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Cervical Cancer

Clinical Practice Guidelines in Oncology

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Overview

An estimated 12,200 new cases of carcinoma of the uterine cervix (ie, cervical cancer) were diagnosed in the United States in 2012, and 4200 people died of the disease.[1,2] Cervical cancer rates are decreasing among women in the United States, although incidence remains high among Hispanic/Latino, Black, and Asian women.[3-6] However, cervical cancer is a major world health problem for women. In 2008, the global yearly incidence of cervical cancer was 529,800, and the annual death rate was 275,100.[7] It is the third most common cancer in women worldwide,[8,9] with 85% of cases occurring in developing countries, where cervical cancer is the second most frequent cause of cancer death in women.[7] This portion of the NCCN Clinical Practice Guidelines in

Abstract

These NCCN Clinical Practice Guidelines in Oncology for Cervical Cancer focus on early-stage disease, because it occurs more frequently in the United States. After careful clinical evaluation and staging, the primary treatment of early-stage cervical cancer is either surgery or radiotherapy. These guidelines include fertility-sparing and non–fertility-sparing treatment for those with early-stage disease, which is disease confined to the uterus. A new fertility-sparing algorithm was added for select patients with stage IA and IB1 disease..

(JNCCN 2013;11:320–343)

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.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Cervical Cancer are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.**

Disclosures for the Cervical Cancer Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Cervical Cancer Panel members can be found on page 343. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

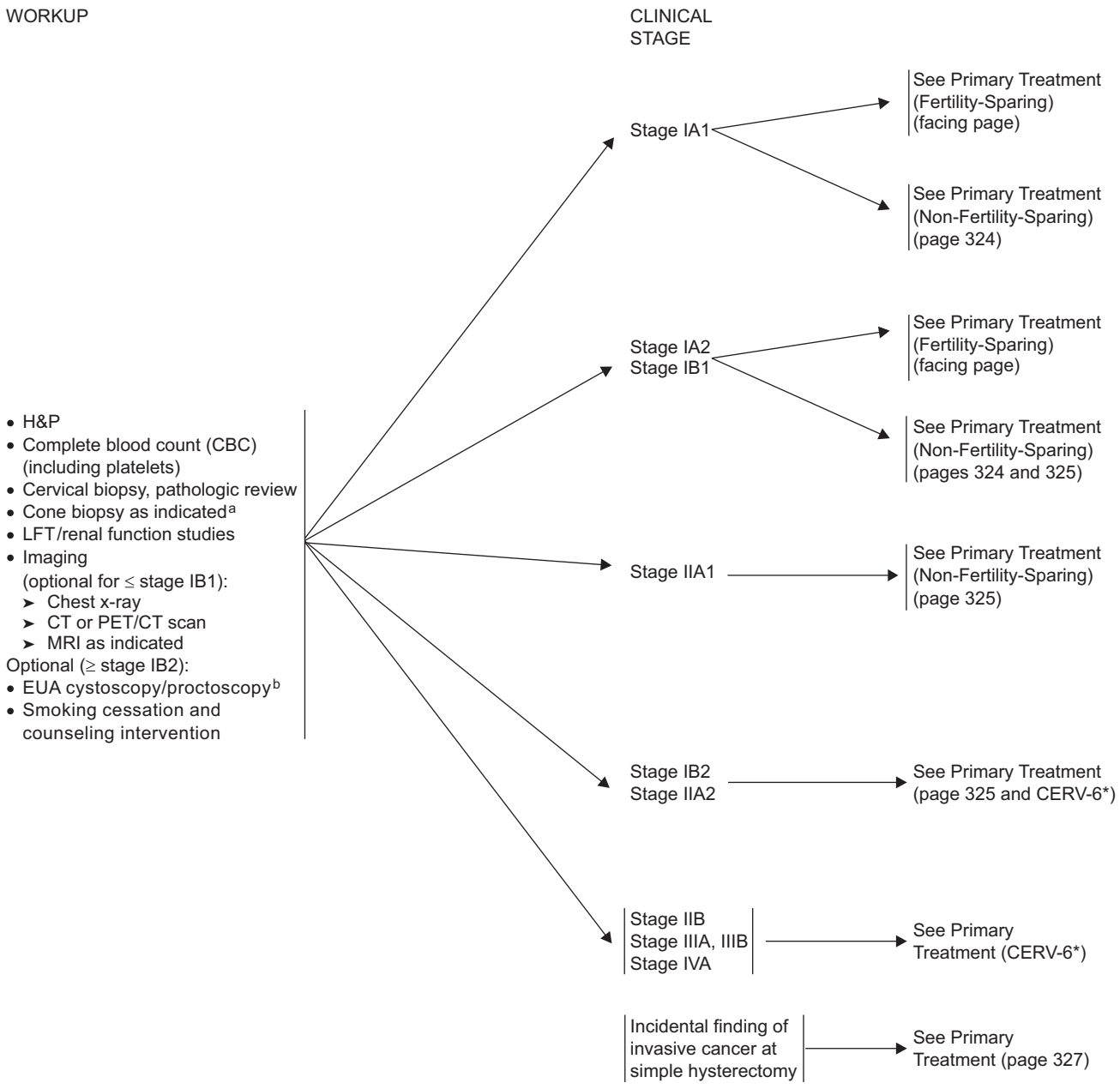
Oncology (NCCN Guidelines) focuses on early-stage disease (ie, disease confined to the uterus), because it occurs more frequently (http://seer.cancer.gov/statfacts/html/cervix.html). The guideline includes fertility-sparing and non–fertility-sparing treatment for those with early-stage disease. The complete version of these guidelines is available on the NCCN Web site (NCCN.org).

Persistent human papillomavirus (HPV) infection is the most important factor in the development of cervical cancer.[10,11] The incidence of cervical cancer seems to be related to the prevalence of HPV in the population. In countries with a high incidence of cervical cancer, the prevalence of chronic HPV is approximately 10% to 20%, whereas the prevalence in low-incidence countries is 5% to 10%.[8] Immunization against HPV prevents infection with the types of HPV against which the vaccine is designed and, thus, is expected to prevent specific HPV cancer in women (see the NCCN Guidelines for Cervical Cancer Screening; to view the most recent version of these guidelines, visit NCCN.org).[12–16] Other epidemiologic risk factors associated with cervical cancer are a history of smoking, parity, oral contraceptive use, early age of onset of coitus, larger number of sexual partners, history of sexually transmitted disease, and chronic immunosuppression.[17] Smoking cessation should be advised in current smokers, and former smokers should continue to avoid smoking (http://smokefree.gov/).

Squamous cell carcinomas account for approximately 80% of all cervical cancers, and adenocarci-

Text continues on p. 331

NCCN Cervical Cancer Panel Members



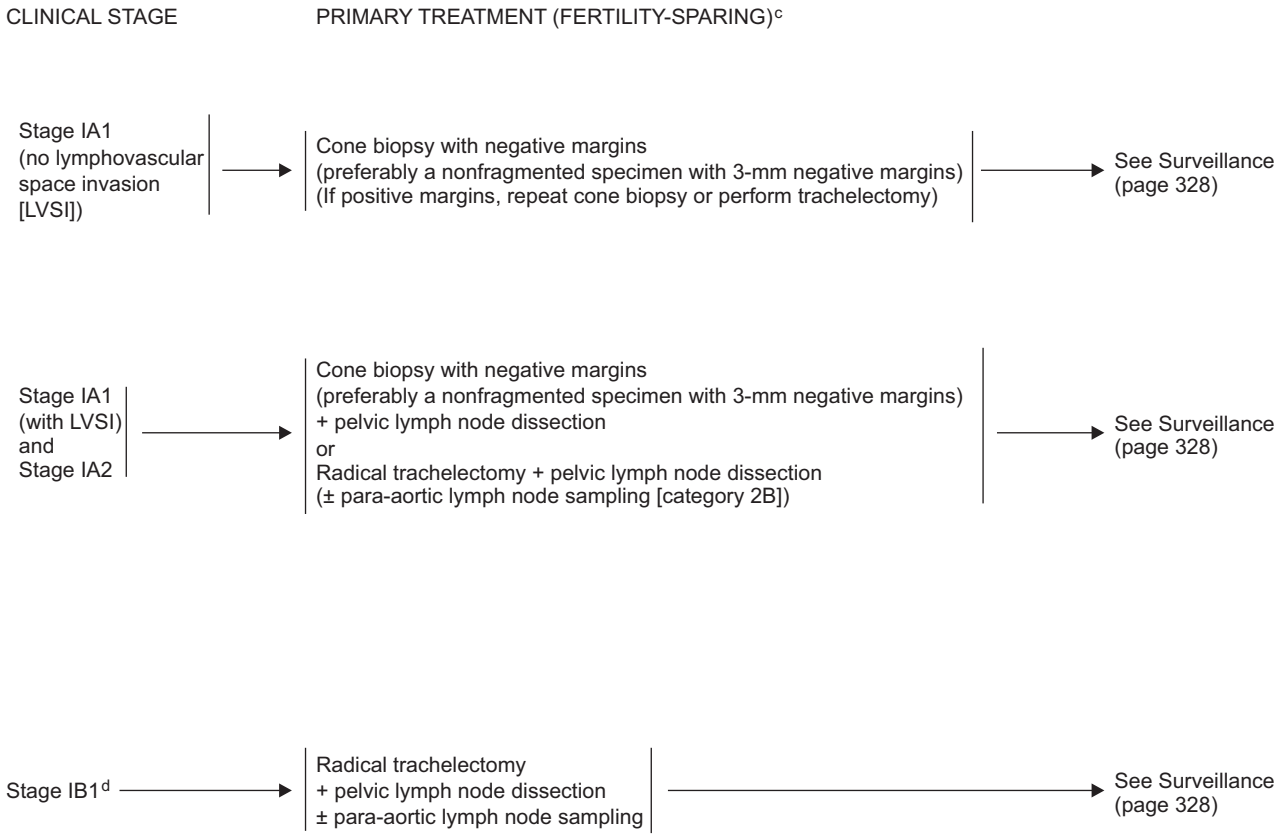
*Available online, in these guidelines, at NCCN.org.

All staging in guideline is based on updated 2010 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.

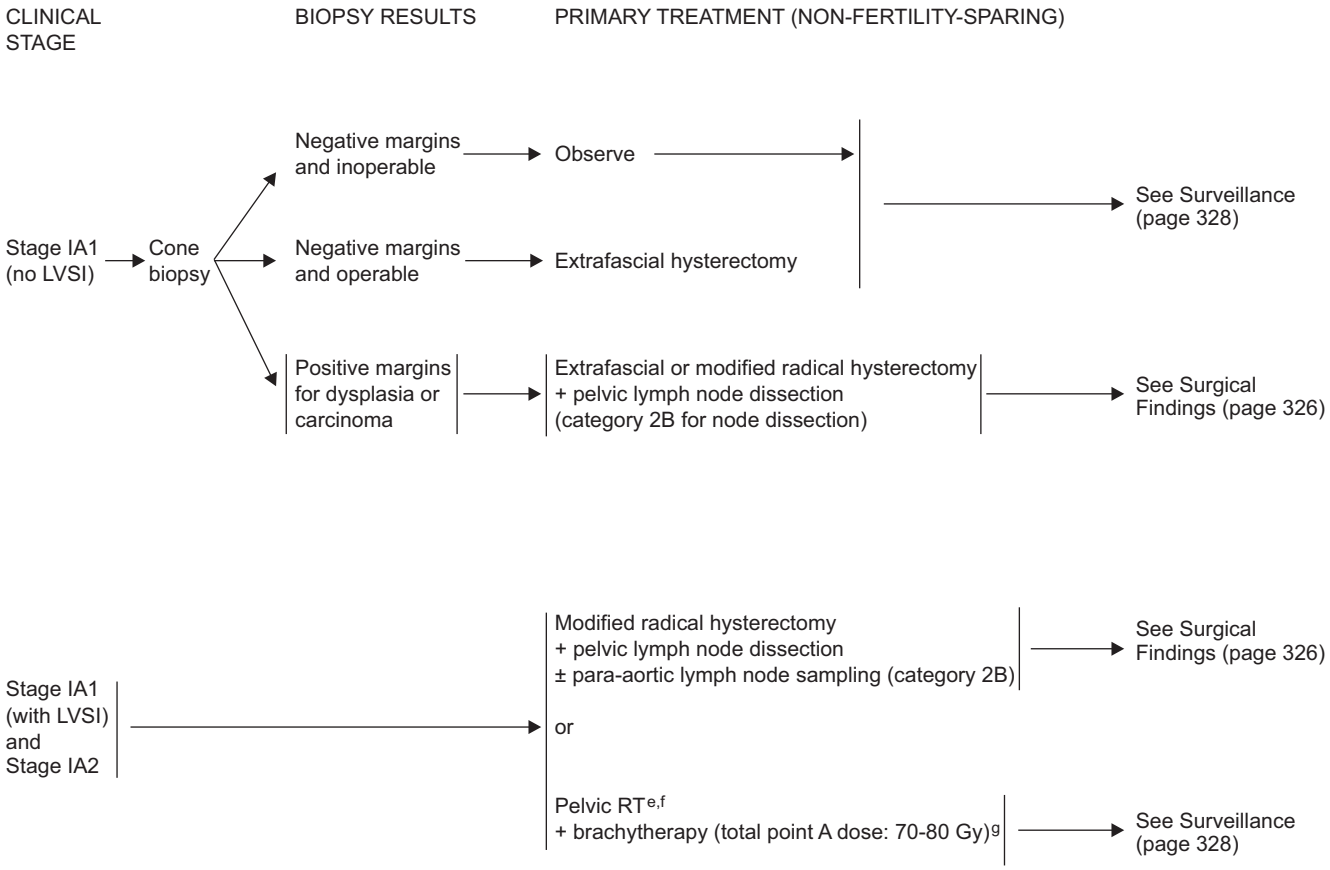
CERV-1

Cervical Cancer, Version 2.2013



[c] No data support a fertility-sparing approach in small cell neuroendocrine tumors or minimal deviation adenocarcinoma (also known as adenoma malignum). Total hysterectomy after completion of childbearing is at the patient's and surgeon's discretion, but is strongly advised in women with continued abnormal Papanicolaou (Pap) smears or chronic persistent HPV infection.

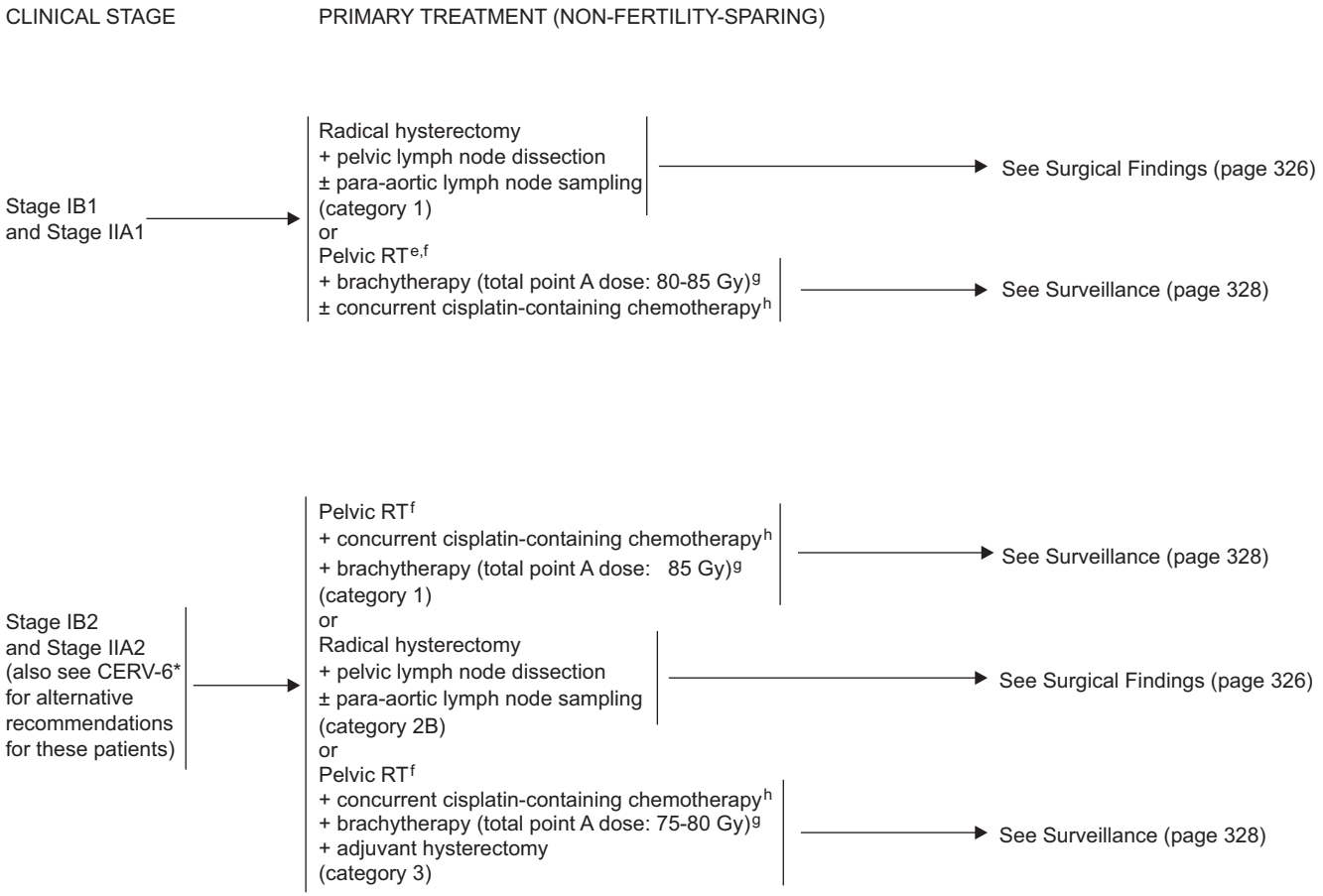
[d] Fertility-sparing surgery for stage IB1 has been most validated for tumors ≤2 cm.



[e] Radiation can be an option for medically inoperable patients or those who refuse surgery.
[f] See Principles of Radiation Therapy for Cervical Cancer (pages 329-330).
[g] 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)

CERV-3

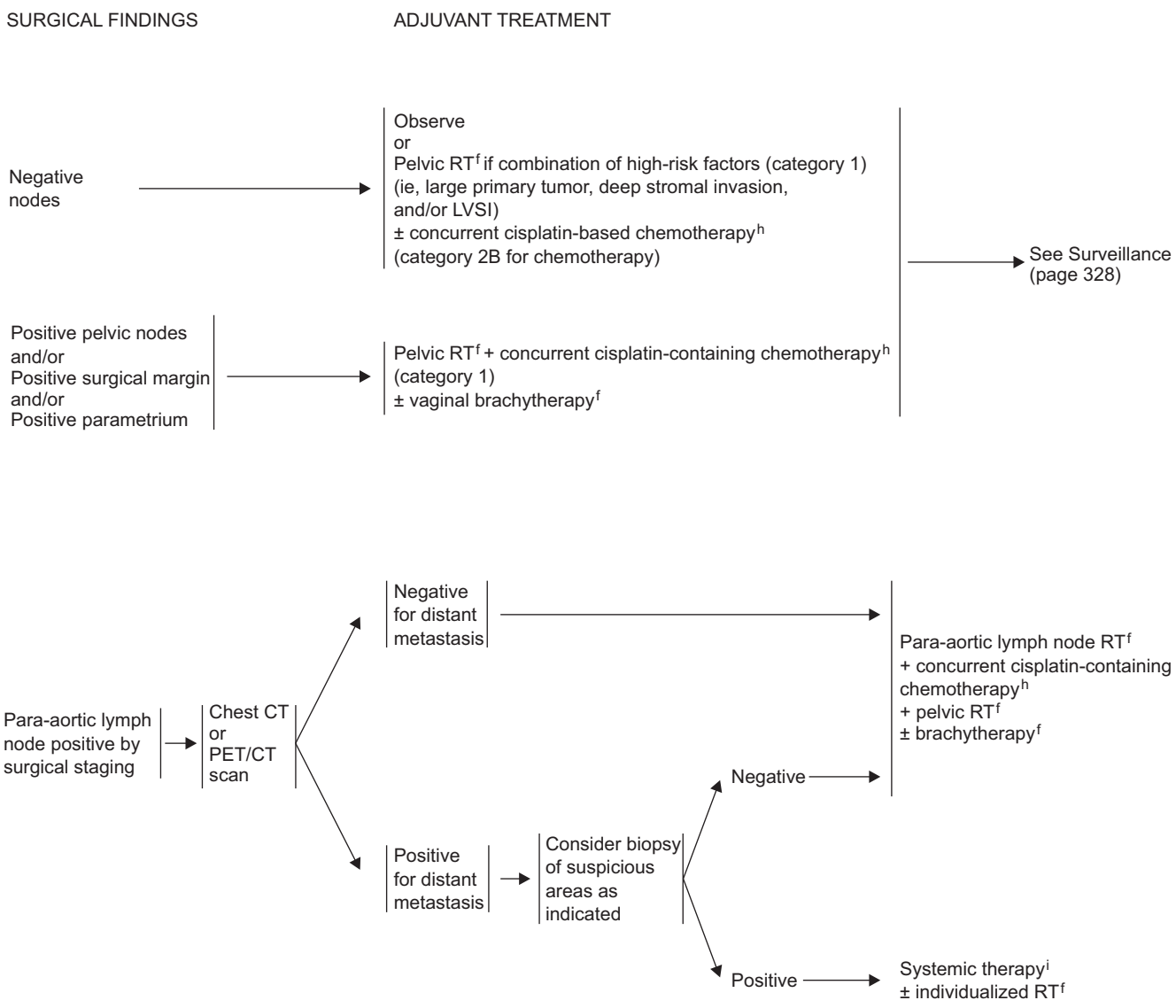
Cervical Cancer, Version 2.2013



*Available online, in these guidelines, at NCCN.org.

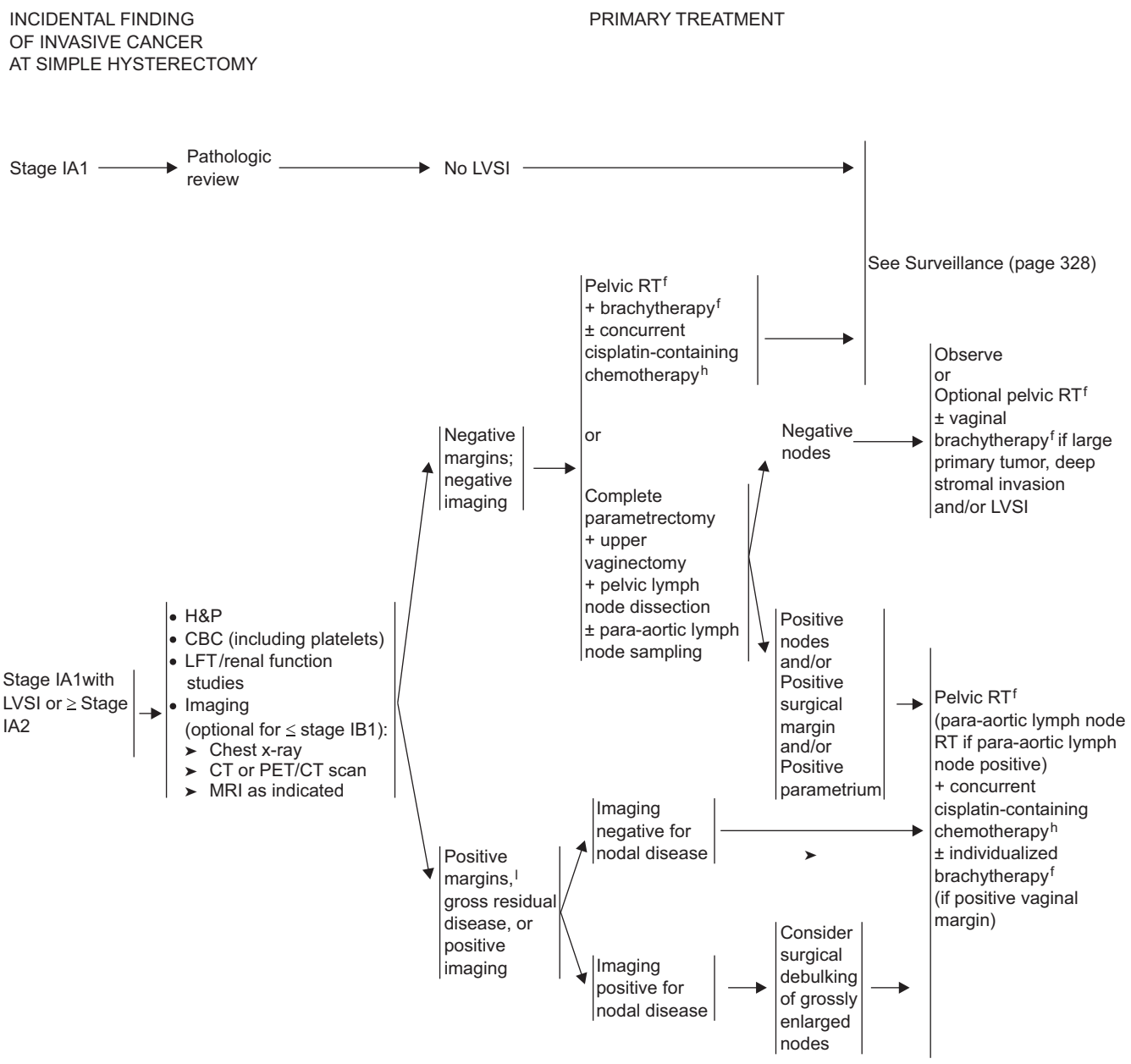
[e] Radiation can be an option for medically inoperable patients or those who refuse surgery.
[f] See Principles of Radiation Therapy for Cervical Cancer (pages 329-330).
[g] These doses are recommended for most patients based on summation of conventional external-beam fractionation and low-dose-rate (40-70 cGy/h) brachytherapy equivalents. Modify treatment based on normal tissue tolerance. (See Discussion)
[h] Concurrent cisplatin-based chemotherapy with RT uses cisplatin as a single agent or cisplatin plus 5-fluorouracil.

CERV-4



[f]See Principles of Radiation Therapy for Cervical Cancer (pages 329-330).
[h]Concurrent cisplatin-based chemotherapy with RT uses cisplatin as a single agent or cisplatin plus 5-fluorouracil.
[i]See Chemotherapy Regimens for Recurrent or Metastatic Cervical Cancer (CERV-B; available online, in these guidelines, at NCCN.org).

Cervical Cancer, Version 2.2013



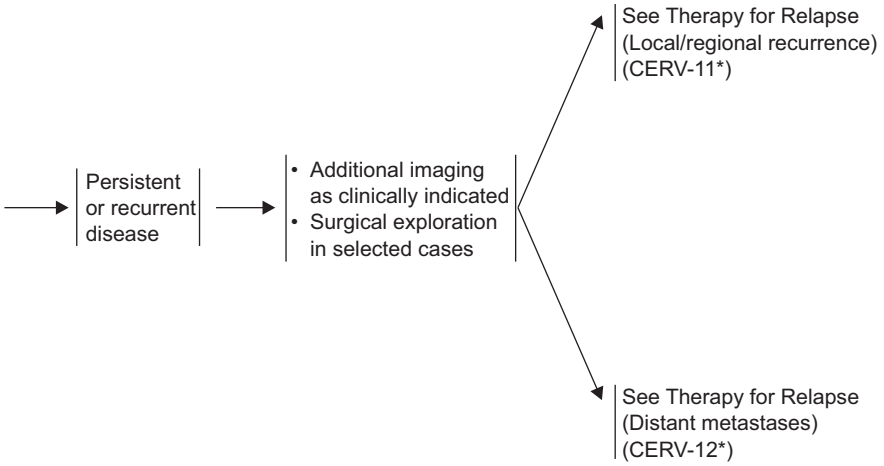
[f]See Principles of Radiation Therapy for Cervical Cancer (pages 329-330).
[h]Concurrent cisplatin-based chemotherapy with RT uses cisplatin as a single agent or cisplatin plus 5-fluorouracil.
[l]Invasive cancer at surgical margin.

CERV-9

SURVEILLANCE[m]

- Interval H&P
  every 3-6 mo for 2 y,
  every 6-12 mo for 3-5 y,
  then annually based on patient's risk of disease recurrence
- Cervical/vaginal cytology annually[n]
  as indicated for the detection of lower genital tract neoplasia
- Imaging (chest radiography, CT, PET, PET/CT, MRI) as indicated based on symptoms or examination findings suspicious for recurrence[o]
- Laboratory assessment (CBC, blood urea nitrogen [BUN], creatinine) as indicated based on symptoms or examination findings suspicious for recurrence
- Recommend use of vaginal dilator after RT
- Patient education regarding symptoms

WORKUP



*Available online, in these guidelines, at NCCN.org.

[m] Salani R, Backes FJ, Fung MF, et al. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. Am J Obstet Gynecol 2011;204:466-478.
[n] Regular cytology can be considered for detection of lower genital tract dysplasia, although its value in detection of recurrent cervical cancer is limited. The likelihood of picking up asymptomatic recurrences by cytology alone is low.
[o] A single PET/CT scan performed at 3-6 months after chemoradiation for locally advanced cervical cancer can be used to identify early or asymptomatic persistence/recurrence. Other imaging studies (such as chest x-ray, CT scan, MRI, and subsequent PET/CT) may also be used to assess or follow recurrence when clinically indicated but are not recommended for routine surveillance. (See Discussion)

PRINCIPLES OF RADIATION THERAPY FOR CERVICAL CANCER

External-Beam Radiation Therapy (EBRT)

- The use of CT-based treatment planning and conformal blocking is considered the 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 also cover the common iliacs. In patients with documented common iliac and/or para-aortic nodal involvement, extended-field pelvic and para-aortic radiotherapy is recommended, 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 to 15 Gy may be considered for limited volumes of gross unresected adenopathy. For most 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 posthysterectomy setting and in treating the para-aortic nodes when 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.

Brachytherapy

- Brachytherapy is a critical component of definitive therapy for all patients with primary cervical cancer who are not candidates for surgery. 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 an intact cervix may be delivered using ovoids, ring, or cylinder brachytherapy (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 posthysterectomy patients (especially those with positive vaginal mucosal surgical margins), vaginal cylinder brachytherapy may be used as a boost to EBRT.

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PRINCIPLES OF RADIATION THERAPY FOR CERVICAL CANCER (cont.)

Radiation Dosing Considerations

- The most common historical dosing parameters for brachytherapy use 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-dimensional image-guided brachytherapy seek to optimize implant dose coverage of tumor, while potentially reducing the dose to adjacent bladder, rectum, and bowel structures.[1] Nonetheless, the weight of experience and tumor control results and most 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 (LDRs). In these provided dose recommendations, for EBRT, the dose is delivered at 1.8 to 2.0 Gy per daily fraction. For brachytherapy, the dose at point A assumes an LDR delivery of 40 to 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 a 6-Gy nominal dose to point A. This scheme results in a nominal HDR point A dose of 30 Gy in 5 fractions, which is generally accepted to be the equivalent of 40 Gy to point A (tumor surrogate dose) using LDR brachytherapy.

Definitive Radiation Therapy for an Intact Cervix

- In patients with an intact cervix (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 to 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 to 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).

Posthysterectomy Adjuvant Radiation Therapy

- After primary hysterectomy, the presence of 1 or more pathologic risk factors may warrant the use of adjuvant radiotherapy. At a minimum, the following should be covered: upper 3 to 4 cm of the vaginal cuff, the parametria, and immediately adjacent nodal basins (such as the external and internal iliacs). For documented nodal metastasis, the superior border of the radiation field should be appropriately increased (as previously described). A dose of 45 to 50 Gy in standard fractionation is generally recommended. Grossly involved unresected nodes may be evaluated for boosting with an additional 10 to 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.

[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;78:67-77.
[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;76:104-109.
[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;5:18-25.

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noma accounts for approximately 20%. In developed countries, the substantial decline in incidence and mortality of squamous cell carcinoma of the cervix is presumed to be the result of effective screening, although racial, ethnic, and geographic disparities exist.[3,4,18,19] However, adenocarcinoma of the cervix has increased over the past 3 decades, probably because cervical cytologic screening methods are less effective for adenocarcinoma.[20–23] 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.[22,24]

By definition, the NCCN 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 carcinomas, 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, CT, MRI, combined PET/CT, and surgical staging are often used to guide treatment options and design.[25–29]

The earliest stages of cervical carcinoma may be asymptomatic or associated with a watery vaginal discharge and postcoital bleeding or intermittent spotting. Often these early symptoms are not recognized 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 the NCCN Guidelines for Cervical Cancer Screening, available at NCCN.org). Cone biopsy (ie, 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 (ie, endocervical canal).[6,23] The College of American Pathologists (CAP) protocol for cervical carcinoma is a useful guide (http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2012/Cervix_12protocol.pdf). This CAP protocol was revised in June 2012 and reflects recent updates in the AJCC/FIGO staging (ie, AJCC Cancer Staging Manual, 7th edition).

Workup for these patients with suspicious symptoms includes history and physical examination, CBC (including platelets), and liver and renal function tests. Recommended radiologic imaging includes chest radiograph, CT, combined PET/CT, and MRI as indicated (eg, to rule out disease high in the endocervix).[26,30] However, imaging is optional for patients with stage IB1 or smaller tumors (see page 322 [CERV-1]). Cystoscopy and proctoscopy are only recommended if bladder or rectal extension is suspected.

Panel members discussed whether laparoscopic and robotic approaches should be recommended for staging and treatment. These techniques are being used more frequently, but long-term outcomes data are not yet available.[31] Laparoscopic staging, lymphadenectomies, and radical hysterectomies can be performed satisfactorily and are used routinely in selected patients in several NCCN Member Institutions.[32–35] Data from studies overseas suggest that recurrence rates are low for laparoscopic radical hysterectomy after 3 to 6 years of follow-up.[36,37] Robotic radical hysterectomy (which is another minimally invasive surgical technique) is currently being performed for patients with early-stage cervical cancer. Potential advantages associated with laparoscopic and robotic approaches include decreased hospital stay and more rapid patient recovery.[38–40]

Staging

Because noninvasive radiographic imaging may not be routinely available in low-resource countries, the FIGO system limits the imaging to chest radiography, intravenous pyelography, and barium enema. The staging of carcinoma of the cervix is largely a clinical evaluation. Although surgical staging is more accurate than clinical staging, it often cannot

be performed in low-resource countries.[28,41,42] The panel currently uses the 2009 FIGO definitions and staging system (see the complete version of these guidelines, available online at NCCN.org).[41,43] This staging system from FIGO has been approved by the AJCC (2010).[44] Early-stage disease includes disease confined to the uterus (eg, stages IA, IB1, and selected IIA1). Advanced disease has traditionally included patients with stage IIB to IVA disease (ie, locally advanced disease). However, many oncologists now include patients with IB2 and IIA2 disease in the advanced disease category.

Importantly, lymphovascular space invasion (LVSI) does not alter the FIGO classification.[41] FIGO did not include LVSI because pathologists do not always agree on whether LVSI is present in tissue samples. Some panel members believe that patients with stage IA1 who have extensive LVSI should be treated using stage IB1 guidelines.

The use of MRI, CT, or combined PET/CT scans may aid in treatment planning but is not accepted for formal staging purposes.[28,42,45,46] 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 (ie, CT and MRI) are used to guide treatment options and design.[30,47,48] 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 early-stage disease and smaller lesions, such as stage IA, IB1, and selected IIA1.[27] The panel agrees that concurrent chemoradiation is generally the primary treatment of choice for stages IB2 to IVA disease based on the results of 5 randomized clinical trials.[49,50] Chemoradiation can also be used for patients who are not candidates for hysterectomy. Although few studies have assessed treatment specifically for adenocarcinomas, they are typically treated in a similar manner to squamous cell carcinomas.[51–53]

Pelvic RT or chemoradiation will invariably lead to ovarian failure in premenopausal women.[54] To preserve intrinsic hormonal function, ovarian transposition may be considered before pelvic RT for select women younger than 45 years with squamous cell cancers.[55,56]

Clinical Trials and Basis for Treatment Selection

A randomized Italian study compared RT alone versus radical hysterectomy and lymph node dissection in patients with clinical early-stage disease.[57] In surgical patients, adjuvant RT was given to those with parametrial extension, less than 3 cm of uninvolved cervical stroma, positive margins, 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.

Concurrent chemoradiation, using cisplatin-based chemotherapy (either cisplatin alone or cisplatin/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 the complete version of these guidelines, available online at NCCN.org).[58–63] Although chemoradiation is tolerated, acute and long-term side effects have been reported.[64–66] Some oncologists prefer concurrent single-agent cisplatin chemoradiation over cisplatin plus 5-FU chemoradiation, because the latter may be more toxic.[50,67] Concurrent carboplatin or nonplatinum chemoradiation regimens are options for patients who may not tolerate cisplatin-containing chemoradiation.[64,68–72] Note that when concurrent chemoradiation is used, the chemotherapy is typically given when the external-beam pelvic radiation is administered.[50]

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 the complete version of these guidelines, available online at NCCN.org). A new fertility-sparing algorithm was added in 2012 for select patients with stage IA and IB1 disease (see page 323 [CERV-2]). Fertility-sparing surgery is generally not recommended for patients with small cell neuroendocrine tumors or those with minimal deviation adenocarcinoma because of a lack of data.

Stage IA1 Disease: Recommended options for stage IA1 depend on the results of cone biopsy and on whether patients 1) want to preserve their fertility; 2) are medically operable; or 3) have LVSI (see pages 323 and 324 [CERV-2 and CERV-3]). Node dissection is performed on all cancers greater than stage

IA1. The extent of the lymph node dissection depends on whether pelvic nodal disease and/or LVSI is present and the size of the tumors.

Fertility-Sparing: For patients who desire fertility preservation, cone biopsy with or without pelvic lymph node dissection is recommended.[73,74] For patients with negative margins after cone biopsy, observation is an option for select patients without LVSI if they desire fertility preservation. For patients with positive margins after cone biopsy, options include either a radical trachelectomy or a repeat cone biopsy. For patients with LVSI, radical trachelectomy and pelvic lymph node dissection is recommended with (or without) para-aortic lymph node sampling (category 2B for para-aortic lymph node sampling; see page 323 [CERV-2]).[75–79] Pelvic lymph node dissection is recommended for patients with LVSI who have negative margins after cone biopsy.

After childbearing is complete, hysterectomy can be considered for patients who have had either radical trachelectomy or a cone biopsy for early-stage disease if they have chronic persistent HPV infection, they have persistent abnormal Pap tests, or they desire this surgery. Note that trachelectomy (also known as *cervicectomy*) refers to removal of the cervix and upper vagina (ie, uterus remains intact).

One 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 was higher.[80] For young (<45 years of age) premenopausal women with early-stage squamous cell carcinoma who opt for ovarian preservation (ie, hysterectomy only), the rate of ovarian metastases is low.[81,82]

Non–Fertility-Sparing: For medically operable patients who do not desire fertility preservation, extrafascial (ie, simple or total) hysterectomy is commonly recommended for patients without LVSI and with either negative margins after cone biopsy or with positive margins for dysplasia. For patients with positive margins for carcinoma, modified radical hysterectomy is recommended with pelvic lymph node dissection (category 2B for node dissection; see page 324 [CERV-3]). If LVSI is present, then modified radical hysterectomy with lymph node dissection is recommended (category 2B for para-aortic lymph node sampling only). Para-aortic node dissection is indicated for patients with known or suspected pelvic nodal disease. For patients with negative margins after cone biopsy, observation is recommended for those who are medically inoperable or those who refuse surgery.

Stage IA2 Disease:

Fertility-Sparing: Recommended options for stage IA2 depend on whether patients want to preserve their fertility and whether they are medically operable. For patients who wish to preserve their fertility, radical trachelectomy and pelvic lymph node dissection with (or without) para-aortic lymph node sampling (category 2B for para-aortic node sampling) is recommended. Cone biopsy followed by observation is another option if the margins are negative and pelvic lymph node dissection is negative.

Non–Fertility-Sparing: For medically operable patients who do not desire fertility preservation, recommended treatment includes either surgery or RT (see page 324 [CERV-3]). The recommended surgical option is radical hysterectomy and pelvic lymph node dissection with (or without) para-aortic lymph node sampling (category 2B for para-aortic node sampling). Para-aortic node dissection is indicated for patients with known or suspected pelvic nodal disease.

Pelvic radiation with brachytherapy (total point A dose: 70–80 Gy) is a treatment option for patients who are medically inoperable or refuse surgery and do not desire fertility preservation.[83] 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 "Radiation Therapy," page 336).

Stage IB and IIA1 Disease: Depending on their stage and disease bulk, patients with stage IB or IIA1 tumors can be treated with surgery or RT (with or without concurrent chemoradiation). Fertility-sparing surgery is only recommended for select patients with stage IB1 disease (see the next section). A combined PET/CT scan can be performed to rule out extrapelvic disease before deciding how to treat these patients. The Gynecologic Oncology Group (GOG) considers that surgical staging is an option for patients with advanced cervical cancer. Radiologic imaging is recommended for assessing stage IB2 tumors.

Stage IB1:

Fertility-Sparing: For patients who desire fertility preservation, radical trachelectomy and pelvic lymph node dissection with (or without) para-aortic lymph node sampling is an option for those with stage IB1 disease, but typically only for tumors 2 cm or less (see page 323 [CERV-2]).[76–79,84,85] Tumors that are 2 to 4 cm are left to the surgeon's discretion. However, some surgeons suggest that a 2-cm cutoff may be used for vaginal trachelectomy, whereas a 4-cm cutoff may be used for abdominal (eg, laparotomy, laparoscopic, robotic) trachelectomy. In one study, oncologic outcomes were similar after 4 years when comparing radical trachelectomy with radical hysterectomy for patients with stage IB1 cervical carcinoma.[85]

Stage IB and IIA1:

Non–Fertility-Sparing: The surgical option includes radical hysterectomy plus bilateral pelvic lymph node dissection with (or without) para-aortic lymph node sampling.[57,86] Panel members feel that surgery is the most appropriate option for patients with stage IB1 or IIA1 disease, whereas concurrent chemoradiation is the most appropriate option for those with stage IB2 or IIA2 disease based on randomized trials.[57–59,61,62] Thus, the surgical option is category 1 for patients with stage IB1 or IIA1 disease.[57] Para-aortic node dissection may be performed for patients with larger tumors and suspected or known pelvic nodal disease. Some panel members feel that a pelvic lymph node dissection should be performed first, and if negative, then the radical hysterectomy should be performed. If the lymph nodes are positive, then the hysterectomy should be abandoned; these patients should undergo chemoradiation.

Recent data suggest that sentinel lymph node biopsy may be useful for decreasing the need for pelvic lymphadenectomy in patients with early-stage cervical cancer.[87,88] However, panel members believe the technique is not yet sufficiently validated for routine use.[89–92] The role of sentinel lymph node biopsy continues to be evaluated in large prospective trials.[93–96] 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.

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. Pelvic radiation is recommended (category 1) with (or without) concurrent cisplatin-based chemotherapy (category 2B for chemotherapy) for patients with stage IA2, IB1, or IIA1 disease who have *negative* lymph nodes after surgery but have large primary tumors, deep stromal invasion, and/or LVSI (see page 326 [CERV-5]).[97–101]

Adjuvant pelvic RT alone versus no further therapy was tested in a randomized trial (GOG 92) of selected patients with node-negative stage IB carcinoma of the cervix after hysterectomy and pelvic lymphadenectomy.[101] Patients were considered to be intermediate risk and were eligible for this trial 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 adjuvant RT versus 79% for the group not receiving adjuvant treatment. After long-term follow-up (12 years), an updated analysis confirmed that adjuvant pelvic RT increased progression-free survival; a clear trend toward improved overall survival was noted (P=.07).[97] The role of concurrent cisplatin/RT in these intermediate-risk patients is currently being evaluated in an international phase III randomized trial (GOG 263).

Postoperative pelvic radiation with concurrent cisplatin-containing chemotherapy (category 1)[60] with (or without) vaginal brachytherapy is recommended for patients with positive pelvic nodes, positive surgical margin, and/or positive parametrium; these patients are considered to be high risk (see page 326 [CERV-5]). Vaginal brachytherapy may be a useful boost for those with positive vaginal mucosal margins. Adjuvant concurrent chemoradiation significantly improves overall survival for these high-risk patients with early-stage disease (those with positive pelvic nodes, parametrial extension, and/or positive margins) who undergo radical hys-

terectomy and pelvic lymphadenectomy.[60] 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.[60]

Depending on the results of primary surgery, imaging (chest CT or combined PET/CT scan) may be recommended to determine whether distant metastases are present (see the complete version of these guidelines, available online at NCCN.org). For patients without distant metastases, recommended treatment is extended-field RT (including pelvic and para-aortic lymph nodes) with concurrent cisplatin-based chemotherapy and with (or without) brachytherapy. Although neoadjuvant chemotherapy followed by surgery has been used in areas where RT is not available, data suggest no improvement in survival when compared with surgery alone for early-stage cervical cancer.[102–104] The panel does not recommend the use of neoadjuvant chemotherapy.

Surveillance

The panel agrees with the Society of Gynecologic Oncology's new recommendations for posttreatment surveillance.[105] The recommended surveillance is based on the patient's risk for recurrence and personal preferences. History and physical examination is recommended every 3 to 6 months for 2 years, every 6 to 12 months for another 3 to 5 years, and then annually (see page 328 [CERV-10]). High-risk patients can be assessed more frequently (eg, every 3 months for the first 2 years) than low-risk patients (eg, every 6 months).

Annual cervical/vaginal cytology tests can be considered as indicated for detection of lower genital tract dysplasia (eg, for those who have had fertility-sparing surgery). 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 or II cervical cancer who were asymptomatic after treatment.[105–107] 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.[108] Patient education regarding symptoms suggestive of recurrence is recommended (eg, vaginal discharge; weight loss; anorexia; pain in the pelvis, hips, back, or legs; persistent coughing). Smoking cessation and abstinence should be encouraged.[105]

Imaging is not routinely recommended for surveillance but may be indicated in patients with symptoms or findings that are suspicious for recurrence.[105,108,109] In patients at high risk for locoregional (central or para-aortic) failure, a combined PET/CT scan (eg, 3–6 months after treatment) or other radiologic imaging may be useful for detecting asymptomatic disease that is potentially curable.[110–112] Many other tests remain optional based on clinical indications, such as semiannual CBCs, blood urea nitrogen, and serum creatinine determinations (see page 328 [CERV-10]). Patients with persistent or recurrent disease need to be evaluated (see the complete version of these guidelines, available online at NCCN.org).[113]

Patients treated with RT are prone to vaginal stenosis, which can impair sexual function. Anecdotal evidence suggests that vaginal dilators may be used to prevent or treat vaginal stenosis.[114] Dilator use can start 2 to 4 weeks after RT is completed and can be performed indefinitely (http://www.mskcc.org/patient_education/_assets/downloads-english/571.pdf).

Cervical cancer survivors are at risk for second cancers.[115] Reports suggest that patients who undergo RT for pelvic cancers are at risk for radiation-induced second cancers, especially at radiated sites near the cervix (eg, colon, rectum/anus, urinary bladder); therefore, careful surveillance is appropriate for these patients.[116,117]

Drug Reactions

Virtually all drugs have the potential to cause adverse reactions, either during or after infusion.[118] Allergic reactions (ie, true drug allergies) are more common with platinum agents (eg, cisplatin).[119,120] Management of drug reactions is discussed in the NCCN Guidelines for Ovarian Cancer (to view the most recent version of these guidelines, visit NCCN.org).[119]

Incidental Cervical Cancer

Invasive cervical carcinoma is sometimes found incidentally after extrafascial hysterectomy. Workup for these patients includes history and physical examination, CBC (including platelets), and liver and re-

nal function tests. Recommended radiologic imaging includes chest radiography, CT, or combined PET/CT; MRI may be performed if indicated to rule out gross residual disease. However, imaging is optional for patients with stage IB1 or smaller tumors (see page 327 [CERV-9]).

No definitive data are available to guide the appropriate adjuvant treatment of these patients. Surveillance is recommended for patients with stage IA1 cervical cancer who do not have LVSI. For patients with either stage IA1 with LVSI or with stage IA2 or higher tumors (pathologic findings), the panel believes that a reasonable treatment schema 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 is recommended (see page 327 [CERV-9]).

If margins or imaging results are negative in stage IA2 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. Typically, observation is recommended for patients with negative lymph nodes. However, pelvic radiation with (or without) vaginal brachytherapy is an option if they have high-risk factors (ie, large primary tumor, deep stromal invasion, LVSI; see page 327 [CERV-9]).[101] 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

RT is often used in the management of patients with cervical cancer either as 1) definitive therapy for those with locally advanced disease or for those who are poor surgical candidates, or 2) adjuvant therapy after radical hysterectomy for those who have one or more pathologic risk factors (eg, positive lymph nodes, parametrial infiltration, positive surgical margins, large tumor size, deep stromal invasion, LVSI).

The algorithm provides general RT dosage recommendations, which are expanded in Principles of Radiation Therapy (see page 329 [CERV-A]). These RT dosages should not be interpreted as stand-alone recommendations, because RT techniques and clinical judgment are essential parts of developing an appropriate treatment regimen. Contemporary imaging studies must be correlated with careful assessment of clinical findings to define tumor extent, especially with regard to vaginal or parametrial extension.

RT Planning

Technologic advances in imaging, computer treatment planning systems, and linear accelerator technology have enabled more precise delivery of radiation doses to the pelvis. However, physical accuracy of dose delivery must be matched with a clear understanding of tumor extent, potential pathways of spread, and historical patterns of locoregional recurrence to avoid geographic misses.

CT-based treatment planning with conformal blocking and dosimetry is considered standard care for external-beam RT. Brachytherapy is a critical component of definitive therapy in patients with cervical cancer who are not candidates for surgery (ie, those with an intact cervix); it may also be used as adjuvant therapy. Brachytherapy is typically combined with external-beam radiation in an integrated treatment plan.

For patients with locally advanced cancers, initial RT of 40 to 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 (http://www.americanbrachytherapy.org/guidelines/cervical_cancer_taskgroup.pdf).[49]

For lesions in the lower third of the vagina, the inguinal lymph nodes must be treated. The use of extended-field radiation to treat occult or macroscopic para-aortic lymph node disease must be carefully planned to ensure an adequate dose (45 Gy for microscopic disease) without exceeding bowel, spinal cord, or renal tolerances.[121] General recommendations for radiation volumes and doses are discussed in the algorithm (see page 329 [CERV-A]).

Intensity-modulated RT (IMRT) is becoming more widely available; however, issues regarding target definition, patient and target immobilization, tissue deformation, and reproducibility remain to be

validated.[122–128] The role of IMRT in cervical cancer continues to be evaluated in several prospective multicenter clinical trials.[129]

Several retrospective analyses suggest that prolonged RT treatment duration has an adverse effect on outcome.[130–134] 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 performed, it is generally accepted that the entire RT course (including both external-beam RT 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 RT 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 (ie, diarrhea, bladder irritation, fatigue) occur to some degree in most patients undergoing radiation and are typically magnified by concurrent chemotherapy. However, acute effects can often be managed with medications and supportive care, and they generally resolve soon after completion of radiation. To avoid treatment-related menopause, ovarian transposition can be considered before pelvic RT in select young patients (<45 years with early-stage disease).[54–56]

After therapy for cervical cancer, late side effects may include potential injury to bladder, rectum, bowel, and pelvic skeletal structures.[135] The risk of major complications (ie, obstruction, fibrosis/necrosis, fistula) is related to the volume, total dose, dose per fraction, and specific intrinsic radiosensitivity of the normal tissue that is irradiated.[121,136] Careful blocking to minimize normal tissue exposure while not compromising tumor coverage is critical to achieving optimal outcomes. In addition, patient-related conditions (ie, 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 to 50 Gy. Gross disease in the parametria or unresected nodes may be treated with tightly contoured external-beam boosts to 60 to 65 Gy. Intracavitary brachytherapy boosts require attention to proper placement of the applicators within the uterus and against the cervix and vaginal apex, and appropriate packing to maximally displace the bladder and rectum.

Cervical Cancer and Pregnancy

Cervical cancer is the most frequently diagnosed gynecologic malignancy in pregnant women; however, most women have stage I disease.[137–140] Invasive cervical cancer during pregnancy creates a clinical dilemma and requires multidisciplinary care.[137,141] Women must make the difficult decision either to delay treatment until documented fetal maturity or to undergo immediate treatment based on their stage of disease.[138,141] Women who delay treatment until fetal maturity should have their children delivered by cesarean section.[140,142,143] Vaginal radical trachelectomy has been successfully performed in a few pregnant patients with early-stage cervical cancer.[144–147]

Patients with early-stage disease may prefer to have radical hysterectomy and node dissection instead of RT to avoid radiation fibrosis and preserve their ovaries. Patients with early-stage disease who delay treatment until fetal maturity can undergo cesarean section with concurrent radical hysterectomy and pelvic node dissection. For those choosing RT, traditional RT with (or without) chemotherapy protocols (described previously) may need to be modified.[140]

Summary

Cervical cancer is decreasing in the United States because of the wide use of screening; however, it is increasing in developing countries (≈275,000 deaths per year), because screening is not available to many women. Effective treatment for cervical cancer (including surgery and concurrent chemoradiation) can yield cures in 80% of women with early-stage disease. The hope is that immunization against HPV (using vaccines) will prevent persistent infection by the types of HPV against which the vaccine is designed and will therefore prevent specific HPV cancer in women.[15,16,148]

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Individual Disclosures for the NCCN Cervical Cancer Panel

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