National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Cervical Cancer

Version 1.2011

NCCN.org

Continue

NCCN Guidelines™ Version 1.2011 Panel Members
Cervical Cancer

NCCN Guidelines Index
Cervical Cancer TOC
Discussion

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

* **Wui-Jin Koh, MD/Co-Chair** §
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
H. Lee Moffitt Cancer Center & Research Institute

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

John Chan, MD Ω
UCSF Helen Diller Family Comprehensive Cancer Center

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

Larry Copeland, 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

Nefertiti DuPont, MD, MPH Ω
Roswell Park Cancer Institute

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

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

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

Daniel S. Kapp, MD, PhD §
Stanford Comprehensive Cancer Center

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

Lainie Martin, MD †
Fox Chase Cancer Center

Mark A. Morgan, MD Ω
Fox Chase Cancer Center

Robert J. Morgan, Jr., MD † ‡
City of Hope Comprehensive Cancer Center

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

Steven W. Remmenga, MD Ω
UNMC Eppley Cancer Center at The Nebraska Medical Center

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

William Small, Jr., MD §
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Nelson Teng, MD, PhD Ω
Stanford Comprehensive Cancer Center

Fidel A. Valea, MD Ω
Duke Comprehensive Cancer Center

NCCN
Miranda Hughes, PhD
Nicole McMillian, MS

NCCN Guidelines Panel Disclosures

Continue

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

NCCN Guidelines™ Version 1.2011 Table of Contents
Cervical Cancer

NCCN Guidelines Index
Cervical Cancer TOC
Discussion

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

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

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

See NCCN Categories of Evidence and Consensus

The NCCN Cervical Cancer Guidelines include the management of squamous cell carcinoma, adenosquamous carcinoma, and adenocarcinoma of the cervix.

NCCN Guidelines™ Version 1.2011 Updates Cervical Cancer

NCCN Guidelines Index
Cervical Cancer TOC
Discussion

Updates in Version 1.2011 of the NCCN Cervical Cancer Guidelines from Version 1.2010 include:

Global Changes:

- The Staging tables were updated to reflect the 2009 FIGO Staging (ST-1) and (ST-2).
- The Cervical Cancer algorithms were revised to reflect the new FIGO staging.
- "Principles of Radiation Therapy" is a new page that provides specific recommendations and dosing for radiation therapy throughout the NCCN Cervical Cancer Guidelines (CERV-A).

CERV-1

- Workup: The "CBC" and "Imaging" bullets were revised for clarity. (Also for CERV-7)

CERV-2

- Stage IA1; Primary Treatment: The third option changed to "Modified radical hysterectomy or trachelectomy + pelvic lymph node dissection if lymphovascular invasion (category 2B for node dissection)".
- Stage IA2; Primary Treatment: The second option changed from "Brachytherapy + pelvic RT..." to "Brachytherapy ± pelvic RT..."
- Stage IB1 and stage IIA1; Primary treatment: "Radical trachelectomy for fertility preservation for lesions (Stage IB1)..." changed to "Radical trachelectomy for tumors ≤ 2 cm (Stage IB1)..."

CERV-3

- Surgical Findings: "Positive pelvic nodes or Positive surgical margin or Positive parametrium" changed to "Positive pelvic nodes and/or Positive surgical margin and/or Positive parametrium" (Also for CERV-7)
- Para-aortic lymph node postive..."; Bottom pathway:
  - "Chest CT/PET scan" was clarified as "Chest CT or PET-CT scan".
  - "Systemic therapy/individualized RT" changed to "Systemic therapy ± individualized RT". (Also for CERV-5 and CERV-6)

CERV-4

- Radiologic imaging only; Positive adenopathy: "FNA if clinically indicated" changed to "Consider needle biopsy".

CERV-5

- "Pelvic lymph node positive/para-aortic lymph...." changed to "Pelvic lymph node positive and para-aortic lymph node..."

CERV-6

- "Retroperitoneal lymph node dissection" changed to "Extraperitoneal lymph node dissection".

CERV-7

- "Stage IA1 with lymphovascular space invasion" pathway: "Optional (≥ Stage IB2): EUA cystoscopy/proctoscopy" was removed as a recommendation.

CERV-8

- Surveillance: "Patient education regarding symptoms" was added.
- Workup: "Pelvic/abdominal/chest CT/PET scan" changed to "Additional imaging as clinically indicated".
- Footnote "h" regarding PET-CT scan is new to the page.

CERV-9

- Noncentral disease: "Pelvic exenteration" was removed before "Resection with IORT for close or positive margins".
- "Platinum-based chemotherapy" changed to "Chemotherapy".

CERV-10

- Resectable: "RT + concurrent chemotherapy" changed to "RT ± concurrent chemotherapy".

CERV-B Chemotherapy Regimens for Recurrent or Metastatic Disease

- First-line combination therapy: "Cisplatin/paclitaxel" changed from "category 1" to "category 2A".
- Second-line therapy:
  - Statement changed to "Agents listed are category 2B unless otherwise noted".
  - "Epirubicin" and "liposomal doxorubicin" were removed.
  - "Pemetrexed" and "vinorelbine" changed from "category 2B" to "category 3."
- Footnote referencing the Management of Drug Reactions (OV-C) page from the NCCN Ovarian Cancer Guidelines is new to the page.

WORKUP

- H&P
- CBC (including platelets)
- Cervical biopsy, pathologic review
- Cone biopsy as indicated[a]
- LFT/renal function studies
- Imaging

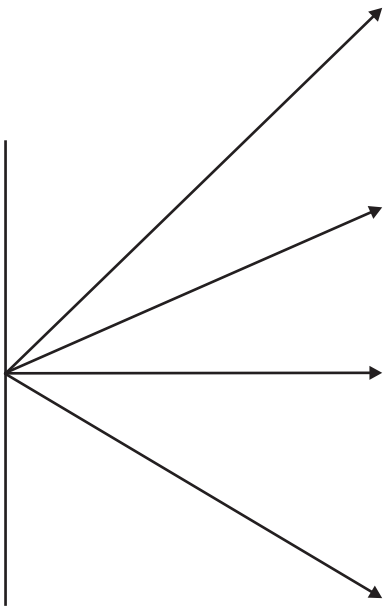
(optional for ≤ stage IB1):

- Chest x-ray
- CT or PET-CT scan
- MRI as indicated

Optional (≥ Stage IB2):

- EUA cystoscopy/proctoscopy[b]

CLINICAL STAGE



Stage IA1	See Primary Treatment (CERV- 2)
Stage IA2 Stage IB1 Stage IIA1	See Primary Treatment (CERV-2)
Stage IB2 Stage IIA2	See Primary Treatment (CERV-2) and (CERV-4)
Stage IIB Stage IIIA, IIIB Stage IVA	See Primary Treatment (CERV-4)
Incidental finding of invasive cancer at simple hysterectomy	See Primary Treatment (CERV-7)

All staging in guideline is based on updated 2009 FIGO staging. (See ST-1)

[a] See Discussion for indications for cone biopsy (MS-2).

[b] For suspicion of bladder/bowel involvement, cystoscopy/proctoscopy with biopsy is required.

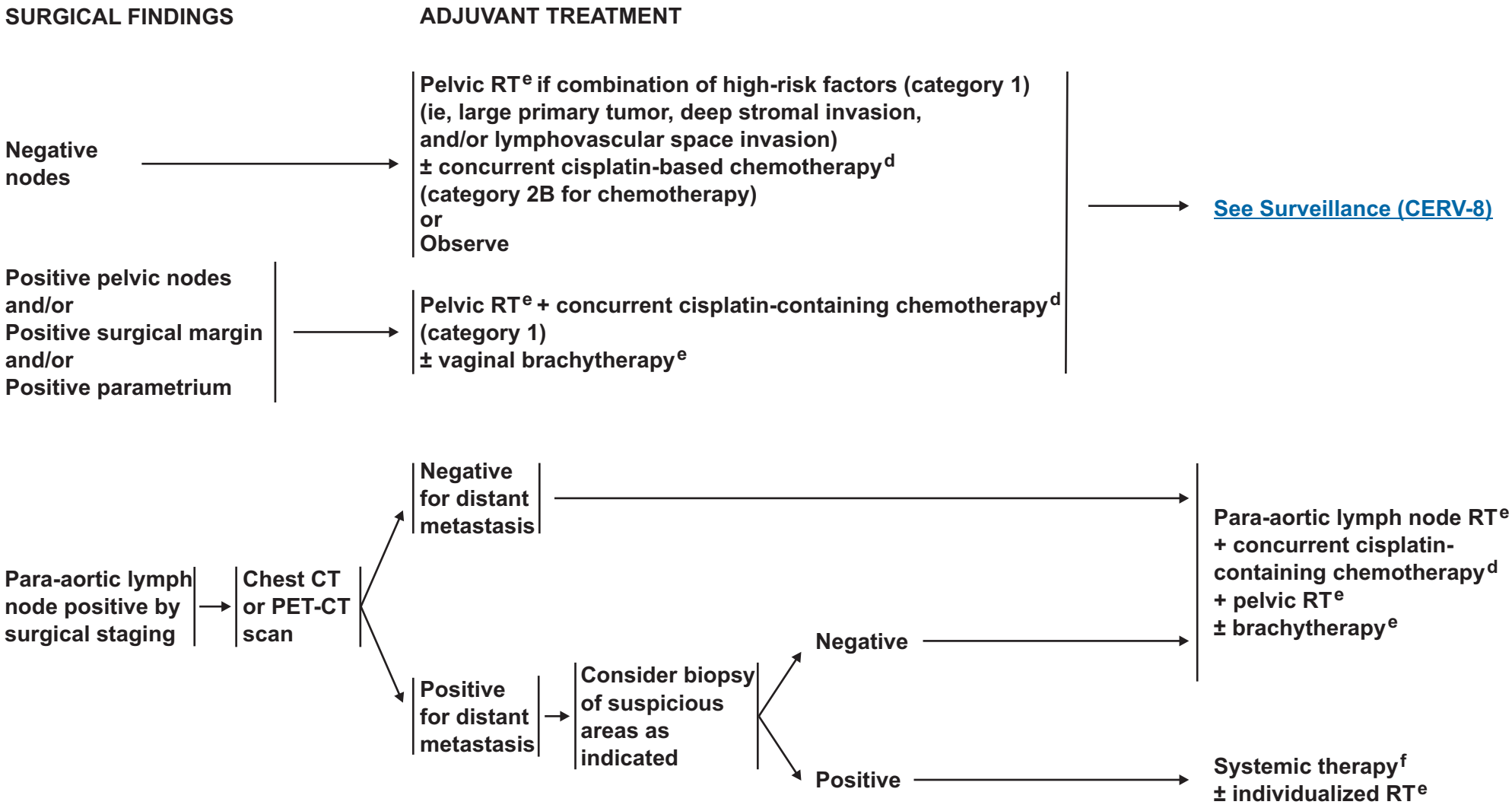
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL STAGE	PRIMARY TREATMENT	
Stage IA1	Extrafascial hysterectomy or Observe if patient desires fertility or if inoperable (only if cone biopsy has negative margins)	→ See Surveillance (CERV-8)
	or Modified radical hysterectomy or trachelectomy + pelvic lymph node dissection if lymphovascular invasion (category 2B for node dissection)	→ See Surgical Findings (CERV-3)
Stage IA2	Radical hysterectomy + pelvic lymph node dissection ± para-aortic lymph node sampling	→ See Surgical Findings (CERV-3)
	or Brachytherapy ± pelvic RT (total point A dose: 75-80 Gy)[c] or Radical trachelectomy + pelvic lymph node dissection ± para-aortic lymph node sampling	→ See Surveillance (CERV-8)
Stage IB1 and stage IIA1	Radical hysterectomy + pelvic lymph node dissection ± para-aortic lymph node sampling (category 1)	→ See Surgical Findings (CERV-3)
	or Pelvic RT + brachytherapy (total point A dose: 80-85 Gy)[c] or Radical trachelectomy for tumors ≤ 2 cm (Stage IB1) + pelvic lymph node dissection ± para-aortic lymph node sampling	→ See Surveillance (CERV-8)
Stage IB2 and stage IIA2 (also see CERV-4)	Pelvic RT + concurrent cisplatin-containing chemotherapy[d] + brachytherapy (total point A dose ≥ 85 Gy)[c] (category 1)	→ See Surveillance (CERV-8)
	or Radical hysterectomy + pelvic lymph node dissection + para-aortic lymph node sampling (category 2B)	→ See Surgical Findings (CERV-3)
	or Pelvic RT + concurrent cisplatin-containing chemotherapy[d] + brachytherapy (total point A dose 75-80 Gy)[c] + adjuvant hysterectomy (category 3)	→ See Surveillance (CERV-8)

[c] These doses are recommended for most patients based on summation of conventional external-beam fractionation and low-dose rate (40-70 cGy/h) brachytherapy equivalents. Modify treatment based on normal tissue tolerance. (See Discussion [MS-12])

[d] Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.

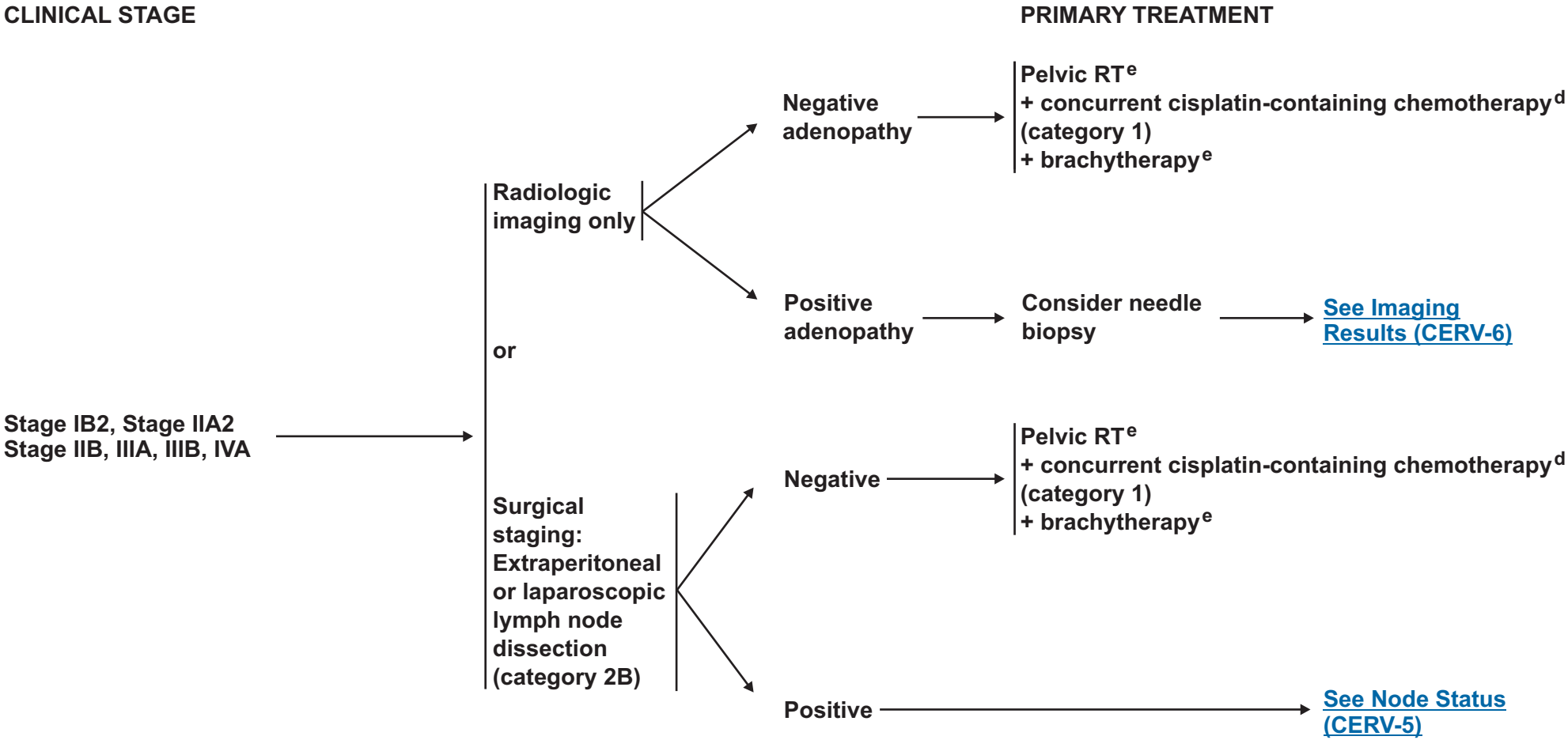
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[d] Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.
[e] See Principles of Radiation Therapy for Cervical Cancer (CERV-A).
[f] See Chemotherapy Regimens for Recurrent or Metastatic Cervical Cancer (CERV-B).

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

See Surveillance (CERV-8)



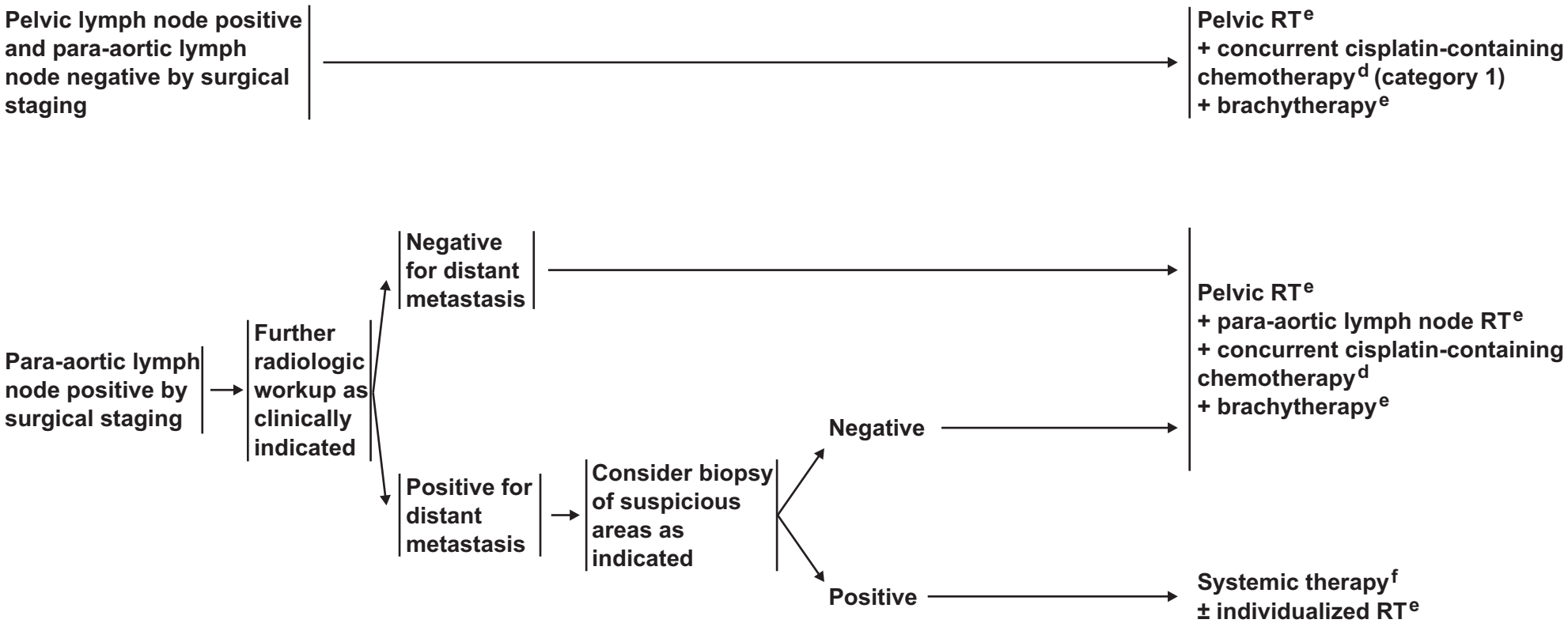
[d] Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.
[e] See Principles of Radiation for Cervical Cancer (CERV-A).

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

See Surveillance (CERV-8)

Stage IB2, IIA2; Stage IIB, IIIA, IIIB, IVA
NODE STATUS

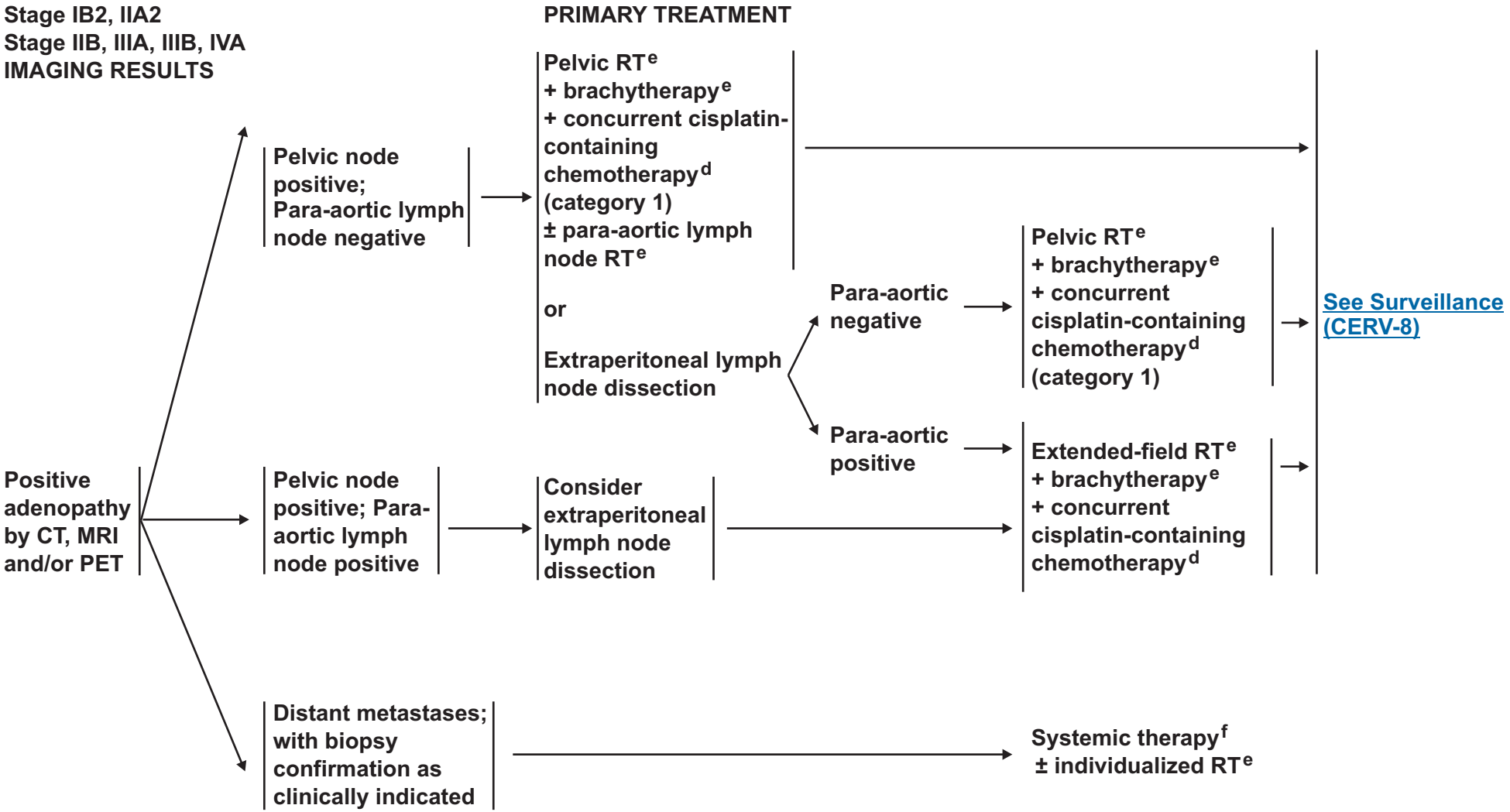
PRIMARY TREATMENT



[d] Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.
[e] See Principles of Radiation Therapy for Cervical Cancer (CERV-A).
[f] See Chemotherapy Regimens for Recurrent or Metastatic Cervical Cancer (CERV-B).

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

See Surveillance (CERV-8)



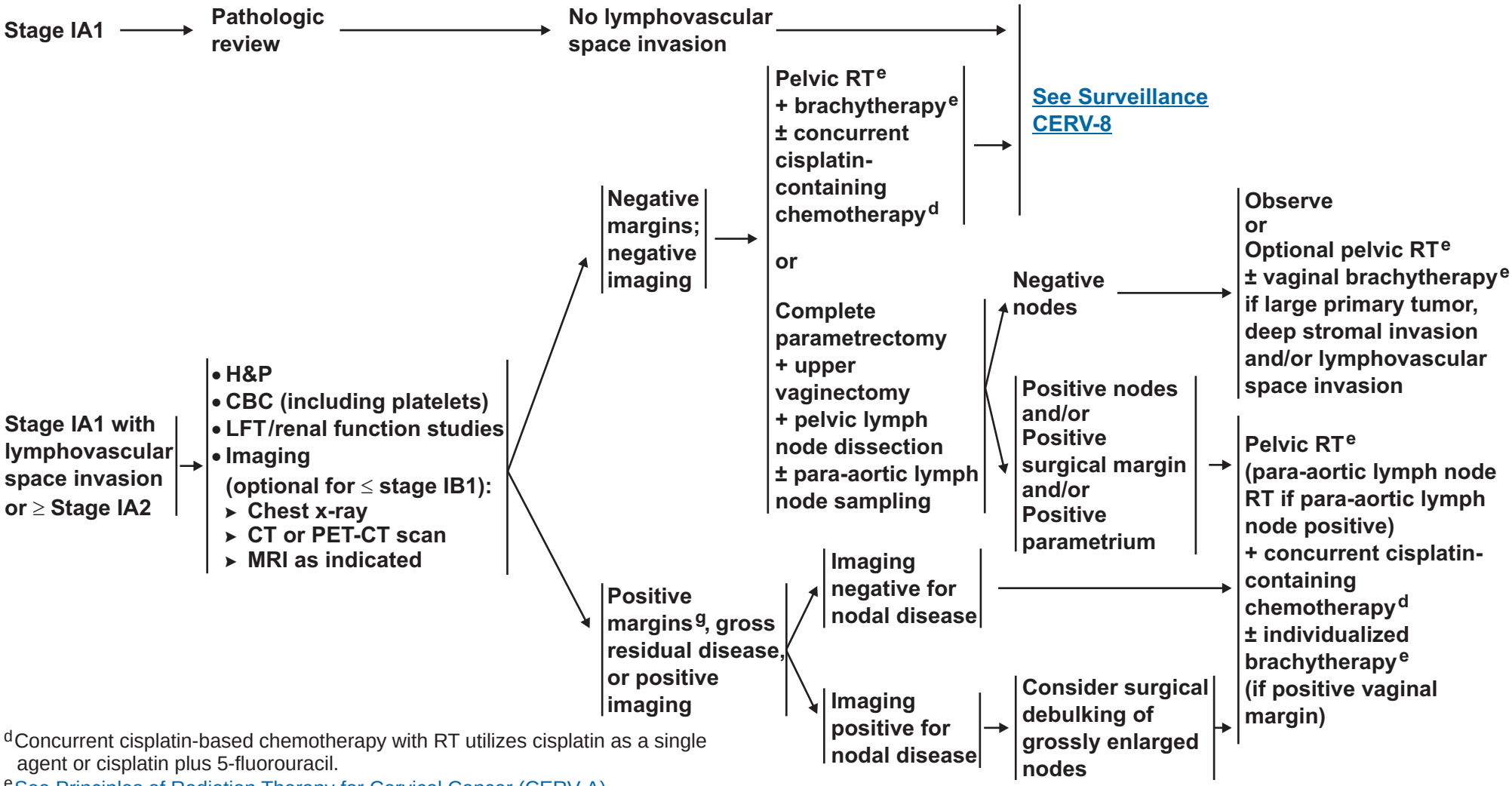
[d] Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.
[e] See Principles of Radiation Therapy for Cervical Cancer (CERV-A).
[f] See Chemotherapy Regimens for Recurrent or Metastatic Cervical Cancer (CERV-B).

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

See Surveillance (CERV-8)

INCIDENTAL FINDING OF INVASIVE CANCER AT SIMPLE HYSTERECTOMY

PRIMARY TREATMENT



[d] Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.

[e] See Principles of Radiation Therapy for Cervical Cancer (CERV-A).

[g] Invasive cancer at surgical margin.

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.

See Surveillance (CERV-8)

SURVEILLANCE

- Interval H&P
- Cervical/vaginal cytology every 3-6 mo for 2 y, then every 6 mo for 3-5 yrs, then annually
- Chest x-ray annually (optional)
- CBC, BUN, creatinine every 6 mo (optional)
- PET-CT scan as clinically indicated[h]
- Recommend use of vaginal dilator after RT
- Patient education regarding symptoms

→ Persistent or recurrent disease →

WORKUP

- Additional imaging as clinically indicated
- Surgical exploration in selected cases

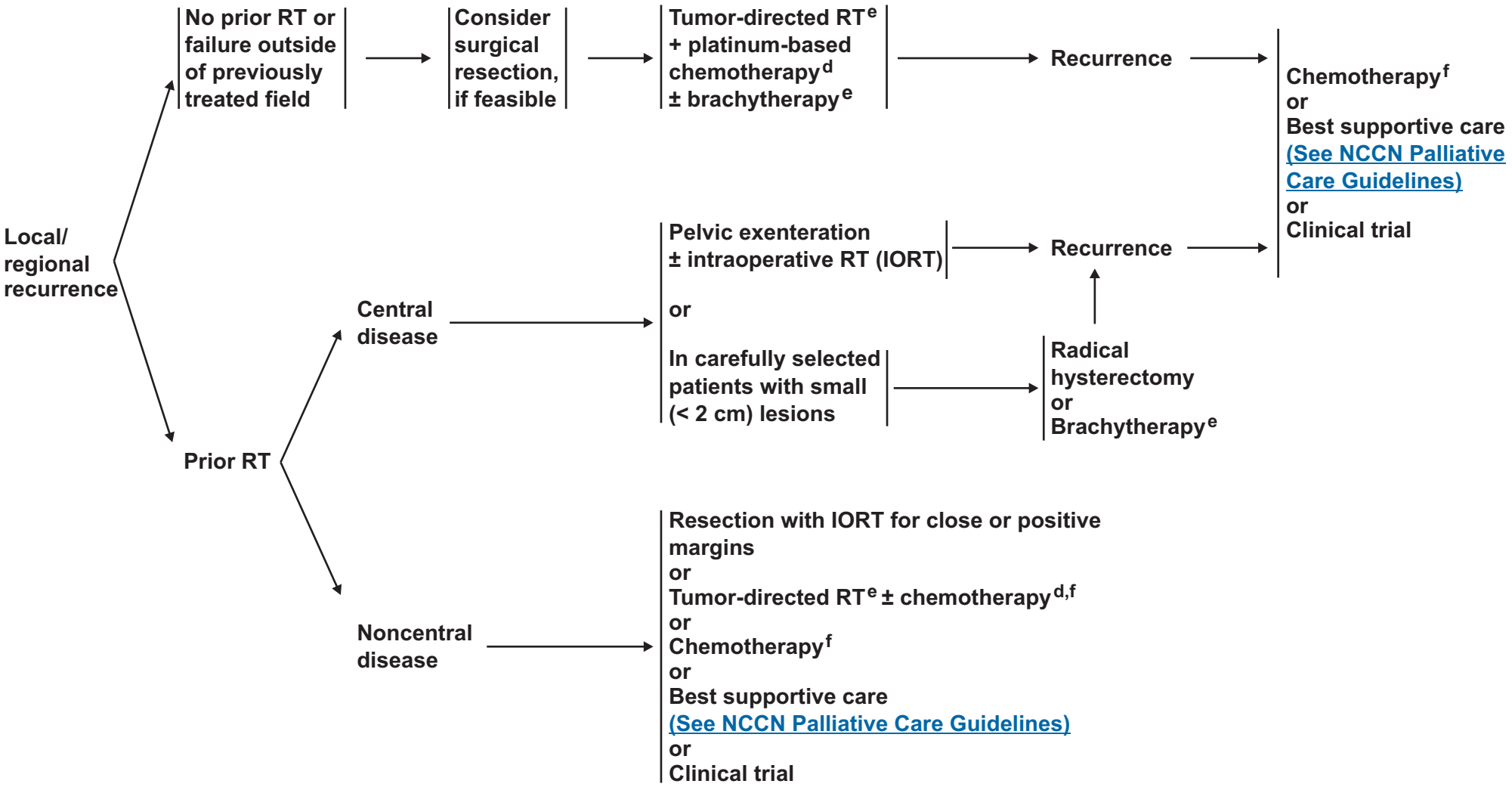
→ See Therapy for Relapse (Local/regional recurrence) (CERV-9)

→ See Therapy for Relapse (Distant metastases) (CERV-10)

[h]PET-CT scan may be useful in detecting isolated recurrences or persistent disease that is amenable to potentially curative salvage therapy. (See Discussion [MS-7])

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.

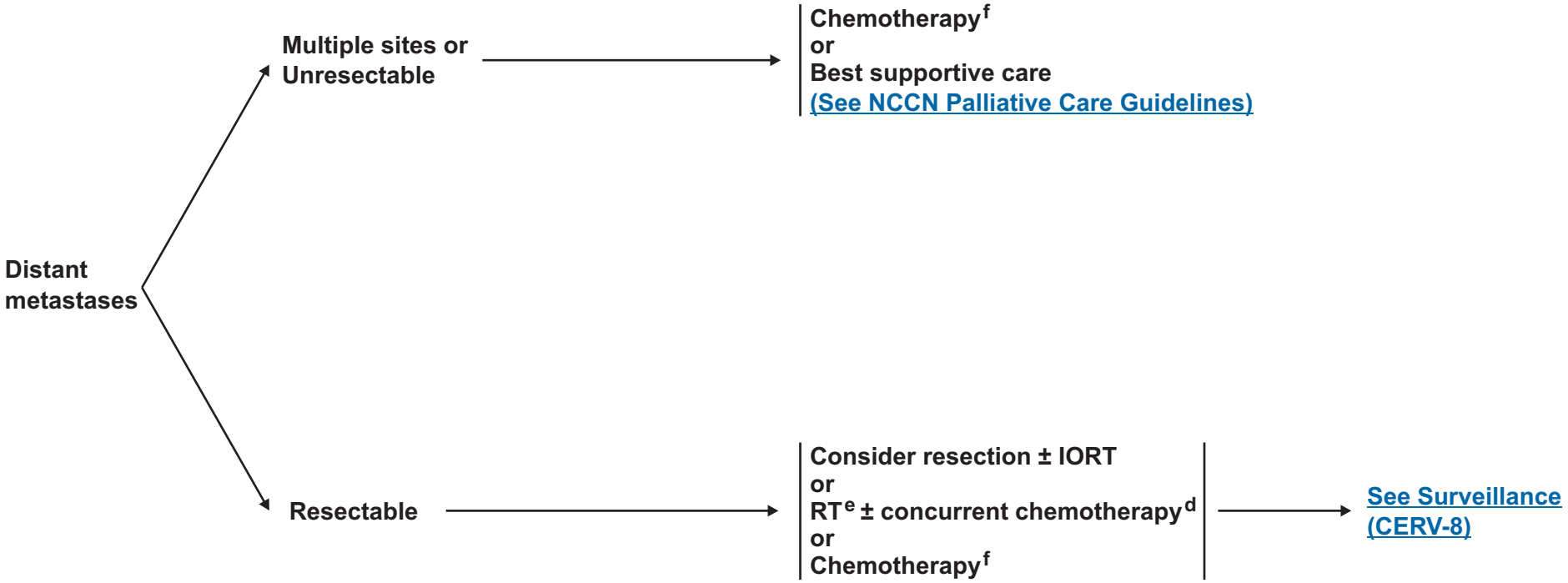
THERAPY FOR RELAPSE



[d] Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.
[e] See Principles of Radiation Therapy for Cervical Cancer (CERV-A).
[f] See Chemotherapy Regimens for Recurrent or Metastatic Cervical Cancer (CERV-B).

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

THERAPY FOR RELAPSE



[d] Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.
[e] See Principles of Radiation Therapy for Cervical Cancer (CERV-A).
[f] See Chemotherapy Regimens for Recurrent or Metastatic Cervical Cancer (CERV-B).

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

PRINCIPLES OF RADIATION THERAPY FOR CERVICAL CANCER

External-Beam Radiation Therapy (EBRT)

- **The use of computed tomography (CT)–based treatment planning and conformal blocking is considered standard of care for EBRT. MRI is the best imaging modality for determining soft tissue and parametrial involvement in patients with advanced tumors. In patients who are not surgically staged, PET imaging is useful to help define the nodal volume of coverage.**
- **The volume of EBRT should cover the gross disease (if present), parametria, uterosacral ligaments, sufficient vaginal margin from the gross disease (at least 3 cm), presacral nodes, and other nodal volumes at risk. For patients with negative nodes on surgical or radiologic imaging, the radiation volume should include the entirety of the external iliac, internal iliac, and obturator nodal basins. For patients deemed at higher risk of lymph node involvement (eg, bulkier tumors, or suspected or confirmed nodes confined to the low true pelvis), the radiation volume should be increased to cover the common iliacs as well. In patients with documented common iliac and/or para-aortic nodal involvement, extended-field pelvic and para-aortic radiotherapy would be required, up to the level of the renal vessels (or even more cephalad as directed by involved nodal distribution).**
- **Coverage of microscopic nodal disease requires an EBRT dose of approximately 45 Gy (in conventional fractionation of 1.8-2.0 Gy daily), and highly conformal boosts of an additional 10-15 Gy may be considered for limited volumes of gross unresected adenopathy. For the majority of patients who receive EBRT for cervical cancer, concurrent cisplatin-based chemotherapy (either cisplatin alone, or cisplatin + 5-fluorouracil) is given during the time of EBRT.**

Brachytherapy

- **Brachytherapy is a critical component of therapy for all patients with intact cervical cancer. This is usually performed using an intracavitary approach, with an intrauterine tandem and vaginal colpostats. Depending on the patient and tumor anatomy, the vaginal component of brachytherapy in patients with intact cervical cancer may be delivered using ovoids, ring, or cylinder (combined with the intrauterine tandem). When combined with EBRT, brachytherapy is often initiated towards the latter part of treatment, when sufficient primary tumor regression has been noted to permit satisfactory brachytherapy apparatus geometry. In highly selected very early disease (ie, stage IA2), brachytherapy alone, without external-beam radiation, may be an option.**
- **In rare cases, patients whose tumor geometry renders intracavitary brachytherapy infeasible may be best treated using an interstitial approach; however, such interstitial brachytherapy should only be performed by individuals and at institutions with appropriate experience and expertise.**
- **In selected post-hysterectomy patients (especially those with positive vaginal mucosal surgical margins), vaginal cylinder brachytherapy may be used as a boost to EBRT.**

Continued

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

PRINCIPLES OF RADIATION THERAPY FOR CERVICAL CANCER

Radiation Dosing Considerations

- The most common historical dosing parameters for brachytherapy utilize a system that includes specifying dose at point A, and that incorporates specific guidelines for 'radioactive source loading and distribution of activity' within the uterus and vagina, based on anatomic considerations. Doses are also calculated at standardized point B and bladder and rectal points. Current efforts at '3-D' image-guided brachytherapy seek to optimize implant dose coverage of tumor, while potentially reducing dose to adjacent bladder, rectum, and bowel structures.[1] Nonetheless, the weight of experience and tumor control results, and the majority of continuing clinical practice, have been based on the point A dosing system.[2] Attempts to improve dosing with image-guided brachytherapy should take care not to underdose tumors relative to the point A system dose recommendations.
- The point A dose recommendations provided in the NCCN Guidelines™ are based on traditional, and widely validated, dose fractionation and brachytherapy at low dose rates. In these provided dose recommendations, for EBRT, the dose is delivered at 1.8-2.0 Gy per daily fraction. For brachytherapy, the dose at point A assumes a low-dose rate (LDR) delivery of 40-70 cGy/h. Clinicians using high-dose rate (HDR) brachytherapy would depend on the linear-quadratic model equation to convert nominal HDR dose to point A to a biologically equivalent LDR dose to point A (http://www.americanbrachytherapy.org/guidelines/). Multiple brachytherapy schemes have been used, when combined with EBRT. However, one of the more common HDR approaches is 5 insertions with tandem and colpostats, each delivering 6 Gy nominal dose to point A. This results in a nominal HDR point A dose of 30 Gy in 5 fractions, which is generally accepted to be the equivalent to 40 Gy to point A (tumor surrogate dose) using LDR brachytherapy.

Definitive Radiation Therapy for Intact Cervical Cancer

- In patients with intact cervical cancer (ie, those who do not have surgery), the primary tumor and regional lymphatics at risk are typically treated with definitive EBRT to a dose of approximately 45 Gy (40-50 Gy). The volume of the EBRT would depend on the nodal status as determined surgically or radiographically (as previously described). The primary cervical tumor is then boosted, using brachytherapy, with an additional 30-40 Gy to point A (in LDR equivalent dose), for a total point A dose (as recommended in the guidelines) of 80 Gy (small volume cervical tumors) to 85 Gy or greater (larger volume cervical tumors). Grossly involved unresected nodes may be evaluated for boosting with an additional 10-15 Gy of highly conformal (and reduced volume) EBRT. With higher doses, especially of EBRT, care must be taken to exclude, or to severely limit, the volume of normal tissue included in the high-dose region(s) (see Discussion).

Continued

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

PRINCIPLES OF RADIATION THERAPY FOR CERVICAL CANCER

Post-Hysterectomy Adjuvant Radiation Therapy

- **Following primary hysterectomy, the presence of one or more pathologic risk factors may warrant the use of adjuvant radiotherapy. At a minimum, the following should be covered: upper 3-4 cm of the vaginal cuff, the parametria, and immediately adjacent nodal basins (such as the external and internal iliacs). Where there is documented nodal metastasis, the superior border of the radiation field should be appropriately increased (as previously described). A dose of 45-50 Gy in standard fractionation is generally recommended. Grossly involved unresected nodes may be evaluated for boosting with an additional 10-15 Gy of highly conformal (and reduced volume) EBRT. With higher doses, especially of EBRT, care must be taken to exclude, or to severely limit, the volume of normal tissue included in the high-dose region(s) (see Discussion).**

Intraoperative Radiation Therapy (IORT)

- **IORT is a specialized technique that delivers a single, highly focused dose of radiation to a tumor bed at risk, or isolated unresectable residual, during an open surgical procedure.[3] It is particularly useful in patients with recurrent disease within a previously radiated volume. During IORT, overlying normal tissue (such as bowel or other viscera) can be manually displaced from the region at risk. IORT is typically delivered with electrons using pre-formed applicators of variable sizes (matched to the surgically defined region at risk), which further constrain the area and depth of radiation exposure to avoid surrounding normal structures.**

Continued

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

PRINCIPLES OF RADIATION THERAPY FOR CERVICAL CANCER (REFERENCES)

[1]Pötter R, Haie-Meder C, Van Limbergen E, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol 2006;78(1):67-77. Epub 2006 Jan 5.

[2]Viswanathan AN, Erickson BA. Three-dimensional imaging in gynecologic brachytherapy: a survey of the American Brachytherapy Society. Int J Radiat Oncol Biol Phys 2010;76(1):104-109.

[3]del Carmen MG, McIntyre JF, Goodman A. The role of intraoperative radiation therapy (IORT) in the treatment of locally advanced gynecologic malignancies. Oncologist 2000;5(1):18-25.

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.

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC CERVICAL CANCER†
(Strongly consider clinical trial)

First-line combination therapy
- Cisplatin/paclitaxel[1,2]
- Carboplatin/paclitaxel[3]
- Cisplatin/topotecan[4]
- Cisplatin/gemcitabine (category 2B)[5]

Possible first-line single agent therapy
- Cisplatin (preferred as a single agent)[2]
- Carboplatin[6]
- Paclitaxel[7]

Second-line therapy††
(Agents listed are category 2B unless otherwise noted)
- Bevacizumab
- Docetaxel
- 5-FU (5-fluorouracil)
- Gemcitabine
- Ifosfamide
- Irinotecan
- Mitomycin
- Topotecan
- Pemetrexed (category 3)
- Vinorelbine (category 3)

Continued

†Cisplatin, carboplatin, docetaxel, and paclitaxel may cause drug reactions (See NCCN Ovarian Cancer Guidelines--Management of Drug Reactions [OV-C])
††References for second-line therapy are provided in the Discussion.

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.

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC CERVICAL CANCER (References)

[1] Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: A Gynecologic Oncology Group Study. J Clin Oncol 2009; 27:4649-4655.

[2] Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol. 2004;22:3113-3119.

[3] Moore KN, Herzog TJ, Lewin S, et al. A comparison of cisplatin/paclitaxel and carboplatin/paclitaxel in stage IVB, recurrent or persistent cervical cancer. Gynecol Oncol 2007;105:299-303.

[4] Long HJ, 3rd, Bundy BN, Grendys EC, Jr., et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. J Clin Oncol. 2005;23:4626-4633.

[5] Brewer CA, Blessing JA, Nagourney RA, et al. Cisplatin plus gemcitabine in previously treated squamous cell carcinoma of the cervix. Gynecol Oncol 2006;100:385-388.

[6] Weiss GR, Green S, Hannigan EV, et al. A phase II trial of carboplatin for recurrent or metastatic squamous carcinoma of the uterine cervix: a Southwest Oncology Group study. Gynecol Oncol. 1990;39:332-336.

[7] Kudelka AP, Winn R, Edwards CL, et al. An update of a phase II study of paclitaxel in advanced or recurrent squamous cell cancer of the cervix. Anticancer Drugs 1997;8:657-661.

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.

Table 1 AJCC Tumor-Node-Metastases (TNM) and International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging Systems for Carcinoma of the Uterine Cervix

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	Cervical carcinoma confined to cervix (extension to corpus should be disregarded)
T1a**	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification
T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion more than 3.0mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2[#]
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or nonfunctioning kidney[##]
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
T4	IVA	Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)

*Note: FIGO no longer includes Stage 0 (Tis).

**Note: All macroscopically visible lesions – even with superficial invasion – are T1b/IB.

[#]All macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not >7.00 mm. Depth of invasion should not be > 5.00mm taken from the base of the epithelium of the original tissue—superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with "early (minimal) stromal invasion" (~1 mm). The involvement of vascular/lymphatic spaces should not change the stage allotment.

[##]On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

Continued...

Staging-Cervical Cancer

Table 1-Continued AJCC Tumor-Node-Metastases (TNM) and International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging Systems for Carcinoma of the Uterine Cervix

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

TNM Categories	FIGO Stages	
M0		No distant metastasis
M1	IVB	Distant metastasis (including peritoneal spread, involvement of supraclavicular, mediastinal, or paraaortic lymph nodes, lung, liver, or bone)

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.
and Reprinted from: Pecorelli S. 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.

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Overview

An estimated 12,200 new cases of cervical cancer will be diagnosed in the United States in the year 2010; 4200 deaths will result from the disease.[1] Cervical cancer rates are decreasing among women in the United States, although incidence remains high among Hispanic/Latino, Black, and Asian women.[2-5] However, cervical cancer is a major world health problem for women. The global yearly incidence of cervical cancer for 2002 was 493,200; the annual death rate was 273,500. It is the third most common cancer in women worldwide;[6, 7] 78% of cases occur in developing countries, where cervical cancer is the second most frequent cause of cancer death in women.

Persistent human papillomavirus (HPV) infection is regarded as the most important factor contributing to the development of cervical cancer. There appears to be a relationship between the incidence of cervical cancer and the prevalence of HPV in the population. The prevalence of chronic HPV in countries with a high incidence of cervical cancer is about 10% to 20%, whereas the prevalence in low-incidence countries is 5% to 10%.[6] Immunization against HPV prevents infection with certain types of HPV and, thus, is expected to prevent specific HPV cancer in women (see NCCN Cervical Cancer Screening Guidelines).[8-12] Other epidemiologic risk factors associated with cervical cancer are a history of smoking, parity, contraceptive use, early age of onset of coitus, larger number of sexual partners, history of sexually transmitted disease, and chronic immunosuppression.[13]

Squamous cell carcinomas account for about 80% of all cervical cancers and adenocarcinoma for about 20%. In developed countries, the substantial decline in incidence and mortality of squamous cell carcinoma of the cervix is thought to be a result of effective screening, although there are racial, ethnic, and geographic disparities.[2, 3, 14, 15] However, adenocarcinoma of the cervix has increased over the last 3 decades, probably because cervical cytologic screening methods are less effective for adenocarcinoma.[16-19] Screening methods using HPV testing may increase detection of adenocarcinoma. Vaccination with HPV vaccines may also decrease the incidence of both squamous cell carcinoma and adenocarcinoma.[18, 20]

By definition, the NCCN practice guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. “Many exceptions to the rule” were discussed among the members of the cervical cancer panel during the process of developing these guidelines.

Diagnosis and Workup

These NCCN guidelines discuss squamous cell carcinoma, adenosquamous carcinoma, and adenocarcinoma of the cervix. Neuroendocrine carcinoma, small cell tumors, glassy-cell carcinomas, sarcomas, and other histologic types are not within the scope of these guidelines.

Currently, the International Federation of Gynecology and Obstetrics (FIGO) evaluation procedures for staging are limited to colposcopy, biopsy, conization of the cervix, cystoscopy, and proctosigmoidoscopy. More complex radiologic and surgical staging procedures are not addressed in the FIGO classification. In the United States, however, computed tomography (CT), magnetic resonance imaging (MRI), combined positron emission tomography (PET)-CT, and surgical staging are often used to guide treatment options and design.[21-23]

The earliest stages of cervical carcinoma may be asymptomatic or associated with a watery vaginal discharge and postcoital bleeding or intermittent spotting. These early symptoms frequently are unrecognized by the patient. Because of the accessibility of the uterine cervix, cervical cytology or Papanicolaou (Pap) smears and cervical biopsies can usually result in an accurate diagnosis (see NCCN Cervical Cancer Screening Guidelines). Cone biopsy (i.e., conization) is recommended if the cervical biopsy is inadequate to define invasiveness or if accurate assessment of microinvasive disease is required. However, cervical cytologic screening methods are less useful for diagnosing adenocarcinoma, because adenocarcinoma in situ affects areas of the cervix that are harder to sample (i.e., endocervical canal).[5, 19]

Workup for these patients with suspicious symptoms includes history and physical examination, complete blood count (including platelets), and liver and renal function tests. Radiologic imaging includes chest x-ray, CT or combined PET-CT, and MRI as indicated (e.g., to rule out disease high in the endocervix); however, imaging is optional for patients with stage IB1 or smaller tumors (see CERV-1). Cystoscopy and proctoscopy should be reserved for patients in whom there is clinical concern for bladder or rectal extension.

Panel members discussed whether laparoscopic and robotic approaches should be included as part of these NCCN guidelines in both staging and treatment. These techniques are being used more frequently, but long-term outcome data are not available yet. Laparoscopic staging, lymphadenectomies, and radical hysterectomies can be performed satisfactorily and are used routinely in selected patients in several member institutions.[24-26] Data from studies overseas suggest that recurrence rates are low for laparoscopic radical hysterectomy after 3-6 years of follow-up.[27, 28] Robotic radical hysterectomy (which is another minimally invasive surgical technique) is currently being done for patients with early cervical cancer. Potential advantages associated with laparoscopic and robotic approaches include decreased hospital stay and more rapid patient recovery.[29-31]

Staging

Because of the variability of the availability and worldwide use of noninvasive radiographic imaging, the FIGO system limits the imaging to chest radiography, intravenous pyelography (IVP), and barium enema. The staging of carcinoma of the cervix remains largely a clinical evaluation. Although surgical staging is more accurate than clinical staging, surgical staging often cannot be used in low resource countries.[22, 32, 33] The guidelines panel currently uses the 2009 FIGO definitions and staging system (see Table 1).[32, 34] This staging system from FIGO has been approved by the American Joint Committee on

Cancer (AJCC) .[35] With the new staging, stage IIA is now subdivided into stage IIA1 (tumor size 4 cm or less) and stage IIA2 (tumor size more than 4 cm), which is the only change from the previous 1994 FIGO staging system.

It is important to note that lymphatic vascular space involvement (LVSI) does not alter the FIGO classification.[32] FIGO did not include vascular space involvement, because pathologists do not always agree on whether LVSI is present in tissue samples. Some panel members believe that the presence of frank LVSI should exclude the lesion from the treatment schema for stage IA1 and that these patients should be treated using stage 1B1 guidelines.

The use of MRI, CT, or combined PET-CT scans may aid in treatment planning but is not accepted for formalized staging purposes.[22, 33, 36, 37] In addition, FIGO has always maintained that staging is intended for comparison purposes only and not as a guide for therapy. As a result, the panel uses the FIGO definitions as the stratification system for these guidelines, although the findings on imaging studies (i.e., CT and MRI) are used to guide treatment options and design. MRI is useful to rule out disease high in the endocervix.

Primary Treatment

The primary treatment of early stage cervical cancer is either surgery or radiation therapy (RT). Surgery is typically reserved for lower-stage disease and smaller lesions, such as stage IA, IB1, and selected IIA1. The NCCN panel agrees that concurrent chemoradiation is the primary treatment of choice for stages IB2-IVA disease based on the results of 5 randomized clinical trials (see Table 2). Chemoradiation can also be used for patients who are not candidates for hysterectomy. Although there are few studies assessing treatment specifically for adenocarcinoma, a recent analysis suggests that they can be effectively treated in a similar manner to squamous cell carcinomas.[38,39]

Clinical Trials and Basis for Treatment Selection

A randomized Italian study compared RT alone versus radical hysterectomy and lymph node dissection.[40] This study used adjuvant RT after surgery for women with surgical stage pT2b (which corresponds to FIGO stage IIB) or more extensive disease, less than 3 mm of uninvolved cervical stroma, and cut-through or positive nodes. Identical outcomes were noted for patients treated with radiation versus surgery, with (or without) postoperative radiation, but higher complication rates were noted for the combined modality approach. This study has been criticized by surgeons for its broad use of postoperative RT in the surgery arm and the high complication rate.

Concurrent chemoradiation, using cisplatin-based chemotherapy (either cisplatin alone or cisplatin/5-fluorouracil [5-FU]), is the treatment of choice for stages IB2, II, III, and IVA disease based on the results of 5 randomized clinical trials (see Table 2).[41-46] These 5 trials have shown that the use of concurrent chemoradiation results in a 30% to 50% decrease in the risk of death compared to RT alone. Although the optimal concurrent chemotherapy regimen to use with RT requires further investigation, these 5 trials clearly established a role for concurrent cisplatin-based chemoradiation. Based on this data, the National Cancer Institute issued an alert stating that strong consideration should be given to using chemoradiation instead of RT alone for invasive cervical cancer (http://www.nih.gov/news/pr/feb99/nci-22.htm). Long-term follow-up of 3 of these trials has confirmed that concurrent cisplatin-based chemoradiation improves progression-free and overall survival when compared with RT with or without hydroxyurea.[47-49] A recent meta-analysis reported that chemoradiotherapy leads to a 6% improvement

in 5-year survival (hazard ratio [HR] = 0.81, *P*<.001).[50] A large population-based registry analysis in Canada (n=4069) confirmed that chemoradiotherapy improved outcomes when compared with radiotherapy alone.[51]

Although chemoradiation is tolerated, acute and long-term side effects have been reported.[50, 52, 53] Some oncologists feel that concurrent single-agent cisplatin chemoradiation is preferred to cisplatin plus 5-FU chemoradiation, because the latter may be more toxic.[54] Concurrent carboplatin or non-platinum chemoradiation regimens are options for patients who may not tolerate cisplatin-containing chemoradiation.[50,55-59] Note that when concurrent chemoradiation is used, the chemotherapy is typically given when the external-beam pelvic radiation is administered.[54] The NCCN panel believes that using "systemic consolidation" (i.e., adding chemotherapy after chemoradiation) should only be used in clinical trials (e.g., RTOG 0724).[50, 60, 61]

Early Stage Disease

After careful clinical evaluation and staging, the primary treatment of early stage cervical cancer is either surgery or RT. The treatment schema is stratified using the FIGO staging system (see Table 1).

Stage IA1 Disease

Extrafascial (i.e., simple) hysterectomy is commonly recommended for patients with clinical stage IA1 disease; another option is modified radical hysterectomy with pelvic lymph node dissection if lymphovascular space invasion is present (category 2B for node dissection only). However, if the patient is medically inoperable or if fertility is desired, patients with negative margins from cone biopsy could undergo observation.[62, 63] For patients who desire fertility preservation, trachelectomy and pelvic lymph node dissection can be considered with (or without) para-aortic lymph node sampling for stage IA cervical cancer (see CERV-2).[64-67]

Stage IA2 Disease

Stage IA2 tumors can be treated with radical hysterectomy or radical trachelectomy and pelvic lymph node dissection with (or without) para-aortic lymph node sampling. Para-aortic node dissection is indicated for patients with known or suspected pelvic nodal disease.

Brachytherapy with (or without) pelvic radiation (total point A dose: 75-80 Gy) is another treatment option for stage IA2 disease. These doses are recommended for most patients based on summation of conventional external-beam fractionation and low-dose-rate (40-70 cGy/h) brachytherapy equivalents. Treatment should be modified based on normal tissue tolerance or on biologic equivalence calculations when using high dose rate brachytherapy (see also "Radiation Therapy" section on MS-10).

Stage IB and IIA Disease

Depending on their stage and disease bulk, patients with stage IB or IIA tumors can be treated with surgery, RT, or concurrent chemoradiation. A combined PET-CT scan can be done to rule out extrapelvic disease prior to deciding how to treat these patients. The surgical option includes radical hysterectomy plus bilateral pelvic lymph node dissection with or without para-aortic lymph node sampling.[40] Para-aortic node dissection is indicated for patients with larger tumors and suspected or known pelvic nodal disease. Some panel members feel that a pelvic lymph node dissection should be done first and if negative, then the radical hysterectomy should be done. If the lymph nodes are positive, then the hysterectomy should be abandoned; these patients should receive chemoradiation.

For patients who desire fertility preservation, radical trachelectomy and pelvic lymph node dissection with (or without) para-aortic lymph node sampling can be considered for stage IB1 tumors 2 cm or less (see CERV-2).[64-68] In one study, oncologic outcomes were similar after 4 years when comparing radical trachelectomy with radical hysterectomy for patients with stage 1B1 cervical carcinoma.[68] A study found that among women attempting to conceive after radical trachelectomy for early stage cervical cancer, the 5-year cumulative pregnancy rate was 52.8%; the cancer recurrence rate was low, but the miscarriage rate is higher.[69] For young (< 45 years) premenopausal women with early stage squamous cell carcinoma who opt for ovarian preservation (i.e., hysterectomy only), the rate of ovarian metastases is low.[70, 71]

Recent data have suggested that sentinel lymph node biopsy may be useful for decreasing the need for pelvic lymphadenectomy in patients with early stage cervical cancer, but panel members believe the technique is not yet sufficiently validated.[72-74] However, this is an interesting area for further research.[75-78]

For patients with stage IB or IIA tumors (including those who are not candidates for hysterectomy), another option is combined pelvic radiotherapy and brachytherapy with or without concurrent cisplatin-containing chemotherapy (see CERV-2). Although concurrent chemoradiation has been proven effective in the definitive treatment of more advanced stage disease, this approach has not been specifically studied in patients with stage IB1 or IIA1 disease. Careful consideration of the risk/benefit ratio should be undertaken in these patients with smaller tumors.

For patients with clinical stage IB2 or IIA2 tumors who are treated with definitive radiation, concurrent cisplatin-containing chemotherapy has been shown to significantly improve patient survival.[41, 42] For stage IB2 or IIA2 tumors, the panel disagreed (category 3) about recommending adjuvant hysterectomy for patients undergoing primary chemoradiation.[41]

Advanced Disease

This category has traditionally included patients with stage IIB-IVA disease (i.e., locally advanced disease). However, many oncologists now include patients with IB2 and IIA2 disease in the advanced disease category. For patients with more advanced tumors who are undergoing primary chemoradiation, the volume of RT is critical and is guided by assessment of nodal involvement in the pelvic and para-aortic nodes. Radiologic imaging studies (including PET-CT) are recommended for stage IB2 or greater disease. MRI is useful to rule out disease high in the endocervix. However, needle biopsy can be considered for questionable imaging findings. Surgical staging (i.e., extraperitoneal or laparoscopic lymph node dissection) is also an option (category 2B) for these patients. Surgical staging may also detect microscopic nodal disease that is not discernable with radiologic imaging.[79]

For patients without nodal disease or with disease limited to the pelvis only by surgical staging, treatment consists of pelvic RT with concurrent cisplatin-based chemotherapy and brachytherapy (category 1).[42, 44-46, 54] However, for patients with positive para-aortic and pelvic lymph nodes by imaging, extraperitoneal lymph node dissection should be considered followed by extended-field RT, concurrent cisplatin-containing chemotherapy, and brachytherapy (see CERV-6). Patients with positive para-aortic lymph nodes who are positive for distant metastases are treated with systemic chemotherapy (see CERV-B) and individualized RT.

Metastatic Disease

For patients who present with distant metastatic disease (i.e., stage IVB), primary treatment is often cisplatin-based chemotherapy (see "Systemic Therapy for Metastatic Disease" [MS-8]). In these situations, individualized RT may be considered for control of pelvic disease and all other symptoms.

Adjuvant Treatment

Adjuvant treatment is indicated after radical hysterectomy depending on surgical findings and disease stage. Observation is appropriate for patients with stage IA2, IB1, or IIA1 disease who have negative nodes and no risk factors after radical hysterectomy. However, adjuvant treatment is indicated after radical hysterectomy if pathologic risk factors are discovered. For patients with stage IA2, IB1, or IIA1 disease who have *negative* lymph nodes after surgery but have large primary tumor size, deep stromal invasion, and/or LVSI, pelvic radiation is recommended (category 1) with (or without) concurrent cisplatin-based chemotherapy (category 2B for chemotherapy).[80-83]

Adjuvant pelvic RT alone versus no further therapy was tested in a randomized trial (Gynecologic Oncology Group [GOG] 92) of selected patients with node-negative stage IB carcinoma of the cervix after hysterectomy and pelvic lymphadenectomy.[83] Patients were eligible for this trial after radical hysterectomy and pelvic lymphadenectomy if they had at least 2 of the following risk factors: (1) greater than one-third stromal invasion; (2) capillary lymphatic space involvement; or (3) cervical tumor diameters more than 4 cm. Patients with positive lymph nodes or involved surgical margins were excluded. At 2 years, the recurrence-free rates were 88% for the RT group versus 79% for the no further treatment group. After long-term follow-up (12 years), an updated analysis confirmed that pelvic RT increased progression-free survival; there was also a clear trend towards improved overall survival (*P*=.07).[84]

Patients with *positive* pelvic nodes, positive surgical margin, and/or positive parametrium should be treated with postoperative pelvic radiation with concurrent cisplatin-containing chemotherapy (category 1)[43] with (or without) vaginal brachytherapy (see CERV-3). Vaginal brachytherapy may be a useful boost for those with positive vaginal mucosal margins. The addition of concurrent chemoradiation significantly improves overall survival for high-risk patients with early stage disease (those with positive lymph nodes, parametrial extension, and/or positive margins) who undergo radical hysterectomy and pelvic lymphadenectomy.[43] The Intergroup Trial 0107 showed a statistically significant benefit of adjuvant pelvic radiation with concurrent cisplatin and 5-FU in the treatment of patients with stage IA2, IB, or IIA disease who had positive lymph nodes, positive margins, and/or microscopic parametrial involvement found at surgery.[43]

If para-aortic lymph nodes are found positive during surgical staging, patients must undergo further screening with chest CT or combined PET-CT scan. In women who are positive for distant metastases, biopsy of suspicious areas should be considered as indicated (see CERV-3). For patients without distant metastases, recommended treatment is extended-field RT (including pelvis and para-aortic lymph nodes), concurrent cisplatin-based chemotherapy with (or without) brachytherapy. For patients with distant metastases, recommended treatment is systemic chemotherapy (see CERV-B) and individualized radiotherapy.

Surveillance

Because no definitive study or uniform agreement exists on the best method for post-treatment surveillance for cervical cancer, the panel

combined the practice patterns of member institutions and issued consensus recommendations. Patient follow-up includes interval history and physical examination, with cervical/vaginal cytology every 3-6 months for 2 years, every 6 months for another 3-5 years, and then annually (see CERV-8). Some clinicians have suggested that rigorous cytology follow-up is not warranted because of studies stating that Pap smears did not detect recurrences in patients with stage I-II cervical cancer who were asymptomatic after treatment.[85, 86] It is important to emphasize good clinical evaluation and a high index of suspicion, because the detection rate of recurrent cervical cancer is low using cervical and vaginal cytology alone.[87] Patient education regarding symptoms suggestive of recurrence is appropriate.

In patients at high risk for local-regional (central or para-aortic) failure, a combined PET-CT scan may be useful for detecting asymptomatic disease that is potentially curable.[88-90] Annual chest radiographs are optional.[87, 91] Many other tests remain optional based on clinical indications, such as semiannual complete blood counts, blood urea nitrogen, and serum creatinine determinations (see CERV-8). Patients with persistent or recurrent disease need to be evaluated using additional imaging studies as clinically indicated and surgical exploration in selected cases followed by therapy for relapse (see next section).[92]

Vaginal dilators are recommended after pelvic RT, because patients who receive RT are prone to vaginal stenosis, which can impair sexual function. Women can use vaginal dilators to prevent or treat vaginal stenosis. Dilator use can start 2-4 weeks after RT is completed and can be done indefinitely (http://www.ukons.org/storage/dilators_guidelines.pdf).

Cervical cancer survivors are at risk for second cancers.[93] Data suggest that patients who receive radiation therapy for pelvic cancers are at risk for radiation-induced second cancers, especially at radiated sites near the cervix (e.g., colon, rectum/anus, urinary bladder); therefore, careful surveillance is appropriate for these patients.[94, 95]

Therapy for Relapse

Local/Regional Therapy

Patients with a localized recurrence of cervical cancer after initial treatment should be evaluated to determine whether radiotherapy or surgery can be utilized for relapse. Long-term disease-free survival rates of approximately 40% have been reported in some situations.[96]

For patients who experience local/regional recurrences who have not previously had RT or who experience recurrences outside of the previously treated RT field, therapy for relapse includes tumor-directed RT and platinum-based chemotherapy with (or without) brachytherapy; surgical resection can be considered if feasible (see CERV-9). Typically the chemoradiation for recurrence uses cisplatin as a single agent or cisplatin plus 5-FU.[97, 98]

Patients with central pelvic recurrent disease after RT should be evaluated for pelvic exenteration, with (or without) intraoperative RT (IORT).[99-105] Surgical mortality is generally 5% or lower, with survival rates approaching 50%.[101] Concomitant measures with such radical procedures include adequate rehabilitation programs dealing with the psychosocial and psychosexual consequences of the operation as well as reconstructive procedures.[100, 106-108] Although exenteration is the common surgical approach in post-radiation patients, in carefully selected patients with small central lesions (less than 2 cm), options may include radical hysterectomy or brachytherapy.

For patients with noncentral recurrent disease, options include resection with IORT for close or positive margins, tumor-directed RT with (or without) chemotherapy, chemotherapy, best supportive care (see NCCN Palliative Care Guidelines), or participation in a clinical trial. Patients who recur after second-line definitive therapy, either surgery or RT, have a poor prognosis. They can be treated with chemotherapy, best supportive care, or be enrolled in a clinical trial.

Systemic Therapy for Metastatic Disease

Patients who develop distant metastases, either at initial presentation or at relapse, are rarely curable. For highly selected patients with isolated distant metastases, occasional long-term survival has been reported with 1) surgical resection with (or without) IORT; 2) RT with (or without) concurrent chemotherapy; or 3) chemotherapy (see CERV-10). For most of the other patients with distant metastases, appropriate treatment is either chemotherapy (see CERV-B) or best supportive care.

The palliation of pelvic recurrences in heavily irradiated sites that are not amenable to local pain control techniques or to surgical resection is an unresolved clinical issue. Such sites are generally not responsive to chemotherapy. It is clinically challenging to adequately palliate the complications of pain and fistulae from such recurrences (http://emedicine.medscape.com/article/270646-overview). However, short-courses of RT may provide symptomatic relief to patients with bone metastases, painful para-aortic nodes, or supraclavicular adenopathy.[109, 110]

Chemotherapy has a limited role in prolonging survival or in improving quality of life and is recommended for patients with extrapelvic metastases or recurrent disease who are not candidates for RT or exenterative surgery. Patients who respond to chemotherapy may achieve pain relief of a transient nature. If cisplatin was previously used as a radiosensitizer, combination platinum-based regimens are preferred over single agents in the metastatic disease setting based on several randomized phase III trials (see next paragraph).[111, 112]

First-Line Combination Chemotherapy

Cisplatin has been considered the most effective agent for metastatic cervical cancer.[113] However, most patients who develop metastatic disease have received concurrent cisplatin/RT as primary treatment and may no longer be sensitive to single-agent platinum therapy.[111, 112] Cisplatin-based combination chemotherapy regimens, such as cisplatin/paclitaxel and cisplatin/topotecan, have been extensively investigated in clinical studies.[111, 112, 114-116] A randomized phase III study (GOG 169) in 264 eligible patients comparing paclitaxel and cisplatin versus cisplatin alone showed that the 2-drug combination had a higher response rate (36% versus 19%) and improved progression-free survival (4.8 versus 2.8 months; P>.001), although no improvement was seen in median survival.[111] For patients who responded to cisplatin/paclitaxel, there was a significant improvement in quality of life. Although carboplatin/paclitaxel has not been studied in a prospective randomized setting, many physicians used carboplatin/paclitaxel because of ease of administration and tolerability.

Another randomized phase III GOG study (GOG 179) investigated the combination of cisplatin and topotecan versus cisplatin alone in recurrent or persistent cervical cancer. In this study of 294 eligible patients, the topotecan combination regimen was shown to be superior to single-agent cisplatin with respect to overall response rate (27% versus 13%, P =.004), progression-free survival (4.6 versus 2.9 months; P=.014), and median survival (9.4 versus 6.5 months, P=.017).[112] The FDA has approved cisplatin/topotecan for advanced cervical cancer. However, the cisplatin/paclitaxel or

carboplatin/paclitaxel regimens are less toxic and easier to administer when compared with cisplatin/topotecan.

A recent phase III trial (GOG 204) in 513 patients with advanced metastatic or recurrent cancer assessed 4 cisplatin-doublet regimens (cisplatin/paclitaxel, cisplatin/topotecan, cisplatin/gemcitabine, versus cisplatin/vinorelbine).[116] The trial was closed early, because it was apparent that cisplatin/topotecan, cisplatin/gemcitabine, and cisplatin/vinorelbine were not superior to cisplatin/paclitaxel. No significant differences in overall survival were seen; however, the trends for response rate, progression-free survival, and overall survival (12.9 versus 10 months) suggest that cisplatin/paclitaxel is superior to the other regimens. Cisplatin/paclitaxel was associated with less thrombocytopenia and anemia (but with more nausea, vomiting, infection, and alopecia), than the other regimens. Although cisplatin/gemcitabine was not shown to be a superior regimen in GOG 204, it was tolerable. Based on a phase III randomized trial for locally advanced cervical cancer, cisplatin/gemcitabine is included as an option in the NCCN guidelines.[61] Cisplatin/gemcitabine may be a useful regimen for patients with neuropathy who cannot tolerate other regimens.

Many clinicians prefer using carboplatin rather than cisplatin because of ease of administration, tolerability, and preservation of renal function. A retrospective trial assessing cisplatin/paclitaxel versus carboplatin/paclitaxel confirmed these opinions.[117] Paclitaxel and carboplatin have been assessed for recurrent or persistent cancer of the cervix. In a study using paclitaxel and carboplatin in 25 women, the median overall survival was 21 months.[118] Recently, a study using paclitaxel and carboplatin in 51 women had an median overall survival of 13 months.[119] A phase III trial assessing carboplatin/paclitaxel versus cisplatin/paclitaxel is currently in progress.[120] Non-platinum doublets are also being studied.[121]

Single Agents

Cisplatin is generally regarded as the most active agent and is recommended as possible first-line single agent chemotherapy in recurrent or metastatic cervical cancer; reported response rates are approximately 20% to 30%, with an occasional complete response.[111,113, 122, 123] Overall survival with cisplatin is about 6-9 months. Carboplatin or paclitaxel have been reported to be tolerable and efficacious and are also possible first-line single agent chemotherapy.[124-127] Therefore, palliation with single agents—cisplatin, carboplatin, or paclitaxel—is a reasonable approach in patients with recurrent disease not amenable to surgical or radiotherapeutic approaches. Complete responses were also observed with topotecan or paclitaxel; however, topotecan is associated with more toxicity than carboplatin or paclitaxel. Other agents (these are category 2B unless otherwise indicated) that have shown responses or prolongation of PFS and may be useful as second-line therapy include bevacizumab,[128] docetaxel,[129] 5-FU,[130] gemcitabine,[131] ifosfamide,[132, 133] irinotecan,[134] mitomycin,[135] topotecan,[136, 137] pemetrexed (category 3),[138] and vinorelbine (category 3).[139]

Drug Reactions

Virtually all drugs have the potential to cause adverse reactions, either during or after the infusion.[140] In cervical cancer treatment, drugs that more commonly cause adverse reactions include carboplatin, cisplatin, docetaxel, liposomal doxorubicin, and paclitaxel. Most of these drug reactions are mild infusion reactions (i.e., skin reactions, cardiovascular reactions, respiratory or throat tightness), but more severe allergic reactions (i.e., life-threatening anaphylaxis) can occur.[141, 142] In addition, patients can have severe infusion reactions and mild allergic reactions.

Infusion reactions are more common with paclitaxel.[143] Allergic reactions (i.e., true drug allergies) are more common with platinum agents (i.e., carboplatin, cisplatin).[143, 144]

Management of drug reactions is discussed in the NCCN Ovarian Cancer guidelines (see OV-C).[143] It is important to note that patients who have had severe life-threatening reactions should not receive the implicated agent again. 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.[144-146] Patients must be desensitized with each infusion if they previously had a reaction. Almost all patients can be desensitized.[140] To maximize safety; patients should be desensitized in the intensive care unit.[140]

Other Agents

Vaccine therapies have no established role in the treatment of cervical cancer at the present time, except in the setting of a clinical trial.[147-149] Targeted therapy (using small molecules or monoclonal antibodies) is currently in clinical trials.[60, 128, 150, 151]

Best Supportive Care

Patients with refractory systemic cancer warrant a comprehensive coordinated approach involving hospice care, pain consultants, and emotional and spiritual support, suited to the individual situation (see NCCN Palliative Care Guidelines).

Incidental Cervical Cancer

Invasive cervical carcinoma is sometimes found incidentally after extrafascial hysterectomy. Workup for these patients includes history and physical examination, complete blood count (including platelets), and liver and renal function tests. Radiologic imaging includes chest radiography, CT or combined PET-CT, or MRI as indicated (e.g., to rule out disease high in the endocervix); although imaging is optional for patients with stage IB1 or smaller tumors (see CERV-7).

No definitive data exist regarding the appropriate primary treatment of these patients. The panel believes that a reasonable treatment schema for patients with either stage IAI with LVSI or with stage 1A2 or higher tumors (pathologic findings) should be based on the status of the surgical margins. If margins are positive and imaging is negative for nodal disease, then pelvic RT with concurrent cisplatin-containing chemotherapy with or without individualized brachytherapy should be recommended (see CERV-7). Stage 1A1 patients with no LVSI should undergo surveillance.

If margins or imaging is negative in stage 1A2 or greater tumors, options include (1) pelvic RT with (or without) concurrent cisplatin-containing chemotherapy and brachytherapy; or (2) a complete parametrectomy, upper vaginectomy, and pelvic lymph node dissection with (or without) para-aortic lymph node sampling. Patients with negative lymph nodes should be observed or treated with optional pelvic radiation with (or without) vaginal brachytherapy if they have high-risk factors (i.e., large primary tumor, deep stromal invasion, and/or LVSI (see CERV-7).[83] Concurrent cisplatin-based chemoradiation is recommended for gross residual disease, positive imaging, disease in the lymph nodes and/or parametrium, and/or a positive surgical margin; individualized brachytherapy is clearly indicated for a positive vaginal margin.

Radiation Therapy

Radiotherapy is often used in the management of patients with cervical cancer, either for patients with intact cervical cancer who are not

amenable to surgery (e.g., definitive therapy for those with locally advanced disease or for those who are poor operative candidates), or in patients following radical hysterectomy (i.e., adjuvant RT) who have one or more pathologic risk factors (e.g., positive lymph nodes, parametrial infiltration, positive surgical margins, large tumor size, deep stromal invasion, lymphovascular space invasion).

The NCCN algorithm provides general RT dosage recommendations, which are expanded upon in the Principles of RT section (see CERV-A). These RT dosages should not be interpreted as stand-alone recommendations, because RT techniques and clinical judgment are an essential part of developing an appropriate treatment regimen.

Optimum staging of patients to precisely delineate the primary tumor volume and draining lymph nodes, including abdominopelvic radiologic studies (CT, MRI, or combined PET-CT scans), is recommended in patients with stage IB2, IIA2, or advanced-stage tumors. Contemporary imaging studies must be correlated with careful assessment of clinical findings to define tumor extent, especially with regard to vaginal or parametrial extension.

Radiation Treatment Planning

Technological advances in imaging, computer treatment planning systems, and linear accelerator technology have provided the capability to more precisely deliver radiation dose to the pelvis. However, physical accuracy of dose delivery must be matched to a clear understanding of tumor extent, potential pathways of spread, and historical patterns of local-regional recurrence to avoid geographic misses.

CT-based treatment planning with conformal blocking and dosimetry is considered standard of care for external-beam radiotherapy. Brachytherapy is a critical component of therapy in patients with intact cervical cancer and is typically combined with external-beam radiation in an integrated treatment plan.

For patients with locally advanced cancers, initial radiation treatment of 40-45 Gy to the whole pelvis is often necessary to obtain tumor shrinkage to permit optimal intracavitary placements. With low-dose-rate intracavitary systems, total doses from brachytherapy and external-beam radiation to point A of at least 80 Gy are currently recommended for small tumors, with doses of 85 Gy or higher recommended for larger tumors.

For lesions in the lower one third of the vagina, the inguinal lymph nodes need to be treated. The use of extended-field radiation to treat occult or macroscopic para-aortic lymph node disease needs to be carefully planned to ensure an adequate dose (45 Gy for microscopic disease) without exceeding bowel, spinal cord, or renal tolerances.[152] General recommendations for radiation volumes and doses are discussed in the algorithm (see CERV-A).

Intensity-modulated radiotherapy (IMRT) is becoming more widely available; however, issues regarding target definition, patient and target immobilization, tissue deformation and reproducibility remain to be validated.[153-157] The role of IMRT in cervical cancer continues to be actively evaluated in several prospective multicenter clinical trials.

Several retrospective analyses have suggested an adverse effect of prolonged treatment duration on outcome.[158-162] Extending the overall treatment beyond 6 to 8 weeks can result in approximately a 0.5% to 1% decrease in pelvic control and cause-specific survival for each extra day of overall treatment time. Thus, although no prospective randomized trials have been done, it is generally accepted that the entire RT course (including both external beam and brachytherapy

components) should be completed in a timely fashion (within 8 weeks); delays or splits in the radiation treatment should be avoided whenever possible.

Normal Tissue Considerations

Planning for radiotherapy in cervical cancer must take into account the potential impact on surrounding critical structures, such as rectum, bladder, sigmoid, small bowel, and bone. Acute effects (i.e., diarrhea, bladder irritation, fatigue) occur to some degree in most patients undergoing radiation and are typically magnified by concurrent chemotherapy. However, acute effects are often manageable by medications and supportive care, and they generally resolve soon after completion of radiation.

The risk of more significant late effects (i.e., obstruction, fibrosis/necrosis, or fistula) is related to the volume, total dose, dose per fraction, and specific intrinsic radiosensitivity of the normal tissue irradiated.[152] Careful blocking to minimize normal tissue exposure while not compromising tumor coverage is critical to achieving optimal outcomes. In addition, patient-related conditions (i.e., inflammatory bowel disease, collagen-vascular disease, multiple abdominal/pelvic surgeries, history of pelvic inflammatory disease, diabetes) influence determination of radiation dose and volumes.

For most patients, it is generally accepted that the whole pelvis can tolerate an external-beam radiation dose of 40-50 Gy. Gross disease in the parametria or unresected nodes may undergo tightly contoured external beam boosts to 60-65 Gy. Intracavitary brachytherapy boosts require attention to proper placement of the applicators within the uterus and against the cervix and vaginal apex, as well as appropriate packing to maximally displace the bladder and rectum.

Pregnancy and Cervical Cancer

For pregnant women, cervical cancer is the most frequently diagnosed type of cancer; however, most pregnant women with cervical cancer have stage I disease.[163] Invasive cervical cancer during pregnancy creates a clinical dilemma. Women need to make the difficult decision either to delay treatment until documented fetal maturity or to receive immediate treatment based on their stage of disease. For women diagnosed with cervical cancer during pregnancy who wish to continue their pregnancies, delaying cancer treatment until the fetus has matured has been reported.[163] Women who delay treatment until fetal maturity should have their children delivered by cesarean section. Patients with early stage disease may prefer to have radical hysterectomy and node dissection instead of RT to avoid radiation fibrosis and to preserve their ovaries. Those patients with early stage disease who delay treatment until fetal maturity can undergo cesarean section with radical hysterectomy and pelvic node dissection. For those opting for RT, traditional RT with (or without) chemotherapy protocols (which have been previously described) may need modification.[163] Vaginal radical trachelectomy has been successfully performed in a few pregnant patients with early stage cancer.[164-167]

Summary

Cervical cancer is decreasing in the United States, because screening has been widely used; however, cervical cancer is increasing in developing countries (about 270,000 deaths/year), because screening is not available to many women. Effective treatment for cervical cancer (i.e., surgery, concurrent chemo/RT) can yield cures in 80% of women with early stage disease (stages I and II) and in 60% of women with stage III disease. Hopefully, immunization against HPV (using the new vaccines) will prevent persistent infection with certain types of HPV and, thus, is expected to prevent specific HPV cancer in women.[11, 12, 168]

Table 2:
Estimates of the Relative Risk of Death in Five Clinical Trials of Concurrent Chemotherapy and Radiotherapy.

Study	FIGO Stage	Control Group	Comparison Group	Relative Risk of Death in Comparison Group
Keys et al.*	IB2	Radiotherapy	Radiotherapy plus weekly cisplatin	0.54
Rose, Bundy, Watkins et al.*	IIB-IVA	Radiotherapy plus hydroxyurea	Radiotherapy plus weekly cisplatin	0.61
			Radiotherapy plus cisplatin, fluorouracil, and hydroxyurea	0.58
Morris et al.*	IB2-IVA	Extended-field radiotherapy	Radiotherapy plus cisplatin and fluorouracil	0.52
Whitney et al.	IIB-IVA	Radiotherapy plus hydroxyurea	Radiotherapy plus cisplatin and fluorouracil	0.72
Peters et al.	IB or IIA (selected postoperatively)	Radiotherapy	Radiotherapy plus cisplatin and fluorouracil	0.50

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

*These studies have been updated (see Discussion).

Used with permission, from: Thomas GM. Improved treatment for cervical cancer concurrent chemotherapy and radiotherapy. N Engl J Med 1999;340(15):1198-1200. Copyright© 1999 Massachusetts Medical Society. All rights reserved.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277-300. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20610543.

2. Barnholtz-Sloan J, Patel N, Rollison D, et al. Incidence trends of invasive cervical cancer in the United States by combined race and ethnicity. Cancer Causes Control 2009;20:1129-1138. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19253025.

3. Wang SS, Carreon JD, Gomez SL, Devesa SS. Cervical cancer incidence among 6 asian ethnic groups in the United States, 1996 through 2004. Cancer 2010;116:949-956. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20029972.

4. Howe HL, Wu X, Ries LAG, et al. Annual report to the nation on the status of cancer, 1975-2003, featuring cancer among U.S. Hispanic/Latino populations. Cancer 2006;107:1711-1742. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16958083.

5. Sherman ME, Wang SS, Carreon J, Devesa SS. Mortality trends for cervical squamous and adenocarcinoma in the United States. Relation to incidence and survival. Cancer 2005;103:1258-1264. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15693030.

6. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-7108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15761078.

7. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006;24:2137-2150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16682732.

8. Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 2005;6:271-278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15863374.

9. Ault KA. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet 2007;369:1861-1868. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17544766.

10. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-1927. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17494925.

11. Arbyn M, Dillner J. Review of current knowledge on HPV vaccination: an appendix to the European Guidelines for Quality Assurance in Cervical Cancer Screening. J Clin Virol 2007;38:189-197. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17258503.

12. Rambout L, Hopkins L, Hutton B, Fergusson D. Prophylactic vaccination against human papillomavirus infection and disease in women: a systematic review of randomized controlled trials. CMAJ 2007;177:469-479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17671238.

13. Comparison of risk factors for invasive squamous cell carcinoma and adenocarcinoma of the cervix: collaborative reanalysis of individual data on 8,097 women with squamous cell carcinoma and 1,374 women with adenocarcinoma from 12 epidemiological studies. Int J Cancer 2007;120:885-891. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17131323.

14. Bray F, Loos AH, McCarron P, et al. Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. Cancer Epidemiol Biomarkers Prev 2005;14:677-686. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15767349.

15. Watson M, Saraiya M, Benard V, et al. Burden of cervical cancer in the United States, 1998-2003. Cancer 2008;113:2855-2864. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18980204.

16. Bray F, Carstensen B, Moller H, et al. Incidence trends of adenocarcinoma of the cervix in 13 European countries. Cancer Epidemiol Biomarkers Prev 2005;14:2191-2199. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16172231.

17. Wang SS, Sherman ME, Hildesheim A, et al. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976-2000. Cancer 2004;100:1035-1044. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14983500.

18. Castellsague X, Diaz M, de Sanjose S, et al. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. J Natl Cancer Inst 2006;98:303-315. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16507827.

19. Sasieni P, Castanon A, Cuzick J. Screening and adenocarcinoma of the cervix. Int J Cancer 2009;125:525-529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19449379.

20. Dahlstrom LA, Ylitalo N, Sundstrom K, et al. Prospective study of human papillomavirus and risk of cervical adenocarcinoma. Int J Cancer 2010;127:1923-1930. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20473898.

21. ACOG practice bulletin. Diagnosis and treatment of cervical carcinomas. Number 35, May 2002. American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet 2002;78:79-91. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12197489.

22. Gold MA, Tian C, Whitney CW, et al. Surgical versus radiographic determination of para-aortic lymph node metastases before chemoradiation for locally advanced cervical carcinoma: a Gynecologic Oncology Group Study. Cancer 2008;112:1954-1963. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18338811.

23. Monk BJ, Tian C, Rose PG, Lanciano R. Which clinical/pathologic factors matter in the era of chemoradiation as treatment for locally advanced cervical carcinoma? Analysis of two Gynecologic Oncology Group (GOG) trials. Gynecol Oncol 2007;105:427-433. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17275889.

24. Ramirez PT, Slomovitz BM, Soliman PT, et al. Total laparoscopic radical hysterectomy and lymphadenectomy: the M. D. Anderson Cancer Center experience. Gynecol Oncol 2006;102:252-255. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16472844.

25. Abu-Rustum NR, Gemignani ML, Moore K, et al. Total laparoscopic radical hysterectomy with pelvic lymphadenectomy using the argon-beam coagulator: pilot data and comparison to laparotomy. Gynecol Oncol 2003;91:402-409. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14599873.

26. Chi DS. Laparoscopy in gynecologic malignancies. Oncology (Williston Park) 1999;13:773-782. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10378217.

27. Chen Y, Xu H, Li Y, et al. The outcome of laparoscopic radical hysterectomy and lymphadenectomy for cervical cancer: a prospective analysis of 295 patients. Ann Surg Oncol 2008;15:2847-2855. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18649105.

28. Puntambekar SP, Palep RJ, Puntambekar SS, et al. Laparoscopic total radical hysterectomy by the Pune technique: our experience of 248 cases. J Minim Invasive Gynecol 2007;14:682-689. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17980327.

29. Lowe MP, Chamberlain DH, Kamelle SA, et al. A multi-institutional experience with robotic-assisted radical hysterectomy for early stage cervical cancer. Gynecol Oncol 2009;113:191-194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19249082.

30. Nezhat FR, Datta MS, Liu C, et al. Robotic radical hysterectomy versus total laparoscopic radical hysterectomy with pelvic lymphadenectomy for treatment of early cervical cancer. JSLS 2008;12:227-237. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18765043.

31. Cantrell LA, Mendivil A, Gehrig PA, Boggess JF. Survival outcomes for women undergoing type III robotic radical hysterectomy for cervical cancer: a 3-year experience. Gynecol Oncol 2010;117:260-265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20153886.

32. Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. Int J Gynaecol Obstet 2009;105:107-108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19342051.

33. Moore DH. Surgical staging and cervical cancer: after 30 years, have we reached a conclusion? Cancer 2008;112:1874-1876. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18348308.

34. 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.

35. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual, 7th ed. New York: Springer; 2010.

36. Park JY, Kim EN, Kim DY, et al. Comparison of the validity of magnetic resonance imaging and positron emission tomography/computed tomography in the preoperative evaluation of patients with uterine corpus cancer. Gynecol Oncol 2008;108:486-492. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18201753.

37. Boughanim M, Leboulleux S, Rey A, et al. Histologic results of para-aortic lymphadenectomy in patients treated for stage IB2/II cervical cancer with negative [18F]fluorodeoxyglucose positron emission tomography scans in the para-aortic area. J Clin Oncol 2008;26:2558-2561. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18487573.

38. Baalbergen A, Veenstra Y, Stalpers LL, Ansink AC. Primary surgery versus primary radiation therapy with or without chemotherapy for early adenocarcinoma of the uterine cervix. Cochrane Database Syst Rev 2010:CD006248. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20091590.

39. Park JY, Kim DY, Kim JH, et al. Outcomes after radical hysterectomy in patients with early-stage adenocarcinoma of uterine cervix. Br J Cancer 2010;102:1692-1698. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20531414.

40. Landoni F, Maneo A, Colombo A, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet 1997;350:535-540. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9284774.

41. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 1999;340:1154-1161. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10202166.

42. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 1999;340:1137-1143. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10202164.

43. Peters WA, Liu PY, Barrett RJ, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000;18:1606-1613. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10764420.

44. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and

Southwest Oncology Group study. J Clin Oncol 1999;17:1339-1348. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10334517.

45. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999;340:1144-1153. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10202165.

46. Thomas GM. Improved treatment for cervical cancer--concurrent chemotherapy and radiotherapy. N Engl J Med 1999;340:1198-1200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10202172.

47. Rose PG, Ali S, Watkins E, et al. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:2804-2810. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17502627.

48. Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. J Clin Oncol 2004;22:872-880. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14990643.

49. Stehman FB, Ali S, Keys HM, et al. Radiation therapy with or without weekly cisplatin for bulky stage 1B cervical carcinoma: follow-up of a Gynecologic Oncology Group trial. Am J Obstet Gynecol 2007;197:1-6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17980189.

50. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol 2008;26:5802-5812. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19001332.

51. Pearcey R, Miao Q, Kong W, et al. Impact of adoption of chemoradiotherapy on the outcome of cervical cancer in Ontario: results of a population-based cohort study. J Clin Oncol 2007;25:2383-2388. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17557951.

52. King M, McConkey C, Latief TN, et al. Improved survival after concurrent weekly cisplatin and radiotherapy for cervical carcinoma with assessment of acute and late side-effects. Clin Oncol (R Coll Radiol) 2006;18:38-45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16477918.

53. Tan LT, Zahra M. Long-term survival and late toxicity after chemoradiotherapy for cervical cancer--the Addenbrooke's experience. Clin Oncol (R Coll Radiol) 2008;20:358-364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18395427.

54. Monk BJ, Tewari KS, Koh W-J. Multimodality therapy for locally advanced cervical carcinoma: state of the art and future directions. J Clin Oncol 2007;25:2952-2965. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17617527.

55. Cetina L, Garcia-Arias A, Uribe MdJ, et al. Concurrent chemoradiation with carboplatin for elderly, diabetic and hypertensive patients with locally advanced cervical cancer. Eur J Gynaecol Oncol 2008;29:608-612. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19115688.

56. Dubay RA, Rose PG, O'Malley DM, et al. Evaluation of concurrent and adjuvant carboplatin with radiation therapy for locally advanced cervical cancer. Gynecol Oncol 2004;94:121-124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15262129.

57. Higgins RV, Naumann WR, Hall JB, Haake M. Concurrent carboplatin with pelvic radiation therapy in the primary treatment of cervix cancer. Gynecol Oncol 2003;89:499-503. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12798718.

58. Lorvidhaya V, Chitapanarux I, Sangruchi S, et al. Concurrent mitomycin C, 5-fluorouracil, and radiotherapy in the treatment of locally advanced carcinoma of the cervix: a randomized trial. Int J Radiat

Oncol Biol Phys 2003;55:1226-1232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12654431.

59. Wong LC, Ngan HY, Cheung AN, et al. Chemoradiation and adjuvant chemotherapy in cervical cancer. J Clin Oncol 1999;17:2055-2060. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561258.

60. Poveda A, Gonzalez-Martin A. Multimodality treatment in locoregional gynecological cancer: cervical cancer treatment update. Ann Oncol 2008;19 Suppl 7:vii70-76. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18790983.

61. Duenas-Gonzalez A, Zarba JJ, Alcedo JC, et al. A phase III study comparing concurrent gemcitabine (Gem) plus cisplatin (Cis) and radiation followed by adjuvant Gem plus Cis versus concurrent Cis and radiation in patients with stage IIB to IVA carcinoma of the cervix [abstract]. J Clin Oncol 2009 27(Suppl 18):Abstract CRA5507. Available at: http://meeting.ascopubs.org/cgi/content/abstract/27/18S/CRA5507.

62. Koliopoulos G, Sotiriadis A, Kyrgiou M, et al. Conservative surgical methods for FIGO stage IA2 squamous cervical carcinoma and their role in preserving women's fertility. Gynecol Oncol 2004;93:469-473. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15099964.

63. Wright JD, NathavithArana R, Lewin SN, et al. Fertility-conserving surgery for young women with stage IA1 cervical cancer: safety and access. Obstet Gynecol 2010;115:585-590. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20177290.

64. Bernardini M, Barrett J, Seaward G, Covens A. Pregnancy outcomes in patients after radical trachelectomy. Am J Obstet Gynecol 2003;189:1378-1382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14634572.

65. Boss EA, van Golde RJT, Beerendonk CCM, Massuger LFAG. Pregnancy after radical trachelectomy: a real option? Gynecol Oncol 2005;99:152-156. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16140367.

66. Plante M, Renaud M-C, Hoskins IA, Roy M. Vaginal radical trachelectomy: a valuable fertility-preserving option in the management of early-stage cervical cancer. A series of 50 pregnancies and review of the literature. Gynecol Oncol 2005;98:3-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15936061.

67. Marchiole P, Benchaib M, Buenerd A, et al. Oncological safety of laparoscopic-assisted vaginal radical trachelectomy (LARVT or Dargent's operation): a comparative study with laparoscopic-assisted vaginal radical hysterectomy (LARVH). Gynecol Oncol 2007;106:132-141. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17493666.

68. Diaz JP, Sonoda Y, Leitao MM, et al. Oncologic outcome of fertility-sparing radical trachelectomy versus radical hysterectomy for stage IB1 cervical carcinoma. Gynecol Oncol 2008;111:255-260. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18755500.

69. Shepherd JH, Spencer C, Herod J, Ind TEJ. Radical vaginal trachelectomy as a fertility-sparing procedure in women with early-stage cervical cancer-cumulative pregnancy rate in a series of 123 women. BJOG 2006;113:719-724. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16709216.

70. Landoni F, Zanagnolo V, Lovato-Diaz L, et al. Ovarian metastases in early-stage cervical cancer (IA2-IIA): a multicenter retrospective study of 1965 patients (a Cooperative Task Force study). Int J Gynecol Cancer 2007;17:623-628. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17309669.

71. Shimada M, Kigawa J, Nishimura R, et al. Ovarian metastasis in carcinoma of the uterine cervix. Gynecol Oncol 2006;101:234-237. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16300819.

72. Lecuru F, Bats A, Mathevet P, et al. Impact of sentinel lymph node biopsy on staging of early cervical cancer: Results of a prospective, multicenter study [abstract]. J Clin Oncol 2009;27(Suppl 18):Abstract CRA5506. Available at: http://meeting.ascopubs.org/cgi/content/abstract/27/18S/CRA5506.

73. Altgassen C, Hertel H, Brandstadt A, et al. Multicenter validation study of the sentinel lymph node concept in cervical cancer: AGO Study Group. J Clin Oncol 2008;26:2943-2951. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18565880.

74. Fader AN, Edwards RP, Cost M, et al. Sentinel lymph node biopsy in early-stage cervical cancer: utility of intraoperative versus postoperative assessment. Gynecol Oncol 2008;111:13-17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18684499.

75. Selman TJ, Mann C, Zamora J, et al. Diagnostic accuracy of tests for lymph node status in primary cervical cancer: a systematic review and meta-analysis. CMAJ 2008;178:855-862. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18362381.

76. van de Lande J, Torrenga B, Raijmakers PGHM, et al. Sentinel lymph node detection in early stage uterine cervix carcinoma: a systematic review. Gynecol Oncol 2007;106:604-613. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17628644.

77. Schneider A. The sentinel concept in patients with cervical cancer. J Surg Oncol 2007;96:337-341. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17726665.

78. Pandit-Taskar N, Gemignani ML, Lyall A, et al. Single photon emission computed tomography SPECT-CT improves sentinel node detection and localization in cervical and uterine malignancy. Gynecol Oncol 2010;117:59-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20117827.

79. Goff BA, Muntz HG, Paley PJ, et al. Impact of surgical staging in women with locally advanced cervical cancer. Gynecol Oncol 1999;74:436-442. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10479506.

80. Monk BJ, Wang J, Im S, et al. Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical-pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial. Gynecol Oncol 2005;96:721-728. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15721417.

81. Chernofsky MR, Felix JC, Muderspach LI, et al. Influence of quantity of lymph vascular space invasion on time to recurrence in women with early-stage squamous cancer of the cervix. Gynecol Oncol 2006;100:288-293. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16182347.

82. Marchiole P, Buenerd A, Benchaib M, et al. Clinical significance of lympho vascular space involvement and lymph node micrometastases in early-stage cervical cancer: a retrospective case-control surgico-pathological study. Gynecol Oncol 2005;97:727-732. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15943983.

83. Sedlis A, Bundy BN, Rotman MZ, et al. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. Gynecol Oncol 1999;73:177-183. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10329031.

84. Rotman M, Sedlis A, Piedmonte MR, et al. A phase III randomized trial of postoperative pelvic irradiation in Stage IB cervical carcinoma with poor prognostic features: follow-up of a gynecologic oncology group study. Int J Radiat Oncol Biol Phys 2006;65:169-176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16427212.

85. Bodurka-Bevers D, Morris M, Eifel PJ, et al. Posttherapy surveillance of women with cervical cancer: an outcomes analysis. Gynecol Oncol 2000;78:187-193. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10926801.

86. Morice P, Deyrolle C, Rey A, et al. Value of routine follow-up procedures for patients with stage I/II cervical cancer treated with combined surgery-radiation therapy. Ann Oncol 2004;15:218-223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14760112.

87. Elit L, Fyles AW, Devries MC, et al. Follow-up for women after treatment for cervical cancer: a systematic review. Gynecol Oncol 2009;114:528-535. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19560188.

88. Brooks RA, Rader JS, Dehdashti F, et al. Surveillance FDG-PET detection of asymptomatic recurrences in patients with cervical cancer. Gynecol Oncol 2009;112:104-109. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18929403.

89. Schwarz JK, Siegel BA, Dehdashti F, Grigsby PW. Association of posttherapy positron emission tomography with tumor response and survival in cervical carcinoma. JAMA 2007;298:2289-2295. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18029833.

90. Sironi S, Picchio M, Landoni C, et al. Post-therapy surveillance of patients with uterine cancers: value of integrated FDG PET/CT in the detection of recurrence. Eur J Nucl Med Mol Imaging 2007;34:472-479. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17106701.

91. Zanagnolo V, Ming L, Gadducci A, et al. Surveillance procedures for patients with cervical carcinoma: a review of the literature. Int J Gynecol Cancer 2009;19:194-201. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19395993.

92. Chung HH, Jo H, Kang WJ, et al. Clinical impact of integrated PET/CT on the management of suspected cervical cancer recurrence. Gynecol Oncol 2007;104:529-534. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17049971.

93. Chaturvedi AK, Kleinerman RA, Hildesheim A, et al. Second cancers after squamous cell carcinoma and adenocarcinoma of the cervix. J Clin Oncol 2009;27:967-973. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19114696.

94. Chaturvedi AK, Engels EA, Gilbert ES, et al. Second cancers among 104,760 survivors of cervical cancer: evaluation of long-term risk. J Natl Cancer Inst 2007;99:1634-1643. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17971527.

95. Kumar S, Shah JP, Bryant CS, et al. Radiation-associated endometrial cancer. Obstet Gynecol 2009;113:319-325. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19155901.

96. Thomas GM, Dembo AJ, Myhr T, et al. Long-term results of concurrent radiation and chemotherapy for carcinoma of the cervix recurrent after surgery. Int J Gynecol Cancer 1993;3:193-198. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11578344.

97. Kim JS, Kim SY, Kim KH, Cho MJ. Hyperfractionated radiotherapy with concurrent chemotherapy for para-aortic lymph node recurrence in carcinoma of the cervix. Int J Radiat Oncol Biol Phys 2003;55:1247-1253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12654434.

98. Chung YL, Jian JJ, Cheng SH, et al. Extended-field radiotherapy and high-dose-rate brachytherapy with concurrent and adjuvant cisplatin-based chemotherapy for locally advanced cervical cancer: a phase I/II study. Gynecol Oncol 2005;97:126-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15790448.

99. Berek JS, Howe C, Lagasse LD, Hacker NF. Pelvic exenteration for recurrent gynecologic malignancy: survival and morbidity analysis of the 45-year experience at UCLA. Gynecol Oncol 2005;99:153-159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16054678.

100. Goldberg GL, Sukumvanich P, Einstein MH, et al. Total pelvic exenteration: the Albert Einstein College of Medicine/Montefiore Medical Center Experience (1987 to 2003). Gynecol Oncol 2006;101:261-268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16426668.

101. Morley GW, Hopkins MP, Lindenauer SM, Roberts JA. Pelvic exenteration, University of Michigan: 100 patients at 5 years. Obstet Gynecol 1989;74:934-943. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2586960.

102. 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.

103. 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.

104. Rutledge FN, Smith JP, Wharton JT, O'Quinn AG. Pelvic exenteration: analysis of 296 patients. Am J Obstet Gynecol 1977;129:881-892. Available at: http://www.ncbi.nlm.nih.gov/pubmed/930972.

105. Symmonds RE, Pratt JH, Webb MJ. Exenterative operations: experience with 198 patients. Am J Obstet Gynecol 1975;121:907-918. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1115180.

106. Soper JT, Secord AA, Havrilesky LJ, et al. Comparison of gracilis and rectus abdominis myocutaneous flap neovaginal reconstruction performed during radical pelvic surgery: flap-specific morbidity. Int J Gynecol Cancer 2007;17:298-303. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17291272.

107. Mirhashemi R, Averette HE, Lambrou N, et al. Vaginal reconstruction at the time of pelvic exenteration: a surgical and psychosexual analysis of techniques. Gynecol Oncol 2002;87:39-45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12468340.

108. Turns D. Psychosocial issues: pelvic exenterative surgery. J Surg Oncol 2001;76:224-236. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11276026.

109. Spanos WJ, Jr., Perez CA, Marcus S, et al. Effect of rest interval on tumor and normal tissue response--a report of phase III study of accelerated split course palliative radiation for advanced pelvic malignancies (RTOG-8502). Int J Radiat Oncol Biol Phys 1993;25:399-403. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7679668.

110. Lutz ST, Chow EL, Hartsell WF, Konski AA. A review of hypofractionated palliative radiotherapy. Cancer 2007;109:1462-1470. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17330854.

111. Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol 2004;22:3113-3119. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15284262.

112. Long HJ, 3rd, Bundy BN, Grendys EC, Jr., et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. J Clin Oncol 2005;23:4626-4633. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15911865.

113. Thigpen T, Shingleton H, Homesley H, et al. Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Cancer 1981;48:899-903. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7196794.

114. Moore DH. Chemotherapy for advanced, recurrent, and metastatic cervical cancer. J Natl Compr Canc Netw 2008;6:53-57. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18267059.

115. Tao X, Hu W, Ramirez PT, Kavanagh JJ. Chemotherapy for recurrent and metastatic cervical cancer. Gynecol Oncol 2008;110:67-71. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18533239.

116. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 2009;27:4649-4655. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19720909.

117. Moore KN, Herzog TJ, Lewin S, et al. A comparison of cisplatin/paclitaxel and carboplatin/paclitaxel in stage IVB, recurrent or persistent cervical cancer. Gynecol Oncol 2007;105:299-303. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17303230.

118. Tinker AV, Bhagat K, Swenerton KD, Hoskins PJ. Carboplatin and paclitaxel for advanced and recurrent cervical carcinoma: the British Columbia Cancer Agency experience. Gynecol Oncol 2005;98:54-58. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15904950.

119. Pectasides D, Fountzilas G, Papaxoinis G, et al. Carboplatin and paclitaxel in metastatic or recurrent cervical cancer. Int J Gynecol Cancer 2009;19:777-781. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19509587.

120. Saito I, Kitagawa R, Fukuda H, et al. A phase III trial of paclitaxel plus carboplatin versus paclitaxel plus cisplatin in stage IVB, persistent or recurrent cervical cancer: Gynecologic Cancer Study Group/Japan Clinical Oncology Group Study (JCOG0505). Jpn J Clin Oncol 2010;40:90-93. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19825815.

121. Tewari KS, Monk BJ. Recent achievements and future developments in advanced and recurrent cervical cancer: trials of the Gynecologic Oncology Group. Semin Oncol 2009;36:170-180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19332251.

122. Thigpen JT, Blessing JA, DiSaia PJ, et al. A randomized comparison of a rapid versus prolonged (24 hr) infusion of cisplatin in therapy of squamous cell carcinoma of the uterine cervix: a Gynecologic Oncology Group study. Gynecol Oncol 1989;32:198-202. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2910782.

123. Pectasides D, Kamposioras K, Papaxoinis G, Pectasides E. Chemotherapy for recurrent cervical cancer. Cancer Treat Rev 2008;34:603-613. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18657909.

124. McGuire WP, Arseneau J, Blessing JA, et al. A randomized comparative trial of carboplatin and iproplatin in advanced squamous carcinoma of the uterine cervix: a Gynecologic Oncology Group study. J Clin Oncol 1989;7:1462-1468. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2674333.

125. Weiss GR, Green S, Hannigan EV, et al. A phase II trial of carboplatin for recurrent or metastatic squamous carcinoma of the uterine cervix: a Southwest Oncology Group study. Gynecol Oncol 1990;39:332-336. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2258080.

126. Kudelka AP, Winn R, Edwards CL, et al. An update of a phase II study of paclitaxel in advanced or recurrent squamous cell cancer of the cervix. Anticancer Drugs 1997;8:657-661. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9311440.

127. McGuire WP, Blessing JA, Moore D, et al. Paclitaxel has moderate activity in squamous cervix cancer. A Gynecologic Oncology Group study. J Clin Oncol 1996;14:792-795. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8622025.

128. Monk BJ, Sill MW, Burger RA, et al. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol 2009;27:1069-1074. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19139430.

129. Garcia AA, Blessing JA, Vaccarello L, Roman LD. Phase II clinical trial of docetaxel in refractory squamous cell carcinoma of the cervix: a Gynecologic Oncology Group Study. Am J Clin Oncol 2007;30:428-431. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17762444.

130. Look KY, Blessing JA, Gallup DG, Lentz SS. A phase II trial of 5-fluorouracil and high-dose leucovorin in patients with recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Am J Clin Oncol 1996;19:439-441. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8823469.

131. Schilder RJ, Blessing J, Cohn DE. Evaluation of gemcitabine in previously treated patients with non-squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol 2005;96:103-107. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15589587.

132. Coleman RE, Harper PG, Gallagher C, et al. A phase II study of ifosfamide in advanced and relapsed carcinoma of the cervix. Cancer Chemother Pharmacol 1986;18:280-283. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3802384.

133. Sutton GP, Blessing JA, McGuire WP, et al. Phase II trial of ifosfamide and mesna in patients with advanced or recurrent squamous carcinoma of the cervix who had never received chemotherapy: a Gynecologic Oncology Group study. Am J Obstet Gynecol 1993;168:805-807. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8456884.

134. Verschraegen CF, Levy T, Kudelka AP, et al. Phase II study of irinotecan in prior chemotherapy-treated squamous cell carcinoma of the cervix. J Clin Oncol 1997;15:625-631. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9053486.

135. Wagenaar HC, Pecorelli S, Mangioni C, et al. Phase II study of mitomycin-C and cisplatin in disseminated, squamous cell carcinoma of the uterine cervix. A European Organization for Research and Treatment of Cancer (EORTC) Gynecological Cancer Group study. Eur J Cancer 2001;37:1624-1628. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11527687.

136. Bookman MA, Blessing JA, Hanjani P, et al. Topotecan in squamous cell carcinoma of the cervix: A Phase II study of the Gynecologic Oncology Group. Gynecol Oncol 2000;77:446-449. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10831357.

137. Muderspach LI, Blessing JA, Levenback C, Moore JL. A Phase II study of topotecan in patients with squamous cell carcinoma of the cervix: a gynecologic oncology group study. Gynecol Oncol 2001;81:213-215. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11354055.

138. Miller DS, Blessing JA, Bodurka DC, et al. Evaluation of pemetrexed (Alimta, LY231514) as second line chemotherapy in persistent or recurrent carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol 2008;110:65-70. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18455781.

139. Muggia FM, Blessing JA, Method M, et al. Evaluation of vinorelbine in persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92:639-643. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14766259.

140. 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.

141. 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.

142. 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.

143. 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.

144. 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.

145. 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.

146. 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.

147. Monie A, Tsen S-WD, Hung C-F, Wu TC. Therapeutic HPV DNA vaccines. Expert Rev Vaccines 2009;8:1221-1235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19722895.

148. Hung C-F, Ma B, Monie A, et al. Therapeutic human papillomavirus vaccines: current clinical trials and future directions. Expert Opin Biol Ther 2008;8:421-439. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18352847.

149. Huang CF, Monie A, Weng WH, Wu T. DNA vaccines for cervical cancer. Am J Transl Res 2010;2:75-87. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20182584.

150. Gonzalez-Cortijo L, Carballo N, Gonzalez-Martin A, et al. Novel chemotherapy approaches in chemoradiation protocols. Gynecol Oncol 2008;110:S45-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18678399.

151. Gonzalez Martin A. Molecular biology of cervical cancer. Clin Transl Oncol 2007;9:347-354. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17594948.

152. Erickson-Whitmann B, Rownd J, Khater K. Biologic and physical aspects of radiation oncology. In: Barakat R, Markman M, Randall M, eds. Principles and Practice of Gynecology Oncology, 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:325-380.

153. Beriwal S, Gan GN, Heron DE, et al. Early clinical outcome with concurrent chemotherapy and extended-field, intensity-modulated radiotherapy for cervical cancer. Int J Radiat Oncol Biol Phys 2007;68:166-171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17321070.

154. Chen M-F, Tseng C-J, Tseng C-C, et al. Clinical outcome in posthysterectomy cervical cancer patients treated with concurrent Cisplatin and intensity-modulated pelvic radiotherapy: comparison with conventional radiotherapy. Int J Radiat Oncol Biol Phys 2007;67:1438-1444. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17394944.

155. Chen M-F, Tseng C-J, Tseng C-C, et al. Adjuvant concurrent chemoradiotherapy with intensity-modulated pelvic radiotherapy after surgery for high-risk, early stage cervical cancer patients. Cancer J 2008;14:200-206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18536561.

156. Salama JK, Mundt AJ, Roeske J, Mehta N. Preliminary outcome and toxicity report of extended-field, intensity-modulated radiation therapy for gynecologic malignancies. Int J Radiat Oncol Biol Phys 2006;65:1170-1176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16730136.

157. Small W, Mell LK, Anderson P, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int J Radiat Oncol Biol Phys 2008;71:428-434. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18037584.

158. Fyles A, Keane TJ, Barton M, Simm J. The effect of treatment duration in the local control of cervix cancer. Radiother Oncol

1992;25:273-279. Available at: http://www.ncbi.nlm.nih.gov/pubmed1480773.

159. Girinsky T, Rey A, Roche B, et al. Overall treatment time in advanced cervical carcinomas: a critical parameter in treatment outcome. Int J Radiat Oncol Biol Phys 1993;27:1051-1056. Available at: http://www.ncbi.nlm.nih.gov/pubmed8262826.

160. Lanciano RM, Pajak TF, Martz K, Hanks GE. The influence of treatment time on outcome for squamous cell cancer of the uterine cervix treated with radiation: a patterns-of-care study. Int J Radiat Oncol Biol Phys 1993;25:391-397. Available at: http://www.ncbi.nlm.nih.gov/pubmed8436516.

161. Perez CA, Grigsby PW, Castro-Vita H, Lockett MA. Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. Int J Radiat Oncol Biol Phys 1995;32:1275-1288. Available at: http://www.ncbi.nlm.nih.gov/pubmed7635767.

162. Petereit DG, Sarkaria JN, Chappell R, et al. The adverse effect of treatment prolongation in cervical carcinoma. Int J Radiat Oncol Biol Phys 1995;32:1301-1307. Available at: http://www.ncbi.nlm.nih.gov/pubmed7635769.

163. Swenson RE, Goff BA, Koh W-J, et al. Cancer in the pregnant patient. In: Hoskins WJ, Perez CA, Young RC, eds. Principles and Practice of Gynecologic Oncology, 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2004 1279-1311.

164. van de Nieuwenhof HP, van Ham MAPC, Lotgering FK, Massuger LFAG. First case of vaginal radical trachelectomy in a pregnant patient. Int J Gynecol Cancer 2008;18:1381-1385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18298565.

165. Ben-Arie A, Levy R, Lavie O, et al. Conservative treatment of stage IA2 squamous cell carcinoma of the cervix during pregnancy. Obstet Gynecol 2004;104:1129-1131. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15516424.

166. Abu-Rustum NR, Tal MN, DeLair D, et al. Radical abdominal trachelectomy for stage IB1 cervical cancer at 15-week gestation. Gynecol Oncol 2010;116:151-152. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19878979.

167. Gurney EP, Blank SV. Postpartum radical trachelectomy for IB1 squamous cell carcinoma of the cervix diagnosed in pregnancy. Am J Obstet Gynecol 2009;201:e8-e10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19695559.

168. Chan JK, Berek JS. Impact of the human papilloma vaccine on cervical cancer. J Clin Oncol 2007;25:2975-2982. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17617529.