National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Cervical Cancer

Version 1.2012

NCCN.org

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Discussion

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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 Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

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

NCCN Guidelines™ Version 1.2012 Updates Cervical Cancer

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Updates in Version 1.2012 of the NCCN Cervical Cancer Guidelines from Version 1.2011 include:

CERV-3
- **Clinical Stage: "Also see CERV-5 for alternative recommendations for these patients" was added after "Stage IB2 and Stage IIA2".**
- **Primary Treatment for Stage IB1 and Stage IIA1: For clarity, the last recommendation changed to "Radical trachelectomy for tumors ≤ 2 cm (Stage IB1 only) + pelvic lymph node..."**

CERV-5
- **Clinical Stage: "See CERV-3 for alternatives for these patients" was added after Stage IB2, Stage IIA2**
- **Additional Workup: For clarity, "category 2B" was removed after "laparoscopic lymph node dissection" and placed after "Surgical staging".**

CERV-7
- **Primary Treatment:**
  - **"Extraperitoneal lymph node dissection" changed to "Extraperitoneal or laparoscopic lymph node dissection".**
  - **New footnote "g" that states, "Consider post-operative imaging to confirm the adequacy of node removal" was added.**

CERV-9

Surveillance:
- **Second bullet: "Cervical/vaginal cytology every 6 mo for 3-5 y..." changed to "...every 6-12 mo for 3-5 y..."**
- **Third bullet: "Chest x-ray annually (optional)" changed to "Chest x-ray annually for 5 y".**

CERV-A---Principles of Radiation Therapy
- **Page 1 of 4: Under External-Beam Radiation Therapy (EBRT), a fourth bullet regarding IMRT was added that states, "Intensity-modulated radiation therapy (IMRT) and similar highly conformal methods of dose delivery may be helpful in minimizing the dose to the bowel and other critical structures in the post-hysterectomy setting and in treating the para-aortic nodes when this is necessary. These techniques can also be useful when high doses are required to treat gross disease in regional lymph nodes. However, conformal external beam therapies (such as IMRT) should not be used as routine alternatives to brachytherapy for treatment of central disease in patients with an intact cervix. Very careful attention to detail and reproducibility (including consideration of target and normal tissue definitions, patient and internal organ motion, soft tissue deformation, and rigorous dosimetric and physics quality assurance) is required for proper delivery of IMRT and related highly conformal technologies."**

WORKUP

- H&P
- CBC (including platelets)
- Cervical biopsy, pathologic review
- Cone biopsy as indicated[a]
- LFT/renal function studies
- Imaging

(optional for ≤ stage IB1):

- Chest x-ray
- CT or PET-CT scan
- MRI as indicated

Optional (≥ Stage IB2):

- EUA cystoscopy/proctoscopy[b]

CLINICAL STAGE

Stage IA1	See Primary Treatment (CERV- 2)
Stage IA2 Stage IB1 Stage IIA1	See Primary Treatment (CERV-2) and (CERV-3)
Stage IB2 Stage IIA2	See Primary Treatment (CERV-3) and (CERV-5)
Stage IIB Stage IIIA, IIIB Stage IVA	See Primary Treatment (CERV-5)
Incidental finding of invasive cancer at simple hysterectomy	See Primary Treatment (CERV-8)

All staging in guideline is based on updated 2009 FIGO staging. (See ST-1)

[a] See Discussion for indications for cone biopsy.
[b] For suspicion of bladder/bowel involvement, cystoscopy/proctoscopy with biopsy is required.

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CLINICAL STAGE	PRIMARY TREATMENT	
Stage IA1	Extrafascial hysterectomy or Observe if patient desires fertility or if inoperable (only if cone biopsy has negative margins)	See Surveillance (CERV-9)
	or Modified radical hysterectomy or trachelectomy + pelvic lymph node dissection if lymphovascular invasion (category 2B for node dissection)	See Surgical Findings (CERV-4)
Stage IA2	Radical hysterectomy + pelvic lymph node dissection ± para-aortic lymph node sampling	See Surgical Findings (CERV-4)
	or Brachytherapy ± pelvic RT (total point A dose: 75-80 Gy)[c] or Radical trachelectomy + pelvic lymph node dissection ± para-aortic lymph node sampling	See Surveillance (CERV-9)

[c]These doses are recommended for most patients based on summation of conventional external-beam fractionation and low-dose rate (40-70 cGy/h) brachytherapy equivalents. Modify treatment based on normal tissue tolerance. (See Discussion)

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CLINICAL STAGE	PRIMARY TREATMENT	
Stage IB1 and stage IIA1	Radical hysterectomy + pelvic lymph node dissection ± para-aortic lymph node sampling (category 1)	→ See Surgical Findings (CERV-4)
	or	
	Pelvic RT + brachytherapy (total point A dose: 80-85 Gy)[c]	→ See Surveillance (CERV-9)
	or	
	Radical trachelectomy for tumors ≤ 2 cm (Stage IB1 only) + pelvic lymph node dissection ± para-aortic lymph node sampling	→ See Surveillance (CERV-9)
Stage IB2 and stage IIA2 (also see CERV-5 for alternative recommendations for these patients)	Pelvic RT + concurrent cisplatin-containing chemotherapy[d] + brachytherapy (total point A dose ≥ 85 Gy)[c] (category 1)	→ See Surveillance (CERV-9)
	or	
	Radical hysterectomy + pelvic lymph node dissection + para-aortic lymph node sampling (category 2B)	→ See Surgical Findings (CERV-4)
	or	
	Pelvic RT + concurrent cisplatin-containing chemotherapy[d] + brachytherapy (total point A dose 75-80 Gy)[c] + adjuvant hysterectomy (category 3)	→ See Surveillance (CERV-9)

[c] These doses are recommended for most patients based on summation of conventional external-beam fractionation and low-dose rate (40-70 cGy/h) brachytherapy equivalents. Modify treatment based on normal tissue tolerance. (See Discussion)

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

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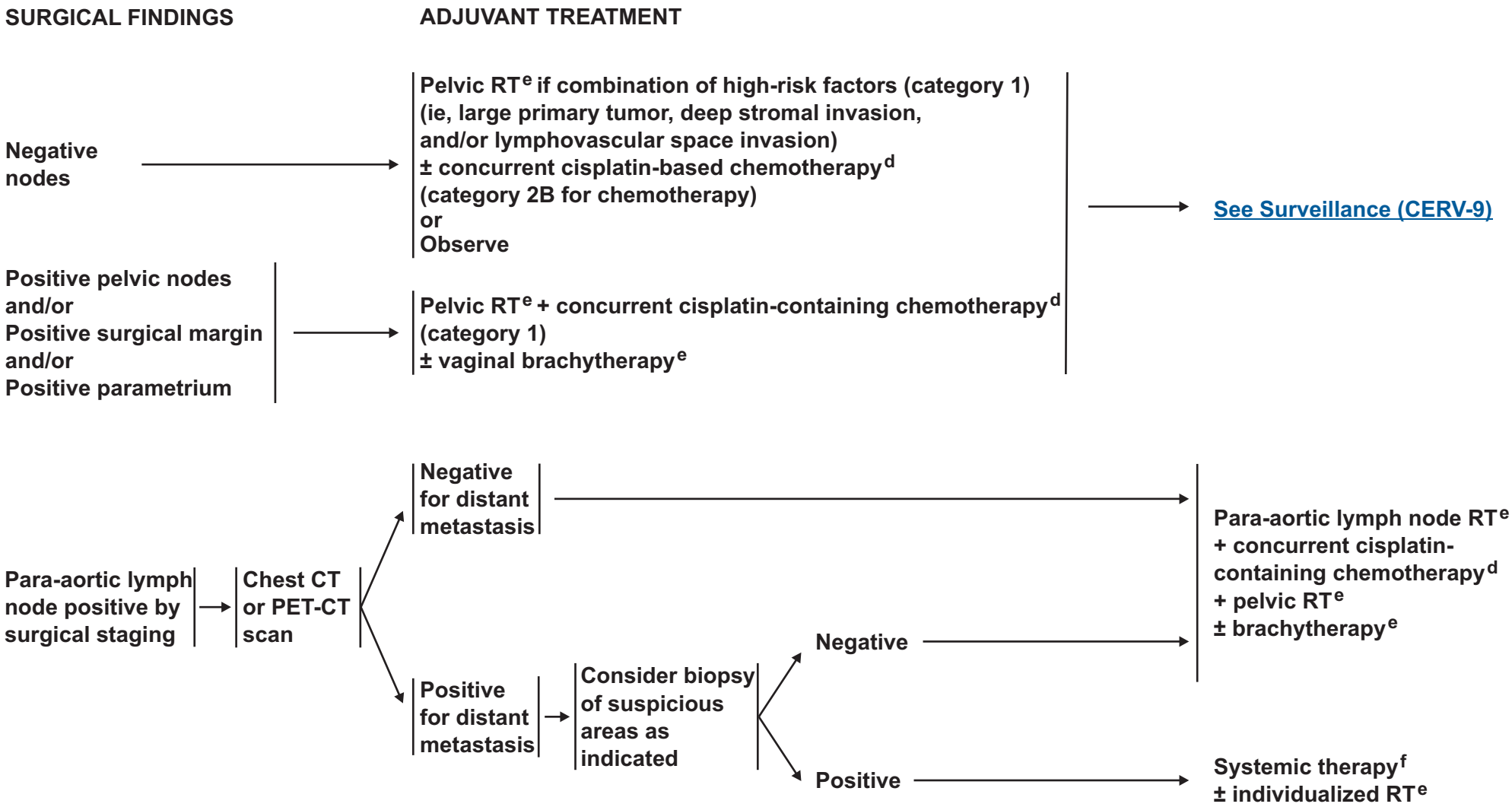

[d] Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.
[e] See Principles of Radiation Therapy for Cervical Cancer (CERV-A).
[f] See Chemotherapy Regimens for Recurrent or Metastatic Cervical Cancer (CERV-B).

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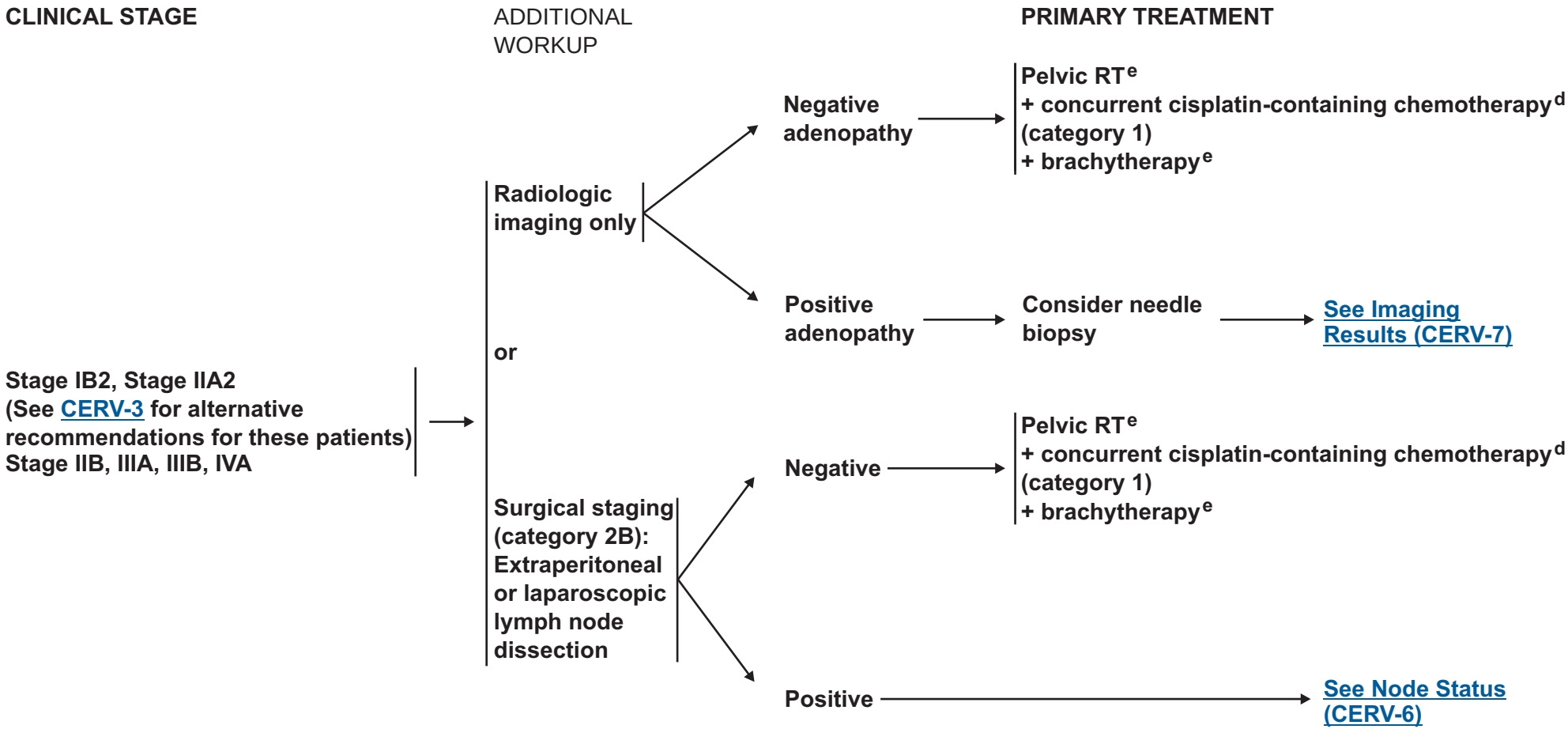
See Surveillance (CERV-9)



[d] Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.
[e] See Principles of Radiation for Cervical Cancer (CERV-A).

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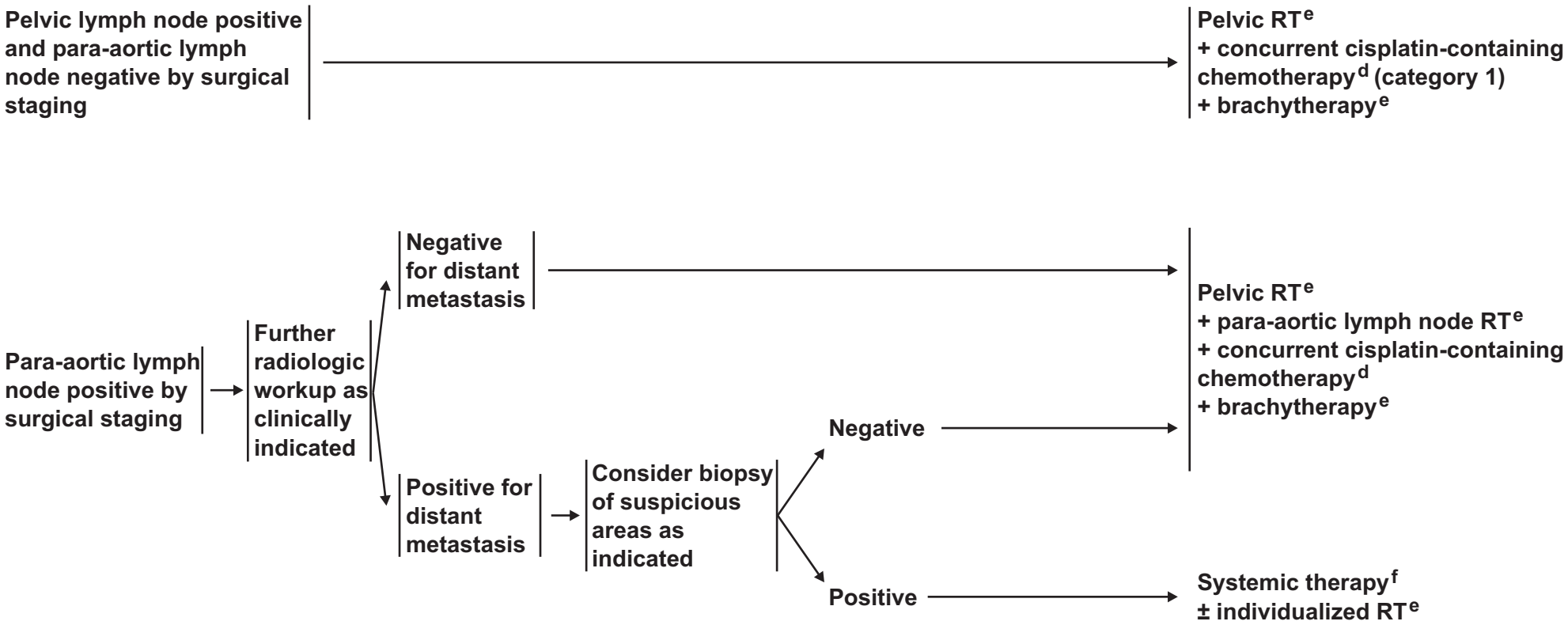
See Surveillance (CERV-9)

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

PRIMARY TREATMENT



[d] Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.
[e] See Principles of Radiation Therapy for Cervical Cancer (CERV-A).
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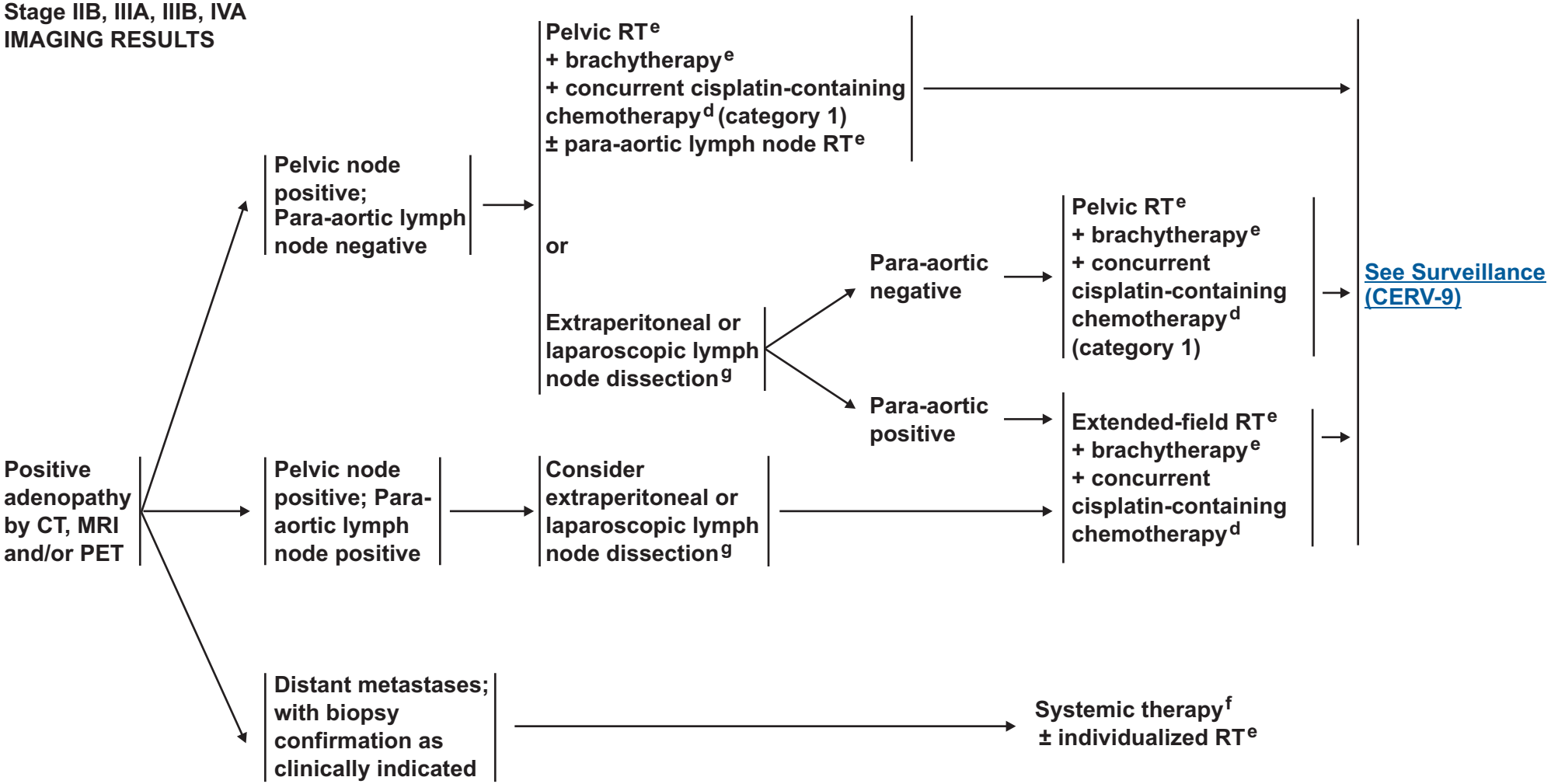
See Surveillance (CERV-9)

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

PRIMARY TREATMENT



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

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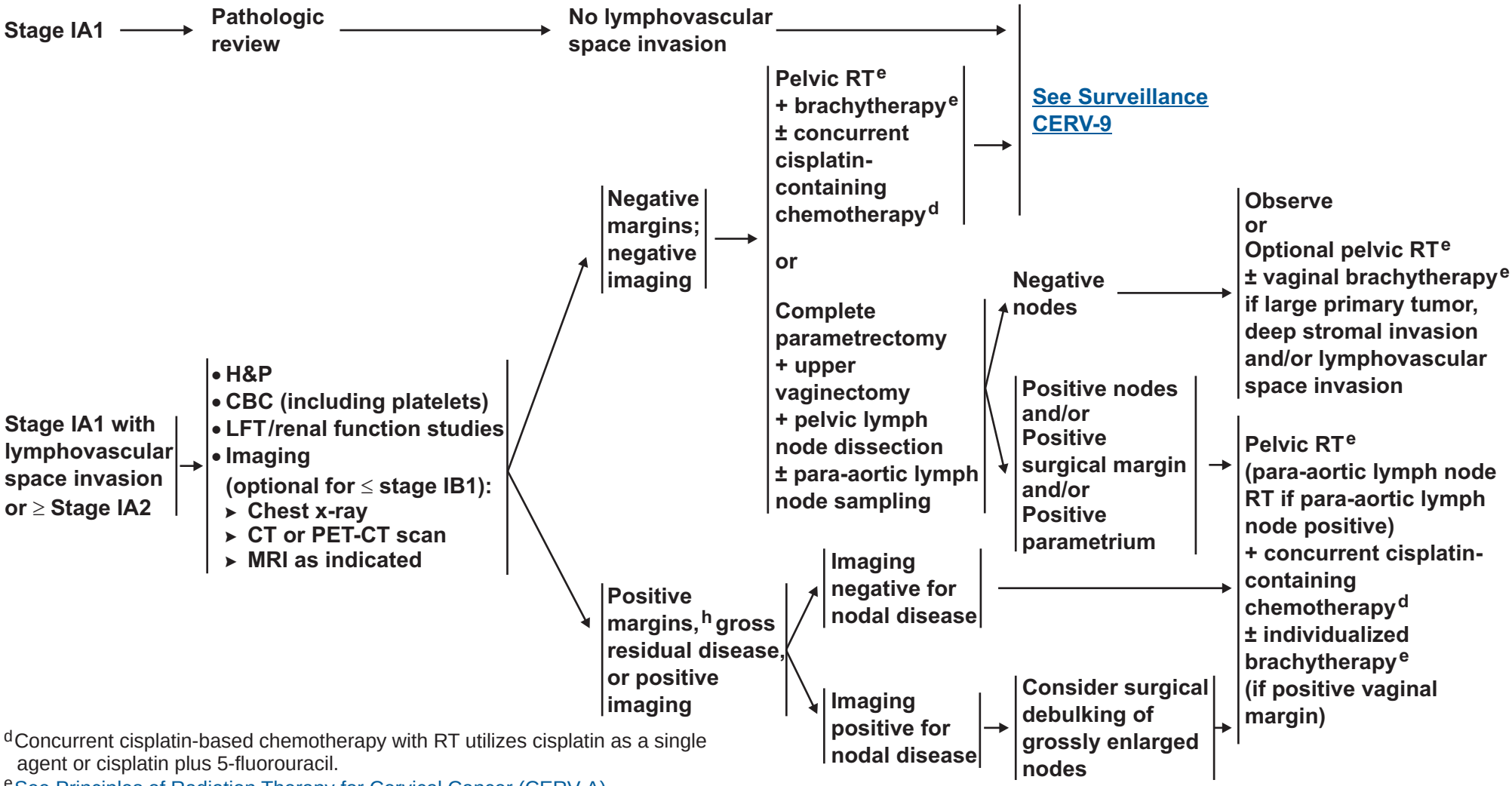
See Surveillance (CERV-9)

INCIDENTAL FINDING OF INVASIVE CANCER AT SIMPLE HYSTERECTOMY

PRIMARY TREATMENT



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

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

[h] Invasive cancer at surgical margin.

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See Surveillance (CERV-9)

SURVEILLANCE

- Interval H&P
- Cervical/vaginal cytology every 3-6 mo for 2 y, then every 6-12 mo for 3-5 y, then annually
- Chest x-ray annually for 5 y
- CBC, BUN, creatinine every 6 mo (optional)
- PET-CT scan as clinically indicated[i]
- Recommend use of vaginal dilator after RT
- Patient education regarding symptoms

→ Persistent or recurrent disease →

WORKUP

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

→ See Therapy for Relapse (Local/regional recurrence) (CERV-10)

→ See Therapy for Relapse (Distant metastases) (CERV-11)

[i]PET-CT scan may be useful in detecting isolated recurrences or persistent disease that is amenable to potentially curative salvage therapy. (See Discussion)

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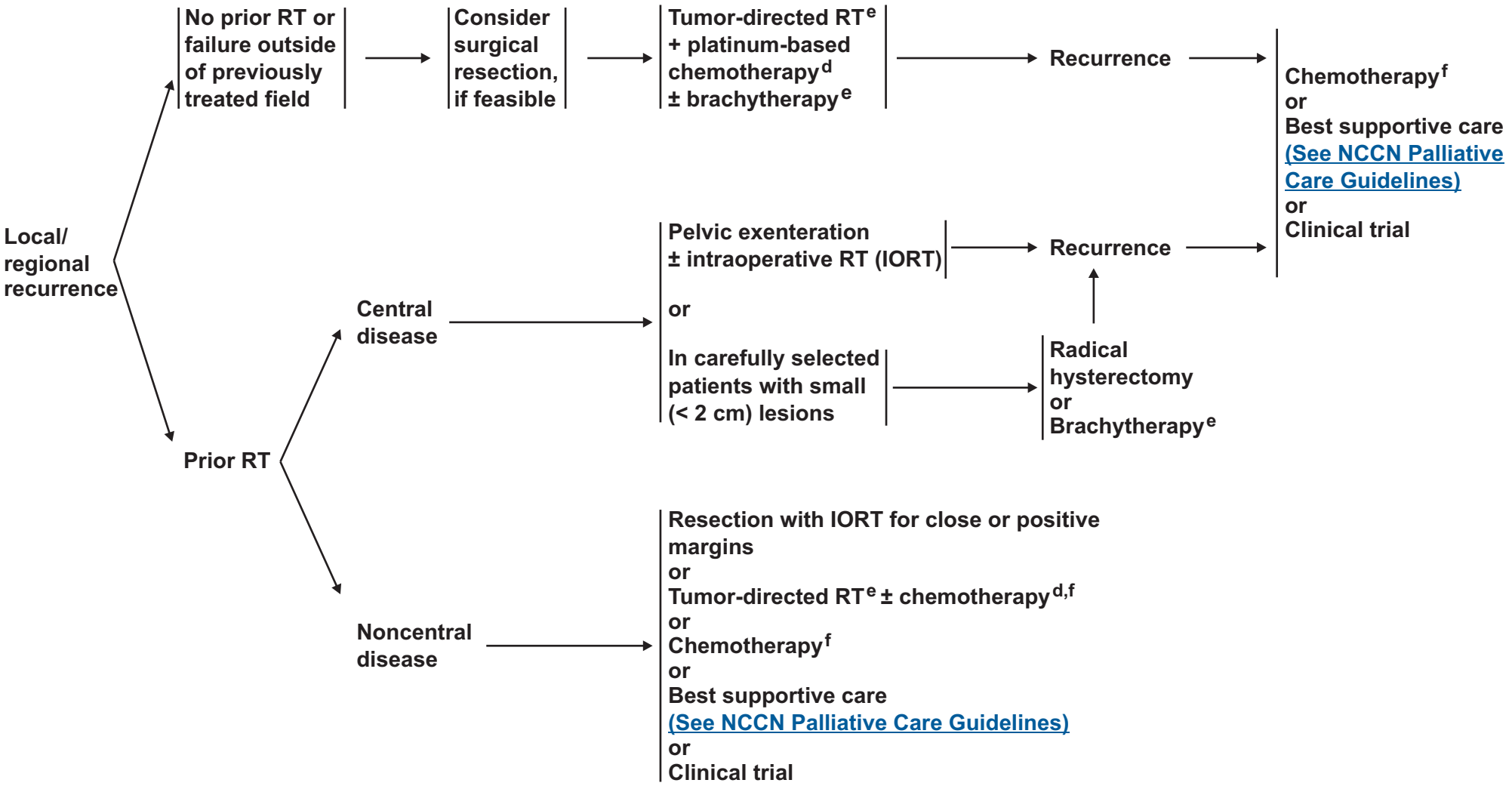
THERAPY FOR RELAPSE



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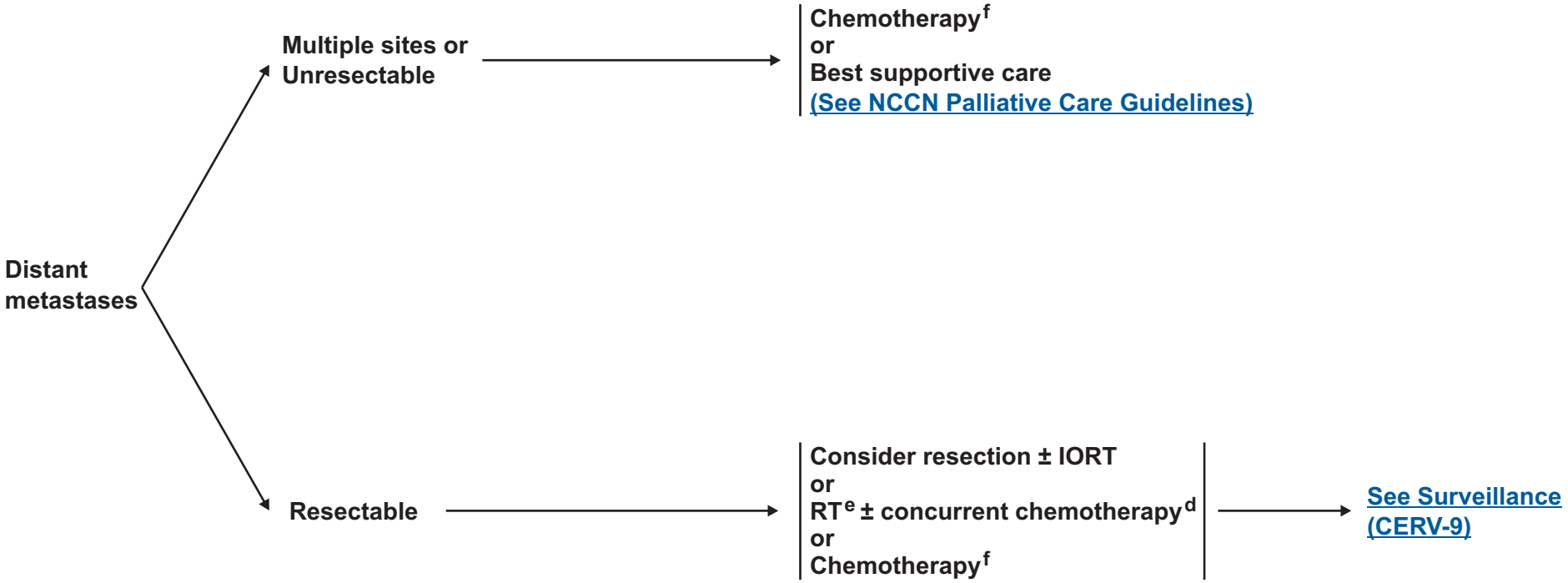

[d] Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.
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PRINCIPLES OF RADIATION THERAPY FOR CERVICAL CANCER

External-Beam Radiation Therapy (EBRT)

- The use of computed tomography (CT)–based treatment planning and conformal blocking is considered standard of care for EBRT. MRI is the best imaging modality for determining soft tissue and parametrial involvement in patients with advanced tumors. In patients who are not surgically staged, PET imaging is useful to help define the nodal volume of coverage.
- The volume of EBRT should cover the gross disease (if present), parametria, uterosacral ligaments, sufficient vaginal margin from the gross disease (at least 3 cm), presacral nodes, and other nodal volumes at risk. For patients with negative nodes on surgical or radiologic imaging, the radiation volume should include the entirety of the external iliac, internal iliac, and obturator nodal basins. For patients deemed at higher risk of lymph node involvement (eg, bulkier tumors, or suspected or confirmed nodes confined to the low true pelvis), the radiation volume should be increased to cover the common iliacs as well. In patients with documented common iliac and/or para-aortic nodal involvement, extended-field pelvic and para-aortic radiotherapy would be required, up to the level of the renal vessels (or even more cephalad as directed by involved nodal distribution).
- Coverage of microscopic nodal disease requires an EBRT dose of approximately 45 Gy (in conventional fractionation of 1.8-2.0 Gy daily), and highly conformal boosts of an additional 10-15 Gy may be considered for limited volumes of gross unresected adenopathy. For the majority of patients who receive EBRT for cervical cancer, concurrent cisplatin-based chemotherapy (either cisplatin alone, or cisplatin + 5-fluorouracil) is given during the time of EBRT.
- Intensity-modulated radiation therapy (IMRT) and similar highly conformal methods of dose delivery may be helpful in minimizing the dose to the bowel and other critical structures in the post-hysterectomy setting and in treating the para-aortic nodes when this is necessary. These techniques can also be useful when high doses are required to treat gross disease in regional lymph nodes. However, conformal external beam therapies (such as IMRT) should not be used as routine alternatives to brachytherapy for treatment of central disease in patients with an intact cervix. Very careful attention to detail and reproducibility (including consideration of target and normal tissue definitions, patient and internal organ motion, soft tissue deformation, and rigorous dosimetric and physics quality assurance) is required for proper delivery of IMRT and related highly conformal technologies.

Continued

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PRINCIPLES OF RADIATION THERAPY FOR CERVICAL CANCER

Brachytherapy

- Brachytherapy is a critical component of therapy for all patients with intact cervical cancer. This is usually performed using an intracavitary approach, with an intrauterine tandem and vaginal colpostats. Depending on the patient and tumor anatomy, the vaginal component of brachytherapy in patients with intact cervical cancer may be delivered using ovoids, ring, or cylinder (combined with the intrauterine tandem). When combined with EBRT, brachytherapy is often initiated towards the latter part of treatment, when sufficient primary tumor regression has been noted to permit satisfactory brachytherapy apparatus geometry. In highly selected very early disease (ie, stage IA2), brachytherapy alone, without external-beam radiation, may be an option.
- In rare cases, patients whose tumor geometry renders intracavitary brachytherapy infeasible may be best treated using an interstitial approach; however, such interstitial brachytherapy should only be performed by individuals and at institutions with appropriate experience and expertise.
- In selected post-hysterectomy patients (especially those with positive vaginal mucosal surgical margins), vaginal cylinder brachytherapy may be used as a boost to EBRT.

Radiation Dosing Considerations

- **The most common historical dosing parameters for brachytherapy utilize a system that includes specifying dose at point A, and that incorporates specific guidelines for 'radioactive source loading and distribution of activity' within the uterus and vagina, based on anatomic considerations. Doses are also calculated at standardized point B and bladder and rectal points. Current efforts at '3-D' image-guided brachytherapy seek to optimize implant dose coverage of tumor, while potentially reducing dose to adjacent bladder, rectum, and bowel structures.[1] Nonetheless, the weight of experience and tumor control results, and the majority of continuing clinical practice, have been based on the point A dosing system.[2] Attempts to improve dosing with image-guided brachytherapy should take care not to underdose tumors relative to the point A system dose recommendations.**
- **The point A dose recommendations provided in the NCCN Guidelines™ are based on traditional, and widely validated, dose fractionation and brachytherapy at low dose rates. In these provided dose recommendations, for EBRT, the dose is delivered at 1.8-2.0 Gy per daily fraction. For brachytherapy, the dose at point A assumes a low-dose rate (LDR) delivery of 40-70 cGy/h. Clinicians using high-dose rate (HDR) brachytherapy would depend on the linear-quadratic model equation to convert nominal HDR dose to point A to a biologically equivalent LDR dose to point A (http://www.americanbrachytherapy.org/guidelines/). Multiple brachytherapy schemes have been used, when combined with EBRT. However, one of the more common HDR approaches is 5 insertions with tandem and colpostats, each delivering 6 Gy nominal dose to point A. This results in a nominal HDR point A dose of 30 Gy in 5 fractions, which is generally accepted to be the equivalent to 40 Gy to point A (tumor surrogate dose) using LDR brachytherapy.**

Continued

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PRINCIPLES OF RADIATION THERAPY FOR CERVICAL CANCER

Definitive Radiation Therapy for Intact Cervical Cancer

- In patients with intact cervical cancer (ie, those who do not have surgery), the primary tumor and regional lymphatics at risk are typically treated with definitive EBRT to a dose of approximately 45 Gy (40-50 Gy). The volume of the EBRT would depend on the nodal status as determined surgically or radiographically (as previously described). The primary cervical tumor is then boosted, using brachytherapy, with an additional 30-40 Gy to point A (in LDR equivalent dose), for a total point A dose (as recommended in the guidelines) of 80 Gy (small volume cervical tumors) to 85 Gy or greater (larger volume cervical tumors). Grossly involved unresected nodes may be evaluated for boosting with an additional 10-15 Gy of highly conformal (and reduced volume) EBRT. With higher doses, especially of EBRT, care must be taken to exclude, or to severely limit, the volume of normal tissue included in the high-dose region(s) (**see Discussion**).

Post-Hysterectomy Adjuvant Radiation Therapy

- **Following primary hysterectomy, the presence of one or more pathologic risk factors may warrant the use of adjuvant radiotherapy. At a minimum, the following should be covered: upper 3-4 cm of the vaginal cuff, the parametria, and immediately adjacent nodal basins (such as the external and internal iliacs). Where there is documented nodal metastasis, the superior border of the radiation field should be appropriately increased (as previously described). A dose of 45-50 Gy in standard fractionation is generally recommended. Grossly involved unresected nodes may be evaluated for boosting with an additional 10-15 Gy of highly conformal (and reduced volume) EBRT. With higher doses, especially of EBRT, care must be taken to exclude, or to severely limit, the volume of normal tissue included in the high-dose region(s) (see Discussion).**

Intraoperative Radiation Therapy (IORT)

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

Continued

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PRINCIPLES OF RADIATION THERAPY FOR CERVICAL CANCER (REFERENCES)

[1]Pötter R, Haie-Meder C, Van Limbergen E, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol 2006;78(1):67-77.

[2]Viswanathan AN, Erickson BA. Three-dimensional imaging in gynecologic brachytherapy: a survey of the American Brachytherapy Society. Int J Radiat Oncol Biol Phys 2010;76(1):104-109.

[3]del Carmen MG, McIntyre JF, Goodman A. The role of intraoperative radiation therapy (IORT) in the treatment of locally advanced gynecologic malignancies. Oncologist 2000;5(1):18-25.

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

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

Possible first-line single agent therapy
- Cisplatin (preferred as a single agent)[2]
- Carboplatin[6]
- Paclitaxel[7]

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

Continued

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

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CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC CERVICAL CANCER
(References)

[1] Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: A Gynecologic Oncology Group Study. J Clin Oncol 2009; 27:4649-4655.

[2] Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol. 2004;22:3113-3119.

[3] Moore KN, Herzog TJ, Lewin S, et al. A comparison of cisplatin/paclitaxel and carboplatin/paclitaxel in stage IVB, recurrent or persistent cervical cancer. Gynecol Oncol 2007;105:299-303.

[4] 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.

[5] Brewer CA, Blessing JA, Nagourney RA, et al. Cisplatin plus gemcitabine in previously treated squamous cell carcinoma of the cervix. Gynecol Oncol 2006;100:385-388.

[6] Weiss GR, Green S, Hannigan EV, et al. A phase II trial of carboplatin for recurrent or metastatic squamous carcinoma of the uterine cervix: a Southwest Oncology Group study. Gynecol Oncol. 1990;39:332-336.

[7] Kudelka AP, Winn R, Edwards CL, et al. An update of a phase II study of paclitaxel in advanced or recurrent squamous cell cancer of the cervix. Anticancer Drugs 1997;8:657-661.

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

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

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

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

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

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

Continued...

Staging-Cervical Cancer

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

Regional Lymph Nodes (N)

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

Distant Metastasis (M)

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

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 11/19/10

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

An estimated 12,200 new cases of cervical cancer will be diagnosed in the United States in the year 2010; 4200 deaths will result from the disease.[1] Cervical cancer rates are decreasing among women in the United States, although incidence remains high among Hispanic/Latino, Black, and Asian women.[2-5] However, cervical cancer is a major world health problem for women. The global yearly incidence of cervical cancer for 2002 was 493,200; the annual death rate was 273,500. It is the third most common cancer in women worldwide;[6, 7] 78% of cases occur in developing countries, where cervical cancer is the second most frequent cause of cancer death in women.

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%.[6] Immunization against HPV prevents infection with certain types of HPV and, thus, is expected to prevent specific HPV cancer in women (see NCCN Cervical Cancer Screening Guidelines).[8-12] 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.[13]

Squamous cell carcinomas account for about 80% of all cervical cancers and adenocarcinoma for about 20%. In developed countries, the substantial decline in incidence and mortality of squamous cell carcinoma of the cervix is thought to be a result of effective screening, although there are racial, ethnic, and geographic disparities.[2, 3, 14, 15] However, adenocarcinoma of the cervix has increased over the last 3 decades, probably because cervical cytologic screening methods are less effective for adenocarcinoma.[16-19] Screening methods using HPV testing may increase detection of adenocarcinoma. Vaccination with HPV vaccines may also decrease the incidence of both squamous cell carcinoma and adenocarcinoma.[18, 20]

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

Diagnosis and Workup

These NCCN guidelines discuss squamous cell carcinoma, adenosquamous carcinoma, and adenocarcinoma of the cervix.

Neuroendocrine carcinoma, small cell tumors, glassy-cell carcinomas, sarcomas, and other histologic types are not within the scope of these guidelines.

Currently, the International Federation of Gynecology and Obstetrics (FIGO) evaluation procedures for staging are limited to colposcopy, biopsy, conization of the cervix, cystoscopy, and proctosigmoidoscopy. More complex radiologic and surgical staging procedures are not addressed in the FIGO classification. In the United States, however, computed tomography (CT), magnetic resonance imaging (MRI), combined positron emission tomography (PET)-CT, and surgical staging are often used to guide treatment options and design.[21-23]

The earliest stages of cervical carcinoma may be asymptomatic or associated with a watery vaginal discharge and postcoital bleeding or intermittent spotting. These early symptoms frequently are unrecognized by the patient. Because of the accessibility of the uterine cervix, cervical cytology or Papanicolaou (Pap) smears and cervical biopsies can usually result in an accurate diagnosis (see NCCN Cervical Cancer Screening Guidelines). Cone biopsy (i.e., conization) is recommended if the cervical biopsy is inadequate to define invasiveness or if accurate assessment of microinvasive disease is required. However, cervical cytologic screening methods are less useful for diagnosing adenocarcinoma, because adenocarcinoma in situ affects areas of the cervix that are harder to sample (i.e., endocervical canal).[5, 19]

Workup for these patients with suspicious symptoms includes history and physical examination, complete blood count (including platelets), and liver and renal function tests. Radiologic imaging includes chest x-ray, CT or combined PET-CT, and MRI as indicated (e.g., to rule out disease high in the endocervix); however, imaging is optional for patients with stage IB1 or smaller tumors (see “Workup” in the NCCN Cervical Cancer algorithm). Cystoscopy and proctoscopy should be reserved for patients in whom there is clinical concern for bladder or rectal extension.

Panel members discussed whether laparoscopic and robotic approaches should be included as part of these NCCN guidelines in both staging and treatment. These techniques are being used more frequently, but long-term outcome data are not available yet. Laparoscopic staging, lymphadenectomies, and radical hysterectomies can be performed satisfactorily and are used routinely in selected patients in several member institutions.[24-26] Data from studies overseas suggest that recurrence rates are low for laparoscopic radical hysterectomy after 3-6 years of follow-up.[27, 28] Robotic radical hysterectomy (which is another minimally invasive surgical technique) is currently being done for patients with early cervical cancer. Potential advantages associated with laparoscopic and robotic approaches include decreased hospital stay and more rapid patient recovery.[29-31]

Staging

Because of the variability of the availability and worldwide use 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. Although surgical staging is more accurate than clinical staging, surgical staging often cannot be used in low resource countries.[22, 32, 33] The guidelines panel currently uses the 2009 FIGO definitions and staging system (see Table 1).[32, 34] This staging system from FIGO has been approved by the American Joint Committee on Cancer (AJCC).[35] With the new staging, stage IIA is now subdivided into stage IIA1 (tumor size 4 cm or less) and stage IIA2 (tumor size

more than 4 cm), which is the only change from the previous 1994 FIGO staging system.

It is important to note that lymphatic vascular space involvement (LVSI) does not alter the FIGO classification.[32] 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 frank 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 combined PET-CT scans may aid in treatment planning but is not accepted for formalized staging purposes.[22, 33, 36, 37] 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 (i.e., CT and MRI) are used to guide treatment options and design. MRI is useful to rule out disease high in the endocervix.

Primary Treatment

The primary treatment of early stage cervical cancer is either surgery or radiation therapy (RT). Surgery is typically reserved for lower-stage disease and smaller lesions, such as stage IA, IB1, and selected IIA1. The NCCN panel agrees that concurrent chemoradiation is the primary treatment of choice for stages IB2-IVA disease based on the results of 5 randomized clinical trials (see Table 2). Chemoradiation can also be used for patients who are not candidates for hysterectomy. Although there are few studies assessing treatment specifically for adenocarcinoma, a recent analysis suggests that they can be effectively treated in a similar manner to squamous cell carcinomas.[38,39]

Clinical Trials and Basis for Treatment Selection

A randomized Italian study compared RT alone versus radical hysterectomy and lymph node dissection.[40] 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.

Concurrent chemoradiation, using cisplatin-based chemotherapy (either cisplatin alone or cisplatin/5-fluorouracil [5-FU]), is the treatment of choice for stages IB2, II, III, and IVA disease based on the results of 5 randomized clinical trials (see Table 2).[41-46] 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 clearly established a role for concurrent cisplatin-based chemoradiation. Based on this data, the National Cancer Institute issued an alert stating that strong consideration should be given to using chemoradiation instead of RT alone for invasive cervical cancer (http://www.nih.gov/news/pr/feb99/nci-22.htm). Long-term follow-up of 3 of these trials has confirmed that concurrent cisplatin-based chemoradiation improves progression-free and overall survival when compared with RT with or without hydroxyurea.[47-49] A recent meta-analysis reported that chemoradiotherapy leads to a 6% improvement in 5-year survival (hazard ratio [HR] = 0.81, P<.001).[50] A large population-based registry analysis in Canada (n=4069) confirmed that

chemoradiotherapy improved outcomes when compared with radiotherapy alone.[51]

Although chemoradiation is tolerated, acute and long-term side effects have been reported.[50, 52, 53] Some oncologists feel that concurrent single-agent cisplatin chemoradiation is preferred to cisplatin plus 5-FU chemoradiation, because the latter may be more toxic.[54] Concurrent carboplatin or non-platinum chemoradiation regimens are options for patients who may not tolerate cisplatin-containing chemoradiation.[50,55-59] Note that when concurrent chemoradiation is used, the chemotherapy is typically given when the external-beam pelvic radiation is administered.[54] The NCCN panel believes that using "systemic consolidation" (i.e., adding chemotherapy after chemoradiation) should only be used in clinical trials (e.g., RTOG 0724).[50, 60, 61]

Early Stage Disease

After careful clinical evaluation and staging, the primary treatment of early stage cervical cancer is either surgery or RT. The treatment schema is stratified using the FIGO staging system (see Table 1).

Stage IA1 Disease

Extrafascial (i.e., simple) hysterectomy is commonly recommended for patients with clinical stage IA1 disease; another option is modified radical hysterectomy with pelvic lymph node dissection if lymphovascular space invasion is present (category 2B for node dissection only). However, if the patient is medically inoperable or if fertility is desired, patients with negative margins from cone biopsy could undergo observation.[62, 63] For patients who desire fertility preservation, trachelectomy and pelvic lymph node dissection can be considered with (or without) para-aortic lymph node sampling for stage IA cervical cancer (see "Primary Treatment" in the NCCN Cervical Cancer algorithm).[64-67]

Stage IA2 Disease

Stage IA2 tumors can be treated with radical hysterectomy or radical trachelectomy and pelvic lymph node dissection with (or without) para-aortic lymph node sampling. Para-aortic node dissection is indicated for patients with known or suspected pelvic nodal disease.

Brachytherapy with (or without) pelvic radiation (total point A dose: 75-80 Gy) is another treatment option for stage IA2 disease. These doses are recommended for most patients based on summation of conventional external-beam fractionation and low-dose-rate (40-70 cGy/h) brachytherapy equivalents. Treatment should be modified based on normal tissue tolerance or on biologic equivalence calculations when using high dose rate brachytherapy (see also "Radiation Therapy" in this manuscript [i.e., Discussion]).

Stage IB and IIA Disease

Depending on their stage and disease bulk, patients with stage IB or IIA tumors can be treated with surgery, RT, or concurrent chemoradiation. A combined PET-CT scan can be done to rule out extrapelvic disease prior to deciding how to treat these patients. The surgical option includes radical hysterectomy plus bilateral pelvic lymph node dissection with or without para-aortic lymph node sampling.[40] Para-aortic node dissection is indicated for patients with larger tumors and suspected or known pelvic nodal disease. Some panel members feel that a pelvic lymph node dissection should be done first and if negative, then the radical hysterectomy should be done. If the lymph nodes are positive, then the hysterectomy should be abandoned; these patients should receive chemoradiation.

For patients who desire fertility preservation, radical trachelectomy and pelvic lymph node dissection with (or without) para-aortic lymph node sampling can be considered for stage IB1 tumors 2 cm or less (see "Primary Treatment" in the NCCN Cervical Cancer algorithm).[64-68] In one study, oncologic outcomes were similar after 4 years when comparing radical trachelectomy with radical hysterectomy for patients with stage 1B1 cervical carcinoma.[68] A study found that among women attempting to conceive after radical trachelectomy for early stage cervical cancer, the 5-year cumulative pregnancy rate was 52.8%; the cancer recurrence rate was low, but the miscarriage rate is higher.[69] For young (< 45 years) premenopausal women with early stage squamous cell carcinoma who opt for ovarian preservation (i.e., hysterectomy only), the rate of ovarian metastases is low.[70, 71]

Recent data have suggested that sentinel lymph node biopsy may be useful for decreasing the need for pelvic lymphadenectomy in patients with early stage cervical cancer, but panel members believe the technique is not yet sufficiently validated.[72-74] However, this is an interesting area for further research.[75-78]

For patients with stage IB or IIA tumors (including those who are not candidates for hysterectomy), another option is combined pelvic radiotherapy and brachytherapy with or without concurrent cisplatin-containing chemotherapy (see "Primary Treatment" in the NCCN Cervical Cancer algorithm). Although concurrent chemoradiation has been proven effective in the definitive treatment of more advanced stage disease, this approach has not been specifically studied in patients with stage IB1 or IIA1 disease. Careful consideration of the risk/benefit ratio should be undertaken in these patients with smaller tumors.

For patients with clinical stage IB2 or IIA2 tumors who are treated with definitive radiation, concurrent cisplatin-containing chemotherapy has been shown to significantly improve patient survival.[41, 42] For stage IB2 or IIA2 tumors, the panel disagreed (category 3) about recommending adjuvant hysterectomy for patients undergoing primary chemoradiation.[41]

Advanced Disease

This category has traditionally included patients with stage IIB-IVA disease (i.e., locally advanced disease). However, many oncologists now include patients with IB2 and IIA2 disease in the advanced disease category. For patients with more advanced tumors who are undergoing primary chemoradiation, the volume of RT is critical and is guided by assessment of nodal involvement in the pelvic and para-aortic nodes. Radiologic imaging studies (including PET-CT) are recommended for stage IB2 or greater disease. MRI is useful to rule out disease high in the endocervix. However, needle biopsy can be considered for questionable imaging findings. Surgical staging (i.e., extraperitoneal or laparoscopic lymph node dissection) is also an option (category 2B) for these patients. Surgical staging may also detect microscopic nodal disease that is not discernable with radiologic imaging.[79]

For patients without nodal disease or with disease limited to the pelvis only by surgical staging, treatment consists of pelvic RT with concurrent cisplatin-based chemotherapy and brachytherapy (category 1).[42, 44-46, 54] However, for patients with positive para-aortic and pelvic lymph nodes by imaging, extraperitoneal lymph node dissection should be considered followed by extended-field RT, concurrent cisplatin-containing chemotherapy, and brachytherapy (see "Primary Treatment" in the NCCN Cervical Cancer algorithm). Patients with positive para-aortic lymph nodes who are positive for distant metastases are treated with systemic chemotherapy (see "Chemotherapy Regimens for

Recurrent or Metastatic Disease" in the NCCN Cervical Cancer algorithm) and individualized RT.

Metastatic Disease

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

Adjuvant Treatment

Adjuvant treatment is indicated after radical hysterectomy depending on surgical findings and disease stage. Observation is appropriate for patients with stage IA2, IB1, or IIA1 disease who have negative nodes and no risk factors after radical hysterectomy. However, adjuvant treatment is indicated after radical hysterectomy if pathologic risk factors are discovered. For patients with stage IA2, IB1, or IIA1 disease who have *negative* lymph nodes after surgery but have large primary tumor size, deep stromal invasion, and/or LVSI, pelvic radiation is recommended (category 1) with (or without) concurrent cisplatin-based chemotherapy (category 2B for chemotherapy).[80-83]

Adjuvant pelvic RT alone versus no further therapy was tested in a randomized trial (Gynecologic Oncology Group [GOG] 92) of selected patients with node-negative stage IB carcinoma of the cervix after hysterectomy and pelvic lymphadenectomy.[83] Patients were eligible for this trial after radical hysterectomy and pelvic lymphadenectomy if they had at least 2 of the following risk factors: (1) greater than one-third stromal invasion; (2) capillary lymphatic space involvement; or (3) cervical tumor diameters more than 4 cm. Patients with positive lymph nodes or involved surgical margins were excluded. At 2 years, the recurrence-free rates were 88% for the RT group versus 79% for the no further treatment group. After long-term follow-up (12 years), an updated analysis confirmed that pelvic RT increased progression-free survival; there was also a clear trend towards improved overall survival (*P*=.07).[84]

Patients with *positive* pelvic nodes, positive surgical margin, and/or positive parametrium should be treated with postoperative pelvic radiation with concurrent cisplatin-containing chemotherapy (category 1)[43] with (or without) vaginal brachytherapy (see "Adjuvant Treatment" in the NCCN Cervical Cancer algorithm). Vaginal brachytherapy may be a useful boost for those with positive vaginal mucosal margins. The addition of concurrent chemoradiation significantly improves 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.[43] The Intergroup Trial 0107 showed a statistically significant benefit of adjuvant pelvic radiation with concurrent cisplatin and 5-FU in the treatment of patients with stage IA2, IB, or IIA disease who had positive lymph nodes, positive margins, and/or microscopic parametrial involvement found at surgery.[43]

If para-aortic lymph nodes are found positive during surgical staging, patients must undergo further screening with chest CT or combined PET-CT scan. In women who are positive for distant metastases, biopsy of suspicious areas should be considered as indicated (see "Adjuvant Treatment" in the NCCN Cervical Cancer algorithm). For patients without distant metastases, recommended treatment is extended-field RT (including pelvis and para-aortic lymph nodes), concurrent cisplatin-based chemotherapy with (or without) brachytherapy. For patients with distant metastases, recommended treatment is systemic chemotherapy (see "Chemotherapy Regimens for

Recurrent or Metastatic Disease" in the NCCN Cervical Cancer algorithm) 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 cervical/vaginal cytology every 3-6 months for 2 years, every 6 months for another 3-5 years, and then annually (see "Surveillance" in the NCCN Cervical Cancer algorithm). Some clinicians have suggested that rigorous cytology follow-up is not warranted because of studies stating that Pap smears did not detect recurrences in patients with stage I-II cervical cancer who were asymptomatic after treatment.[85, 86] It is important to emphasize good clinical evaluation and a high index of suspicion, because the detection rate of recurrent cervical cancer is low using cervical and vaginal cytology alone.[87] Patient education regarding symptoms suggestive of recurrence is appropriate.

In patients at high risk for local-regional (central or para-aortic) failure, a combined PET-CT scan may be useful for detecting asymptomatic disease that is potentially curable.[88-90] Annual chest radiographs are optional.[87, 91] Many other tests remain optional based on clinical indications, such as semiannual complete blood counts, blood urea nitrogen, and serum creatinine determinations (see "Surveillance" in the NCCN Cervical Cancer algorithm). Patients with persistent or recurrent disease need to be evaluated using additional imaging studies as clinically indicated and surgical exploration in selected cases followed by therapy for relapse (see next section).[92]

Vaginal dilators are recommended after pelvic RT, because patients who receive RT are prone to vaginal stenosis, which can impair sexual function. Women can use vaginal dilators to prevent or treat vaginal stenosis. Dilator use can start 2-4 weeks after RT is completed and can be done indefinitely (http://www.ukons.org/storage/dilators_guidelines.pdf).

Cervical cancer survivors are at risk for second cancers.[93] Data suggest that patients who receive radiation therapy for pelvic cancers are at risk for radiation-induced second cancers, especially at radiated sites near the cervix (e.g., colon, rectum/anus, urinary bladder); therefore, careful surveillance is appropriate for these patients.[94, 95]

Therapy for Relapse

Local/Regional Therapy

Patients with a localized recurrence of cervical cancer after initial treatment should be evaluated to determine whether radiotherapy or surgery can be utilized for relapse. Long-term disease-free survival rates of approximately 40% have been reported in some situations.[96]

For patients who experience local/regional recurrences who have not previously had RT or who experience recurrences outside of the previously treated RT field, therapy for relapse includes tumor-directed RT and platinum-based chemotherapy with (or without) brachytherapy; surgical resection can be considered if feasible (see "Therapy for Relapse" in the NCCN Cervical Cancer algorithm). Typically the chemoradiation for recurrence uses cisplatin as a single agent or cisplatin plus 5-FU.[97, 98]

Patients with central pelvic recurrent disease after RT should be evaluated for pelvic exenteration, with (or without) intraoperative RT (IORT).[99-105] Surgical mortality is generally 5% or lower, with survival

rates approaching 50%.[101] Concomitant measures with such radical procedures include adequate rehabilitation programs dealing with the psychosocial and psychosexual consequences of the operation as well as reconstructive procedures.[100, 106-108] Although exenteration is the common surgical approach in post-radiation patients, in carefully selected patients with small central lesions (less than 2 cm), options may include radical hysterectomy or brachytherapy.

For patients with noncentral recurrent disease, options include resection with IORT for close or positive margins, tumor-directed RT with (or without) chemotherapy, chemotherapy, best supportive care (see the NCCN Palliative Care Guidelines), or participation in a clinical trial. Patients who recur after second-line definitive therapy, either surgery or RT, have a poor prognosis. They can be treated with chemotherapy, best supportive care, or be enrolled in a clinical trial.

Systemic Therapy for Metastatic Disease

Patients who develop distant metastases, either at initial presentation or at relapse, are rarely curable. For highly selected patients with isolated distant metastases, occasional long-term survival has been reported with 1) surgical resection with (or without) IORT; 2) RT with (or without) concurrent chemotherapy; or 3) chemotherapy (see "Therapy for Relapse" in the NCCN Cervical Cancer algorithm). For most of the other patients with distant metastases, appropriate treatment is either chemotherapy (see "Chemotherapy Regimens for Recurrent or Metastatic Disease" in the NCCN Cervical Cancer algorithm) or best supportive care.

The palliation of pelvic recurrences in heavily irradiated sites that are not amenable to local pain control techniques or to surgical resection is 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 (http://emedicine.medscape.com/article/270646-overview). However, short-courses of RT may provide symptomatic relief to patients with bone metastases, painful para-aortic nodes, or supraclavicular adenopathy.[109, 110]

Chemotherapy has a limited role in prolonging survival or in improving quality of life and is recommended for patients with extrapelvic metastases or recurrent disease who are not candidates for RT or exenterative surgery. Patients who respond to chemotherapy may achieve pain relief of a transient nature. If cisplatin was previously used as a radiosensitizer, combination platinum-based regimens are preferred over single agents in the metastatic disease setting based on several randomized phase III trials (see next paragraph).[111, 112]

First-Line Combination Chemotherapy

Cisplatin has been considered the most effective agent for metastatic cervical cancer.[113] However, most patients who develop metastatic disease have received concurrent cisplatin/RT as primary treatment and may no longer be sensitive to single-agent platinum therapy.[111, 112] Cisplatin-based combination chemotherapy regimens, such as cisplatin/paclitaxel and cisplatin/topotecan, have been extensively investigated in clinical studies.[111, 112, 114-116] A randomized phase III study (GOG 169) in 264 eligible patients comparing paclitaxel and cisplatin versus cisplatin alone showed that the 2-drug combination had a higher response rate (36% versus 19%) and improved progression-free survival (4.8 versus 2.8 months; *P*>.001), although no improvement was seen in median survival.[111] For patients who responded to cisplatin/paclitaxel, there was a significant improvement in quality of life. Although carboplatin/paclitaxel has not been studied in a prospective randomized setting, many physicians used carboplatin/paclitaxel because of ease of administration and tolerability.

Another randomized phase III GOG study (GOG 179) 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).[112] The FDA has approved cisplatin/topotecan for advanced cervical cancer. However, the cisplatin/paclitaxel or carboplatin/paclitaxel regimens are less toxic and easier to administer when compared with cisplatin/topotecan.

A recent phase III trial (GOG 204) in 513 patients with advanced metastatic or recurrent cancer assessed 4 cisplatin-doublet regimens (cisplatin/paclitaxel, cisplatin/topotecan, cisplatin/gemcitabine, versus cisplatin/vinorelbine).[116] The trial was closed early, because it was apparent that cisplatin/topotecan, cisplatin/gemcitabine, and cisplatin/vinorelbine were not superior to cisplatin/paclitaxel. No significant differences in overall survival were seen; however, the trends for response rate, progression-free survival, and overall survival (12.9 versus 10 months) suggest that cisplatin/paclitaxel is superior to the other regimens. Cisplatin/paclitaxel was associated with less thrombocytopenia and anemia (but with more nausea, vomiting, infection, and alopecia), than the other regimens. Although cisplatin/gemcitabine was not shown to be a superior regimen in GOG 204, it was tolerable. Based on a phase III randomized trial for locally advanced cervical cancer, cisplatin/gemcitabine is included as an option in the NCCN guidelines.[61] Cisplatin/gemcitabine may be a useful regimen for patients with neuropathy who cannot tolerate other regimens.

Many clinicians prefer using carboplatin rather than cisplatin because of ease of administration, tolerability, and preservation of renal function. A retrospective trial assessing cisplatin/paclitaxel versus carboplatin/paclitaxel confirmed these opinions.[117] Paclitaxel and carboplatin have been assessed for recurrent or persistent cancer of the cervix. In a study using paclitaxel and carboplatin in 25 women, the median overall survival was 21 months.[118] Recently, a study using paclitaxel and carboplatin in 51 women had an median overall survival of 13 months.[119] A phase III trial assessing carboplatin/paclitaxel versus cisplatin/paclitaxel is currently in progress.[120] Non-platinum doublets are also being studied.[121]

Single Agents

Cisplatin is generally regarded as the most active agent and is recommended as possible first-line single agent chemotherapy in recurrent or metastatic cervical cancer; reported response rates are approximately 20% to 30%, with an occasional complete response.[111,113, 122, 123] Overall survival with cisplatin is about 6-9 months. Carboplatin or paclitaxel have been reported to be tolerable and efficacious and are also possible first-line single agent chemotherapy.[124-127] Therefore, palliation with single agents—cisplatin, carboplatin, or paclitaxel—is a reasonable approach in patients with recurrent disease not amenable to surgical or radiotherapeutic approaches. Complete responses were also observed with topotecan or paclitaxel; however, topotecan is associated with more toxicity than carboplatin or paclitaxel. Other agents (these are category 2B unless otherwise indicated) that have shown responses or prolongation of PFS and may be useful as second-line therapy include bevacizumab,[128] docetaxel,[129] 5-FU,[130] gemcitabine,[131] ifosfamide,[132, 133] irinotecan,[134] mitomycin,[135] topotecan,[136, 137] pemetrexed (category 3),[138] and vinorelbine (category 3).[139]

Drug Reactions

Virtually all drugs have the potential to cause adverse reactions, either during or after the infusion.[140] In cervical cancer treatment, drugs that more commonly cause adverse reactions include carboplatin, cisplatin, docetaxel, liposomal doxorubicin, and paclitaxel. Most of these drug reactions are mild infusion reactions (i.e., skin reactions, cardiovascular reactions, respiratory or throat tightness), but more severe allergic reactions (i.e., life-threatening anaphylaxis) can occur.[141, 142] In addition, patients can have severe infusion reactions and mild allergic reactions. Infusion reactions are more common with paclitaxel.[143] Allergic reactions (i.e., true drug allergies) are more common with platinum agents (i.e., carboplatin, cisplatin).[143, 144]

Management of drug reactions is discussed in the NCCN Ovarian Cancer guidelines.[143] It is important to note that patients who have had severe life-threatening reactions should not receive the implicated agent again. If a mild allergic reaction has previously occurred and it is appropriate to administer the drug again, a desensitization regimen should be used even if the symptoms have resolved; various desensitization regimens have been published and should be followed.[144-146] Patients must be desensitized with each infusion if they previously had a reaction. Almost all patients can be desensitized.[140] To maximize safety; patients should be desensitized in the intensive care unit.[140]

Other Agents

Vaccine therapies have no established role in the treatment of cervical cancer at the present time, except in the setting of a clinical trial.[147-149] Targeted therapy (using small molecules or monoclonal antibodies) is currently in clinical trials.[60, 128, 150, 151]

Best Supportive Care

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 (see the NCCN Palliative Care Guidelines).

Incidental Cervical Cancer

Invasive cervical carcinoma is sometimes found incidentally after extrafascial hysterectomy. Workup for these patients includes history and physical examination, complete blood count (including platelets), and liver and renal function tests. Radiologic imaging includes chest radiography, CT or combined PET-CT, or MRI as indicated (e.g., to rule out disease high in the endocervix); although imaging is optional for patients with stage IB1 or smaller tumors (see “Incidental Finding of Invasive Cancer at Simple Hysterectomy” in the NCCN Cervical Cancer algorithm).

No definitive data exist regarding the appropriate primary treatment of these patients. The panel believes that a reasonable treatment schema for patients with either stage IAI with LVSI or with stage 1A2 or higher tumors (pathologic findings) should be based on the status of the surgical margins. If margins are positive and imaging is negative for nodal disease, then pelvic RT with concurrent cisplatin-containing chemotherapy with or without individualized brachytherapy should be recommended (see “Primary Treatment” in the NCCN Cervical Cancer algorithm). Stage 1A1 patients with no LVSI should undergo surveillance.

If margins or imaging is negative in stage 1A2 or greater tumors, options include (1) pelvic RT with (or without) concurrent cisplatin-containing chemotherapy and brachytherapy; or (2) a complete parametrectomy, upper vaginectomy, and pelvic lymph node dissection

with (or without) para-aortic lymph node sampling. Patients with negative lymph nodes should be observed or treated with optional pelvic radiation with (or without) vaginal brachytherapy if they have high-risk factors (i.e., large primary tumor, deep stromal invasion, and/or LVSI (see "Primary Treatment" in the NCCN Cervical Cancer algorithm).[83] Concurrent cisplatin-based chemoradiation is recommended for gross residual disease, positive imaging, disease in the lymph nodes and/or parametrium, and/or a positive surgical margin; individualized brachytherapy is clearly indicated for a positive vaginal margin.

Radiation Therapy

Radiotherapy is often used in the management of patients with cervical cancer, either for patients with intact cervical cancer who are not amenable to surgery (e.g., definitive therapy for those with locally advanced disease or for those who are poor operative candidates), or in patients following radical hysterectomy (i.e., adjuvant RT) who have one or more pathologic risk factors (e.g., positive lymph nodes, parametrial infiltration, positive surgical margins, large tumor size, deep stromal invasion, lymphovascular space invasion).

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

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

Radiation Treatment Planning

Technological advances in imaging, computer treatment planning systems, and linear accelerator technology have provided the capability to more precisely deliver radiation dose to the pelvis. However, physical accuracy of dose delivery must be matched to a clear understanding of tumor extent, potential pathways of spread, and historical patterns of local-regional recurrence to avoid geographic misses.

CT-based treatment planning with conformal blocking and dosimetry is considered standard of care for external-beam radiotherapy. Brachytherapy is a critical component of therapy in patients with intact cervical cancer and is typically combined with external-beam radiation in an integrated treatment plan.

For patients with locally advanced cancers, initial radiation treatment of 40-45 Gy to the whole pelvis is often necessary to obtain tumor shrinkage to permit optimal intracavitary placements. With low-dose-rate intracavitary systems, total doses from brachytherapy and external-beam radiation to point A of at least 80 Gy are currently recommended for small tumors, with doses of 85 Gy or higher recommended for larger tumors.

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 an adequate dose (45 Gy for microscopic disease) without exceeding bowel, spinal cord, or renal tolerances.[152] General recommendations for radiation volumes and doses are

discussed in the algorithm (see “Principles of Radiation Therapy” in the NCCN Cervical Cancer algorithm).

Intensity-modulated radiotherapy (IMRT) is becoming more widely available; however, issues regarding target definition, patient and target immobilization, tissue deformation and reproducibility remain to be validated.[153-157] The role of IMRT in cervical cancer continues to be actively evaluated in several prospective multicenter clinical trials.

Several retrospective analyses have suggested an adverse effect of prolonged treatment duration on outcome.[158-162] Extending the overall treatment beyond 6 to 8 weeks can result in approximately a 0.5% to 1% decrease in pelvic control and cause-specific survival for each extra day of overall treatment time. Thus, although no prospective randomized trials have been done, it is generally accepted that the entire RT course (including both external beam and brachytherapy components) should be completed in a timely fashion (within 8 weeks); delays or splits in the radiation treatment should be avoided whenever possible.

Normal Tissue Considerations

Planning for radiotherapy in cervical cancer must take into account the potential impact on surrounding critical structures, such as rectum, bladder, sigmoid, small bowel, and bone. Acute effects (i.e., diarrhea, bladder irritation, fatigue) occur to some degree in most patients undergoing radiation and are typically magnified by concurrent chemotherapy. However, acute effects are often manageable by medications and supportive care, and they generally resolve soon after completion of radiation.

The risk of more significant late effects (i.e., obstruction, fibrosis/necrosis, or fistula) is related to the volume, total dose, dose per fraction, and specific intrinsic radiosensitivity of the normal tissue irradiated.[152] Careful blocking to minimize normal tissue exposure while not compromising tumor coverage is critical to achieving optimal outcomes. In addition, patient-related conditions (i.e., inflammatory bowel disease, collagen-vascular disease, multiple abdominal/pelvic surgeries, history of pelvic inflammatory disease, diabetes) influence determination of radiation dose and volumes.

For most patients, it is generally accepted that the whole pelvis can tolerate an external-beam radiation dose of 40-50 Gy. Gross disease in the parametria or unresected nodes may undergo tightly contoured external beam boosts to 60-65 Gy. Intracavitary brachytherapy boosts require attention to proper placement of the applicators within the uterus and against the cervix and vaginal apex, as well as appropriate packing to maximally displace the bladder and rectum.

Pregnancy and Cervical Cancer

For pregnant women, cervical cancer is the most frequently diagnosed type of cancer; however, most pregnant women with cervical cancer have stage I disease.[163] Invasive cervical cancer during pregnancy creates a clinical dilemma. Women need to make the difficult decision either to delay treatment until documented fetal maturity or to receive immediate treatment based on their stage of disease. For women diagnosed with cervical cancer during pregnancy who wish to continue their pregnancies, delaying cancer treatment until the fetus has matured has been reported.[163] Women who delay treatment until fetal maturity should have their children delivered by cesarean section. Patients with early stage disease may prefer to have radical hysterectomy and node dissection instead of RT to avoid radiation fibrosis and to preserve their ovaries. Those patients with early stage disease who delay treatment until fetal maturity can undergo cesarean

section with radical hysterectomy and pelvic node dissection. For those opting for RT, traditional RT with (or without) chemotherapy protocols (which have been previously described) may need modification.[163] Vaginal radical trachelectomy has been successfully performed in a few pregnant patients with early stage cancer.[164-167]

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 (i.e., surgery, concurrent chemo/RT) can yield cures in 80% of women with early stage disease (stages I and II) and in 60% of women with stage III disease. Hopefully, immunization against HPV (using the new vaccines) will prevent persistent infection with certain types of HPV and, thus, is expected to prevent specific HPV cancer in women.[11, 12, 168]

Table 2:

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

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

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

*These studies have been updated (see Discussion).

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