



**NCCN Clinical Practice Guidelines in Oncology™**

# **Cervical Cancer**

V.1.2008

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

See [NCCN Categories of Evidence and Consensus](#)

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## Summary of the Guidelines updates

Summary of changes in the 1.2008 version of the Cervical Cancer guidelines from the 1.2007 version include:

### **(CERV-1)**

- **Workup: Fifth bullet:** The recommendation “PET scan for  $\geq$  Stage IB2” was changed to “PET scan” and incorporated into the fifth bullet as “Chest x-ray, PET scan, CT/MRI...”

### **(CERV-2)**

- **Under Primary Treatment for “Stage IB1 and stage IIA ( $\leq 4$  cm)” patients:** The recommendation “Radical trachelectomy...  $\pm$  para-aortic lymph node sampling” was changed to “Radical trachelectomy... + para-aortic lymph node sampling”.
- **Under Clinical Stage, “Stage IB2 and Stage IIA ( $> 4$  cm),”** the phrase “(also see CERV-4)” was added.

### **(CERV-4)**

- **Clinical Stage:** “Selected bulky Stage IB2, IIA” was changed to “Selected bulky Stage IB2, Stage IIA ( $> 4$  cm)”. (Also for CERV-4, CERV-5 and CERV-6)
- **After Clinical Stage:** “Imaging studies: CT, MRI and/or PET scan” was deleted.
- **“Surgical staging: Extraperitoneal or laparoscopic lymph node dissection”; Positive:** The panel deleted the recommendation to “Consider intraoperative RT for bulky residual nodes”.

### **(CERV-5)**

- **Lower Pathway, after “Para-aortic lymph node positive by surgical staging”:** “Chest CT, PET scan” was changed to “Further radiologic workup as clinically indicated”.

### **(CERV-6)**

- **Top branch; “Pelvic node positive; para-aortic lymph node negative” pathway; Primary treatment:** The “category 1” designation was moved to after “cisplatin-containing chemotherapy”.

### **(CERV-7)**

- **“PET scan”** was changed from “Optional  $\geq$  Stage IB2” to part of the imaging studies that are “Optional for  $\leq$  Stage IB1” patients
- **LFT/renal function studies** is no longer listed as “optional”

### **(CERV-8)**

- **The phrase “Salvage Therapy”** was changed to “Therapy for Relapse” throughout the guideline.

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WORKUP

- H&P
- CBC, platelets
- Cervical biopsy, pathologic review
- Cone biopsy as indicated
- Chest x-ray, PET scan, CT/MRI (optional for  $\leq$  stage IB1)
- LFT/renal function studies

- Optional ( $\geq$  Stage IB2):
- EUA
  - cystoscopy/proctoscopy<sup>a</sup>

CLINICAL STAGE

Stage IA1 → [See Primary Treatment \(CERV-2\)](#)

Stage IA2  
Stage IB1  
Stage IIA ( $\leq$  4 cm) → [See Primary Treatment \(CERV-2\)](#)

Stage IB2  
Stage IIA ( $>$  4 cm) → [See Primary Treatment \(CERV-2\)](#)

Selected bulky:  
Stage IB2, IIA  
Stage IIB  
Stage IIIA, IIIB  
Stage IVA → [See Primary Treatment \(CERV-4\)](#)

Incidental finding of invasive cancer at simple hysterectomy → [See Primary Treatment \(CERV-7\)](#)

<sup>a</sup>For suspicion of bladder/bowel involvement, cystoscopy/proctoscopy with biopsy is required.

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CLINICAL STAGE	PRIMARY TREATMENT	
Stage IA1	Extrafascial hysterectomy or Observe if patient desires fertility or if inoperable (only if cone biopsy has negative margins) or Modified radical hysterectomy + pelvic lymph node dissection if lymphovascular invasion (category 2B)	→ <a href="#">See Surveillance (CERV-8)</a>
		→ <a href="#">See Surgical Findings (CERV-3)</a>
Stage IA2	Radical hysterectomy + pelvic lymph node dissection ± para-aortic lymph node sampling or Brachytherapy + pelvic RT (point A dose: 75-80 Gy) <sup>b</sup> or Radical trachelectomy for fertility preservation + pelvic lymph node dissection ± para-aortic lymph node sampling	→ <a href="#">See Surgical Findings (CERV-3)</a>
		→ <a href="#">See Surveillance (CERV-8)</a>
Stage IB1 and stage IIA (≤ 4 cm) <sup>a</sup>	Radical hysterectomy + pelvic lymph node dissection + para-aortic lymph node sampling (category 1) or Pelvic RT + brachytherapy (point A dose: 80-85 Gy) <sup>b</sup> or Radical trachelectomy for fertility preservation for lesions ≤ 2 cm (Stage IB1) + pelvic lymph node dissection + para-aortic lymph node sampling	→ <a href="#">See Surgical Findings (CERV-3)</a>
		→ <a href="#">See Surveillance (CERV-8)</a>
Stage IB2 and stage IIA (> 4 cm) <sup>a</sup> (also see <a href="#">CERV-4</a> )	Radical hysterectomy + pelvic lymph node dissection + para-aortic lymph node sampling (category 2B) or Pelvic RT + concurrent cisplatin-containing chemotherapy + brachytherapy (point A dose ≥ 85 Gy) <sup>b</sup> (category 1) or Pelvic RT + concurrent cisplatin-containing chemotherapy + brachytherapy (point A dose 75-80 Gy) <sup>b</sup> + adjuvant hysterectomy (category 3)	→ <a href="#">See Surgical Findings (CERV-3)</a>
		→ <a href="#">See Surveillance (CERV-8)</a>

<sup>a</sup>For suspicion of bladder/bowel involvement, cystoscopy/proctoscopy with biopsy is required.

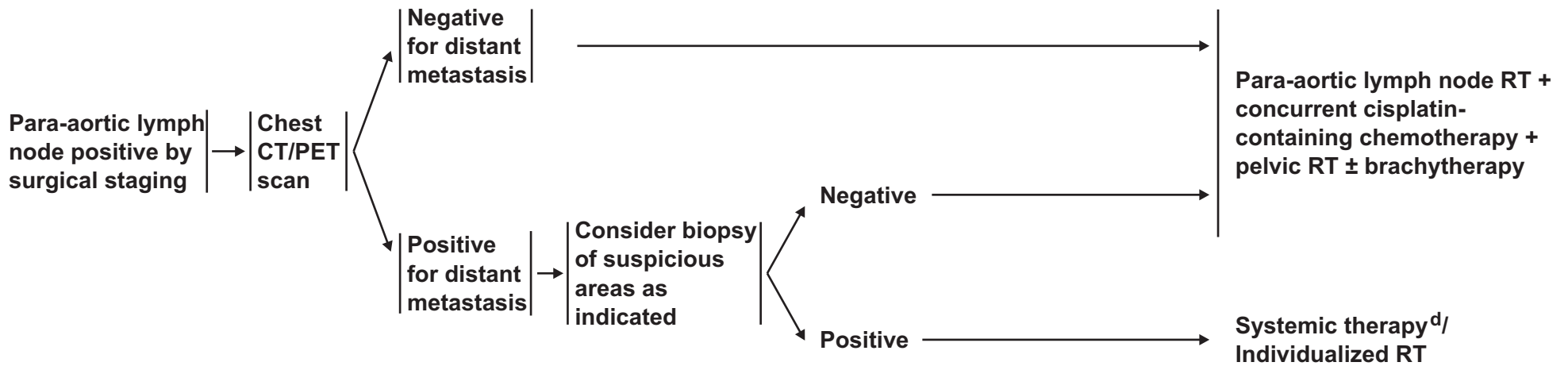
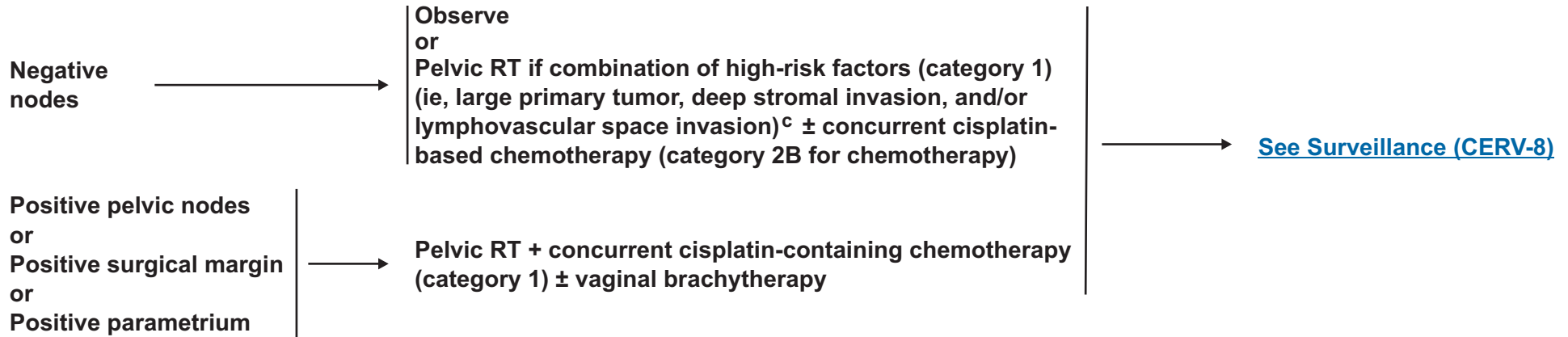
<sup>b</sup>These doses are recommended for most patients based on summation of conventional external-beam fractionation and low-dose rate (40-70 cGy/h) brachytherapy equivalents. Modify treatment based on normal tissue tolerance.

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**SURGICAL FINDINGS**

**ADJUVANT TREATMENT**



<sup>c</sup>Sedlis A, Bundy BN, Rotman MZ, et al. A randomized trial of pelvic radiation therapy vs. no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. *Gynecol Oncol* 1999;73:177-183.

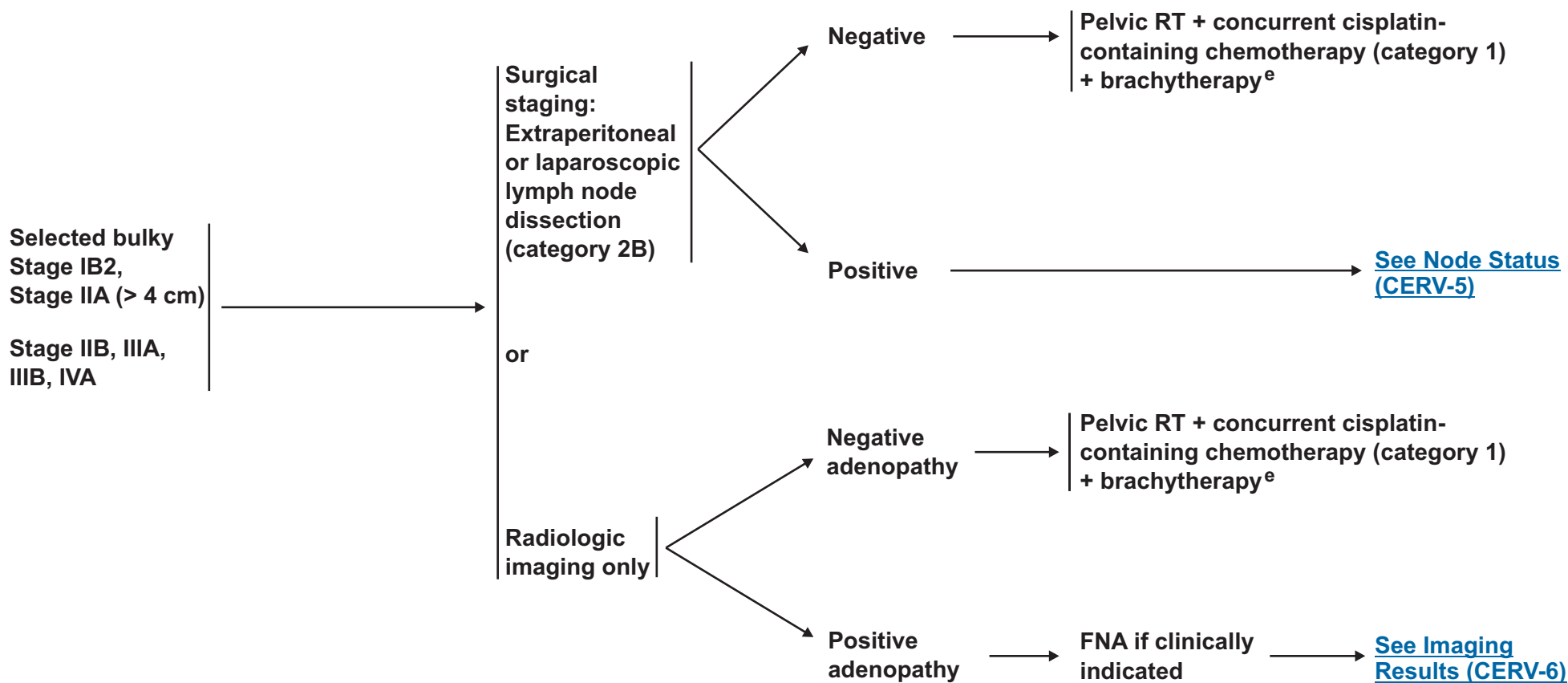
<sup>d</sup>See [Chemotherapy Regimens for Cervical Cancer \(CERV-A\)](#).

[See Surveillance \(CERV-8\)](#)

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CLINICAL STAGE

PRIMARY TREATMENT



<sup>e</sup>Pelvic RT + brachytherapy total point A dose ≥ 85 Gy.

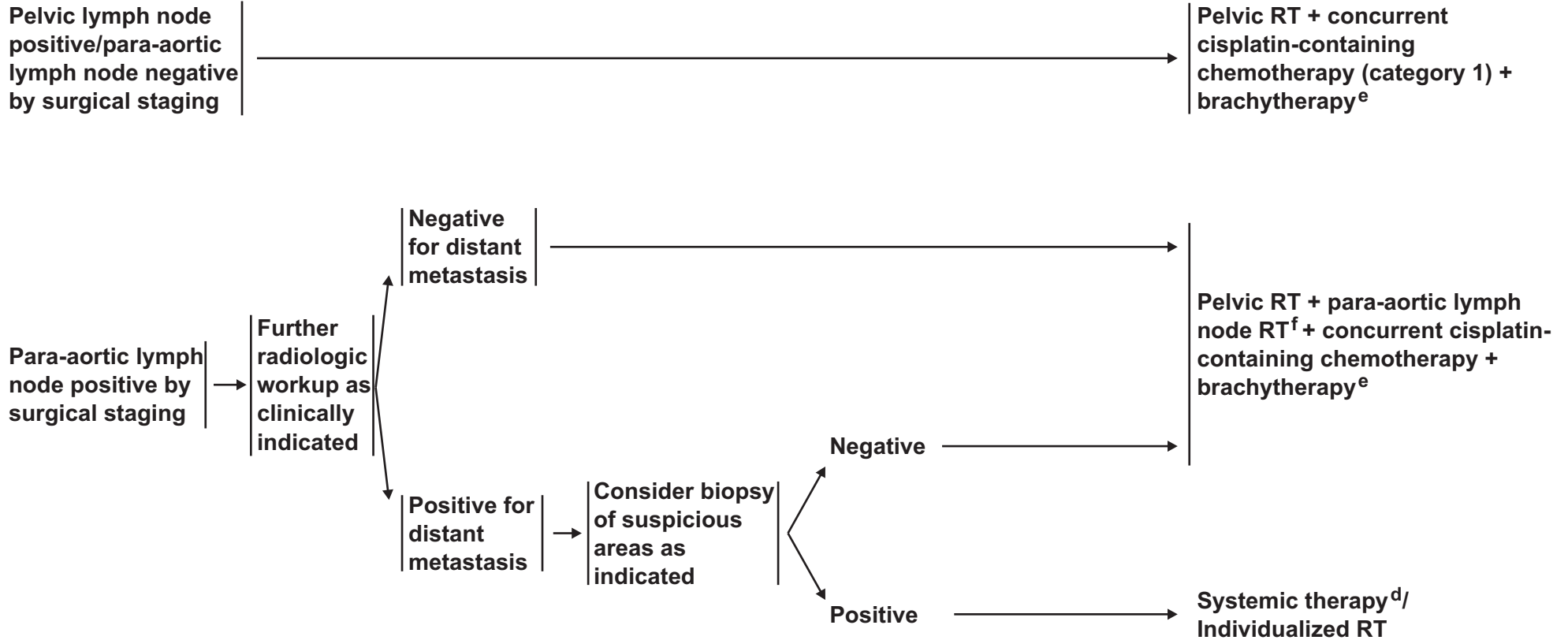
[See Surveillance \(CERV-8\)](#)

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SELECTED BULKY Stage IB2, IIA (> 4 cm);  
Stage IIB, IIIA, IIIB, IVA  
NODE STATUS

PRIMARY TREATMENT



<sup>d</sup>See [Chemotherapy Regimens for Cervical Cancer \(CERV-A\)](#).

<sup>e</sup>Pelvic RT + brachytherapy total point A dose ≥ 85 Gy.

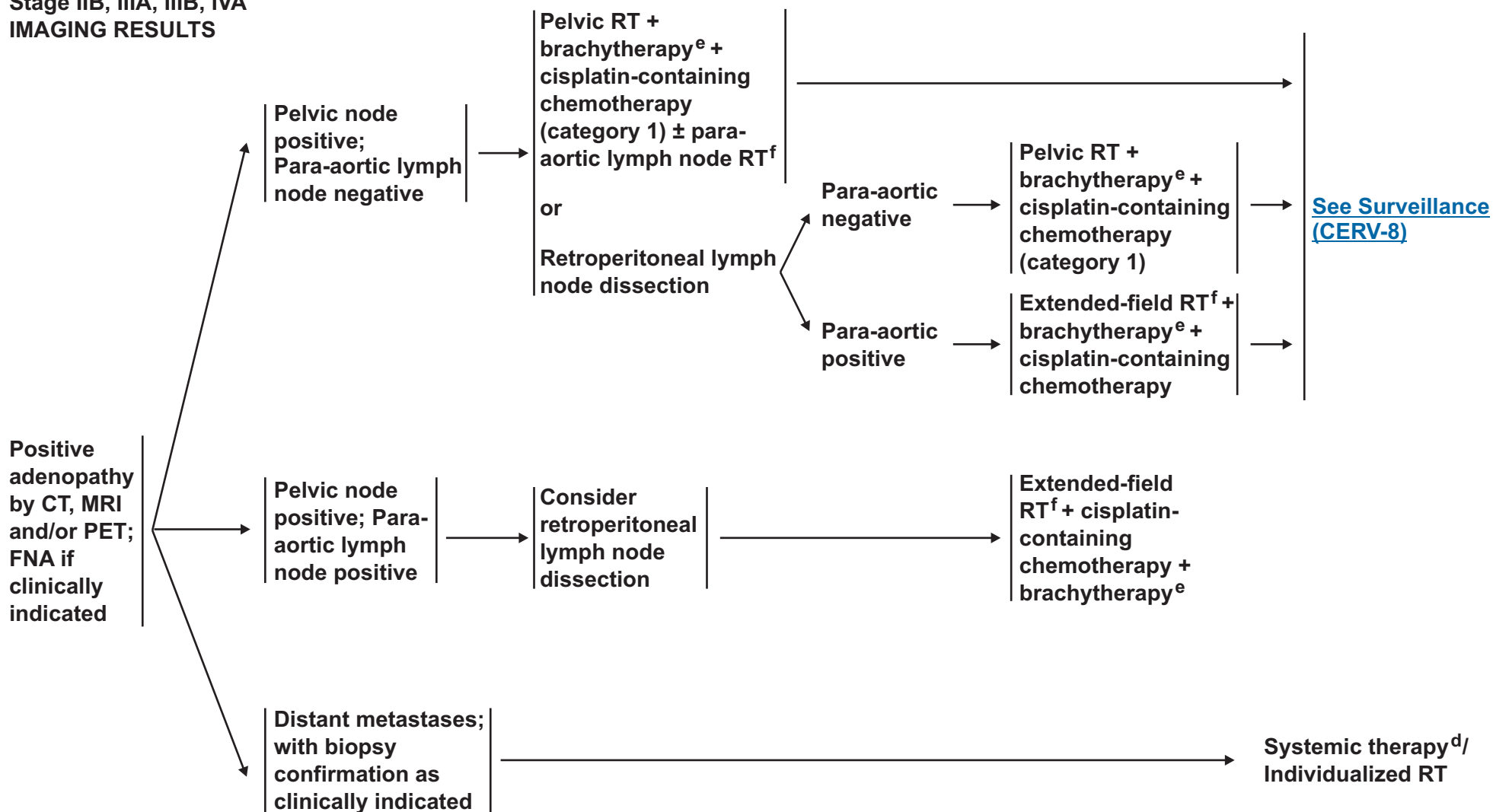
<sup>f</sup>RT dose is 45-50 Gy to clinical tumor volume (CTV).

[See Surveillance \(CERV-8\)](#)

**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.

SELECTED BULKY Stage IB2, IIA (> 4 cm)  
Stage IIB, IIIA, IIIB, IVA  
IMAGING RESULTS

PRIMARY TREATMENT



<sup>d</sup>See [Chemotherapy Regimens for Cervical Cancer \(CERV-A\)](#).

<sup>e</sup>Pelvic RT + brachytherapy total point A dose ≥ 85 Gy.

<sup>f</sup>RT dose is 45-50 Gy to clinical tumor volume (CTV).

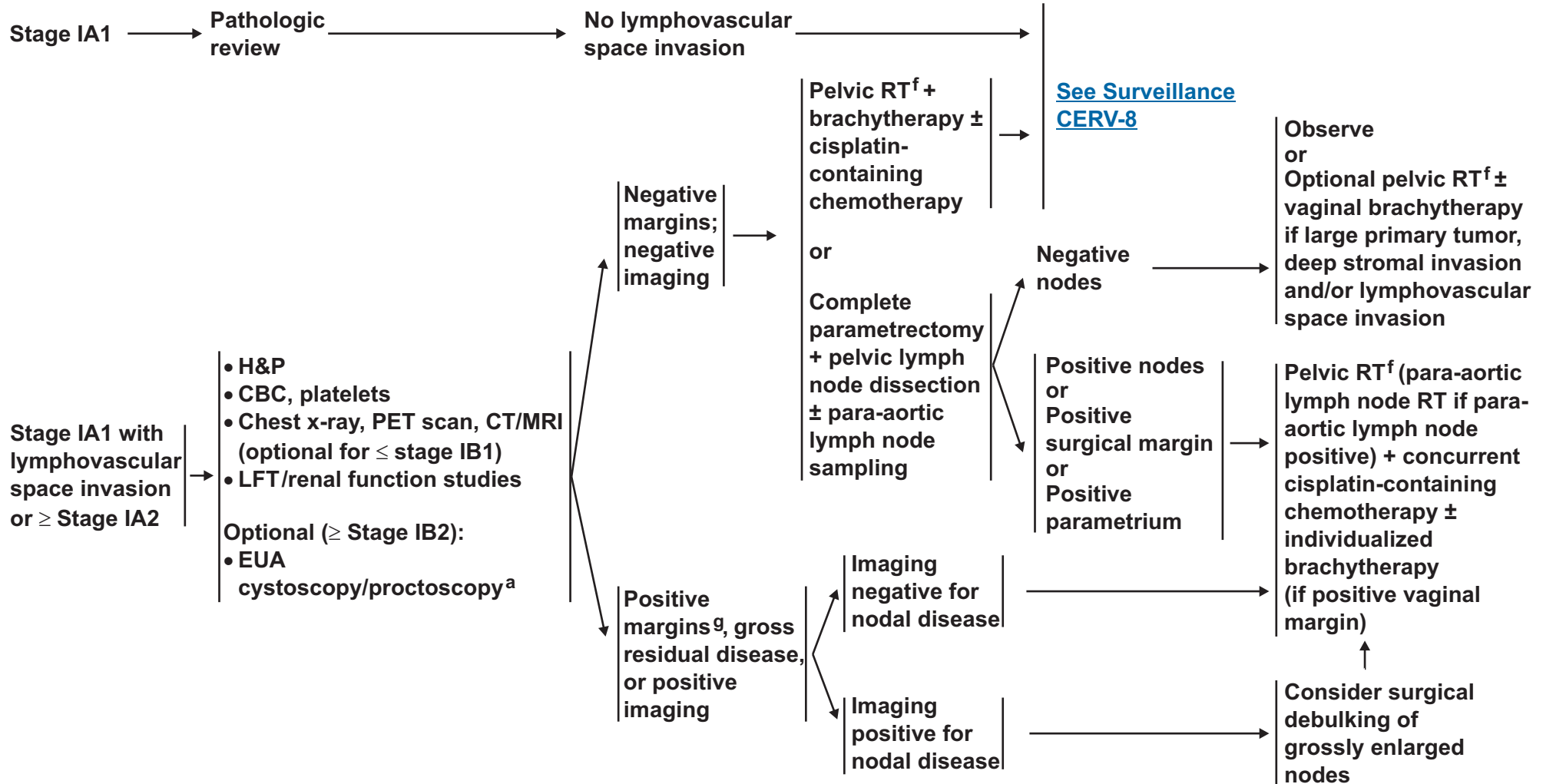
[See Surveillance \(CERV-8\)](#)

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INCIDENTAL FINDING  
OF INVASIVE CANCER  
AT SIMPLE HYSTERECTOMY

PRIMARY TREATMENT



<sup>a</sup>For suspicion of bladder/bowel involvement, cystoscopy/proctoscopy with biopsy is required.

<sup>f</sup> RT dose is 45-50 Gy to clinical tumor volume (CTV).

<sup>g</sup>Invasive cancer at surgical margin.

[See Surveillance \(CERV-8\)](#)

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SURVEILLANCE

WORKUP

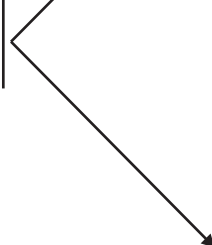
- Interval H&P
- Pap test + visit every 3 mo for 1 y, every 4 mo for 1 y, every 6 mo for 3 y, then annually
- Chest x-ray annually (category 2B)
- CBC, BUN, creatinine every 6 mo (optional)
- CT/PET scan as clinically indicated
- Suggest use of vaginal dilator after RT



Persistent or recurrent disease



- Pelvic/abdominal/chest CT/PET scan
- Surgical exploration in selected cases

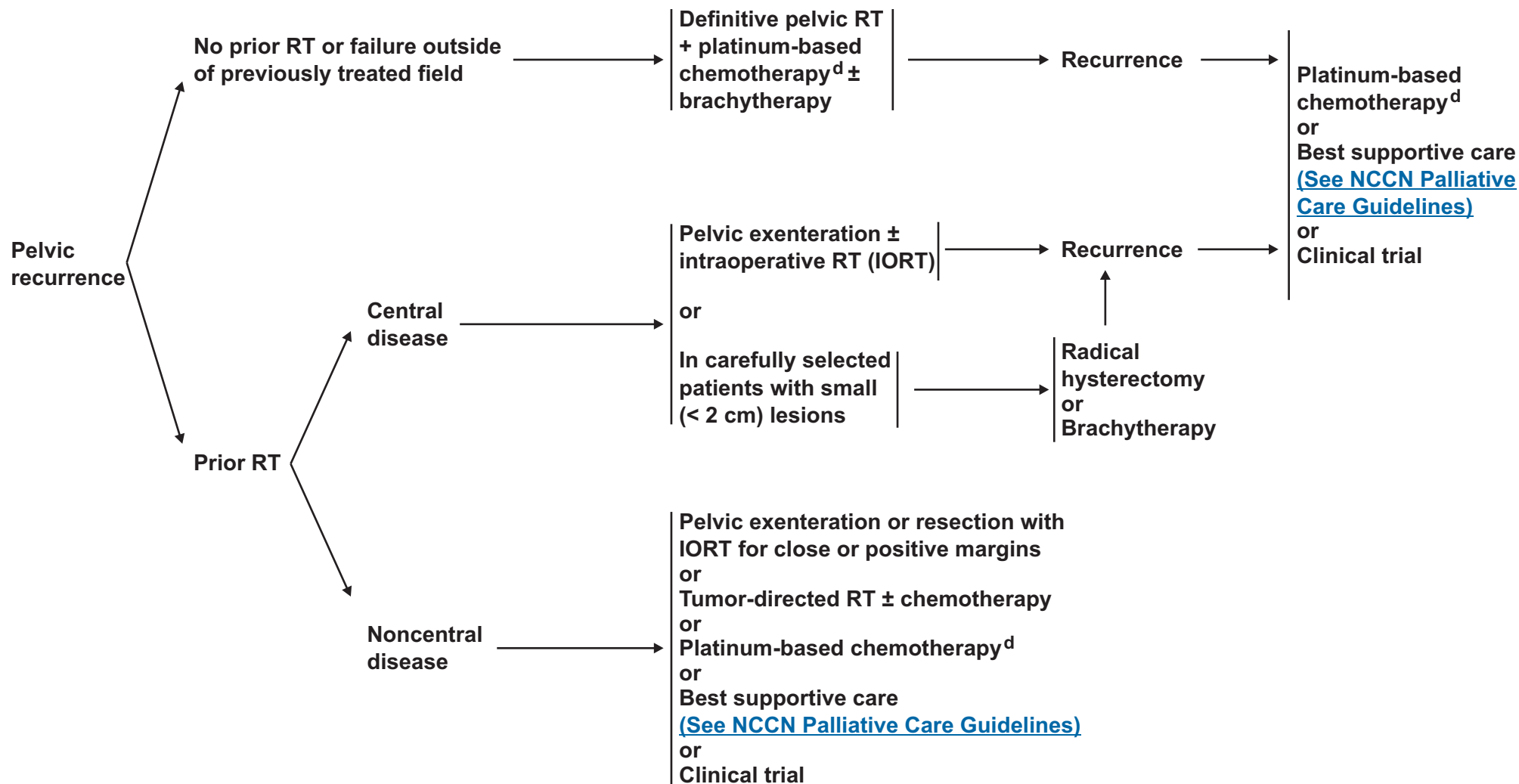


[See Therapy for Relapse \(pelvic recurrence\) \(CERV-9\)](#)

[See Therapy for Relapse \(extrapelvic or para-aortic recurrence\) \(CERV-10\)](#)

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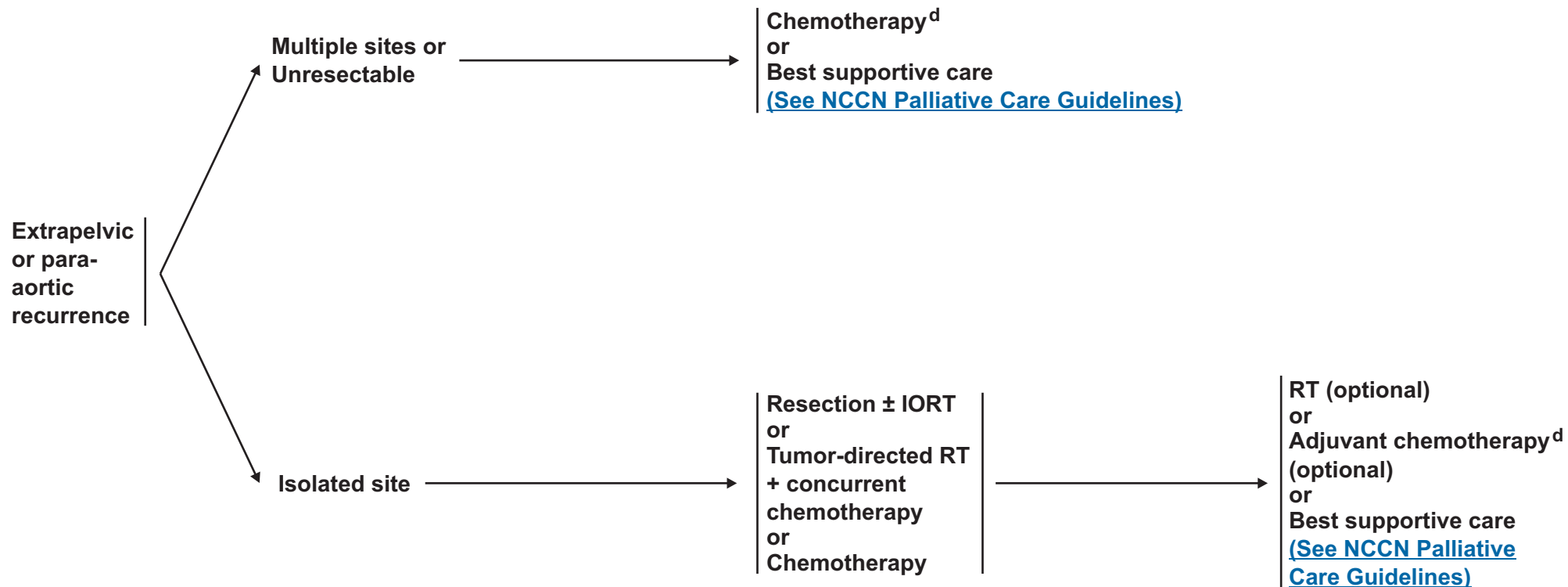
THERAPY FOR RELAPSE



<sup>d</sup>See [Chemotherapy Regimens for Cervical Cancer \(CERV-A\)](#).

**Note:** All recommendations are category 2A unless otherwise indicated.  
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THERAPY FOR RELAPSE



<sup>d</sup>[See Chemotherapy Regimens for Cervical Cancer \(CERV-A\).](#)

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## CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC CERVICAL CANCER

**First-line combination therapy**<sup>1</sup>

- Cisplatin/paclitaxel (category 1)
- Cisplatin/topotecan (category 1)
- Cisplatin/gemcitabine (category 2B)
- Carboplatin/paclitaxel

**Possible first-line single agent therapy**

- Cisplatin
- Carboplatin
- Paclitaxel
- Topotecan  
(category 2B)

**Second-line therapy**

(All agents listed are category 2B)

- Docetaxel
- Ifosfamide
- Vinorelbine
- Irinotecan
- Epirubicin
- Mitomycin
- 5-FU

<sup>1</sup>Preferred if cisplatin was previously used as a radiosensitizer.

**Note:** All recommendations are category 2A unless otherwise indicated.

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

## Staging

### Staging

Table 1

#### International Federation of Gynecology and Obstetrics (FIGO) and Tumor-Node-Metastases (TNM) Surgical Staging Systems for Carcinoma of the Uterine Cervix\*

FIGO Stages	Surgical-Pathologic Findings	TNM Categories
	Primary tumor cannot be assessed	TX
	No evidence of primary tumor	T0
0	Carcinoma in situ (preinvasive carcinoma)	Tis
I	Cervical carcinoma confined to uterus (extension to the corpus should be disregarded)	T1
IA	Invasive carcinoma diagnosed only by microscopy. All macroscopically visible lesions---even with superficial invasion---are stage IB/T1b.	T1a
IA1	Stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread	T1a1
IA2	Stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less†	T1a2
IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2/T1a2	T1b
IB1	Clinically visible lesion 4.0 cm or less in greatest dimension	T1b1
IB2	Clinically visible lesion more than 4.0 cm in greatest dimension	T1b2
II	Tumor invades beyond the uterus but not to pelvic wall or lower third of the vagina	T2
IIA	Without parametrial invasion	T2a
IIB	With parametrial invasion	T2b

III	Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or nonfunctioning kidney	T3
IIIA	Tumor involves lower third of vagina, no extension to pelvic wall	T3a
IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney	T3b
IVA	Tumor invades mucosa of bladder or rectum, and/or extends beyond true pelvis. The presence of bullous edema is not sufficient to classify a tumor as T4	T4
IVB	Distant metastasis	M1

#### Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

#### Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

\*Reprinted from: Benedet JL, Bender H, Jones H 3rd, et al. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. *Int J Gynaecol Obstet* 2000;70:209-262. Copyright © 2000, with permission from International Federation of Gynecology and Obstetrics.

†The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial epithelial papilla to the deepest point of invasion. Vascular space involvement, venous or lymphatic, does not affect classification.



## Manuscript

### NCCN Categories of Evidence and Consensus

**Category 1:** There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

**Category 2A:** There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

**Category 2B:** There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

**Category 3:** There is major NCCN disagreement that the recommendation is appropriate.

**All recommendations are category 2A unless otherwise noted.**

## Overview

An estimated 11,150 new cases of cervical cancer will be diagnosed in the United States in the year 2007; 3670 deaths will result from the disease.<sup>1</sup> Cervical cancer rates are decreasing among women in all racial and ethnic groups in the United States, although incidence remains high among Hispanic/Latino women.<sup>2,3</sup> However, cervical cancer is a major world health problem for women. The global yearly incidence of cervical cancer for 2002 was 493,243; the annual death rate was 273,505. It is the third most common cancer in women worldwide;<sup>4,5</sup> 78% of cases occur in developing countries, where cervical cancer is the second most frequent cause of cancer death in women.

The substantial decline in incidence and mortality of cervical cancer, in developed countries, is thought to be a result of effective screening. Persistent human papillomavirus (HPV) infection is regarded as the most important factor contributing to the development of cervical cancer. There appears to be a relationship between the incidence of cervical cancer and the prevalence of HPV in the population. The prevalence of chronic HPV in countries with a high incidence of cervical cancer is about 10% to 20%, whereas the prevalence in low-incidence countries is 5% to 10%.<sup>4</sup> Immunization against HPV (using Gardasil, which was approved by the US Food and Drug Administration [FDA] in 2006) prevents persistent infection with certain types of HPV and, thus, is expected to prevent specific HPV cancer in women (see “Vaccination Against HPV”).<sup>6-9</sup> 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.

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

## Diagnosis and Workup

These NCCN guidelines discuss squamous cell carcinoma, adenosquamous carcinoma, and adenocarcinoma of the cervix. Squamous cell carcinomas account for about 80% of all cervical cancers. Neuroendocrine carcinoma, small cell tumors, glassy-cell carcinomas, sarcomas, and other histologic types are not within the scope of these guidelines. Currently, the International Federation of Gynecology and Obstetrics (FIGO) evaluation procedures for staging are limited to colposcopy, biopsy, conization of the cervix, cystoscopy, and proctosigmoidoscopy. More complex radiologic and surgical

staging procedures are not addressed in the FIGO classification. In the United States, however, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and surgical staging are often used to guide treatment options and design.<sup>10</sup>

The earliest stages of cervical carcinoma may be asymptomatic or associated with a watery vaginal discharge and postcoital bleeding or intermittent spotting. These early symptoms frequently are unrecognized by the patient. Because of the accessibility of the uterine cervix to the physician, cervical cytology or Papanicolaou (Pap) smears and cervical biopsies can usually result in an accurate diagnosis (see [NCCN Cervical Cancer Screening Guidelines](#)). Cone biopsy is recommended if the cervical biopsy is inadequate to define invasiveness or if accurate assessment of microinvasive disease is required.

Workup for these patients includes history and physical examination, complete blood count, platelets, and liver and renal function tests. Radiologic imaging includes chest x-ray, CT, MRI, or PET; although these tests are optional for patients with stage IB1 or smaller tumors. Cystoscopy and proctoscopy examination under anesthesia should be reserved for patients in whom there is clinical concern for bladder or rectal cancer (that is, stage IB2 or higher).

Panel members discussed whether laparoscopy should be included as part of these NCCN guidelines in both staging and treatment. The consensus is that the techniques are not uniformly used. Laparoscopic staging, lymphadenectomies, and radical hysterectomies can be performed satisfactorily and are used routinely in selected patients in several member institutions.<sup>11</sup>

## Staging

Because of the controversial nature of noninvasive radiographic imaging, the FIGO system limits the imaging to chest radiography,

intravenous pyelography (IVP), and barium enema. The staging of carcinoma of the cervix remains largely a clinical evaluation. The guidelines panel adopted the 1994 FIGO definitions and staging system, which have been revised (see [Table 1](#)).<sup>12</sup>

Historically, FIGO has made numerous definition changes, mostly in the area of microinvasive carcinoma of the cervix. Currently, the FIGO definition of stage IA is limited to invasive cancer that can be identified only microscopically on pathology. Stage IA1 cancer includes invasive cancer with a measured invasion of the stroma of up to 3.0 mm in depth. Stage IA2 includes invasion of the stroma greater than 3.0 mm but not more than 5.0 mm in depth. For stages IA1 and IA2, the horizontal spread is less than 7.0 mm.

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

The use of MRI, CT, or PET scans may aid in treatment planning but is not accepted for formalized staging purposes. 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 (such as CT and MRI) are used to guide treatment options and design.

## Primary Treatment

After careful clinical evaluation and staging, the primary treatment of early stage cervical cancer is either surgery or radiation therapy (RT). A randomized Italian study compared RT alone versus radical

hysterectomy and lymph node dissection.<sup>13</sup> This study used adjuvant RT after surgery for women with surgical stage pT2b (which corresponds to FIGO stage IIB) or more extensive disease, less than 3 mm of uninvolved cervical stroma, and cut-through or positive nodes. Identical outcomes were noted for patients treated with radiation versus surgery, with (or without) postoperative radiation, but higher complication rates were noted for the combined modality approach. This study has been criticized by surgeons for its broad use of postoperative RT in the surgery arm and the high complication rate.

The treatment schema is stratified using the FIGO staging system (see [Table 1](#)). Surgery is typically reserved for lower-stage disease and smaller lesions, such as stage 1A and 1B1. The NCCN panel reached a general agreement, based on the results of 5 randomized clinical trials (see [Table 2](#)), that RT and concurrent cisplatin-based chemotherapy (either cisplatin alone or cisplatin/5-fluorouracil [5-FU]) should be the treatment of choice for stages IIB, IIIA, IIIB, and IVA disease. Long-term follow-up (106 months) of one of these trials has confirmed that concurrent cisplatin-based chemoradiation improves progression-free and overall survival when compared with hydroxyurea plus RT.<sup>14</sup> Some oncologists feel that concurrent single-agent cisplatin chemoradiation is preferred to cisplatin plus 5-FU chemoradiation, because the latter may be more toxic.<sup>15</sup> Recently, a large population-based pattern-of-care study in Canada (n=4069) confirmed that chemoradiotherapy improved outcomes when compared with radiotherapy alone.<sup>16</sup> Of interest, the French National Federation of Cancer Centres (FNCLCC) have also updated their guidelines (Standards, Options, and Recommendations [SOR] project) by stating that chemoradiotherapy should be the standard for women with cervical cancer.<sup>17</sup> Note that when concurrent chemoradiation is used, the chemotherapy is typically given when the external-beam pelvic radiation is administered.<sup>15</sup>

Extrafascial hysterectomy is commonly recommended for patients with clinical stage IA1 disease; another option is modified radical hysterectomy with pelvic lymph node dissection if lymphovascular invasion is present (category 2B). However, if the patient is medically inoperable or if fertility is desired, patients with negative margins from cone biopsy could undergo observation.<sup>18</sup> Stage IA2 tumors can be treated with radical hysterectomy and pelvic lymph node dissection with (or without) para-aortic lymph node sampling. Brachytherapy with pelvic radiation (point A dose: 75-80 Gy) is another treatment option. 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.

For patients who desire fertility preservation, radical trachelectomy and pelvic lymph node dissection are recommended (with or without para-aortic lymph node sampling) for early stage (stage IA2 or stage IBI < 2 cm) cervical cancer (see [CERV-2](#)).<sup>19-22</sup> A recent 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.<sup>23</sup> For young (< 45 years) premenopausal women with early stage squamous cell carcinoma who opt for ovarian preservation (ie, hysterectomy only), there is a low rate of ovarian metastases.<sup>24,25</sup>

Patients with stage IB or IIA tumors can be treated effectively with radical hysterectomy plus bilateral pelvic lymph node dissection with para-aortic node sampling<sup>13</sup> (category 1 for stage IB1 or IIA tumors [4 cm or less]; category 2B for stage IB2 or IIA bulky [greater than 4 cm]) tumors. Another option for these patients (with stage IB or IIA tumors) is combined pelvic radiotherapy and brachytherapy (plus concurrent cisplatin-containing chemotherapy for bulky stage IB2 or IIA disease

[category 1]) (see [CERV-2](#)). For patients with bulky clinical stage IB2 or IIA tumors who are treated with radiation, concurrent cisplatin-containing chemotherapy has been shown to significantly improve patient survival.<sup>26,27</sup> The addition of concurrent chemoradiation significantly improves progression-free and overall survival for high-risk patients with early stage disease (those with positive lymph nodes, parametrial extension, and/or positive margins) who undergo radical hysterectomy and pelvic lymphadenectomy.<sup>28</sup> For stage IB2 or IIA bulky (greater than 4 cm) tumors, the panel disagreed (category 3) about recommending adjuvant hysterectomy for patients undergoing primary chemoradiation.<sup>26</sup> The EORTC is currently conducting a phase III randomized trial (EORTC 55994) of neoadjuvant cisplatin-based chemotherapy followed by surgery compared with RT plus chemotherapy in patients with stage IB or II cervical cancer.

For patients with more advanced tumors who are undergoing primary chemoradiation, the volume of RT is critical and is guided by assessment of nodal involvement in the pelvis and para-aortic nodes. Radiologic imaging studies are recommended for selected bulky stage IB2 or higher disease. However, fine-needle aspiration (FNA) should be considered for questionable findings seen on radiologic imaging. Surgical staging (ie, extraperitoneal or laparoscopic lymph node dissection) is also an option (category 2B) for these patients. For patients without nodal disease or with disease limited to the pelvis only by surgical staging, treatment consists of pelvic RT with concurrent cisplatin-based chemotherapy (category 1) and brachytherapy.<sup>27</sup> However, for patients with positive para-aortic and pelvic lymph nodes, retroperitoneal lymph node dissection should be considered followed by extended-field RT, cisplatin-containing chemotherapy, and brachytherapy (see [CERV-6](#)). Patients with positive para-aortic lymph nodes who are positive for distant metastases are treated with systemic chemotherapy (see [CERV-A](#)) and individualized RT.

## Adjuvant Treatment

Adjuvant treatment is indicated after radical hysterectomy depending on surgical findings and disease stage. For small-volume tumors (4 cm or less) in stage IA2, IB1, or IIA, if lymph nodes are found negative in the surgery options include 1) close observation or 2) pelvic radiation for high-risk factors (category 1) (large primary tumor, deep stromal invasion, and/or LVSI) with (or without) concurrent cisplatin-based chemotherapy (category 2B for chemotherapy).<sup>29,30</sup> Adjuvant pelvic RT alone versus no further therapy was tested in a randomized trial (Gynecologic Oncology Group [GOG] 92) of selected patients with stage IB carcinoma of the cervix after hysterectomy and pelvic lymphadenectomy.<sup>31</sup> Patients were eligible for this trial after radical hysterectomy and pelvic lymphadenectomy if they had at least 2 of the following risk factors: (1) greater than one-third stromal invasion; (2) capillary lymphatic space involvement; or (3) cervical tumor diameters more than 4 cm. Patients with positive lymph nodes or involved surgical margins were excluded. A statistically significant decrease in recurrence was found in the RT arm compared with the “no additional treatment” arm (15% versus 28%). Life-table analysis indicated a statistically significant (47%) reduction in risk of recurrence (relative risk = 0.53;  $P = .008$ ) in the RT group. At 2 years, the recurrence-free rates were 88% for the RT group versus 79% for the no further treatment group. After extensive follow-up, survival differences did not reach statistical significance ( $P = .07$ ).<sup>32</sup>

Patients with positive pelvic nodes, positive surgical margin, or positive parametrium should be treated with postoperative pelvic radiation with concurrent cisplatin-containing chemotherapy (category 1)<sup>28</sup> with (or without) vaginal brachytherapy (see [CERV-3](#)). As previously noted, Intergroup Trial 0107 showed a statistically significant benefit of adjuvant pelvic radiation with 5-FU and cisplatin in the treatment of patients with stage IA2, IB, or IIA disease who had positive lymph

nodes, positive margins, or microscopic parametrial involvement found at surgery.<sup>28</sup>

If para-aortic lymph nodes are found positive during surgical staging, patients must undergo further screening with chest CT or PET scan. In women who are positive for distant metastases, biopsy of suspicious areas should be considered as indicated (see [CERV-3](#)). If all findings are negative, patients should be treated with para-aortic lymph node RT, concurrent cisplatin-based chemotherapy, and pelvic RT with (or without) brachytherapy. However, patients with positive results should be treated with systemic chemotherapy (see [CERV-A](#)) and individualized radiotherapy.

## Surveillance

Because no definitive study or uniform agreement exists on the best method for post-treatment surveillance for cervical cancer, the panel combined the practice patterns of member institutions and issued consensus recommendations. Patient follow-up includes interval history and physical examination, with a Pap test every 3 months for 1 year, every 4 months for the second year, every 6 months for another 3 years, and then annually. Chest radiographs can be done annually (category 2B). Many of the tests remain optional, such as semiannual complete blood counts, blood urea nitrogen, and serum creatinine determinations. Patients with persistent or recurrent disease need to be evaluated using imaging studies (such as pelvic/abdominal/chest CT/PET scan) and surgical exploration in selected cases followed by salvage therapy (that is, therapy for relapse). Use of a vaginal dilator is suggested after RT for women who wish to remain sexually active.

## Therapy for Relapse

### Local/Regional Therapy

Patients with a localized recurrence of cervical cancer after surgery should be evaluated for radiotherapy for relapse. Salvage rates of

approximately 40% have been reported in such situations.<sup>33</sup> For patients who experience pelvic recurrences with no prior RT or who experience recurrences outside of the previously treated field, therapy for relapse includes definitive pelvic radiation and platinum-based chemotherapy with (or without) brachytherapy. Patients with central pelvic recurrent disease after RT should be evaluated for pelvic exenteration, with (or without) intraoperative RT (IORT); in carefully selected patients with small lesions (less than 2 cm), options include radical hysterectomy or brachytherapy. Surgical mortality is generally 5% or lower, with survival rates between 20% and 60%. Concomitant measures with such radical procedures include adequate rehabilitation programs dealing with the psychosocial and psychosexual consequences of the operation<sup>34,35</sup> as well as reconstructive procedures. Women with recurrence after pelvic exenteration should be treated with platinum-based chemotherapy, best supportive care, or be enrolled in a clinical trial. Patients with isolated recurrences may benefit from surgical resection with (or without) IORT, tumor-directed RT with concurrent chemotherapy, or chemotherapy. Those with noncentral disease should be treated with pelvic exenteration or resection with IORT for close or positive margins, tumor-directed RT with (or without) chemotherapy, platinum-based chemotherapy, best supportive care, or participation in a clinical trial.

### Systemic Therapy and Palliation

Patients with extrapelvic or para-aortic recurrence(s) at multiple sites or with unresectable recurrence(s) should be treated with chemotherapy (see [CERV-A](#)) or best supportive care. Isolated site recurrence(s) can be managed with surgical resection with (or without) IORT, tumor-directed RT with concurrent chemotherapy, or chemotherapy. Patients may then undergo RT (optional), adjuvant chemotherapy (optional), or best supportive care (see [NCCN Palliative Care Guidelines](#)).

The palliation of pelvic recurrences in heavily irradiated sites that are not amenable to local pain control techniques or to surgical resection is an unresolved clinical issue. Such sites are generally not responsive to chemotherapy. It is clinically challenging to adequately palliate the complications of pain and fistulae from such recurrences. Occasionally, patients may benefit from radiotherapy to a localized recurrence(s). Generally, these areas would be supraclavicular, bone metastases, or painful para-aortic nodal recurrences. Clearly, pain relief of a transient nature may be achieved in responders to chemotherapy.

Chemotherapy has a limited role in prolonging survival or in improving quality of life and is recommended for patients with extrapelvic metastases or recurrent disease who are not candidates for RT or exenterative surgery. Cisplatin is generally regarded as the most active agent and is recommended as possible first-line chemotherapy in recurrent or metastatic cervical cancer; reported response rates are approximately 20% to 30%, with an occasional complete response.<sup>36,37</sup> However, combination regimens (see next paragraph) are preferred (and are first-line therapy) if cisplatin was previously used as a radiosensitizer. Carboplatin, topotecan (category 2B), and paclitaxel have also been reported to be tolerable and efficacious. Complete responses were also observed with topotecan and paclitaxel; however, topotecan is associated with more toxicity than carboplatin or paclitaxel.<sup>38-42</sup> Therefore, palliation with single-agent cisplatin, carboplatin, paclitaxel, or topotecan is a reasonable approach in patients with recurrent disease not amenable to surgical or radiotherapeutic approaches. Other agents (category 2B) reported to show a partial response and useful as second-line therapy include ifosfamide,<sup>43,44</sup> vinorelbine,<sup>45</sup> irinotecan,<sup>46</sup> epirubicin,<sup>47</sup> mitomycin, and 5-FU. A phase II study evaluating the effectiveness of docetaxel in patients who have persistent or recurrent cervical cancer is ongoing (GOG-0127S).

Cisplatin-based combination chemotherapy regimens such as cisplatin/paclitaxel and cisplatin/topotecan (category 1 for both) have been extensively investigated in clinical studies. A randomized phase III study comparing paclitaxel and cisplatin versus cisplatin alone showed that the 2-drug combination had a higher response rate (36% versus 19%) and improved progression-free survival (4.8 versus 2.8 months;  $P > .001$ ), although no improvement was seen in median survival.<sup>48</sup> Another randomized phase III GOG study investigated the combination of cisplatin and topotecan versus cisplatin alone in recurrent or persistent cervical cancer. In this study of 294 eligible patients, the topotecan combination regimen was shown to be superior to single-agent cisplatin with respect to overall response rate (27% versus 13%,  $P = .004$ ), progression-free survival (4.6 versus 2.9 months;  $P = .014$ ), and median survival (9.4 versus 6.5 months,  $P = .017$ ).<sup>49</sup>

A phase II study assessed cisplatin and gemcitabine (category 2B) in patients with advanced, recurrent, or persistent cervical cancer; 17 patients were evaluated.<sup>50</sup> The response rate was 57% in patients who had not previously received RT; there was one complete response of 14 months. Paclitaxel and carboplatin have recently been assessed for recurrent or persistent cancer of the cervix; 4 of 15 patients had complete response and 5 had partial response for an overall response rate of 60%. The median survival of all 15 patients treated was 17 months (range, 4 to 39 months).<sup>51</sup> The combination of vinorelbine and cisplatin has also been assessed in 42 patients with recurrent or metastatic cervical cancer; the overall response rate was 48%.<sup>52</sup> The GOG is currently conducting a phase III trial (GOG 204) assessing 4 cisplatin-doublet regimens in patients with advanced metastatic or recurrent cancer (cisplatin/paclitaxel, cisplatin/topotecan, cisplatin/gemcitabine, versus cisplatin/vinorelbine).

Biologic molecular and vaccine therapies have no established role at the present time,<sup>53,54</sup> except in the setting of a clinical trial. Therefore,

patients with refractory systemic cancer warrant a comprehensive coordinated approach involving hospice care, pain consultants, and emotional and spiritual support, suited to the individual situation.

### Incidental Cervical Cancer

A clinical scenario requiring oncologic management is the finding of invasive cervical carcinoma after simple hysterectomy. Workup for these patients includes history and physical examination, complete blood count, platelets, and liver and renal function tests. Radiologic imaging includes chest radiography, CT, MRI, or PET; although these tests are optional for patients with stage IB1 or smaller tumors. Cystoscopy and proctoscopy examination under anesthesia should be reserved for patients in whom there is clinical concern for bladder or rectal cancer (that is, stage IB2 or higher).

No definitive data exist regarding the appropriate follow-up treatment of these patients. The panel believes that a reasonable treatment schema for patients with either stage IA1 with LVSI or with stage 1A2 or higher tumors (pathologic findings) should be based on the status of the surgical margins. If margins are positive and imaging is negative for nodal disease, then concurrent chemoradiation should be recommended (see [CERV-7](#)).

If margins or imaging is negative in stage 1A2 or higher tumors, options include (1) pelvic RT and brachytherapy with (or without) cisplatin-containing chemotherapy; or (2) a complete parametrectomy with pelvic lymph node dissection with (or without) para-aortic lymph node sampling. Patients with negative lymph nodes should be observed or treated with optional pelvic radiation with (or without) vaginal brachytherapy if they have high-risk factors (ie, large primary tumor, deep stromal invasion, and/or LVSI). Concurrent cisplatin-based chemoradiation is recommended for gross residual disease, positive imaging, disease in the lymph nodes or parametrium, or a positive

surgical margin; individualized brachytherapy is clearly indicated for a positive vaginal margin. Stage 1A1 patients with no LVSI should undergo surveillance (see [CERV-8](#)).

### Radiation Therapy

The NCCN algorithm provides RT dosage recommendations. 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.

The external-beam doses represent the range of doses employing conventionally fractionated regimens of treatment (45-50 Gy to CTV). The brachytherapy doses used are for low-dose-rate applications (40 to 70 cGy/h), with doses to point A added to the external-beam doses to permit treatments to be compared. These doses may be modified for individual patients to provide adequate tumor coverage and to take into account normal tissue tolerances.

External-beam RT and brachytherapy techniques have improved, as well as a better understanding of the influence of overall treatment time on outcome. Optimum staging of patients to precisely delineate the primary tumor volume and draining lymph nodes, including abdominopelvic radiologic studies (CT, MRI, or PET scans), is recommended in patients with bulky or advanced-stage tumors.

### Planning Treatment Fields

The use of 3-dimensional treatment planning for both the external-beam RT fields and the brachytherapy placements may assist in customized shaping of dose distributions to ensure adequate tumor coverage in all dimensions and to minimize normal tissue exposure. The anterior field margins should include, where indicated, possible extensions of the tumor into the body of the uterus. The posterior field margins should include tumor extension into the uterosacral ligament

and presacral lymph nodes. Lateral field margins need to adequately include the pelvic lymph nodes. IMRT is becoming more widely used; however, its role in the primary management of gynecologic cancer is undefined.

For lesions in the lower one third of the vagina, the inguinal lymph nodes need to be treated. The use of extended-field radiation to treat occult or macroscopic para-aortic lymph node disease needs to be carefully planned to ensure adequate dose (45 Gy for microscopic disease) without exceeding bowel, spinal cord, or renal tolerances. Intracavitary or interstitial brachytherapy techniques have proven to be a vital component in treatment of invasive cervical tumors. This is particularly true for more advanced stages of disease.

Initial radiation treatment of 40 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 at least 85 Gy recommended for larger tumors.

### Minimizing Tissue Damage

Adjustments must be made to minimize radiation doses to normal surrounding tissues (eg, bladder, rectum, and sigmoid colon). Coned-down shaped boost fields should be used with involved pelvic lymph nodes and areas of parametrial extension. These regions should be treated with total doses of 60 to 65 Gy. Individualized central blocking techniques should be used to shield from the intracavitary placements those portions of the small bowel, rectum, and bladder that had been included in the high-dose regions. Similar recommendations apply to high-dose-rate intracavitary systems, for which a wide range of treatment regimens have been used (generally using between 3 and 6 fractions, with doses usually between 5 and 10 Gy per fraction). Dose

modifications may be needed for patients who will undergo hysterectomy or for postoperative treatment.

Several, but not all, retrospective analyses have suggested an adverse effect of prolonged treatment duration on outcome. 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, the entire RT course should be completed in a timely fashion (eg, less than 8 weeks); delays or splits in the radiation treatment should be avoided whenever possible, although no prospective randomized trials have been done.

### Concurrent Chemoradiation

Five randomized phase III trials have shown a statistically significant benefit of concurrent cisplatin--based chemoradiation for advanced cervical cancers (see [Table 2](#)).<sup>26-28,55-57</sup> These 5 trials have shown that the use of concurrent chemoradiation results in a 30% to 50% decrease in the risk of death compared to RT alone. Although the optimal concurrent chemotherapy regimen to use with RT requires further investigation, these 5 trials have clearly established a role for concurrent cisplatin-based chemoradiation. For concurrent chemoradiation, the currently accepted regimens are cisplatin alone (weekly) or cisplatin combined with infusion 5-FU on an every 3 to 4 week basis. Use of 5-FU alone (with RT) is not an optimal regimen.<sup>58</sup>

Peters and colleagues in the Intergroup Trial INT-0107 (SWOG-8797) assessed postoperative pelvic RT with (or without) 5-FU and cisplatin for the treatment of stages IA2, IB, and IIA cervical cancer with positive lymph nodes, positive margins, or microscopic parametrial involvement at the time of surgery.<sup>28</sup> The 4-year progression-free survival was significantly improved with the use of radiation plus chemotherapy, compared with RT alone (81% versus 63%, respectively;  $P = .01$ ). The



relative risk of death was reduced by 50% for the group receiving adjuvant 5-FU and cisplatin in conjunction with radiation.

Keys and colleagues in the GOG Trial 123 studied the use of cisplatin as an adjunct to RT in patients who subsequently underwent extrafascial hysterectomies. The study included patients with bulky stage IB tumors that were 4 cm or more in diameter or barrel-shaped in configuration. The 3-year survival rates were 83% for the radiation plus cisplatin plus hysterectomy group compared with 74% for the radiation plus hysterectomy group. The addition of cisplatin resulted in a relative risk of death of 0.54.<sup>26</sup>

Rose and colleagues in the GOG Trial 120 investigated the use of standard pelvic radiation with 1 of 3 concurrent chemotherapy regimens---hydroxyurea alone, cisplatin alone, or cisplatin plus 5-FU plus hydroxyurea---in patients with stage IIB, III, or IVA cancer and with negative para-aortic lymph nodes. The 3-year survival rate in both cisplatin-containing treatment arms was 65%, compared with 47% for the pelvic radiation plus hydroxyurea treatment group. The relative risk of death was 0.61 for pelvic radiation plus cisplatin, and 0.58 for cisplatin plus 5-FU plus hydroxyurea plus pelvic radiation, compared with patients treated with pelvic radiation plus hydroxyurea alone.<sup>57</sup>

Morris and colleagues in the RTOG Trial 9001 assessed pelvic plus para-aortic radiation compared with pelvic radiation plus 5-FU plus cisplatin treatment in patients with stage IIB to IVA cervical cancer and in patients with stage IB or IIA disease with tumors 5 cm or larger or with metastases to the pelvic lymph nodes. The 5-year survival rate for the cisplatin treatment arm was 73%, compared with 58% for patients treated with pelvic plus para-aortic radiation ( $P = .004$ ). The addition of chemotherapy resulted in a relative risk of death of 0.52.<sup>27</sup> After 8 years, the overall survival was still significantly greater for patients receiving concomitant cisplatin treatment (67% versus 41%,  $P < .0001$ ).<sup>59</sup>

Whitney and colleagues (GOG Trial 85) also showed a significant benefit for the concurrent use of cisplatin-based chemotherapy.<sup>56</sup> Patients enrolled in this study had stage IIB to IVA cervical cancer with surgically staged negative para-aortic lymph nodes. These patients were randomly assigned either to pelvic radiation with concurrent hydroxyurea or to pelvic radiation with cisplatin plus 5-FU. A statistically significant improvement in the 3-year survival rate was noted for the cisplatin-containing regimen (67% versus 57%), resulting in a relative risk of death of 0.72.

### Vaccination Against HPV

Gardasil is a prophylactic vaccine against certain types of human papillomavirus, (types 6, 11, 16, 18), which cause cervical cancer and genital warts.<sup>6-9</sup> The Gardasil vaccine is currently approved for use in girls and women ages 9 to 26 years; however, it is most effective if given before sexual intercourse is initiated. Guidelines from the American College of Obstetricians and Gynecologists (ACOG), Centers for Disease Control and Prevention (CDC), and American Cancer Society (ACS) all agree that 11 to 12 year old females should receive routine vaccination with the HPV vaccine, but they differ regarding recommendations for other age groups.<sup>60-62</sup> The Gardasil vaccine is not recommended for women older than 26 years. After 3 years, the efficacy of Gardasil was 99% for preventing cervical intraepithelial neoplasia grades 2 and 3 (CIN2/3, which are precursors of cervical cancer) caused by HPV 16 or 18 in females who were not previously infected with either HPV 16 or 18 before vaccination; however, efficacy was only 44% in those who had been infected prior to vaccination.<sup>7</sup> Cervarix is another prophylactic HPV vaccine; however, it is not currently approved in the United States. If women have been vaccinated against HPV, they still must receive routine Pap tests and other appropriate cervical cancer screening tests, because HPV vaccination is currently only effective against certain types of HPV.

## Pregnancy and Cervical Cancer

Women who are treated for CIN (for example, using the loop electrosurgical excision procedure [LEEP]) have an increased risk for premature rupture of membranes<sup>63</sup> or for preterm delivery during subsequent pregnancies.<sup>64-66</sup> For women diagnosed with early stage cervical cancer during pregnancy who wish to continue their pregnancies, delaying cancer treatment until the fetus has matured has been successful. Chemotherapy has been administered during pregnancy to women with cervical carcinoma;<sup>67</sup> however, it should be administered after 13-weeks gestation to avoid major congenital malformations.<sup>68</sup> Short-term follow-up has indicated that there were no abnormalities in the offspring whose mothers were treated; however, the long-term effect of neoadjuvant chemotherapy during pregnancy is unknown.

## Summary

Cervical cancer is decreasing in the United States, because screening has been widely used; however, cervical cancer is increasing in developing countries (about 270,000 deaths/year), because screening is not available to many women. Effective treatment for cervical cancer (including surgery, concurrent chemoradiation) can yield cures in 80% of women with early stage disease (stages I and II) and in 60% of women with stage III disease. Hopefully, immunization against HPV (using the new vaccines) will prevent persistent infection with certain types of HPV and, thus, is expected to prevent specific HPV cancer in women.<sup>9,69</sup>

## Disclosures for the NCCN Cervical Cancer Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed the names of companies, foundations, and/or funding agencies from which they received research support; for which they participate in speakers' bureau, advisory boards; and/or in which

they have equity interest or patents. Members of the panel indicated that they have received support from the following: Cardinal Health; Cell Therapeutics Inc.; Eli Lilly; EMD Pharmaceuticals; Genentech Inc.; GlaxoSmithKline; Gynecologic Oncology Group; InterMune; Lilly Oncology; MedImmune; Merck & Co.; Myriad Genetics, Inc; Novartis Pharmaceuticals; Nucletron Corporation; Ross Products; sanofi-aventis; Sanofi-Synthelabo Inc.; Schering-Plough; Telik, Inc.; Tibotec Therapeutics; and Wyeth. Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.

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

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

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

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