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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Cervical Cancer

Version 4.2019 — March 29, 2019

NCCN.org

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NCCN Guidelines Panel Disclosures

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

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.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/clinicians.aspx.

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, and adenocarcinoma of the cervix.

Updates in Version 4.2019 of the NCCN Guidelines for Cervical Cancer from Version 3.2019 include:

<u>General</u>
• The algorithms have been updated to include the new 2018 International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging system. The staging tables have also been updated **(ST-1)**.
• The following FIGO Staging reference has been added and footnoted where appropriate: "*Bhatla N, Aoki D, Sharma DN, et al. FIGO Cancer Report 2018. Cancer of the cervix uteri. Int J Gynecol Obstet 2018;143(Suppl):22-36.*"

CERV-2
• Footnote f revised: "Fertility-sparing surgery for stage ~~IB4~~ 1B has been most validated for tumors ≤2 cm. Small cell neuroendocrine histology and ~~adenoma malignum~~ *gastric type adenocarcinoma* (also known as minimal deviation adenocarcinoma *or adenoma malignum*)..."

CERV-10
• Footnote bb is new: "*The accuracy of cytology results may be affected in patients who have received pelvic radiation.*"

CERV-A Principles of Pathology
• Pathologic assessment for carcinoma
  ‣ Uterus: Revised, "Longitudinal/length horizontal extent in mm *(no longer included in FIGO 2018 staging)*."
  ‣ Lymph nodes (when resected): Sub-bullet added, "*Isolated tumor cells are noted as pN0(i+).*"
• Footnote b revised: "Ultrastaging commonly entails ~~thin~~ serial sectioning of the ~~gross~~ SLN and review of multiple H&E stained sections..."

CERV-B Principles of Imaging
• Suspected Recurrence or Metastasis
  ‣ ~~Consider~~ Whole body PET/CT.
  ‣ *Consider pelvic MRI* added as an option.

CERV-C Principles of Evaluation and Surgical Staging
• Footnote a is new: "*Recommendations by stage are based on the revised 2018 FIGO staging (Bhatla N, Aoki D, Sharma DN, et al. FIGO Cancer Report 2018. Cancer of the cervix uteri. Int J Gynecol Obstet 2018;143(Suppl):22-36.). However, trial data cited within this section utilized the 2009 FIGO staging system.*"
• Table 1 (Resection of Cervical Cancer as Primary Therapy) and Table 2 (Resection of Locally Recurrent Cervical Cancer With No Distant Metastasis) have been extensively revised.
• Footnote k is a new reference regarding double barrel wet colostomy: "*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.*"

MS-1
• The Discussion has been updated to reflect the 2018 FIGO Surgical Staging system.

UPDATES

Updates in Version 3.2019 of the NCCN Guidelines for Cervical Cancer from Version 2.2019 include:

CERV-C 1 of 7 Principles of Evaluation and Surgical Staging
• Types of Resection and Appropriateness for Treatment of Cervical Cancer: The following bullets were added:
  ‣ The standard and historical approach for radical hysterectomy is an open abdominal approach. Previous iterations of the guidelines indicated that radical hysterectomy could be performed via open laparotomy or minimally invasive surgery (MIS) laparoscopic approaches, using either conventional or robotic techniques. However, several key contemporary reports have questioned the presumed therapeutic equivalency of open vs. MIS approaches. A prospective randomized trial demonstrated that minimally invasive radical hysterectomy was associated with lower rates of DFS and OS than open abdominal radical hysterectomy. Moreover, 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. See Discussion for additional details.
  ‣ *Given recently presented findings of significantly poorer survival outcomes with the minimally invasive approach compared to the open approach in a randomized controlled trial of women with early-stage cervical cancer, women should be carefully counseled about the short-term versus long-term outcomes and oncologic risks of the different surgical approaches.*

MS-1
• The Discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 2.2019 of the NCCN Guidelines for Cervical Cancer from Version 1.2019 include:
General
• Recommendation revised "concurrent ~~cisplatin~~ *platinum*-containing chemotherapy" throughout the guidelines.

CERV-4
• Footnote q revised: "Concurrent ~~cisplatin-based~~ *platinum-containing* chemotherapy with EBRT utilizes cisplatin as a single agent *(or carboplatin if cisplatin intolerant)* or cisplatin plus 5-fluorouracil."

CERV-A Principles of Pathology
• This is a new section that provides recommendations for pathologic assessment after radical hysterectomy.

CERV-C Principles of Evaluation and Surgical Staging
• Types of Resection and Appropriateness for Treatment of Cervical Cancer
  ‣ Third bullet revised: "Radical hysterectomy with bilateral pelvic lymph node dissection (with or without SLN mapping) is the preferred treatment for FIGO stage IA2, ~~IB, and IIA~~ *IB1, and select IB2/IIA1* lesions when fertility preservation is not desired."

CERV-D Principles of Radiation Therapy
• This section has been extensively revised.

CERV-F Systemic Therapy Regimens for Cervical Cancer
• The NCCN Categories of Preference have been applied to all of the suggested regimens.
• Footnote c was revised: "*If not used previously*, these agents can be used as second-line therapy ~~if not used previously~~ *as clinically appropriate*."

MS-1
• The Discussion section has been updated to reflect the changes in the algorithm.

UPDATES

Updates in Version 1.2019 of the NCCN Guidelines for Cervical Cancer from Version 1.2018 include:

CERV-1
- **Workup:**
  - ▸ Ninth bullet: Revised to "*Consider* examination under anesthesia (EUA) cystoscopy...". Previously this recommendation was listed as "optional."
  - ▸ "*Consider options for fertility sparing*" added.

CERV-2
- **Primary Treatment (Fertility Sparing)**
  - ▸ Stage IA1 with LVSI and Stage IA2: For both treatment recommendations, "± para-aortic lymph node sampling (category 2B)" was removed. The same change was also made under Non-Fertility Sparing recommendations for Stage IA1 with LVSI and Stage IA2 on CERV-3.
  - ▸ Stage IB1: Revised, "... ± para-aortic lymph node ~~sampling~~ *dissection.*" Also for CERV-4 under the non-fertility sparing options. Same changes made for all stages under Non-Fertility Sparing treatment options on CERV-4.
- Footnote "g" is new: "*Consultation with reproductive endocrinology fertility experts is suggested.*"

CERV 5
- Negative nodes, negative margins, negative parametrium: Revised, "Pelvic EBRT if combination of ~~high-~~risk factors..."
- Para-aortic lymph node positive by surgical staging; Imaging workup for maetastatic disease: Revised, "~~Para-aortic lymph node~~ *Extended-field* EBRT + concurrent cisplatin-containing chemotherapy ~~+ pelvic EBRT~~ ± brachytherapy."
- Footnote removed: "Patients undergoing trachelectomy with high-risk pathologic features meeting Sedlis criteria and/or with positive nodes and/or positive parametrium are no longer candidates for fertility sparing uterine preservation for fertility."

CERV-7
- Footnote v: New reference added, *Kim JY, Kim JY, Kim JH, et al. Curative chemoradiotherapy in patients with stage IVB cervical cancer presenting with paraortic and left supraclavicular lymph node metastases. Int J Radiat Oncol Biol Phys 2012;84:741-747.*

CERV-9
- Negative margins; negative imaging: New pathway added for "*Optional if Sedlis criteria not met on hysterectomy specimen*" was added.

CERV-10
- Surveillance; Last bullet: *Hormone replacement therapy* added as part of sexual health patient education.

CERV-B Principles of Evaluation and Surgical Staging
- Revisions made throughout this section for clarity.

1 of 7
- Third bullet revised: "...conventional or robotic techniques. *However, given recently presented findings of significantly poorer survival outcomes with the laparoscopic approach compared to the open approach in a randomized controlled trial of women with early-stage cervical cancer, women should be carefully counseled about the risks and benefits of the different surgical approaches until more data become available.* The Querleu and Morrow classification system..."
- New bullet added: "*Para-aortic lymph node dissection 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.*"

7 of 7
- Two new references were added:
  - ▸ *Ramirez PT, Frumovitz M, Pareja R, et al. Phase III randomized trial of laparoscopic or robotic versus abdominal hysterectomy in patients with early-stage cervical cancer: LACC Trial. Society of Gynecologic Oncology Annual Metting on Women's Cancer; New Orleans 2018.*
  - ▸ *Margul DJ, Yang J, Seagle BL, et al. Outcomes and costs of open, robotic, and laparoscopic radical hysterectomy for stage IB1 cervical cancer. J Clin Oncol 36, 2018 (suppl; abstr 5502).*

CERV-C Principles of Radiation Therapy
- Revisions made throughout this section for clarity.

1 of 5
- External Beam Radiation Therapy: New bullet added: "*Parametrial boosting should be considered in select cases with bulky parametrial/pelvic side wall disease after completion of initial whole pelvic radiation.*"

CERV-E Systemic Therapy Regimens
- Chemoradiation (preferred regimens): "*Carboplatin if patient is cisplatin intolerant*" was added as an option.
- First-line Combination Therapy for Recurrent or Metastatic Disease: "Cisplatin/gemcitabine (category 3)" was removed as an option.

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WORKUP

CLINICAL STAGE

- History and physical (H&P)
- Complete blood count (CBC) (including platelets)
- Cervical biopsy, pathologic review[a]
- Cone biopsy as indicated[b]
- Liver function test (LFT)/renal function studies
- Imaging[c]
- Smoking cessation and counseling intervention if indicated
- Consider HIV testing[d]
- Consider examination under anesthesia (EUA) cystoscopy/proctoscopy[e] (≥ stage IB3)
- Consider options for fertility sparing

Stage IA1 → See Primary Treatment (Fertility Sparing) (CERV-2)
→ See Primary Treatment (Non-Fertility Sparing) (CERV-3)

Stage IA2 / Stage IB1 / Stage IB2 → See Primary Treatment (Fertility Sparing) (CERV-2)
→ See Primary Treatment (Non-Fertility Sparing) (CERV-3) and (CERV-4)

Stage IIA1 → See Primary Treatment (Non-Fertility Sparing) (CERV-4)

Stage IB3 / Stage IIA2 → See Primary Treatment (CERV-4) and (CERV-6)

Stage IIB / Stage III / Stage IVA → See Primary Treatment (CERV-6)

Stage IVB → See Treatment (CERV-12)

Incidental finding of invasive cancer at simple hysterectomy → See Treatment (CERV-9)

[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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CERV-1

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NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

CLINICAL STAGE[c] **PRIMARY TREATMENT (FERTILITY SPARING)[g,h]**

Stage IA1
no lymphovascular
space invasion
(LVSI)
→
Cone biopsy[i] with negative margins[j]
(preferably a non-fragmented specimen with 3-mm negative margins[j])
(If positive margins, repeat cone biopsy or perform trachelectomy)
→ **See Surveillance (CERV-10)**

Stage IA1
with LVSI
and
Stage IA2
→
Cone biopsy[i] with negative margins[j]
(preferably a non-fragmented specimen with 3-mm negative margins[j])
(if positive margins, repeat cone biopsy or perform trachelectomy)
+ pelvic lymph node dissection
(consider sentinel lymph node [SLN] mapping)[k]
or
Radical trachelectomy
+ pelvic lymph node dissection[k]
(consider SLN mapping)[k]
→ **See Surgical Findings (CERV-5)**

Stage IB1[f]
Select IB2[f,k]
→
Radical trachelectomy
+ pelvic lymph node dissection[k]
± para-aortic lymph node dissection
(consider SLN mapping)[k,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 (also known as minimal deviation adenocarcinoma or adenoma malignum) are not considered suitable tumors for this procedure.
[g]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.
[h]Consultation with reproductive endocrinology fertility experts is suggested.
[i]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.
[j]Negative for invasive disease or histologic high-grade squamous intraepithelial lesion (HSIL) at margins.
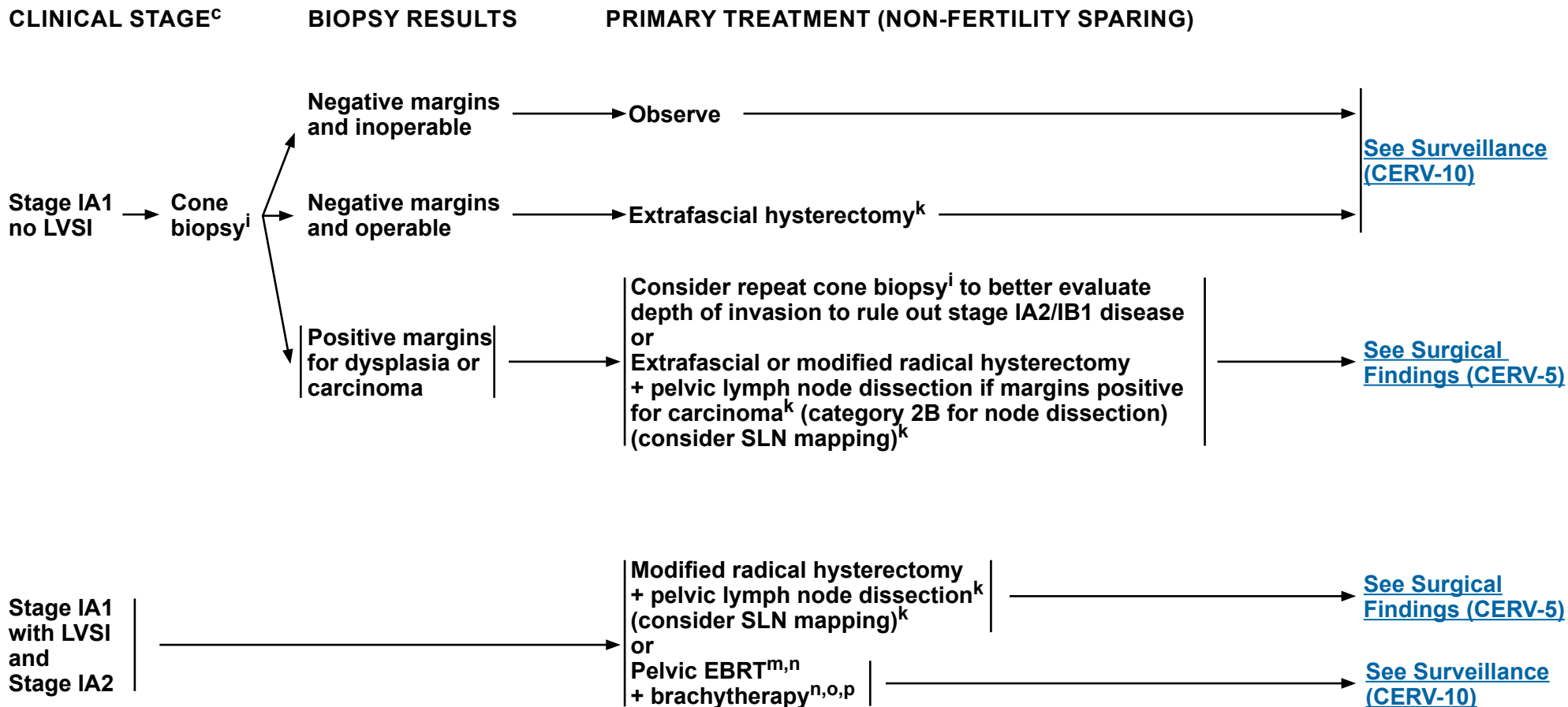[k]See Principles of Evaluation and Surgical Staging (CERV-C).
[l]For SLN mapping, the best detection rates and mapping results are in tumors <2 cm.

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CLINICAL STAGE[c]   **BIOPSY RESULTS**   **PRIMARY TREATMENT (NON-FERTILITY SPARING)**

Stage IA1 no LVSI → **Cone biopsy[i]** →

- **Negative margins and inoperable** → **Observe** → See Surveillance (CERV-10)
- **Negative margins and operable** → **Extrafascial hysterectomy[k]** → See Surveillance (CERV-10)
- **Positive margins for dysplasia or carcinoma** → **Consider repeat cone biopsy[i] to better evaluate depth of invasion to rule out stage IA2/IB1 disease** or **Extrafascial or modified radical hysterectomy + pelvic lymph node dissection if margins positive for carcinoma[k] (category 2B for node dissection) (consider SLN mapping)[k]** → See Surgical Findings (CERV-5)

Stage IA1 with LVSI and Stage IA2 →
- **Modified radical hysterectomy + pelvic lymph node dissection[k] (consider SLN mapping)[k]** → See Surgical Findings (CERV-5)
- or
- **Pelvic EBRT[m,n] + brachytherapy[n,o,p]** → See Surveillance (CERV-10)

[c]See Principles of Imaging (CERV-B).
[i]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.
[k]See Principles of Evaluation and Surgical Staging (CERV-C).
[m]Radiation can be an option for medically inoperable patients or those who refuse surgery.
[n]See Principles of Radiation Therapy (CERV-D).
[o]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)
[p]The traditional dose would be 70–80 Gy to total point A dose.

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**NCCN Guidelines Version 4.2019
Cervical Cancer**

NCCN Guidelines Index
Table of Contents
Discussion

CLINICAL STAGE[c]

PRIMARY TREATMENT (NON-FERTILITY SPARING)

Stage IB1, IB2 and Stage IIA1

**Radical hysterectomy + pelvic lymph node dissection[k] (category 1)
± para-aortic lymph node dissection (category 2B)
(consider SLN mapping)[k,l]**
or
Pelvic EBRT[m,n]
→ See Surgical Findings (CERV-5)

**+ brachytherapy (total point A dose: 80–85 Gy)[n,o]
± concurrent platinum-containing chemotherapy[q]**
→ See Surveillance (CERV-10)

**Stage IB3 and Stage IIA2
([also see CERV-6](#) for additional recommendations for non-primary surgery patients)**

**Definitive pelvic EBRT[n]
+ concurrent platinum-containing chemotherapy[q]
+ brachytherapy (total point A dose ≥85 Gy)[n,o]
(category 1 for primary chemoradiation)**
→ See Surveillance (CERV-10)

or
**Radical hysterectomy
+ pelvic lymph node dissection[k]
± para-aortic lymph node dissection (category 2B)**
→ See Surgical Findings (CERV-5)

or
**Pelvic EBRT[n]
+ concurrent platinum-containing chemotherapy[q]
+ brachytherapy[n,o,r]
+ adjuvant hysterectomy[s]
(category 3)**
→ See Surveillance (CERV-10)

[c]See Principles of Imaging (CERV-B).
[k]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).
[o]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)
[q]Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant) or cisplatin plus 5-fluorouracil.
[r]The traditional dose would be 75–80 Gy to total point A dose.
[s]This approach can be considered in patients whose extent of disease, response to EBRT, or uterine anatomy precludes adequate coverage by brachytherapy.
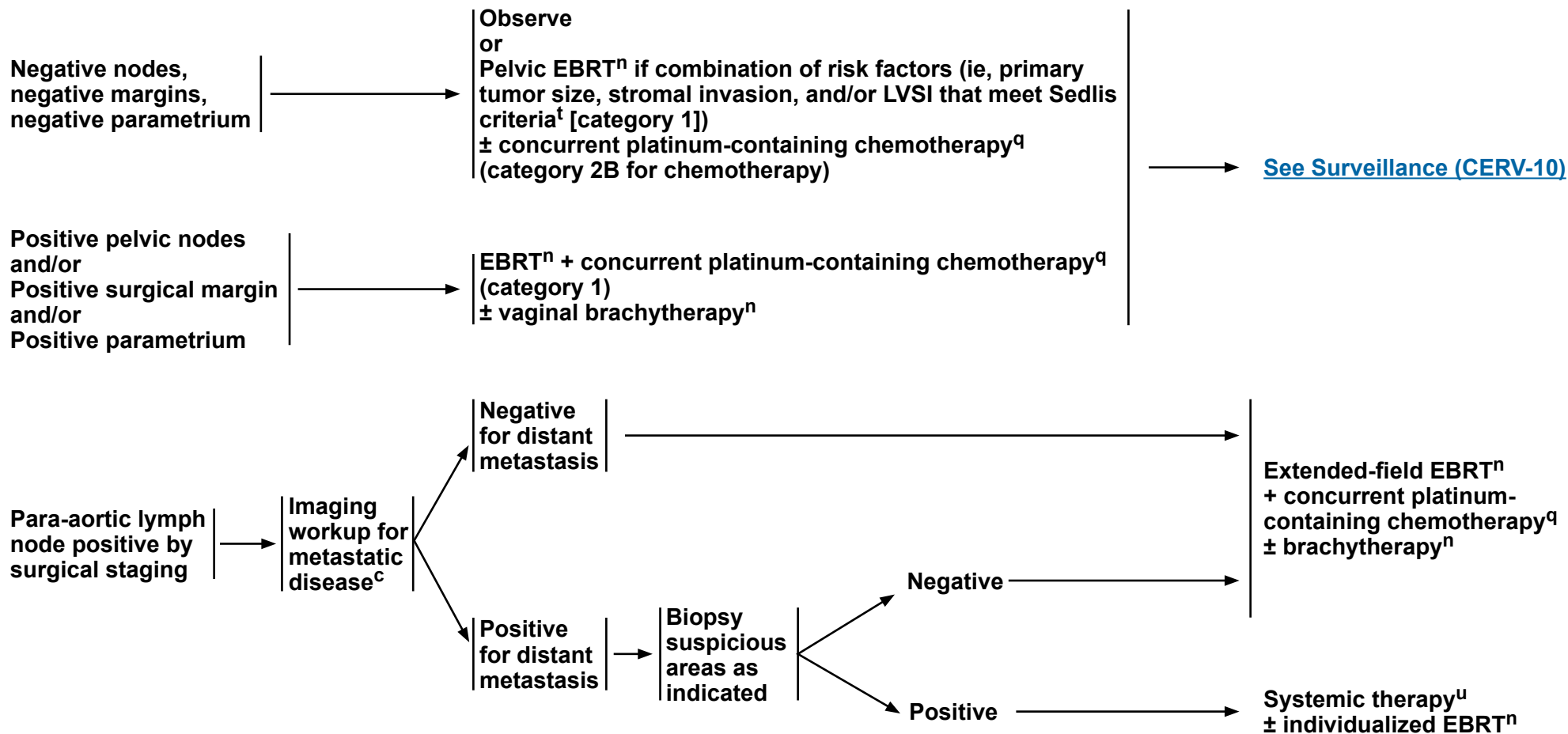
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SURGICAL FINDINGS

ADJUVANT TREATMENT

Negative nodes, negative margins, negative parametrium →

Observe
or
Pelvic EBRT[n] if combination of risk factors (ie, primary tumor size, stromal invasion, and/or LVSI that meet Sedlis criteria[t] [category 1])
± concurrent platinum-containing chemotherapy[q]
(category 2B for chemotherapy)

→ **See Surveillance (CERV-10)**

Positive pelvic nodes and/or
Positive surgical margin and/or
Positive parametrium →

EBRT[n] + concurrent platinum-containing chemotherapy[q]
(category 1)
± vaginal brachytherapy[n]

Para-aortic lymph node positive by surgical staging → **Imaging workup for metastatic disease[c]**

Negative for distant metastasis →

Extended-field EBRT[n] + concurrent platinum-containing chemotherapy[q] ± brachytherapy[n]

Positive for distant metastasis → **Biopsy suspicious areas as indicated**

Negative →

Positive → **Systemic therapy[u] ± individualized EBRT[n]**

[c]See Principles of Imaging (CERV-B).
[n]See Principles of Radiation Therapy (CERV-D).
[q]Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant) or cisplatin plus 5-fluorouracil.
[t]Risk factors may not be limited to the Sedlis criteria. See Sedlis Criteria (CERV-E).
[u]See Systemic Therapy Regimens for Cervical Cancer (CERV-F).

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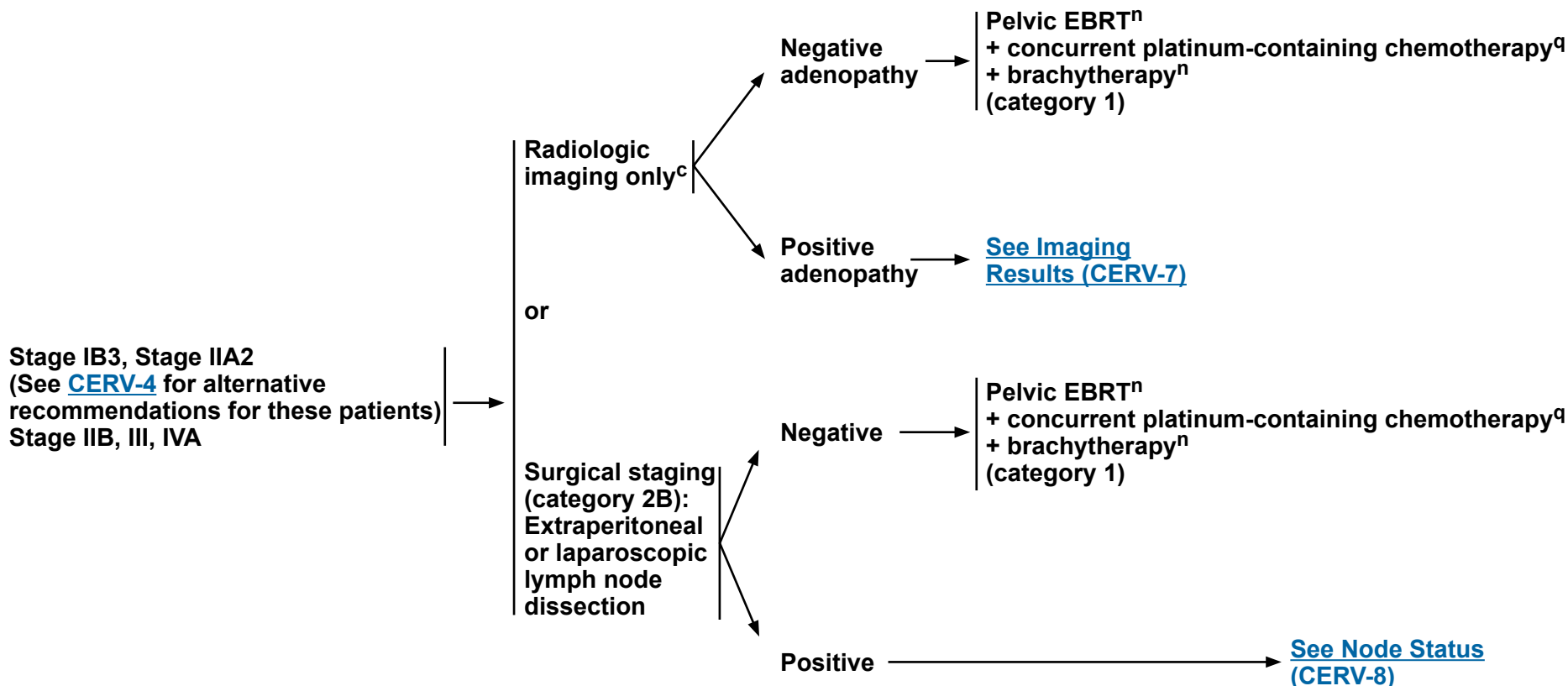
See Surveillance (CERV-10)

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NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

CLINICAL STAGE

ADDITIONAL WORKUP

PRIMARY TREATMENT

Stage IB3, Stage IIA2
(See CERV-4 for alternative recommendations for these patients)
Stage IIB, III, IVA

Radiologic imaging only[c]

→ Negative adenopathy →

Pelvic EBRT[n]
+ concurrent platinum-containing chemotherapy[q]
+ brachytherapy[n]
(category 1)

→ Positive adenopathy → **See Imaging Results (CERV-7)**

or

Surgical staging (category 2B): Extraperitoneal or laparoscopic lymph node dissection

→ Negative →

Pelvic EBRT[n]
+ concurrent platinum-containing chemotherapy[q]
+ brachytherapy[n]
(category 1)

→ Positive → **See Node Status (CERV-8)**

[c]See Principles of Imaging (CERV-B).
[n]See Principles of Radiation Therapy (CERV-D).
[q]Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant) or cisplatin plus 5-fluorouracil.

See Surveillance (CERV-10)

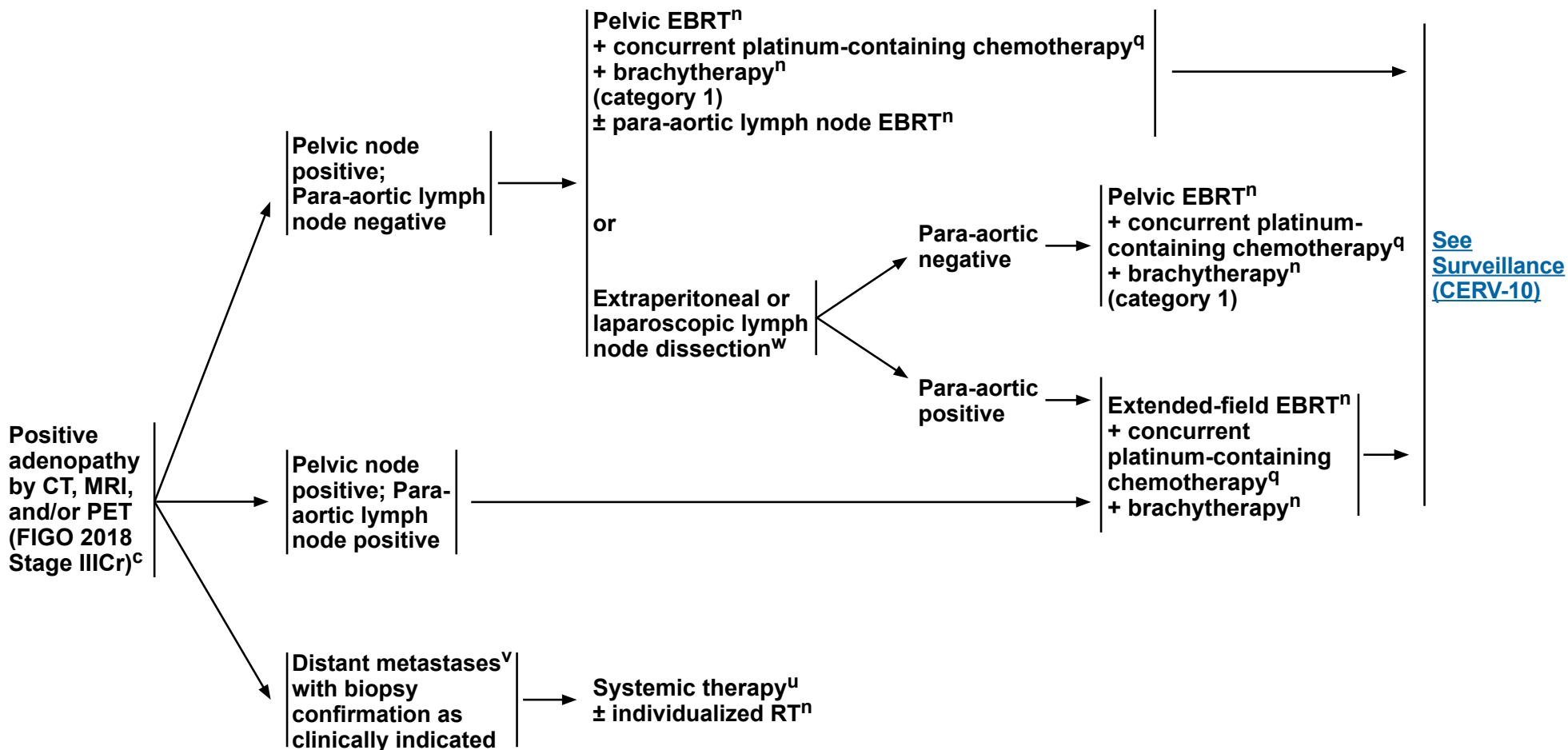Note: All recommendations are category 2A unless otherwise indicated.
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NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

IMAGING RESULTS

PRIMARY TREATMENT

Positive adenopathy by CT, MRI, and/or PET (FIGO 2018 Stage IIICr)[c]

→ **Pelvic node positive; Para-aortic lymph node negative** →

Pelvic EBRT[n]
+ concurrent platinum-containing chemotherapy[q]
+ brachytherapy[n]
(category 1)
± para-aortic lymph node EBRT[n]

→ **See Surveillance (CERV-10)**

or

Extraperitoneal or laparoscopic lymph node dissection[w]

→ **Para-aortic negative** → Pelvic EBRT[n] + concurrent platinum-containing chemotherapy[q] + brachytherapy[n] (category 1) → **See Surveillance (CERV-10)**

→ **Para-aortic positive** → Extended-field EBRT[n] + concurrent platinum-containing chemotherapy[q] + brachytherapy[n] →

→ **Pelvic node positive; Para-aortic lymph node positive** → Extended-field EBRT[n] + concurrent platinum-containing chemotherapy[q] + brachytherapy[n] → **See Surveillance (CERV-10)**

→ **Distant metastases[v] with biopsy confirmation as clinically indicated** → Systemic therapy[u] ± individualized RT[n]

[c] See Principles of Imaging (CERV-B).
[n] See Principles of Radiation Therapy (CERV-D).
[q] Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant) or cisplatin plus 5-fluorouracil.
[u] See Systemic Therapy Regimens for Cervical Cancer (CERV-F).
[v] Patients with distant metastatic disease confined to the surpaclavicular nodes may be treated definitively. (Kim JY, Kim JY, Kim JH, et al. Curative chemoradiotherapy in patients with stage IVB cervical cancer presenting with paraortic and left supraclavicular lymph node metastases. Int J Radiat Oncol Biol Phys 2012;84:741-747.)
[w] Consider postoperative imaging (abdominal/pelvic CT or MRI with contrast) to confirm the adequacy of node removal.

See Surveillance (CERV-10)

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NCCN Guidelines Version 4.2019
Cervical Cancer
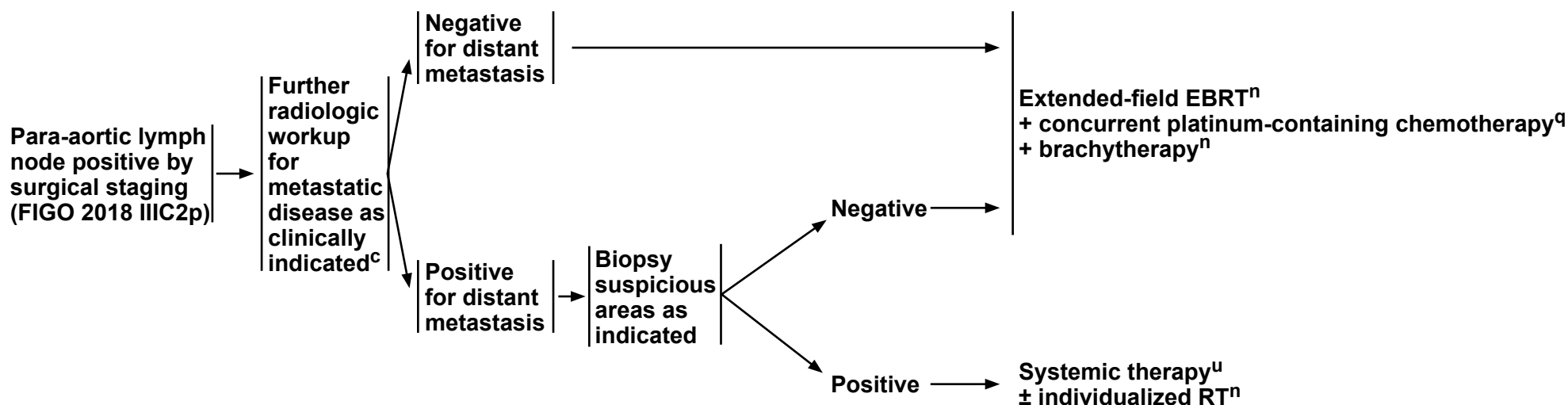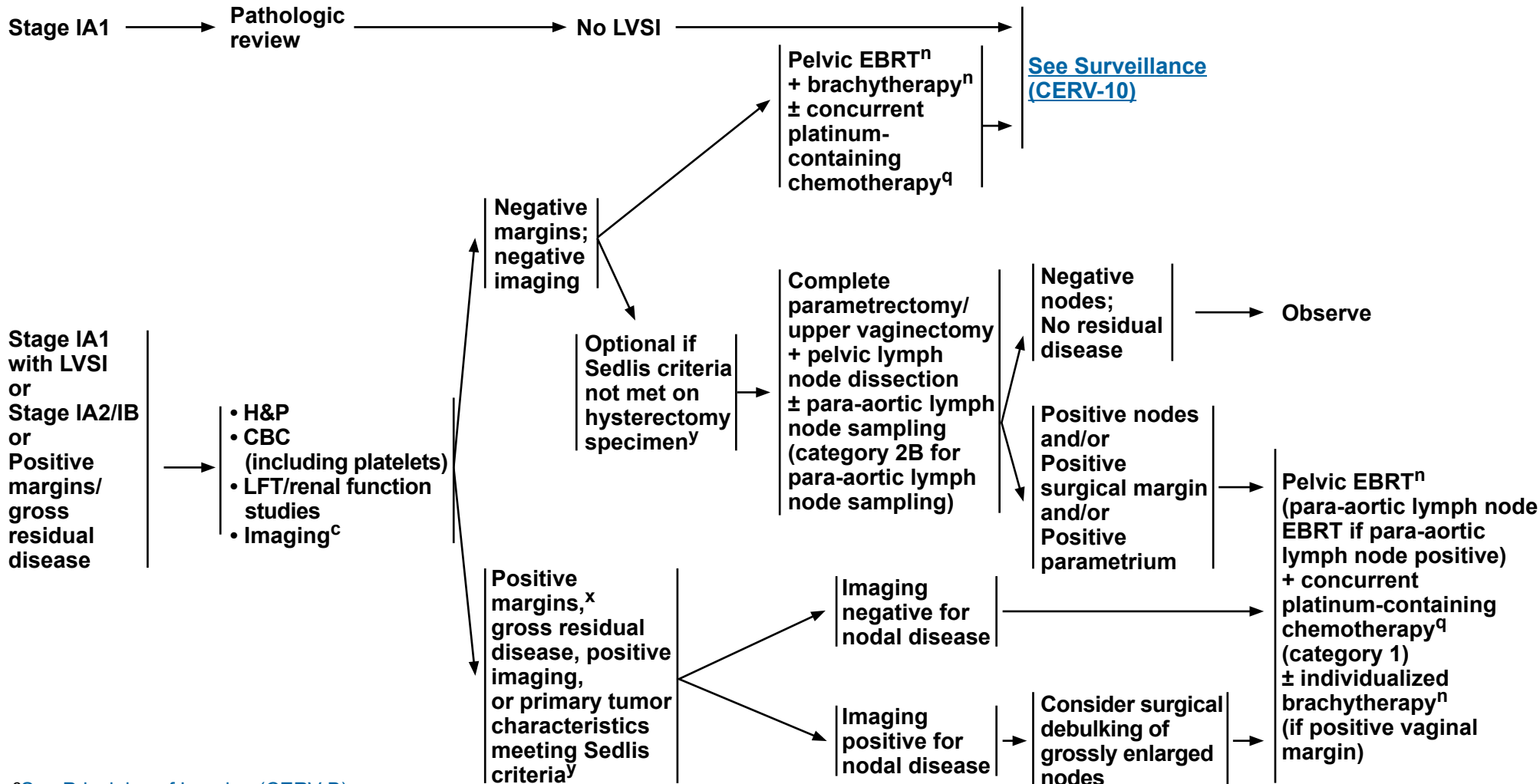
NCCN Guidelines Index
Table of Contents
Discussion

SURGICAL NODE STATUS

PRIMARY TREATMENT

Pelvic lymph node positive and para-aortic lymph node negative by surgical staging (FIGO 2018 IIIC1p) → **Pelvic EBRT[n] + concurrent platinum-containing chemotherapy[q] + brachytherapy[n] (category 1)**

Para-aortic lymph node positive by surgical staging (FIGO 2018 IIIC2p) → **Further radiologic workup for metastatic disease as clinically indicated[c]**

- **Negative for distant metastasis** → **Extended-field EBRT[n] + concurrent platinum-containing chemotherapy[q] + brachytherapy[n]**

- **Positive for distant metastasis** → **Biopsy suspicious areas as indicated**
  - **Negative** → **Extended-field EBRT[n] + concurrent platinum-containing chemotherapy[q] + brachytherapy[n]**
  - **Positive** → **Systemic therapy[u] ± individualized RT[n]**

[c]See Principles of Imaging (CERV-B).
[n]See Principles of Radiation Therapy (CERV-D).
[q]Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant) or cisplatin plus 5-fluorouracil.
[u]See Systemic Therapy Regimens for Cervical Cancer (CERV-F).

See Surveillance (CERV-10)

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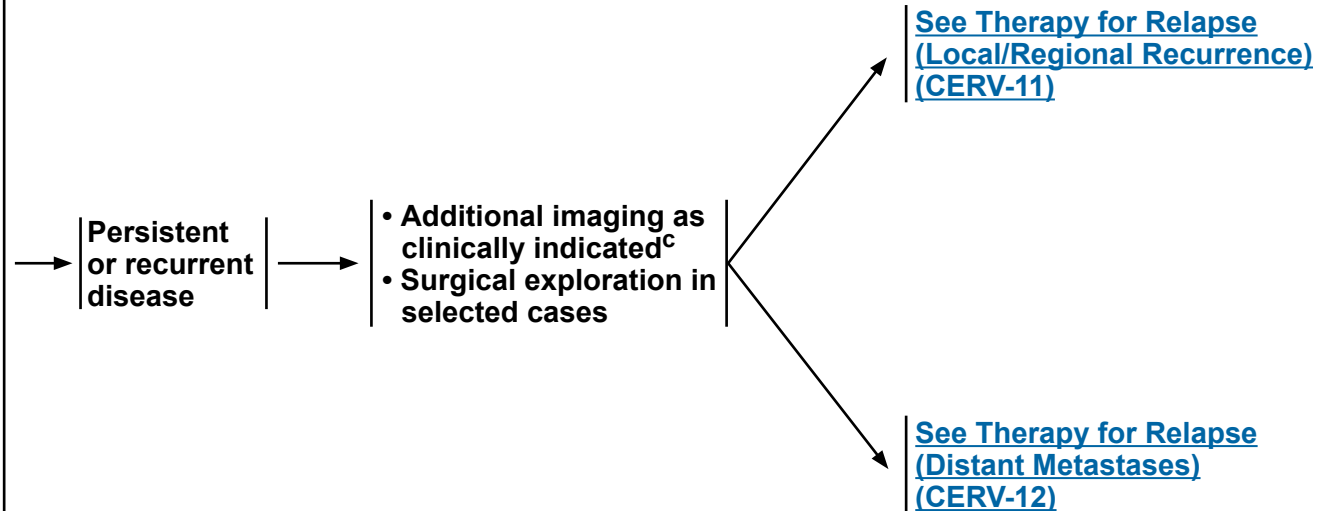
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Cervical Cancer**

NCCN Guidelines Index
Table of Contents
Discussion

**INCIDENTAL FINDING OF INVASIVE CANCER
AFTER SIMPLE HYSTERECTOMY**

TREATMENT

Stage IA1 → **Pathologic review** → **No LVSI** → See Surveillance (CERV-10)

Stage IA1 with LVSI or Stage IA2/IB or Positive margins/ gross residual disease
→
- **H&P**
- **CBC (including platelets)**
- **LFT/renal function studies**
- **Imaging[c]**

Negative margins; negative imaging
→ **Pelvic EBRT[n] + brachytherapy[n] ± concurrent platinum-containing chemotherapy[q]** → See Surveillance (CERV-10)

Optional if Sedlis criteria not met on hysterectomy specimen[y]
→ **Complete parametrectomy/ upper vaginectomy + pelvic lymph node dissection ± para-aortic lymph node sampling (category 2B for para-aortic lymph node sampling)**

→ **Negative nodes; No residual disease** → **Observe**

→ **Positive nodes and/or Positive surgical margin and/or Positive parametrium** → **Pelvic EBRT[n] (para-aortic lymph node EBRT if para-aortic lymph node positive) + concurrent platinum-containing chemotherapy[q] (category 1) ± individualized brachytherapy[n] (if positive vaginal margin)**

Positive margins,[x] gross residual disease, positive imaging, or primary tumor characteristics meeting Sedlis criteria[y]

→ **Imaging negative for nodal disease** → **Pelvic EBRT[n] ... chemotherapy[q] (category 1) ± individualized brachytherapy[n] (if positive vaginal margin)**

→ **Imaging positive for nodal disease** → **Consider surgical debulking of grossly enlarged nodes** →
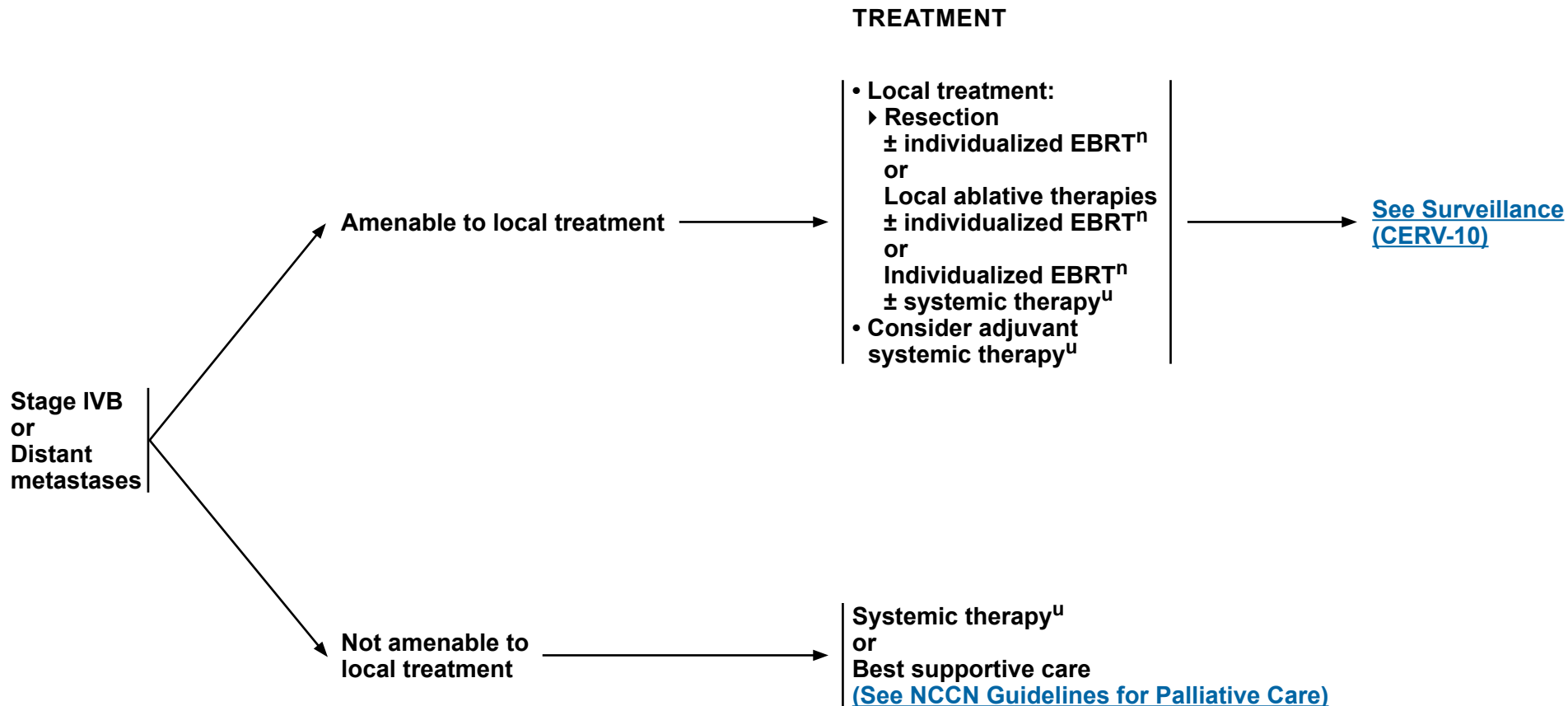
[c]See Principles of Imaging (CERV-B).
[n]See Principles of Radiation Therapy (CERV-D).
[q]Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant) or cisplatin plus 5-fluorouracil.

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

See Surveillance (CERV-10)

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Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SURVEILLANCE[z]

WORKUP

- **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 annually[aa,bb]**
  as indicated for the detection of lower genital
  tract neoplasia
- **Imaging as indicated based on symptoms**
  or examination findings suspicious for
  recurrence[c,cc]
- **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 (including vaginal dilator use,
  lubricants/moisturizers, hormone replacement
  therapy), smoking cessation, nutrition
  counseling, and potential long-term and late
  effects of treatment (See NCCN Guidelines
  for Survivorship and NCCN Guidelines for
  Smoking Cessation)

Persistent
or recurrent
disease
→
- **Additional imaging as**
  clinically indicated[c]
- **Surgical exploration in**
  selected cases

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

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

[c]See Principles of Imaging (CERV-B).
[z]Salani R, Khanna N, Frimer M, et al. An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncology (SGO) recommendations. Gynecol Oncol 2017;146:3-10.
[aa]Regular cytology can be considered for detection of lower genital tract dysplasia, although its value in detection of recurrent cervical cancer is limited. The likelihood of picking up asymptomatic recurrences by cytology alone is low.
[bb]The accuracy of cytology results may be affected in patients who have received pelvic radiation.
[cc]Recurrences should be proven by biopsy before proceeding to treatment planning.

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NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

THERAPY FOR RELAPSE

Local/ regional recurrence

No prior RT or failure outside of previously treated field → **Consider surgical resection, if feasible** → **Individualized EBRT[n] ± systemic therapy[q,u] ± brachytherapy[n]** → **Recurrence**

Prior RT

Central disease →

Pelvic exenteration[k] ± intraoperative RT (IORT)[n] (category 3 for IORT) → **Recurrence**

or

In carefully selected patients with small (<2 cm) lesions → **Radical hysterectomy[k] or Brachytherapy[n]** → **Recurrence**

Noncentral disease → **Individualized EBRT[n] ± systemic therapy[q,u] or Resection ± IORT[n] (category 3 for IORT) or Systemic therapy[u]** → **Recurrence**

Systemic therapy[u] or Best supportive care (See NCCN Guidelines for Palliative Care)

[k]See Principles of Evaluation and Surgical Staging (CERV-C).
[n]See Principles of Radiation Therapy (CERV-D).
[q]Concurrent platinum-containing chemotherapy with EBRT utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant) or cisplatin plus 5-fluorouracil.
[u]See Systemic Therapy Regimens for Cervical Cancer (CERV-F).

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NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

TREATMENT

Stage IVB
or
Distant
metastases

Amenable to local treatment →

- **Local treatment:**
  ‣ **Resection**
    ± individualized EBRT[n]
    or
    Local ablative therapies
    ± individualized EBRT[n]
    or
    Individualized EBRT[n]
    ± systemic therapy[u]
- **Consider adjuvant**
  systemic therapy[u]

→ See Surveillance (CERV-10)

Not amenable to
local treatment →

Systemic therapy[u]
or
Best supportive care
(See NCCN Guidelines for Palliative Care)

[n]See Principles of Radiation Therapy (CERV-D).
[u]See Systemic Therapy Regimens for Cervical Cancer (CERV-F).

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NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF PATHOLOGY[1]

- **Procedure:**
  - ▸ **Radical hysterectomy**
- **Pathologic assessment for carcinoma:**
  - ▸ **Uterus**
    - ◊ **Hysterectomy type (where applicable)**
    - ◊ **Tumor site**
    - ◊ **Tumor size, include greatest dimension and additional two dimensions**
    - ◊ **Histologic type**
    - ◊ **Histologic grade**
    - ◊ **Stromal invasion (depth of invasion in mm/cervical wall thickness in mm)**
    - ◊ **Longitudinal/length horizontal extent in mm (no longer included in FIGO 2018 staging[2])**
    - ◊ **Circumferential/width horizontal extent in mm**
    - ◊ **Surgical resection margin status**
      - **– If negative, include closest margin and distance to closest margin (in mm).[a]**
      - **– If positive, include location of positive margin.[a]**
    - ◊ **Lymphovascular invasion (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.[b]**
    - ◊ **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, macrometastasis**
    - ◊ **Isolated tumor cells are noted as pN0(i+)**
  - ▸ **Consider MMR/MSI testing or PD-L1 testing for patients with recurrent, progressive, or metastatic disease[3,4]**

Footnotes
[a]While reporting of this information is not required, knowledge of this information is useful for multidisciplinary treatment planning.
[b]Ultrastaging commonly entails serial sectioning of the SLN and review of multiple H&E stained sections and cytokeratin immunohistochemistry for all blocks of the SLN. There is not a standard protocol for lymph node ultrastaging.

References
[1]Krishnamurti U, Movahedi-Lankarani S, Bell DA, et al. Protocol for the Examination of Specimens from Patients with Primary Carcinoma of the Uterine Cervix. College of American Pathologists 2017.
[2]Bhatla N, Aoki D, Sharma DN, et al. FIGO Cancer Report 2018. Cancer of the cervix uteri. Int J Gynecol Obstet 2018;143(Suppl):22-36.
[3]Minion LE, Tewari KS. Cervical cancer - State of science: From angiogenesis blockade to checkpoint inhibition. Gynecol Oncol 2018; Mar;148(3):609-621.
[4]Chung HC, Schellens JH, Delord J-P, et al. Pembrolizumab treatment of advanced cervical cancer: Updated results from the phase 2 KEYNOTE-158 study. J Clin Oncol 2018:36; (suppl; abstr 5522).

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CERV-A

PRINCIPLES OF IMAGING[a,1-9]

Initial Workup
- **Stage I**
  - ▸ **Non-Fertility Sparing**
    - ◊ **Consider chest imaging with plain radiography (chest x-ray). If an abnormality is seen, then chest CT without contrast may be performed.**
    - ◊ **Consider pelvic MRI with contrast to assess local disease extent (preferred for FIGO stage IB2-IB3).**
    - ◊ **Consider whole body PET/CT or chest/abdomen/pelvic CT in FIGO stage IB1-IB2.**
    - ◊ **Whole body PET/CT or chest/abdomen/pelvic CT in FIGO stage IB3.**
    - ◊ **For patients who underwent total hysterectomy (TH) with incidental finding of cervical cancer, consider whole body PET/CT or chest/abdomen/pelvic CT to evaluate for metastatic disease and pelvic MRI to assess pelvic residual disease.**
  - ▸ **Fertility Sparing**
    - ◊ **Consider chest imaging with plain radiography (chest x-ray). If an abnormality is seen, then chest CT without contrast may be performed.**
    - ◊ **Pelvic MRI (preferred) to assess local disease extent and proximity of tumor to internal cervical os; perform pelvic transvaginal ultrasound if MRI is contraindicated.**
    - ◊ **Consider whole body PET/CT or chest/abdomen/pelvic CT in FIGO stage IB1-IB2.**
    - ◊ **Other imaging should be based on symptomatology and clinical concern for metastatic disease.[b]**

- **Stage II–IV**
  - ▸ **Whole body PET/CT (preferred) or chest/abdomen/pelvic CT to evaluate for metastatic disease.**
  - ▸ **Consider pelvic MRI with contrast to assess local disease extent.**
  - ▸ **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 whole body PET/CT or chest/abdomen/pelvic 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.

Continued
References

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CERV-B
1 OF 3

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 whole body 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**
  - ▸ **Whole body 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]**

Suspected Recurrence or Metastasis
- **Whole body 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.

References

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NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF IMAGING
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[1]Salani R, Khanna N, Frimer M, et al. An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncology (SGO) recommendations. Gynecol Oncol 2017;146:3-10.

[2]Atri M, Zhang Z, Dehdashti F, et al. Utility of PET-CT to evaluate retroperitoneal lymph node metastasis in advanced cervical cancer: Results of ACRIN6671/GOG0233 trial. Gynecol Oncol 2016;142:413-419.

[3]Rajendran JG, Greer BE. Expanding role of positron emission tomography in cancer of the uterine cervix. J Natl Compr Canc Netw 2006;4:463-469.

[4]Lakhman Y, Akin O, Park KJ, et al. Stage IB1 cervical cancer: role of preoperative MR imaging in selection of patients for fertility-sparing radical trachelectomy. Radiology 2013;269:149-158.

[5]Elit L, Reade CJ. Recommendations for follow-up care for gynecologic cancer survivors. Obstet Gynecol 2015;126:1207-1214.

[6]Sala E, Rockall AG, Freeman SJ, et al. The added role of MR imaging in treatment stratification of patients with gynecologic malignancies: what the radiologist needs to know. Radiology 2013;266:717-740.

[7]Balleyguier C, Sala E, Da Cunha T, et al. Staging of uterine cervical cancer with MRI: guidelines of the European Society of Urogenital Radiology. Eur Radiol 2011;21:1102-1110.

[8]Sala E, Micco M, Burger IA, et al. Complementary prognostic value of pelvic MRI and whole-body FDG PET/CT in the pretreatment assessment of patients with cervical cancer. Int J Gynecol Cancer 2015;25:1461-1467.

[9]Bhatla N, Aoki D, Sharma DN, et al. FIGO Cancer Report 2018. Cancer of the cervix uteri. Int J Gynecol Obstet 2018;143(Suppl):22-36.

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PRINCIPLES OF EVALUATION AND SURGICAL STAGING[a]

<u>Types of Resection and Appropriateness for Treatment of Cervical Cancer</u>
- Treatment of cervical cancer is stratified by stage as delineated in the Guidelines.
- Microinvasive disease, defined as FIGO stage IA1 with no lymphovascular space invasion (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. 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 lymph node dissection (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[1] is a modern surgical classification that describes degree of resection and nerve preservation in three-dimensional (3D) planes of resection.[2] Procedural details for the most commonly used types of hysterectomy are described in Table 1 (see CERV-C 5 of 7).
- The standard and historical approach for radical hysterectomy is with an open abdominal approach. Previous iterations of the guidelines indicated that radical hysterectomy could be performed via open laparotomy or minimally invasive surgery (MIS) laparoscopic approaches, using either conventional or robotic techniques. However, several key contemporary reports have questioned the presumed therapeutic equivalency of open vs. MIS approaches. A prospective randomized trial[3] demonstrated that minimally invasive radical hysterectomy was associated with lower rates of DFS and OS than open abdominal radical hysterectomy. Moreover, two 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.[4,5] See Discussion for additional details.
- Given recently presented findings of significantly poorer survival outcomes with the minimally invasive approach compared to the open approach in a randomized controlled trial of women with early-stage cervical cancer, women should be carefully counseled about the short-term versus long-term outcomes and oncologic risks of the different surgical approaches.[3-5]

[a]Recommendations by stage are based on the revised 2018 FIGO staging (Bhatla N, Aoki D, Sharma DN, et al. FIGO Cancer Report 2018. Cancer of the cervix uteri. Int J Gynecol Obstet 2018;143(Suppl):22-36.). 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).

Continued
References

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NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF EVALUATION AND SURGICAL STAGING[a]

<u>Types of Resection and Appropriateness for Treatment of Cervical Cancer</u> — continued

- Para-aortic lymph node dissection 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.[a,1,2,7-10]
- 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 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, Aoki D, Sharma DN, et al. FIGO Cancer Report 2018. Cancer of the cervix uteri. Int J Gynecol Obstet 2018;143(Suppl):22-36.). However, trial data cited within this section utilized the 2009 FIGO staging system.

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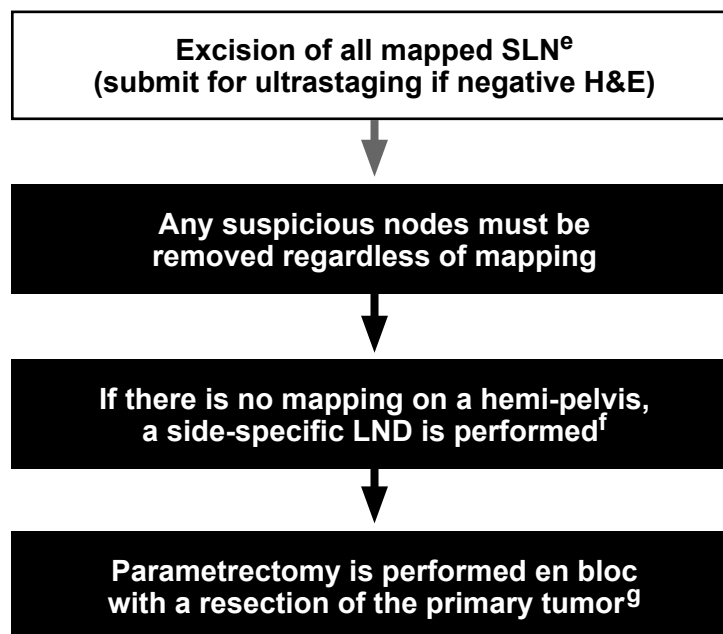
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NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF EVALUATION AND SURGICAL STAGING[a]

<u>Sentinel Lymph Node Mapping for Cervical Cancer:</u>

• 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 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) 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.[4,16]

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]
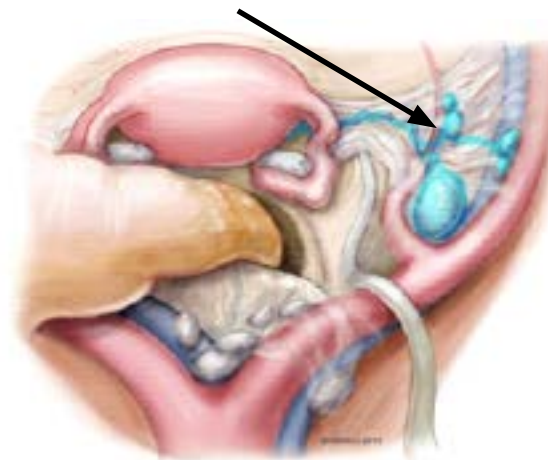
[a]Recommendations by stage are based on the revised 2018 FIGO staging (Bhatla N, Aoki D, Sharma DN, et al. FIGO Cancer Report 2018. Cancer of the cervix uteri. Int J Gynecol Obstet 2018;143(Suppl):22-36.). However, trial data cited within this section utilized the 2009 FIGO staging system.
[c]Figures 1 and 2 are reproduced with permission from Memorial Sloan Kettering Cancer Center. © 2013 Memorial Sloan Kettering Cancer Center.

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References

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Cervical Cancer**

NCCN Guidelines Index
Table of Contents
Discussion

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 nodal dissection 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[d]

Excision of all mapped SLN[e]
(submit for ultrastaging if negative H&E)

↓

Any suspicious nodes must be
removed regardless of mapping

↓

If there is no mapping on a hemi-pelvis,
a side-specific LND is performed[f]

↓

Parametrectomy is performed en bloc
with a resection of the primary tumor[g]

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

[d]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 Aug;122:275-280.
[e]Intracervical injection with dye, 99Tc, or both.
[f]Including interiliac/subaortic nodes.
[g]Exceptions made for select cases (see CERV-C 1 of 7).

Continued

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**CERV-C
4 OF 7**

PRINCIPLES OF EVALUATION AND SURGICAL STAGING

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

	Comparison of Hysterectomy Types			Comparison of Fertility-Sparing Trachelectomy Types	
	Extrafascial Hysterectomy (Type A)[i]	Modified Radical Hysterectomy (Type B)[i]	Radical Hysterectomy (Type C1)[i]	Simple Trachelectomy	Radical Trachelectomy[j]
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 5mm of the cranial aspect of the cervix typically left for cerclage)	Majority removed (approximately 5mm 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 Disesection	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 1-2cm)	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 1-2cm)
Recto-uterine (Uterosacral ligaments)	Divided at cervical border	1-2cm dorsal from cervix (preserves hypogastric nerve plexus)	Type C1 is nerve preserving, divided at least 2cm 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	Laparotomy or minimally invasive	Laparotomy or minimally invasive	Laparotomy or minimally invasive	Vaginal or laparotomy or minimally invasive	Vaginal or laparotomy or minimally invasive

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

[i]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 radican hysterectomy. Lancet Oncology 2008;9:297-303.)

[j]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.

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NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF EVALUATION AND SURGICAL STAGING

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

	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,[k] ileal conduit or continent diversion	N/A	Double barrel wet colostomy,[k] ileal conduit or continent diversion
Reconstruction options GI system	N/A	End colostomy	Double barrel wet colostomy[k] or end colostomy	End colostomy or anastomosis with temporary ileostomy	Double barrel wet colostomy,[k] end colostomy, or anastomosis with temporary ileostomy
Neovaginal reconstruction options	Myocutaneous flap (rectus, gracilis, etc.), or Split thickness skin graft with omental J-flap				

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

[k]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 Jan;128:60-64.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
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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 ± interstitial approach.
- For the majority of patients who receive EBRT for cervical cancer, concurrent platinum-containing chemotherapy (either cisplatin alone [carboplatin if cisplatin intolerant], or cisplatin + 5-fluorouracil) 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 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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NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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 intensity-modulated radiation therapy (IMRT)/volumetric-modulated arc therapy (VMAT)/tomotherapy.
- IMRT may be 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 45 Gy (in conventional fractionation of 1.8–2.0 Gy daily possible 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 (either cisplatin alone [carboplatin if cisplatin intolerant], or cisplatin + 5-fluorouracil) is given during the time of EBRT.

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CERV-D
2 OF 6

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**NCCN Guidelines Version 4.2019
Cervical Cancer**

NCCN Guidelines Index
Table of Contents
Discussion

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 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. Grossly involved unresected nodes may be evaluated for boosting with an additional 10 to 15 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)**.

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 iliacs). 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 is generally recommended. 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.[8] It is particularly useful in patients with recurrent disease within a previously radiated volume. During IORT, overlying normal tissue (such as bowel or other viscera) can be manually displaced from the region at risk. IORT is typically delivered with electrons using 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.

Continued

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PRINCIPLES OF RADIATION THERAPY

<u>General Treatment Information—Continued</u>
<u>Treatment Information-Brachytherapy</u>

• **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 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 dosed at the vaginal surface.**

• **SBRT is not considered an appropriate routine alternative to brachytherapy.**

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NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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 three-dimensional (3D) shape of tumors, nor individual tumor to normal tissue structure correlations. Typical point A prescription doses are 5.5 Gy X 5 fractions for early disease and 6 Gy X 5 for large tumors or those demonstrating a poor response. 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) of ≥80 Gy; however, with large disease or poor response dose goals should be ≥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.[4,5]**
- **Image-guided brachytherapy is encouraged with prescribing to a HR-CTV. The most common historical dosing parameters for brachytherapy use a system that includes specifying the dose at point A and incorporates specific guidelines for "radioactive source loading and distribution of activity" within the uterus and vagina, based on anatomic considerations. Doses are also calculated at standardized point B and bladder and rectal points. Current efforts at 3D image-guided brachytherapy seek to optimize implant dose coverage of the tumor, while potentially reducing the dose to adjacent bladder, rectum, and bowel structures.[6] Nonetheless, the weight of experience and tumor control results and the majority of continuing clinical practice have been based on the point A dosing system.[7] Attempts to improve dosing with image-guided brachytherapy should take care not to underdose tumors relative to the point A system dose recommendations.**
- **The point A dose recommendations provided in the NCCN Guidelines are based on traditional, and widely validated, dose fractionation and brachytherapy at 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/hr. Clinicians using high dose-rate (HDR) brachytherapy would depend on the linear-quadratic model equation to convert nominal HDR dose to point A to a biologically equivalent LDR dose to point A (http://www.americanbrachytherapy.org/guidelines/). Multiple brachytherapy schemes have been used when combined with EBRT. However, one of the more common HDR approaches is 5 insertions with tandem and colpostats, each delivering 6 Gy nominal dose to point A. This scheme results in a nominal HDR point A dose of 30 Gy in 5 fractions, which is generally accepted to be the equivalent to 40 Gy to point A (tumor surrogate dose) using LDR brachytherapy. 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.**

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NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY
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NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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 REGIMENS FOR CERVICAL CANCER[a]
(Strongly consider clinical trial)

Chemoradiation
Preferred Regimens   • Cisplatin   • Carboplatin if patient is cisplatin intolerant   **Other Recommended Regimens**   • Cisplatin/fluorouracil

Recurrent or Metastatic Disease		
First-line combination therapy[b,c]	**Possible first-line single-agent therapy[c]**	**Second-line therapy[d]**

Preferred Regimens
 • Cisplatin/paclitaxel/bevacizumab[1]
   (category 1)
 • Carboplatin/paclitaxel/bevacizumab
 • Topotecan/paclitaxel/bevacizumab[1]
   (category 1)
 • Cisplatin/paclitaxel (category 1)[2,3]
 • Carboplatin/paclitaxel[4,5]
   (category 1 for patients who have received
   prior cisplatin therapy)
 • Topotecan/paclitaxel[1]
 	
 Other Recommended Regimens
 • Cisplatin/topotecan[6]
	Preferred Regimens
	 • Cisplatin[3]
	
	 Other Recommended Regimens
	 • Carboplatin[7]
	 • Paclitaxel[8,9]
		Preferred Regimens
		 • Pembrolizumab for PD-L1–positive[e] or
		   MSI-H/dMMR tumors
		
		 Other Recommended Regimens
		 (All agents listed here are category 2B unless
		 otherwise noted)
		 • Bevacizumab
		 • Albumin-bound paclitaxel
		 • Docetaxel
		 • Fluorouracil
		 • Gemcitabine
		 • Ifosfamide
		 • Irinotecan
		 • Mitomycin
		 • Pemetrexed
		 • Topotecan
		 • Vinorelbine

[a]Cisplatin, carboplatin, docetaxel, and paclitaxel may cause drug reactions (See NCCN Guidelines for Ovarian Cancer--Management of Drug Reactions [OV-C]).
[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 therapy as clinically appropriate.
[d]References for second-line therapy are provided in the Discussion.
[e]Recommended for disease progression on or after chemotherapy in patients whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

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Cervical Cancer**

NCCN Guidelines Index
Table of Contents
Discussion

**SYSTEMIC THERAPY REGIMENS FOR CERVICAL CANCER
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CERV-F
2 OF 2

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Cervical Cancer**

NCCN Guidelines Index
Table of Contents
Discussion

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 uterine 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[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 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 involvement
		IIA1	Invasive carcinoma <4 cm in greatest dimension
		IIA2	Invasive carcinoma ≥4 cm in greatest dimension
	IIB		With parametrial involvement 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 nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes[c]
	IIIA		The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
	IIIB		Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
	IIIC		Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[c]
		IIIC1	Pelvic lymph node metastasis only
		IIIC2	Para-aortic 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 to adjacent pelvic organs
	IVB		Spread to distant organs

When in doubt, the lower staging should be assigned.
[a] Imaging and pathology can be used, where available, to supplement clinical findings with respect to tumor size and extent, in all stages.
[b] The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.
[c] 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.

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Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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

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 between 2017 and 2018, 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 PubMed search resulted in 170 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section

(eg, e-publications ahead of print, meeting abstracts). 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, and adenocarcinoma of the cervix. Neuroendocrine carcinoma, small cell tumors, glassy-cell carcinomas, sarcomas, and other histologic types are not within the scope of these guidelines.

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 metaanalysis, 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

MS-10

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

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NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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 at www.NCCN.org).

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

MS-16

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

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NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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

MS-19

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

MS-20

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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National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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National Comprehensive Cancer Network®

**NCCN Guidelines Version 4.2019
Cervical Cancer**

NCCN Guidelines Index
Table of Contents
Discussion

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NCCN Guidelines Index
Table of Contents
Discussion

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National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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National Comprehensive Cancer Network® (NCCN)

NCCN Guidelines Version 4.2019
Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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Cervical Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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