National Comprehensive Cancer Network

Clinical Practice Guidelines in Oncology – v.1.2003

Cervical Cancer

Version 1.2003

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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

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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 → Primary Treatment (see CERV-2)

Stage IA2
Stage IB1
Stage IIA (< 4 cm) → Primary Treatment (see CERV-2)

Stage IB2
Stage IIA (> 4 cm) → Primary Treatment (see CERV-2)

Selected bulky:
Stage IB2, IIA
Stage IIB
Stage IIIA, IIIB
Stage IV → Primary Treatment (see CERV-4)

Incidental finding of invasive cancer at simple hysterectomy → Primary Treatment (see 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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CLINICAL STAGE	PRIMARY TREATMENT	
Stage IA1	Extrafascial hysterectomy or Observe if patient desires fertility or if inoperable (only if cone biopsy has negative margins)	Surveillance (see CERV-8)
Stage IA2 [b]	Radical hysterectomy + pelvic lymph node dissection ± para-aortic lymph node sampling (category 2B) or Brachytherapy ± pelvic RT (point A dose: 75-80 Gy) [d]	Surgical Findings (see CERV-3) Surveillance (see CERV-8)
Stage IB1 [b] and stage IIA (< 4 cm)	Radical hysterectomy + pelvic lymph node dissection + sample para-aortic nodes (category 1) or Pelvic RT + brachytherapy (point A dose: 80-85 Gy) [d]	Surgical Findings (see CERV-3) Surveillance (see CERV-8)
Stage IB2 and stage IIA (> 4 cm)	Radical hysterectomy + pelvic lymph node dissection + para-aortic lymph node sampling (category 2B) or Pelvic RT + concurrent cisplatin-containing chemotherapy + brachytherapy Point A dose ≥ 85 Gy [d] or Pelvic RT + concurrent cisplatin-containing chemotherapy + brachytherapy Point A dose 75-80 Gy [d] + adjuvant hysterectomy (category 2B)	Surgical Findings (see CERV-3) Surveillance (see CERV-8) Surveillance (see 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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STAGE IA2, IB1 AND IIA (< 4 cm) SURGICAL FINDINGS

ADJUVANT TREATMENT

Negative nodes

Observe
Optional pelvic RT ± vaginal brachytherapy if deep stromal invasion or lymph vascular 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)**

Surveillance (see 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 → **Pelvic + para-aortic lymph node RT[e+] concurrent cisplatin-containing chemotherapy + brachytherapy**

Biopsy positive → **Systemic therapy[f]/ Individualized RT**

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

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

Positive → **Systemic therapy[f]/ Individualized RT**

Surveillance (see CERV-8)

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

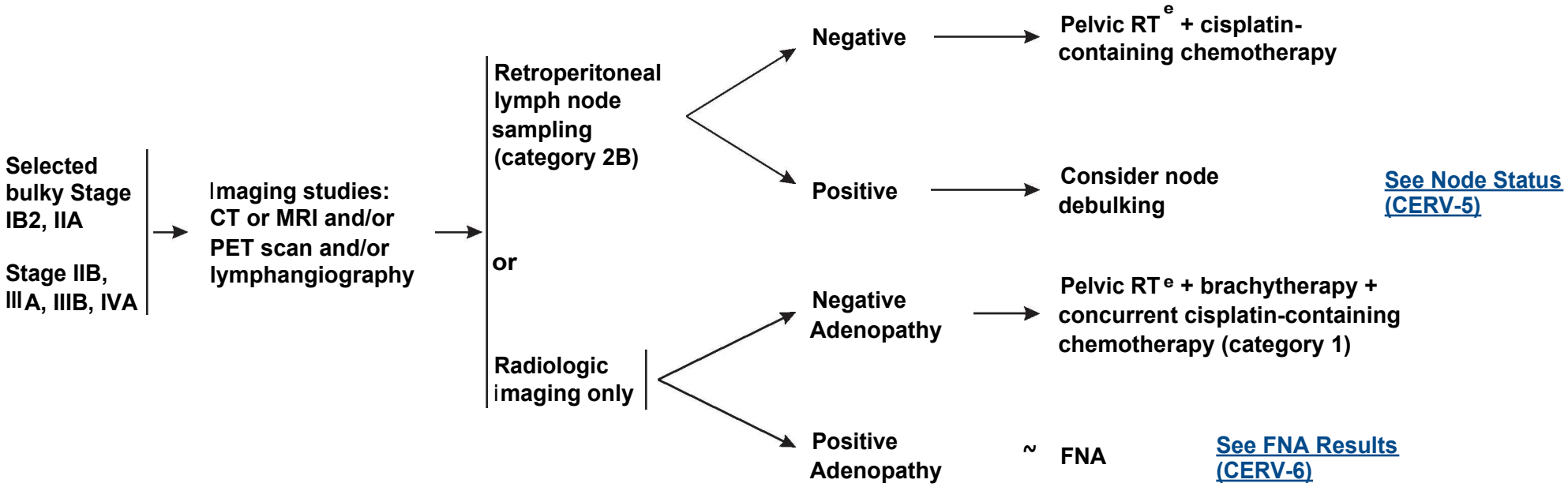
[f] Chemotherapy Regimens for Cervical Cancer (see CERV-A).

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CLINICAL STAGE

PRIMARY TREATMENT



Surveillance (see CERV-8)

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

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SELECTED BULKY STAGE IB2, IIA, IIB, IIIA, IIIB, IV NODE STATUS

PRIMARY TREATMENT

Pelvic lymph node positive/para-aortic lymph node negative by surgical staging → **Pelvic RT[e] + brachytherapy + concurrent cisplatin-containing chemotherapy (category 1)**

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

- **Negative** → **Consider left scalene node biopsy (category 2B)**
  - **Biopsy not done or negative** → **Pelvic + para-aortic lymph node RT[e+] concurrent cisplatin-containing chemotherapy + brachytherapy**
  - **Biopsy positive** → **Systemic therapy[f]/ Individualized RT**
- **Positive** → **Consider biopsy of suspicious areas as indicated**
  - **Negative** → **Consider left scalene node biopsy (category 2B)**
  - **Positive** → **Systemic therapy[f]/ Individualized RT**

Surveillance (see CERV-8)

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

[f] Chemotherapy Regimens for Cervical Cancer (see CERV-A).

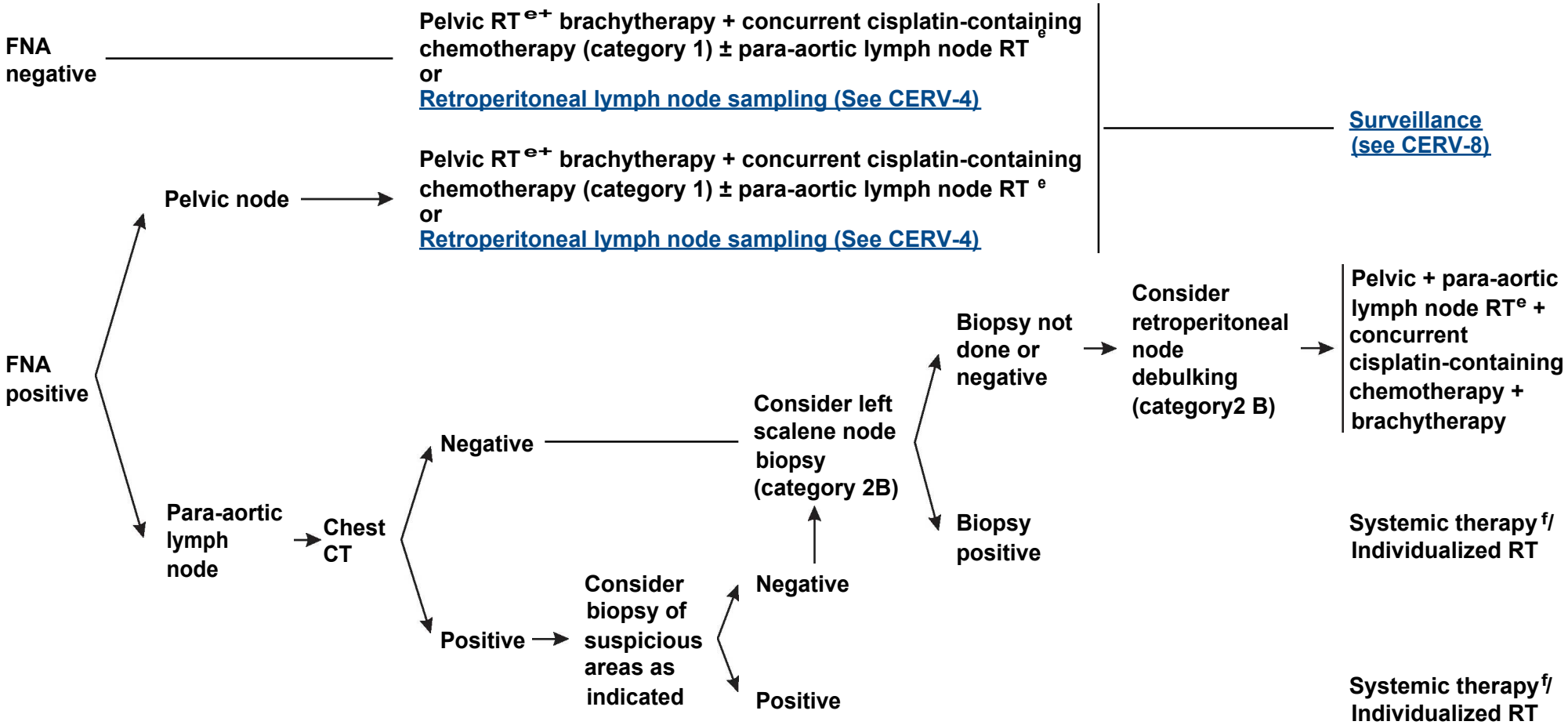
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Cervical Cancer

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

PRIMARY TREATMENT



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

f Chemotherapy Regimens for Cervical Cancer (see CERV-A).

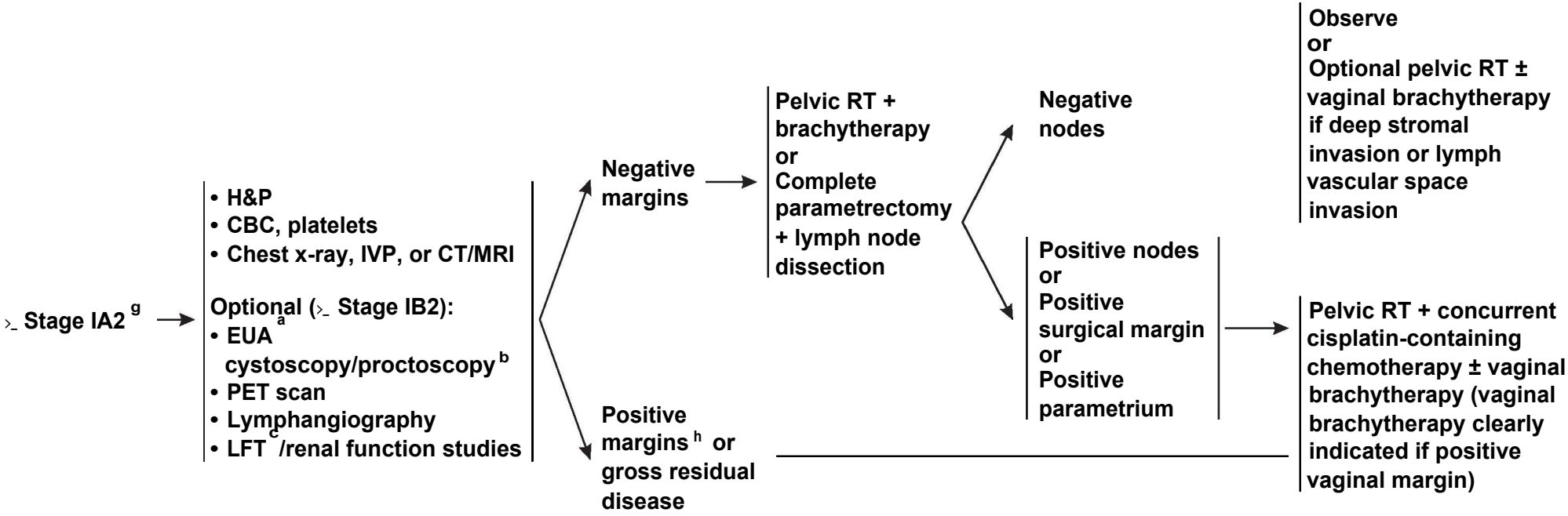
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Cervical Cancer

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.
[g] Incidental stage IA1 cervical cancer is adequately managed by the initial hysterectomy.
[h] Invasive cancer at surgical margin.

Surveillance (see 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 for advanced stage annually (optional)

WORKUP

Persistent or recurrent disease →

- 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)

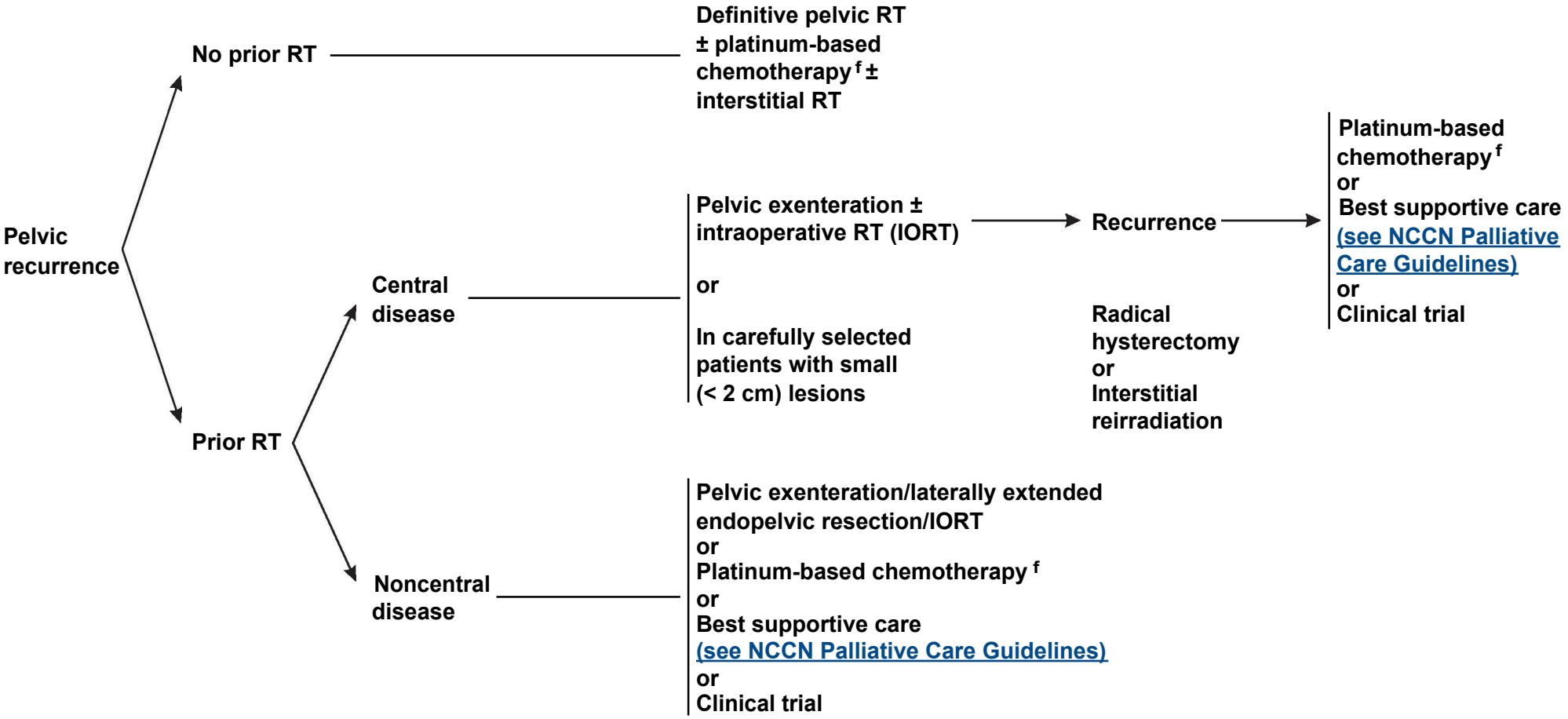
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SALVAGE THERAPY



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[f] Chemotherapy Regimens for Cervical Cancer (see CERV-A).

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Cervical Cancer

SALVAGE THERAPY

Extrapelvic or para-aortic recurrence

- **Multiple sites or Unresectable** → **Platinum-based chemotherapy [f] or Best supportive care (see NCCN Palliative Care Guidelines)**
- **Isolated site** → **Lung resection or Consider liver metastasis resection or Nodal RT ± resection or RT (optional) or Adjuvant chemotherapy [f] (optional)** → **RT (optional) or Adjuvant chemotherapy [f] (optional) or Best supportive care (see NCCN Palliative Care Guidelines)**
- **Isolated nodal site (para-aortic, inguinal, scalene)** → **Consider resection and/or Chemotherapy [f]/RT**

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[f] Chemotherapy Regimens for Cervical Cancer (see CERV-A).

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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

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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.

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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 12,200 new cases will be diagnosed in the United States in the year 2003, and 4,100 deaths will result from the disease (Jemal et al, 2003). 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 (Parkin et al, 1999). 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 in low-incidence countries it is 5% to 10% (Parkin et al, 1999). Other epidemiological risk factors associated with cervical cancer are a history of smoking, parity, contraceptive use, early age of onset of coitus, 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. There were “many exceptions to the rule” 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

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cytology/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.

There is debate as to the value of a noninvasive workup, such as chest x-ray, intravenous pyelography (IVP), computed tomography (CT) or magnetic resonance imaging (MRI). These tests are considered optional for patients with stage IB1 or less.

Lymphangiography and PET scan (positron emission tomography) have been found to be useful in those institutions with 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 and/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 stages IB2 or higher. Although these tests are informative, they are considered optional for patients during their workup.

Staging

Due to the controversial nature of noninvasive radiographic imaging, the International Federation of Gynecology and Obstetrics (FIGO) system limits the imaging methodology to chest x-ray, 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 feel 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, and/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 substratify 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. There was considerable discussion among panel members about the inclusion of laparoscopy as part of the guideline in both staging and treatment. The consensus is that while laparoscopic staging, lymphadenectomies, and radical hysterectomies can be performed satisfactorily and are used routinely in selected patients in several

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member institutions, the techniques are not uniformly used and remain investigational (Chi, 1999).

Primary Treatment

The primary treatment of early-stage cervical cancer following 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 (Landoni et al, 1997). 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). There is general agreement among the representatives of the participating institutions based on the results of five randomized clinical trials that radiation therapy and concurrent cisplatin-based chemotherapy should be the treatment of choice for stage IIB, IIIA, IIIB, and IVA disease (see below). Surgery is reserved for lower-stage disease and smaller lesions.

Extrafascial hystectomy is recommended for clinical stage IA1 patients. However, if medically inoperable or fertility is desired, patients with negative margins from cone biopsy could be observed. 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 or without 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 equilavents. Modify treatment based on normal tissue tolerance.

There was significant discussion about the optimal treatment of bulky stage IB2 and bulky IIA disease. Patients with stage IB or stage IIA tumors can be managed 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 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 4cm who are treated with radiation, concurrent cisplatin-containing chemotherapy has demonstrated to significantly improve patient survival (Keys et al, 1999; Morris 1999). The addition of concurrent cisplatin-based chemotherapy to postoperative radiation significantly improves progression-free and overall survival for high-risk, early-stage patients (those with positive lymph nodes, parametrial extension, and/or positive margins) who undergo radical hysterectomy and pelvic lymphadenectomy (Peters et al, 2000). Another recommended treatment option for stage IB2 or IIA tumors (4cm) is pelvic radiation and concurrent cisplatin-containing chemotherapy with brachytherapy and adjuvant hysterectomy (Category 2B) (Keys et al, 1999).

As explained in Work-up, although imaging studies (CT, MRI, Pet scan, and/or lymphangiography) are optional for selective bulky stage IB2 or higher disease, they can aid in making treatment

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decisions. There was no uniform consensus on recommending retroperitoneal lymph node sampling for these patients (Category 2B). However, if node sampling is carried out and positive findings are indicated, node debulking should be considered. Otherwise, patients with negative nodes are treated with pelvic radiotherapy and cisplatin-containing chemotherapy. For patients evaluated with radiologic imaging only, negative adenopathy results indicate the treatment with pelvic radiotherapy with brachytherapy and concurrent cisplatin-containing chemotherapy (Category 1). However, fine needle aspiration (FNA) is needed for confirmation of suspicious lymph nodes. Patients with negative FNA or positive FNA for pelvic nodes are managed by 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 positive para-aortic lymph node in stage IB, IIA (4cm) (see CERV-3) as will be explained later.

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). For patients with positive para-aortic lymph nodes findings, the same treatment guidelines are followed for those with positive para-aortic lymph node in stage IB, IIA (4cm) (see CERV-3).

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 small volume tumors (4cm) in stage IA2, IB1 or IIA, if lymph nodes are found negative in the surgery, patients should be observed closely, or treated with optional pelvic radiation with or without vaginal brachytherapy if deep stromal invasion or lymph vascular 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 (Sedis et al, 1999). Patients were eligible for this trial following 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. There was a statistically significant diminution in recurrence 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 managed 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 stage IA2, IB, and IIA patients who

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had positive lymph nodes, positive margins, or microscopic parametrial involvement found at surgery (Peters et al, 2000).

If para-aortic lymph nodes are found positive during surgical staging, patients need to be further screened by 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 and brachytherapy. However, patients with positive results from either biopsy should be treated with systemic therapy and individualized radiotherapy.

Surveillance

Because there is no definitive study or uniform agreement on the best methodology for posttreatment surveillance for cervical cancer, the practice guidelines panel combined the practice patterns of member institutions and issued consensus recommendations. Follow-up of the patient includes history and physical examination, 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 by imaging studies, i.e. Pelvic/abdominal CT, chest x-ray (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 x-rays, and annual CT scans for advanced-stage patients.

Salvage Therapy

Patients with a localized recurrence of cervical cancer following surgery should be evaluated for salvage radiotherapy. Salvage rates of approximately 40% have been reported in such situations (Thomas et al, 1993). For patients having pelvic recurrences without prior radiation therapy, salvage therapy includes definitive pelvic radiation with or without platinum-based chemotherapy with or without interstitial radiotherapy. Patients with central pelvic recurrent disease following 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). Operative 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 (Averette et al, 1984; Morley et al, 1984) and reconstructive procedures. Recurrence following pelvic exenteration should be treated with platinum-based chemotherapy, best supportive care, or be enrolled in a clinical trial. Patients with isolated pulmonary, liver, or nodal recurrences may benefit from surgical resection. Those with non-central disease should be managed with pelvic exenteration/laterally extended endopelvic resection/IORT, platinum-based chemotherapy, best supportive care, or participating 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,

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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/or 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. Chemotherapy has a limited role in prolonging survival or improving quality of life. Clearly, pain relief of a transient nature may be achieved in responders to chemotherapy. The efficacy of combination therapy versus single-agent therapy in the treatment of metastatic disease has not been proven.

Cisplatin is generally considered to be the most active drug. Response rates are approximately 20% to 30%, with an occasional complete response. Carboplatin has also been reported to have a 19% response rate. Other drugs with reported positive response rates include ifosfamide, epirubicin, and vindesine. The use of combination chemotherapy in patients who have had primary treatment with surgery or radiotherapy is associated in some studies with a higher response rate. Durations of response are usually 3 to 6 months, and median survival remains around 1 year. Palliation with single-agent cisplatin or carboplatin is a reasonable approach in patients with recurrent disease not amenable to surgical or radiotherapeutic approaches. Biologic molecular and vaccine therapies have no established role at the present time (Vermorken, 1993; Lopez et al, 1996), 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/spiritual support, suited to the individual situation.

Incidental Cervical Cancer

A clinical scenario requiring oncologic management is the finding of invasive cervical carcinoma following simple hysterectomy. Work-up for these patients includes history and physical exam, complete blood and platelet count, chest x-ray, 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 feels that a reasonable treatment schema for patients with tumors that were stage 1A2 or higher was based on the status of the margins. If margins were positive, pelvic radiation therapy plus 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 there is deep stromal invasion or lymph vascular space invasion. If gross residual disease exists, or disease is found in the lymph nodes, parametrium, or 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.

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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, in order 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 radiological 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 need to be made to minimize radiation doses to normal surrounding tissues (e.g., bladder, rectum, and sigmoid colon). Coned-down shaped boost fields should be employed to 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, where a wide range of treatment regimens have been

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employed (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 (e.g., less than 8 weeks) and avoid, whenever possible, delays or splits in the radiation treatment.

Concurrent Chemoradiation

As these practice guidelines developed, five randomized trials matured that demonstrated the statistically significant benefit of concurrent cisplatin-containing chemotherapy regimens with radiation in the treatment of advanced cervical cancers (Table2).

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 stage IA2, IB, and IIA cervical cancer with positive lymph nodes, and/or positive margins, and/or microscopic parametrial involvement at the time of surgery (Peters et al, 2000). 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 (Keys et al, 1999).

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 (Rose et al, 1999).

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 (Morris et al, 1999).

The final study, which demonstrated a significant benefit for the concurrent use of cisplatin-based chemotherapy, was GOG Trial 85

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(Whitney et al, 1999). 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 demonstrated 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.

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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

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.

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References

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.

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

Jemal A, Murray T, Samuels A et al. Cancer statistics, 2003. CA Cancer J Clin 2003;53:5-26.

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.

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.

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.

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.

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.

Parkin DM, Pisani P, Ferlay J. Global cancer statistics. CA Cancer J Clin 1999;49:33-64.

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.

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.

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.

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.

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

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.

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