National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Cervical Cancer

Version 1.2022 — October 26, 2021

NCCN.org

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National Comprehensive Cancer Network®

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Cervical Cancer

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

***Catheryn M. Yashar, MD §/Vice Chair**
UC San Diego Moores Cancer Center

Kristin Bradley, MD §
University of Wisconsin
Carbone Cancer Center

Rebecca Brooks, MD Ω
UC Davis Comprehensive Cancer Center

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

Junzo Chino, MD §
Duke Cancer Institute

Hye Sook Chon, MD Ω
Moffitt Cancer Center

Christina Chu, MD Ω
Fox Chase Cancer Center

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

Marta Ann Crispens, MD Ω
Vanderbilt-Ingram Cancer Center

Shari Damast, MD §
Yale Cancer Center/
Smilow Cancer Hospital

Elisabeth Diver, MD Ω
Stanford Cancer Institute

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

Peter Frederick, MD Ω
Roswell Park Cancer Institute

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

Robert Giuntoli II, MD Ω
Abramson Cancer Center at
the University of Pennsylvania

Ernest Han, MD, PhD Ω
City of Hope
National Medical Center

Brooke E. Howitt, MD ≠
Stanford Cancer Institute

Warner K. Huh, MD Ω
O'Neal Comprehensive
Cancer Center at UAB

Jayanthi Lea, MD Ω
UT Southwestern Simmons
Comprehensive Cancer Center

Andrea Mariani, MD Ω
Mayo Clinic Cancer Center

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

Larissa Nekhlyudov, MD, MPH Þ
Dana-Farber/Brigham and Women's
Cancer Center

Mirna Podoll, MD ≠
Vanderbilt-Ingram Cancer Center

Steven W. Remmenga, MD Ω
Fred & Pamela Buffett Cancer Center

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

Ritu Salani, MD, MBA Ω
UCLA Jonsson Comprehensive Cancer Center

Rachel Sisodia, MD Ω
Massachusetts General Hospital Cancer Center

Pamela Soliman, MD, MPH Ω
The University of Texas MD Anderson Cancer Center

Edward Tanner, MD Ω
Robert H. Lurie Comprehensive
Cancer Center of Northwestern University

Stefanie Ueda, MD Ω
UCSF Helen Diller Family
Comprehensive Cancer Center

Renata Urban, MD Ω
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

Stephanie L. Wethington, MD, MSc Ω
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Emily Wyse ¥
Patient Advocate

Kristine Zanotti, MD Ω
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer Center and
Cleveland Clinic Taussig Cancer Institute

NCCN
Nicole McMillian, MS
Angela Motter, PhD

Ω Gynecologic oncology
Þ Internal medicine
† Medical oncology
§ Radiotherapy/Radiation oncology
≠ Pathology
¥ Patient advocacy
* Discussion Section Writing Committee

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NCCN Guidelines Panel Disclosures

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

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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

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Updates in Version 1.2022 of the NCCN Guidelines for Cervical Cancer from Version 1.2021 include:

CERV-3
- Footnotes removed (Also for CERV-4)
  - 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, fractionation, and size of target volume. (See Discussion)
  - The traditional dose would be 70–80 Gy to total point A dose.

CERV-10
- Persistent or recurrent disease pathway; Under "Workup" two new bullets added:
  - Consider comprehensive genomic profiling (CGP) via a validated and/or FDA-approved assay
  - If tissue biopsy of metastatic site is not feasible or tissue not available, consider CGP via a validated plasma ctDNA assay

CERV-A Principles of Pathology
Page 1 of 3
- Pathologic assessment
  - New sub-bullet added: Recommend PD-L1 testing for patients with recurrent, progressive, or metastatic disease
  - Sub-bullet revised: Recommend MMR/MSI~~; or PD-L1, and/or NTRK gene fusion~~ testing for patients with recurrent, progressive, or metastatic disease; *and/or NTRK gene fusion testing for patients with cervical sarcoma*.

Page 2 of 3
- Neuroendocrine Carcinoma of the Cervix
  - Histologic description; 4th Sub-bullet revised: ~~Resembles counterpart in lung~~ *This carcinoma type morphologically resembles neuroendocrine carcinomas of the lung.*
- Immunohistochemistry
  - Small cell NECC is variably positive for chromogranin, CD56 ~~and~~ synaptophysin~~, and PGP9.5~~.

CERV-B Prinicples of Imaging
Page 1 of 4
- Initial Workup
  - Stage I: This section was extensively revised.

CERV-B Prinicples of Imaging (continued)
- Intial Workup; Stage II-IVA
  - First arrow sub-bullet revised: ~~Consider~~ Pelvic MRI with contrast to assess local disease extent *(preferred)*.
  - Sub-bullet removed: Consider pelvic MRI with contrast to assess local disease extent.

Page 3 of 4
- Small Cell NECC: This section was extensively revised.

CERV-D Principles of Radiation Therapy
Page 3 of 6
- Intraoperative Radiation Therapy: "... IORT is typically delivered with electrons, *brachytherapy, or miniaturized x-ray sources* using preformed applicators of variable sizes..."

Page 4 of 6
- Treatment Information - Brachytherapy; First bullet revised: "... MRI immediately preceding *or during* brachytherapy may be helpful in delineating residual tumor geometry..."

Page 5 of 6
- Dosing Prescription Regimen - Brachytherapy
  - First bullet revised: "... nor individual tumor to normal tissue structure correlations. *Traditionally point A doses were based on widely validated, dose fractionation for brachytherapy with LDR. The dose at point A assumes an LDR delivery of 40–70 cGy/h. The traditional LDR Point A prescription dose was 70 – 80 Gy*. Typical point A prescription doses are 5.5 Gy X 5 fractions for early disease and 6 Gy X 5 fractions for large tumors or those demonstrating a poor response. *Another reasonable choice that has been well-studied in European trials for intracavity dosing to the high-risk CTV is 28 Gy in 4 fractions*."
  - New bullet added: For brachytherapy in combination with EBRT, the external dose is delivered at 1.8–2.0 Gy per daily fraction. Clinicians using high dose-rate (HDR) brachytherapy use dosing based on the linear-quadratic model equation to convert nominal HDR dose to a biologically equivalent LDR dose. (http://www.americanbrachytherapy.org/guidelines/). The HDR fractionation schedule of 5 fractions delivering 6 Gy nominal dose results in a nominal HDR 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.

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UPDATES

CERV-D Principles of Radiation Therapy (continued)
Page 5 of 6

- **Bullet removed: The point A dose recommendations provided in the NCCN Guidelines are based on traditional, and widely validated, dose fractionation and brachytherapy at LDRs. 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 an 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 a biologically equivalent LDR dose (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. This scheme results in a nominal HDR 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. Another reasonable choice that has been well-studied in European trials for intracavity dosing to the high-risk CTV is 28 Gy in 4 fractions.**

CERV-F Systemic Therapy for Cervical Cancer
Page 1 of 3

- **Squamous Cell Carcinoma, Adenocarcinoma, or Adenosquamous Carcinoma**
  - **First-line Combination Therapy; Preferred Regimens; The following were added:**
    - **Pembrolizumab + cisplatin/paclitaxel ± bevacizumab for PD-L1–positive tumors (category 1)**
    - **Pembrolizumab + carboplatin/paclitaxel ± bevacizumab for PD-L1–positive tumors (category 1)**
  - **Column header clarified as Second-line *or Subsequent* Therapy (Also for CERV-F 2 of 3)**
    - **Preferred regimens: Nivolumab for PD-L1–positive tumors was added as a category 2A recommendation.**
    - **Other Recommended Regimens: Tisotumab vedotin-tftv was added as a category 2A recommendation.**
- **Footnote c revised: If not used previously, these agents can be used as second-line *or subsequent* therapy as clinically appropriate.**
- **Footnote e revised: Recommended ~~for disease progression on or after chemotherapy~~ in patients whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.**
- **Footnote f revised: *Additional* references for second-line therapy are provided in the Discussion.**
- **Footnote h revised: "... as determined by ~~an~~ *a validated and/or* FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.**

Page 2 of 3

- **Footnote k revised: "...may be used as second-line *or subsequent* therapy for small cell neuroendocrine carcinoma if not used previously.**

Page 3 of 3

- **References were updated.**

CERV-G Principles of Gynecologic Survivorship

- **Psychosocial effects revised: Psychosocial effects after cancer may ~~include~~ *be* psychological (eg, depression, anxiety, fear of recurrence, altered body image), financial (eg, return to work, insurance concerns), and*/or* interpersonal (eg, relationships, sexuality, intimacy) ~~effects~~ *in nature*.**
- **Clinical approach**
  - **1st bullet: "...focuses on *managing* chronic disease ~~management~~, monitoring ~~of~~ cardiovascular risk factors, *providing* recommended vaccinations..."**
  - **2nd bullet: "...physical examination, and ~~conduct~~ *provide any* necessary imaging and/or laboratory testing. All ~~women~~ *patients*, whether sexually active or not, should be asked about genitourinary symptoms, including vulvovaginal dryness..."**
  - **New bullet added: For premenopausal patients, hormone replacement therapy should be considered.**

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UPDATES

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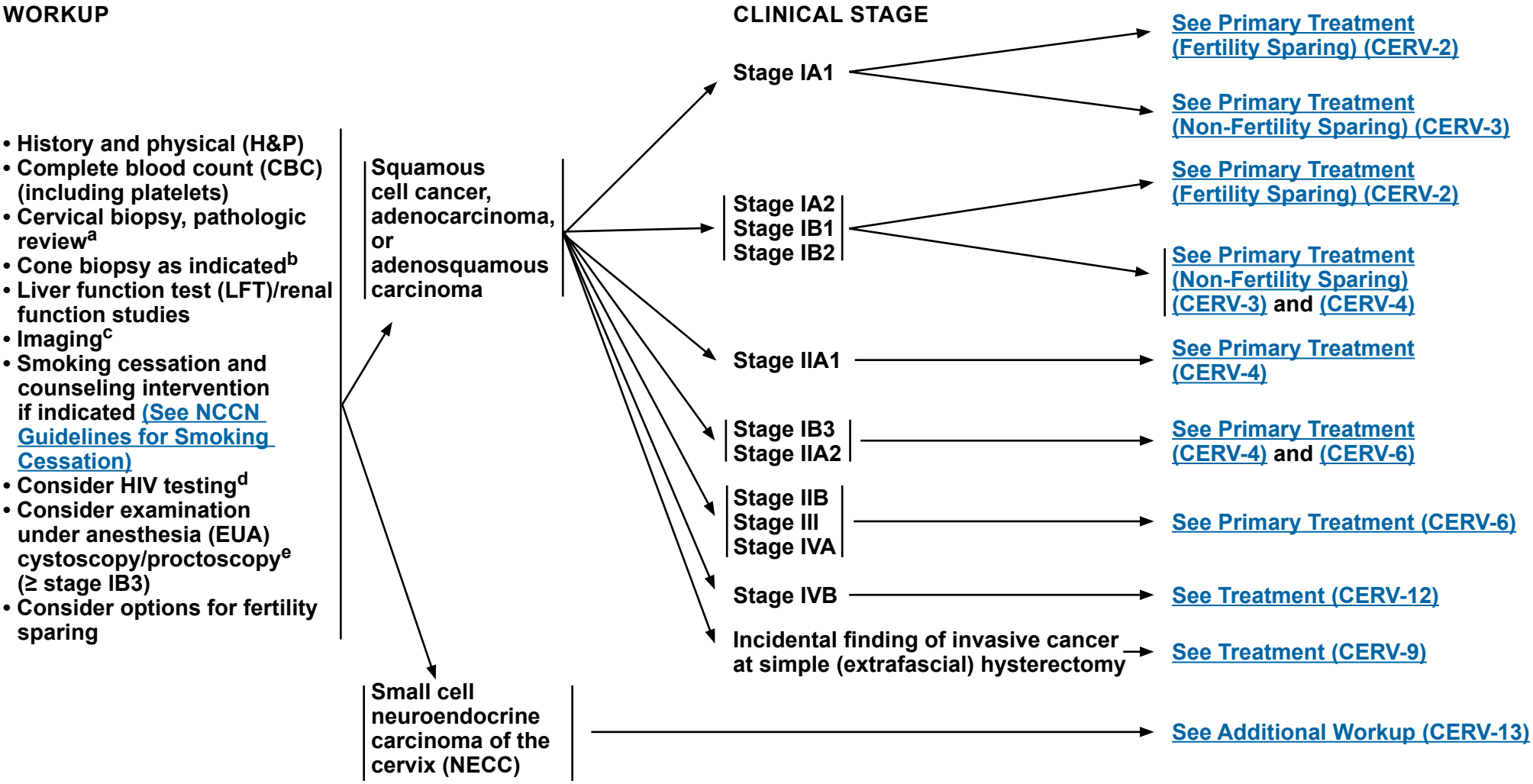

[a] See Principles of Pathology (CERV-A).
[b] See Discussion for indications for cone biopsy.
[c] See Principles of Imaging (CERV-B).
[d] Consider HIV testing, especially in younger patients. Patients with cervical cancer and HIV should be referred to an HIV specialist and should be treated for cervical cancer as per these guidelines. Modifications to cancer treatment should not be made solely on the basis of HIV status.
[e] For suspicion of bladder/bowel involvement, cystoscopy/proctoscopy with biopsy is required.

All staging in guidelines is based on updated 2018 FIGO staging. (See ST-1)

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

CLINICAL STAGE[c]	PRIMARY TREATMENT (FERTILITY SPARING)[h,i]	
Stage IA1 no lymphovascular space invasion (LVSI)	**Cone biopsy[j] with negative margins[k] (preferably a non-fragmented specimen with at least 3-mm negative margins[k]) (If positive margins, repeat cone biopsy or perform trachelectomy)**	**See Surveillance (CERV-10)**
Stage IA1 with LVSI and Stage IA2	**Radical trachelectomy + pelvic lymphadenectomy[g] (consider sentinel lymph node [SLN] mapping)[g] or Cone biopsy[j] with negative margins[k] (preferably a non-fragmented specimen with at least 3-mm negative margins[k]) (if positive margins, repeat cone biopsy or perform trachelectomy) + pelvic lymphadenectomy (consider SLN mapping)[g]**	**See Surgical Findings (CERV-5)**
Stage IB1[f] Select IB2[f,g]	**Radical trachelectomy + pelvic lymphadenectomy[g] ± para-aortic lymphadenectomy (consider SLN mapping)[g,l]**	**See Surgical Findings (CERV-5)**

[c] See Principles of Imaging (CERV-B).
[f] Fertility-sparing surgery for stage IB has been most validated for tumors ≤2 cm. Small cell neuroendocrine histology and gastric type adenocarcinoma are not considered suitable tumors for this procedure.
[g] See Principles of Evaluation and Surgical Staging (CERV-C).
[h] There are no data to support a fertility-sparing approach in small neuroendocrine tumors, gastric type adenocarcinoma, or adenoma malignum. Total hysterectomy after completion of childbearing is at the patient's and surgeon's discretion, but is strongly advised in women with continued abnormal pap smears or chronic persistent HPV infection.
[i] Consultation with reproductive endocrinology fertility experts is suggested.
[j] Cold knife conization (CKC) is the preferred method of diagnostic excision, but loop electrosurgical excision procedure (LEEP) is acceptable, provided adequate margins and proper orientation are obtained. Endocervical curettage (ECC) should be added as clinically indicated.
[k] Negative for invasive disease or histologic high-grade squamous intraepithelial lesion (HSIL) at margins.
[l] For SLN mapping, the best detection rates and mapping results are in tumors <2 cm.

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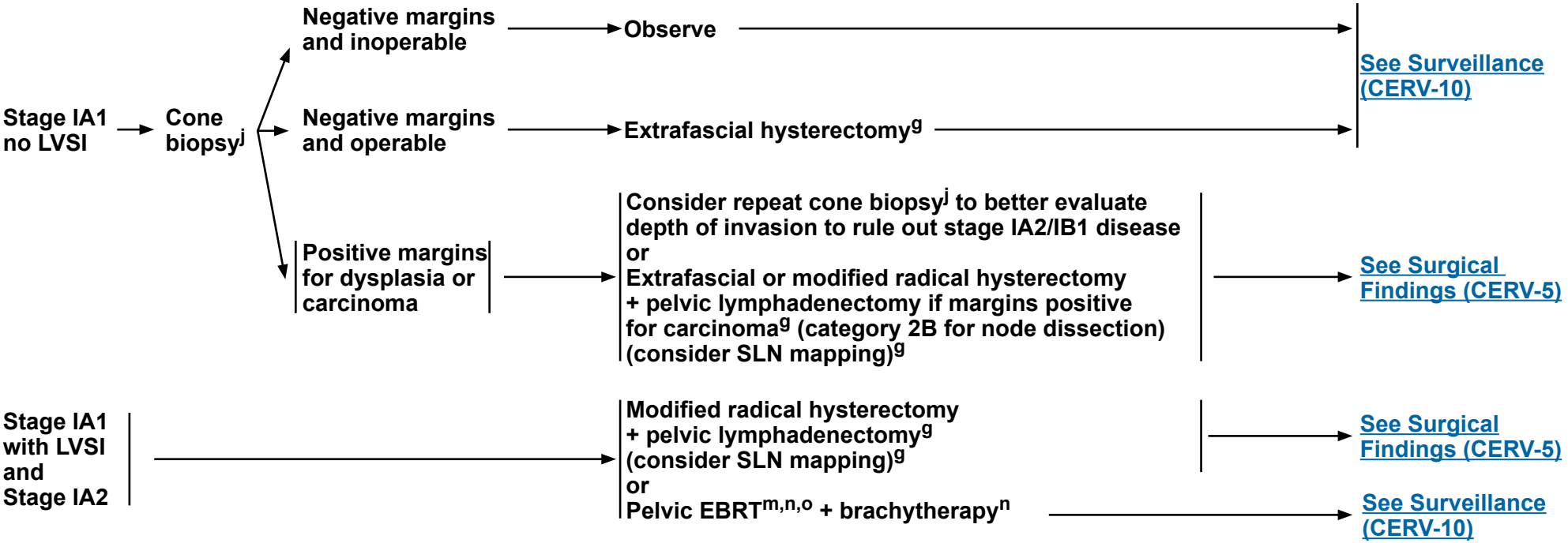

[c] See Principles of Imaging (CERV-B).
[g] See Principles of Evaluation and Surgical Staging (CERV-C).
[j] CKC is the preferred method of diagnostic excision, but LEEP is acceptable, provided adequate margins and proper orientation are obtained. ECC should be added as clinically indicated.
[m] Radiation can be an option for medically inoperable patients or those who refuse surgery.
[n] See Principles of Radiation Therapy (CERV-D).
[o] For higher risk patients such as those who are IA2 with LVSI, consideration can be given to adding concurrent platinum-containing chemotherapy with external beam RT (EBRT) utilizing cisplatin as a single agent (or carboplatin if cisplatin intolerant).

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CLINICAL STAGE[c]	PRIMARY TREATMENT (NON-FERTILITY SPARING)	
Stage IB1, IB2 and Stage IIA1	Radical hysterectomy + pelvic lymphadenectomy[g] (category 1) ± para-aortic lymphadenectomy (category 2B) (consider SLN mapping)[g,l] or Pelvic EBRT[m,n] + brachytherapy[n] ± concurrent platinum-containing chemotherapy[p]	See Surgical Findings (CERV-5) See Surveillance (CERV-10)
Stage IB3 and Stage IIA2 (also see CERV-6 for additional recommendations for non-primary surgery patients)	Pelvic EBRT[n] + concurrent platinum-containing chemotherapy[p] + brachytherapy[n] (category 1) or Radical hysterectomy + pelvic lymphadenectomy[g] ± para-aortic lymphadenectomy (category 2B) or Pelvic EBRT[n] + concurrent platinum-containing chemotherapy[p] + brachytherapy[n] + selective completion hysterectomy[q] (category 3)	See Surveillance (CERV-10) See Surgical Findings (CERV-5) See Surveillance (CERV-10)

[c] See Principles of Imaging (CERV-B).
[g] See Principles of Evaluation and Surgical Staging (CERV-C).
[l] For SLN mapping, the best detection rates and mapping results are in tumors <2 cm.
[m] Radiation can be an option for medically inoperable patients or those who refuse surgery.
[n] See Principles of Radiation Therapy (CERV-D).
[p] Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant).
[q] This approach can be considered in patients whose extent of disease, response to EBRT, or uterine anatomy precludes adequate coverage by brachytherapy.

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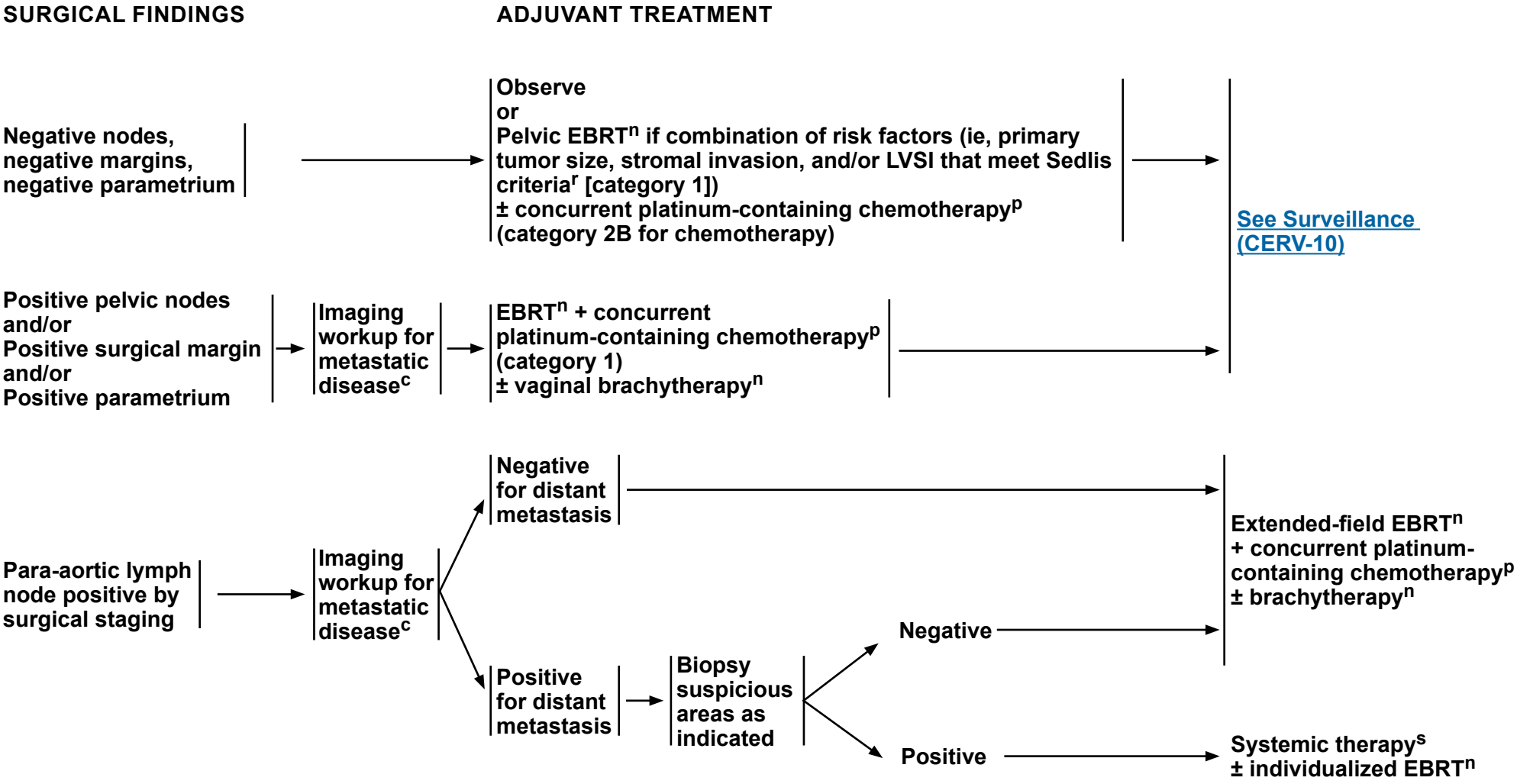

[c] See Principles of Imaging (CERV-B).
[n] See Principles of Radiation Therapy (CERV-D).
[p] Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant).
[r] Risk factors may not be limited to the Sedlis criteria. See Sedlis Criteria (CERV-E).
[s] See Systemic Therapy for Cervical Cancer (CERV-F).

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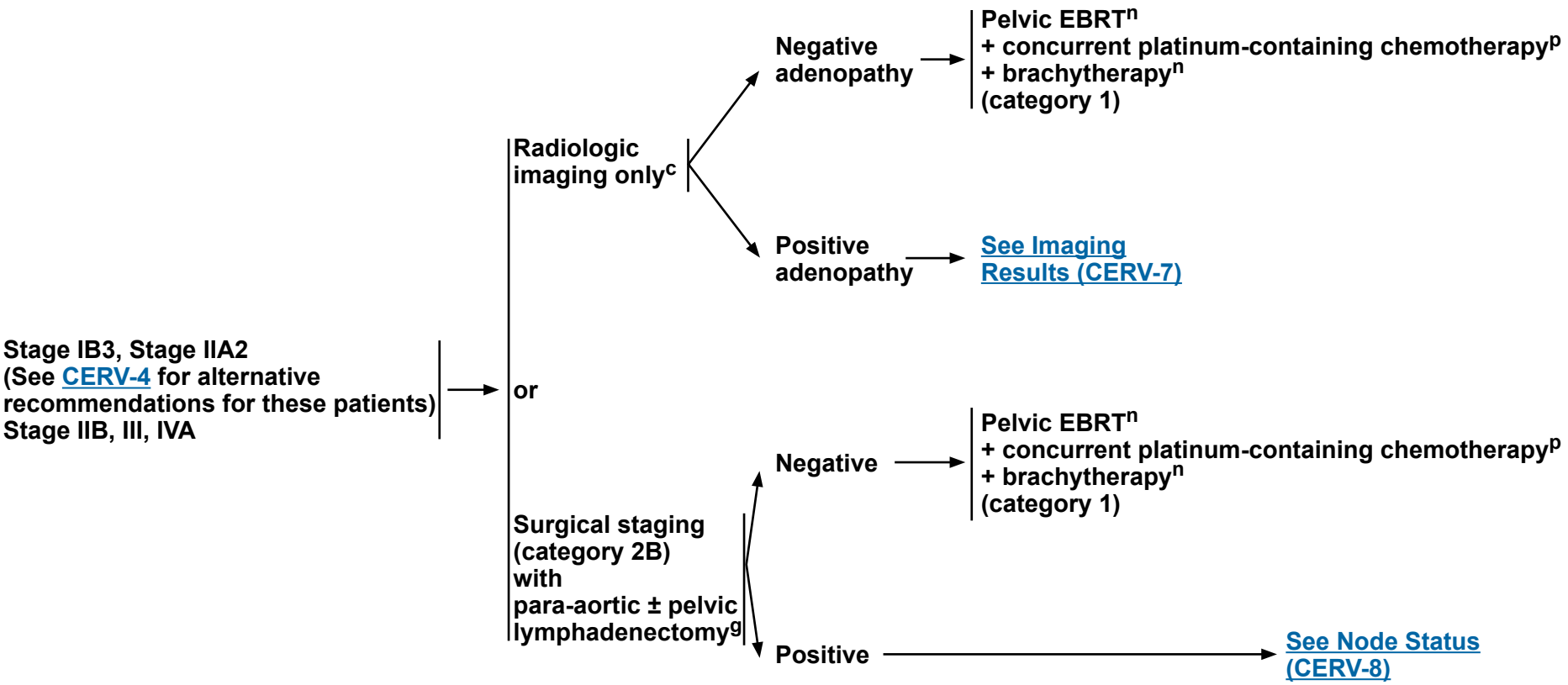
See Surveillance (CERV-10)



[c] See Principles of Imaging (CERV-B).
[g] See Principles of Evaluation and Surgical Staging (CERV-C).
[n] See Principles of Radiation Therapy (CERV-D).
[p] Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant).

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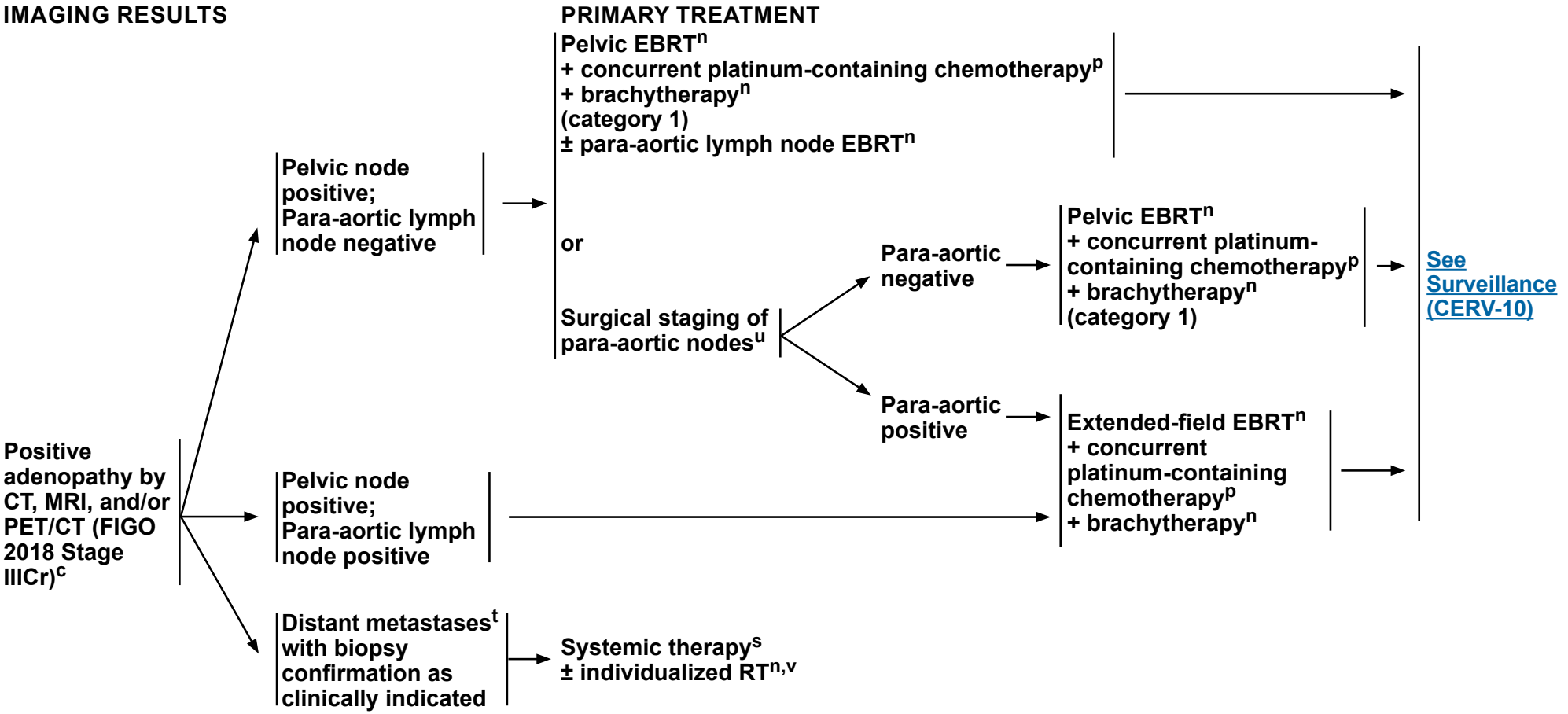
See Surveillance (CERV-10)



c See Principles of Imaging (CERV-B).
n See Principles of Radiation Therapy (CERV-D).
p Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant).
s See Systemic Therapy for Cervical Cancer (CERV-F).
t Patients with distant metastatic disease confined to the supraclavicular nodes may be treated definitively. (Kim JY, et al. Int J Radiat Oncol Biol Phys 2012;84:741-747.)
u Consider postoperative imaging (abdominal/pelvic CT or MRI with contrast) to confirm the adequacy of node removal.
v Consider ablative therapy for 1–5 metastatic lesions (category 2B) if the primary has been controlled. (Palma D, et al. Lancet 2019;393:2051-2058.)

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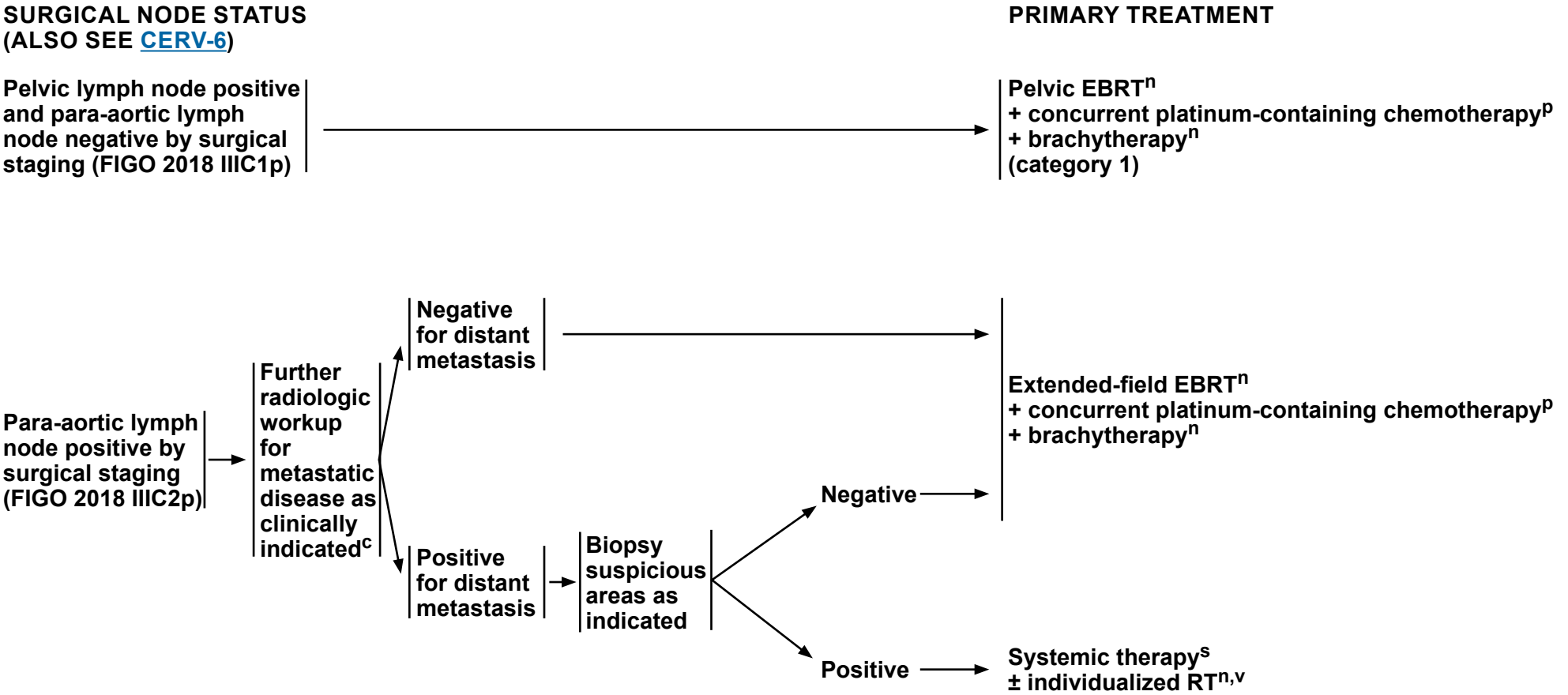
See Surveillance (CERV-10)



c See Principles of Imaging (CERV-B).
n See Principles of Radiation Therapy (CERV-D).
p Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant).
s See Systemic Therapy for Cervical Cancer (CERV-F).
v Consider ablative therapy for 1–5 metastatic lesions (category 2B) if the primary has been controlled. (Palma D, et al. Lancet 2019;393:2051-2058.)

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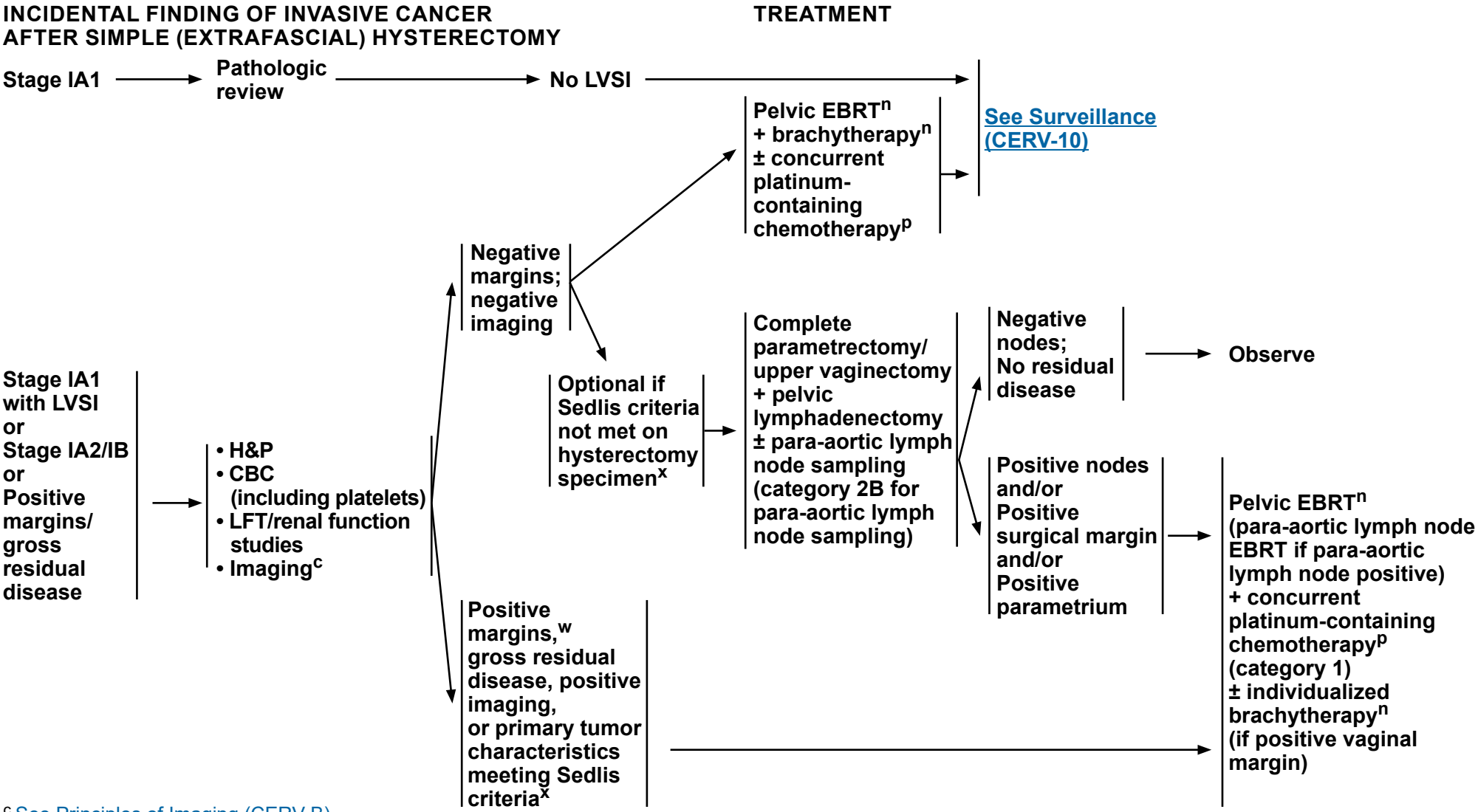
See Surveillance (CERV-10)



[c] See Principles of Imaging (CERV-B).
[n] See Principles of Radiation Therapy (CERV-D).
[p] Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant).

[w] Invasive cancer at surgical margin.
[x] See Sedlis Criteria (CERV-E).

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See Surveillance (CERV-10)

SURVEILLANCE[y]

- **Interval H&P every 3–6 mo for 2 y, every 6–12 mo for 3–5 y, then annually based on patient's risk of disease recurrence**
- **Cervical/vaginal cytology screening annually[z,aa] as indicated for the detection of lower genital tract neoplasia**
- **Stage-dependent imaging for follow-up[c,bb]**
- **Laboratory assessment (CBC, blood urea nitrogen [BUN], creatinine) as indicated based on symptoms or examination findings suspicious for recurrence**
- **Patient education regarding symptoms of potential recurrence, periodic self-examinations, lifestyle, obesity, exercise, sexual health (eg, vaginal dilator use, lubricants/moisturizers, hormone replacement therapy), smoking cessation, nutrition counseling, and potential long-term and late effects of treatment[cc] (Also See NCCN Guidelines for Survivorship and NCCN Guidelines for Smoking Cessation)**

→ **Persistent or recurrent disease** →

WORKUP

- **Additional imaging as clinically indicated[c]**
- **Surgical exploration in selected cases**
- **Consider comprehensive genomic profiling (CGP) via a validated and/or FDA-approved assay**
- **If tissue biopsy of metastatic site is not feasible or tissue not available, consider CGP via a validated plasma ctDNA assay**

→ **See Therapy for Relapse (Local/Regional Recurrence) (CERV-11)**

→ **See Therapy for Relapse (Distant Metastases) (CERV-12)**

[c] See Principles of Imaging (CERV-B).
[y] Salani R et al. Gynecol Oncol 2017;146:3-10.
[z] Regular cytology can be considered for detection of lower genital tract dysplasia and for immunocompromised patients, although its value in detection of recurrent cervical cancer is limited. The likelihood of picking up asymptomatic recurrences by cytology alone is low.
[aa] The accuracy of cytology results may be affected in patients who have received pelvic radiation.
[bb] Recurrences should be proven by biopsy before proceeding to treatment planning.
[cc] See Principles of Gynecologic Survivorship (CERV-G).

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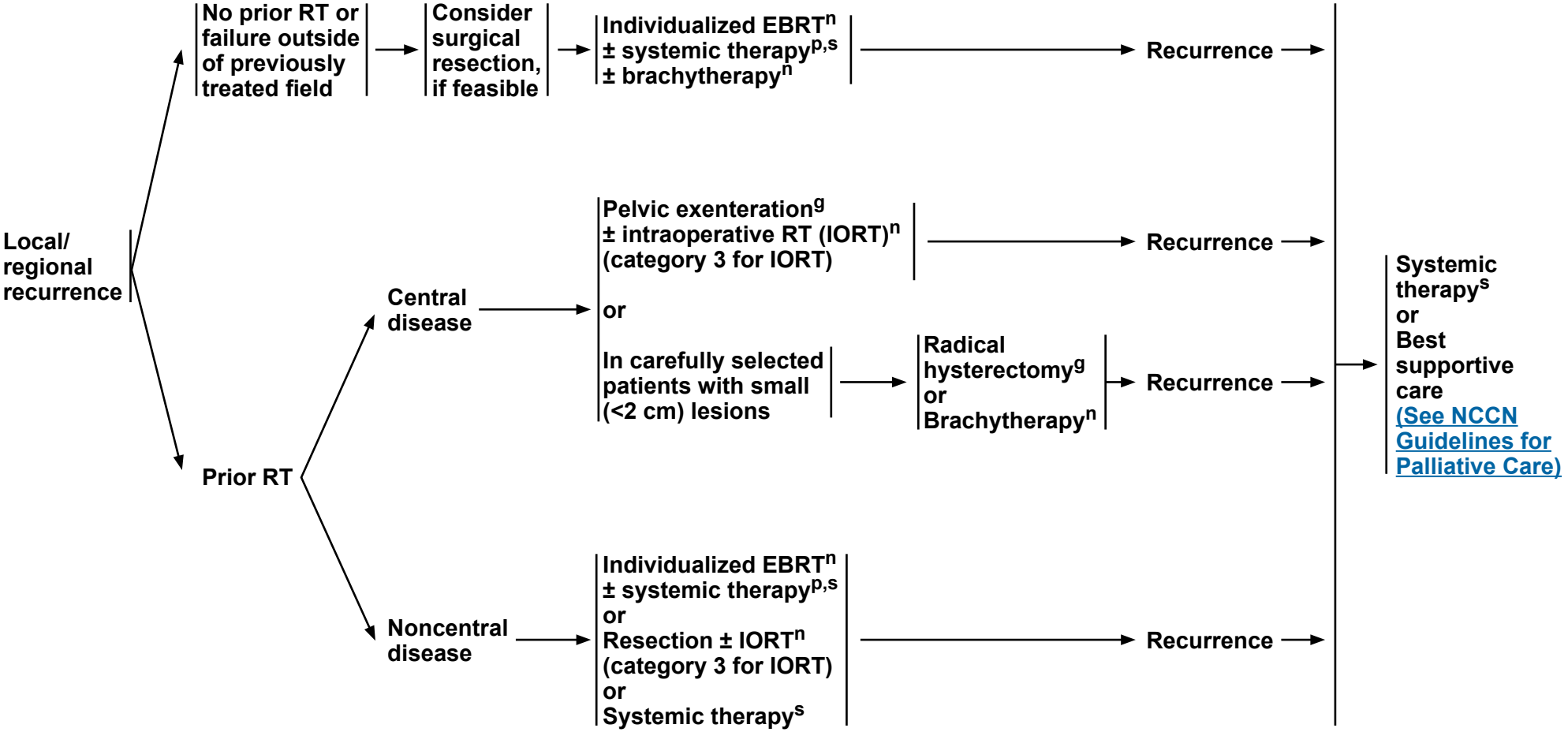
THERAPY FOR RELAPSE



g See Principles of Evaluation and Surgical Staging (CERV-C).
n See Principles of Radiation Therapy (CERV-D).
p Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant).
s See Systemic Therapy for Cervical Cancer (CERV-F).

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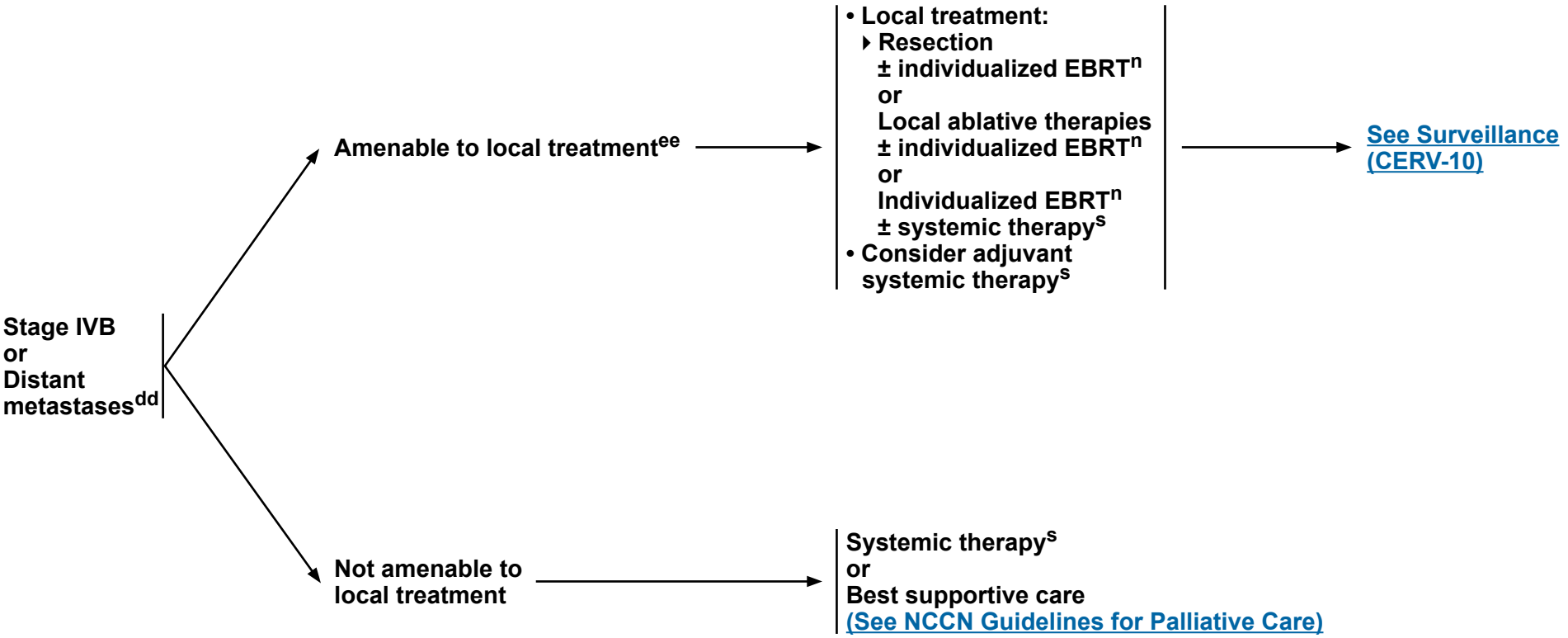
TREATMENT



[n] See Principles of Radiation Therapy (CERV-D).
[s] See Systemic Therapy for Cervical Cancer (CERV-F).
[dd] Consider tumor mutational burden (TMB) testing as determined by a validated and/or FDA-approved assay.
[ee] Perkins V, Gynecol Oncol 2020;156:100-106.

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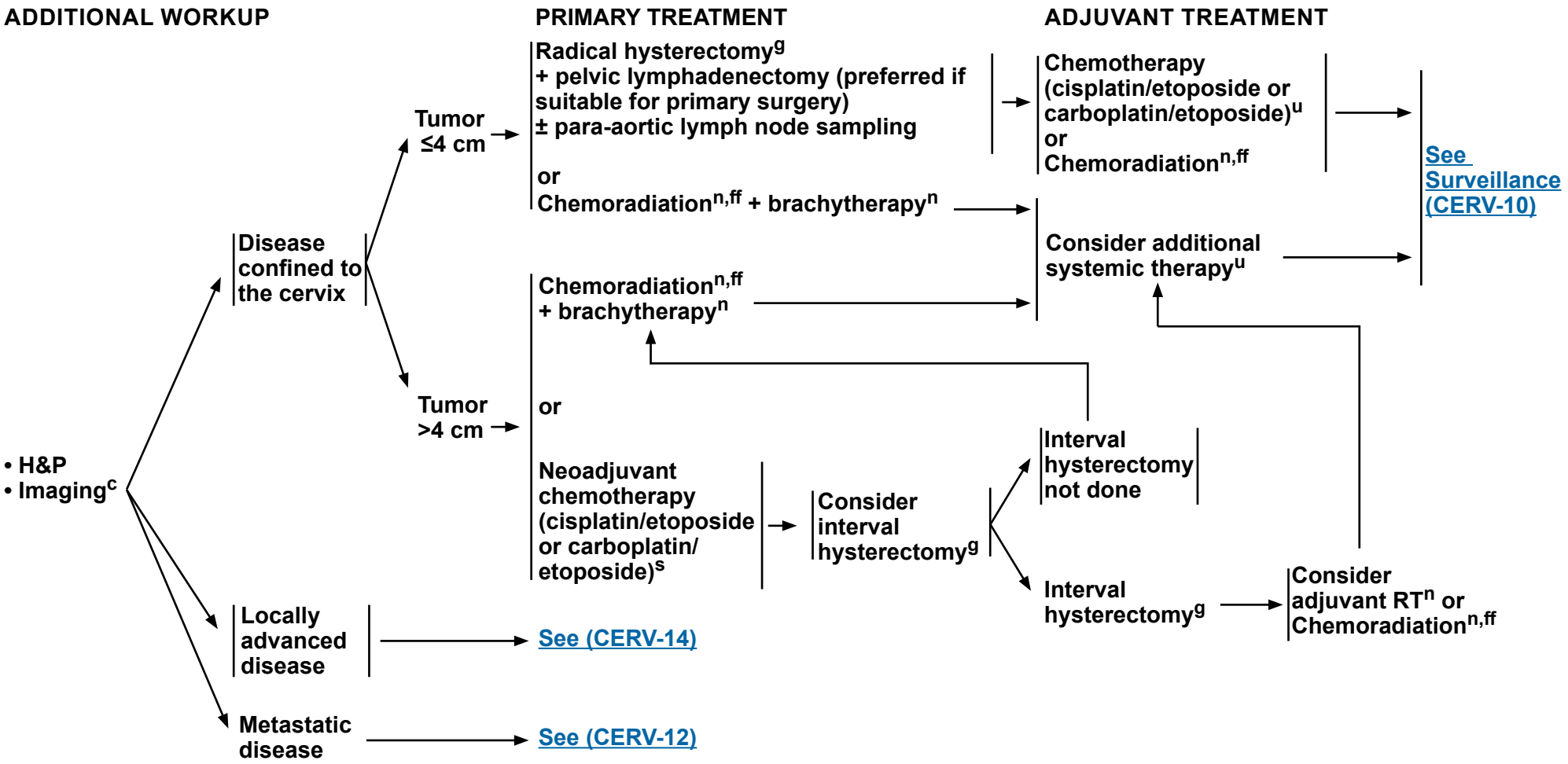
SMALL CELL NECC[a]



[a] See Principles of Pathology (CERV-A).
[c] See Principles of Imaging (CERV-B).
[g] See Principles of Evaluation and Surgical Staging (CERV-C).
[n] See Principles of Radiation Therapy (CERV-D).
[s] See Systemic Therapy for Cervical Cancer (CERV-F).
[ff] Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin (or carboplatin if cisplatin intolerant) + etoposide.

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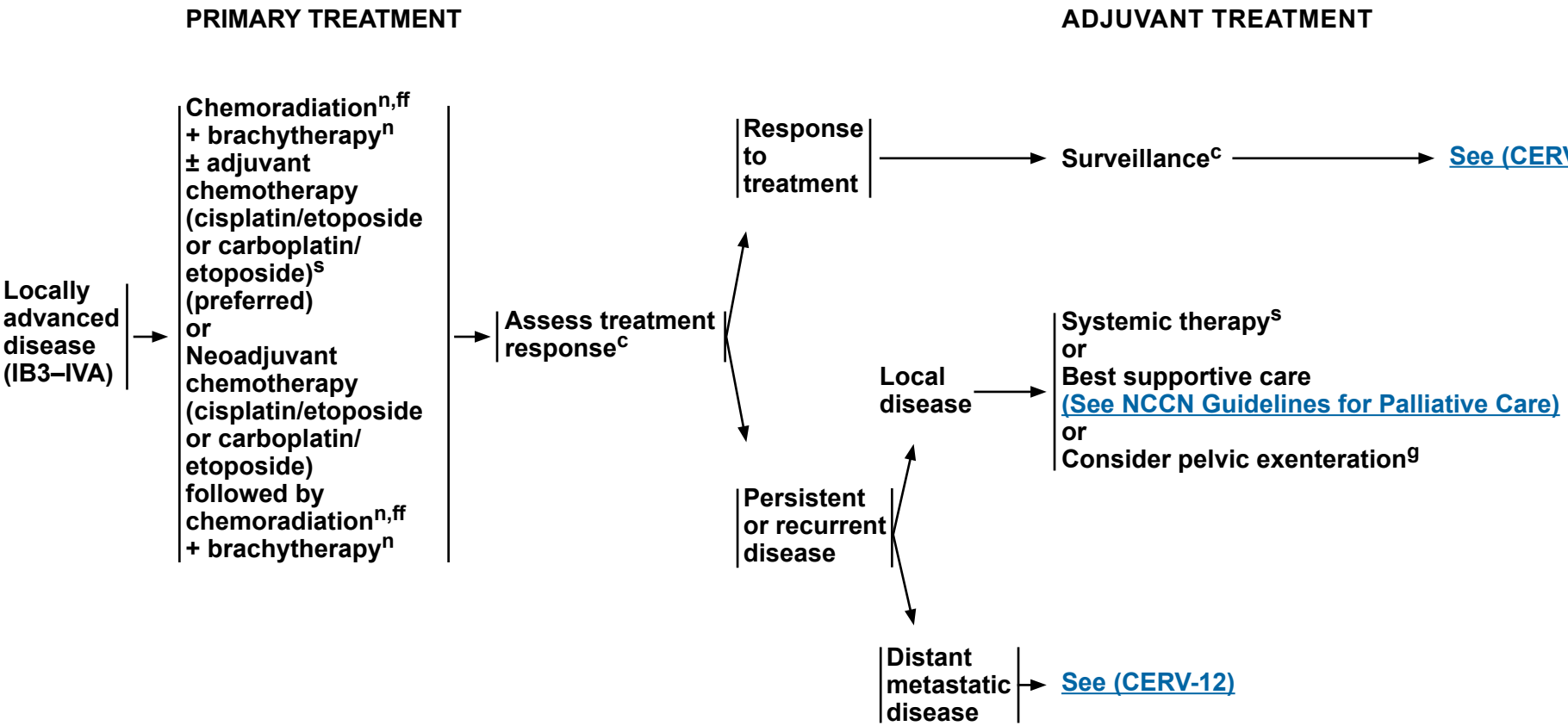
SMALL CELL NECC



[c] See Principles of Imaging (CERV-B).
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PRINCIPLES OF PATHOLOGY[1]

Squamous Cell Carcinoma, Adenocarcinoma, or Adenosquamous Carcinoma

- **Procedure**
  - **Radical hysterectomy**

- **Pathologic assessment:**
  - **Uterus**
    - ◊ **Hysterectomy type (where applicable)**
    - ◊ **Tumor site**
    - ◊ **Tumor size, including greatest dimension and additional two dimensions**
    - ◊ **Histologic type[a]**
    - ◊ **Histologic grade**
    - ◊ **Stromal invasion (depth of invasion in mm/cervical wall thickness in mm)[b]**
    - ◊ **Tumor width extent in mm**
    - ◊ **Surgical resection margin status**
      - **– If negative, include closest margin and distance to closest margin (in mm)[c]**
      - **– If positive, include location of positive margin[c]**
    - ◊ **LVSI (does not impact FIGO 2018 staging[2])**
  - **Other tissue/organ involvement (parametrium, vaginal cuff, fallopian tubes, ovaries, peritoneum, omentum, other)**
  - **Lymph nodes (when resected)**
    - ◊ **SLNs should undergo ultrastaging for detection of low-volume metastasis[d]**
    - ◊ **Non-SLNs do not require ultrastaging and can be processed as per routine protocols**
    - ◊ **Include the number of lymph nodes with isolated tumor cells, micrometastasis, and macrometastasis**
    - ◊ **Isolated tumor cells are noted as pN0(i+)**
  - **Recommend PD-L1 testing for patients with recurrent, progressive, or metastatic disease**
  - **Recommend MMR/MSI; testing for patients with recurrent, progressive, or metastatic disease; and/or *NTRK* gene fusion testing for patients with cervical sarcoma [3,4]**
  - **Consider TMB testing through a validated and/or FDA-approved assay[5]**

[a] According to the 2018 International Endocervical Adenocarcinoma Criteria and Classification (IECC),[6] morphologic features (luminal mitotic figures and apoptosis) can be used to distinguish between human papillomavirus (HPV)-associated endocervical adenocarcinomas and non-HPV–associated adenocarcinomas. Tumors can be further subtyped based on morphologic features.

[b] Evaluation of histologic pattern of invasion for endocervical adenocarcinomas is an emerging concept.[7,8,9] Three clinically significant histologic patterns of invasion for endocervical adenocarcinoma have been described. Tumors with so-called pattern A invasion (defined by well-demarcated glands with round contours, an absence of single cells, an absence of desmoplastic stromal response, and no lymphatic vascular invasion) have excellent survival and do not have lymph node metastases or recurrences.[7]

[c] While reporting of this information is not required, knowledge of this information is useful for multidisciplinary treatment planning.

[d] Ultrastaging commonly entails serial sectioning of the SLN and review of multiple hematoxylin and eosin (H&E)-stained sections with or without cytokeratin immunohistochemistry for all blocks of the SLN. There is not a standard protocol for lymph node ultrastaging.

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Continued

PRINCIPLES OF PATHOLOGY[10-13]

Neuroendocrine Carcinoma of the Cervix (NECC)

- **Histologic description**
  - **Although rare, comprising <5% of cervical cancers, the cervix is the most common site for high-grade neuroendocrine carcinoma (eg, small cell and large cell neuroendocrine carcinoma) in the female genital tract.**
  - **NECC is clinically aggressive, with rapid metastasis and a frequently poor clinical outcome.**
  - **NECC is usually HPV-associated; types 16 and 18 are the most common (18 more often than 16).**
  - **This carcinoma type morphologically resembles neuroendocrine carcinomas of the lung.**
  - **Small cell NECC is a morphologic diagnosis regardless of immunohistochemical staining profile.**
  - **The predominant growth pattern is diffuse. Additional growth patterns include insular (solid nests/islands of cells with peripheral palisading and retraction of stroma), as well as perivascular and thick trabeculae with serpiginous (wavy) growth. Pseudoglandular and rosette-like structures are variably present.**
  - **Cytologic features include a uniform population of cells with indistinct cell borders, scant cytoplasm, and hyperchromatic nuclei with fine granular chromatin. Abundant mitotic activity and apoptotic debris is common. Nuclear molding and indistinct nucleoli are additional features. Necrosis is common.**
  - **Associated cervical glandular lesions (pre- or overtly malignant) may be seen. Consider diagnoses such as adenocarcinoma mixed with neuroendocrine carcinoma as appropriate.**
  - **Differentiating between small cell and large cell NECC may be difficult or impossible; the term "high-grade NECC" is preferred in these circumstances.**

- **Immunohistochemistry**
  - **Small cell NECC is variably positive for chromogranin, CD56, and synaptophysin.**
    - **CD56 and synaptophysin are the most sensitive neuroendocrine markers, but CD56 lacks specificity.**
    - **Chromogranin is the most specific neuroendocrine marker, but lacks sensitivity with only about 50%–60% of small cell NECC beinpositive.[14,15]**
    - **Neuron-specific enolase (NSE) and synaptophysin are other neuroendocrine markers, with 80% and 70% positivity, respectively.[14,15]**
  - **If the tumor demonstrates classic morphologic features of small cell NECC, the diagnosis can be made in the absence of immunohistochemical neuroendocrine positivity (this is NOT true for large cell NECC).**
  - **Small cell NECC may be only focally positive (often punctuate cytoplasmic staining) or even negative with broad-spectrum cytokeratins.**
  - **A high percentage of primary high-grade NECCs are TTF1-positive, including some with diffuse immunoreactivity, and this marker is of no value in distinction from a pulmonary metastasis.**
  - **Most high-grade NECCs are diffusely positive for p16 due to the presence of high-risk HPV. However, p16 positivity cannot be used to aid in determining the site of origin; neuroendocrine carcinomas arising at other sites may strongly express p16 due to a non-HPV–related process.**
  - **Peptide hormones, including ACTH, serotonin, somatostatin, calcitonin, glucagon, and gastrin, have been demonstrated in some high-grade NECCs.**

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Continued

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PRINCIPLES OF IMAGING[a,1-9]

Initial Workup

- **Stage I**
  - **Non-Fertility Sparing**
    - ◊ **Consider pelvic MRI with contrast to assess local disease extent (preferred for FIGO stage IB1–IB3).**
    - ◊ **Neck/chest/abdomen/pelvis/groin PET/CT (preferred) or chest/abdomen/pelvis CT or PET/MRI for FIGO stage IB1–IB3.**
    - ◊ **For patients who underwent total hysterectomy (TH) with incidental finding of cervical cancer, consider neck/chest/abdomen/pelvis/groin PET/CT or chest/abdomen/pelvis CT to evaluate for metastatic disease and pelvic MRI to assess pelvic residual disease.**
    - ◊ **Other imaging should be based on symptomatology and clinical concern for metastatic disease.[b]**
  - **Fertility Sparing**
    - ◊ **Pelvic MRI (preferred) to assess local disease extent and proximity of tumor to internal cervical os; perform pelvic transvaginal ultrasound if MRI is contraindicated.**
    - ◊ **Neck/chest/abdomen/pelvis/groin PET/CT (preferred) or chest/abdomen/pelvis CT in FIGO stage IB1–IB3.**
    - ◊ **Consider chest CT with or without contrast.**
    - ◊ **Other imaging should be based on symptomatology and clinical concern for metastatic disease.[b]**

- **Stage II–IVA**
  - **Pelvic MRI with contrast to assess local disease extent (preferred).**
  - **Neck/chest/abdomen/pelvis/groin PET/CT (preferred) or chest/abdomen/pelvis CT to evaluate for metastatic disease.**
  - **Other initial imaging should be based on symptomatology and clinical concern for metastatic disease.[c]**
  - **For patients who underwent TH with incidental finding of cervical cancer, consider neck/chest/abdomen/pelvis/groin PET/CT or chest/abdomen/pelvis CT to evaluate for metastatic disease and pelvic MRI with contrast to assess pelvic residual disease.**

[a] MRI and CT are performed with contrast throughout the guidelines unless contraindicated. Contrast is not required for screening chest CT.
[b] These factors may include abnormal physical exam findings or pelvic, abdominal, or pulmonary symptoms.
[c] These factors may include abnormal physical exam findings, bulky pelvic tumor (>4 cm), delay in presentation or treatment, and pelvic abdominal or pulmonary symptoms.

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Continued
References

PRINCIPLES OF IMAGING[a,1-9]

Follow-up/Surveillance

- **Stage I**
  - **Non-Fertility Sparing**
    - ◊ **Imaging should be based on symptomatology and clinical concern for recurrent/metastatic disease.[b]**
    - ◊ **For patients with FIGO stage IB3 or patients who required postoperative adjuvant radiation or chemoradiation due to high-risk factors,[d] a neck/chest/abdomen/pelvis/groin PET/CT may be performed at 3–6 months after completion of treatment.**
  - **Fertility Sparing**
    - ◊ **Consider pelvic MRI with contrast 6 months after surgery and then yearly for 2–3 years.**
    - ◊ **Other imaging should be based on symptomatology and clinical concern for recurrent/metastatic disease.[b]**

- **Stage II–IV**
  - **Neck/chest/abdomen/pelvis/groin PET/CT (preferred) or chest/abdomen/pelvic CT with contrast within 3–6 months of completion of therapy.**
  - **Consider pelvic MRI with contrast at 3–6 months post completion of therapy.**
  - **Other imaging should be based on symptomatology and clinical concern for recurrent/metastatic disease.[e]**

- **Stage IVB or Recurrence**
  - **Imaging as appropriate (CT, MRI, or PET/CT) to assess response or determine further therapy.**

Suspected Recurrence or Metastasis

- **Neck/chest/abdomen/pelvis/groin PET/CT.**
- **Consider pelvic MRI.**

[a] MRI and CT are performed with contrast throughout the guidelines unless contraindicated. Contrast is not required for screening chest CT.
[b] These factors may include abnormal physical exam findings or pelvic, abdominal, or pulmonary symptoms.
[d] Risk factors may include positive nodes, positive parametria, positive margins, or local cervical factors (See Sedlis Criteria CERV-E).
[e] These factors may include abnormal physical exam findings such as palpable mass or adenopathy, or new pelvic, abdominal, or pulmonary symptoms.

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References

PRINCIPLES OF IMAGING[a,1-9]

Small Cell NECC

- **Additional Workup**
  - **Neck/chest/abdomen/pelvis/groin PET/CT + brain MRI (preferred)**
    or
  - **Chest/abdomen/pelvis CT + brain MRI**

- **Treatment Response Assessment**
  - **If primary treatment is chemoradiation, then neck/chest/abdomen/pelvis/groin PET/CT ± brain MRI (preferred) or chest/abdomen/pelvis CT ± brain MRI**
  - **If neoadjuvant chemotherapy is used, consider reassessment to rule out metastatic disease prior to chemoradiation and brachytherapy.**

- **Surveillance**
  - **Neck/chest/abdomen/pelvis/groin PET/CT ± brain MRI (preferred)**
    or
  - **Chest/abdomen/pelvis CT ± brain MRI**

[a] MRI and CT are performed with contrast throughout the guidelines unless contraindicated. Contrast is not required for screening chest CT.

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PRINCIPLES OF EVALUATION AND SURGICAL STAGING[a]

Types of Resection and Appropriateness for Treatment of Cervical Cancer

- **Treatment of cervical cancer is stratified by stage as delineated in the Guidelines.**
- **Microinvasive disease, defined as FIGO stage IA1 with no LVSI, has less than a 1% chance of lymphatic metastasis and may be managed conservatively with cone biopsy for preservation of fertility (with negative margins) or with simple hysterectomy when preservation of fertility is not desired or relevant. The intent of a cone biopsy is to remove the ectocervix and endocervical canal en bloc using a scalpel. This provides the pathologist with an intact, non-fragmented specimen without electrosurgical artifact, which facilitates margin status evaluation. If a loop electrosurgical excision procedure (LEEP) is chosen for treatment, the specimen should not be fragmented, and care must be undertaken to minimize electrosurgical artifact at the margins. The shape and depth of the cone biopsy may be tailored to the size, type, and location of the neoplastic lesion. For example, if there is concern for invasive adenocarcinoma versus adenocarcinoma in situ in the cervical canal, the cone biopsy would be designed as a narrow, long cone extending to the internal os in order not to miss possible invasion in the endocervical canal. Length of the cold cone of at least 10 mm is preferred and can be increased to 18–20 mm in patients who have completed childbearing.[1] Endocervical sampling above the cone apex to evaluate for residual disease is recommended. Cone biopsy is indicated for triage and treatment of small cancers where there is no likelihood of cutting across gross neoplasm. In cases of stage IA1 with LVSI, a conization (with negative margins) with pelvic SLN mapping/lymphadenectomy is a reasonable strategy.**
- **Radical hysterectomy with bilateral pelvic lymphadenectomy (with or without SLN mapping) is the preferred treatment for FIGO stage IA2, IB1, IB2, and select IB3–IIA1 lesions when fertility preservation is not desired. Radical hysterectomy results in resection of much wider margins compared with a simple hysterectomy, including removal of parts of the cardinal and uterosacral ligaments and the upper 1–2 cm of the vagina; in addition, pelvic and sometimes para-aortic nodes are removed. The Querleu and Morrow classification system[2] is a modern surgical classification that describes degree of resection and nerve preservation in three-dimensional (3D) planes of resection.[3] Procedural details for the most commonly used types of hysterectomy are described in Table 1 (see CERV-C 5 of 7).**
- **The standard and recommended approach for radical hysterectomy is with an open abdominal approach (category 1). A prospective randomized trial[4] demonstrated that minimally invasive radical hysterectomy was associated with lower rates of disease-free survival (DFS) and overall survival than open abdominal radical hysterectomy. Moreover, two recent epidemiologic studies also demonstrated that minimally invasive radical hysterectomy was associated with shorter overall survival than open surgery among women with stage IA2–IB1 cervical cancer.[5] See Discussion for additional details.**

[a] Recommendations by stage are based on the revised 2018 FIGO staging (Bhatla N, Berek JS, Fredes MC, et al. Revised FIGO Staging for carcinoma of the cervix uteri. Int J Gynecol Obstet 2019;145:129-135 and Corrigendum to "Revised FIGO Staging for carcinoma of the cervix uteri" [Int J Gynecol Obstet 2019;145:129-135] Int J Gynecol Obstet 2019;147:279-280). However, trial data cited within this section utilized the 2009 FIGO staging system.

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Continued
References

PRINCIPLES OF EVALUATION AND SURGICAL STAGING[a]

Types of Resection and Appropriateness for Treatment of Cervical Cancer — continued

- **Para-aortic lymphadenectomy for staging is typically done to the level of the inferior mesenteric artery (IMA). The cephalad extent of dissection can be modified based on clinical and radiologic findings.**
- **The radical vaginal trachelectomy with laparoscopic lymphadenectomy procedure (with or without SLN mapping) offers a fertility-sparing option for carefully selected individuals with stage IA2 or stage IB1 lesions (less than 2-cm diameter). The cervix, upper vagina, and supporting ligaments are removed as with a type B radical hysterectomy, but the uterine corpus is preserved. In the more than 300 subsequent pregnancies currently reported, there is a 10% likelihood of second trimester loss, but 72% of patients carry their gestation to 37 weeks or more.[6] The abdominal radical trachelectomy is a reasonable fertility-sparing strategy. It provides larger resection of parametria than the vaginal approach,[7] is suitable for select stage IB1–IB2 cases, and has been utilized in lesions between 2–4 cm in diameter. The operation mimics a type C radical hysterectomy.[b,2,3,7-10]**
- **Advanced-stage disease, including FIGO stage IIB and above, is not usually treated with hysterectomy, as delineated in the Guidelines. The majority of advanced-stage disease in the United States is treated with definitive chemoradiation. In some countries, select cases of stage IIB may be treated with upfront radical hysterectomy or neoadjuvant chemotherapy followed by radical hysterectomy.**
- **Recurrent or persistent disease in the central pelvis following radiation therapy may potentially be cured with the pelvic exenteration procedure. Preoperative assessment for exenteration is designed to identify or rule out distant metastasis. If the recurrence is confined to the pelvis, then surgical exploration is carried out. If intraoperative margin and node assessment are negative, then resection of pelvic viscera is completed. Depending on the location of the tumor, resection may include anterior exenteration, posterior exenteration, or total pelvic exenteration. In cases where the location of tumor allows for adequate margins, the pelvic floor and anal sphincter may be preserved as a supralevator exenteration. Table 2 summarizes the tissues typically removed with differing types of pelvic exenteration (See CERV-C 6 of 7). These are highly complex procedures and should be performed in centers with a high level of expertise for exenteration procedures. Primary pelvic exenteration (without prior pelvic radiation) is restricted to the rare case where pelvic radiation is contraindicated or to women who received prior pelvic radiation for another indication and then developed a metachronous, locally advanced cervical carcinoma and further radiation therapy is not feasible.**

[a] Recommendations by stage are based on the revised 2018 FIGO staging (Bhatla N, Berek JS, Fredes MC, et al. Revised FIGO Staging for carcinoma of the cervix uteri. Int J Gynecol Obstet 2019;145:129-135 and Corrigendum to "Revised FIGO Staging for carcinoma of the cervix uteri" [Int J Gynecol Obstet 2019;145:129-135] Int J Gynecol Obstet 2019;147:279-280). However, trial data cited within this section utilized the 2009 FIGO staging system.

[b] For a description of a type C radical hysterectomy, see Table 1 (CERV-C 5 of 7).

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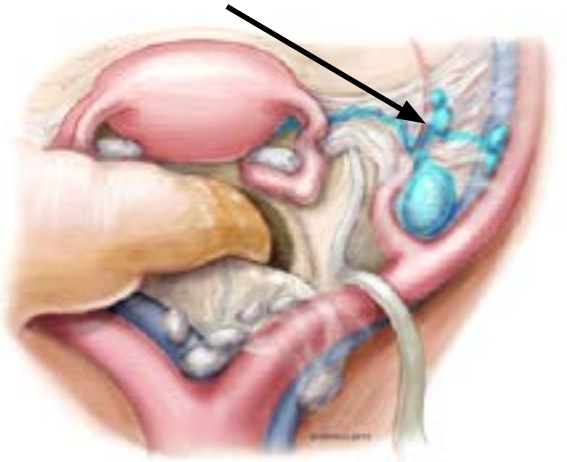
PRINCIPLES OF EVALUATION AND SURGICAL STAGING[a]

Sentinel Lymph Node Mapping for Cervical Cancer:

- **SLN mapping as part of the surgical management of select stage I cervical cancer is considered in gynecologic oncology practices worldwide. While this technique has been used in tumors up to 4 cm in size, the best detection rates and mapping results are in tumors less than 2 cm.[11-15] This simple technique utilizes a direct cervical injection with dye[c] or radiocolloid technetium-99 (99Tc) into the cervix, usually at 2 or 4 points as shown in Figure 1 (below). The SLNs are identified at the time of surgery with direct visualization of colored dye; a fluorescent camera is used if indocyanine green (ICG)[16] was used, and a gamma probe is used if 99Tc was used. SLNs following a cervical injection are commonly located medial to the external iliac vessels, ventral to the hypogastric vessels, or in the superior part of the obturator space (Figure 2). SLNs usually undergo ultrastaging by pathologists, which allows for higher detection of micrometastasis that may alter postoperative management.[4,17]**

Figure 1: Options of SLN Cervical Injection Sites[c]

Figure 2: SLNs (blue, arrow) After Cervical Injection Are Commonly Located Medial to the External Iliac, Ventral to the Hypogastric, or in the Superior Part of the Obturator Space[c]



[a] Recommendations by stage are based on the revised 2018 FIGO staging (Bhatla N, Berek JS, Fredes MC, et al. Revised FIGO Staging for carcinoma of the cervix uteri. Int J Gynecol Obstet 2019;145:129-135 and Corrigendum to "Revised FIGO Staging for carcinoma of the cervix uteri" [Int J Gynecol Obstet 2019;145:129-135] Int J Gynecol Obstet 2019;147:279-280). However, trial data cited within this section utilized the 2009 FIGO staging system.

[c] In the phase III randomized FILM trial, ICG was shown to be superior to isosulfan blue dye. (Frumovitz M, Plante M, Lee PS, et al. Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers (FILM): a randomised, phase 3, multicentre, non-inferiority trial. Lancet Oncol 2018;19:1394-1403).

[d] Figures 1 and 2 are reproduced with permission from Memorial Sloan Kettering Cancer Center. © 2013 Memorial Sloan Kettering Cancer Center.

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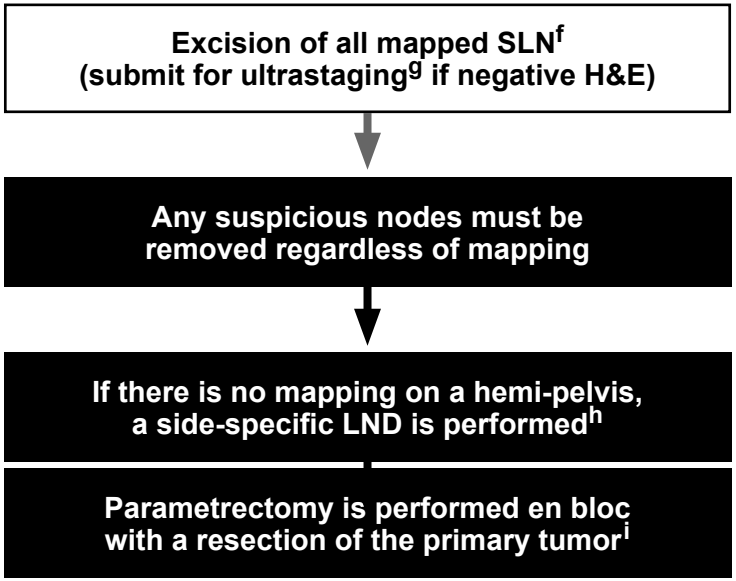
PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

The key to a successful SLN mapping is adherence to the SLN algorithm, which requires the performance of a side-specific lymphadenectomy in cases of failed mapping and removal of any suspicious or grossly enlarged nodes regardless of mapping (Figure 3).

Figure 3: Surgical/SLN Mapping Algorithm for Early-Stage Cervical Cancer[e]



H&E: Hematoxylin and eosin staining
LND: Lymphadenectomy
SLN: Sentinel lymph node

[e] Reproduced with permission from Cormier B, Diaz JP, Shih K, et al. Establishing a sentinel lymph node mapping algorithm for the treatment of early cervical cancer. Gynecol Oncol 2011;122:275-280.
[f] Intracervical injection with dye, 99Tc, or both.
[g] There is no standard protocol for ultrastaging. Ultrastaging typically includes serial sectioning of the gross lymph node with review of H&E with or without cytokeratin IHC staining. See Principles of Pathology (CERV-A).
[h] Including interiliac/subaortic nodes.
[i] Exceptions made for select cases (see CERV-C 1 of 7).

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PRINCIPLES OF EVALUATION AND SURGICAL STAGING

TABLE 1: Resection of Cervical Cancer as Primary Therapy[j]

	Comparison of Hysterectomy Types			Comparison of Fertility-Sparing Trachelectomy Types	
	Extrafascial Hysterectomy (Type A)[k]	Modified Radical Hysterectomy (Type B)[k]	Radical Hysterectomy (Type C1)[k]	Simple Trachelectomy	Radical Trachelectomy[l]
Indication	Stage IA1	Stage IA1 with LVSI and IA2	Local disease without obvious metastasis, including: Stage IB1–IB2 Selected stage IB3-IIA1	Carcinoma in situ and stage IA1	Stage IA2–IB1 Select IB2
Intent	Curative for microinvasion	Curative for small lesions	Curative for larger lesions	Curative for microinvasion Fertility preserved	Curative for select stage IA2-IB2 Fertility preserved
Uterus	Removed	Removed	Removed	Spared	Spared
Ovaries	Optional removal	Optional removal	Optional removal	Spared	Spared
Cervix	Completely removed	Completely removed	Completely removed	Majority removed (approximately 5 mm of the cranial aspect of the cervix typically left for cerclage)	Majority removed (approximately 5 mm of the cranial aspect of the cervix typically left for cerclage)
Vaginal margin	Minimal	1–2 cm margin	Upper 1/4 to 1/3 of vagina	Minimal	1–2 cm margin
Ureteral dissection	Not mobilized	Ureters unroofed and dissected from cervix	Ureters unroofed and dissected from cervix and from lateral parametria	Not mobilized	Ureters unroofed and dissected from cervix
Paracervix/Parametrial resection	None	Resection at the level of ureter bed (horizontal resection 1–2 cm)	Divided at medial aspect of internal iliac vessels. The deep margin is the deep uterine vein	Resected at cervical border	Resection at the level of ureter bed (horizontal resection 1–2 cm)
Recto-uterine (Uterosacral ligaments)	Divided at cervical border	1–2 cm dorsal from cervix (preserves hypogastric nerve plexus)	Type C1 is nerve preserving, divided at least 2 cm dorsal from cervix	Divided at cervical border	1–2cm dorsal from cervix (preserves hypogastric nerve plexus)
Bladder	Mobilized caudal to cervix	Mobilized to upper vagina	Mobilized to middle vagina	Mobilized to peritoneal reflection	Mobilized to upper vagina
Rectum	Not mobilized	Mobilized below cervix	Mobilized below middle vagina	Mobilized to peritoneal reflection	Mobilized below cervix
Surgical approach	Vaginal or laparotomy or minimally invasive	Laparotomy	Laparotomy	Vaginal or laparotomy or minimally invasive[m]	Vaginal or laparotomy or minimally invasive (category 2B for MIS)[m]

[j] Cibula D, Abu-Rustum NR, Benedetti-Panici P, et al. New classification system of radical hysterectomy: Emphasis on a three-dimensional anatomic template for parametrial resection. Gynecol Oncol 2011;122:264-268.

[k] The Querleu and Morrow surgical classification system describes the degree of resection and nerve preservation for radical hysterectomy in three-dimensional planes and updates the previously used Piver-Rutledge-Smith classifications. (Querleu D, Morrow CP. Classification of radical hysterectomy. Lancet Oncol 2008;9:297-303.)

[l] Fertility-sparing radical trachelectomy is most validated for lesions ≤2 cm in diameter. Small cell neuroendocrine histology and gastric type adenocarcinoma are not considered suitable tumors for this procedure.

[m] There is a lack of data on oncologic outcomes for minimally invasive surgical approaches to trachelectomy.

Continued

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PRINCIPLES OF EVALUATION AND SURGICAL STAGING

TABLE 2: Resection of Locally Recurrent Cervical Cancer with No Distant Metastasis[j]

	Comparison of Infralevator Exenteration Types			Comparison of Supralevator Exenteration Types	
	Anterior	Posterior	Total	Posterior	Total
Indication	Central pelvic recurrence Primary therapy for select FIGO stage IVA when primary radiation not feasible				
Intent	Curative				
Uterus, tubes, ovaries	Removed if still present	Removed if still present	Removed if still present	Removed if still present	Removed if still present
Vagina	Removed	Removed	Removed	Removed	Removed
Bladder and urethra	Removed	Preserved	Removed	Preserved	Removed
Rectum	Preserved	Removed	Removed	Removed	Removed
Anal sphincter	Preserved	Removed	Removed	Preserved, colonic anastomosis possible	Preserved, colonic anastomosis possible
Reconstruction options Urinary system	Ileal conduit or Continent diversion	N/A	Double barrel wet colostomy,[n] ileal conduit, or continent diversion	N/A	Double barrel wet colostomy,[n] ileal conduit, or continent diversion
Reconstruction options GI system	N/A	End colostomy	Double barrel wet colostomy[n] or end colostomy	End colostomy or anastomosis with temporary ileostomy	Double barrel wet colostomy,[n] end colostomy, or anastomosis with temporary ileostomy
Neovaginal reconstruction options	Myocutaneous flap (rectus, gracilis, etc.), or split-thickness skin graft with omental J-flap				

[j] Cibula D, Abu-Rustum NR, Benedetti-Panici P, et al. New classification system of radical hysterectomy: Emphasis on a three-dimensional anatomic template for parametrial resection. Gynecol Oncol 2011;122:264-268.

[n] Backes FJ, Tierney BJ, Eisenhauer EL, et al. Complications after double-barreled wet colostomy compared to separate urinary and fecal diversion during pelvic exenteration: time to change back? Gynecol Oncol 2013;128:60-64.

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PRINCIPLES OF RADIATION THERAPY

General Principles

- The use of CT-based treatment planning and conformal blocking is considered the standard of care for external-beam RT (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, and may be useful postoperatively to confirm removal of abnormal nodes.
- RT is directed at sites of known or suspected tumor involvement. EBRT is directed to the pelvis with or without the para-aortic region.
- Brachytherapy is a critical component of definitive therapy for all patients with primary cervical cancer who are not candidates for surgery. This is performed using an intracavitary and/or an interstitial approach.
- For the majority of patients who receive EBRT for cervical cancer, concurrent platinum-containing chemotherapy is given during the time of EBRT.
- Optimal results are achieved when treatment is completed within 8 weeks.

General Treatment Information

- Target Volumes
  - Concepts regarding the gross target volume (GTV), clinical target volume (CTV), planning target volume (PTV), organs at risk (OARs), internal organ motion, and dose-volume histogram (DVH) have been defined for use in conformal radiotherapy, especially for intensity-modulated radiation therapy (IMRT).
  - Very careful attention to detail and reproducibility (including consideration of target and normal tissue definitions, patient and internal organ motion, soft tissue deformation, and rigorous dosimetric and physics quality assurance) is required for proper delivery of IMRT and related highly conformal technologies. Routine image guidance, such as cone-beam CT (CBCT), should be used for defining daily internal soft tissue positioning.
  - 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, obturator, and presacral nodal basins. For patients deemed at higher risk of lymph node involvement (eg, bulkier tumors; 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 is recommended, up to the level of the renal vessels (or even more cephalad as directed by involved nodal distribution). For patients with lower 1/3 vaginal involvement, the bilateral groins should be covered as well.

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Continued
References

PRINCIPLES OF RADIATION THERAPY

General Treatment Information—Continued

Treatment Information - External Beam

- **EBRT is delivered using multiple conformal fields or intensity-modulated volumetric techniques, such as IMRT/volumetric-modulated arc therapy (VMAT)/tomotherapy.**
- **IMRT is helpful in minimizing the dose to the bowel and other critical structures in the post-hysterectomy setting[1] and in treating the para-aortic nodes when necessary. These techniques can also be useful when high doses are required to treat gross disease in regional lymph nodes. However, conformal external beam therapies (such as IMRT or stereotactic body radiation therapy, SBRT) should not be used as routine alternatives to brachytherapy for treatment of central disease in patients with an intact cervix.**
- **A parametrial boost of 5 to 10 Gy can be considered in select cases with bulky parametrial/pelvic sidewall disease after completion of initial whole pelvic radiation.**
- **IMRT can be planned to deliver a higher dose to gross disease in the lymph nodes, while simultaneously delivering a lower dose to control microscopic disease to the other targets, termed a simultaneous integrated boost (SIB). Using a combination of IMRT with SIB can deliver higher doses to grossly positive nodal disease in a shorter time frame, while sparing normal tissues. In general, an SIB target may be boosted up to approximately 2.10 to 2.2 Gy/fraction, depending on target and OAR volumes. At times, additional external boosts may be necessary. Target doses for nodes can range from 54 to 63 Gy, with strict attention to the contribution from brachytherapy, and respecting normal tissue doses while paying attention to adjacent normal tissue doses.**
- **SBRT is an approach that allows for delivery of very high doses of focused EBRT in 1–5 fractions and may be applied to isolated metastatic sites; consideration can be given for limited disease in the re-irradiation setting.[2,3]**

Dosing Prescription Regimen - External Beam

- **Coverage of microscopic nodal disease requires an EBRT dose of approximately 40–45 Gy (in conventional fractionation of 1.8–2.0 Gy daily possibly with an SIB if IMRT is used), and highly conformal boosts of an additional 10–20 Gy may be considered for limited volumes of gross unresected adenopathy, with consideration of the dose given by brachytherapy. For the majority of patients who receive EBRT for cervical cancer, concurrent platinum-containing chemotherapy is given during the time of EBRT.**

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Continued
References

PRINCIPLES OF RADIATION THERAPY

General Treatment Information—Continued

Definitive Radiation Therapy for an Intact Cervix

- **In patients with an intact cervix (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 to 40 Gy using either image guidance (preferred) or to point A (in low dose-rate [LDR] equivalent dose), for a total point A dose (as recommended in the guidelines) of 80 Gy for small-volume cervical tumors or ≥85 Gy for larger-volume cervical tumors. For very small tumors (medically inoperable IA1 or IA2) EQD2 D90 doses of 75–80 Gy may be considered. Grossly involved unresected nodes may be evaluated for boosting with an additional 10 to 15 Gy of highly conformal (and reduced-volume) EBRT. When using image guidance for EBRT, care must be taken to exclude or severely limit the volume of normal tissue included in the high-dose region(s) (see Discussion).**

Posthysterectomy 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 to 4 cm of the vaginal cuff, the parametria, and immediately adjacent nodal basins (such as the external and internal iliac, obturator, and presacral nodes). For documented nodal metastasis, the superior border of the radiation field should be appropriately increased (as previously described). A dose of 45 to 50 Gy in standard fractionation with IMRT is generally recommended.[4] Grossly involved unresected nodes may be evaluated for boosting with an additional 10 to 20 Gy of highly conformal (and reduced-volume) EBRT. With higher doses, especially of EBRT, care must be taken to exclude or severely limit the volume of normal tissue included in the high-dose region(s) (see Discussion).**

Intraoperative Radiation Therapy

- **IORT is a specialized technique that delivers a single, highly focused dose of radiation to an at-risk tumor bed or isolated unresectable residual disease during an open surgical procedure.[5] 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, brachytherapy, or miniaturized x-ray sources using preformed applicators of variable sizes matched to the surgically defined region at risk, which further constrains the area and depth of radiation exposure to avoid surrounding normal structures.**

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Continued
References

PRINCIPLES OF RADIATION THERAPY

General Treatment Information—Continued

Treatment Information - Brachytherapy

- **Brachytherapy is a critical component of definitive therapy for all patients with primary cervical cancer who are not candidates for surgery. 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 an intact cervix may be delivered using ovoids, ring, or cylinder brachytherapy (combined with the intrauterine tandem). For more advanced disease, or without sufficient regression, interstitial needles may allow increased dose to the target, while minimizing dose to the normal tissues. MRI immediately preceding or during brachytherapy may be helpful in delineating residual tumor geometry. 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 EBRT) may be an option.**
- **In rare cases, patients whose anatomy or 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, and early referral for timely use of their expertise is critical.**
- **In selected post-hysterectomy patients (especially those with positive or close vaginal mucosal surgical margins), vaginal cylinder brachytherapy may be used as a boost to EBRT. The prescription is typically to the vaginal surface or at 5 mm below the surface. Typical fractionation schemes include 5.5 Gy X 2 fractions dosed at 5 mm or 6 Gy X 3 fractions dosed at the vaginal surface.**
- **SBRT is not considered an appropriate routine alternative to brachytherapy.**

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Continued
References

PRINCIPLES OF RADIATION THERAPY

Dosing Prescription Regimen - Brachytherapy

- **Point A, representing a paracervical reference point, has been the most widely used dosing parameter to date. However, limitations of the point A dosing system include the fact that it does not take into account the 3D shape of tumors, nor individual tumor to normal tissue structure correlations. Traditionally point A doses were based on widely validated, dose fractionation for brachytherapy with LDR. The dose at point A assumes an LDR delivery of 40–70 cGy/h. The traditional LDR Point A prescription dose was 70 – 80 Gy. Typical point A prescription doses are 5.5 Gy X 5 fractions for early disease and 6 Gy X 5 fractions for large tumors or those demonstrating a poor response. Another reasonable choice that has been well-studied in European trials for intracavity dosing to the high-risk CTV is 28 Gy in 4 fractions.**
- **Interstitial brachytherapy is an advanced technique where multiple needles/catheters are inserted in the gross disease/target. Interstitial brachytherapy may be preferred to maximize dose to the target and minimize dose to the OARs for cases where intracavitary brachytherapy is not possible, or anatomy favors interstitial. 3D treatment planning allows for volumetric delineation of targets and OARs on CT and/or MRI with DVHs. Dose and fractionation depend on prior RT dose, target volume, and OAR doses.**
- **There is evidence that image-guided brachytherapy improves outcomes and decreases toxicity. MRI gives the best soft tissue imaging for residual disease and while it is best to have an MRI with the instruments in place, an MRI prior to brachytherapy can help guide therapy. In the absence of MRI, CT can be used but is inferior for determination of residual disease and contouring is less accurate. The goals of care would include an equivalent dose at 2 Gy (EQD2) to the high-risk CTV (HR-CTV) with a D90 of 80–85 Gy; however, with large disease or poor response dose goals should be HR-CTV D90 ≥87 Gy. Normal tissues should be limited according to published guidelines with 2-cc rectal dose ≤65–75 Gy, sigmoid 2-cc dose ≤70–75 Gy, and 2-cc bladder dose ≤80–90 Gy. If those parameters cannot be achieved, supplemental dosing with interstitial needles should be considered.[6-9]**
- **For brachytherapy in combination with EBRT, the external dose is delivered at 1.8–2.0 Gy per daily fraction. Clinicians using high dose-rate (HDR) brachytherapy use dosing based on the linear-quadratic model equation to convert nominal HDR dose to a biologically equivalent LDR dose (http://www.americanbrachytherapy.org/guidelines/). The HDR fractionation schedule of 5 fractions delivering 6 Gy nominal dose results in a nominal HDR 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.**

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PRINCIPLES OF RADIATION THERAPY
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SEDLIS CRITERIA FOR EXTERNAL PELVIC RADIATION AFTER RADICAL HYSTERECTOMY IN NODE-NEGATIVE, MARGIN-NEGATIVE, PARAMETRIA-NEGATIVE CASES[1-4]

LVSI	Stromal Invasion	Tumor Size (cm) (determined by clinical palpation)
+	Deep 1/3	Any
+	Middle 1/3	≥2
+	Superficial 1/3	≥5
-	Middle or deep 1/3	≥4

LVSI: Lymphovascular space invasion

[1] Modified with permission from 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 study group. Gynecol Oncol 1999;73:177-183.
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[4] Risk factors may not be limited to the Sedlis criteria.

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SYSTEMIC THERAPY FOR CERVICAL CANCER[a]

Squamous Cell Carcinoma, Adenocarcinoma, or Adenosquamous Carcinoma			
Chemoradiation	**Recurrent or Metastatic Disease**		
	First-line Combination Therapy[b,c]	**Possible First-line Single-agent therapy[c]**	**Second-line or Subsequent Therapy[g]**
Preferred Regimens • Cisplatin • Carboplatin if patient is cisplatin intolerant	**Preferred Regimens** • Pembrolizumab + cisplatin/paclitaxel ± bevacizumab for PD-L1–positive tumors (category 1)[d,e,f,1] • Pembrolizumab + carboplatin/paclitaxel ± bevacizumab for PD-L1–positive tumors (category 1)[d,e,f,1] • Cisplatin/paclitaxel/bevacizumab[d,2] (category 1) • Carboplatin/paclitaxel/bevacizumab[d] **Other Recommended Regimens** • Cisplatin/paclitaxel (category 1)[3,4] • Carboplatin/paclitaxel[5,6] (category 1 for patients who have received prior cisplatin therapy) • Topotecan/paclitaxel/bevacizumab[d,2] (category 1) • Topotecan/paclitaxel[2] • Cisplatin/topotecan[7]	**Preferred Regimens** • Cisplatin[4] **Other Recommended Regimens** • Carboplatin[8] • Paclitaxel[9,10]	**Preferred Regimens** • Pembrolizumab for PD-L1–positive or MSI-H/dMMR tumors[e,f,11] • Nivolumab for PD-L1–positive tumors[e,f,12] **Other Recommended Regimens** (All agents listed here are category 2B unless otherwise noted) • Bevacizumab[d] • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Ifosfamide • Irinotecan • Mitomycin • Pemetrexed • Topotecan • Vinorelbine • Tisotumab vedotin-tftv (category 2A)[13] **Useful in Certain Circumstances** • Pembrolizumab for TMB-H tumors[e,h] • Larotrectinib or entrectinib for *NTRK* gene fusion-positive tumors (category 2B)

[a] Cisplatin, carboplatin, docetaxel, and paclitaxel may cause drug reactions (See NCCN Guidelines for Ovarian Cancer--Management of Drug Reactions [OV-D]).
[b] Cost and toxicity should be carefully considered when selecting an appropriate regimen for treatment.
[c] If not used previously, these agents can be used as second-line or subsequent therapy as clinically appropriate.
[d] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[e] See NCCN Guidelines for the Management of Immunotherapy-Related Toxicities.
[f] Recommended in patients whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.
[g] Additional references for second-line therapy are provided in the Discussion.
[h] For the treatment of patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors, as determined by a validated and/or FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

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References
Continued

SYSTEMIC THERAPY FOR CERVICAL CANCER[i]

Small Cell NECC[j]		
Chemoradiation	**Neoadjuvant Therapy, Adjuvant Therapy, Recurrent or Metastatic Disease**	
	First-line Therapy	**Second-line or Subsequent Therapy**
Preferred Regimens • Cisplatin + etoposide[j] **Other Recommended Regimens** • Carboplatin + etoposide if patient is cisplatin intolerant[j]	**Preferred Regimens** • Cisplatin/etoposide • Carboplatin/etoposide	• See first-line or second-line therapy on CERV-F (1 of 3)[k]

[i] Cisplatin or carboplatin may cause drug reactions (See NCCN Guidelines for Ovarian Cancer--Management of Drug Reactions [OV-D]).
[j] For dosing and schedules, see Principles of Systemic Therapy (page SCL-E) in the NCCN Guidelines for Small Cell Lung Cancer.
[k] Any of the regimens recommended for first-line or second-line treatment on CERV-F (1 of 3) may be used as second-line or subsequent therapy for small cell neuroendocrine carcinoma if not used previously.

References

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

PRINCIPLES OF GYNECOLOGIC SURVIVORSHIP

Physical Effects

- Gynecologic cancer treatment typically involves surgery, chemotherapy, hormone therapy, radiation therapy, and/or immunotherapy. These treatments cause acute, short-term, and long-term toxicities.
- Surgical approaches may be extensive and pose risks such as adhesion formation, which may cause pain and may contribute to small bowel obstruction, urinary or gastrointestinal complications (eg, incontinence, diarrhea), pelvic floor dysfunction (manifested by a variety of urinary, bowel, and/or sexual effects), and lymphedema.
- Chemotherapy agents vary, though commonly used regimens may pose a significant risk of neurotoxicity, cardiac toxicity, development of hematologic cancers, and cognitive dysfunction.
- Long-term estrogen deprivation may cause symptoms such as hot flashes, vaginal dryness, and bone loss.
- Radiation therapy may cause long-term complications (eg, fibrosis, vulvovaginal atrophy) and may predispose patients to secondary cancers of the subcutaneous tissue, and/or underlying organs that are proximal to the radiation field.
- Immunotherapy use is emerging, and to date, long-term effects of these treatments are unknown.

Psychosocial Effects

- Psychosocial effects after cancer may be psychological (eg, depression, anxiety, fear of recurrence, altered body image), financial (eg, return to work, insurance concerns), and/or interpersonal (eg, relationships, sexuality, intimacy) in nature.

Clinical Approach

- All gynecologic cancer survivors should receive regular general medical care that focuses on managing chronic disease, monitoring cardiovascular risk factors, providing recommended vaccinations, and encouraging adoption of a healthy lifestyle.
- In order to assess the late and long-term effects of gynecologic cancers, clinicians should comprehensively document the patient's history, conduct a thorough physical examination, and provide any necessary imaging and/or laboratory testing. All patients, whether sexually active or not, should be asked about genitourinary symptoms, including vulvovaginal dryness. Referral to appropriate specialty providers (eg, physical therapy, pelvic floor therapy, sexual therapy, psychotherapy) is recommended. As most treatments for gynecologic cancers will cause sexual dysfunction, early menopause, and infertility, special attention to the resultant medical and psychosocial implications is needed.
- Post-radiation use of vaginal dilators and moisturizers is recommended.
- For premenopausal women, hormone replacement therapy should be considered.
- Communication and coordination with all clinicians involved in the care of survivors, including primary care clinicians, is critical. Providing cancer survivors with a summary of their treatment and recommendations for follow-up is recommended.

Additional Guidance

- See NCCN Guidelines for Distress Management
- See NCCN Guidelines for Smoking Cessation
- See NCCN Guidelines for Survivorship

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

Table 1: International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging of Cancer of the Cervix Uteri (2018)

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the corpus should be disregarded).
IA	Invasive carcinoma that can be diagnosed only by microscopy with maximum depth of invasion ≤5 mm[a]
IA1	Measured stromal invasion ≤3 mm in depth
IA2	Measured stromal invasion >3 mm and ≤5 mm in depth
IB	Invasive carcinoma with measured deepest invasion >5 mm (greater than stage IA); lesion limited to the cervix uteri with size measured by maximum tumor diameter[b]
IB1	Invasive carcinoma >5 mm depth of stromal invasion and ≤2 cm in greatest dimension
IB2	Invasive carcinoma >2 cm and ≤4 cm in greatest dimension
IB3	Invasive carcinoma >4 cm in greatest dimension
II	The cervical carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial invasion
IIA1	IIA1 Invasive carcinoma ≤4 cm in greatest dimension
IIA2	Invasive carcinoma >4 cm in greatest dimension
IIB	With parametrial invasion but not up to the pelvic wall
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non- functioning kidney and/or involves pelvic and/or paraaortic lymph nodes
IIIA	Carcinoma involves lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or paraaortic lymph nodes (including micrometastases)[c], irrespective of tumor size and extent (with r and p notations).
IIIC1	Pelvic lymph node metastasis only
IIIC2	Paraaortic lymph node metastasis
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

[a] Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumor size and extent, in all stages. Pathological findings supercede imaging and clinical findings.
[b] The involvement of vascular/lymphatic spaces should not change the staging. The lateral extent of the lesion is no longer considered.
[c] Isolated tumor cells do not change the stage but their presence should be recorded.
[d] Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC. Example: If imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r, and if confirmed by pathologic findings, it would be Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented.

Reprinted from: Bhatla N, Berek JS, Fredes MC, et al. Revised FIGO Staging for carcinoma of the cervix uteri. Int J Gynecol Obstet 2019;145:129-135 and Corrigendum to "Revised FIGO Staging for carcinoma of the cervix uteri" [Int J Gynecol Obstet 2019;145:129-135] Int J Gynecol Obstet 2019;147:279-280. Copyright 2019, with permission from International Federation of Gynecology and Obstetrics.

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Discussion

This discussion corresponds to the NCCN Guidelines for Cervical Cancer. Last (partially) updated: March 29, 2019.

Table of Contents

Overview

An estimated 13,170 new cases of carcinoma of the uterine cervix (ie, cervical cancer) will be diagnosed in the United States in 2019, and 4250 people will die of 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 in 2012 was 528,000; the annual death rate was 266,000.[6] It is the fourth most common cancer in women worldwide,[7,8] with 85% of cases occurring in developing countries—where cervical cancer is a leading cause of cancer death in women.[6,9]

Persistent human papillomavirus (HPV) infection is the most important factor in the development of cervical cancer.[10,11] The incidence of cervical cancer appears to be related to the prevalence of HPV in the population. In countries with a high incidence of cervical cancer, the prevalence of chronic HPV is approximately 10% to 20%, whereas the prevalence in low-incidence countries is 5% to 10%.[7] Immunization against HPV prevents infection with the types of HPV against which the vaccine is designed and, thus, is expected to prevent specific HPV cancer in women.[12-16] Other epidemiologic risk factors associated with cervical cancer are a history of smoking, parity, oral contraceptive use, early age of onset of coitus, larger number of sexual partners, history of sexually transmitted disease, certain autoimmune diseases, and chronic immunosuppression.[17,18] Smoking cessation should be advised in current smokers, and former smokers should continue to avoid smoking (see the NCCN Guidelines for Smoking Cessation and http://smokefree.gov/).

Squamous cell carcinomas account for approximately 80% of all cervical cancers and adenocarcinoma accounts for approximately 20%. In developed countries, the substantial decline in incidence and mortality of squamous cell carcinoma of the cervix is presumed to be the result of effective screening, although racial, ethnic, and geographic disparities exist.[2,3,19,20] However, adenocarcinoma of the cervix has increased over the past 3 decades, probably because cervical cytologic screening methods are less effective for adenocarcinoma.[21-24] 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.[23,25]

By definition, the NCCN 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.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Cervical Cancer, an electronic search of the PubMed database was performed to obtain key literature in cervical cancer published since the previous Guidelines update, using the following search terms: cervical cancer or cervical carcinoma or carcinoma of the cervix. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines as discussed by the panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence

is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Diagnosis and Workup

These NCCN Guidelines discuss squamous cell carcinoma, adenosquamous carcinoma, adenocarcinoma of the cervix, and small cell neuroendocrine carcinoma. Glassy-cell carcinomas, sarcomas, and other histologic types are not within the scope of these Guidelines.

The earliest stages of cervical carcinoma may be asymptomatic or associated with a watery vaginal discharge and postcoital bleeding or intermittent spotting. Often these early symptoms are not recognized 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. Cone biopsy (ie, 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 (ie, endocervical canal).[5,24] The College of American Pathologists (CAP) protocol for cervical carcinoma is a useful guide (https://cap.objects.frb.io/protocols/cp-femalereproductive-uterine-cervix-18protocol-4100.pdf). This CAP protocol was revised in August 2018 and reflects recent updates in AJCC staging (ie, AJCC Cancer Staging Manual, 8th edition).

Workup for these patients with suspicious symptoms includes history and physical examination, complete blood count (CBC; including platelets), and liver and renal function tests. Recommended radiologic imaging includes chest radiograph, CT, or combined PET/CT, and MRI as indicated (eg, to rule out disease high in the endocervix).[26,27] For detailed imaging recommendations by stage and planned treatment approach, see *Principles of Imaging* in the NCCN Guidelines for Cervical Cancer). Smoking cessation and counseling, as well as HIV testing (especially in younger patients), are recommended. Cystoscopy and proctoscopy are only recommended if bladder or rectal extension is suspected (ie, for ≥ stage IB3). Options for fertility sparing should be considered.

Principles of Staging and Surgery

Clinical Staging

The panel has updated the Guidelines according to the revised 2018 FIGO staging system.[28] The definitions for lesion size and microinvasion for stage I have been revised. For stage IA, the lateral extent of the lesion no longer affects staging. Stage IB is now divided into 3 subgroups as follows: IB1 includes invasive carcinomas ≥5 mm and <2 cm in greatest diameter; IB2 includes tumors 2–4 cm; and IB3 designates tumors ≥4 cm. Consideration of nodal metastasis has also been revised; radiology (r) or pathology (p) findings may be used to assess retroperitoneal nodal involvement and are indicated for stage IIIC. Nodal involvement is now designated as stage IIIC, which is subdivided into IIIC1 for pelvic nodes only, and IIIC2 for para-aortic node involvement. Importantly, lymphovascular space invasion (LVSI) does not alter the FIGO classification. FIGO did not include LVSI because pathologists do not always agree on whether LVSI is present in tissue samples. Some panel members believe that patients with stage IA1 who have extensive LVSI should be treated using stage IB1 guidelines.[28]

Although staging and treatment recommendations by stage have been revised according to FIGO 2018 in the algorithm, much of the data cited within this section utilized the previous 2009 FIGO staging system.[29,30]

Surgical Staging

Pathologic Assessment

Surgicopathologic factors may be used to guide the extent of surgical staging and treatment decisions. Findings from pathologic assessment of the surgical specimen should be carefully documented. Important elements of primary tumor evaluation include tumor site; primary tumor volume (in multiple dimensions); histologic type and grade; stromal invasion; surgical margin status; and the presence of lymphovascular invasion. When resected, the number of lymph nodes with isolated tumor cells, micrometastases, and macrometastases should be recorded. When sentinel lymph node (SLN) mapping is performed, SLNs should undergo ultrastaging for detection of low-volume metastasis; non-sentinel nodes do not require ultrastaging. Other important factors include tumor involvement of tissues/organs such as the parametrium, vaginal cuff, fallopian tubes, ovaries, peritoneum, omentum, and others.

The "Sedlis Criteria," which are intermediate risk factors used to guide adjuvant treatment decisions, include: 1) greater than one-third stromal invasion; 2) capillary lymphatic space involvement; or 3) cervical tumor diameters more than 4 cm.[31] However, potentially important risk factors for recurrence may not be limited to the Sedlis Criteria. Additional risk factors for consideration include tumor histology (eg, adenocarcinoma component)[32,33] and close or positive surgical margins.[34,35]

Recent findings suggest that predictive factors for lymph node metastasis in endocervical adenocarcinoma may differ from squamous cell carcinoma. Data from retrospective studies suggest that the pattern of cervical stromal invasion and presence of LVSI, but not primary tumor size, predict risk of nodal metastasis. Alternative classification systems incorporating stromal invasion pattern have been proposed for adenocarcinoma.[36-38] These systems remain to be validated for clinical use.

Conservative/Fertility-Sparing Approaches

Fertility-sparing approaches may be considered in highly selected patients who have been thoroughly counseled regarding disease risk as well as prenatal and perinatal issues.[39] Consultation with reproductive endocrinology fertility experts is suggested.

Microinvasive disease (FIGO stage IA1 with no LVSI) is associated with an extremely low incidence of lymphatic metastasis,[40-43] and conservative treatment with conization is an option (category 2A) for individuals with no evidence of LVSI. In stage IA1 individuals with evidence of LVSI, a reasonable conservative approach is conization (with negative margins) in addition to SLN mapping algorithm or pelvic lymphadenectomy.

The goal of conization is *en bloc* removal of the ectocervix and endocervical canal; the shape of the cone can be tailored to the size, type, and location of the lesion (ie, narrow, long cone in cases of suspected invasive adenocarcinoma). The panel recommends cold knife conization as the preferred approach to conization. However, LEEP (loop electrosurgical excision procedure) is acceptable as long as adequate margins, proper orientation, and a non-fragmented specimen without electrosurgical artifact can be obtained.[44-49] Endocervical curettage should be added as clinically indicated.

Select patients with stage IA2 and IB1, especially for those with tumors of less than 2 cm in diameter, may be eligible for conservative surgery.[50,51] Radical trachelectomy may offer a reasonable fertility-sparing treatment option for patients with stage IA2, IB1, and select IB2 cervical cancer with lesions that are less than or equal to 2 cm in diameter.[52-54] In a radical trachelectomy, the cervix, vaginal margins, and supporting ligaments are removed while leaving the main body and fundus of the uterus intact.[55] Laparoscopic pelvic lymphadenectomy accompanies the procedure and can be performed with or without SLN mapping (see *Lymph Node Mapping and Dissection* below). Due to their aggressive nature, tumors of

small cell neuroendocrine histology are considered inappropriate for radical trachelectomy.[56] Trachelectomy is also inappropriate for treating gastric type cervical adenocarcinoma and adenoma malignum (minimal deviation adenocarcinoma) due to their diagnostic challenges and potentially aggressive nature.[57]

Vaginal radical trachelectomy (VRT) may be used for carefully selected patients with lesions of 2 cm diameter or less.[58-60] Abdominal radical trachelectomy (ART) provides a broader resection of the parametria[52,60] than the vaginal approach and is commonly used in stage IB1 lesions. Multiple case series have evaluated safety and outcomes with vaginal versus abdominal approaches to radical trachelectomy,[58,61-63] including systematic reviews on VRT[64] and ART.[65] A limited number of studies have specifically examined this approach in patients with tumors between 2 cm and 4 cm in diameter and reported safe oncologic outcomes; however, as expected, more patients in this subgroup will require adjuvant therapy that may reduce fertility.[66-68]

Studies that examined pregnancy in women who underwent radical trachelectomy have provided differing success rates. One case series of 125 patients with cervical cancer who underwent VRT reported 106 pregnancies among 58 women.[59] In a systematic review of 413 women who underwent ART, 113 women attempted pregnancy and 67 (59%) successfully conceived.[62] However, miscarriage and pre-term labor rates were elevated among women who underwent radical trachelectomy.[59,69-71]

Non–Fertility-Sparing Approaches

The Querleu and Morrow surgical classification system[72,73] describes the degree of resection and nerve preservation for radical hysterectomy in three-dimensional planes and updates the previously used Piver-Rutledge classifications.[74] Approaches to hysterectomy include simple/extrafascial hysterectomy (Type A), modified radical hysterectomy (Type B), and radical hysterectomy (Type C).[75,76]

For patients with IA1 disease, cone excision, simple/extrafascial hysterectomy, and modified radical hysterectomy are options. Radical hysterectomy with bilateral pelvic lymph node dissection (with or without SLN mapping) is the preferred treatment approach for patients with FIGO stage IA2, IB1, IB2, and IIA1 cervical cancers. Radical hysterectomy is preferred over simple hysterectomy due to its wider paracervix margin of resection that also includes aspects of the cardinal and uterosacral ligaments, upper vagina, pelvic nodes, and at times, para-aortic nodes. In the United States, definitive chemoradiation is typically preferred over radical surgery for select patients with FIGO IB3 lesions and the vast majority of FIGO stage IIA2 or greater cervical cancers. Abroad, select FIGO IB3-IIB cases may be treated with radical hysterectomy or neoadjuvant chemotherapy followed by radical hysterectomy.

For recurrent or persistent cervical cancers that are confined to the central pelvis (ie, no distant metastasis), pelvic exenteration may be a potentially curative surgical option.[77,78] Discussion of the various approaches to pelvic exenteration are offered by Chi and colleagues,[75] and in the Gynecologic Oncology Group (GOG) Surgical Manual.[76]

Lymph Node Mapping and Dissection

Sentinel Lymph Node Mapping

Recent data suggest that SLN biopsy may be useful for decreasing the need for pelvic lymphadenectomy in patients with early-stage cervical cancer.[79,80]

Prospective studies generally support the feasibility of SLN detection in patients with early-stage cervical cancer and suggest that extensive pelvic lymph node dissection may be safely avoided in a significant proportion of early-stage cases.[79-90]

Meta-analyses of pooled data from SLN mapping studies have generated SLN detection rates of 89% to 92% and sensitivity of 89% to 90%.[91,92] Factors determined to be important for detection included laparoscopy, dual blue dye/radiocolloid tracer approaches, and pathologic assessment using immunohistochemistry. However, based on a recent meta-analysis, indocyanine green (ICG) tracer appears to provide similar overall and bilateral detection rates to the standard dual blue dye/technetium-99 approach.[93] The randomized phase III FILM trial demonstrated that ICG tracer identified more SLNs (overall and bilateral) than blue dye.[94]

Study data also highlight limited sensitivity of this approach and potential to miss SLN micrometastases and isolated tumor cells using intraoperative assessment (ie, frozen section or imprint cytology).[82,86,88] The sensitivity of this approach appears to be better in patients with tumors equal to or less than 2 cm in diameter.[79,81,83,95] Ultrastaging of detected SLNs has been shown to provide enhanced detection of micrometastases.[84,85]

The SENTICOL longitudinal study demonstrated the utility of SLN mapping to uncover unusual lymph drainage patterns.[83,96] It also highlighted limited agreement between lymphoscintigraphy and intraoperative SLN mapping.[96] Additionally, this study revealed that bilateral SLN detection and biopsy provided a more reliable assessment of sentinel nodal metastases and led to fewer false negatives than unilateral SLN biopsy.[80] Generally, research supports ipsilateral lymphadenectomy if no sentinel nodes are detected on a given side of the pelvis as outlined in the SLN mapping algorithm.[79,80,97]

Based on these collective data, the panel recommends consideration of SLN mapping algorithm and emphasizes that best detection and mapping results are in tumors of less than 2 cm diameter. Adherence to the SLN mapping algorithm is important; surgeons should perform side-specific nodal dissection in any cases of failed mapping and remove all suspicious or grossly enlarged nodes regardless of SLN mapping.[79]

Para-Aortic Lymph Node Assessment

Studies of the incidence and distribution of lymph node metastases in women with stage IB to IIB cervical cancers suggest that para-aortic lymph node involvement is closely tied to the presence of pelvic lymph node metastases, larger primary tumor size (>2 cm), and metastasis to the common iliac nodes.[98,99]

Analysis of outcomes data from 555 women who participated in GOG trials (GOG 85, GOG 120, and GOG 165) revealed a more positive prognosis for patients who underwent surgical exclusion of para-aortic lymph node involvement versus those who underwent radiographic determination of para-aortic node involvement.[100] One study examined the efficacy of extending the radiation therapy (RT) field to the para-aortic region in patients with para-aortic lymph node involvement, and showed therapeutic benefit especially in patients with small-volume nodal disease.[101] A randomized controlled trial examining surgical versus radiologic staging and treatment of para-aortic lymph node involvement is ongoing.[102]

The panel recommends para-aortic lymph node dissection for patients with ≥ stage IB1 disease.

Minimally Invasive Surgical Approaches

The standard and historical approach for radical hysterectomy is with an open abdominal approach.

Previous iterations of the Guidelines had indicated that radical hysterectomy could be performed either via open laparotomy or minimally invasive surgery (MIS) laparoscopic approaches, using either conventional or robotic techniques. Data from previous retrospective reviews and prospective observational studies demonstrated oncologic outcomes following conventional laparoscopic radical hysterectomy that were comparable to open abdominal approaches after 3 to 6 years of follow-up.[103-106] Similarly, multicenter retrospective reviews and matched

cohort studies showed comparable oncologic outcomes (disease recurrence and survival rates) for open abdominal and robotic radical hysterectomy after 3 to 5 years of follow-up.[106-109] Additionally, a systematic review and meta-analysis of data from 26 studies found that laparoscopic and robotic radical hysterectomy approaches appeared to provide equivalent intraoperative and short-term postoperative outcomes.[110]

However, several key contemporary reports have questioned the presumed therapeutic equivalency of open vs MIS approaches. A recently published prospective randomized trial demonstrated that minimally invasive radical hysterectomy was associated with lower rates of DFS and OS than open abdominal radical hysterectomy.[111] This phase III LACC trial (NCT00614211) was designed to provide a definitive comparison of outcomes data in patients with early-stage cervical cancer undergoing total abdominal radical hysterectomy (TARH) or total laparoscopic radical hysterectomy/total robotic radical hysterectomy. At closure, 319 patients had received MIS (84% laparoscopy, 16% robotic) and 312 patients underwent a TARH. Ninety-two percent of participants in both surgical arms had stage IB1 disease. MIS was associated with lower rate of disease-free survival than open surgery (3-year DFS, 91.2% vs. 97.1%; HR 3.74; 95% CI, 1.63 to 8.58), as well as a decrease in overall survival (3-year OS, 93.8% vs. 99.0%; HR 6.00; 95% CI, 1.77 to 20.30).[111] MIS did not meet predetermined non-inferiority criteria compared with standard-of-care laparotomy (P = 0.88).

Two other recent epidemiologic studies also demonstrated that minimally invasive radical hysterectomy was associated with shorter OS than open surgery among women with stage IA2-IB1 cervical cancer.[112,113] Melamed et al reported on a SEER-based cohort study that compared females with stage IA2 or IB1 cervical cancer who underwent laparotomy (n = 1236) or MIS (n = 1225).[112] Four-year mortality was higher among patients undergoing MIS versus laparotomy (9.1% versus 5.3%, P = 0.002). Relative survival rates were stable prior to the adoption of MIS techniques (2000-2006), but a significant decline was noted in the years following adoption. Margul et al examined National Cancer Database data from 2010 to 2013 to compare outcomes of patients with stage IB1 cervical cancer who underwent radical hysterectomy performed by open abdominal versus MIS approaches.[114] Although MIS was associated with decreased surgical morbidity and costs, patients with tumor sizes ≥2 cm who underwent MIS had decreased 5-year survival compared to those undergoing open radical hysterectomy (81.3% vs. 90.8%, P < .001).[114]

These most recent findings stand in contradiction to the earlier referenced series that had suggested therapeutic equivalency of MIS compared to open approaches along with the MIS-associated potential advantages of decreased hospital stay and more rapid patient recovery.[106,107,109,110,115-118]

Given the recently presented findings of poorer oncologic outcomes and survival with the MIS techniques compared to open laparotomy, women should be carefully counseled about the oncologic risks and potential short-term benefits of the different surgical approaches.

Primary Treatment

Note: Recommendations by stage are based on the revised 2018 FIGO staging by Bhatla et al.[28] However, trial data cited within this section primarily utilized the previous 2009 FIGO staging system.[29,30]

The primary treatment of early-stage cervical cancer is either surgery or RT. Surgery is typically reserved for early-stage disease, fertility-preservation, and smaller lesions, such as stage IA, IB1, IB2, and selected IIA1.[119] The panel agrees that concurrent chemoradiation is generally the primary treatment of choice for stages IB3 to IVA disease based on the results of 5 randomized clinical trials.[120,121] Chemoradiation can also be used for patients who are not candidates for hysterectomy. Although few

studies have assessed treatment specifically for adenocarcinomas, they are typically treated in a similar manner to squamous cell carcinomas.[122-124]

Pelvic RT or chemoradiation will invariably lead to ovarian failure in premenopausal women.[125] To preserve intrinsic hormonal function, ovarian transposition may be considered before pelvic RT for select women younger than 45 years of age with squamous cell cancers.[126,127]

Important Phase III Clinical Trials Underpinning Treatment Recommendations

A randomized Italian study compared RT alone versus radical hysterectomy and lymph node dissection in patients with clinical early-stage disease (stage IB–IIA).[128] Adjuvant RT was given to those with parametrial extension, less than 3 cm of uninvolved cervical stroma, positive margins, 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.

Concurrent chemoradiation, using platinum-containing chemotherapy (cisplatin alone [preferred] or cisplatin/fluorouracil), is the treatment of choice for stages IB3, II, III, and IVA disease based on the results of randomized clinical trials.[129-134] These trials have shown that the use of concurrent chemoradiation results in a 30% to 50% decrease in the risk of death compared with RT alone. Although the optimal concurrent chemotherapy regimen to use with RT requires further investigation, these trials clearly established a role for concurrent cisplatin-containing chemoradiation. Based on these data, the NCI issued an alert stating that strong consideration should be given to using chemoradiation instead of RT alone for invasive cervical cancer.[134] Long-term follow-up of 3 of these trials has confirmed that concurrent cisplatin-containing chemoradiation improves progression-free survival (PFS) and overall survival when compared with RT with (or without) hydroxyurea.[135-137] A recent meta-analysis reported that chemoradiotherapy leads to a 6% improvement in 5-year survival (hazard ratio [HR], 0.81; $P < .001$).[138] A large, population-based registry analysis in Canada (n = 4069) confirmed that chemoradiotherapy improved outcomes when compared with RT alone.[139]

Although chemoradiation is tolerated, acute and long-term side effects have been reported.[138,140,141] Concurrent single-agent cisplatin chemoradiation may be preferred over cisplatin/fluorouracil chemoradiation due to lesser toxicity.[121,142] Concurrent carboplatin (preferred if cisplatin intolerant) or non-platinum chemoradiation regimens are options for patients who may not tolerate cisplatin-containing chemoradiation.[138,143-148] Carboplatin has been added to the Guidelines as a preferred radiosensitizing agent for patients who are cisplatin intolerant.

Note that when concurrent chemoradiation is used, the chemotherapy is typically given when the external-beam pelvic radiation is administered.[121] The panel believes that using “systemic consolidation” (ie, adding chemotherapy after chemoradiation) should only be used in clinical trials (eg, OUTBACK [ANZGOG-0902/GOG 274, NCT01414608] and RTOG 724 [NCT00980954]).[149]

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. A fertility-sparing algorithm may be applied for select patients with stage IA, IB1, and certain cases of IB2 disease. Fertility-sparing surgery is generally not recommended for patients with small cell neuroendocrine tumors, gastric type adenocarcinoma, or adenoma malignum (minimal deviation adenocarcinoma) because of its high-risk nature and a paucity of data.

Stage IA1 Disease

Recommended options for stage IA1 disease depend on the results of cone biopsy and whether patients 1) want to preserve their fertility; 2) are medically operable; or 3) have LVSI. The extent of the lymph node dissection depends on whether pelvic nodal disease and/or LVSI are present and the size of the tumors. SLN mapping can be considered.

Fertility-Sparing

For patients who desire fertility preservation, cone biopsy with or without pelvic lymph node dissection is recommended.[90,150,151]

The goal of cone biopsy is margins that are negative for invasive disease and high-grade squamous intraepithelial lesion (HSIL). For patients with negative margins after cone biopsy and no findings of LVSI, observation may be an option if fertility preservation is desired. For patients with positive margins after cone biopsy, options include repeat cone biopsy to better evaluate depth of invasion (to rule out stage IA2/IB disease) or a radical trachelectomy. In studies of patients who had positive margins after conization, predictors of residual disease included positive endocervical curettage, combined endocervical margin and endocervical curettage, and volume of disease.[34,152,153]

For patients with stage IA1 disease with LVSI, conization (with negative margins) plus laparoscopic pelvic SLN mapping/lymphadenectomy is a reasonable strategy. In addition, these patients may also be treated with a radical trachelectomy and SLN mapping/pelvic lymph node dissection.[63,154-157]

After childbearing is complete, hysterectomy can be considered for patients who have had either radical trachelectomy or a cone biopsy for early-stage disease if they have chronic, persistent HPV infection, they have persistent abnormal Pap tests, or they desire this surgery.

For young (<45 years) premenopausal women with early-stage squamous cell carcinoma who opt for ovarian preservation (ie, hysterectomy only), the rate of ovarian metastases is low.[158,159]

Non–Fertility-Sparing

For medically and technically operable patients with stage IA1 disease who do not desire fertility preservation, extrafascial (ie, simple) hysterectomy is commonly recommended for patients without LVSI and with either negative margins after cone biopsy or with positive margins for dysplasia. For patients with positive margins for carcinoma, modified radical hysterectomy is recommended with SLN mapping/pelvic lymph node dissection (category 2B for node dissection). SLN mapping can be considered. Physicians can also consider repeat cone biopsy to better evaluate depth of invasion. If LVSI is present, then modified radical hysterectomy with SLN mapping/pelvic lymph node dissection is recommended. For patients with negative margins after cone biopsy, observation is recommended for those who are medically inoperable or those who refuse surgery.

Stage IA2 Disease

Recommendations for stage IA2 depend upon whether a patient wishes to preserve her fertility and if the disease is medically operable.

Fertility-Sparing

For patients who wish to preserve their fertility, radical trachelectomy and pelvic lymph node dissection is recommended. SLN mapping can also be considered. Cone biopsy followed by observation is another option if the margins are negative and pelvic lymph node dissection is negative.

Non–Fertility-Sparing

For medically operable patients who do not desire fertility preservation, recommended treatment includes either surgery or RT. The recommended surgical option is radical hysterectomy and bilateral pelvic lymph node

dissection. SLN mapping can also be considered. Para-aortic node dissection is indicated for patients with known or suspected pelvic nodal disease. Less radical surgical approaches for patients with stage IA2 disease are the subject of ongoing investigation.[153,160]

Pelvic external beam RT (EBRT) with brachytherapy (traditionally 70–80 Gy to total point A dose) is a treatment option for patients who are medically inoperable or who refuse surgery.[161] 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, fractionation, and size of target volume or on biologic equivalence calculations when using high dose-rate brachytherapy.

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. Fertility-sparing surgery is only recommended for patients with stage IB1 or select cases of stage IB2 disease (see next section). A combined PET/CT scan can be performed to rule out extrapelvic disease before deciding how to treat these patients. The GOG considers that surgical staging is an option for patients with advanced cervical cancer. Radiologic imaging is recommended for assessing stage IB3 and IIA2 tumors (see *Principles of Imaging* in the NCCN Guidelines for Cervical Cancer).

Stage IB1: Fertility-Sparing

For patients who desire fertility preservation, radical trachelectomy and pelvic lymph node dissection with (or without) para-aortic lymph node dissection is an option for stage IB1 and select cases of IB2 disease, but typically only for tumors 2 cm or less in the NCCN Guidelines for Cervical Cancer].[52,154-157,162] SLN mapping can also be considered. Tumors that are 2 to 4 cm have to be carefully selected for a fertility-sparing approach as many of these patients may require postoperative adjuvant therapy due to pathologic risk factors (eg, Sedlis Criteria or positive nodes). However, some surgeons suggest that a 2cm cutoff may be used for vaginal trachelectomy, whereas a 4cm cutoff may be used for abdominal trachelectomy.[163] In one study, oncologic outcomes were similar after 4 years when comparing radical trachelectomy with radical hysterectomy for patients with stage IB1 cervical carcinoma.[52] Stage IB1 or IB2 small cell neuroendocrine histology, gastric type adenocarcinoma, and adenoma malignum are not considered suitable for fertility-sparing surgery.

Stage IB and IIA: Non–Fertility-Sparing

For stage IB1, IB2, and IIA1 disease, primary surgery consists of radical hysterectomy plus bilateral pelvic lymph node dissection (category 1), with (or without) para-aortic lymph node dissection (category 2B for para-aortic lymph node dissection).[128,164] SLN mapping can also be considered for stages IB1, IB2, and IIA1. Panel members feel that surgery is the most appropriate option for patients with stage IB1, IB2, or IIA1 disease, whereas concurrent chemoradiation is the most appropriate option for those with stage IB3 or IIA2 disease based on randomized trials.[128-130,132,133] Thus, the primary surgical option is a category 1 recommendation for patients with stage IB1, IB2, or IIA1 disease; however, primary chemoradiation is the category 1 recommendation for those with stage IB3 or IIA2 disease. Para-aortic node dissection may be performed for patients with larger tumors and suspected or known pelvic nodal disease. Some panel members feel that a pelvic lymph node dissection should be performed first and if negative, then the radical hysterectomy should be performed. If the lymph nodes are positive, then the hysterectomy should be abandoned; these patients should undergo chemoradiation. For patients with stage IBI, IB2, or IIA tumors (including those who are not candidates for hysterectomy), another option is combined pelvic EBRT and brachytherapy with (or without) concurrent platinum-containing chemotherapy. Preferred radiosensitizing regimens include cisplatin or

carboplatin for patients who are cisplatin-intolerant. Other recommended regimens include cisplatin/fluorouracil. 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, IB2, or IIA1 disease. Careful consideration of the risk/benefit ratio should be undertaken in these patients with smaller tumors.

For patients with clinical stage IB3 or IIA2 tumors who are treated with definitive radiation, concurrent cisplatin-containing chemotherapy has been shown to significantly improve patient survival. The panel recommends definitive EBRT with concurrent platinum-containing chemotherapy and brachytherapy (traditionally 75–80 Gy to total point A dose). Again, treatment should be modified based on normal tissue tolerance, fractionation, and size of target volume. Primary chemoradiation has a category 1 recommendation.[129,130]

For stage IB3 or IIA2 tumors, the panel had a major disagreement about recommending adjuvant hysterectomy (category 3) (also known as completion surgery) after primary chemoradiation.[129] Adjuvant hysterectomy after RT has been shown to improve pelvic control, but not overall survival, and is associated with increased morbidity.[165] A recent Cochrane review examined whether the addition of hysterectomy to standard non-surgical treatments benefitted women with locally advanced cervical cancer, finding insufficient data to demonstrate a survival benefit associated with surgery.[166] The morbidity is higher after completion surgery, but this may be reduced using a laparoscopic technique.[167-170] Although routine completion hysterectomy is not typically performed, this approach may be considered in patients whose extent of disease or uterine anatomy precludes adequate coverage by brachytherapy.

Advanced Disease

This category has traditionally included patients with stage IIB to IVA disease (ie, locally advanced disease). However, many oncologists now include patients with IB3 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 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, especially for evaluation of nodal or extrapelvic tumor (see *Principles of Imaging* in the NCCN Guidelines for Cervical Cancer). MRI is useful to describe local disease extent and assist in radiation treatment planning. However, needle biopsy of extrauterine abnormality can be considered for questionable imaging findings. Surgical staging (ie, extraperitoneal or laparoscopic lymph node dissection) is also an option (category 2B) for these patients.[171] Surgical staging may also detect microscopic nodal disease that is not discernable with radiologic imaging.[172]

For patients without nodal disease or with disease limited to the pelvis only through surgical staging, treatment consists of pelvic EBRT with concurrent platinum-containing chemotherapy and brachytherapy (category 1).[120,121,130,132-134,173] Currently, acceptable concurrent platinum-containing regimens include either weekly cisplatin (preferred), carboplatin (preferred if cisplatin intolerant), or cisplatin/fluorouracil, given every 3 to 4 weeks during RT. An international phase III randomized trial reported that concurrent cisplatin/gemcitabine and EBRT followed by 2 additional cycles of cisplatin/gemcitabine after RT improved PFS and overall survival when compared with a standard regimen of concurrent cisplatin with pelvic EBRT.[174] However, this trial is controversial because of changes in its statistical design and because the reported superior regimen of concurrent cisplatin/gemcitabine and EBRT has unresolved toxicity issues.[174-177]

However, for patients with positive para-aortic and pelvic lymph nodes by imaging, imaging workup for metastatic disease is recommended. Extended-field EBRT, concurrent platinum-containing chemotherapy, and brachytherapy is recommended. Patients with positive para-aortic lymph nodes who are positive for distant metastases are treated with systemic chemotherapy with (or without) individualized EBRT.[178]

Metastatic Disease

For patients who present with distant metastatic disease (ie, stage IVB), primary treatment is often platinum-containing chemotherapy (see *Therapy for Metastatic Disease* in this Discussion). In these situations, individualized EBRT may be considered for control of pelvic disease and other symptoms.[178]

Adjuvant Treatment

Adjuvant treatment is indicated after radical hysterectomy depending on surgical findings and disease stage. Observation is appropriate for patients with stage IA2, IB or IIA1 disease who have negative nodes, negative margins, negative parametria, and no cervical risk factors after radical hysterectomy (Sedlis Criteria). However, adjuvant treatment is indicated after radical hysterectomy if pathologic risk factors are discovered.

Pelvic EBRT is recommended (category 1) with (or without) concurrent platinum-containing chemotherapy (category 2B for chemotherapy) for patients with stage IA2, IB, or IIA1 disease who have *negative* lymph nodes after surgery but have large primary tumors, deep stromal invasion, and/or LVSI.[31,179-182] Recommended radiosensitizing regimens include cisplatin (preferred), carboplatin (preferred if cisplatin intolerant), or cisplatin/fluorouracil.

Adjuvant pelvic RT alone versus no further therapy was tested in a randomized trial (GOG 92) of selected patients with node-negative stage IB carcinoma of the cervix after hysterectomy and pelvic lymphadenectomy.[31] Patients were considered to have "intermediate-risk" disease and were eligible for this trial if they had at least 2 of the following risk factors (commonly referred to as Sedlis Criteria): 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 adjuvant RT versus 79% for the no-adjuvant-treatment group. After long-term follow-up (12 years), an updated analysis confirmed that adjuvant pelvic RT increased PFS; a clear trend towards improved overall survival was noted (P = .07).[179] The role of concurrent cisplatin/RT in patients with intermediate-risk disease is currently being evaluated in an international phase III randomized trial (GOG 263, NCT01101451).

Potentially important risk factors for recurrence may not be limited to the Sedlis Criteria" (ie, stromal invasion, LVSI, primary tumor size). Additional risk factors for consideration include tumor histology (eg, adenocarcinoma component)[32,33] and close or positive surgical margins.[34,35]

Postoperative pelvic EBRT with concurrent platinum-containing chemotherapy (category 1)[131] with (or without) vaginal brachytherapy is recommended for patients with positive pelvic nodes, positive surgical margin, and/or positive parametrium; these patients are considered to have "high-risk" disease. Vaginal brachytherapy may be a useful boost for those with positive vaginal mucosal margins. Adjuvant concurrent chemoradiation significantly improves overall survival for patients with high-risk, early-stage disease (those with positive pelvic nodes, parametrial extension, and/or positive margins) who undergo radical hysterectomy and pelvic lymphadenectomy.[131] The Intergroup trial 0107/GOG 109 showed a statistically significant benefit of adjuvant pelvic radiation with concurrent cisplatin and fluorouracil 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.[131] A recent study re-evaluated these findings from GOG 109 in a population-based cohort (n = 3053) in the National Cancer Database, confirming the survival benefit of adjuvant chemoradiation but suggesting that this benefit may be best realized in patients with lymph node involvement.[183]

Depending on the results of primary surgery, imaging may be recommended to determine whether distant metastases are present. In women who are positive for distant metastases, perform biopsy of suspicious areas as indicated. For patients without distant metastases, recommended treatment is extended-field EBRT (including pelvic and para-aortic lymph nodes) with concurrent platinum-containing chemotherapy and with (or without) brachytherapy. Recommended radiosensitizing regimens include cisplatin (preferred), carboplatin (preferred if cisplatin intolerant), or cisplatin/fluorouracil. For patients with distant metastases, recommended treatment is systemic chemotherapy with (or without) individualized EBRT.[178]

Although neoadjuvant chemotherapy followed by surgery has been used in areas where RT is not available, data suggest no improvement in survival when compared with surgery alone for early-stage cervical cancer[184-186] or locally advanced cervical cancer.[187,188] A meta-analysis of data on patients with stage IB1 to IIA cervical cancer found that neoadjuvant chemotherapy may reduce the need for adjuvant RT by decreasing tumor size and metastases, but indicated no overall survival benefit.[188] However, data from a second meta-analysis suggested that response to neoadjuvant chemotherapy was a strong prognostic factor for PFS and overall survival.[189,190] Outside of the clinical trial, the panel does not recommend the use of neoadjuvant chemotherapy.

Surveillance

The panel agrees with the new Society of Gynecologic Oncology's recommendations for post-treatment surveillance.[191] The recommended surveillance is based on the patient's risk for recurrence and personal preferences. History and physical examination is recommended every 3 to 6 months for 2 years, every 6 to 12 months for another 3 to 5 years, and then annually. Patients with high-risk disease can be assessed more frequently (eg, every 3 months for the first 2 years) than patients with low-risk disease (eg, every 6 months).

Annual cervical/vaginal cytology tests can be considered as indicated for detection of lower genital tract dysplasia (eg, for those who have had fertility-sparing surgery). 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 or II cervical cancer who were asymptomatic after treatment.[191-193] Noting the inherent differences between these patients and the general screening population, the panel does not recommend workup of low-grade squamous dysplasia detected during surveillance, but suggests that patients should follow up with a provider with specific expertise in this area. 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.[194]

For patients with stage I disease, follow-up imaging should be based on symptomatology and clinical concern for recurrent/metastatic disease, such as abnormal physical exam finding or new pelvic, abdominal, or pulmonary symptoms. If fertility-sparing treatment was provided, pelvic MRI should be considered 6 months after surgery and yearly for 2 to 3 years. PET/CT can be considered if metastasis is suspected.[195] For patients with stage II disease or greater, PET/CT (preferred) or CT should be performed within 3 to 6 months of completing therapy; pelvic MRI is

optional. Additional imaging should be guided by symptomatology and clinical concern for recurrent/metastatic disease. Specific indications and recommendations for surveillance imaging are detailed in *Principles of Imaging* in the NCCN Guidelines for Cervical Cancer.[191,196-204]

Many other tests remain optional based on clinical indications, such as semiannual CBCs, blood urea nitrogen (BUN), and serum creatinine determinations. 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).[205]

Patient education regarding symptoms suggestive of recurrence is recommended (eg, vaginal discharge; weight loss; anorexia; pain in the pelvis, hips, back, or legs; persistent coughing). Patients should also be counseled on healthy lifestyle, obesity, nutrition, exercise, sexual health, hormone replacement therapy, and potential long-term and late effects of treatment. Smoking cessation and abstinence should be encouraged.[191] See the NCCN Guidelines for Survivorship, the NCCN Guidelines for Smoking Cessation, and http://www.cancer.org/treatment/survivorship).

Patients who have received RT for cervical cancer may experience vaginal stenosis and dryness and should receive education on important issues regarding sexual health and vaginal health. Providers should inform patients about regular vaginal intercourse and/or vaginal dilator use and on the use of vaginal moisturizers/lubricants (eg, estrogen creams). Anecdotal evidence suggests that vaginal dilators may be used to prevent or treat vaginal stenosis.[206] Dilator use can start 2 to 4 weeks after RT is completed and can be performed indefinitely.

Cervical cancer survivors are at risk for second cancers.[207] Data suggest that patients who undergo RT for pelvic cancers are at risk for radiation-induced second cancers, especially at radiated sites near the cervix (eg, colon, rectum/anus, urinary bladder); therefore, careful surveillance is appropriate for these patients.[208,209]

Therapy for Relapse

Recurrences should be proven by biopsy before proceeding to treatment planning for recurrent disease.

Locoregional Therapy

Patients with a localized recurrence of cervical cancer after initial treatment may be candidates for radical retreatment; options include: 1) RT and/or chemotherapy; or 2) surgery.[120,210] After treatment for relapse, long-term, disease-free survival rates of approximately 40% have been reported in some situations.[211]

For patients who experience locoregional recurrences who have not undergone previous RT or who experience recurrences outside of the previously treated RT field, therapy for relapse includes tumor-directed EBRT with (or without) chemotherapy and/or brachytherapy; surgical resection can be considered if feasible. Typically, the chemoradiation for recurrence uses cisplatin or carboplatin as single agents or cisplatin/fluorouracil.[212,213] However, in those patients who have relapsed soon after completing initial chemoradiation with these regimens, alternative concurrent chemotherapy agents such as carboplatin, paclitaxel, and gemcitabine may be considered.

Patients with central pelvic recurrent disease after RT should be evaluated for pelvic exenteration, with (or without) intraoperative RT (IORT), although IORT is category 3.[214-221] Surgical mortality is generally 5% or less, with survival rates approaching 50% in carefully selected patients.[217] Concomitant measures with these radical procedures include adequate rehabilitation programs dealing with the psychosocial and psychosexual consequences of the surgery as well as reconstructive procedures.[216,222-224]

Although exenteration is the common surgical approach in postradiation patients with isolated central pelvic relapse, radical hysterectomy or brachytherapy may be an option in carefully selected patients with small central lesions (<2 cm).

For patients with noncentral recurrent disease, options include EBRT with (or without) chemotherapy, resection with (or without) IORT (category 3 for IORT), or chemotherapy (see the NCCN Guidelines for Palliative Care), or participation in a clinical trial. Patients who experience recurrence after second-line definitive therapy, either surgery or RT, have a poor prognosis. They can be treated with systemic therapy or best supportive care, or can be enrolled in a clinical trial.

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 amendable to local treatment, occasional long-term survival has been reported with: 1) surgical resection with (or without) EBRT; 2) local ablative therapies with (or without) EBRT; or 3) EBRT with (or without) chemotherapy. Systemic adjuvant chemotherapy can be considered. For example, patients who may benefit from aggressive local therapy for oligometastatic disease include those with nodal, lung, liver, or bone metastases.[225,226] Following local therapy, additional adjuvant chemotherapy can be considered. For most other patients with distant metastases, an appropriate approach is a clinical trial, chemotherapy, or best supportive care (see NCCN Guidelines for Palliative Care).

The palliation of pelvic recurrences in heavily irradiated sites that are not amenable to local pain control techniques or to surgical resection is difficult. These sites are generally not responsive to chemotherapy. Adequately palliating the complications of pain and fistulae from these recurrences is clinically challenging (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.[178,227,228]

Chemotherapy is often recommended for patients with extrapelvic metastases or recurrent disease who are not candidates for RT or exenterative surgery. Patients whose disease responds to chemotherapy may have relief from pain and other symptoms. 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).[229,230] However, responses to chemotherapy are often of short duration and survival is rarely increased.

First-Line Combination Chemotherapy

Cisplatin has been considered the most effective agent for metastatic cervical cancer.[231] 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.[229,230] Cisplatin-containing combination chemotherapy regimens, such as cisplatin/paclitaxel/bevacizumab (preferred regimen, category 1), cisplatin/paclitaxel (preferred, category 1), and cisplatin/topotecan (category 2A), have been extensively investigated in clinical studies.[229,230,232-235] A randomized phase III study (GOG 169) in 264 patients compared cisplatin/paclitaxel versus cisplatin alone for metastatic, recurrent, or persistent cervical cancer. Patients receiving the 2-drug combination had a higher response rate (36% vs. 19%) and improved PFS (4.8 months vs. 2.8 months; $P > .001$) compared to single-agent cisplatin, although no improvement was seen in median survival.[229] Patients who responded to cisplatin/paclitaxel had a significant improvement in quality of life.

Another randomized phase III study (GOG 179) in 294 patients investigated cisplatin/topotecan versus cisplatin alone for recurrent or persistent cervical cancer. The topotecan combination regimen was shown to be superior to single-agent cisplatin with respect to overall response rate (27% vs. 13%, *P* = .004), PFS (4.6 months vs. 2.9 months; *P* = .014), and median survival (9.4 months vs. 6.5 months; *P* =.017).[230] The FDA (U.S. Food and Drug Administration) has approved cisplatin/topotecan for advanced cervical cancer. However, the cisplatin/paclitaxel or carboplatin/paclitaxel regimens are less toxic and easier to administer than cisplatin/topotecan.[236]

A phase III trial (GOG 204) compared 4 cisplatin-doublet regimens (cisplatin/paclitaxel, cisplatin/topotecan, cisplatin/gemcitabine, and cisplatin/vinorelbine) in 513 patients with advanced metastatic or recurrent cancer.[234] The trial was closed early based on futility analysis, because it was apparent that the cisplatin/topotecan, cisplatin/gemcitabine, and cisplatin/vinorelbine regimens were not superior to the control arm of cisplatin/paclitaxel. No significant differences in overall survival were seen; however, the trends for response rate, PFS, and overall survival (12.9 months vs. 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.

A recent randomized phase III trial (GOG 240) studied the addition of bevacizumab to combination chemotherapy regimens (cisplatin/paclitaxel/bevacizumab or topotecan/paclitaxel/bevacizumab) in 452 patients in the first-line setting of metastatic, persistent, or recurrent cervical cancer. Analysis of pooled data from the two chemotherapy regimens revealed significant improvements in overall survival among patients receiving bevacizumab (16.8 months vs. 13.3 months; *P* =.007).[235] While topotecan/paclitaxel (category 2A) was not shown to be superior to cisplatin/paclitaxel, it may be considered as an alternative in patients who are not candidates for cisplatin.[235] While bevacizumab led to higher toxicity (eg, hypertension, thromboembolic events, gastrointestinal fistula), it was not associated with a statistically significant decrease in patient-reported quality of life (*P* = .27).[237] A 2017 systemic review and meta-analysis of data from 19 trials of systemic therapy for patients with recurrent, persistent, or metastatic cervical cancer found a trend towards improved OS for the addition of bevacizumab to cisplatin/paclitaxel or topotecan/paclitaxel when compared with all other non-bevacizumab–containing chemotherapy regimens.[238] Both bevacizumab-containing regimens are included as preferred category 1 options for treating persistent, recurrent, or metastatic cervical cancer.

Recently published data from a phase III randomized trial (JCOG0505) suggested that carboplatin/paclitaxel was non-inferior to cisplatin/paclitaxel in 253 women with metastatic or recurrent cervical cancer.[239] Many physicians use carboplatin/paclitaxel because of ease of administration and tolerability.[240] Results from JCOG0505 showed that the carboplatin/paclitaxel (TC) regimen was non-inferior to cisplatin/paclitaxel (TP) in terms of median overall survival (18.3 months for TP vs. 17.5 months for TC; HR = 0.994 (90% CI, 0.79–1.25); *P* = .032) and non-hospitalization periods were significantly longer for patients receiving TC.[239] However, among patients who had not received prior cisplatin, OS for TC and TP was 13.0 and 23.2 months, respectively (HR = 1.571; 95% CI, 1.06–2.32).[239] Based on these data, the panel recommends carboplatin/paclitaxel as a preferred category 1 option for patients who have received prior cisplatin therapy (category 2A for other indications).

A recent systematic review of the data on cisplatin/paclitaxel and carboplatin/paclitaxel regimens also suggested that lower toxicity carboplatin-based regimens appear to be an equally effective alternative to cisplatin-containing regimens for treating recurrent or metastatic cervical

cancer.[241] Based on the collective findings from GOG 240 and JGOG0505, the panel has opted to include carboplatin/paclitaxel/bevacizumab as an additional preferred regimen for recurrent or metastatic cervical cancer (category 2A). Based on the previous studies, cisplatin/paclitaxel and carboplatin/paclitaxel have become the most widely used systemic regimens for metastatic or recurrent cervical cancer. However, for patients who may not be candidates for taxanes, cisplatin/topotecan remains a reasonable alternative regimen.[230] In 2019, the panel voted to remove cisplatin/gemcitabine as a first-line combination therapy option. Non-platinum regimens are also being studied and may be considered in patients who cannot tolerate platinum-based chemotherapy.[242]

Single Agents

Cisplatin is generally regarded as the most active agent and is recommended as the preferred first-line single-agent chemotherapy option for recurrent or metastatic cervical cancer; reported response rates are approximately 20% to 30%, with an occasional complete response.[229,231,243,244] Overall survival with cisplatin is approximately 6 to 9 months. Both carboplatin and paclitaxel have each been reported to be tolerable and efficacious and are also possible first-line single-agent chemotherapy options.[245-248] 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.

Pembrolizumab has been added as a preferred regimen for second-line option for treating PD-L1–positive or MSI-H/dMMR cervical tumors (category 2A). [249-251] Other recommended agents (all category 2B) that have shown responses or prolongation of PFS and may be useful as second-line therapy include bevacizumab,[252] albumin-bound paclitaxel (ie, nab-paclitaxel),[253] docetaxel,[254] fluorouracil,[255] gemcitabine,[256] ifosfamide,[257,258] irinotecan,[259] mitomycin,[260] pemetrexed,[261] topotecan,[262,263] and vinorelbine.[264]

Other Agents

Targeted therapies and biologics have an established role for selected cases of cervical cancer. Pembrolizumab and bevacizumab have been included in the Guidelines for treating recurrent or metastatic disease. Use of these and other targeted or biologic agents remain an active area of investigation.

Drug Reactions

Virtually all drugs have the potential to cause adverse reactions, either during or after infusion.[265] 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 (ie, skin reactions, cardiovascular reactions, respiratory or throat tightness), but more severe allergic reactions (ie, life-threatening anaphylaxis) can occur.[266,267] In addition, patients can have severe infusion reactions and mild allergic reactions. Infusion reactions are more common with paclitaxel.[268] Allergic reactions (ie, true drug allergies) are more common with platinum agents (eg, cisplatin).[268,269]

Management of drug reactions is discussed in the NCCN Guidelines for Ovarian Cancer.[268] Importantly, patients who experienced severe life-threatening reactions should not receive the implicated agent again unless evaluated by an allergist or specialist in drug desensitization. If a mild allergic reaction previously occurred and it is appropriate to re-administer the drug, a desensitization regimen is recommended even if the symptoms have resolved. Various desensitization regimens have been published and should be followed.[269-271] Patients must be desensitized with each infusion if they have had a previous reaction. Almost all patients can

be desensitized.[265] To maximize safety, patients should be desensitized in the intensive care unit.[265]

Best Supportive Care

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

Incidental Cervical Cancer

Invasive cervical carcinoma is sometimes found incidentally after extrafascial hysterectomy. Workup for these patients includes history and physical examination, CBC (including platelets), and liver and renal function tests. Recommended radiologic imaging includes chest radiography, CT, or combined PET/CT; MRI may be performed if indicated to rule out gross residual disease. However, imaging is optional for patients with stage IB1 or smaller tumors.

No definitive data are available to guide the appropriate adjuvant treatment of these patients. Surveillance is recommended for patients with stage IA1 cervical cancer who do not have LVSI. For patients with either stage IAI with LVSI, stage IA2/IB disease, or positive margins/gross residual disease, the panel believes that a reasonable treatment schema 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 platinum-containing chemotherapy with (or without) individualized brachytherapy is recommended. Recommended radiosensitizing regimens include cisplatin (preferred), carboplatin (preferred if patient is cisplatin-intolerant), or cisplatin/fluorouracil.

If margins or imaging is negative in stage IA2 or greater tumors, options include: 1) pelvic RT with brachytherapy, with (or without) concurrent platinum-containing chemotherapy; or 2) if Sedlis Criteria are not met on the hysterectomy specimen, consideration of complete parametrectomy, upper vaginectomy, and pelvic lymph node dissection with (or without) para-aortic lymph node sampling (category 2B for para-aortic lymph node sampling). Typically, observation is recommended for patients with negative lymph nodes and no residual disease. However, chemoradiation with (or without) vaginal brachytherapy is recommended for subsequent findings of positive nodes, surgical margins, and/or parametrium.

For hysterectomy specimens with positive margins, gross residual disease, positive imaging, or primary tumor characteristics meeting Sedlis Criteria, pelvic EBRT with concurrent platinum-containing chemotherapy (with individualized brachytherapy for positive vaginal margins) is recommended.[31]

Radiation Therapy

RT is often used in the management of patients with cervical cancer either 1) as definitive therapy for those with locally advanced disease or for those who are poor surgical candidates; or 2) as adjuvant therapy following radical hysterectomy for those who have one or more pathologic risk factors (eg, positive lymph nodes, parametrial infiltration, positive surgical margins, large tumor size, deep stromal invasion, LVSI).

The algorithm provides general RT dosage recommendations, which 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 disease 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

Technologic advances in imaging, computer treatment planning systems, and linear accelerator technology have enabled the more precise delivery radiation doses 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 locoregional recurrence to avoid geographic misses.

CT-based treatment planning with conformal blocking and dosimetry is considered standard care for EBRT. Brachytherapy is a critical component of definitive therapy in patients with cervical cancer who are not candidates for surgery (ie, those with an intact cervix); it may also be used as adjuvant therapy. Brachytherapy is typically combined with EBRT in an integrated treatment plan. MRI imaging immediately preceding brachytherapy may be helpful in delineating residual tumor geometry. Stereotactic body radiotherapy (SBRT) allows delivery of very high doses of focused external beam radiation and may be applied to isolated metastatic sites.[272,273]

Routine image guidance, such as cone-beam CT (CBCT), may be helpful in defining daily internal soft tissue positioning. Concepts regarding the gross target volume (GTV), clinical target volume (CTV), planning target volume (PTV), organs at risk (OARs) and dose-volume histogram (DVH) have been defined for use in conformal radiotherapy, especially for IMRT.[274-276]

Point A, representing a paracervical reference point, has been the most widely used, validated, and reproducible dosing parameter used to date. However, limitations of the Point A dosing system include the fact that it does not take into account the three-dimensional shape of tumors, nor individual tumor to normal tissue structure correlations. There are increasing efforts to use and standardize image-based volumetric brachytherapy approaches using MR, CT or ultrasound – international validation efforts are underway (EMBRACE, NCT00920920).[277-280]

For patients with locally advanced cancers, initial radiation treatment of 40 to 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 (http://www.americanbrachytherapy.org/guidelines/cervical_cancer_taskgroup.pdf).[120]

For lesions in the lower one third of the vagina, the inguinal lymph nodes must be treated. The use of extended-field radiation to treat occult or macroscopic para-aortic lymph node disease must be carefully planned to ensure an adequate dose (45 Gy for microscopic disease) without exceeding bowel, spinal cord, or renal tolerances.[281] General recommendations for radiation volumes and doses are discussed in the algorithm.

Intensity-modulated RT (IMRT) is becoming more widely available; however, issues regarding target definition, patient and target immobilization, tissue deformation, toxicity, and reproducibility remain to be validated.[282-289] Initial phase II hematologic toxicity data from RTOG 418 suggested that limiting the volume of bone marrow treated with IMRT was an important consideration for patients with cervical cancer who were receiving concurrent chemotherapy.[290] The recently reported TIME-C trial (RTOG 1203, NCT01672892) compared post-hysterectomy patients receiving adjuvant IMRT or standard four-field RT to determine whether IMRT reduced acute toxicity. Among the 278 patients with cervical and endometrial cancer included in the analysis, pelvic IMRT was associated

with significantly lower scores for gastrointestinal and urinary toxicity than standard RT.[291]

Several retrospective analyses suggest that prolonged RT treatment duration has an adverse effect on outcome.[292-296] 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 performed, it is generally accepted that the entire RT course (including both EBRT 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 RT 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 (ie, diarrhea, bladder irritation, fatigue) occur to some degree in most patients undergoing radiation and are typically magnified by concurrent chemotherapy. However, acute effects can often be managed with medications and supportive care, and they generally resolve soon after completion of radiation. To avoid treatment-related menopause, ovarian transposition can be considered before pelvic RT in select young patients (<45 years with early-stage disease).[125-127]

After therapy for cervical cancer, late side effects may include potential injury to bladder, rectum, bowel, and pelvic skeletal structures.[297] The risk of major complications (eg, obstruction, fibrosis/necrosis, and fistula) is related to the volume, total dose, dose per fraction, and specific intrinsic radiosensitivity of the normal tissue that is irradiated.[281,298,299] Careful blocking in order to minimize normal tissue exposure while maintaining tumor coverage is critical for optimal outcomes. In addition, patient-related conditions (ie, 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 to 50 Gy. Gross disease in the parametria or unresected nodes may be treated with tightly contoured external-beam boosts to 60 to 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. SBRT is not considered an appropriate routine alternative to brachytherapy.

Cervical Cancer and Pregnancy

Cervical cancer is the most frequently diagnosed gynecologic malignancy in pregnant women; however, most women have stage I disease.[300-303] Invasive cervical cancer during pregnancy creates a clinical dilemma and requires multidisciplinary care.[300,304] Women must make the difficult decision either to delay treatment until documented fetal maturity or to undergo immediate treatment based on their stage of disease.[301,304] Women who delay treatment until fetal maturity should have their children delivered by cesarean section.[303,305,306] Radical trachelectomy with preservation of pregnancy has been successfully performed in a few pregnant patients with early-stage cervical cancer.[53,307-309]

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. Patients with stage I disease who delay treatment until fetal maturity can undergo cesarean section with concurrent radical hysterectomy and pelvic node dissection. For those choosing RT, traditional RT with (or without) chemotherapy protocols (described previously) may need to be modified.[303]

Summary

Cervical cancer is decreasing in the United States because of the wide use of screening; however, it is increasing in developing countries (~275,000 deaths/year), because screening is not available to many women. Effective treatment for cervical cancer (including surgery and concurrent chemoradiation) can yield cures in 80% of women with early-stage disease (stages I–II) and in 60% of women with stage III disease. The hope is that immunization against HPV (using vaccines) will prevent persistent infection with the types of HPV against which the vaccine is designed, and will therefore prevent specific HPV cancer in women.[15,16,310]

Table 1:

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.

*See Discussion for all references.

†These studies have been updated (see Discussion).

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