NCCN Guidelines® Insights

Cervical Cancer, Version 2.2015

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Cervical Cancer provide interdisciplinary recommendations for treating cervical cancer. These NCCN Guidelines Insights summarize the NCCN Cervical Cancer Panel's discussion and major guideline updates from 2014 and 2015. The recommended systemic therapy options for recurrent and metastatic cervical cancer were amended upon panel review of new survival data and the FDA's approval of bevacizumab for treating late-stage cervical cancer. This article outlines relevant data and provides insight into panel decisions regarding various combination regimens. Additionally, a new section was added to provide additional guidance on key principles of evaluation and surgical staging in cervical cancer. This article highlights 2 areas of active investigation and debate from this new section: sentinel lymph node mapping and fertility-sparing treatment approaches. (J Natl Compr Canc Netw 2015;13:395–404)

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Cervical Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Cervical Cancer

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PRINCIPLES OF EVALUATION AND SURGICAL STAGING¶

Types of Resection and Appropriateness for Treatment of Cervical Cancer

- Treatment of cervical cancer is stratified by stage as delineated in the Guideline.
- Microinvasive disease, defined as FIGO stage IA-1 with no lymphovascular invasion (LVSI), has less than a 1% chance of lymphatic metastasis and may be managed conservatively with cone biopsy for preservation of fertility (with negative margins) or with simple hysterectomy when preservation of fertility is not desired or relevant. The intent of a cone biopsy is to remove the ectocervix and endocervical canal *en bloc* using a scalpel. This provides the pathologist with an intact, non-fragmented specimen without electrosurgical artifact, which facilitates margin status evaluation. If a loop electrosurgical excision procedure (LEEP) is chosen for treatment, the specimen should not be fragmented, and care must be undertaken to minimize electrosurgical artifact at the margins. The shape and depth of the cone biopsy may be tailored to the size, type, and location of the neoplastic lesion. For example, if there is concern for invasive adenocarcinoma versus adenocarcinoma *in situ* in the cervical canal, the cone biopsy would be designed as a narrow, long cone extending to the internal os in order not to miss possible invasion in the endocervical canal. Cone biopsy is indicated for triage and treatment of small cancers where there is no likelihood of cutting across gross neoplasm. In cases of stage IA1 with LVSI, a conization (with negative margins) with laparoscopic pelvic SLN mapping (category 2B for SLN)/lymphadenectomy is a reasonable strategy.

- Radical hysterectomy with bilateral pelvic lymph node dissection (with or without SLN mapping [category 2B for SLN]) is the preferred treatment for FIGO stage IA-2, IB, and IIA lesions when fertility preservation is not desired. Radical hysterectomy results in resection of much wider margins compared with a simple hysterectomy, including removal of parts of the cardinal and uterosacral ligaments and the upper 1–2 cm of the vagina; in addition, pelvic and sometimes para-aortic nodes are removed. Radical hysterectomy procedures may be performed either via laparotomy or laparoscopy, and the laparoscopy approach may be either with conventional or robotic techniques. The Querleu & Morrow classification system[1] is a modern surgical classification that describes degree of resection and nerve preservation in 3-dimensional planes of resection.[2] Procedural details for the most commonly used types of hysterectomy are described in Table 1 (see CERV-A 5 of 7).

- The radical vaginal trachelectomy with laparoscopic lymphadenectomy procedure (with or without SLN mapping [category 2B for SLN]) offers a fertility-sparing option for carefully selected individuals with stage IA-2 or stage IB-1 lesions of 2 cm diameter or less. The cervix, upper vagina, and supporting ligaments are removed as with a type B radical hysterectomy, but the uterine corpus is preserved. In the more than 300 subsequent pregnancies currently reported, there is a 10% likelihood of second trimester loss, but 72% of patients carry their gestation to 37 weeks or more.[3] The abdominal radical trachelectomy has emerged as a reasonable fertility-sparing strategy. It provides larger resection of parametria than the vaginal approach,[4] is suitable for select stage IB1 cases, and has been utilized in lesions up to 4 cm in diameter. The operation mimics a type C radical hysterectomy.*,[1,2,5-8]

*For a description of a type C radical hysterectomy See Table 1 (CERV-A 5 of 7)
¶References appearing on CERV-A 1 of 7 can be accessed online, in these guidelines, at NCCN.org.

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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.

Overview

The NCCN Cervical Cancer Panel is an interdisciplinary group of representatives from NCCN Member Institutions consisting of specialists in gynecologic oncology, medical oncology, radiation oncology, and pathology. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Cervical Cancer include evidence-based recommendations for the assessment and management of cervical cancer. The panel updates the NCCN Guidelines on an annual basis, with additional interim updates as appropriate. Notable recent updates include modifications to the recommended systemic therapy regimens for recurrent or metastatic cervical cancer, and new information and guidance related to surgical staging and evaluation. The latest full version of these guidelines is available online at NCCN.org.

Background

Carcinoma of the uterine cervix, commonly known as cervical cancer, remains a significant public health

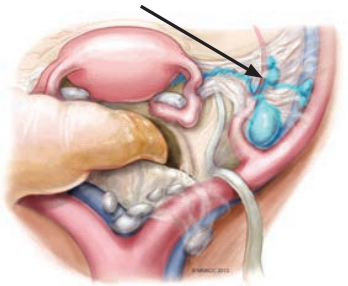
PRINCIPLES OF EVALUATION AND SURGICAL STAGING¶

Sentinel Lymph Node Mapping for Cervical Cancer:

- SLN mapping as part of the surgical management of select stage I cervical cancer is considered in gynecologic oncology practices worldwide. While this technique has been used in tumors up to 4 cm in size, the best detection rates and mapping results are in tumors less than 2 cm.[9-12] This simple technique utilizes a direct cervical injection with dye or radiocolloid Technetium-99 (99Tc) into the cervix, usually at 2 or 4 points as shown in Figure 1 (below). The SLNs are identified at the time of surgery with direct visualization of colored dye, a fluorescent camera if indocyanine green (ICG) was used, or a gamma probe if 99Tc was used. SLNs following a cervical injection are commonly located medial to the external iliac vessels, ventral to the hypogastric vessels, or in the superior part of the obturator space (Figure 2). SLNs usually undergo ultrastaging by pathologists, which allows for higher detection of micrometastasis that may alter postoperative management.[2,13]

Figure 1: Options of SLN Cervical Injection Sites†

Figure 2: SLNs (blue, arrow) After Cervical Injection Are Commonly Located Medial to the External Iliac, Ventral to the Hypogastric, or in the Superior Part of the Obturator Space†



†Figures 1 and 2 are reproduced with permission from Memorial Sloan Kettering Cancer Center. © 2013 Memorial Sloan Kettering Cancer Center.
¶References appearing on CERV-A 3 of 7 can be accessed online, in these guidelines, at NCCN.org.

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concern for women worldwide despite the existence of highly effective prevention and screening methods. Research has shown that persistent human papillomavirus (HPV) infection is the most important factor in the development of cervical cancer.[1,2] Major strides have been made in cervical cancer prevention with the development of vaccines that immunize against multiple oncogenic HPV strains.[3–5] In addition to cytology-based screening methods (ie, the Papanicolaou or "Pap" test), screening tests that detect high-risk HPV infections provide a valuable tool that can lead to early detection and treatment of precancerous lesions and cervical cancer.

Despite these advancements, cervical cancer is the fourth most common cancer among women worldwide.[6] In 2012, an estimated 528,000 new cases of cervical cancer were diagnosed and 266,000 women died from the disease.[6] Importantly, cervical cancer has a dramatically uneven impact across the globe; more than 85% of all cervical cancers and cervical cancer–related deaths occur in developing countries.[6–9] Although cervical cancer rates are generally decreasing among women in developed countries because of the availability of effective prevention and screening methods, incidence in the United States remains high among Hispanic/Latino, black, and Asian women.[10–14] An estimated 12,900 new cases of cervical cancer are expected in the United States in 2015, and 4100 people will die of the disease.[15] Cervical cancer can often be successfully treated when detected early. The current 5-year survival rates for women with early-stage, locally advanced, and metastatic cervical cancers are 91%, 57%, and 16%, respectively.[16]

Newly-Approved Combination Regimens for Advanced Disease

Recent research has focused on systemic regimens that are able to improve survival for patients with persistent, recurrent, or metastatic cervical cancer.

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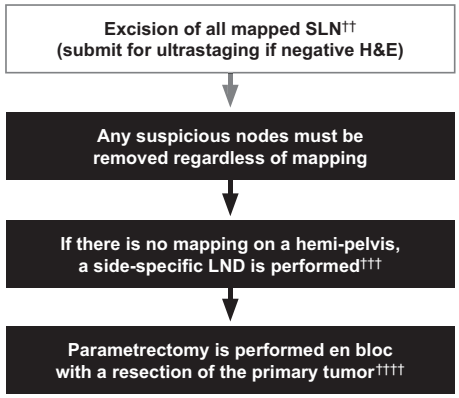
PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED¶

The key to a successful SLN mapping (category 2B) is the adherence to the SLN algorithm, which requires the performance of a side-specific nodal dissection in cases of failed mapping and removal of any suspicious or grossly enlarged nodes regardless of mapping (Figure 3)

Figure 3: Surgical/SLN Mapping Algorithm for Early-Stage Cervical Cancer†



H&E: Hematoxylin and eosin staining
LND: Lymphadenectomy
SLN: Sentinel lymph node

†Reproduced with permission from Cormier B, Diaz JP, Shih K, et al. Establishing a sentinel lymph node mapping algorithm for the treatment of early cervical cancer. Gynecol Oncol. 2011 Aug;122:275-280.
††Intracervical injection with dye, 99m technetium, or both.
†††Including interiliac/subaortic nodes.
††††Exceptions made for select cases (see CERV-A 1 of 7).
¶References appearing on CERV-A 4 of 7 can be accessed online, in these guidelines, at NCCN.org.

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CERV-A
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Historically, cisplatin has been considered the most active and effective agent for metastatic cervical cancer.[17] However, most patients who develop metastatic disease have typically received concurrent cisplatin-based chemoradiation as a primary treatment regimen and may no longer be sensitive to single-agent platinum therapy. Combination platinum-based regimens are preferred over single agents in the metastatic disease setting based on several randomized phase III trials.[18,19] Cisplatin is a standard backbone of combination chemotherapy regimens, and cisplatin-based chemotherapy regimens (eg, cisplatin/paclitaxel/bevacizumab; cisplatin/paclitaxel; cisplatin/topotecan) have been extensively investigated in clinical studies.[18–23] Alternatives to the cisplatin backbone (eg, topotecan/paclitaxel,[23] carboplatin/paclitaxel[24,25]) have also been investigated to determine whether these alternatives can further improve survival and tolerability compared with standard regimens.

A recent randomized phase III trial from the Gynecologic Oncology Group (GOG 240) examined 2 primary questions: (1) whether topotecan/paclitaxel was superior to the standard cisplatin/paclitaxel regimen for treating persistent, recurrent, or metastatic cervical cancer; and (2) whether the addition of bevacizumab to cisplatin/paclitaxel or topotecan/paclitaxel could improve survival. Accordingly, this trial included patients with advanced cervical cancer (n=452) who received 1 of 4 possible combination regimens: cisplatin/paclitaxel; topotecan/paclitaxel; cisplatin/paclitaxel/bevacizumab; or topotecan/paclitaxel/bevacizumab. Analysis of pooled data from the 2 bevacizumab-containing regimens revealed significant improvements in overall survival among patients receiving the antiangiogenic agent (17.0 vs 13.3 months; P=.004).[23] Compared with cisplatin/paclitaxel, topotecan/paclitaxel was not shown to be superior.[23] Although bevacizumab led to higher toxicity (eg, hypertension, thromboembolic events,

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

First-line combination therapy††
- Cisplatin/paclitaxel/bevacizumab[1] (category 1)
- Cisplatin/paclitaxel (category 1)[2,3]
- Topotecan/paclitaxel/bevacizumab[1] (category 1)
- Carboplatin/paclitaxel[4,5]
- Cisplatin/topotecan[6]
- Topotecan/paclitaxel
- Cisplatin/gemcitabine (category 3)[7]

Possible first-line single-agent therapy
- Cisplatin (preferred as a single agent)[3]
- Carboplatin[8]
- Paclitaxel[9]

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

†Cisplatin, carboplatin, docetaxel, and paclitaxel may cause drug reactions (See NCCN Guidelines for Ovarian Cancer--Management of Drug Reactions [OV-C]).
††Cost and toxicity should be carefully considered when selecting an appropriate regimen for treatment.
†††References for second-line therapy are provided in the Discussion.
¶References appearing on CERV-D 1 of 2 can be accessed online, in these guidelines, at NCCN.org.

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gastrointestinal fistula), it was not associated with a statistically significant decrease in patient-reported quality of life (P=.3).[26] Based on these data, the FDA recently approved bevacizumab as part of combination therapy with paclitaxel and either cisplatin or topotecan for treating persistent, recurrent, or metastatic cervical cancer.[27]

NCCN Recommendations

During the 2015 NCCN Cervical Cancer Guidelines update, the panel made several revisions to the systemic therapy recommendations for advanced disease based on new clinical trial data (see CERV-D 1 of 2, above). After discussing the clinical data and recent drug approvals, the panel voted to modify the category assigned to several existing recommendations (see NCCN Categories of Evidence and Consensus on page 397 for category descriptions).

Based on GOG 240 data recently published by Tewari et al,[23] the list of recommended first-line combination therapies was modified (see CERV-D 1 of 2, above). First, the panel voted to recategorize cisplatin/paclitaxel/bevacizumab from category 2A to category 1 based on the availability of positive survival data from a phase III randomized trial. For patients who cannot receive or access bevacizumab, the panel also voted to recommend cisplatin/paclitaxel, a preexisting standard of care regimen, as an alternative category 1 option. Combination regimens using a nonplatinum chemotherapy backbone (eg, topotecan/paclitaxel/bevacizumab and topotecan/paclitaxel) were also added to the list of recommended combination regimens. During the panel's initial 2014 guideline update, topotecan/paclitaxel/bevacizumab was included as a category 2B regimen and topotecan/paclitaxel was added as a category 2A recommendation. Upon the FDA's August 2014 approval of bevacizumab in combination with cisplatin/paclitaxel or topotecan/paclitaxel for treating cervical cancer, the panel voted to include topotecan/paclitaxel/bevacizumab as a category 1 recommendation.

Several other regimens were recategorized after panel discussions. After considering the strength of

the data supporting cisplatin/gemcitabine relative to that for alternative combination regimens, this recommendation was changed to category 3 (see CERV-D 1 of 2, opposite page). The panel also revisited the recommended single-agent second-line therapies (see CERV-D 1 of 2, opposite page). Although most of the second-line therapy options were recognized as category 2B recommendations, the panel noted the categorization of pemetrexed and vinorelbine, which were category 3 at that time. After reevaluating data for each of the second-line single-therapy options, the panel came to consensus that each option had data of relatively equivalent strength and quality. Therefore, the panel decided to change pemetrexed and vinorelbine to category 2B recommendations.

Surgical Approaches for Evaluating and Treating Cervical Cancer

Bolstered by the publication of new clinical data, advances in imaging, radiotherapy, and surgical techniques have expanded the range of treatment options available for staging and treating early-stage cervical cancer. New data suggest that fertility-sparing treatment options can be considered in select patients without negatively impacting oncologic outcomes (reviewed by Ramirez et al[28]). Additionally, recent data suggest that conservative approaches to lymph node assessment/dissection may reduce morbidity without harming survival. However, because of the complex nature of treatment decisions and the need to consider individual disease risk factors, considerable debate still surrounds the decision to forego more aggressive therapy for conservative approaches. Because high levels of expertise and experience are required to safely and effectively execute fertility-sparing/conservative treatment approaches, a new section describing recommended principles of evaluation and surgical staging was incorporated into the NCCN Guidelines during the annual 2014 update. This Insights article discusses relevant data and panel recommendations for various surgical approaches.

Sentinel Lymph Node Mapping

Recent data suggest that sentinel lymph node (SLN) biopsy may be useful for decreasing the need for pelvic lymphadenectomy in patients with early-stage cervical cancer.[29,30] Prospective studies generally support the feasibility of SLN detection in patients with early-stage cervical cancer and suggest that pelvic lymph node dissection can be safely avoided in a significant proportion of early-stage cases.[29–40] In a meta-analysis of data from 1112 patients with cervical cancer who underwent SLN biopsy, pooled data generated a detection rate of 92.2%, pooled sensitivity was 88.8%, and negative predictive values were 95%.[41] Subgroup analyses were performed according to route of surgery (laparoscopy vs laparotomy), detection method (dye only, isotope only, or combination of both tracers), and pathologic assessment method (hematoxylin-eosin only vs hematoxylin-eosin with immunohistochemistry). Higher SLN detection rates were observed for laparoscopy, dual-tracer approaches, and pathologic assessment using immunohistochemistry.

However, study data also highlight the limited sensitivity of this approach and potential to miss SLN micrometastases and isolated tumor cells using intraoperative assessment (ie, frozen section or imprint cytology).[32,36,38] The sensitivity of this approach seems to be better in patients with tumors 2 cm or less in diameter.[29,31,33,42] Ultrastaging of detected SLNs has been shown to provide enhanced detection of micrometastases.[34,35]

The SENTICOL longitudinal study demonstrated the utility of SLN mapping to uncover unusual lymph drainage patterns.[33] Additionally, this study revealed that bilateral SLN detection and biopsy provided a more reliable assessment of sentinel nodal metastases and led to fewer false-negatives than unilateral SLN biopsy.[30] Generally, research supports ipsilateral lymphadenectomy if no SLNs are detected on a given side of the pelvis.[30,43]

NCCN Recommendations: Lymph Node Assessment: Panel members were divided over whether the SLN technique has been sufficiently validated for routine use.[31,32,36,37] Based on existing data, the panel recommends consideration of SLN mapping (category 2B) for early-stage disease and emphasizes that best detection and mapping results are in tumors with a diameter of less than 2 cm. The panel strongly emphasizes that adherence to the SLN mapping algorithm is important; surgeons should perform side-specific nodal dissection in any cases of failed mapping and remove all suspicious or grossly enlarged nodes regardless of SLN mapping.[29] To provide additional detail and guidance on this procedure, the panel added new SLN treatment principles to the guidelines during the 2014 update (see CERV-A 3 and 4 of 7, pages 398 and 399).

Fertility-Sparing Treatment for Early-Stage Cervical Cancer

Microinvasive disease (International Federation of Gynecology and Obstetrics [FIGO] stage IA1 with no lymphovascular space invasion [LVSI]) is associated with an extremely low incidence of lymphatic metastasis,[44–47] and conservative treatment with conization seems to be safe in individuals with no evidence of LVSI.[48]

For stage IA2 and IB1 cervical cancers with lesions that are 2 cm or less in diameter, radical trachelectomy provides a fertility-sparing option that may be appropriate for select patients. In a radical trachelectomy, the cervix, vaginal margins, and supporting ligaments are removed while leaving the main body and fundus of the uterus intact.[49] Laparoscopic pelvic lymphadenectomy accompanies the procedure and can be performed with or without SLN mapping.[50] Research suggests that radical trachelectomy is oncologically safe for patients with stage IA2 or IB1 cervical cancer with lesions that are 2 cm or less in diameter.[51–56] However, select studies have begun to investigate the safety of this procedure for patients with stage IA2 or IB1 cervical cancer with lesions that are more than 2 cm in diameter.[57–59]

Both vaginal and abdominal approaches to the radical trachelectomy procedure have been examined. Abdominal radical trachelectomy provides a broader resection of the parametria than a vaginal approach, but provides a less conservative alternative for fertility preservation.[55,60] Multiple case series have evaluated safety and outcomes with vaginal versus abdominal approaches to radical trachelectomy,[54,61–63] including systematic reviews on vaginal[50] and abdominal[64] radical trachelectomy.

NCCN Recommendations: The panel agrees that fertility-sparing approaches may be considered in highly selected patients who have been thoroughly counseled regarding disease risk and prenatal and perinatal issues (see CERV-A 1 of 7, page 397). In stage IA1 individuals with evidence of LVSI, a reasonable conservative approach is conization (with negative margins) in addition to pelvic lymphadenectomy (category 2A) with the option for SLN mapping (category 2B for SLN). Based on existing data, the panel suggests that radical trachelectomy with lymph node dissection (category 2A) offers a reasonable fertility-sparing treatment option for select patients with stage IA2 or IB1 cervical cancer with lesions that are 2 cm or less in diameter.[28,55,65] Vaginal radical trachelectomy (category 2A) is recommended for carefully selected patients with lesions with a diameter of 2 cm or less.[56,60,61] Laparoscopic pelvic lymphadenectomy should accompany the procedure and can be performed with or without SLN mapping (category 2B for SLN).

Conclusions

Important recent updates to the NCCN Guidelines for Cervical Cancer are highlighted in this report. The NCCN Guidelines are updated at least annually and more often when new high-quality clinical data become available in the interim. The most up-to-date version of these continuously evolving guidelines is available at NCCN.org. The recommendations in the NCCN Guidelines are based on evidence from clinical trials, when available, combined with expert consensus of the NCCN Cervical Cancer Panel. Independent medical judgment is required to apply these guidelines individually to provide optimal care. The physician and patient have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, consistent with NCCN philosophy, the NCCN panel strongly encourages participation in prospective clinical trials.

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Posttest Questions

1. Bevacizumab is a category 1 recommendation for treating recurrent or metastatic cervical cancer in combination with which of the following chemotherapy regimens?
   a. Topotecan/paclitaxel
   b. Cisplatin/gemcitabine
   c. Cisplatin/paclitaxel
   d. A and C
   e. All of the above
2. True or False: SLN mapping should be considered for patients with cervical tumors >4 cm in diameter.
3. Vaginal radical trachelectomy is included as fertility-sparing treatment option for select patients with:
   a. Stage IA1 disease with no LVSI
   b. Stage IA2 disease with lesions ≤2 cm in diameter
   c. Stage IIA2 disease with nodal involvement
   d. All of the above