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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

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

Kerrin M. Rosenthal, MA; Kimberly Callan, MS; Genevieve Emberger Hartzman, MA; Erin Hesler; Kristina M. Gregory, RN, MSN, OCN; Rashmi Kumar, PhD; Karen Kanefield; and Kathy Smith.

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Nadeem R. Abu-Rustum, MD, Panel Chair, has disclosed that he has received grant/research support from GRAIL and Stryker/Novadaq.

Catheryn M. Yashar, MD, Panel Vice Chair, has disclosed that she has no relevant financial relationships.

Nicole R. McMillian, MS, CHES, Guidelines Coordinator, NCCN, has disclosed that she has no relevant financial relationships.

Angela D. Motter, PhD, Oncology Scientist/Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.

To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/disclosures/guidelinepanellisting.aspx.

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Cervical Cancer, Version 1.2020

Featured Updates to the NCCN Guidelines

Nadeem R. Abu-Rustum, MD[1,*]; Catheryn M. Yashar, MD[2,*]; Sarah Bean, MD[3]; Kristin Bradley, MD[4]; Susana M. Campos, MD, MPH, MS[5]; Hye Sook Chon, MD[6]; Christina Chu, MD[7]; David Cohn, MD[8]; Marta Ann Crispens, MD[9]; Shari Damast, MD[10]; Christine M. Fisher, MD, MPH[11]; Peter Frederick, MD[12]; David K. Gaffney, MD, PhD[13]; Robert Giuntoli II, MD[14]; Ernest Han, MD, PhD[15]; Warner K. Huh, MD[16]; John R. Lurain III, MD[17]; Andrea Mariani, MD[18]; David Mutch, MD[19]; Christa Nagel, MD[20]; Larissa Nekhlyudov, MD, MPH[5]; Amanda Nickles Fader, MD[21]; Steven W. Remmenga, MD[22]; R. Kevin Reynolds, MD[23]; Rachel Sisodia, MD[24]; Todd Tillmanns, MD[25]; Stefanie Ueda, MD[26]; Renata Urban, MD[27]; Emily Wyse[28]; Nicole R. McMillian, MS, CHES[29,*]; and Angela D. Motter, PhD[29,*]

ABSTRACT

The NCCN Guidelines for Cervical Cancer provide recommendations for diagnostic workup, staging, and treatment of patients with the disease. These NCCN Guidelines Insights focus on recent updates to the guidelines, including changes to first- and second-line systemic therapy recommendations for patients with recurrent or metastatic disease, and emerging evidence on a new histopathologic classification system for HPV-related endocervical adenocarcinoma.

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[1]Memorial Sloan Kettering Cancer Center; [2]UC San Diego Moores Cancer Center; [3]Duke Cancer Institute; [4]University of Wisconsin Carbone Cancer Center; [5]Dana-Farber/Brigham and Women's Cancer Center; [6]Moffitt Cancer Center; [7]Fox Chase Cancer Center; [8]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [9]Vanderbilt-Ingram Cancer Center; [10]Yale Cancer Center/Smilow Cancer Hospital; [11]University of Colorado Cancer Center; [12]Roswell Park Comprehensive Cancer Center; [13]Huntsman Cancer Institute at the University of Utah; [14]Abramson Cancer Center at the University of Pennsylvania; [15]City of Hope National Medical Center; [16]O'Neal Comprehensive Cancer Center at UAB; [17]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [18]Mayo Clinic Cancer Center; [19]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [20]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [21]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [22]Fred & Pamela Buffett Cancer Center; [23]University of Michigan Rogel Cancer Center; [24]Massachusetts General Hospital Cancer Center; [25]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; [26]UCSF Helen Diller Family Comprehensive Cancer Center; [27]Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; [28]Patient Advocate; and [29]National Comprehensive Cancer Network

*Provided content development and/or authorship assistance.

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 of any patient with cancer 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 evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

The NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their application or use in any way.

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PRINCIPLES OF PATHOLOGY[1]

- **Procedure:**
  - **Radical hysterectomy**
- **Pathologic assessment for carcinoma:**
  - **Uterus**
    - ◊ **Hysterectomy type (where applicable)**
    - ◊ **Tumor site**
    - ◊ **Tumor size, including greatest dimension and additional two dimensions**
    - ◊ **Histologic type[a]**
    - ◊ **Histologic grade**
    - ◊ **Stromal invasion (depth of invasion in mm/cervical wall thickness in mm)[b]**
    - ◊ **Tumor width extent in mm**
    - ◊ **Surgical resection margin status**
      - – **If negative, include closest margin and distance to closest margin (in mm)[c]**
      - – **If positive, include location of positive margin[c]**
    - ◊ **Lymphovascular invasion (does not impact FIGO 2018 staging[2])**
  - **Other tissue/organ involvement (parametrium, vaginal cuff, fallopian tubes, ovaries, peritoneum, omentum, other)**
  - **Lymph nodes (when resected)**
    - ◊ **SLNs should undergo ultrastaging for detection of low-volume metastasis[d]**
    - ◊ **Non-SLNs do not require ultrastaging and can be processed as per routine protocols**
    - ◊ **Include the number of lymph nodes with isolated tumor cells, micrometastasis, and macrometastasis**
    - ◊ **Isolated tumor cells are noted as pN0(i+)**
  - **Consider MMR/MSI, or PD-L1, and/or *NTRK* gene fusion testing for patients with recurrent, progressive, or metastatic disease[3,4]**

[a]According to the 2018 International Endocervical Adenocarcinoma Criteria and Classification (IECC),[5] morphologic features (luminal mitotic figures and apoptosis) can be used to distinguish between human papillomavirus (HPV)-associated endocervical adenocarcinomas and non-HPV–associated adenocarcinomas. Tumors can be further subtyped based on morphologic features.

[b]Evaluation of histologic pattern of invasion for endocervical adenocarcinomas is an emerging concept.[6,7,8] Three clinically significant histologic patterns of invasion for endocervical adenocarcinoma have been described. Tumors with so-called pattern A invasion (defined by well-demarcated glands with round contours, an absence of single cells, an absence of desmoplastic stromal response, and no lymphatic vascular invasion) have excellent survival and do not have lymph node metastases or recurrences. (Diaz De Vivar A, Roma AA, Park KJ, et al. Invasive endocervical adenocarcinoma: proposal for a new pattern-based classification system with significant clinical implications: a multi-institutional study. Int J Gynecol Pathol 2013;32:592-601.)

[c]While reporting of this information is not required, knowledge of this information is useful for multidisciplinary treatment planning.

[d]Ultrastaging commonly entails serial sectioning of the SLN and review of multiple H&E-stained sections with or without cytokeratin immunohistochemistry for all blocks of the SLN. There is not a standard protocol for lymph node ultrastaging.

Overview

An estimated 13,800 new cases of cervical cancer will be diagnosed in the United States in 2020, and 4,290 people will die of the disease.[1] Although cervical cancer rates are decreasing overall among women in the United States, incidence remains elevated among Hispanic/Latino, Black, and Asian women.[2] The estimated global yearly incidence of cervical cancer in 2018 was 570,000, with corresponding deaths of 311,000. It is the fourth most common cancer in women worldwide, with approximately 84% of cases occurring in developing countries, where cervical cancer is a leading cause of cancer death in women.[3] Squamous cell carcinomas account for approximately 75% to 80% of all cervical cancers, and adenocarcinoma accounts for approximately 20%.[4] Persistent HPV infection is the most important factor in the development of cervical cancer.[5,6] Approximately 70% of cervical cancers are caused by persistent infection with high-risk (oncogenic) HPV type 16 or 18,[7] although persistence of other oncogenic HPV types (eg, 31, 33, 45, 52, 58) also confers an increased risk of cancer.[8]

Regardless of cancer subtype and HPV infection status, primary treatment with curative intent for patients with cervical cancer typically consists of surgery, chemoradiation, or a combination of these treatments; options vary by cancer stage. Chemotherapy with or without radiation forms the basis of treatment of patients with recurrent and/or metastatic disease. Traditionally, cisplatin has been the foundation of systemic therapy, either as a single agent or in combination with other agents. In recent years, double- and triple-agent chemotherapy regimens have increasingly been used for patients with recurrent or metastatic disease. Additionally, the availability of targeted therapies and immunotherapy regimens (eg, bevacizumab, pembrolizumab) in combination with, or as alternatives to, existing first- and second-line treatment options has led to improved outcomes in some patients.

These NCCN Guidelines Insights focus on recent changes to first- and second-line systemic therapy recommendations for recurrent or metastatic disease (see CERV-F page 1 of 2, page 663). Certain novel targeted therapies (ie, entrectinib, larotrectinib, pembrolizumab) were newly added to the NCCN Guidelines, whereas some doublet and triplet chemotherapy regimens (ie, cisplatin/paclitaxel, carboplatin/paclitaxel, topotecan/paclitaxel, and topotecan/paclitaxel/bevacizumab) were restratified according to the NCCN Categories of Preference.

SYSTEMIC THERAPY REGIMENS FOR CERVICAL CANCER[a]

Chemoradiation		
Preferred Regimens • Cisplatin • Carboplatin if patient is cisplatin intolerant		
Recurrent or Metastatic Disease		
First-line combination therapy[b,c]	**Possible first-line single-agent therapy[c]**	**Second-line therapy[e]**
Preferred Regimens • Cisplatin/paclitaxel/bevacizumab[d,1] (category 1) • Carboplatin/paclitaxel/bevacizumab[d] **Other Recommended Regimens** • Cisplatin/paclitaxel (category 1)[2,3] • Carboplatin/paclitaxel[4,5] (category 1 for patients who have received prior cisplatin therapy) • Topotecan/paclitaxel/bevacizumab[d,1] (category 1) • Topotecan/paclitaxel[1] • Cisplatin/topotecan[6]	**Preferred Regimens** • Cisplatin[3] **Other Recommended Regimens** • Carboplatin[7] • Paclitaxel[8,9]	**Preferred Regimens** • Pembrolizumab for PD-L1–positive[f] or MSI-H/dMMR tumors[g] **Other Recommended Regimens** (All agents listed here are category 2B unless otherwise noted) • Bevacizumab[d] • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Ifosfamide • Irinotecan • Mitomycin • Pemetrexed • Topotecan • Vinorelbine **Useful in Certain Circumstances** • Larotrectinib or entrectinib for *NTRK* gene fusion-positive tumors (category 2B)

[a]Cisplatin, carboplatin, docetaxel, and paclitaxel may cause drug reactions (See NCCN Guidelines for Ovarian Cancer--Management of Drug Reactions [OV-C]).
[b]Cost and toxicity should be carefully considered when selecting an appropriate regimen for treatment.
[c]If not used previously, these agents can be used as second-line therapy as clinically appropriate.
[d]An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[e]References for second-line therapy are provided in the Discussion.
[f]Recommended for disease progression on or after chemotherapy in patients whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.
[g]See NCCN Guidelines for the Management of Immunotherapy-Related Toxicities.

In addition, emerging data on a new histopathologic classification system for HPV-related endocervical adenocarcinoma (EAC) are discussed (see footnote "b" on CERV-A page 1 of 2, page 662).

NCCN Categories of Preference

Starting with version 2.2019, the panel assigned a Category of Preference to all systemic therapy regimens included in the NCCN Guidelines for Cervical Cancer. The 3 NCCN Categories of Preference are as follows:

- Preferred: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability
- Other recommended: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes
- Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation)

The Categories of Preference provide increased granularity and specificity of recommended regimens, and supplement information provided by the NCCN Categories of Evidence and Consensus (ie, categories 1, 2A, 2B, and 3).

First- and Second-Line Systemic Therapy Regimens for Recurrent or Metastatic Disease

First-Line Combination Therapy Regimens: Preferred Versus Other Recommended Regimens

Prior to Version 1.2020, the panel included 6 first-line combination therapies (3 doublet, 3 triplet) in the Guidelines as Preferred systemic therapy regimens for recurrent or metastatic disease: cisplatin/paclitaxel/bevacizumab, carboplatin/paclitaxel/bevacizumab, topotecan/paclitaxel/bevacizumab, cisplatin/paclitaxel, carboplatin/paclitaxel, and topotecan/paclitaxel. While discussing potential guidelines updates for Version 1.2020, the panel came to the consensus that an extensive list of Preferred regimens was less likely to provide specific guidance on the most effective treatment options. Additionally, by this time, based on randomized clinical trial data and real-world experience, clinicians had come to widely accept triplet regimens as the first-line standard of care for recurrent or metastatic cervical cancer. Thus, the panel agreed to move all 3 of the doublet regimens to Other Recommended.

Previously, the triplet combination of topotecan/paclitaxel/bevacizumab was listed as a Preferred regimen. Although the FDA did approve bevacizumab in

combination with topotecan and paclitaxel for the treatment of recurrent or metastatic cervical cancer, further review of the final results[9] from the randomized phase III GOG 240 trial suggested that, although not statistically different, this triplet regimen was qualitatively less effective than the corresponding platinum-containing regimen of cisplatin/paclitaxel/bevacizumab. The authors reported that adding bevacizumab to a topotecan/paclitaxel regimen did not significantly improve overall survival (OS) versus topotecan/paclitaxel alone (hazard ratio [HR], 0.80; 95% CI, 0.59–1.08; P=.15). Conversely, adding bevacizumab to cisplatin/paclitaxel significantly improved OS versus cisplatin/paclitaxel alone (HR, 0.73; 95% CI, 0.54–0.99; P=.04).[9] Based on these data, the panel kept the cisplatin/paclitaxel/bevacizumab regimen in the Preferred category, while moving the non-platinum triplet to the Other Recommended group, even as the Category of Evidence and Consensus remained at level 1 based on randomized clinical trial data. Although the GOG 240 trial did not specifically include a carboplatin/paclitaxel/bevacizumab triplet regimen, the panel also considers it a Preferred first-line treatment option for patients who are intolerant to cisplatin, based on results from the randomized phase III JCOG0505 trial that suggested non-inferiority of carboplatin/paclitaxel to cisplatin/paclitaxel.[10]

Pembrolizumab as a Second-Line Therapy for PD-L1–Positive or MSI-H/dMMR Tumors

FDA approved pembrolizumab in May 2017 for treating adult and pediatric patients with unresectable or metastatic microsatellite instability–high (MSI-H) or deficient mismatch repair (dMMR) solid tumors that have progressed after prior treatment and who have no satisfactory alternative treatment options.[11] Data from the nonrandomized phase Ib KEYNOTE-028 basket trial, which included 24 patients with advanced cervical cancer who previously received ≥1 lines of chemotherapy, partially supported the drug's approval for this indication.[12,13] Based on these data, the panel added pembrolizumab as a second-line therapy option in version 1.2018 of the guidelines. At that time, the panel gave the drug a category 2B rating, because they felt that the KEYNOTE-028 trial did not include an adequate number of patients with cervical cancer, and thus, the drug had limited validation in this patient population.

In June 2018, the FDA expanded pembrolizumab's approval to include patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy, whose tumors express PD-L1 as determined by an FDA-approved test.[14] Data from the nonrandomized phase II KEYNOTE-158 basket trial, which included 98 patients with advanced cervical cancer, supported this expanded indication.[15,16] Nearly 84% (n=82) of the enrolled patients with cervical cancer were PD-L1–positive, and of these, 94% (n=77) previously received ≥1 lines of chemotherapy. In PD-L1–positive patients, the objective response rate to pembrolizumab was nearly 15% (3 complete and 9 partial responses). Of these responders, 10 (83%) previously received radiotherapy in addition to chemotherapy. Upon considering pembrolizumab's expanded indication and the publication of these new data, the panel felt that the drug became a more relevant option for patients with cervical cancer, and recategorized it as a category 2A option in version 2.2018 for patients with PD-L1–positive or MSI-H/dMMR tumors. When the panel added the Categories of Preference to version 2.2019 of the guidelines, they designated pembrolizumab a Preferred second-line therapy option for patients with PD-L1–positive or MSI-H/dMMR tumors and recurrent or metastatic disease; its category 2A status stayed the same. The panel has made no further changes to these assignments since version 2.2019.

Silva Classification System for HPV-Related EAC

While discussing potential Guidelines updates for 1.2020, the panel reviewed emerging evidence on the Silva clinicopathologic classification system, which considers the extent of lymphovascular space invasion (LVSI), stromal invasion, and differentiation in patients with HPV-related EAC. The studies describing and validating its use in these patients are retrospective, and only a limited number of expert gynecologic pathologists currently use the Silva system in clinical practice. However, the available data suggest that the system may more accurately stratify patients with HPV-related EAC by risk of metastases, recurrence, and death than the current clinicopathologic features that are used for measuring the extent of disease. The panel felt that it was important to introduce this novel concept to guidelines readers, but acknowledged that there was not yet enough evidence to support the formal addition of the Silva system to the list of clinicopathologic features that are recommended for use in disease assessment. Instead, they briefly described the Silva classification system in a footnote (see footnote "b" on CERV-A page 1 of 2, page 662). Following is an expanded summary of the evidence on the Silva system and insights on how it might be incorporated into more widespread clinical practice in the future.

According to the 2018 FIGO criteria,[17,18] pathologists use tumor size and stromal depth of invasion (DOI) during clinicopathologic staging of cervical cancer. During clinicopathologic assessment, pathologists calculate DOI (in millimeters) starting from the basement membrane of the originating epithelium.[19] Endocervical glands normally vary in size, shape, and distance of extension into the underlying stroma; because of this architectural complexity, determining the DOI in EAC is difficult.[20,21] Obtaining an accurate DOI measurement is important, because it directly informs treatment decisions. The FIGO staging system does not consider the extent of LVSI, but

clinicians also use this information to inform treatment decisions. For instance, patients with stage IA1 cervical cancer (DOI ≤3 mm) whose tumors do not have LVSI may be candidates for fertility-sparing conservative treatment (ie, cone biopsy, trachelectomy), because these patients generally have low risk of metastases and recurrence. Patients with IA2 cervical cancer (DOI >3 mm) may also be candidates for these procedures, but also typically undergo lymphadenectomy with or without sentinel lymph node (SLN) mapping due to an increased risk of nodal metastases and recurrence compared with patients with stage IA1 cervical cancer without LVSI. Lymphadenectomy and SLN mapping both may increase morbidity. Therefore, more accurate and reproducible methods of staging EAC are needed to avoid the use of unnecessary procedures in patients who may be at minimal risk of nodal metastases, recurrence, and/or death.

The Silva classification system has thus been proposed to more accurately stratify patients with invasive usual-type (HPV-related) EAC. A 2013 retrospective study published by Diaz De Vivar et al[22] included patients (n=352) with stage I–IV usual-type EAC, all of whom previously underwent lymphadenectomy. Pathologists classified their tumor samples into 1 of 3 Silva categories according to histologic patterns of invasion:

1. Pattern A tumors are characterized by no LVSI, well-demarcated glands, and no detachment, which may resemble adenocarcinoma in situ
2. Pattern B, some LVSI, focal destructive stromal invasion
3. Pattern C, more widespread LVSI, diffuse destructive stromal invasion

For reference, we included representative images of EAC tumors for each category (Figure 1).

For tumors that had mixed histopathologic characteristics, pathologists assigned the highest classification that they observed in the sample. Mean follow-up time was approximately 4.5 years. Patients with pattern A tumors did not experience any metastases or recurrences during this time. Of those with pattern B tumors, 4.4% experienced metastases and 1.2% had a recurrence. Those with pattern C tumors had a marked increase in the rates of metastases and recurrences (23.8% and 22.1%, respectively).

Since 2013, several other groups independently published retrospective studies on use of the Silva classification system. Spaans et al[23] classified tumor samples from 82 patients with stage IB–IIA usual-type EAC, all of whom previously underwent radical hysterectomy or trachelectomy. Median follow-up time was approximately 10 years. Patients with pattern A tumors did not experience any metastases, recurrences, or deaths during this time. Of patients with pattern B tumors, 17% experienced metastases, 13% had a recurrence, and 10% died. Of patients with pattern C tumors, 37% experienced metastases, 35% had a recurrence, and 35% died. The authors suggested that pattern B and C tumors may be associated with a higher incidence of somatic hotspot mutations, but noted that this observation should be confirmed in prospective studies.

Stolnicu et al[24] used the Silva classification system to stratify 341 patients with usual-type and non–HPV-related stage I–IV EAC who previously underwent surgical resection (ie, cone biopsy, trachelectomy, hysterectomy) and lymphadenectomy. Pathologists first classified tumor specimens into usual-type and non–HPV-related EAC according to International Endocervical Adenocarcinoma Criteria and Classification[25] and then further classified the tumors by Silva criteria. The authors found that the incidence of metastases in usual-type EAC was similar to that observed by Diaz De Vivar et al.[22] They also reported that 100% of the non–HPV-related EAC tumors were classified as pattern C, and therefore concluded that the utility of the Silva classification system is limited to patients with usual-type (HPV-related) EAC.

Data from these retrospective studies suggest that the Silva classification system may help stratify patients with invasive, usual-type EAC by risk of metastases, recurrence, and death. Some expert gynecologic pathologists are already using the Silva classification system

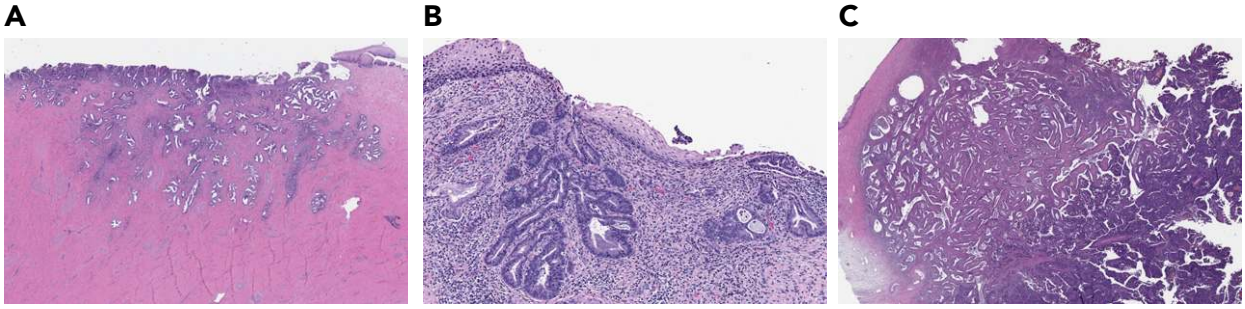

Figure 1. Representative images of HPV-related endocervical adenocarcinoma classified according to Silva criteria: (A) pattern A, (B) pattern B, and (C) pattern C tumors. (Courtesy of Kay Park, MD, and Nadeem Abu-Rustum, MD, New York, NY.)

during clinicopathologic staging. The system could be particularly helpful for identifying low-risk patients with stage I disease who may be candidates for conservative, fertility-sparing treatment without compromising short- and long-term patient health outcomes. However, prospective studies are needed to confirm these observations (ie, studies in which pathologists would use the Silva classification system to stratify patients' tumors into pattern A, B, or C categories, and clinicians would consider this information in addition to other clinicopathologic factors to help inform treatment decisions). If data from future prospective studies agree with the data cited earlier, the Silva classification system could potentially be used in conjunction with, or incorporated into, FIGO/AJCC criteria at the time of diagnostic biopsy. To this end, Roma et al[26] proposed that a new 3-tier FIGO/AJCC classification system could be created for usual-type EAC staging, in which Silva A, B, and C categories would replace DOI measurement. Alternatively, DOI could be revised to specify the depth of *destructive* invasion, and the Silva classification system could then be used in conjunction.

Conclusions

Emerging evidence informs panel recommendations in the NCCN Guidelines for Cervical Cancer and all other NCCN Guidelines. Recent updates to these guidelines include new and restratified treatment option recommendations that may provide safer, more effective care for patients with the disease. The panel also recently discussed and noted new methods of EAC staging that could potentially be incorporated into official guidelines recommendations and more widespread clinical practice in the future.

To participate in this journal CE activity, go to https://education.nccn.org/node/87827

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