National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Cervical Cancer

Version 3.2013

NCCN.org

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NCCN Guidelines® Version 3.2013 Panel Members
Cervical Cancer

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Cervical Cancer TOC
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NCCN Guidelines Panel Disclosures

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

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

See NCCN Categories of Evidence and Consensus

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

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2012.

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NCCN Guidelines Version 3.2013 Updates Cervical Cancer

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Updates in Version 3.2013 of the NCCN Guidelines for Cervical Cancer from Version 2.2013 include:

CERV-B Chemotherapy Regimens for Recurrent or Metastatic Cervical Cancer
- **Cisplatin/paclitaxel/bevacizumab was added as first-line combination therapy for the treatment of recurrent or metastatic cervical cancer.**

The 2.2013 version of the NCCN Guidelines for Cervical Cancer represent the addition of the updated Discussion text (MS-1).

Updates in Version 1.2013 of the NCCN Guidelines for Cervical Cancer from Version 1.2012 include:

CERV-1
- **Workup: "Smoking cessation and counseling intervention" was added.**

CERV-2
- **A new section was added that provides recommendations for fertility sparing treatment options for stages IA and IB1.**

CERV-3 and CERV-4
- **A new section was added that provides recommendations for non-fertility-sparing treatment options for stages IA and IB1.**

CERV-10
- **Surveillance: This section was revised as follows:**
  - **First bullet: "Interval H&P" was modified to include "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."**
  - **Second bullet: "Cervical/vaginal cytology every 3-6 mo for 2 y, then every 6-12 mo for 3-5 y then annually" was changed to "Cervical/vaginal cytology annually as indicated for the detection of lower genital tract neoplasia."**
  - **Third bullet: The imaging recommendations were combined to read "Imaging (chest radiography, CT, PET, PET/CT, MRI) as indicated based on symptoms or examination findings suspicious for recurrence."**
  - **Fourth bullet: Revised to read, "Laboratory assessment (CBC, BUN, creatinine) as indicated based on symptoms or examination findings suspicious for recurrence."**

CERV-10--continued
- **Footnote "n" that states, "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" is new to the algorithm.**
- **Footnote "o" was revised to state, "A single PET-CT scan performed at 3-6 months after chemoradiation for locally advanced cervical cancer can be used to identify early or asymptomatic persistence/recurrence. Other imaging studies (such as chest x-ray, CT scan, MRI, and subsequent PET-CT) may also be used to assess or follow recurrence when clinically indicated but are not recommended for routine surveillance."**

CERV-11
- **Local/regional recurrence; Prior RT; Central disease; Therapy for Relapse: The recommendation changed to "Pelvic exenteration ± intraoperative RT (IORT) (category 3 for IORT)."**
- **Local/regional recurrence; Prior RT; Noncentral disease; Therapy for Relapse: The recommendation "Resection with IORT for close or positive margins" changed from category 2A to category 3.**

CERV-12
- **Distant metastases; Resectable; Therapy for Relapse: In the recommendation "Consider resection ± IORT," the option of IORT changed from category 2A to category 3.**

CERV-A--Principles of Radiation Therapy
- **The Principles of Radiation Therapy pages were revised for clarity.**

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WORKUP

- H&P
- Complete blood count (CBC) (including platelets)
- Cervical biopsy, pathologic review
- Cone biopsy as indicated[a]
- LFT/renal function studies
- Imaging (optional for ≤ stage IB1):
  - Chest x-ray
  - CT or PET-CT scan
  - MRI as indicated

Optional (≥ stage IB2):

- EUA cystoscopy/proctoscopy[b]
- Smoking cessation and counseling intervention

CLINICAL STAGE

Stage IA1	See Primary Treatment (Fertility Sparing) (CERV-2)
	See Primary Treatment (Non-Fertility Sparing) (CERV-3)
Stage IA2 Stage IB1	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 IB2 Stage IIA2	See Primary Treatment (CERV-4) and (CERV-6)
Stage IIB Stage IIIA, IIIB Stage IVA	See Primary Treatment (CERV-6)
Incidental finding of invasive cancer at simple hysterectomy	See Primary Treatment (CERV-9)

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

[a] See Discussion for indications for cone biopsy.

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

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CLINICAL STAGE	PRIMARY TREATMENT (FERTILITY SPARING)[c]	
Stage IA1 (no lymphovascular space invasion [LVSI])	Cone biopsy with negative margins (preferably a non-fragmented specimen with 3-mm negative margins) (If positive margins, repeat cone biopsy or perform trachelectomy)	See Surveillance (CERV-10)
Stage IA1 (with LVSI) and Stage IA2	Cone biopsy with negative margins (preferably a non-fragmented specimen with 3-mm negative margins) + pelvic lymph node dissection or Radical trachelectomy + pelvic lymph node dissection (± para-aortic lymph node sampling [category 2B])	See Surveillance (CERV-10)
Stage IB1[d]	Radical trachelectomy + pelvic lymph node dissection ± para-aortic lymph node sampling	See Surveillance (CERV-10)

[c]No data support a fertility-sparing approach in small cell neuroendocrine tumors or minimal deviation adenocarcinoma (also known as 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.

[d]Fertility-sparing surgery for stage IB1 has been most validated for tumors ≤2 cm.

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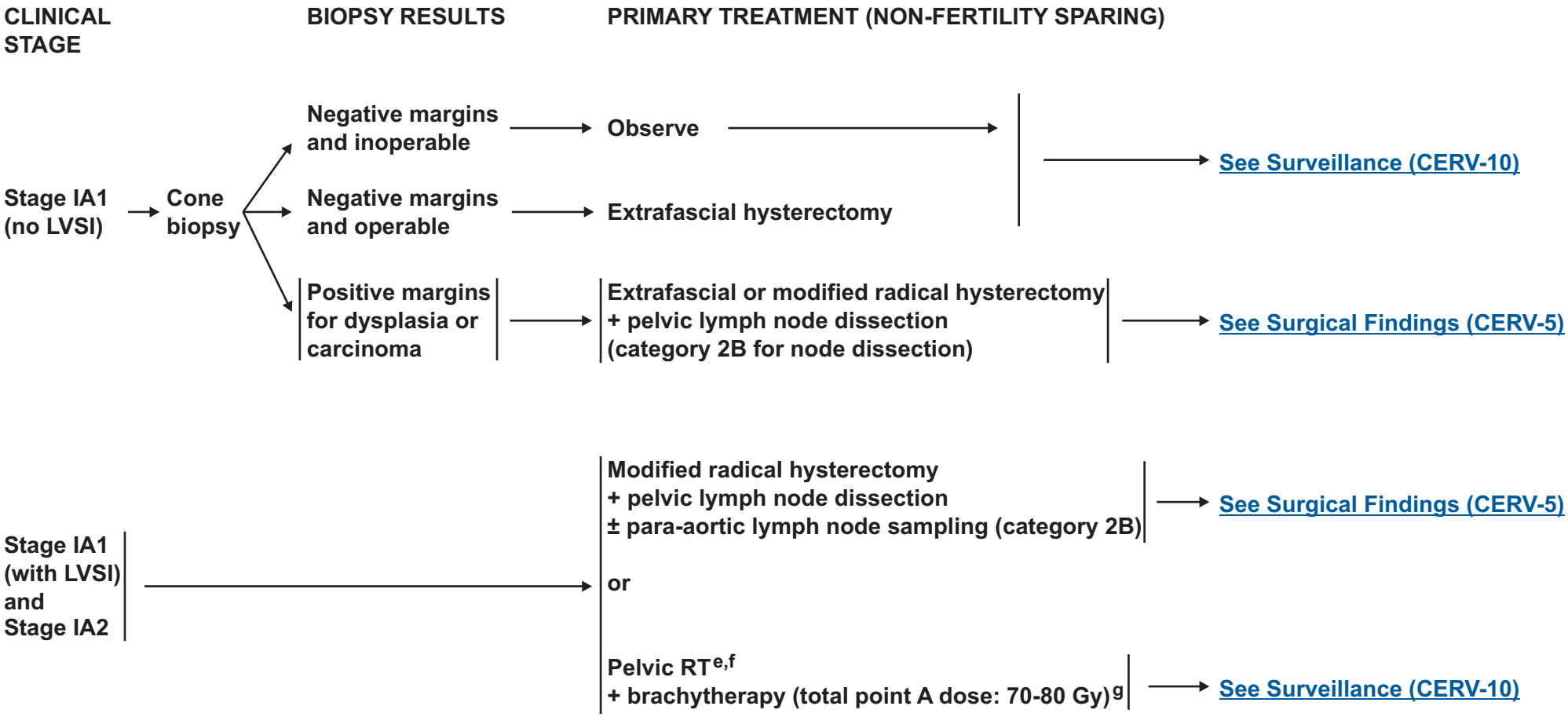

[e] Radiation can be an option for medically inoperable patients or those who refuse surgery.
[f] See Principles of Radiation Therapy for Cervical Cancer (CERV-A).
[g] These doses are recommended for most patients based on summation of conventional external-beam fractionation and low-dose rate (40-70 cGy/h) brachytherapy equivalents. Modify treatment based on normal tissue tolerance. (See Discussion)

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CLINICAL STAGE | **PRIMARY TREATMENT (NON-FERTILITY SPARING)**

Stage IB1 and Stage IIA1 →

- **Radical hysterectomy + pelvic lymph node dissection ± para-aortic lymph node sampling (category 1)** → See Surgical Findings (CERV-5)
- **or**
- **Pelvic RT[e,f] + brachytherapy (total point A dose: 80-85 Gy)[g] ± concurrent cisplatin-containing chemotherapy[h]** → See Surveillance (CERV-10)

Stage IB2 and Stage IIA2 (also see CERV-6 for alternative recommendations for these patients) →

- **Pelvic RT[f] + concurrent cisplatin-containing chemotherapy[h] + brachytherapy (total point A dose ≥85 Gy)[g] (category 1)** → See Surveillance (CERV-10)
- **or**
- **Radical hysterectomy + pelvic lymph node dissection ± para-aortic lymph node sampling (category 2B)** → See Surgical Findings (CERV-5)
- **or**
- **Pelvic RT[f] + concurrent cisplatin-containing chemotherapy[h] + brachytherapy (total point A dose 75-80 Gy)[g] + adjuvant hysterectomy (category 3)** → See Surveillance (CERV-10)

[e] Radiation can be an option for medically inoperable patients or those who refuse surgery.
[f] See Principles of Radiation Therapy for Cervical Cancer (CERV-A).
[g] These doses are recommended for most patients based on summation of conventional external-beam fractionation and low-dose rate (40-70 cGy/h) brachytherapy equivalents. Modify treatment based on normal tissue tolerance. (See Discussion)
[h] Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.

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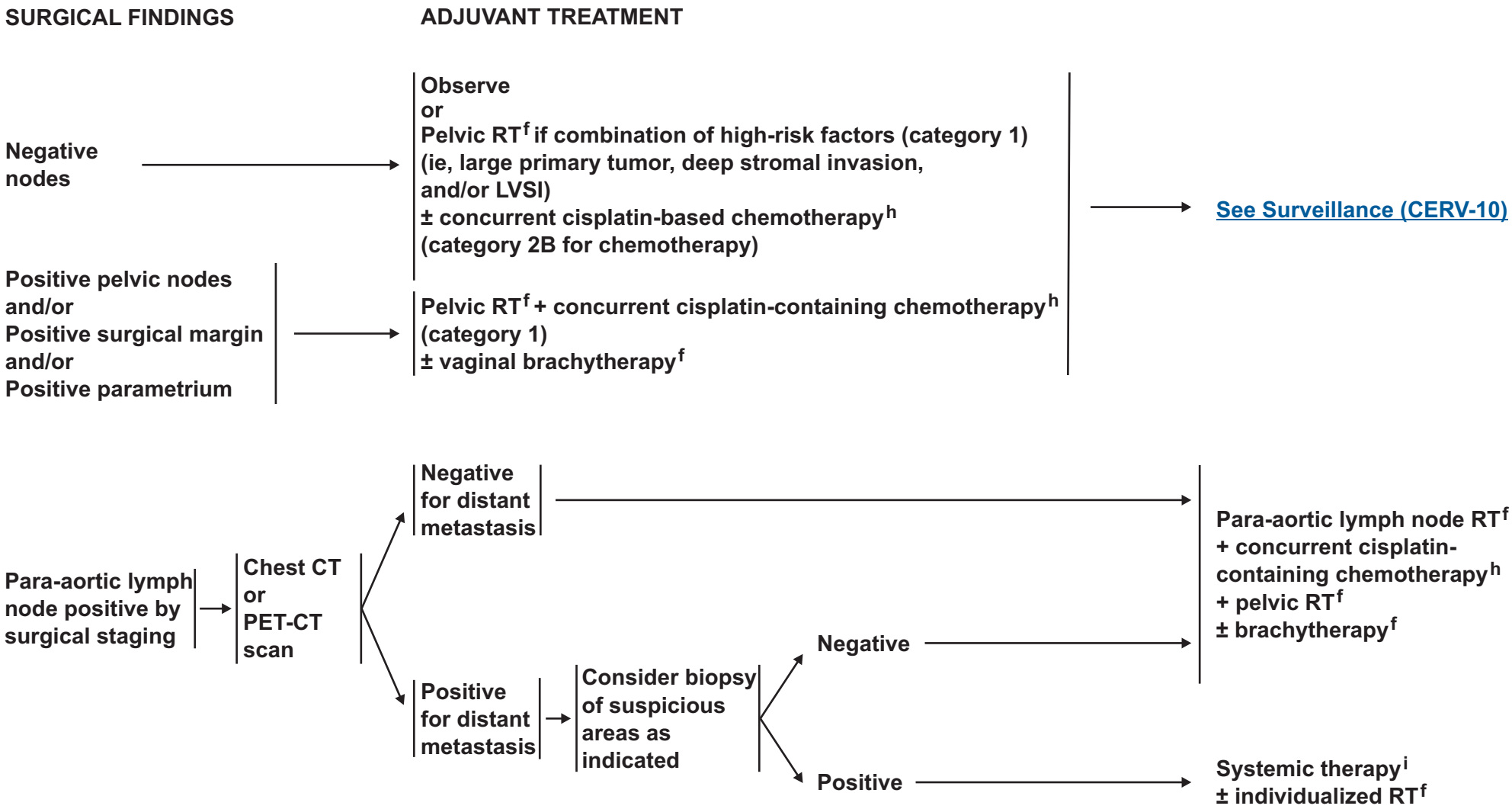

[f] See Principles of Radiation Therapy for Cervical Cancer (CERV-A).
[h] Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.
[i] See Chemotherapy Regimens for Recurrent or Metastatic Cervical Cancer (CERV-B).

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See Surveillance (CERV-10)

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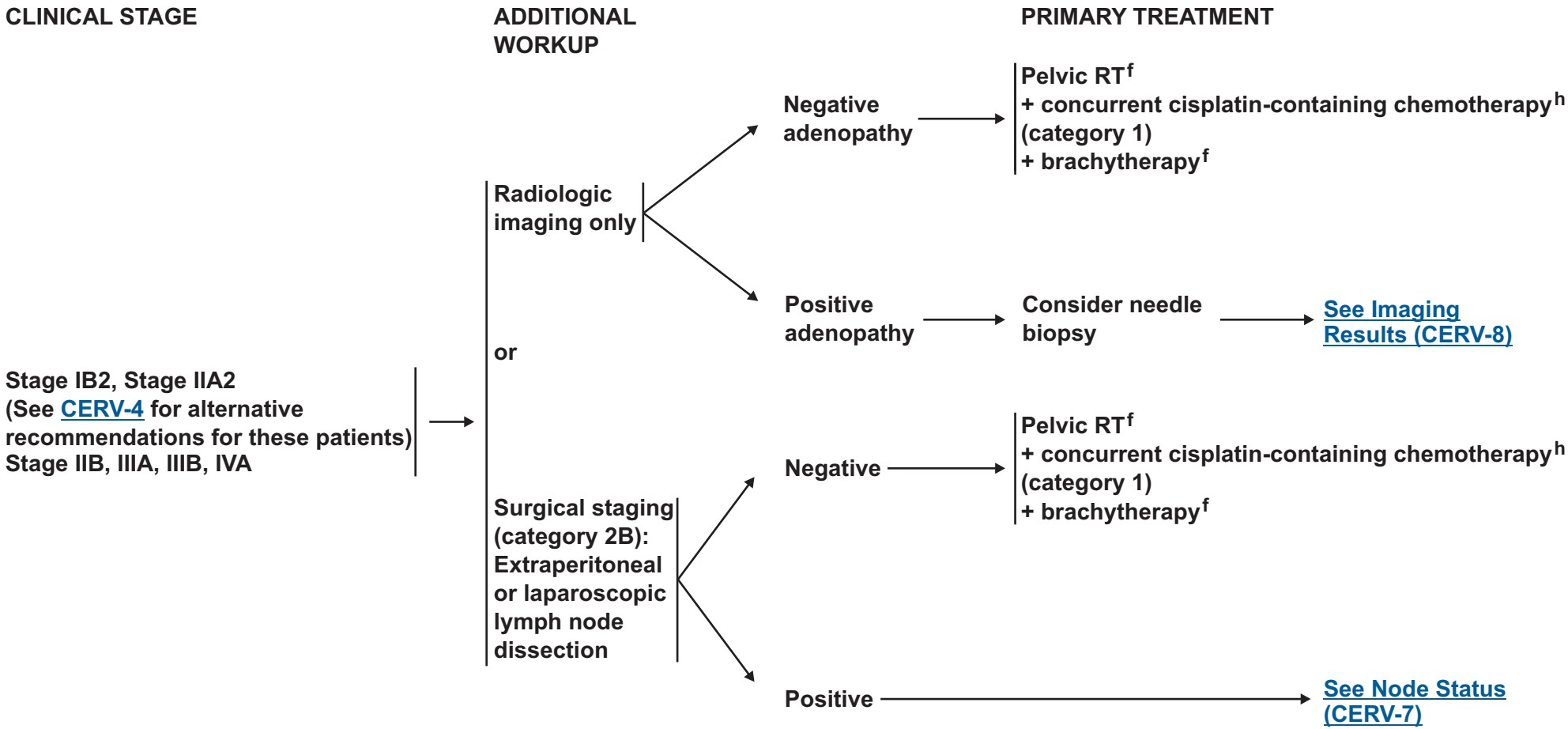

[f] See Principles of Radiation Therapy for Cervical Cancer (CERV-A).

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

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See Surveillance (CERV-10)

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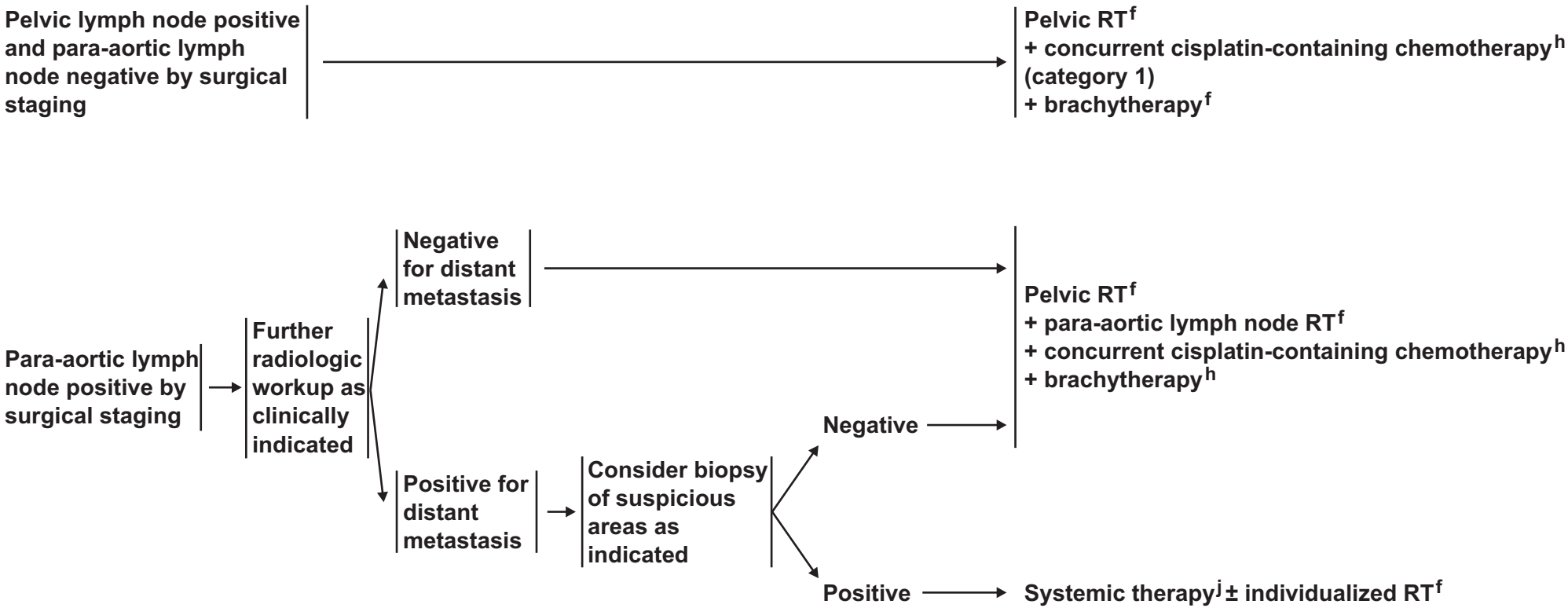
Stage IB2, IIA2; Stage IIB, IIIA, IIIB, IVA
NODE STATUS

PRIMARY TREATMENT



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

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See Surveillance (CERV-10)

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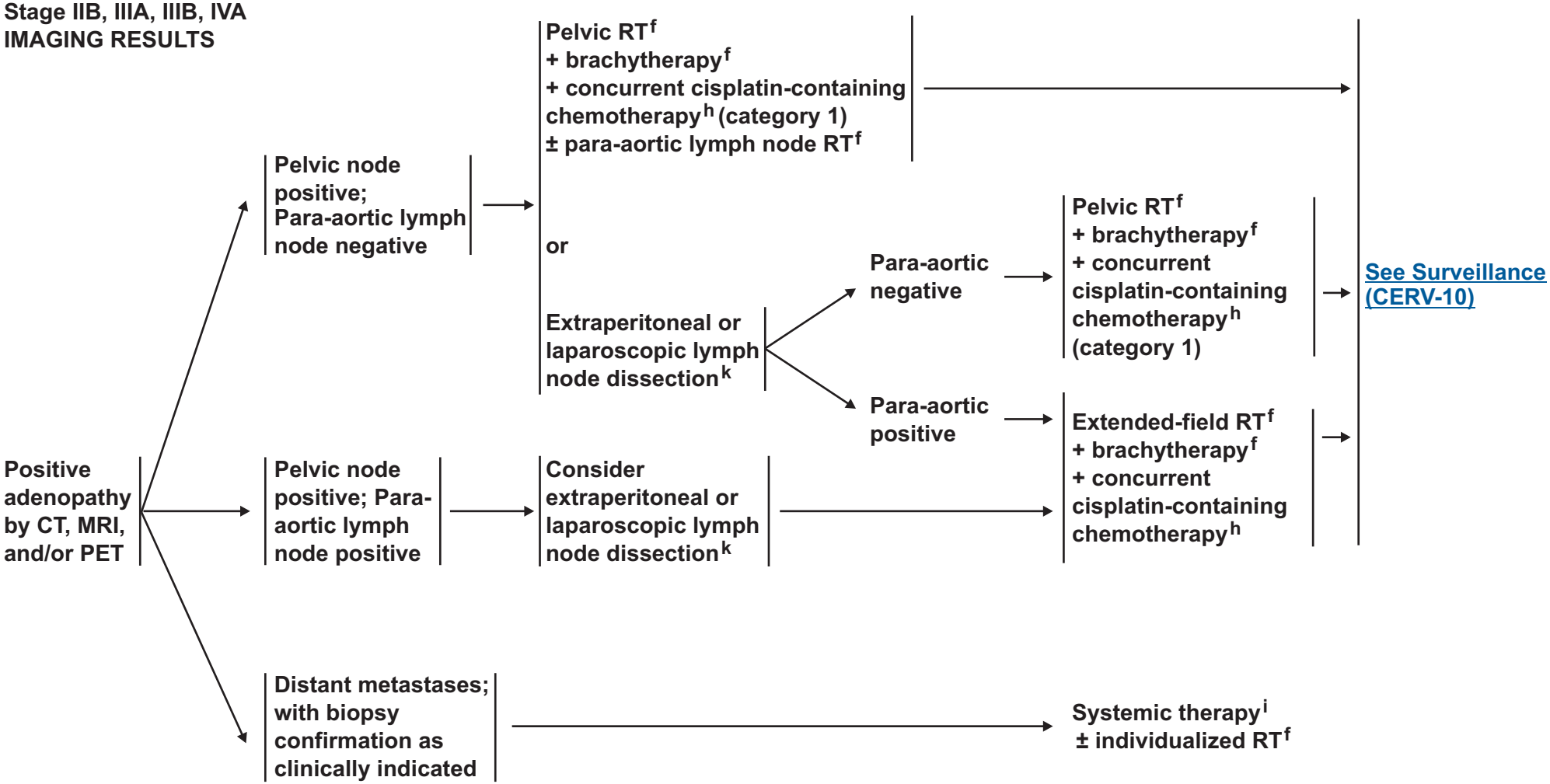
Stage IB2, IIA2
Stage IIB, IIIA, IIIB, IVA
IMAGING RESULTS

PRIMARY TREATMENT



[f] See Principles of Radiation Therapy for Cervical Cancer (CERV-A).
[h] Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.
[i] See Chemotherapy Regimens for Recurrent or Metastatic Cervical Cancer (CERV-B).
[k] Consider postoperative imaging to confirm the adequacy of node removal.

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See Surveillance (CERV-10)

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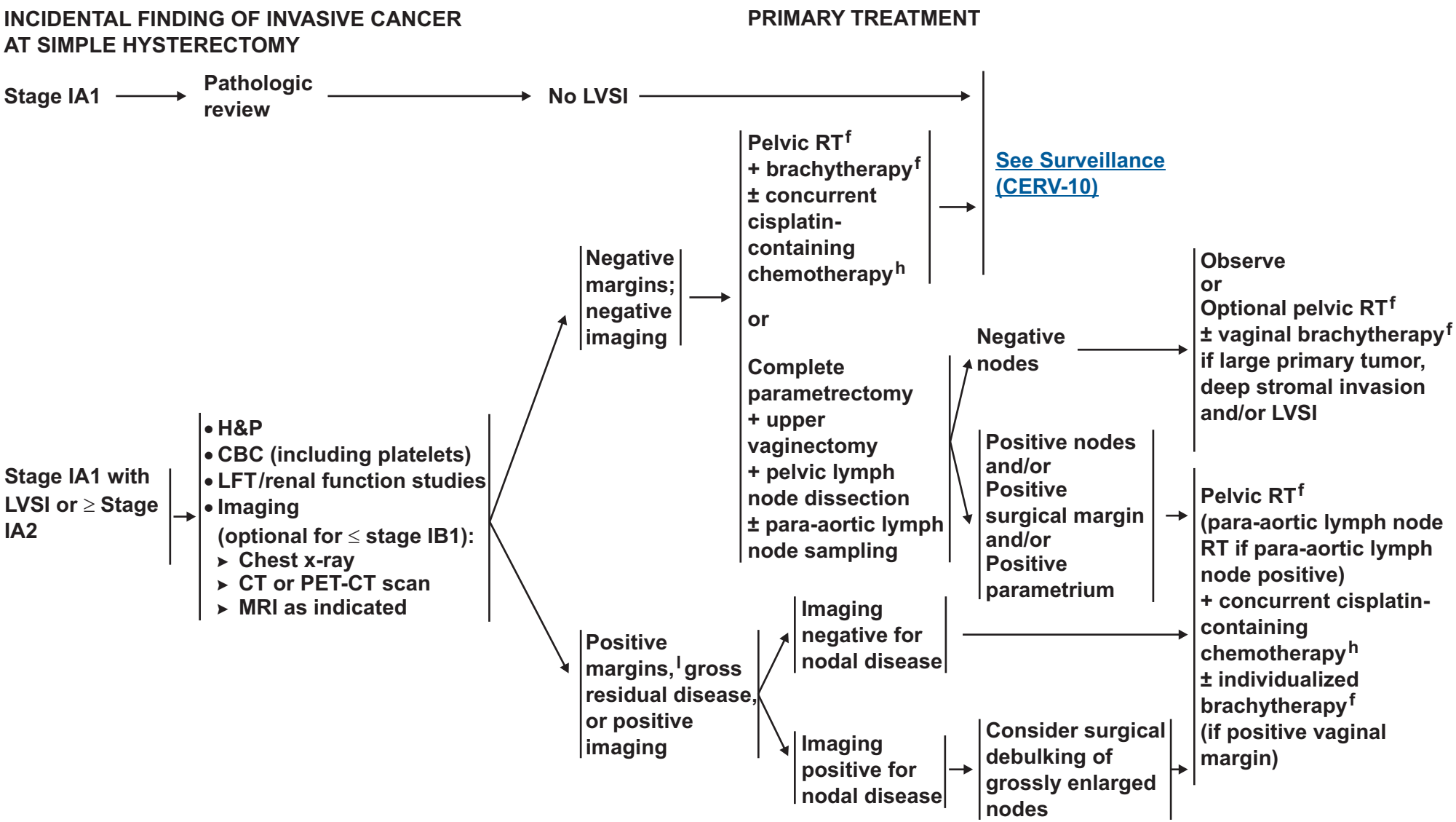

[f] See Principles of Radiation Therapy for Cervical Cancer (CERV-A).
[h] Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.
[l] Invasive cancer at surgical margin.

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See Surveillance (CERV-10)

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SURVEILLANCE[m]

- 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[n] as indicated for the detection of lower genital tract neoplasia
- Imaging (chest radiography, CT, PET, PET/CT, MRI) as indicated based on symptoms or examination findings suspicious for recurrence[o]
- Laboratory assessment (CBC, blood urea nitrogen (BUN), creatinine) as indicated based on symptoms or examination findings suspicious for recurrence
- Recommend use of vaginal dilator after RT
- Patient education regarding symptoms

→ **Persistent or recurrent disease** →

WORKUP

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

→ See Therapy for Relapse (Local/regional recurrence) (CERV-11)

→ See Therapy for Relapse (Distant metastases) (CERV-12)

[m] Salani R, Backes FJ, Fung MF, et al. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. Am J Obstet Gynecol 2011;204:466-478.

[n] 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.

[o] A single PET-CT scan performed at 3-6 months after chemoradiation for locally advanced cervical cancer can be used to identify early or asymptomatic persistence/recurrence. Other imaging studies (such as chest x-ray, CT scan, MRI, and subsequent PET-CT) may also be used to assess or follow recurrence when clinically indicated but are not recommended for routine surveillance. (See Discussion)

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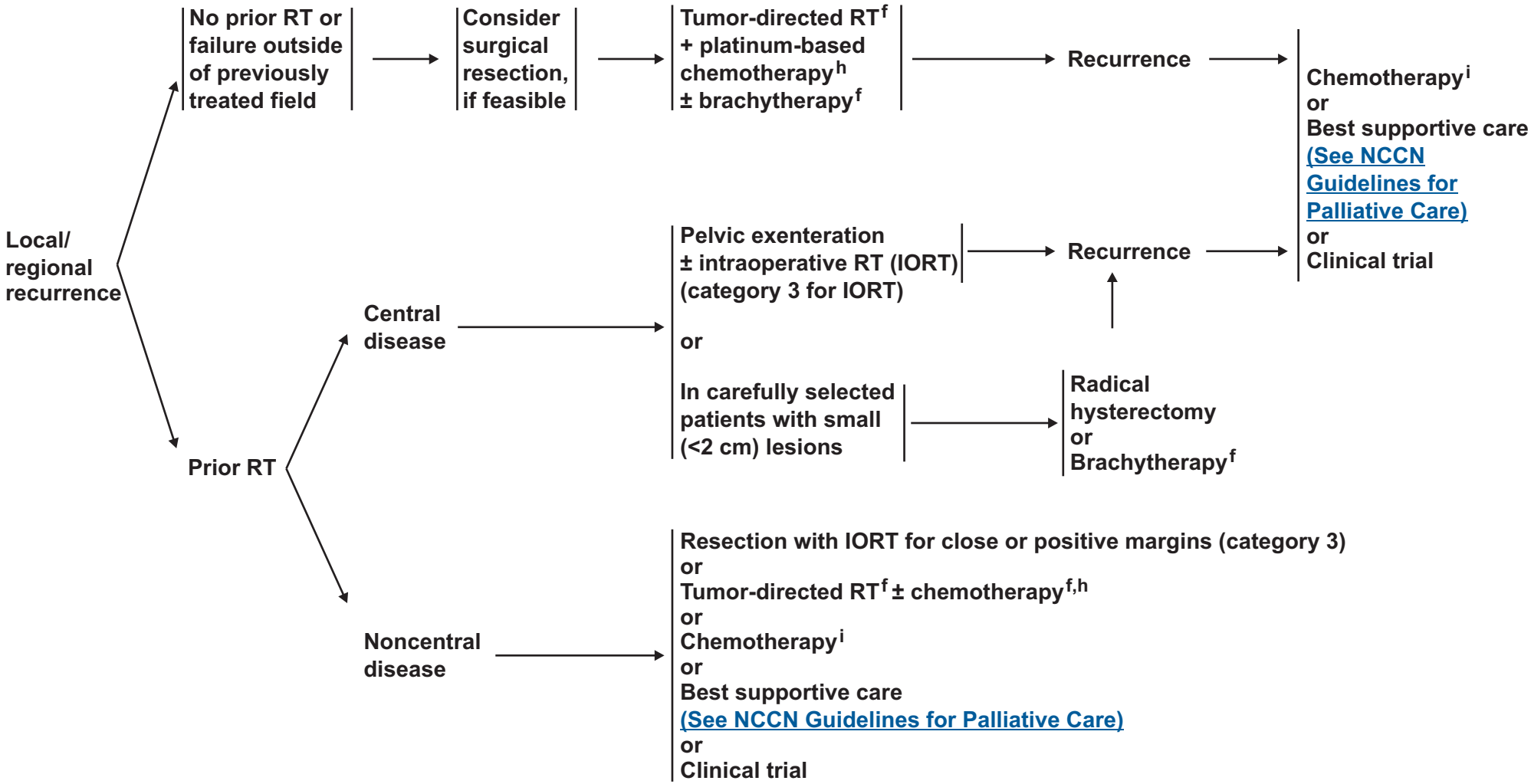
THERAPY FOR RELAPSE



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

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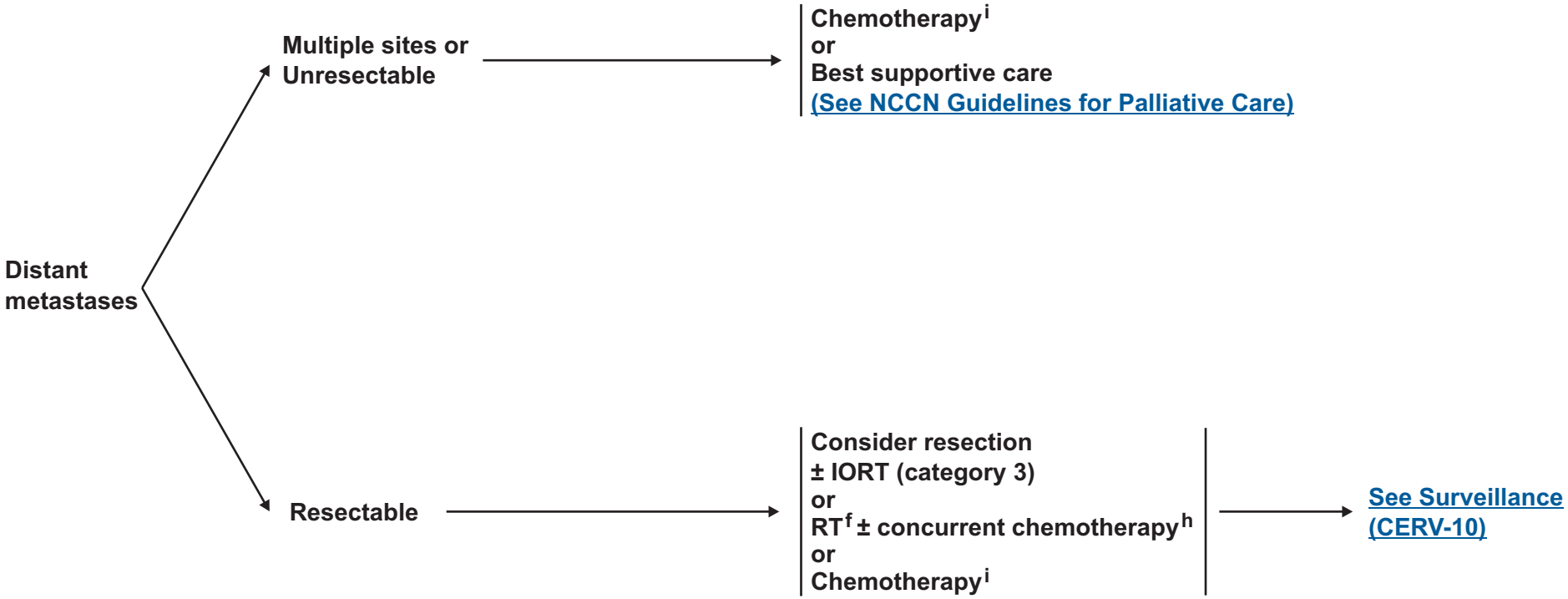

[f] See Principles of Radiation Therapy for Cervical Cancer (CERV-A).
[h] Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.
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PRINCIPLES OF RADIATION THERAPY FOR CERVICAL CANCER

External Beam Radiation Therapy (EBRT)

- **The use of CT–based treatment planning and conformal blocking is considered the standard of care for EBRT. MRI is the best imaging modality for determining soft tissue and parametrial involvement in patients with advanced tumors. In patients who are not surgically staged, PET imaging is useful to help define the nodal volume of coverage.**
- **The volume of EBRT should cover the gross disease (if present), parametria, uterosacral ligaments, sufficient vaginal margin from the gross disease (at least 3 cm), presacral nodes, and other nodal volumes at risk. For patients with negative nodes on surgical or radiologic imaging, the radiation volume should include the entirety of the external iliac, internal iliac, and obturator nodal basins. For patients deemed at higher risk of lymph node involvement (eg, bulkier tumors; 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).**
- **Coverage of microscopic nodal disease requires an EBRT dose of approximately 45 Gy (in conventional fractionation of 1.8-2.0 Gy daily), and highly conformal boosts of an additional 10-15 Gy may be considered for limited volumes of gross unresected adenopathy. For the majority of patients who receive EBRT for cervical cancer, concurrent cisplatin-based chemotherapy (either cisplatin alone, or cisplatin + 5-fluorouracil) is given during the time of EBRT.**
- **Intensity-modulated radiation therapy (IMRT) and similar highly conformal methods of dose delivery may be helpful in minimizing the dose to the bowel and other critical structures in the post-hysterectomy setting 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) should not be used as routine alternatives to brachytherapy for treatment of central disease in patients with an intact cervix. 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.**

Continued

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

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PRINCIPLES OF RADIATION THERAPY FOR CERVICAL CANCER

Brachytherapy

- Brachytherapy is a critical component of definitive therapy for all patients with primary cervical cancer who are not candidates for surgery. This is usually performed using an intracavitary approach, with an intrauterine tandem and vaginal colpostats. Depending on the patient and tumor anatomy, the vaginal component of brachytherapy in patients with an intact cervix may be delivered using ovoids, ring, or cylinder brachytherapy (combined with the intrauterine tandem). When combined with EBRT, brachytherapy is often initiated towards the latter part of treatment, when sufficient primary tumor regression has been noted to permit satisfactory brachytherapy apparatus geometry. In highly selected very early disease (ie, stage IA2), brachytherapy alone (without external-beam radiation) may be an option.
- In rare cases, patients whose tumor geometry renders intracavitary brachytherapy infeasible may be best treated using an interstitial approach; however, such interstitial brachytherapy should only be performed by individuals and at institutions with appropriate experience and expertise.
- In selected post-hysterectomy patients (especially those with positive vaginal mucosal surgical margins), vaginal cylinder brachytherapy may be used as a boost to EBRT.

Radiation Dosing Considerations

- 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 3-D image-guided brachytherapy seek to optimize implant dose coverage of the tumor, while potentially reducing the dose to adjacent bladder, rectum, and bowel structures.[1] Nonetheless, the weight of experience and tumor control results and the majority of continuing clinical practice have been based on the point A dosing system.[2] Attempts to improve dosing with image-guided brachytherapy should take care not to underdose tumors relative to the point A system dose recommendations.
- The point A dose recommendations provided in the NCCN Guidelines are based on traditional, and widely validated, dose fractionation and brachytherapy at low dose rates (LDRs). In these provided dose recommendations, for EBRT, the dose is delivered at 1.8-2.0 Gy per daily fraction. For brachytherapy, the dose at point A assumes an LDR delivery of 40-70 cGy/h. Clinicians using high-dose rate (HDR) brachytherapy would depend on the linear-quadratic model equation to convert nominal HDR dose to 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.

Continued

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PRINCIPLES OF RADIATION THERAPY FOR CERVICAL CANCER

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 30-40 Gy to point A (in LDR equivalent dose), for a total point A dose (as recommended in the guidelines) of 80 Gy (small volume cervical tumors) to 85 Gy or greater (larger volume cervical tumors). Grossly involved unresected nodes may be evaluated for boosting with an additional 10-15 Gy of highly conformal (and reduced volume) EBRT. With higher doses, especially of EBRT, care must be taken to exclude, or to severely limit, the volume of normal tissue included in the high-dose region(s) (see Discussion).

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 3-4 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 45-50 Gy in standard fractionation is generally recommended. Grossly involved unresected nodes may be evaluated for boosting with an additional 10-15 Gy of highly conformal (and reduced volume) EBRT. With higher doses, especially of EBRT, care must be taken to exclude, or to severely limit, the volume of normal tissue included in the high-dose region(s) (see Discussion).

Intraoperative Radiation Therapy (IORT)

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

Continued

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

First-line combination therapy
- Cisplatin/paclitaxel[1,2]
- Carboplatin/paclitaxel[3]
- Cisplatin/topotecan[4]
- Cisplatin/paclitaxel/bevacizumab[5]
- Cisplatin/gemcitabine (category 2B)[6]

Possible first-line single-agent therapy
- Cisplatin (preferred as a single agent)[2]
- Carboplatin[7]
- Paclitaxel[8]

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

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

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CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC CERVICAL CANCER
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Table 1 **AJCC Tumor-Node-Metastases (TNM) and International Federation of Gynecology and Obstetrics (FIGO) Surgical Staging Systems for Carcinoma of the Uterine Cervix**

TNM Categories	FIGO Stages	Surgical-Pathologic Findings
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis*		Carcinoma in situ (preinvasive carcinoma)
T1	I	Cervical carcinoma confined to cervix (extension to corpus should be disregarded)
T1a**	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification
T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2[#]
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or nonfunctioning kidney[##]
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
T4	IVA	Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)

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

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

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

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

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Staging-Cervical Cancer

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

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

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

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 10/25/12

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.

Discussion update in progress

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Overview

An estimated 12,200 new cases of carcinoma of the uterine cervix (ie, cervical cancer) will be diagnosed in the United States in 2012, and 4200 people will die of the disease.[1,2] Cervical cancer rates are decreasing among women in the United States, although incidence remains high among Hispanic/Latino, Black, and Asian women.[3-6] However, cervical cancer is a major world health problem for women. The global yearly incidence of cervical cancer for 2008 was 529,800; the annual death rate was 275,100.[7] It is the third most common cancer in women worldwide,[8,9] with 85% of cases occurring in developing countries, where cervical cancer is the second most frequent cause of cancer death in women.[7]

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%.[8] Immunization against HPV prevents infection with certain types of HPV 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, contraceptive use, early age of onset of coitus, larger number of sexual partners, history of sexually transmitted disease, and chronic immunosuppression.[17] Smoking cessation should be advised in current smokers, and abstinence should be encouraged in former smokers (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.[3,4,18,19] However, adenocarcinoma of the cervix has increased over the past 3 decades, probably because cervical cytologic screening methods are less effective for adenocarcinoma.[20-23] 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.[22,24]

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.

Diagnosis and Workup

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

Currently, the International Federation of Gynecology and Obstetrics (FIGO) evaluation procedures for staging are limited to colposcopy, biopsy, conization of the cervix, cystoscopy, and proctosigmoidoscopy. More complex radiologic and surgical staging procedures are not addressed in the FIGO classification. In the United States, however, CT, MRI, combined PET-CT, and surgical staging are often used to guide treatment options and design.[25-29]

The earliest stages of cervical carcinoma may be asymptomatic or associated with a watery vaginal discharge and postcoital bleeding or

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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).[6,23] The College of American Pathologists (CAP) protocol for cervical carcinoma is a useful guide (http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2012/Cervix_12protocol.pdf). This CAP protocol was revised in June 2012 and reflects recent updates in the AJCC/FIGO staging (ie, AJCC Cancer Staging Manual, 7th edition).

Workup for these patients with suspicious symptoms includes history and physical examination, 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).[26,30] However, imaging is optional for patients with stage IB1 or smaller tumors (see *Workup* in the NCCN Guidelines for Cervical Cancer). Cystoscopy and proctoscopy are only recommended if bladder or rectal extension is suspected.

Panel members discussed whether laparoscopic and robotic approaches should be recommended for staging and treatment. These techniques are being used more frequently, but long-term outcomes data are not yet available.[31] Laparoscopic staging, lymphadenectomies, and radical hysterectomies can be performed satisfactorily and are used routinely in selected patients in several NCCN Member Institutions.[32-35] Data from studies overseas suggest that recurrence rates are low for laparoscopic radical hysterectomy after 3 to 6 years of follow-up.[36,37] Robotic radical hysterectomy (which is another minimally invasive surgical technique) is currently being performed for patients with early-stage cervical cancer. Potential advantages associated with laparoscopic and robotic approaches include decreased hospital stay and more rapid patient recovery.[38-40]

Staging

Because noninvasive radiographic imaging may not be routinely available in low-resource countries, the FIGO system limits the imaging to chest radiography, intravenous pyelography, and barium enema. The staging of carcinoma of the cervix is largely a clinical evaluation. Although surgical staging is more accurate than clinical staging, surgical staging often cannot be performed in low-resource countries.[28,41,42] The panel currently uses the 2010 FIGO definitions and staging system (see Table 1).[41,43] This staging system from FIGO has been approved by the AJCC.[44] With the 2010 staging, stage IIA is now subdivided into stage IIA1 (tumor size ≤4 cm) and stage IIA2 (tumor size >4 cm), which is the only change from the previous 1994 FIGO staging system.

Importantly, lymphovascular space invasion (LVSI) does not alter the FIGO classification.[41] 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 1B1 guidelines.

The use of MRI, CT, or combined PET-CT scans may aid in treatment planning but is not accepted for formal staging purposes.[28,42,45,46] In addition, FIGO has always maintained that staging is intended for comparison purposes only and not as a guide for therapy. As a result, the panel uses the FIGO definitions as the stratification system for these guidelines, although the findings on imaging studies (ie, CT and MRI)

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are used to guide treatment options and design.[30,47,48] MRI is useful to rule out disease high in the endocervix.

Primary Treatment

The primary treatment of early-stage cervical cancer is either surgery or radiation therapy (RT). Surgery is typically reserved for early-stage disease and smaller lesions, such as stage IA, IB1, and selected IIA1.[27] The panel agrees that concurrent chemoradiation is the primary treatment of choice for stages IB2 to IVA disease based on the results of 5 randomized clinical trials (see Table 2).[49,50] 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.[51-53]

Pelvic RT or chemoradiation will invariably lead to ovarian failure in premenopausal women.[54] 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.[55,56]

Clinical Trials and Basis for Treatment Selection

A randomized Italian study compared RT alone versus radical hysterectomy and lymph node dissection in patients with clinical early-stage disease (stage IB–IIA).[57] In surgical patients, 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 cisplatin-based chemotherapy (either cisplatin alone or cisplatin/5-FU), is the treatment of choice for stages IB2, II, III, and IVA disease based on the results of 5 randomized clinical trials (see Table 2).[58-63] These 5 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 5 trials clearly established a role for concurrent cisplatin-based 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 (http://www.nih.gov/news/pr/feb99/nci-22.htm).[63] Long-term follow-up of 3 of these trials has confirmed that concurrent cisplatin-based chemoradiation improves progression-free survival (PFS) and overall survival when compared with RT with (or without) hydroxyurea.[64-66] A recent meta-analysis reported that chemoradiotherapy leads to a 6% improvement in 5-year survival (hazard ratio, 0.81; *P*<.001).[67] A large population-based registry analysis in Canada (n=4069) confirmed that chemoradiotherapy improved outcomes when compared with RT alone.[68]

Although chemoradiation is tolerated, acute and long-term side effects have been reported.[67,69,70] Some oncologists prefer concurrent single-agent cisplatin chemoradiation over cisplatin plus 5-FU chemoradiation, because the latter may be more toxic.[50,71] Concurrent carboplatin or nonplatinum chemoradiation regimens are options for patients who may not tolerate cisplatin-containing chemoradiation.[67,72-76] Note that when concurrent chemoradiation is used, the chemotherapy is typically given when the external-beam pelvic radiation is administered.[50] The panel believes that using “systemic consolidation” (ie, adding chemotherapy after chemoradiation) should only be used in clinical trials (eg, RTOG 0724, International OUTBACK trial [ANZGOG]).[67,77-79]

Discussion Update in progress

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Early-Stage Disease

After careful clinical evaluation and staging, the primary treatment of early-stage cervical cancer is either surgery or RT. The treatment schema is stratified using the FIGO staging system (see Table 1). A new fertility-sparing algorithm was added in 2012 for select patients with stage IA and IB1 disease (see *Primary Treatment (Fertility Sparing)* in the NCCN Guidelines for Cervical Cancer). Fertility-sparing surgery is generally not recommended for patients with small cell neuroendocrine tumors or those with minimal deviation adenocarcinoma because of a lack of data.

Stage IA1 Disease

Recommended options for stage IA1 depend on the results of cone biopsy and on whether patients 1) want to preserve their fertility; 2) are medically operable; and 3) have LVSI (see *Primary Treatment (Fertility Sparing)* and *Primary Treatment (Non–Fertility Sparing)* in the NCCN Guidelines for Cervical Cancer). The extent of the lymph node dissection depends on whether pelvic nodal disease and/or LVSI is present and the size of the tumors.

Fertility Sparing

For patients who desire fertility preservation, cone biopsy with or without pelvic lymph node dissection is recommended.[80,81] For patients with negative margins after cone biopsy, observation is an option for select patients without LVSI if they desire fertility preservation. For patients with positive margins after cone biopsy, options include either a radical trachelectomy or a repeat cone biopsy. For patients with LVSI, radical trachelectomy and pelvic lymph node dissection is recommended with (or without) para-aortic lymph node sampling (category 2B for para-aortic lymph node sampling) (see *Primary Treatment (Fertility Sparing)* in the NCCN Guidelines for Cervical Cancer).[82-86] Pelvic lymph node dissection is recommended for patients with LVSI who have negative margins after cone biopsy.

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. Note that *trachelectomy* (also known as cervicectomy) refers to removal of the cervix and upper vagina (ie, uterus remains intact).

A study found that among women attempting to conceive after radical trachelectomy for early-stage cervical cancer, the 5-year cumulative pregnancy rate was 52.8%; the cancer recurrence rate was low, but the miscarriage rate was higher.[87] 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.[88,89]

Non–Fertility Sparing

For medically operable patients who do not desire fertility preservation, extrafascial (ie, simple or total) 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 pelvic lymph node dissection (category 2B for node dissection) (see *Primary Treatment (Non–Fertility Sparing)* in the NCCN Guidelines for Cervical Cancer). If LVSI is present, then modified radical hysterectomy with lymph node dissection is recommended (category 2B for para-aortic lymph node sampling only). Para-aortic node dissection is indicated for patients with known or suspected pelvic nodal disease. For patients with negative margins after

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cone biopsy, observation is recommended for those who are medically inoperable or those who refuse surgery.

Stage IA2 Disease

Fertility Sparing

For patients who wish to preserve their fertility, radical trachelectomy and pelvic lymph node dissection with (or without) para-aortic lymph node sampling (category 2B for para-aortic node sampling) is recommended. Cone biopsy followed by observation is another option if the margins are negative and pelvic lymph node dissection is negative.

Non–Fertility Sparing

Recommended options for stage IA2 depend on whether patients want to preserve their fertility and whether they are medically operable. For medically operable patients who do not desire fertility preservation, recommended treatment includes either surgery or RT (see *Primary Treatment (Non–Fertility Sparing)* in the NCCN Guidelines for Cervical Cancer). The recommended surgical option is modified radical hysterectomy and pelvic lymph node dissection with (or without) para-aortic lymph node sampling (category 2B for para-aortic node sampling). Para-aortic node dissection is indicated for patients with known or suspected pelvic nodal disease.

Pelvic radiation with brachytherapy (total point A dose: 70–80 Gy) is a treatment option for patients who are medically inoperable or refuse surgery and do not desire fertility preservation.[90] These doses are recommended for most patients based on summation of conventional external-beam fractionation and low–dose-rate (40–70 cGy/h) brachytherapy equivalents. Treatment should be modified based on normal tissue tolerance or on biologic equivalence calculations when using high–dose-rate brachytherapy (see also the *Radiation Therapy* section in this Discussion).

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 select patients with stage IB1 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 Gynecologic Oncology Group (GOG) considers that surgical staging is an option for patients with advanced cervical cancer. Radiologic imaging is recommended for assessing stage IB2 and IIA2 tumors.

Stage IB1: Fertility Sparing

For patients who desire fertility preservation, radical trachelectomy and pelvic lymph node dissection with (or without) para-aortic lymph node sampling is an option for stage IB1 disease, but typically only for tumors 2 cm or less (see *Primary Treatment (Fertility Sparing)* in the NCCN Guidelines for Cervical Cancer).[83-86,91,92] Tumors that are 2 to 4 cm are left to the surgeon's discretion. However, some surgeons suggest that a 2-cm cutoff may be used for vaginal trachelectomy, whereas a 4-cm cutoff may be used for abdominal (eg, laparoscopic, robotic) trachelectomy. In one study, oncologic outcomes were similar after 4 years when comparing radical trachelectomy with radical hysterectomy for patients with stage 1B1 cervical carcinoma.[92]

Stage IB and IIA: Non–Fertility Sparing

The surgical option includes radical hysterectomy plus bilateral pelvic lymph node dissection with (or without) para-aortic lymph node sampling.[57] Panel members feel that surgery is the most appropriate option for patients with stage IB1 or IIA1 disease, whereas concurrent

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chemoradiation is the most appropriate option for those with stage IB2 or IIA2 disease based on randomized trials.[57-59,61,62] Thus, the surgical option is category 1 for patients with stage IB1 or IIA1 disease; however, surgery is category 2B for those with stage IB2 or IIA2 disease.[57] 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.

Recent data suggest that sentinel lymph node biopsy may be useful for decreasing the need for pelvic lymphadenectomy in patients with early-stage cervical cancer.[93,94] However, panel members believe the technique is not yet sufficiently validated for routine use.[95-98] The role of sentinel lymph node biopsy continues to be evaluated in large prospective trials.[99-102] For patients with stage IB or IIA tumors (including those who are not candidates for hysterectomy), another option is combined pelvic RT and brachytherapy with (or without) concurrent cisplatin-containing chemotherapy (see *Primary Treatment (Non–Fertility Sparing)* in the NCCN Guidelines for Cervical Cancer). Although concurrent chemoradiation has been proven effective in the definitive treatment of more advanced-stage disease, this approach has not been specifically studied in patients with stage IB1 or IIA1 disease. Careful consideration of the risk/benefit ratio should be undertaken in these patients with smaller tumors.

For patients with clinical stage IB2 or IIA2 tumors who are treated with definitive radiation, concurrent cisplatin-containing chemotherapy has been shown to significantly improve patient survival. This recommendation has a category 1 recommendation (see *Primary Treatment (Non–Fertility Sparing)* in the NCCN Guidelines for Cervical Cancer).[58,59]

For stage IB2 or IIA2 tumors, the panel had a major disagreement about recommending adjuvant hysterectomy (category 3) (also known as completion surgery) after primary chemoradiation.[58] Adjuvant hysterectomy after RT has been shown to improve pelvic control, but not overall survival, and is associated with increased morbidity.[103] Some clinicians feel that completion surgery may be considered in patients who have residual disease after concurrent chemoradiation but should not be performed if patients have a complete response.[104] A recent study assessed completion hysterectomy in patients who had a complete response after concurrent chemoradiation, but the study was underpowered.[105] The morbidity is higher after completion surgery, and it has not been shown to increase survival.[104,106] However, the morbidity may be reduced if using completion laparoscopic hysterectomy after chemoradiation.[107]

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 IB2 and IIA2 disease in the advanced disease category. For patients with more advanced tumors who are undergoing primary chemoradiation, the volume of RT is critical and guided by assessment of nodal involvement in the pelvic and para-aortic nodes. Radiologic imaging studies (including PET-CT) are recommended for stage IB2 or greater disease. MRI is useful to rule out disease high in the endocervix. However, needle biopsy can be considered for questionable imaging findings. Surgical staging (ie, extraperitoneal or laparoscopic lymph node dissection) is also an option (category 2B) for

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these patients. Surgical staging may also detect microscopic nodal disease that is not discernible with radiologic imaging.[108]

For patients without nodal disease or with disease limited to the pelvis only through surgical staging, treatment consists of pelvic RT with concurrent cisplatin-based chemotherapy (category 1) and brachytherapy.[49,50,59,61-63,109] Currently, acceptable concurrent cisplatin-based regimens include either weekly cisplatin or the combination of cisplatin/5-FU given every 3 to 4 weeks during RT.

A recent international phase III randomized trial reported that concurrent cisplatin/gemcitabine and RT 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 RT.[77] However, this trial is controversial because of changes in its statistical design and because the reported superior regimen of concurrent cisplatin/gemcitabine and RT has unresolved toxicity issues.[77,110-112]

However, for patients with positive para-aortic and pelvic lymph nodes by imaging, extraperitoneal lymph node dissection should be considered followed by extended-field RT, concurrent cisplatin-containing chemotherapy, and brachytherapy (see *Primary Treatment* in the NCCN Guidelines for Cervical Cancer). Patients with positive para-aortic lymph nodes who are positive for distant metastases are treated with systemic chemotherapy (see *Chemotherapy Regimens for Recurrent or Metastatic Cervical Cancer* in the NCCN Guidelines) with (or without) individualized RT.[113]

Metastatic Disease

For patients who present with distant metastatic disease (ie, stage IVB), primary treatment is often cisplatin-based chemotherapy (see *Systemic Therapy for Metastatic Disease* in this Discussion). In these situations, individualized RT may be considered for control of pelvic disease and other symptoms.[113]

Adjuvant Treatment

Adjuvant treatment is indicated after radical hysterectomy depending on surgical findings and disease stage. Observation is appropriate for patients with stage IA2, IB1, or IIA1 disease who have negative nodes and no risk factors after radical hysterectomy. However, adjuvant treatment is indicated after radical hysterectomy if pathologic risk factors are discovered. Pelvic radiation is recommended (category 1) with (or without) concurrent cisplatin-based chemotherapy (category 2B for chemotherapy) for patients with stage IA2, IB1, or IIA1 disease who have *negative* lymph nodes after surgery but have large primary tumors, deep stromal invasion, and/or LVSI (see *Adjuvant Treatment* in the NCCN Guidelines for Cervical Cancer).[114-118]

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.[118] Patients were considered to be “intermediate risk” and were eligible for this trial if they had at least 2 of the following risk factors: 1) greater than one-third stromal invasion; 2) capillary lymphatic space involvement; or 3) cervical tumor diameters more than 4 cm. Patients with positive lymph nodes or involved surgical margins were excluded. At 2 years, the recurrence-free rates were 88% for 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).[114] The role of concurrent cisplatin/RT in these

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intermediate-risk patients is currently being evaluated in an international phase III randomized trial (GOG 263).

Postoperative pelvic radiation with concurrent cisplatin-containing chemotherapy (category 1)[60] 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 be “high risk” (see *Adjuvant Treatment* in the NCCN Guidelines for Cervical Cancer). Vaginal brachytherapy may be a useful boost for those with positive vaginal mucosal margins. Adjuvant concurrent chemoradiation significantly improves overall survival for these high-risk patients with early-stage disease (those with positive pelvic nodes, parametrial extension, and/or positive margins) who undergo radical hysterectomy and pelvic lymphadenectomy.[60] The Intergroup trial 0107 showed a statistically significant benefit of adjuvant pelvic radiation with concurrent cisplatin and 5-FU in the treatment of patients with stage IA2, IB, or IIA disease who had positive lymph nodes, positive margins, and/or microscopic parametrial involvement found at surgery.[60]

Depending on the results of primary surgery, imaging (chest CT or combined PET-CT scan) may be recommended to determine whether distant metastases are present. In women who are positive for distant metastases, biopsy of suspicious areas should be considered as indicated (see *Adjuvant Treatment* in the NCCN Guidelines for Cervical Cancer). For patients without distant metastases, recommended treatment is extended-field RT (including pelvic and para-aortic lymph nodes) with concurrent cisplatin-based chemotherapy and with (or without) brachytherapy. For patients with distant metastases, recommended treatment is systemic chemotherapy (see *Chemotherapy Regimens for Recurrent or Metastatic Cervical Cancer* in the NCCN Guidelines) with (or without) individualized RT.[113]

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.[119-121] 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.[122] 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 (see *Surveillance* in the NCCN Guidelines for Cervical Cancer). High-risk patients can be assessed more frequently (eg, every 3 months for the first 2 years) than low-risk patients (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.[122-124] 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.[125] 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). Smoking cessation and abstinence should be encouraged.[122]

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Imaging is not routinely recommended for surveillance but may be indicated in patients with symptoms or findings that are suspicious for recurrence.[122,125,126] In patients at high risk for locoregional (central or para-aortic) failure, a combined PET-CT scan (eg, 3–6 months after treatment) or other radiologic imaging may be useful for detecting asymptomatic disease that is potentially curable.[127-129] Many other tests remain optional based on clinical indications, such as semiannual CBCs, blood urea nitrogen, and serum creatinine determinations (see *Surveillance* in the NCCN Guidelines for Cervical Cancer). 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).[130]

Patients treated with RT are prone to vaginal stenosis, which can impair sexual function. Anecdotal evidence suggests that vaginal dilators may be used to prevent or treat vaginal stenosis.[131] Dilator use can start 2 to 4 weeks after RT is completed and can be performed indefinitely (http://www.mskcc.org/patient_education/_assets/downloads-english/571.pdf).

Cervical cancer survivors are at risk for second cancers.[132] 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.[133,134]

Therapy for Relapse

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.[49,135] After treatment for relapse, long-term disease-free survival rates of approximately 40% have been reported in some situations.[136]

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 RT and platinum-based chemotherapy with (or without) brachytherapy; surgical resection can be considered if feasible (see *Therapy for Relapse* in the NCCN Guidelines for Cervical Cancer). Typically, the chemoradiation for recurrence uses cisplatin as a single agent or cisplatin plus 5-FU.[137,138]

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.[139-146] Surgical mortality is generally 5% or less, with survival rates approaching 50% in carefully selected patients.[142] 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.[141,147-149] 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 resection (with IORT for close or positive margins, category 3), tumor-directed RT with (or without) chemotherapy, chemotherapy, best supportive care (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 chemotherapy or best supportive care, or can be enrolled in a clinical trial.

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Therapy for Metastatic Disease

Patients who develop distant metastases, either at initial presentation or at relapse, are rarely curable. For highly selected patients with isolated distant metastases, occasional long-term survival has been reported with either 1) surgical resection with (or without) IORT (IORT is category 3); or 2) RT with (or without) concurrent chemotherapy (see *Therapy for Relapse* in the NCCN Guidelines for Cervical Cancer). For example, patients who may benefit from aggressive local therapy for oligometastatic disease include those with lung, liver, or bone metastases. For most other patients with distant metastases, appropriate treatment is either chemotherapy (see *Chemotherapy Regimens for Recurrent or Metastatic Cervical Cancer* in the NCCN Guidelines for Cervical Cancer) or best supportive care.

The palliation of pelvic recurrences in heavily irradiated sites that are not amenable to local pain control techniques or to surgical resection is 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.[113,150,151]

Chemotherapy is often recommended for patients with extrapelvic metastases or recurrent disease who are not candidates for RT or exenterative surgery. Patients who respond 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).[152,153] 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.[154] 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.[152,153] Cisplatin-based combination chemotherapy regimens, such as cisplatin/paclitaxel and cisplatin/topotecan, have been extensively investigated in clinical studies.[152,153,155-157]

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 vs. 2.8 months; *P*>.001) compared to single-agent cisplatin, although no improvement was seen in median survival.[152] Patients who responded to cisplatin/paclitaxel had a significant improvement in quality of life. Preliminary data from a phase III randomized trial suggest that carboplatin/paclitaxel is equivalent to cisplatin/paclitaxel in women with metastatic or recurrent cervical cancer.[158,159] Many physicians use carboplatin/paclitaxel because of ease of administration and tolerability.[160]

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 vs. 2.9 months; *P*=.014), and median survival (9.4 vs. 6.5 months; *P*=.017).[153] The FDA has approved cisplatin/topotecan for advanced cervical cancer.

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However, the cisplatin/paclitaxel or carboplatin/paclitaxel regimens are less toxic and easier to administer than cisplatin/topotecan.

A recent phase III trial (GOG 204) in 513 patients with advanced metastatic or recurrent cancer compared 4 cisplatin-doublet regimens (cisplatin/paclitaxel, cisplatin/topotecan, cisplatin/gemcitabine, and cisplatin/vinorelbine).[157] 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 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.

Based on the previous studies, cisplatin/paclitaxel and carboplatin/paclitaxel have become the most widely used systemic regimens for metastatic or recurrent cervical cancer.[152,157,158] However, for patients who may not be candidates for taxanes, cisplatin/topotecan and cisplatin/gemcitabine remain reasonable alternative regimens.[77,153] Nonplatinum regimens are also being studied and may be considered in patients who cannot tolerate platinum-based chemotherapy.[161]

Single Agents

Cisplatin is generally regarded as the most active agent and is recommended as a possible first-line single-agent chemotherapy in recurrent or metastatic cervical cancer; reported response rates are approximately 20% to 30%, with an occasional complete response.[152,154,162,163] 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.[164-167] 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.

Other agents (that are category 2B unless otherwise indicated) that have shown responses or prolongation of PFS and may be useful as second-line therapy include bevacizumab,[168] docetaxel,[169] 5-FU,[170] gemcitabine,[171] ifosfamide,[172,173] irinotecan,[174] mitomycin,[175] topotecan,[176,177] pemetrexed (category 3),[178] and vinorelbine (category 3).[179]

Drug Reactions

Virtually all drugs have the potential to cause adverse reactions, either during or after infusion.[180] 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.[181,182] In addition, patients can have severe infusion reactions and mild allergic reactions. Infusion reactions are more common with paclitaxel.[183] Allergic reactions (ie, true drug allergies) are more common with platinum agents (ie, carboplatin, cisplatin).[183,184]

Management of drug reactions is discussed in the NCCN Guidelines for Ovarian Cancer.[183] Importantly, patients who have had 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 administer the drug again, a desensitization regimen is recommended

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even if the symptoms have resolved. Various desensitization regimens have been published and should be followed.[184-186] Patients must be desensitized with each infusion if they have had a previous reaction. Almost all patients can be desensitized.[180] To maximize safety, patients should be desensitized in the intensive care unit.[180]

Other Agents

Vaccine therapies currently have no established role in the treatment of cervical cancer at the present time, except in the setting of a clinical trial.[187-189] Targeted therapy (using small molecules or monoclonal antibodies) is currently used in clinical trials.[78,168,190,191]

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 (see *Incidental Finding of Invasive Cervical Cancer at Simple Hysterectomy* in the NCCN Guidelines for Cervical Cancer).

No definitive data are available to guide the appropriate adjuvant treatment of these patients. Surveillance is recommended for patients with stage 1A1 cervical cancer who do not have LVSI. For patients with either stage IAI with LVSI or with stage 1A2 or higher tumors (pathologic findings), 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 cisplatin-containing chemotherapy with (or without) individualized brachytherapy is recommended (see *Primary Treatment* in the NCCN Guidelines for Cervical Cancer).

If margins or imaging is negative in stage 1A2 or greater tumors, options include: 1) pelvic RT with (or without) concurrent cisplatin-containing chemotherapy and brachytherapy; or 2) a complete parametrectomy, upper vaginectomy, and pelvic lymph node dissection with (or without) para-aortic lymph node sampling. Typically, observation is recommended for patients with negative lymph nodes. However, pelvic radiation with (or without) vaginal brachytherapy is an option if they have high-risk factors (ie, large primary tumor, deep stromal invasion, LVSI) (see *Primary Treatment* in the NCCN Guidelines for Cervical Cancer).[118] Concurrent cisplatin-based chemoradiation is recommended for gross residual disease, positive imaging, disease in the lymph nodes and/or parametrium, and/or a positive surgical margin; individualized brachytherapy is clearly indicated for a positive vaginal margin.

Radiation Therapy

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).

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The algorithm provides general RT dosage recommendations, which are expanded in the *Principles of Radiation Therapy* (see the NCCN Guidelines for Cervical Cancer). These RT dosages should not be interpreted as stand-alone recommendations, because RT techniques and clinical judgment are an essential part of developing an appropriate treatment regimen.

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

Radiation Treatment Planning

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 external-beam RT. 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 external-beam radiation in an integrated treatment plan.

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).[49]

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.[192] General recommendations for radiation volumes and doses are discussed in the algorithm (see *Principles of Radiation Therapy for Cervical Cancer* in the NCCN Guidelines for Cervical Cancer).

Intensity-modulated RT (IMRT) is becoming more widely available; however, issues regarding target definition, patient and target immobilization, tissue deformation, and reproducibility remain to be validated.[193-199] The role of IMRT in cervical cancer continues to be evaluated in several prospective multicenter clinical trials.[200]

Several retrospective analyses suggest that prolonged treatment duration has an adverse effect on outcome.[201-205] 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 external-beam RT and brachytherapy components) should be completed in a timely fashion (within 8 weeks);

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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).[54-56]

After therapy for cervical cancer, late side effects may include potential injury to bladder, rectum, bowel, and pelvic skeletal structures.[206] The risk of major complications (ie, obstruction, fibrosis/necrosis, fistula) is related to the volume, total dose, dose per fraction, and specific intrinsic radiosensitivity of the normal tissue that is irradiated.[192,207] Careful blocking to minimize normal tissue exposure while not compromising tumor coverage is critical to achieving 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.

Cervical Cancer and Pregnancy

Cervical cancer is the most frequently diagnosed gynecologic malignancy in pregnant women; however, most women have stage I disease.[208-211] Invasive cervical cancer during pregnancy creates a clinical dilemma and requires multidisciplinary care.[208,212] 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.[209,212] Women who delay treatment until fetal maturity should have their children delivered by cesarean section.[211,213,214] Vaginal radical trachelectomy has been successfully performed in a few pregnant patients with early-stage cervical cancer.[215-218]

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 early-stage 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.[211]

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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 certain types of the virus, and will therefore prevent specific HPV cancer in women.[15,16,219]

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Table 2: 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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