-1167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1186789.

221. Ziel HK, Finkle WD. Increased risk of endometrial carcinoma among users of conjugated estrogens. N Engl J Med 1975;293:1167-1170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/171569.

222. Creasman WT, Henderson D, Hinshaw W, Clarke-Pearson DL. Estrogen replacement therapy in the patient treated for endometrial cancer. Obstet Gynecol 1986;67:326-330. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3003636.

223. Lee RB, Burke TW, Park RC. Estrogen replacement therapy following treatment for stage I endometrial carcinoma. Gynecol Oncol 1990;36:189-191. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2298408.

224. Chapman JA, DiSaia PJ, Osann K, et al. Estrogen replacement in surgical stage I and II endometrial cancer survivors. Am J Obstet Gynecol 1996;175:1195-1200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8942487.

225. Barakat RR, Bundy BN, Spirtos NM, et al. Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2006;24:587-592. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16446331.

226. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 2003;289:3243-3253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12824205.

227. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004;291:1701-1712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15082697.

228. LaCroix AZ, Chlebowski RT, Manson JE, et al. Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial. JAMA 2011;305:1305-1314. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21467283.

229. Pachman DR, Jones JM, Loprinzi CL. Management of menopause-associated vasomotor symptoms: Current treatment options, challenges and future directions. Int J Womens Health 2010;2:123-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21072305.

230. Morrow PK, Mattair DN, Hortobagyi GN. Hot flashes: a review of pathophysiology and treatment modalities. Oncologist 2011;16:1658-1664. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22042786.

231. Levine JP. Treating menopausal symptoms with a tissue-selective estrogen complex. Gend Med 2011;8:57-68. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21536225.

232. Pinkerton JV, Utian WH, Constantine GD, et al. Relief of vasomotor symptoms with the tissue-selective estrogen complex containing bazedoxifene/conjugated estrogens: a randomized, controlled trial. Menopause 2009;16:1116-1124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19546826.

233. Loprinzi CL, Barton DL, Qin R. Nonestrogenic management of hot flashes. J Clin Oncol 2011;29:3842-3846. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21911722.

234. Sideras K, Loprinzi CL. Nonhormonal management of hot flashes for women on risk reduction therapy. J Natl Compr Canc Netw 2010;8:1171-1179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20971841.

235. Jhingran A, Burke TW, Eifel PJ. Definitive radiotherapy for patients with isolated vaginal recurrence of endometrial carcinoma after

hysterectomy. Int J Radiat Oncol Biol Phys 2003;56:1366-1372. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12873682.

236. Creutzberg CL, van Putten WL, Koper PC, et al. Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol Oncol 2003;89:201-209. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12713981.

237. Lin LL, Grigsby PW, Powell MA, Mutch DG. Definitive radiotherapy in the management of isolated vaginal recurrences of endometrial cancer. Int J Radiat Oncol Biol Phys 2005;63:500-504. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16168841.

238. Barakat RR, Goldman NA, Patel DA, et al. Pelvic exenteration for recurrent endometrial cancer. Gynecol Oncol 1999;75:99-9102. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10502433.

239. Fleisch MC, Pantke P, Beckmann MW, et al. Predictors for long-term survival after interdisciplinary salvage surgery for advanced or recurrent gynecologic cancers. J Surg Oncol 2007;95:476-484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17192947.

240. Dowdy SC, Mariani A, Cliby WA, et al. Radical pelvic resection and intraoperative radiation therapy for recurrent endometrial cancer: technique and analysis of outcomes. Gynecol Oncol 2006;101:280-286. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16321431.

241. Tran PT, Su Z, Hara W, et al. Long-term survivors using intraoperative radiotherapy for recurrent gynecologic malignancies. Int J Radiat Oncol Biol Phys 2007;69:504-511. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17560736.

242. Whitney CW, Brunetto VL, Zaino RJ, et al. Phase II study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92:4-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14751130.

243. Herzog TJ. What is the clinical value of adding tamoxifen to progestins in the treatment [correction for treament] of advanced or recurrent endometrial cancer? Gynecol Oncol 2004;92:1-3. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14751129.

244. Singh M, Zaino RJ, Filiaci VJ, Leslie KK. Relationship of estrogen and progesterone receptors to clinical outcome in metastatic endometrial carcinoma: a Gynecologic Oncology Group Study. Gynecol Oncol 2007;106:325-333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17532033.

245. Kauppila A. Oestrogen and progestin receptors as prognostic indicators in endometrial cancer. A review of the literature. Acta Oncol 1989;28:561-566. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2675940.

246. Thigpen JT, Brady MF, Alvarez RD, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. J Clin Oncol 1999;17:1736-1744. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561210.

247. Dellinger TH, Monk BJ. Systemic therapy for recurrent endometrial cancer: a review of North American trials. Expert Rev Anticancer Ther 2009;9:905-916. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19589030.

248. Quinn MA, Campbell JJ. Tamoxifen therapy in advanced/recurrent endometrial carcinoma. Gynecol Oncol 1989;32:1-3. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2909443.

249. Thigpen T, Brady MF, Homesley HD, et al. Tamoxifen in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 2001;19:364-367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11208827.

250. Pandya KJ, Yeap BY, Weiner LM, et al. Megestrol and tamoxifen in patients with advanced endometrial cancer: an Eastern Cooperative

Oncology Group Study (E4882). Am J Clin Oncol 2001;24:43-46. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11232948.

251. McMeekin DS, Gordon A, Fowler J, et al. A phase II trial of arzoxifene, a selective estrogen response modulator, in patients with recurrent or advanced endometrial cancer. Gynecol Oncol 2003;90:64-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12821343.

252. Quinn MA. Hormonal treatment of endometrial cancer. Hematol Oncol Clin North Am 1999;13:163-187. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10080075.

253. Ray M, Fleming G. Management of advanced-stage and recurrent endometrial cancer. Semin Oncol 2009;36:145-154. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19332249.

254. Humber CE, Tierney JF, Symonds RP, et al. Chemotherapy for advanced, recurrent or metastatic endometrial cancer: a systematic review of Cochrane collaboration. Ann Oncol 2007;18:409-420. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17150999.

255. Cella D, Huang H, Homesley HD, et al. Patient-reported peripheral neuropathy of doxorubicin and cisplatin with and without paclitaxel in the treatment of advanced endometrial cancer: Results from GOG 184. Gynecol Oncol 2010;119:538-542. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20863554.

256. Fleming GF, Brunetto VL, Cella D, et al. Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol 2004;22:2159-2166. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15169803.

257. Miller D, Filiaci V, Fleming G, et al. Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: A Gynecologic Oncology Group study [abstract]. Gynecologic Oncology 2012;125:771. Available at:

258. Sovak MA, Dupont J, Hensley ML, et al. Paclitaxel and carboplatin in the treatment of advanced or recurrent endometrial cancer: a large retrospective study. Int J Gynecol Cancer 2007;17:197-203. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17291253.

259. Pectasides D, Xiros N, Papaxoinis G, et al. Carboplatin and paclitaxel in advanced or metastatic endometrial cancer. Gynecol Oncol 2008;109:250-254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18299146.

260. Sorbe B, Andersson H, Boman K, et al. Treatment of primary advanced and recurrent endometrial carcinoma with a combination of carboplatin and paclitaxel-long-term follow-up. Int J Gynecol Cancer 2008;18:803-808. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17944917.

261. Nomura H, Aoki D, Takahashi F, et al. Randomized phase II study comparing docetaxel plus cisplatin, docetaxel plus carboplatin, and paclitaxel plus carboplatin in patients with advanced or recurrent endometrial carcinoma: a Japanese Gynecologic Oncology Group study (JGOG2041). Ann Oncol 2011;22:636-642. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20696677.

262. Wadler S, Levy DE, Lincoln ST, et al. Topotecan is an active agent in the first-line treatment of metastatic or recurrent endometrial carcinoma: Eastern Cooperative Oncology Group Study E3E93. J Clin Oncol 2003;21:2110-2114. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12775736.

263. Traina TA, Sabbatini P, Aghajanian C, Dupont J. Weekly topotecan for recurrent endometrial cancer: a case series and review of the literature. Gynecol Oncol 2004;95:235-241. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15385138.

264. Miller DS, Blessing JA, Lentz SS, Waggoner SE. A phase II trial of topotecan in patients with advanced, persistent, or recurrent endometrial carcinoma: a gynecologic oncology group study. Gynecol

Oncol 2002;87:247-251. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12468321.

265. Moxley KM, McMeekin DS. Endometrial carcinoma: a review of chemotherapy, drug resistance, and the search for new agents. Oncologist 2010;15:1026-1033. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20930101.

266. Muggia FM, Blessing JA, Sorosky J, Reid GC. Phase II trial of the pegylated liposomal doxorubicin in previously treated metastatic endometrial cancer: a Gynecologic Oncology Group study. J Clin Oncol 2002;20:2360-2364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11981008.

267. Garcia AA, Blessing JA, Nolte S, Mannel RS. A phase II evaluation of weekly docetaxel in the treatment of recurrent or persistent endometrial carcinoma: a study by the Gynecologic Oncology Group. Gynecol Oncol 2008;111:22-26. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18675446.

268. Alvarez EA, Brady WE, Walker JL, et al. Phase II trial of combination bevacizumab and temsirolimus in the treatment of recurrent or persistent endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2013;129:22-27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23262204.

269. Aghajanian C, Sill MW, Darcy KM, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: A Gynecologic Oncology Group Study. J Clin Oncol 2011;29:2259-2265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21537039.

270. Oza AM, Elit L, Tsao MS, et al. Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trials Group. J Clin Oncol 2011;29:3278-3285. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21788564.

271. Fleming GF, Filiaci VL, Marzullo B, et al. Temsirolimus with or without megestrol acetate and tamoxifen for endometrial cancer: a gynecologic oncology group study. Gynecol Oncol 2014;132:585-592. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24456823.

272. Slomovitz BM, Jiang Y, Yates MS, et al. Phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma. J Clin Oncol 2015;33:930-936. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25624430.

273. Boruta DM, 2nd, Gehrig PA, Fader AN, Olawaiye AB. Management of women with uterine papillary serous cancer: a Society of Gynecologic Oncology (SGO) review. Gynecol Oncol 2009;115:142-153. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19592079.

274. Olawaiye AB, Boruta DM, 2nd. Management of women with clear cell endometrial cancer: a Society of Gynecologic Oncology (SGO) review. Gynecol Oncol 2009;113:277-283. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19251307.

275. Mendivil A, Schuler KM, Gehrig PA. Non-endometrioid adenocarcinoma of the uterine corpus: a review of selected histological subtypes. Cancer Control 2009;16:46-52. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19078929.

276. Varughese J, Hui P, Lu L, et al. Clear cell cancer of the uterine corpus: the association of clinicopathologic parameters and treatment on disease progression. J Oncol 2011;2011:628084. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22187554.

277. Kernochan LE, Garcia RL. Carcinosarcomas (malignant mixed Mullerian tumor) of the uterus: advances in elucidation of biologic and clinical characteristics. J Natl Compr Canc Netw 2009;7:550-556; quiz 557. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19460280.

278. Cirisano FD, Jr., Robboy SJ, Dodge RK, et al. The outcome of stage I-II clinically and surgically staged papillary serous and clear cell endometrial cancers when compared with endometrioid carcinoma. Gynecol Oncol 2000;77:55-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10739691.

279. Hendrickson MR, Longacre TA, Kempson RL. Uterine papillary serous carcinoma revisited. Gynecol Oncol 1994;54:261-263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8088601.

280. McCluggage WG. Uterine carcinosarcomas (malignant mixed Mullerian tumors) are metaplastic carcinomas. Int J Gynecol Cancer 2002;12:687-690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12445244.

281. Cantrell LA, Havrilesky L, Moore DT, et al. A multi-institutional cohort study of adjuvant therapy in stage I-II uterine carcinosarcoma. Gynecol Oncol 2012;127:22-26. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22727985.

282. Kanthan R, Senger JL. Uterine carcinosarcomas (malignant mixed mullerian tumours): a review with special emphasis on the controversies in management. Obstet Gynecol Int 2011;2011:470795. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22007228.

283. D'Angelo E, Prat J. Pathology of mixed Mullerian tumours. Best Pract Res Clin Obstet Gynaecol 2011;25:705-718. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21742560.

284. de Jong RA, Nijman HW, Wijbrandi TF, et al. Molecular markers and clinical behavior of uterine carcinosarcomas: focus on the epithelial tumor component. Mod Pathol 2011;24:1368-1379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21572397.

285. Vorgias G, Fotiou S. The role of lymphadenectomy in uterine carcinosarcomas (malignant mixed mullerian tumours): a critical literature review. Arch Gynecol Obstet 2010;282:659-664. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20721670.

286. Fader AN, Drake RD, O'Malley DM, et al. Platinum/taxane-based chemotherapy with or without radiation therapy favorably impacts survival outcomes in stage I uterine papillary serous carcinoma. Cancer 2009;115:2119-2127. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19306417.

287. Fader AN, Nagel C, Axtell AE, et al. Stage II uterine papillary serous carcinoma: Carboplatin/paclitaxel chemotherapy improves recurrence and survival outcomes. Gynecol Oncol 2009;112:558-562. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19118888.

288. Vandenput I, Trovik J, Vergote I, et al. The role of adjuvant chemotherapy in surgical stages I-II serous and clear cell carcinomas and carcinosarcoma of the endometrium: A collaborative study. Int J Gynecol Cancer 2011;21:332-336. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21270614.

289. Kelly MG, O'Malley D M, Hui P, et al. Improved survival in surgical stage I patients with uterine papillary serous carcinoma (UPSC) treated with adjuvant platinum-based chemotherapy. Gynecol Oncol 2005;98:353-359. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16005947.

290. Thomas MB, Mariani A, Cliby WA, et al. Role of systematic lymphadenectomy and adjuvant therapy in stage I uterine papillary serous carcinoma. Gynecol Oncol 2007;107:186-189. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17688926.

291. Goldberg H, Miller RC, Abdah-Bortnyak R, et al. Outcome after combined modality treatment for uterine papillary serous carcinoma: a study by the Rare Cancer Network (RCN). Gynecol Oncol 2008;108:298-305. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18096209.

292. Hamilton CA, Cheung MK, Osann K, et al. The effect of adjuvant chemotherapy versus whole abdominopelvic radiation on the survival of patients with advanced stage uterine papillary serous carcinoma. Gynecol Oncol 2006;103:679-683. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16793126.

293. Grice J, Ek M, Greer B, et al. Uterine papillary serous carcinoma: evaluation of long-term survival in surgically staged patients. Gynecol Oncol 1998;69:69-73. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9571001.

294. Havrilesky LJ, Secord AA, Bae-Jump V, et al. Outcomes in surgical stage I uterine papillary serous carcinoma. Gynecol Oncol 2007;105:677-682. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17355889.

295. Sutton G, Axelrod JH, Bundy BN, et al. Adjuvant whole abdominal irradiation in clinical stages I and II papillary serous or clear cell carcinoma of the endometrium: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol 2006;100:349-354. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16213007.

296. Fader AN, Boruta D, Olawaiye AB, Gehrig PA. Uterine papillary serous carcinoma: epidemiology, pathogenesis and management. Curr Opin Obstet Gynecol 2010;22:21-29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19952744.

297. Homesley HD, Filiaci V, Markman M, et al. Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:526-531. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17290061.

298. Einstein MH, Frimer M, Kuo DY, et al. Phase II trial of adjuvant pelvic radiation "sandwiched" between combination paclitaxel and carboplatin in women with uterine papillary serous carcinoma. Gynecol Oncol 2012;124:21-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22035806.

299. Galaal K, van der Heijden E, Godfrey K, et al. Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma. Cochrane Database Syst Rev 2013;2:CD006812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23450572.

300. Wang W, Do V, Hogg R, et al. Uterine papillary serous carcinoma: patterns of failure and survival. Aust N Z J Obstet Gynaecol 2009;49:419-425. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19694700.

301. Mehta N, Yamada SD, Rotmensch J, Mundt AJ. Outcome and pattern of failure in pathologic stage I-II papillary serous carcinoma of the endometrium: implications for adjuvant radiation therapy. Int J Radiat Oncol Biol Phys 2003;57:1004-1009. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14575831.

302. Murphy KT, Rotmensch J, Yamada SD, Mundt AJ. Outcome and patterns of failure in pathologic stages I-IV clear-cell carcinoma of the endometrium: implications for adjuvant radiation therapy. Int J Radiat Oncol Biol Phys 2003;55:1272-1276. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12654437.

303. Sood BM, Jones J, Gupta S, et al. Patterns of failure after the multimodality treatment of uterine papillary serous carcinoma. Int J Radiat Oncol Biol Phys 2003;57:208-216. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12909235.

304. Wolfson AH, Brady MF, Rocereto T, et al. A gynecologic oncology group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I-IV carcinosarcoma (CS) of the uterus. Gynecol Oncol 2007;107:177-185. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17822748.

305. Jhingran A, Ramondetta LM, Bodurka DC, et al. A prospective phase II study of chemoradiation followed by adjuvant chemotherapy for FIGO stage I-IIIA (1988) uterine papillary serous carcinoma of the endometrium. Gynecol Oncol 2013;129:304-309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23385150.

306. Vogel TJ, Knickerbocker A, Shah CA, et al. An analysis of current treatment practice in uterine papillary serous and clear cell carcinoma at two high volume cancer centers. J Gynecol Oncol 2015;26:25-31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25376917.

307. Mahdi H, Rose PG, Elshaikh MA, et al. Adjuvant vaginal brachytherapy decreases the risk of vaginal recurrence in patients with stage I non-invasive uterine papillary serous carcinoma. A multi-

institutional study. Gynecol Oncol 2015;136:529-533. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25575483.

308. Mahdi H, Elshaikh MA, DeBenardo R, et al. Impact of adjuvant chemotherapy and pelvic radiation on pattern of recurrence and outcome in stage I non-invasive uterine papillary serous carcinoma. A multi-institution study. Gynecol Oncol 2015;137:239-244. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25641568.

309. Sutton G, Brunetto VL, Kilgore L, et al. A phase III trial of ifosfamide with or without cisplatin in carcinosarcoma of the uterus: A Gynecologic Oncology Group Study. Gynecol Oncol 2000;79:147-153. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11063636.

310. Hensley ML. Role of chemotherapy and biomolecular therapy in the treatment of uterine sarcomas. Best Pract Res Clin Obstet Gynaecol 2011;25:773-782. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21752717.

311. Sutton G, Kauderer J, Carson LF, et al. Adjuvant ifosfamide and cisplatin in patients with completely resected stage I or II carcinosarcomas (mixed mesodermal tumors) of the uterus: a Gynecologic Oncology Group study. Gynecol Oncol 2005;96:630-634. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15721404.

312. Powell MA, Filiaci VL, Rose PG, et al. Phase II evaluation of paclitaxel and carboplatin in the treatment of carcinosarcoma of the uterus: a Gynecologic Oncology Group study. J Clin Oncol 2010;28:2727-2731. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20421537.

313. Reed NS, Mangioni C, Malmström H, et al. Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). Eur J Cancer 2008;44:808-818. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18378136.

314. Callister M, Ramondetta LM, Jhingran A, et al. Malignant mixed Müllerian tumors of the uterus: analysis of patterns of failure, prognostic factors, and treatment outcome. Int J Radiat Oncol Biol Phys 2004;58:786-796. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14967435.

315. Chi DS, Mychalczak B, Saigo PE, et al. The role of whole-pelvic irradiation in the treatment of early-stage uterine carcinosarcoma. Gynecol Oncol 1997;65:493-498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9190981.

316. Knocke TH, Weitmann HD, Kucera H, et al. Results of primary and adjuvant radiotherapy in the treatment of mixed Müllerian tumors of the corpus uteri. Gynecol Oncol 1999;73:389-395. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10366465.

317. Larson B, Silfverswärd C, Nilsson B, Pettersson F. Mixed müllerian tumours of the uterus--prognostic factors: a clinical and histopathologic study of 147 cases. Radiother Oncol 1990;17:123-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2157241.

318. Gerszten K, Faul C, Kounelis S, et al. The impact of adjuvant radiotherapy on carcinosarcoma of the uterus. Gynecol Oncol 1998;68:8-13. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9454652.

319. Dusenbery KE, Potish RA, Argenta PA, Judson PL. On the apparent failure of adjuvant pelvic radiotherapy to improve survival for women with uterine sarcomas confined to the uterus. Am J Clin Oncol 2005;28:295-300. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15923804.

320. Nemani D, Mitra N, Guo M, Lin L. Assessing the effects of lymphadenectomy and radiation therapy in patients with uterine carcinosarcoma: a SEER analysis. Gynecol Oncol 2008;111:82-88. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18674808.

321. Trope CG, Abeler VM, Kristensen GB. Diagnosis and treatment of sarcoma of the uterus. A review. Acta Oncol 2012;51:694-705. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22793037.

322. Amant F, Coosemans A, Debiec-Rychter M, et al. Clinical management of uterine sarcomas. Lancet Oncol 2009;10:1188-1198. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19959075.

323. Novetsky AP, Powell MA. Management of sarcomas of the uterus. Curr Opin Oncol 2013;25:546-552. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23942299.

324. Lax SF. Molecular genetic changes in epithelial, stromal and mixed neoplasms of the endometrium. Pathology 2007;39:46-54. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17365822.

325. Huang HY, Ladanyi M, Soslow RA. Molecular detection of JAZF1-JJAZ1 gene fusion in endometrial stromal neoplasms with classic and variant histology: evidence for genetic heterogeneity. Am J Surg Pathol 2004;28:224-232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15043312.

326. Leath CA, 3rd, Huh WK, Hyde J, Jr., et al. A multi-institutional review of outcomes of endometrial stromal sarcoma. Gynecol Oncol 2007;105:630-634. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17320937.

327. Koontz JI, Soreng AL, Nucci M, et al. Frequent fusion of the JAZF1 and JJAZ1 genes in endometrial stromal tumors. Proc Natl Acad Sci U S A 2001;98:6348-6353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11371647.

328. Lee CH, Marino-Enriquez A, Ou W, et al. The clinicopathologic features of YWHAE-FAM22 endometrial stromal sarcomas: a histologically high-grade and clinically aggressive tumor. Am J Surg Pathol 2012;36:641-653. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22456610.

329. Sciallis AP, Bedroske PP, Schoolmeester JK, et al. High-grade endometrial stromal sarcomas: a clinicopathologic study of a group of tumors with heterogenous morphologic and genetic features. Am J Surg Pathol 2014;38:1161-1172. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25133706.

330. Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO Classification of Tumours of Female Reproductive Organs. Fourth Edition. Vol. 6: World Health Organization; 2014.

331. Zivanovic O, Leitao MM, Iasonos A, et al. Stage-specific outcomes of patients with uterine leiomyosarcoma: a comparison of the international Federation of gynecology and obstetrics and american joint committee on cancer staging systems. J Clin Oncol 2009;27:2066-2072. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19255317.

332. Prat J. FIGO staging for uterine sarcomas. Int J Gynaecol Obstet 2009;104:177-178. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19135669.

333. Rauh-Hain JA, del Carmen MG. Endometrial stromal sarcoma: a systematic review. Obstet Gynecol 2013;122:676-683. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23921879.

334. Group EESNW. Soft tissue and visceral sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23 Suppl 7:vii92-99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22997462.

335. Barney B, Tward JD, Skidmore T, Gaffney DK. Does radiotherapy or lymphadenectomy improve survival in endometrial stromal sarcoma? Int J Gynecol Cancer 2009;19:1232-1238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19823060.

336. Shah JP, Bryant CS, Kumar S, et al. Lymphadenectomy and ovarian preservation in low-grade endometrial stromal sarcoma. Obstet Gynecol 2008;112:1102-1108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18978112.

337. Signorelli M, Fruscio R, Dell'Anna T, et al. Lymphadenectomy in uterine low-grade endometrial stromal sarcoma: an analysis of 19 cases and a literature review. Int J Gynecol Cancer 2010;20:1363-1366. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21051978.

338. Reichardt P. The treatment of uterine sarcomas. Ann Oncol 2012;23 Suppl 10:x151-157. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22987952.

339. Thanopoulou E, Judson I. Hormonal therapy in gynecological sarcomas. Expert Rev Anticancer Ther 2012;12:885-894. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22845404.

340. Pink D, Lindner T, Mrozek A, et al. Harm or benefit of hormonal treatment in metastatic low-grade endometrial stromal sarcoma: single center experience with 10 cases and review of the literature. Gynecol Oncol 2006;101:464-469. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16368128.

341. Reich O, Regauer S. Estrogen replacement therapy and tamoxifen are contraindicated in patients with endometrial stromal sarcoma. Gynecol Oncol 2006;102:413-414; author reply 414. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16712906.

342. Mansi JL, Ramachandra S, Wiltshaw E, Fisher C. Endometrial stromal sarcomas. Gynecol Oncol 1990;36:113-118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2295442.

343. Berchuck A, Rubin SC, Hoskins WJ, et al. Treatment of endometrial stromal tumors. Gynecol Oncol 1990;36:60-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2295453.

344. Weitmann HD, Knocke TH, Kucera H, Pötter R. Radiation therapy in the treatment of endometrial stromal sarcoma. Int J Radiat Oncol Biol Phys 2001;49:739-748. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11172957.

345. Brenner DJ, Hall EJ. Computed tomography--an increasing source of radiation exposure. N Engl J Med 2007;357:2277-2284. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18046031.

346. Sampath S, Schultheiss TE, Ryu JK, Wong JY. The role of adjuvant radiation in uterine sarcomas. Int J Radiat Oncol Biol Phys 2010;76:728-734. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19700247.

347. Mahdavi A, Monk BJ, Ragazzo J, et al. Pelvic radiation improves local control after hysterectomy for uterine leiomyosarcoma: a 20-year experience. Int J Gynecol Cancer 2009;19:1080-1084. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19820372.

348. Giuntoli RL, 2nd, Metzinger DS, DiMarco CS, et al. Retrospective review of 208 patients with leiomyosarcoma of the uterus: prognostic indicators, surgical management, and adjuvant therapy. Gynecol Oncol 2003;89:460-469. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12798712.

349. Dusenbery KE, Potish RA, Judson P. Limitations of adjuvant radiotherapy for uterine sarcomas spread beyond the uterus. Gynecol Oncol 2004;94:191-196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15262141.

350. Ricci S, Giuntoli RL, 2nd, Eisenhauer E, et al. Does adjuvant chemotherapy improve survival for women with early-stage uterine leiomyosarcoma? Gynecol Oncol 2013;131:629-633. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24016408.

351. Hensley ML, Wathen JK, Maki RG, et al. Adjuvant therapy for high-grade, uterus-limited leiomyosarcoma: results of a phase 2 trial (SARC 005). Cancer 2013;119:1555-1561. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23335221.

352. Maki RG, Wathen JK, Patel SR, et al. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma

alliance for research through collaboration study 002 [corrected]. J Clin Oncol 2007;25:2755-2763. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17602081.

353. Davis EJ, Chugh R, Zhao L, et al. Neo/adjuvant doxorubicin (A) and ifosfamide (I) versus gemcitabine (G) and docetaxel (T) in patients (PTS) with localized, high risk soft tissue sarcoma (STS): A randomized phase II comparative effectiveness trial [abstract]. J Clin Oncol 2013;31(Suppl 15):Abstract 10524. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/10524.

354. Hensley ML, Blessing JA, Mannel R, Rose PG. Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. Gynecol Oncol 2008;109:329-334. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18534250.

355. Hensley ML, Ishill N, Soslow R, et al. Adjuvant gemcitabine plus docetaxel for completely resected stages I-IV high grade uterine leiomyosarcoma: Results of a prospective study. Gynecol Oncol 2009;112:563-567. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19135708.

356. Hensley ML, Maki R, Venkatraman E, et al. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J Clin Oncol 2002;20:2824-2831. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12065559.

357. Garcia-Del-Muro X, Lopez-Pousa A, Maurel J, et al. Randomized phase II study comparing gemcitabine plus dacarbazine versus dacarbazine alone in patients with previously treated soft tissue sarcoma: a Spanish Group for Research on Sarcomas study. J Clin Oncol 2011;29:2528-2533. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21606430.

358. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012;379:1879-1886. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22595799.

359. Mancari R, Signorelli M, Gadducci A, et al. Adjuvant chemotherapy in stage I-II uterine leiomyosarcoma: a multicentric retrospective study of 140 patients. Gynecol Oncol 2014;133:531-536. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24631454.

360. Karavasilis V, Seddon BM, Ashley S, et al. Significant clinical benefit of first-line palliative chemotherapy in advanced soft-tissue sarcoma: retrospective analysis and identification of prognostic factors in 488 patients. Cancer 2008;112:1585-1591. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18278813.

361. Gottlieb JA, Benjamin RS, Baker LH, et al. Role of DTIC (NSC-45388) in the chemotherapy of sarcomas. Cancer Treat Rep 1976;60:199-203. Available at: http://www.ncbi.nlm.nih.gov/pubmed/769974.

362. Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). J Clin Oncol 2009;27:3126-3132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19451427.

363. Somaiah N, von Mehren M. New drugs and combinations for the treatment of soft-tissue sarcoma: a review. Cancer Manag Res 2012;4:397-411. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23226072.

364. Rajendra R, Jones RL, Pollack SM. Targeted treatment for advanced soft tissue sarcoma: profile of pazopanib. Onco Targets Ther 2013;6:217-222. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23524973.

365. Pautier P, Floquet A, Penel N, et al. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and

docetaxel in patients with metastatic or relapsed leiomyosarcomas: a Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). Oncologist 2012;17:1213-1220. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22907974.

366. van Hoesel QG, Verweij J, Catimel G, et al. Phase II study with docetaxel (Taxotere) in advanced soft tissue sarcomas of the adult. EORTC Soft Tissue and Bone Sarcoma Group. Ann Oncol 1994;5:539-542. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7918126.

367. Edmonson JH, Ebbert LP, Nascimento AG, et al. Phase II study of docetaxel in advanced soft tissue sarcomas. Am J Clin Oncol 1996;19:574-576. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8931674.

368. Ridolfi C, Pasini G, Drudi F, et al. Long lasting clinical response to chemotherapy for advanced uterine leiomyosarcoma: a case report. J Med Case Rep 2013;7:29. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23347560.

369. Ferriss JS, Atkins KA, Lachance JA, et al. Temozolomide in advanced and recurrent uterine leiomyosarcoma and correlation with o6-methylguanine DNA methyltransferase expression: a case series. Int J Gynecol Cancer 2010;20:120-125. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20130512.

370. Anderson S, Aghajanian C. Temozolomide in uterine leiomyosarcomas. Gynecol Oncol 2005;98:99-103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15916799.

371. Talbot SM, Keohan ML, Hesdorffer M, et al. A phase II trial of temozolomide in patients with unresectable or metastatic soft tissue sarcoma. Cancer 2003;98:1942-1946. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14584078.

372. Oosten AW, Seynaeve C, Schmitz PI, et al. Outcomes of first-line chemotherapy in patients with advanced or metastatic leiomyosarcoma of uterine and non-uterine origin. Sarcoma 2009;2009:348910. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20066161.

373. Bernstein-Molho R, Grisaro D, Soyfer V, et al. Metastatic uterine leiomyosarcomas: a single-institution experience. Int J Gynecol Cancer 2010;20:255-260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20134269.

374. Look KY, Sandler A, Blessing JA, et al. Phase II trial of gemcitabine as second-line chemotherapy of uterine leiomyosarcoma: a Gynecologic Oncology Group (GOG) Study. Gynecol Oncol 2004;92:644-647. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14766260.

375. Judson I, Radford JA, Harris M, et al. Randomised phase II trial of pegylated liposomal doxorubicin (DOXIL/CAELYX) versus doxorubicin in the treatment of advanced or metastatic soft tissue sarcoma: a study by the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer 2001;37:870-877. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11313175.

376. Sutton G, Blessing J, Hanjani P, Kramer P. Phase II evaluation of liposomal doxorubicin (Doxil) in recurrent or advanced leiomyosarcoma of the uterus: a Gynecologic Oncology Group study. Gynecol Oncol 2005;96:749-752. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15721421.

377. Gallup DG, Blessing JA, Andersen W, Morgan MA. Evaluation of paclitaxel in previously treated leiomyosarcoma of the uterus: a gynecologic oncology group study. Gynecol Oncol 2003;89:48-51. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12694653.

378. George S, Feng Y, Manola J, et al. Phase 2 trial of aromatase inhibition with letrozole in patients with uterine leiomyosarcomas expressing estrogen and/or progesterone receptors. Cancer 2014;120:738-743. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24222211.

379. Schoffski P, Maki RG, Italiano A, et al. Randomized, open-label, multicenter, phase III study of eribulin versus dacarbazine in patients (pts) with leiomyosarcoma (LMS) and adipocytic sarcoma (ADI) [abstract]. ASCO Meeting Abstracts 2015;33:LBA10502. Available at: http://meeting.ascopubs.org/cgi/content/abstract/33/18_suppl/LBA10502.

380. Gajdos C, Elias A. Trabectedin: safety and efficacy in the treatment of advanced sarcoma. Clin Med Insights Oncol 2011;5:35-43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21499557.

381. Demetri GD, Chawla SP, von Mehren M, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. J Clin Oncol 2009;27:4188-4196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19652065.

382. Fayette J, Boyle H, Chabaud S, et al. Efficacy of trabectedin for advanced sarcomas in clinical trials versus compassionate use programs: analysis of 92 patients treated in a single institution. Anticancer Drugs 2010;21:113-119. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19887935.

383. Pautier P, Floquet A, Chevreau C, et al. Trabectedin in combination with doxorubicin for first-line treatment of advanced uterine or soft-tissue leiomyosarcoma (LMS-02): a non-randomised, multicentre, phase 2 trial. Lancet Oncol 2015;16:457-464. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25795402.

384. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial. J Clin Oncol 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26371143.

385. Yoon A, Park JY, Park JY, et al. Prognostic factors and outcomes in endometrial stromal sarcoma with the 2009 FIGO staging system: a multicenter review of 114 cases. Gynecol Oncol 2014;132:70-75. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24184602.

386. Sharma S, Takyar S, Manson SC, et al. Efficacy and safety of pharmacological interventions in second- or later-line treatment of patients with advanced soft tissue sarcoma: a systematic review. BMC Cancer 2013;13:385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23937858.

387. Dhakal S, Corbin KS, Milano MT, et al. Stereotactic body radiotherapy for pulmonary metastases from soft-tissue sarcomas: excellent local lesion control and improved patient survival. Int J Radiat Oncol Biol Phys 2012;82:940-945. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21277105.

388. Mehta N, Selch M, Wang PC, et al. Safety and efficacy of stereotactic body radiation therapy in the treatment of pulmonary metastases from high grade sarcoma. Sarcoma 2013;2013:360214. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24198717.

389. Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122:574-580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18502492.

390. Dizon DS, Sabbatini PJ, Aghajanian C, et al. Analysis of patients with epithelial ovarian cancer or fallopian tube carcinoma retreated with cisplatin after the development of a carboplatin allergy. Gynecol Oncol 2002;84:378-382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11855873.

391. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Ann Emerg Med 2006;47:373-380. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16546624.

392. Manivannan V, Decker WW, Stead LG, et al. Visual representation of National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network criteria for anaphylaxis. Int J Emerg Med 2009;2:3-5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19390910.

393. Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. Oncologist 2007;12:601-609. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17522249.

394. Markman M, Zanotti K, Peterson G, et al. Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. J Clin Oncol 2003;21:4611-4614. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14673050.

395. Lee CW, Matulonis UA, Castells MC. Rapid inpatient/outpatient desensitization for chemotherapy hypersensitivity: standard protocol effective in 57 patients for 255 courses. Gynecol Oncol 2005;99:393-399. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16054201.

396. Lee CW, Matulonis UA, Castells MC. Carboplatin hypersensitivity: a 6-h 12-step protocol effective in 35 desensitizations in patients with gynecological malignancies and mast cell/IgE-mediated reactions. Gynecol Oncol 2004;95:370-376. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15491759.

397. Markman M, Hsieh F, Zanotti K, et al. Initial experience with a novel desensitization strategy for carboplatin-associated hypersensitivity reactions: carboplatin-hypersensitivity reactions. J Cancer Res Clin Oncol 2004;130:25-28. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14564516.