National Comprehensive Cancer Network

NCCN

Clinical Practice Guidelines in Oncology – v.2.2006

Cervical Cancer

Version 2.2006

Continue

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

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

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

See NCCN Categories of Consensus

Summary of Guidelines Updates

Cervical Cancer

WORKUP

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

Optional (≥ Stage IB2):

- EUA cystoscopy/proctoscopy[a]
- PET scan

CLINICAL STAGE

Stage IA1	See Primary Treatment (CERV- 2)
Stage IA2 Stage IBI Stage IIA (≤ 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 IV	See Primary Treatment (CERV-4)
Incidental finding of invasive cancer at simple hysterectomy	See Primary Treatment (CERV-7)

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

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

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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)	See Surveillance (CERV-8)
Stage IA2	Radical hysterectomy + pelvic lymph node dissection ± para-aortic lymph node sampling	See Surgical Findings (CERV-3)
	or Brachytherapy + pelvic RT (point A dose: 75-80 Gy)[b]	See Surveillance (CERV-8)
	or Radical trachelectomy + lymph node dissection for fertility preservation	
Stage IB1 and stage IIA (≤ 4 cm)[a]	Radical hysterectomy + pelvic lymph node dissection + sample para-aortic nodes (category 1)	See Surgical Findings (CERV-3)
	or Pelvic RT + brachytherapy (point A dose: 80-85 Gy)[b]	See Surveillance (CERV-8)
Stage IB2 and stage IIA (> 4 cm)[a]	Radical hysterectomy + pelvic lymph node dissection + para-aortic lymph node sampling (category 2B)	See Surgical Findings (CERV-3)
	or Pelvic RT + concurrent cisplatin-containing chemotherapy + brachytherapy (point A dose ≥ 85 Gy)[b] (category 1)	See Surveillance (CERV-8)
	or Pelvic RT + concurrent cisplatin-containing chemotherapy + brachytherapy (point A dose 75-80 Gy)[b] + adjuvant hysterectomy (category 3)	See Surveillance (CERV-8)

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

[b] These doses are recommended for most patients based on summation of conventional external-beam fractionation and low-dose rate (40-60 cGy/h) brachytherapy equivalents. Modify treatment based on normal tissue tolerance.

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Cervical Cancer

SURGICAL FINDINGS | **ADJUVANT TREATMENT**

Negative nodes → **Observe or Pelvic RT if combination of high-risk factors (ie, large primary tumor, deep stromal invasion or lymphovascular space invasion)[c]** → **See Surveillance (CERV-8)**

Positive pelvic nodes or Positive surgical margin or Positive parametrium → **Pelvic RT + concurrent cisplatin-containing chemotherapy (category 1) ± vaginal brachytherapy if positive vaginal margin)** → **See Surveillance (CERV-8)**

Para-aortic lymph node positive by surgical staging → **Chest CT/PET scan**

- **Negative for distant metastasis** → **Para-aortic lymph node RT + concurrent cisplatin-containing chemotherapy + pelvic RT ± brachytherapy**
- **Positive for distant metastasis** → **Consider biopsy of suspicious areas as indicated**
  - **Negative** → **Para-aortic lymph node RT + concurrent cisplatin-containing chemotherapy + pelvic RT ± brachytherapy**
  - **Positive** → **Systemic therapy[d]/ Individualized RT**

[c] 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.

See Surveillance (CERV-8)

[d] See Chemotherapy Regimens for Cervical Cancer (CERV-A).

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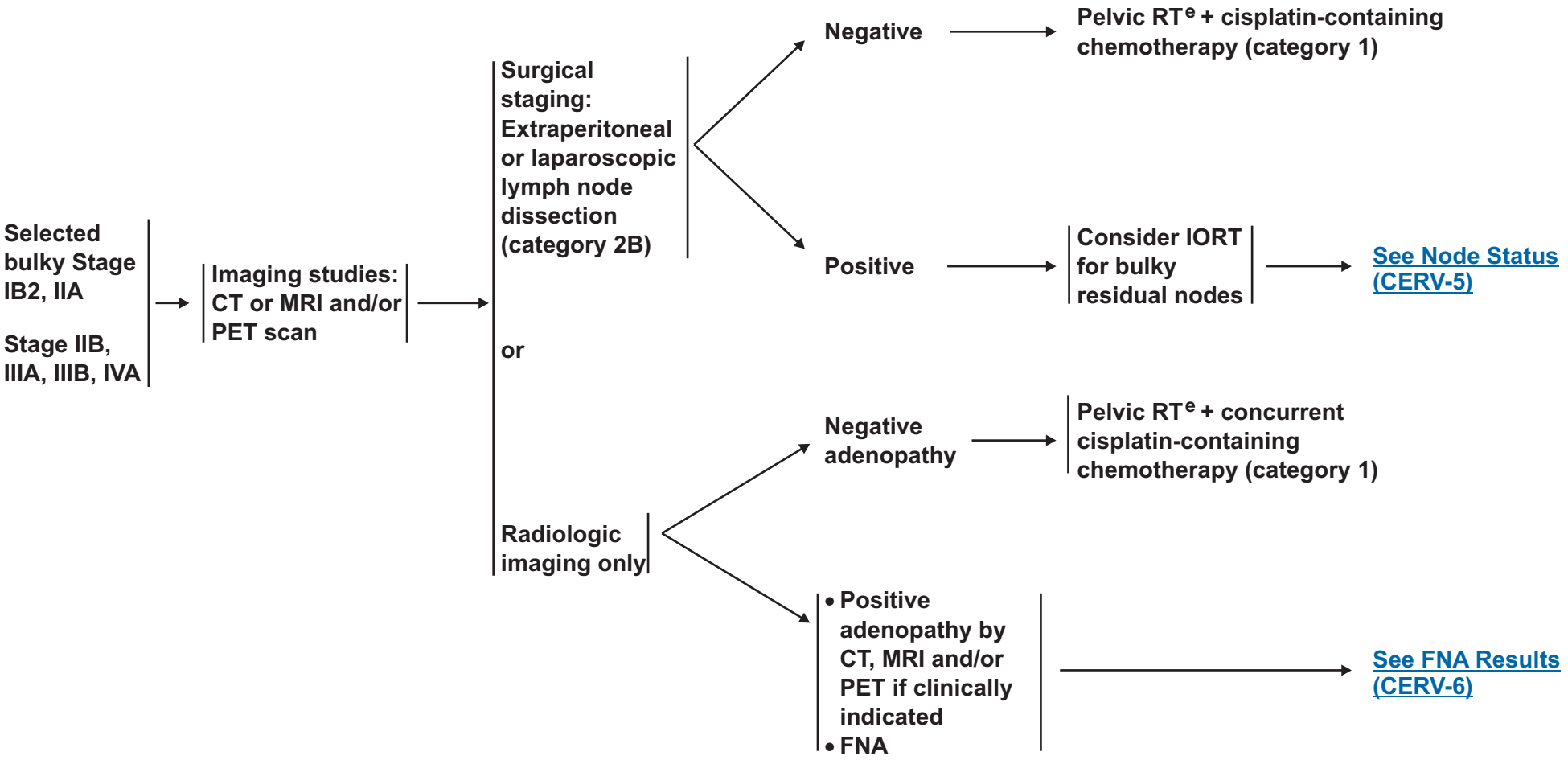
Cervical Cancer

CLINICAL STAGE

PRIMARY TREATMENT



[e]All RT on this page should be pelvic RT + brachytherapy (total point A dose ≥ 85 Gy).

See Surveillance (CERV-8)

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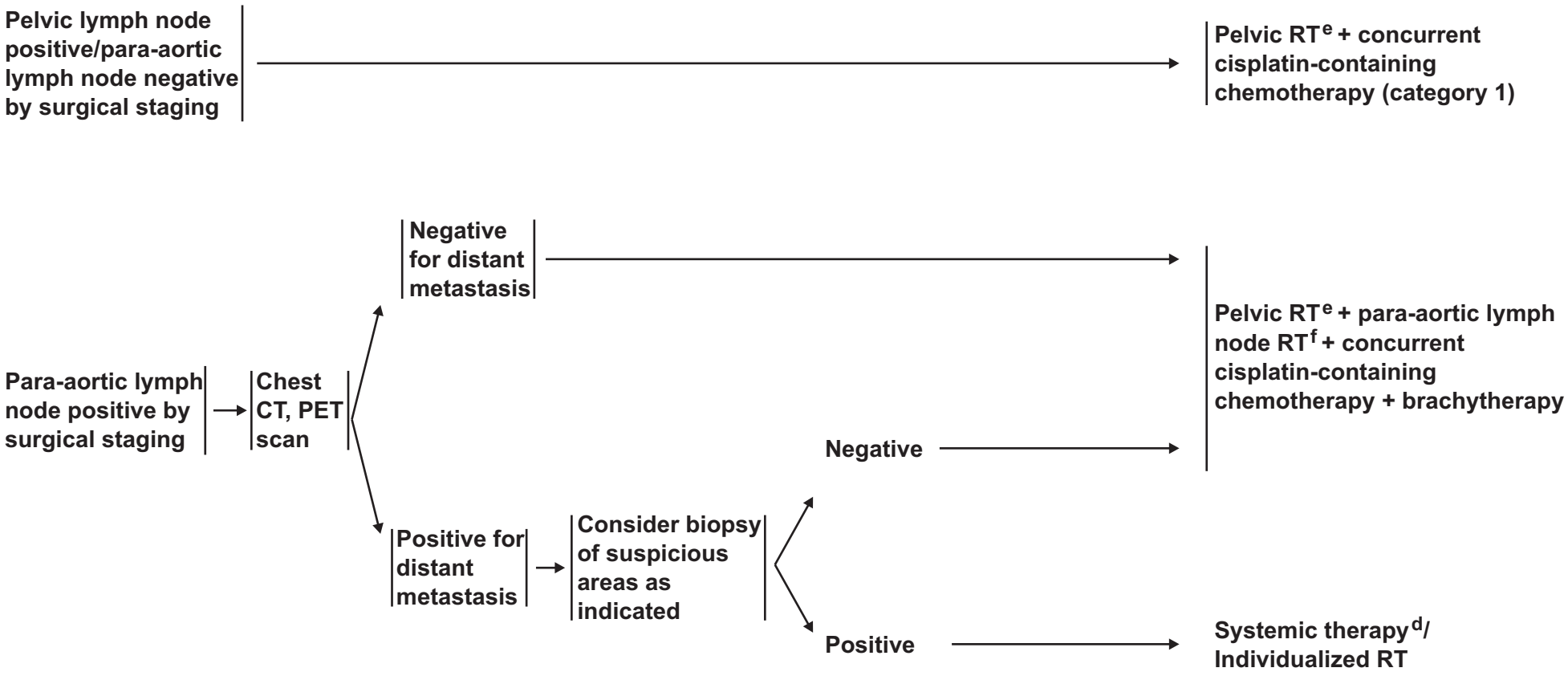
Cervical Cancer

SELECTED BULKY Stage IB2, IIA; Stage IIB, IIIA, IIIB, IV NODE STATUS

PRIMARY TREATMENT



[d] See Chemotherapy Regimens for Cervical Cancer (CERV-A).

[e] All RT on this page should be pelvic RT + brachytherapy (total point A dose ≥ 85 Gy).

[f] RT dose is 45-50 Gy to CTV.

See Surveillance (CERV-8)

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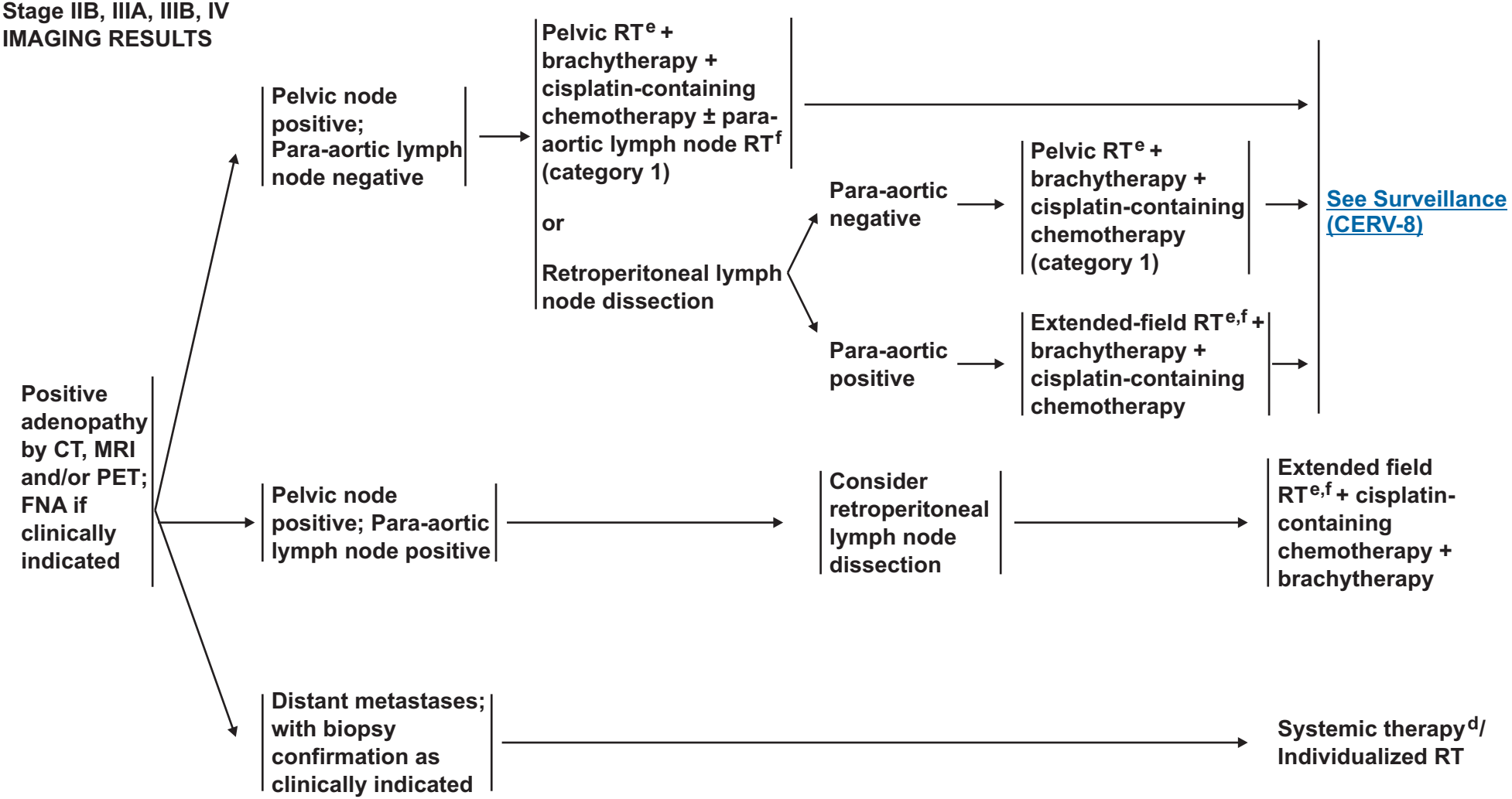
Cervical Cancer

SELECTED BULKY Stage IB2, IIA
Stage IIB, IIIA, IIIB, IV
IMAGING RESULTS

PRIMARY TREATMENT



[d] See Chemotherapy Regimens for Cervical Cancer (CERV-A).

[e] All RT on this page should be pelvic RT + brachytherapy (total point A dose ≥ 85 Gy).

[f] RT dose is 45-50 Gy to CTV.

See Surveillance (CERV-8)

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Cervical Cancer

INCIDENTAL FINDING OF INVASIVE CANCER AT SIMPLE HYSTERECTOMY

PRIMARY TREATMENT

Stage IA1 → **Pathologic review** → **No lymphovascular space invasion** → **See Surveillance CERV-8**

≥ Stage IA2 →
- H&P
- CBC, platelets
- Chest x-ray, or CT/MRI

Optional (≥ Stage IB2):
- EUA cystoscopy/proctoscopy[a]
- PET scan
- LFT/renal function studies

→ **Negative margins; negative imaging** →
- **Pelvic RT[f] + brachytherapy ± cisplatin-containing chemotherapy** → **See Surveillance CERV-8**
- or
- **Complete parametrectomy + lymph node dissection** →
  - **Negative nodes** → **Observe or Optional pelvic RT[f] ± vaginal brachytherapy if deep stromal invasion or lymphovascular space invasion**
  - **Positive nodes or Positive surgical margin or Positive parametrium** → **Pelvic RT[f] (para-aortic lymph node RT if para-aortic lymph node positive) + concurrent cisplatin-containing chemotherapy ± individualized brachytherapy (if positive vaginal margin)**

→ **Positive margins[g], gross residual disease, or positive imaging** →
- **Imaging negative for nodal disease** → **Pelvic RT[f] (para-aortic lymph node RT if para-aortic lymph node positive) + concurrent cisplatin-containing chemotherapy ± individualized brachytherapy (if positive vaginal margin)**
- **Imaging positive for nodal disease** → **Consider surgical debulking of grossly enlarged nodes** → **Pelvic RT[f] (para-aortic lymph node RT if para-aortic lymph node positive) + concurrent cisplatin-containing chemotherapy ± individualized brachytherapy (if positive vaginal margin)**

[a] For suspicion of bladder/bowel involvement cystoscopy/proctoscopy with biopsy is required.
[f] RT dose is 45-50 Gy to CTV.
[g] Invasive cancer at surgical margin.

See Surveillance CERV-8

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Cervical Cancer

SURVEILLANCE

- 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 →

WORKUP

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

→ See Salvage Therapy (pelvic recurrence) (CERV-9)

→ See Salvage Therapy (extrapelvic or para-aortic recurrence) (CERV-10)

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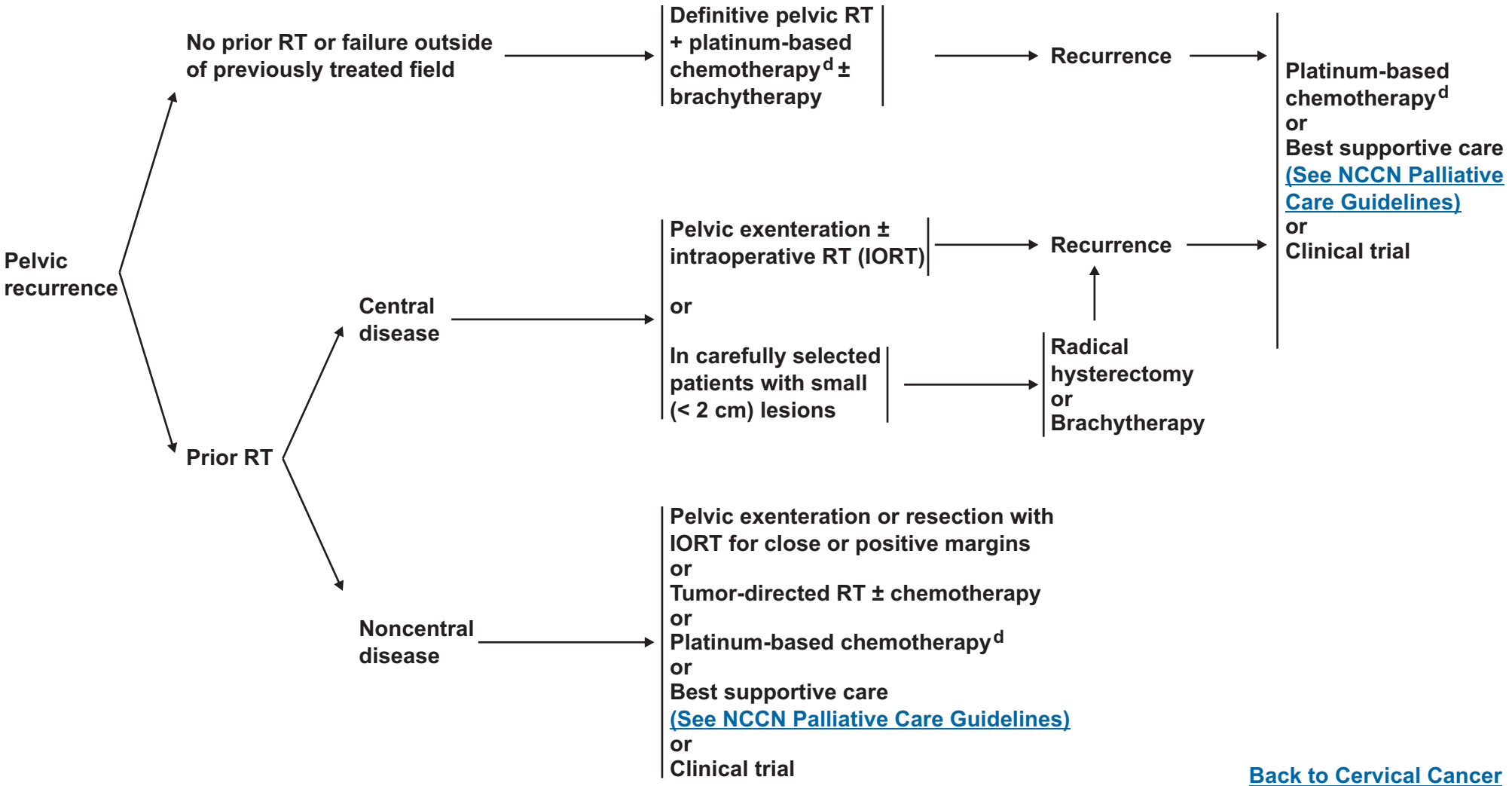
SALVAGE THERAPY



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[d] See Chemotherapy Regimens for Cervical Cancer (CERV-A).

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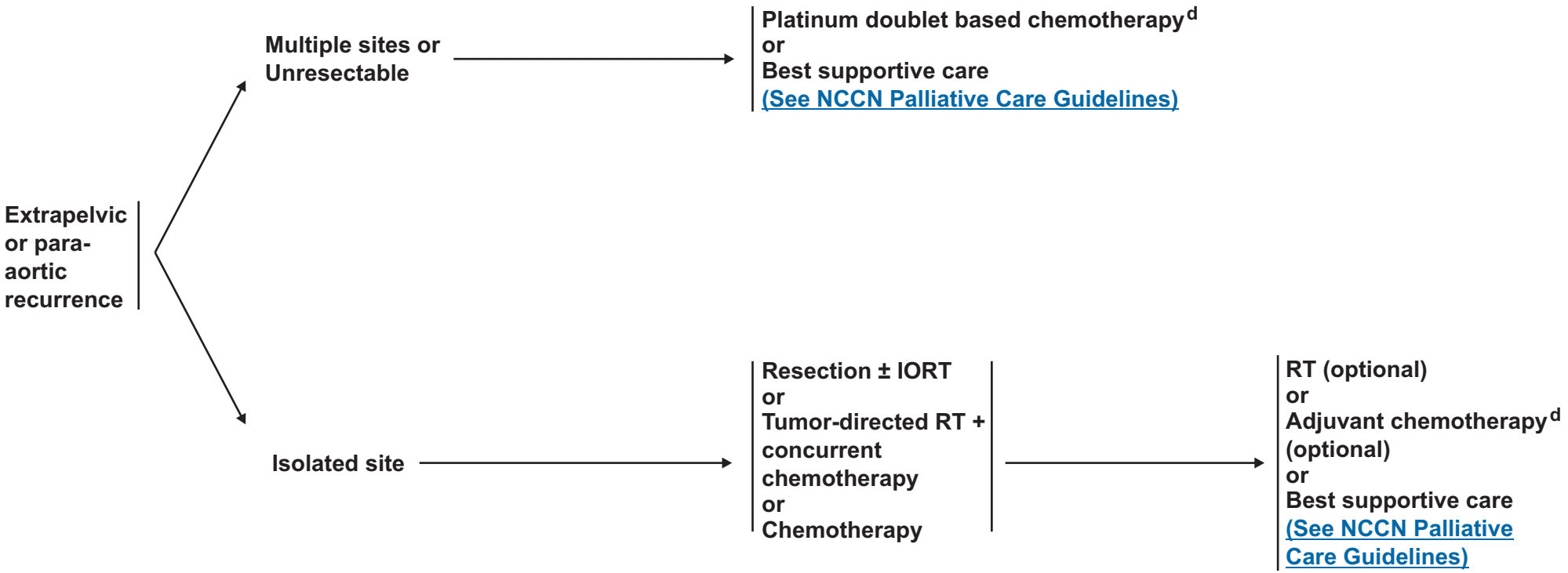
SALVAGE THERAPY



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[d] See Chemotherapy Regimens for Cervical Cancer (CERV-A).

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Cervical Cancer

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC CERVICAL CANCER

First-line therapy
- Cisplatin
- Carboplatin
- Paclitaxel
- Topotecan (category 2B)

Possible first-line combination therapy[1]
- Cisplatin/paclitaxel (category 1)
- Cisplatin/topotecan (category 1)
- Cisplatin/gemcitabine (category 2B)
- Carboplatin/paclitaxel

Second-line therapy
(All agents listed are category 2B)
- Docetaxel
- Ifosfamide
- Vinorelbine
- Irinotecan
- Epirubicin
- Mitomycin
- 5-FU

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[1] Preferred if cisplatin was previously used as a radiosensitizer.

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Summary of the Guidelines updates

Highlights of major changes in the 1.2006 version of the Cervical Cancer guidelines from the 1.2005 version include:

- In the workup section lymphangiography was removed and LFT/renal function studies are no longer optional, but part of the workup (CERV-1).
- Primary treatment options for Stage IA1 and Stage IA2 were expanded, and adjuvant hysterectomy for Stage IB2 is listed as a category 3 (CERV-2).
- PET scan was added to Chest CT and adjuvant treatment for negative nodes includes pelvic RT if combination of high-risk factors is present and a reference was added; vaginal brachytherapy was removed (CERV-3).
- Scalene node biopsy was removed (CERV-3 and CERV-4).
- Surgical staging was added and IORT for bulky residual nodes was added if the result is positive (CERV-4).
- Positive adenopathy is defined by CT, MRI and possibly PET (CERV-4).
- Primary treatment for positive adenopathy by CT, MRI and/or PET was completely updated (CERV-6).
- Primary treatment for Stage IA1 was added (CERV-7).
- Primary treatment for both negative and positive margins was updated (CERV-7).
- CT/PET scan as clinically indicated was added to surveillance and the use of a vaginal dilator after RT was suggested (CERV-8).
- Chest x-ray was removed from the workup (CERV-8).
- Pelvic exenteration or tumor-directed RT with or without chemotherapy were added as salvage therapy options for noncentral disease with history of prior RT (CERV-9).
- Salvage therapy for isolated sites was updated and the isolated nodal site branch was removed (CERV-10).
- Chemotherapy regimens were listed for recurrent or metastatic cancer (CERV-A).
- Topotecan and carboplatin/paclitaxel were added at possible first-line therapies. Combination first-line therapies are preferred if cisplatin was previously used as a radiosensitizer (CERV-A).

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 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 9,710 new cases of cervical cancer will be diagnosed in the United States in the year 2006; 3,700 deaths will result from the disease.[1] Cervical cancer rates are decreasing among women in all racial and ethnic groups in the United States, although incidence remains high among Hispanic/Latina women.[2] 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;[3] 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%.[3] 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 carcinomas, adenosquamous carcinoma, and adenocarcinoma of the cervix. Squamous cell carcinomas account for about 80% of all cervical cancers. Neuroendocrine 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.[4]

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 go 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 Practice Guidelines for Cervical Cancer Screening). Cone biopsy is recommended if the cervical biopsy is inadequate to define invasiveness or if accurate assessment of microinvasive disease is required.

Common radiologic tests include chest radiography, CT, MRI, or PET, although these tests are optional for patients with stage IB1 or smaller tumors. Laboratory tests (such as complete blood count, platelets, liver and renal function tests) are also recommended. Cystoscopy and proctoscopy examination under anesthesia should be reserved for patients with disease that is stage IB2 or higher, or for those in whom there is clinical concern for bladder or rectal cancer.

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 and remain investigational, although laparoscopic staging, lymphadenectomies, and radical hysterectomies can be performed satisfactorily and are used routinely in selected patients in several member institutions.[5]

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 recently revised (see Table 1).[6]

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.[7] 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). The NCCN panel reached a general agreement, based on the results of five randomized clinical trials, 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. Surgery is typically reserved for lower-stage disease and smaller lesions, such as stage 1A and 1B1. 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.[8]

Extrafascial hysterectomy is 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.[9] 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 (40-60 cGy/h) brachytherapy equivalents. Treatment should be modified based on normal tissue tolerance. For patients who desire fertility preservation, radical trachelectomy and lymph node dissection are recommended.[10,11]

Among panel members, there was some disagreement about the primary approach for stage 1B2/IIA disease. 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[7] (category 1 for stage IB1 or IIA tumors 4 cm or less; category 2B for stage IB2 or IIA tumors greater than 4 cm), or with combined pelvic radiotherapy and brachytherapy (see CERV-2). Substantial discussion occurred about the optimal management of stage IB2 and bulky IIA (greater than 4 cm) disease. For patients with clinical stage IB2 or IIA tumors (greater than 4 cm) who are treated with radiation, concurrent cisplatin-containing chemotherapy has been shown to significantly improve patient survival.[12,13] 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.[14] For stage IB2 or IIA tumors (greater than 4 cm), the panel disagreed (category 3) about

recommending adjuvant hysterectomy for patients undergoing primary chemoradiation.[12] 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. Imaging studies (CT or MRI and/or PET scan) are recommended for selected bulky stage IB2 or higher disease (see CERV-4). However, fine-needle aspiration (FNA) is needed to confirm suspicious lymph nodes seen on radiologic imaging. Surgical staging (ie, extraperitoneal or laparoscopic lymph node dissection) is also recommended (category 2B) for these patients. If node sampling is performed and indicates positive findings, intraoperative radiotherapy (IORT) should be considered for bulky residual nodes. For patients without nodal disease or with disease limited to the pelvis only by surgical staging, treatment consists of pelvic RT with concurrent chemotherapy (category 1).[13] 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. 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, patients should undergo close observation or receive pelvic radiation if deep stromal invasion or LVSI is present. 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.[15] Patients were eligible for this trial after radical hysterectomy and pelvic lymphadenectomy if they had at least two of the following risk factors: (1) greater than one-third stromal invasion; (2) capillary lymphatic space involvement; or (3) large cervical tumor diameters. 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.

Patients with positive pelvic nodes, positive surgical margin, or positive parametrium should be treated with postoperative pelvic radiation with concurrent chemotherapy (category 1);[14] vaginal brachytherapy is also indicated if the vaginal margin is positive (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.[14]

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 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. Use of a vaginal dilator is suggested after RT for women who wish to remain sexually active.

Salvage Therapy

Local/Regional Therapy

Patients with a localized recurrence of cervical cancer after surgery should be evaluated for salvage radiotherapy. Salvage rates of approximately 40% have been reported in such situations.[16] For patients who experience pelvic recurrences with no prior RT or who experience recurrences outside of the previously treated field, salvage therapy 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 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[17,18] 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 platinum doublet-based chemotherapy 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 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 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 first-line chemotherapy in recurrent or metastatic cervical cancer; reported response rates are approximately 20% to 30%, with an occasional complete response.[19,20] However, combination regimens (see next paragraph) are preferred if cisplatin was previously used as a radiosensitizer. Carboplatin, topotecan, 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.[21-25] 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 reported to show a partial response include ifosfamide,[26,27] vinorelbine,[28] irinotecan,[29] epirubicin,[30] 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 have been extensively investigated in clinical studies. A randomized phase III study comparing paclitaxel and cisplatin versus cisplatin alone showed that the two-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.[31] 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, $P = .017$).[32] A phase II study assessed cisplatin and gemcitabine in patients with advanced, recurrent, or persistent cervical cancer; 17 patients were evaluated.[33] 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).[34] 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%.[35] 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,[36,37] 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 or extrafascial hysterectomy. Workup for these patients includes history and physical examination, complete blood and platelet counts, and chest radiography or CT and MRI. For stage IB2 or higher, optional tests include cystoscopy or proctoscopy under anesthesia, PET scan, and liver and renal function studies. No definitive data exist regarding the appropriate follow-up treatment of these patients. The panel believes that a reasonable treatment schema for patients with stage 1A2 or higher tumors (pathologic findings) should be based on the status of the surgical margins. If margins are positive and imaging is negative for nodal disease, then pelvic RT and concurrent chemotherapy with or without individualized brachytherapy 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 a lymph node dissection. Patients with negative lymph nodes should be observed or treated with optional pelvic radiation with (or without) vaginal brachytherapy if deep stromal invasion or LVSI has occurred. Concurrent 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. The brachytherapy doses used are for low-dose-rate applications (40 to 60 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 three-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 three and six 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) and 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).[38] 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.[39]

Peters and colleagues in the Intergroup Trial INT-0107 (SWOG-8797) investigated the value of 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.[14] 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.[12]

Rose and colleagues in the GOG Trial 120 investigated the use of standard pelvic radiation with one of three concurrent chemotherapy regimens---hydroxyurea alone, cisplatin alone, or cisplatin plus 5-FU plus hydroxyurea---in patients with stage IIB, III, or IVA cancer and 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.[40]

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.[13] After 8 years, the overall survival was still significantly greater for patients receiving concomitant cisplatin treatment (67% versus 41%, *P* < .0001).[41]

Whitney and colleagues (GOG Trial 85) also showed a significant benefit for the concurrent use of cisplatin-based chemotherapy.[42] 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 to either pelvic radiation with concurrent hydroxyurea or 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.

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 vaccine,[43] which may be approved by the Food and Drug Administration [FDA] in 2006) will prevent persistent infection with HPV and thus prevent cervical cancer in women.

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; CTI; Eli Lilly; EMD Pharmaceuticals; Genentech, Inc; GlaxoSmithKline; Gynecologic Oncology Group; InterMune; Lilly Oncology; MedImmune; Merck & Co.; Novartis Pharmaceuticals; Ross Products; Sanofi-Aventis; Sanofi-Synthelabo, Inc.; Schering-Plough; Telik, Inc.; 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

From: Thomas GM, Improved treatment for cervical cancer concurrent chemotherapy and radiotherapy. New England Journal of Medicine. 340(15):1198-1200, 1999. Copyright© 1999 Massachusetts Medical Society. All rights reserved.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer Statistics, 2006. CA Cancer J Clin 2006;56:106-130.

2. Edwards BK, Brown ML, Wingo PA, et al. Annual report to the nation on the status of cancer, 1975-2002, featuring population-based trends in cancer treatment. J Natl Cancer Inst 2005;97:1407-1427.

3. Parkin DM, Bray F, Ferlay J. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.

4. American College of Obstetricians and Gynecologists. ACOG practice bulletin. Diagnosis and treatment of cervical carcinomas. Number 35, May 2002. Int J Gynaecol Obstet 2002;78:79-91.

5. Chi DS. Laparoscopy in gynecologic malignancies. Oncology 1999;13:773-782.

6. 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.

7. Landoni F, Maneo A, Colombo A, et al. Randomized study of radical surgery vs. radiotherapy for stage Ib-IIa cervical cancer. Lancet 1997;350:535-540.

8. Haie-Meder C, Fervers B, Fondrinier E, et al. SOR guidelines for concomitant chemoradiotherapy for patients with uterine cervical cancers: evidence update bulletin 2004. Ann Oncol 2005;16:1100-1108.

9. Koliopoulos G, Sotiriadis A, Kyrgiou M, et al. Conservative surgical methods for FIGO stage IA2 squamous cervical carcinoma and their role in preserving women's fertility. Gynecol Oncol 2004;93:469-473.

10. Bernardini M, Barrett J, Seaward G, et al. Pregnancy outcomes in patients after radical trachelectomy. Am J Obstet Gynecol 2003;189:1378-1382.

11. Boss EA, van Golde RJ, Beerendonk CC, et al. Pregnancy after radical trachelectomy: A real option? Gynecol Oncol 2005;99:S152-6. Epub 2005 Sep 2.

12. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 1999;340:1154-1161.

13. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 1999;340:1137-1143.

14. Peters WA 3rd, Liu PY, Barrett RJ 2nd, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000;18:1606-1613.

15. 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.

16. Thomas GM, Dembo AJ, Myhr T, et al. Long-term results of concurrent radiation and chemotherapy for carcinoma of the cervix recurrent after surgery. Int J Gynecol Cancer 1993;3:193-198.

17. Averette HE, Lichtinger M, Sevin BU, et al. Pelvic exenteration: A 15-year experience in general metropolitan hospital. Am J Obstet Gynecol 1984;150:179-184.

18. Morley GW. Pelvic exenteration in the treatment of recurrent cervical cancer. In: Heints APM, Griffiths CT, Trimbos JB, eds. Surgery in Gynecological Oncology. The Hague: Martinus Nijhoff, 1984:174.

19. Thigpen T, Shingleton H, Homesley H, et al. Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Cancer 1981;48:899-903.

20. Thigpen JT, Blessing JA, DiSaia PJ, et al. A randomized comparison of a rapid versus prolonged (24 hr) infusion of cisplatin in therapy of squamous cell carcinoma of the uterine cervix: a Gynecologic Oncology Group study. Gynecol Oncol 1989;32:198-202.

21. McGuire WP, Blessing JA, Moore D, et al. Paclitaxel has moderate activity in squamous cervix cancer. A Gynecologic Oncology Group study. J Clin Oncol 1996;14:792-795.

22. Bookman MA, Blessing JA, Hanjani P, et al. Topotecan in squamous cell carcinoma of the cervix: A Phase II study of the Gynecologic Oncology Group. Gynecol Oncol 2000;77:446-449.

23. Dubay RA, Rose PG, O'Malley DM, et al. Evaluation of concurrent and adjuvant carboplatin with radiation therapy for locally advanced cervical cancer. Gynecol Oncol 2004;94:121-124.

24. Muderspach LI, Blessing JA, Levenback C, et al. A Phase II study of topotecan in patients with squamous cell carcinoma of the cervix: a Gynecologic Oncology Group Study. Gynecol Oncol 2001;81:213-215.

25. Higgins RV, Naumann WR, Hall JB, et al. Concurrent carboplatin with pelvic radiation therapy in the primary treatment of cervix cancer. Gynecol Oncol 2003;89:499-503.

26. Coleman RE, Harper PG, Gallagher C, et al. A phase II study of ifosfamide in advanced and relapsed carcinoma of the cervix. Cancer Chemother Pharmacol 1986;18:280-283.

27. Sutton GP, Blessing JA, McGuire WP, et al. Phase II trial of ifosfamide and mesna in patients with advanced or recurrent squamous carcinoma of the cervix who had never received chemotherapy: a Gynecologic Oncology Group study. Am J Obstet Gynecol 1993;168:805-807.

28. Muggia FM, Blessing JA, Method M, et al. Evaluation of vinorelbine in persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92:639-643.

29. Verschraegen CF, Levy T, Kudelka AP, et al. Phase II study of irinotecan in prior chemotherapy-treated squamous cell carcinoma of the cervix. J Clin Oncol 1997;15:625-631.

30. Wong LC, Ngan HYS, Cheung ANY, et al. Chemoradiation and adjuvant chemotherapy in cervical cancer. J Clin Oncol 1999;17:2055-2060.

31. Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IV, recurrent or persistent squamous cell carcinoma of the cervix: A Gynecologic Oncology Group Study. J Clin Oncol 2004;22:3113-3119.

32. Long HJ 3rd, Bundy BN, Grendys EC Jr, et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. J Clin

Oncol 2005;23:4626-4633. Epub 2005 May 23.

33. Burnett AF, Roman LD, Garcia AA, et al. A phase II study of gemcitabine and cisplatin in patients with advanced, persistent, or recurrent squamous cell carcinoma of the cervix. Gynecol Oncol 2000;76:63-66.

34. Sit AS, Kelley JL, Gallion HH, et al. Paclitaxel and carboplatin for recurrent or persistent cancer of the cervix. Cancer Invest 2004;22:368-373.

35. Gebbia V, Caruso M, Testa A, et al. Vinorelbine and cisplatin for the treatment of recurrent and/or metastatic carcinoma of the uterine cervix. Oncology 2002;63:31-37.

36. Vermorken JB. The role of chemotherapy in squamous-cell carcinoma of the uterine cervix: A review. Int J Gynecol Cancer 1993;3:129-142.

37. Lopez A, Kudelka AP, Edwards CL, et al. Carcinoma of the uterine cervix. In: Pazdur R, ed. Medical Oncology: A Comprehensive Review. Huntington, New York: PRR 1996:393-405.

38. Thomas GM. Improved treatment for cervical cancer-concurrent chemotherapy and radiotherapy. N Engl J Med 1999;340:1198-1200.

39. Lanciano R, Calkins A, Bundy BN, et al. Randomized comparison of weekly cisplatin or protracted venous infusion of fluorouracil in combination with pelvic radiation in advanced cervix cancer: A Gynecologic Oncology Group Study. J Clin Oncol 2005;23:8289-8295.

40. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999;340:1144-1153.

41. Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: An update of Radiation Therapy Oncology Group Trial (RTOG) 90-01. J Clin Oncol 2004;22:872-880.

42. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin vs. hydroxyurea as an adjunct to radiation therapy in stage IIB-IIIA carcinoma of the cervix with negative para-aortic lymph nodes: A Gynecologic Oncology Group and Southwest Oncology Group Study. J Clin Oncol 1999;17:1339-1348.

43. Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomized double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 2005;6:271-278.