National Comprehensive Cancer Network

Clinical Practice Guidelines in Oncology – v.1.2004

Cervical Cancer

Version 1.2004

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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

Cervical Cancer

WORKUP

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

Optional (≥ Stage IB2):

- EUA[a] cystoscopy/proctoscopy[b]
- PET scan
- Lymphangiography
- LFT[c]/renal function studies

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]EUA= Evaluation under anesthesia.
[b]Cystoscopy/proctoscopy with biopsy required for suspicion of bladder/bowel involvement.
[c]LFT= liver function tests.

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Cervical Cancer

CLINICAL STAGE	PRIMARY TREATMENT	
Stage IA1	Extrafascial hysterectomy or Observe if patient desires fertility or if inoperable (only if cone biopsy has negative margins)	See Surveillance (CERV-8)
Stage IA2[b]	Radical hysterectomy + pelvic lymph node dissection ± para-aortic lymph node sampling (category 2B)	See Surgical Findings (CERV-3)
	or Brachytherapy + pelvic RT (point A dose: 75-80 Gy[d])	See Surveillance (CERV-8)
Stage IB1[b] and stage IIA (≤ 4 cm)	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)[d]	See Surveillance (CERV-8)
Stage IB2 and stage IIA (> 4 cm)	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[d]	See Surveillance (CERV-8)
	or Pelvic RT + concurrent cisplatin-containing chemotherapy + brachytherapy Point A dose 75-80 Gy[d] + adjuvant hysterectomy (category 2B)	See Surveillance (CERV-8)

[b] Cystoscopy/proctoscopy with biopsy required for suspicion of bladder/bowel involvement.

[d] 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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SURGICAL FINDINGS | **ADJUVANT TREATMENT**

Negative nodes → **Observe**
Optional pelvic RT ± vaginal brachytherapy if deep stromal invasion or lymphovascular space invasion

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

→ **See Surveillance (CERV-8)**

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

Negative → **Consider left scalene node biopsy (category 2B)**

- **Biopsy not done or negative** → **Para-aortic lymph node RT + concurrent cisplatin-containing chemotherapy + pelvic RT ± brachytherapy**
- **Biopsy positive** → **Systemic therapy[e]/ Individualized RT**

Positive → **Consider biopsy of suspicious areas as indicated**

- **Negative** → **See Surveillance (CERV-8)**
- **Positive** → **Systemic therapy[e]/ Individualized RT**

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

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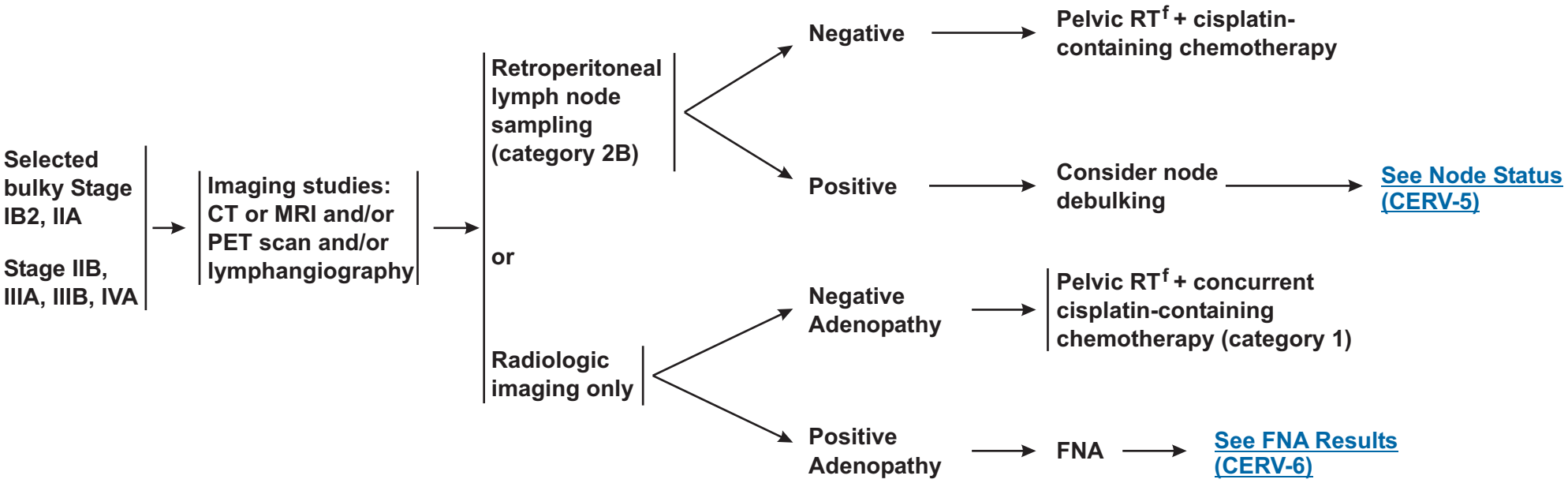
Cervical Cancer

CLINICAL STAGE

PRIMARY TREATMENT



See Surveillance (CERV-8)

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

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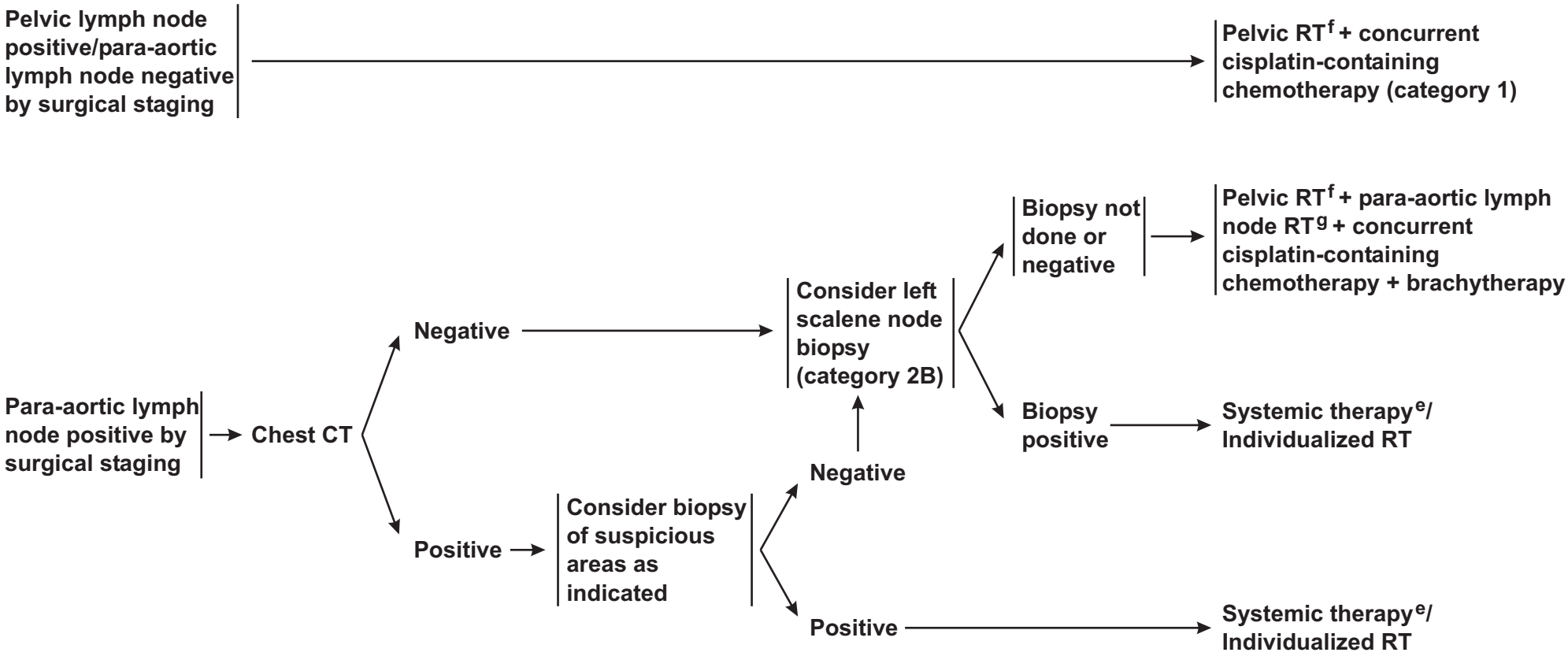
Cervical Cancer

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

PRIMARY TREATMENT



[e] See Chemotherapy Regimens for Cervical Cancer (CERV-A).
[f] All RT on this page should be pelvic RT + brachytherapy (total point A dose ≥ 85 Gy).
[g] RT dose is 45-50 Gy.

See Surveillance (CERV-8)

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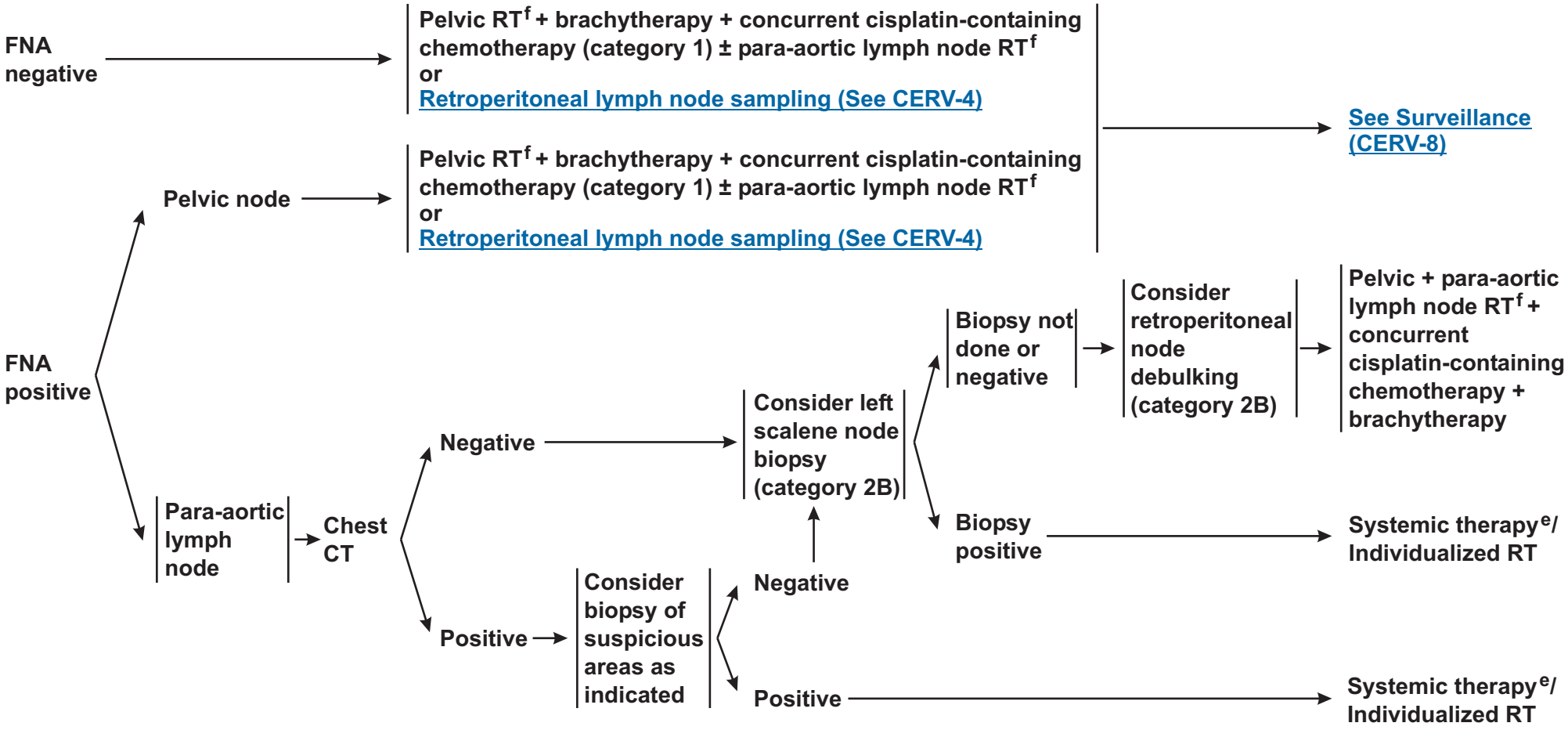
SELECTED BULKY Stage IB2, IIA Stage IIB, IIIA, IIIB, IV FNA RESULTS

PRIMARY TREATMENT



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

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

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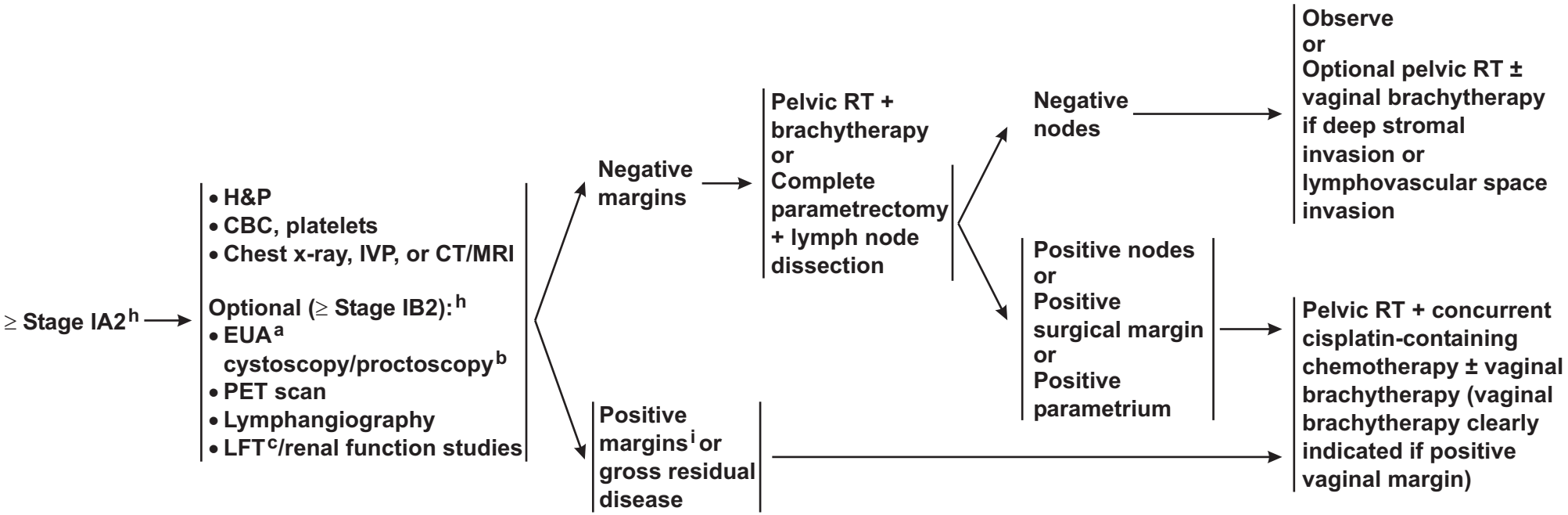
INCIDENTAL FINDING OF INVASIVE CANCER AT SIMPLE HYSTERECTOMY

PRIMARY TREATMENT



[a]EUA= Evaluation under anesthesia.
[b]Cystoscopy/proctoscopy with biopsy required for suspicion of bladder/bowel involvement.
[c]LFT= liver function tests.
[h]Incidental stage IA1 (pathology staging) cervical cancer is adequately managed by the initial hysterectomy.
[i]Invasive cancer at surgical margin.

See Surveillance (CERV-8)

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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 for advanced stage annually (optional)

→ Persistent or recurrent disease →

WORKUP

- Pelvic/abdominal CT
- Chest x-ray (if negative, consider chest CT)
- 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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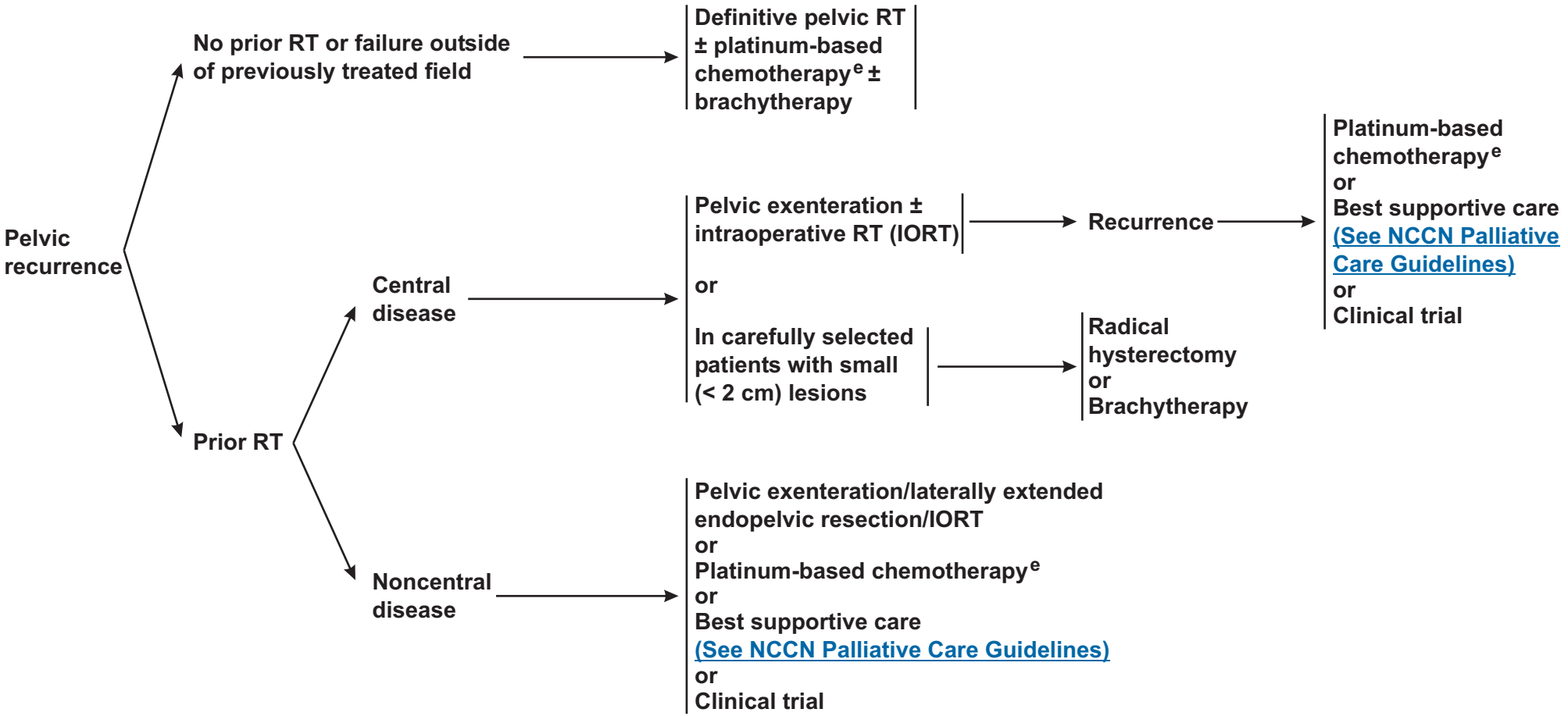
SALVAGE THERAPY



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

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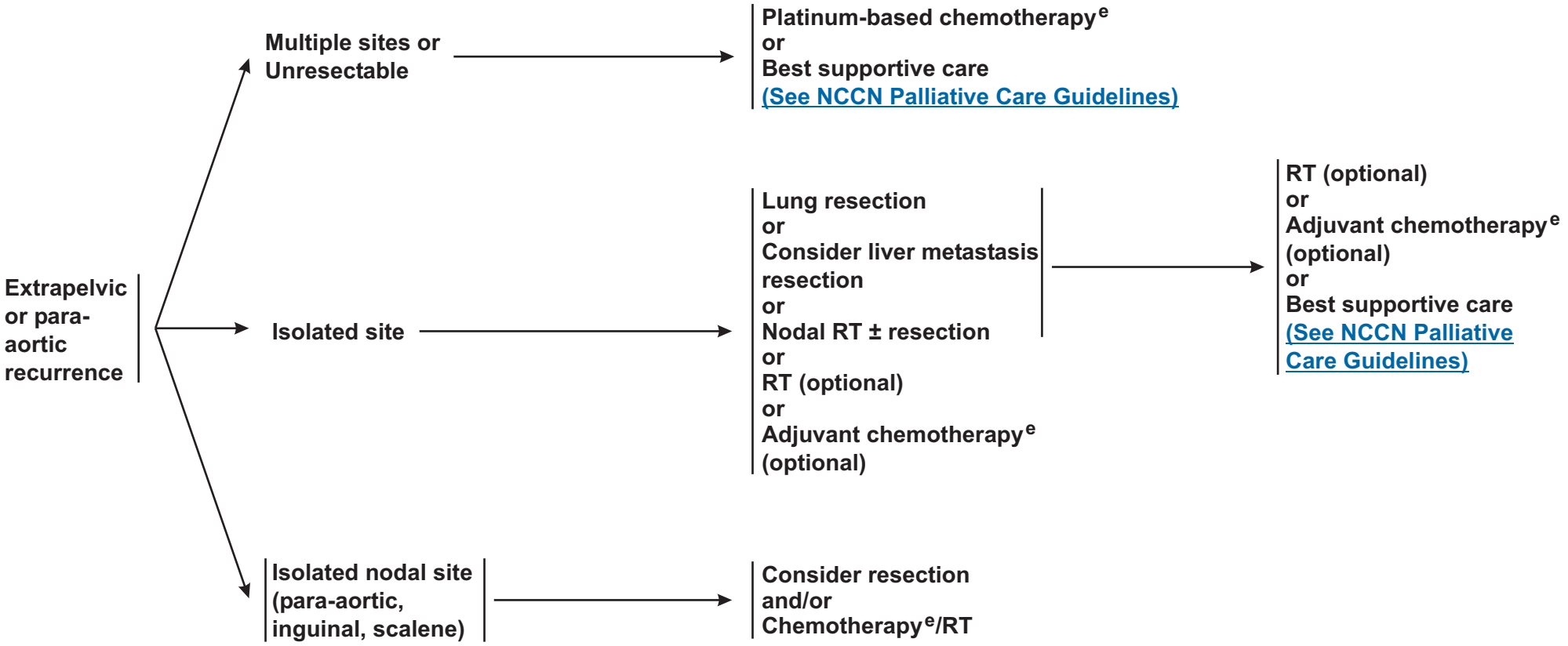
SALVAGE THERAPY



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CHEMOTHERAPY REGIMENS FOR CERVICAL CANCER

First-line therapy
- Cisplatin
- Carboplatin
- Paclitaxel

Second-line therapy
- Docetaxel
- Ifosfamide
- Vinorelbine
- Irinotecan
- Topotecan
- Epirubicin
- Mitomycin
- 5-FU

Possible first-line combination therapy
- Cisplatin/paclitaxel
- Cisplatin/topotecan

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Staging

Table 1

Carcinoma of the Uterine Cervix: FIGO[a] Nomenclature (Montreal, 1994)

Stage 0	Carcinoma in situ, cervical intraepithelial neoplasia grade III.
Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded).
IA	Invasive carcinoma that can be diagnosed only by microscopy. All macroscopically visible lesions – even with superficial invasion – are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.0 mm and a horizontal extension no wider than 7.0 mm. (Depth of invasion should be no greater than 5.0 mm taken from the base of the epithelium of the original tissue superficial or glandular. The involvement of vascular spaces – venous or lymphatic – should not change the stage designation.)
IA1	Measured stromal invasion no greater than 3.0 mm in depth and extension no wider than 7.0 mm.
IA2	Measured stromal invasion greater than 3.0 mm and no greater than 5.0 mm with an extension no wider than 7.0 mm.
IB	Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than stage IA.
IB1	Clinically visible lesions no greater than 4.0 cm.
IB2	Clinically visible lesions greater than 4.0 cm.
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina.
IIA	No obvious parametrial involvement.
IIB	Obvious parametrial involvement.
Stage III	The carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina. All cases with hydronephrosis or nonfunctioning kidney are included, unless they are due to other causes.
IIIA	Tumor involves lower third of the vagina, with no extension to the pelvic wall.
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney.
Stage IV	The carcinoma has extended beyond the true pelvis, or has involved the mucosa of the bladder or rectum (biopsy-proven). (A bullous edema, as such, does not permit a case to be designated as stage IV.)
IVA	Spread to adjacent organs.
IVB	Spread to distant organs.

[a]International Federation of Gynecology and Obstetrics
Benedet JL, Odicino F, Maisonneuve P et al. Caricinoma of the cervix uteri. J Epidemiol Biostat 2001;6(1):5-44.

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

Although cervical cancer is more of a problem in developing countries than in the United States, an estimated 10,520 new cases will be diagnosed in the United States in the year 2004, and 3,900 deaths will result from the disease.[1] Cervical cancer is a major world health problem for women. The global yearly incidence of cervical cancer is 371,000, and the annual death rate is 190,000. It is the third most common cancer in women worldwide.[2] Seventy eight percent of cases occur in developing countries, where cervical cancer is the second most frequent cause of cancer death in women.

The substantial decline in mortality, most significantly in developing countries, is thought to be a result of effective screening. Human papillomavirus (HPV) is considered 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 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%.[2] 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 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. A 5% rule (omitting clinical scenarios that comprise less than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from the schema.

Diagnosis and Workup

These guidelines confine themselves to squamous cell carcinoma and adenocarcinoma of the cervix. Neuroendocrine small cell tumors, glassy-cell carcinomas, and other histologic types are not within the scope of this guideline.

Early cervical carcinoma is often 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.

Debate exists as to the value of a noninvasive workup, such as chest radiography, intravenous pyelography (IVP), computed tomography (CT), or magnetic resonance imaging (MRI). These tests are considered optional for patients with stage IB1 or smaller.

Lymphangiography and positron emission tomography scan (PET) are useful in institutions whose personnel have expertise in performing them. Laboratory tests such as liver and renal function tests and human immunodeficiency virus (HIV) screening are performed as clinically indicated. The appropriate stage for performing cystoscopy or proctoscopy examination under anesthesia is also a subject of disagreement. The majority of the panel members agree that these procedures should be reserved for patients with disease that is stage IB2 or higher. Although these tests are informative, they are considered optional for patients during workup.

Staging

Because of the controversial nature of noninvasive radiographic imaging, the International Federation of Gynecology and Obstetrics (FIGO) system limits the imaging methodology to chest radiography, 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 (Table 1 on ST-1).

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. Both stages IA1 and IA2 require a horizontal spread no wider than 7.0 mm.

It is important to note that lymphatic vascular space involvement (LVSI) would not alter the FIGO classification. FIGO did not include vascular space involvement because of the difficulty of reproducing LVSI among pathologists. Some panel members believe that the presence of LVSI should exclude the lesion from the treatment schema for stage IA1. Because a provision of extrafascial hysterectomy is available as an option, this guideline does not specifically discuss LVSI in staging considerations.

The use of lymphangiography, MRI, or CT scans may aid in treatment planning but is not accepted for 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, although the panel uses the FIGO definitions as the stratification system for this guideline, the findings on imaging studies, such as CT and MRI, are used to sub-stratify treatment options.

Currently, the FIGO surgical procedures for staging are limited to colposcopy, biopsy, conization of the cervix, cystoscopy, and proctosigmoidoscopy. Laparoscopy, hysteroscopy, and retroperitoneal exploration are not accepted. Considerable discussion occurred among panel members about the inclusion of laparoscopy as part of the guideline in both staging and treatment. The consensus is that although laparoscopic staging,

lymphadenectomies, and radical hysterectomies can be performed satisfactorily and are used routinely in selected patients in several member institutions, the techniques are not uniformly used and remain investigational.[3]

Primary Treatment

The primary treatment of early-stage cervical cancer after careful clinical evaluation and staging is either surgery or radiation therapy. A randomized Italian study compared radiation therapy alone versus radical hysterectomy and lymph node dissection.[4] This study employed adjuvant radiation therapy after surgery for women with surgical stage pT2b (which corresponds to FIGO stage IIB) or more extensive disease, 3 mm or more of safe 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 radiation therapy in the surgery arm and the high complication rate.

The treatment schema is stratified using the FIGO staging system (Table 1 on ST-1). The representatives of the participating institutions reached a general agreement, based on the results of five randomized clinical trials, that radiation therapy and concurrent cisplatin-based chemotherapy should be the treatment of choice for stages IIB, IIIA, IIIB, and IVA disease. Surgery is reserved for lower-stage disease and smaller lesions.

Extrafascial hysterectomy is recommended for patients with clinical stage IA1 disease. However, if the cancer is medically inoperable or fertility is desired, patients with negative margins from cone biopsy could undergo observation. Stage IA2 tumors can be treated with radical hysterectomy and pelvic lymph node dissection with or without para-aortic lymph node sampling (category 2B). 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.

Significant discussion occurred about the optimal management of stage IB2 and IIA disease. Patients with stage IB or stage IIA tumors can be treated effectively with radical hysterectomy plus bilateral pelvic lymph node dissection with para-aortic node sampling (category 1 for stage IB1 or IIA tumors 4cm or less; category 2B for stage IB2 or IIA tumors greater than 4cm), or with combined pelvic radiotherapy and brachytherapy to destroy malignant cells in the cervix, paracervical tissues, and regional lymph nodes. For patients with clinical stage IB2 or IIA tumors greater than 4cm who are treated with radiation, concurrent cisplatin-containing chemotherapy has been shown to significantly improve patient survival.[5,6] The addition of concurrent cisplatin-based chemotherapy to postoperative radiation 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.[7] Another recommended treatment option for stage IB2 or IIA tumors (greater than 4cm) is pelvic radiation and concurrent cisplatin-containing chemotherapy with brachytherapy and adjuvant hysterectomy (category 2B).[5]

As explained previously, although imaging studies (CT, MRI, PET scan, lymphangiography) are optional for selective bulky stage IB2 or

higher disease, they can aid in making treatment decisions. No uniform consensus was reached on recommending retroperitoneal lymph node sampling for these patients (category 2B). However, if node sampling is performed and indicate positive findings, node debulking should be considered. Otherwise, patients with negative nodes are treated with pelvic radiotherapy and cisplatin-containing chemotherapy. For patients evaluated using radiologic imaging only, negative adenopathy results indicate treatment with pelvic radiotherapy with brachytherapy and concurrent cisplatin-containing chemotherapy (category 1). However, fine needle aspiration (FNA) is needed to confirm suspicious lymph nodes. Patients whose FNA results are negative or are positive only in the pelvic nodes are treated using pelvic radiotherapy with brachytherapy and concurrent cisplatin-containing chemotherapy (category 1) with or without para-aortic lymph node radiation. Retroperitoneal lymph node sampling is another recommended option. However, for patients with positive FNA for para-aortic lymph nodes, the same treatment is recommended as for those with surgical findings of positive para-aortic lymph node in stage I, IIA (CERV-3) as will be explained later in the text.

For patients undergoing surgical staging, if para-aortic lymph nodes are negative, but pelvic lymph nodes are found positive, treatment with pelvic radiation and brachytherapy with concurrent cisplatin-containing chemotherapy should be considered (category 1). Patients with positive para-aortic lymph nodes findings without chest metastases are treated with pelvic and para-aortic lymph node RT with concurrent cisplatin-containing chemotherapy and brachytherapy.

A phase III neoadjuvant chemotherapy trial comparing chemotherapy followed by radical hysterectomy and lymph node dissection versus radical hysterectomy and lymph node dissection is currently in progress (GOG-141).

Adjuvant Treatment

Adjuvant treatment is indicated after radical hysterectomy depending on surgical findings and disease stage. For stage IA2, IB, or IIA, if lymph nodes are found negative in the surgery, patients should undergo close observation or receive optional pelvic radiation with or without vaginal brachytherapy if deep stromal invasion or lymphovascular space invasion is present. Adjuvant pelvic radiation therapy alone versus no further therapy was tested in a randomized trial (GOG 92) of selected patients with stage IB carcinoma of the cervix after hysterectomy and pelvic lymphadenectomy.[8] 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 diminution in recurrence was found in the radiation therapy arm compared with the no additional treatment arm (15% vs. 28%). Life-table analysis indicated a statistically significant (47%) reduction in risk of recurrence (relative risk = 0.53; P = .008) in the radiation therapy group. At 2 years, the recurrence-free rates were 88% for the radiation therapy 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 cisplatin-containing chemotherapy (category 1). In addition, vaginal brachytherapy is also indicated if vaginal margin is positive. 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.[7]

If para-aortic lymph nodes are found positive during surgical staging, patients must undergo further screening with chest CT. Consideration of biopsy of suspicious areas is indicated by positive CT findings. If biopsy is negative, left scalene node biopsy is considered to rule out metastasis (category 2B), which should also be considered in patients with negative chest CT findings (category 2B). If all biopsies are negative, patients should be treated with pelvic and para-aortic lymph node radiation concurrent with cisplatin-containing chemotherapy with or without brachytherapy depending on findings at surgery. However, patients with positive results from either biopsy should be treated with systemic therapy and individualized radiotherapy.

Surveillance

Because no definitive study or uniform agreement exists on the best methodology for post-treatment surveillance for cervical cancer, the panel combined the practice patterns of member institutions and issued consensus recommendations. Patient follow-up includes history and physical examination, with a Pap test every 3 months for 1 year, every 4 months for the second year, and every 6 months for another 3 years, then annually. Patients with persistent or recurrent disease need to be evaluated using imaging studies, such as pelvic/abdominal CT, chest radiograph (if negative, consider chest CT), and surgical exploration in selected cases. Many of the tests remain optional, such as semiannual complete blood counts, blood urea nitrogen, and serum creatinine determinations, chest radiographs, and annual CT scans for advanced-stage patients.

Salvage 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.[9] For patients who experience pelvic recurrences with no prior radiation therapy or who experience recurrences outside of the previously treated field, salvage therapy includes definitive pelvic radiation with or without platinum-based chemotherapy with or without brachytherapy. Patients with central pelvic recurrent disease after radiation therapy should be evaluated for pelvic exenteration, with or without intraoperative radiotherapy (IORT), (or, in carefully selected patients with small lesions, radical hysterectomy or interstitial reirradiation). 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[10,11] and reconstructive procedures. Recurrence after pelvic exenteration should be treated with platinum-based chemotherapy or best supportive care or be enrolled in a clinical trial. Those with non-central disease should be treated with pelvic exenteration/laterally extended endopelvic resection/IORT, platinum-based chemotherapy, best supportive care, or participation in a clinical trial.

For patients with extrapelvic or para-aortic recurrence, multiple sites or unresectable recurrence should be treated with platinum-based chemotherapy or best supportive care. Isolated recurrence can be managed with surgical resection followed by optional radiation, adjuvant chemotherapy, or best supportive care. Alternatively, patients may undergo radiation therapy (optional) or adjuvant chemotherapy (optional) without surgical resection. For isolated

nodal recurrence (para-aortic, inguinal, or scalene), treatment options include resection and chemoradiation therapy.

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 remains a clinical challenge as to how to adequately palliate the complications of pain and fistulae from such recurrences. Occasionally, patients may benefit from radiotherapy to localized recurrence. 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 candidate for radiation therapy or exenterative surgery. Cisplatin is generally considered to be the most active agent and is recommended as first-line chemotherapy in cervical cancer. The reported response rates are approximately 20% to 30%, with an occasional complete response.[12,13] Carboplatin and paclitaxel have also been reported to have response rates of 19% and 17%, respectively.[14] Therefore, palliation with single-agent cisplatin, carboplatin, or paclitaxel is a reasonable approach in patients with recurrent disease not amenable to surgical or radiotherapeutic approaches.

Other agents reported to show partial response include ifosfamide,[15,16] vinorelbine,[17] irinotecan,[18] topotecan,[19] epirubicin,[20] 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). Recently, cisplatin-based combination chemotherapy regimens such as cisplatin/paclitaxel and cisplatin/topotecan were extensively investigated in clinical studies. Rose et al.[21] reported a phase II GOG study of cisplatin/paclitaxel as first-line therapy with an overall response rate of 46.3% in chemotherapy-naïve squamous cell carcinoma of the cervix.[21] The outcome results from a randomized phase III study comparing the combination of paclitaxel and cisplatin with cisplatin alone showed that the two-drug combination had a higher response rate (36% vs. 19%) and improved PFS (4.8 vs. 2.8 months; $P > .001$), although no improvement was seen in median survival.[22] Another randomized phase III study investigating the combination of cisplatin and topotecan versus cisplatin alone in recurrent or persistent cervical cancer was conducted by GOG. In this study of 356 eligible patients, the combination regimen was shown to be superior to single-agent cisplatin with respect to overall response rate (26% vs 13%, $P = .004$), progression free survival (4.6 vs 2.9 months; $P = .00048$), and median survival (9.2 vs 7.0 months, $P = .015$).[23]

Biologic molecular and vaccine therapies have no established role at the present time,[24,25] 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. Work-up for these patients includes history and physical examination, complete blood and platelet counts, chest radiography, IVP, or CT/MRI. For stage IB2 or higher, optional tests include cystoscopy or proctoscopy under anesthesia, PET scan, lymphangiography, 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) was based on the status of the surgical margins. If margins were positive, pelvic radiation therapy and concurrent cisplatin-containing chemotherapy with or without brachytherapy would be recommended.

If margins are negative, options include pelvic radiation therapy with brachytherapy or 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 or lymph vascular space invasion has occurred. If gross residual disease exists, disease is found in the lymph nodes or parametrium, or the surgical margin is positive, pelvic radiation therapy with concurrent cisplatin-containing chemotherapy is recommended. In addition, vaginal brachytherapy is clearly indicated if vaginal margin is positive.

Use of Radiation Therapy

In developing guideline recommendations for radiation therapy, the panel elected to include dosage as a reference in the schema, but realized that, to be complete, other aspects of radiation therapy techniques would be necessary. These dosages should not be interpreted as stand-alone recommendations; other considerations of radiation therapy techniques and clinical judgment are paramount.

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.

Considerable refinement in external-beam radiation therapy and brachytherapy techniques, as well as a better understanding of the influence of overall treatment time on outcome, has occurred over the past decade. Optimum staging of patients to precisely delineate the primary tumor volume and draining lymph nodes, including abdominopelvic radiologic studies (CT, MRI, or PET scans), should be considered in patients with bulky or advanced-stage tumors.

Planning Treatment Fields

The use of three-dimensional treatment planning for both the external-beam radiation therapy fields and the brachytherapy placements may assist in customized shaping of dose distributions to ensure adequate tumor coverage in all dimensions and minimal 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.

For lesions in the lower 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 of 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 considerations 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 need to be considered 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% diminution in pelvic control and cause-specific survival for each extra day of overall treatment time. Even though prospective randomized trials confirming these findings are lacking, it would be prudent to attempt to complete the entire radiation therapy course in a timely fashion (eg, less than 8 weeks) and avoid, whenever possible, delays or splits in the radiation treatment.

Concurrent Chemoradiation

As listed in Table 2, five randomized trials have shown the statistically significant benefit of concurrent cisplatin-containing chemotherapy regimens with radiation in the treatment of advanced cervical cancers.

Intergroup Trial INT-0107 (SWOG-8797) investigated the value of postoperative pelvic radiation therapy with or without 5-fluorouracil (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.[7] The 4-year progression-free survival was significantly improved with the use of radiation plus chemotherapy, compared with radiation therapy alone (81% vs. 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.

GOG Trial 123 studied the use of cisplatin as an adjunct to radiation therapy 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.[5]

GOG Trial 120 investigated the use of standard pelvic radiation with one of three concurrent chemotherapy regimens---cisplatin alone, hydroxyurea 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.[26]

RTOG Trial 9001 compared pelvic plus para-aortic radiation to pelvic radiation plus 5-FU plus cisplatin treatment in patients with stage IIB through stage IVA cervical cancer and in patients with stage IB or stage 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 0.59.[6]

The final study, which showed a significant benefit for the concurrent use of cisplatin-based chemotherapy, was GOG Trial 85.[27] Patients enrolled in this study had stage IIB through stage IVA cervical cancer with surgically staged negative para-aortic lymph nodes. These patients were randomized between 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% vs. 57%), resulting in a relative risk of death of 0.74.

These five trials have shown that the use of concurrent cisplatin-based chemoradiation therapy results in a decreased risk of death of 30% to 50%. Although the determination of the optimum chemotherapy to be used with concurrent radiation will require further investigation, it appears that cisplatin-containing regimens or cisplatin alone should now be considered as part of the standard treatment regimen in patients with locally advanced cervical cancer.

Table 2:

Estimates of the Relative Risk of Death in Five Clinical Trials of Concurrent Chemotherapy and Radiotherapy.

Study	Stage	Control Group	Comparison Group	Relative Risk of Death in Compaeison Group
Keys et al.	IB2	Radiotherapy	Radiotherapy plus weekly cisplatin	0.54
Rose et al.	IIB-IVA	Radiotherapy plus hydroxyurea	Radiotherapy plus weekly cisplatin	0.61
			Radiotherapy plus cisplati 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 proportionately)	Radiotherapy	Radiotherapy plus cisplatin and fluorouracil	0.50

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