Management and Care of Women with Invasive Cervical Cancer

American Society of Clinical Oncology
Resource-Stratified Clinical Practice Guidelines

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Introduction

• The purpose of this guideline is to provide expert guidance to clinicians and policymakers in all resource settings on the workup, treatment, and palliative care for women diagnosed with invasive cervical cancer.

• Treatment of cervical cancer is dependent on the stage of disease. Treatment may include surgical treatments such as cervical cone biopsy, hysterectomy or radical hysterectomy, radiation therapy, and/or chemotherapy.
Introduction

- Different regions of the world, both among and within countries, differ with respect to access to these treatments. In particular, regions with lower resources tend to have poorer screening programs, and patients present with more advanced disease that requires either radical surgery or chemoradiotherapy, neither of which is readily available in these areas.

- For this reason, standard guidelines that assume ideal availability of surgery and radiotherapy may not be applicable. The goal of this guideline is to recommend options in settings in which ideal treatment regimens may not be available.
ASCO Guidelines
Development Methodology

The ASCO Clinical Practice Guidelines Committee (CPGC) guideline process includes:

- a systematic literature review by ASCO guidelines staff
- an expert panel provides critical review and evidence interpretation to inform guideline recommendations
- final guideline approval by ASCO CPGC

The full ASCO Guideline methodology supplement can be found at:

www.asco.org/rs-cervical-cancer-treatment-guideline
Clinical Questions

This clinical practice guidelines address four overarching clinical questions:

• In the basic, limited, enhanced, and maximal resource settings, what are the appropriate care options for women with invasive cervical cancer for

  (1) Workup
  (2) Treatment
  (3) Follow-up and post-treatment surveillance
  (4) Palliative care
Cost Implications

• There are very few studies of the cost effectiveness of treatment in low- and middle-income countries.

• Concentrating surgical volume in high-risk centers and by high-risk surgeons has been shown in many clinical settings to improve outcome.

• Thus, even in countries without trained gynecologic oncologists or access to ideal radiation therapy facilities, surgical outcomes could be improved by concentrating resources and designating experts.

• These types of changes may be cost-effective both by improving clinical outcomes and by optimally using existing resources.
# Work Up

<table>
<thead>
<tr>
<th>Setting</th>
<th>Basic</th>
<th>Limited</th>
<th>Enhanced</th>
<th>Maximal</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and physical examination, CBC, cervical biopsy, cone biopsy, and LFT/renal function studies</td>
<td>History and physical examination, CBC, cervical biopsy, <strong>pathologic review</strong>, cone biopsy, and LFT/renal function studies</td>
<td>History and physical examination, CBC, cervical biopsy, pathologic review, cone biopsy, and LFT/renal function studies</td>
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<td>History and physical examination, CBC, cervical biopsy, pathologic review, cone biopsy, and LFT/renal function studies</td>
</tr>
<tr>
<td>Imaging (optional in ≤ stage IB1 disease): chest x-ray</td>
<td>Imaging (optional in ≤ stage IB1): chest x-ray, <strong>CT (specifically CT of abdomen and pelvis for women with advanced-stage disease for treatment planning purposed)</strong></td>
<td>Imaging (optional in ≤ stage IB1): chest x-ray, <strong>CT or MRI</strong></td>
<td>Imaging (optional ≤ stage IB1): chest x-ray, CT or MRI <strong>or PET-CT</strong></td>
<td>Imaging (optional ≤ stage IB1): chest x-ray, CT, or MRI <strong>or PET-CT</strong></td>
</tr>
<tr>
<td>Smoking cessation and counseling; may offer HIV testing</td>
<td>Smoking cessation and counseling; may offer HIV testing</td>
<td>Smoking cessation and counseling; may offer HIV testing</td>
<td>Optional: <strong>EUA cystoscopy/proctoscopy only if suspicion of bladder or rectum invasion by CT or MRI</strong></td>
<td>Optional: EUA cystoscopy/proctoscopy only if suspicion of bladder or rectum invasion by CT or MRI</td>
</tr>
</tbody>
</table>

**NOTE.** Bold indicates addition of a recommended action over a previous resource level (e.g., in limited setting, a bold action is one that was not recommended in basic).

Abbreviations: CBC, complete blood count; CT, computed tomography; EUA, examination under anesthesia; LFT, liver function test; MRI, magnetic resonance imaging; PET, positron emission tomography  

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• A majority of patients in basic settings do not have access to trained surgeons to perform radical surgeries and to radiation treatment, either with curative or palliative intent.

• Low-resourced countries face the largest challenges in the supply of routine chemotherapy and radiation therapy equipment and personnel to treat women with locally advanced cervical cancers.
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• One of the most important premises is that some options offered in the Basic, low-resourced settings, is that some may consider the treatment options as suboptimal in the Maximal setting.

• Practitioners should offer options to their patients that are recommended for the enhanced/maximal settings, whenever possible.

• If feasible, patients should be referred for treatments at centers where these options are available.
## Treatment Capacity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgery</strong></td>
<td><strong>Basic</strong></td>
</tr>
<tr>
<td></td>
<td>Simple (extrafascial) hysterectomy or more extensive hysterectomy can be performed*</td>
</tr>
<tr>
<td></td>
<td>*Where medical facilities exist to take care of women who are at high risk for postoperative complications</td>
</tr>
<tr>
<td></td>
<td><strong>Limited</strong></td>
</tr>
<tr>
<td></td>
<td>Modified radical and radical hysterectomy</td>
</tr>
<tr>
<td></td>
<td><strong>Enhanced</strong></td>
</tr>
<tr>
<td></td>
<td>Capable of performing most major surgeries, including radical hysterectomy, radical trachelectomy,* pelvic and para-aortic LN sampling, and pelvic exenteration*</td>
</tr>
<tr>
<td></td>
<td>Following are not available: PET scan, interventional radiology, sentinel node biopsy/IORT, and bevacizumab</td>
</tr>
<tr>
<td></td>
<td>*Can be performed in some enhanced levels</td>
</tr>
<tr>
<td></td>
<td><strong>Maximal</strong></td>
</tr>
<tr>
<td></td>
<td>Radical hysterectomy, radical trachelectomy, pelvic and para-aortic LN sampling, sentinel node biopsy, and pelvic exenteration; radiation therapy, chemotherapy, interventional radiology, palliative care service, and bevacizumab are all available</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td><strong>Basic</strong></td>
</tr>
<tr>
<td></td>
<td>Availability of chemotherapy drugs is unpredictable</td>
</tr>
<tr>
<td></td>
<td><strong>Limited</strong></td>
</tr>
<tr>
<td></td>
<td>Chemotherapy may be available</td>
</tr>
<tr>
<td></td>
<td><strong>Enhanced</strong></td>
</tr>
<tr>
<td></td>
<td>Chemotherapy available; bevacizumab not available</td>
</tr>
<tr>
<td></td>
<td><strong>Maximal</strong></td>
</tr>
<tr>
<td></td>
<td>Chemotherapy available; bevacizumab is available</td>
</tr>
<tr>
<td><strong>Radiation therapy</strong></td>
<td><strong>Basic</strong></td>
</tr>
<tr>
<td></td>
<td>No radiation therapy available</td>
</tr>
<tr>
<td></td>
<td><strong>Limited</strong></td>
</tr>
<tr>
<td></td>
<td>Limited external RT with no brachytherapy available; in some areas where there are only brachytherapy and no external RT, this will be considered as basic level</td>
</tr>
<tr>
<td></td>
<td><strong>Enhanced</strong></td>
</tr>
<tr>
<td></td>
<td>RT including external beam and brachytherapy available; interventional radiology not available</td>
</tr>
<tr>
<td></td>
<td><strong>Maximal</strong></td>
</tr>
<tr>
<td></td>
<td>RT including external beam and brachytherapy available; interventional radiology available</td>
</tr>
</tbody>
</table>

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## Treatment Capacity

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<tr>
<th>Treatment</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basic</td>
</tr>
<tr>
<td>Pathology</td>
<td>Pathology services are not available; if there is a way to send pathology for review when needed, that should occur. (Basic pathology may be available, but diagnosis is often delayed for more than one month. There are no frozen sections or pathology consultations in the region.)</td>
</tr>
<tr>
<td>Palliative care</td>
<td>Palliative care service is in development; basic palliative care, including pain and symptom management, should be provided†</td>
</tr>
</tbody>
</table>

†Palliative care is multifaceted and in some contexts can be provided concurrently with tumor-directed therapy. Pain management and best supportive care are necessary but insufficient parts of palliative care in all settings. Women with advanced cervical cancer with or without access to tumor-directed therapy may have specific late-stage symptoms that require clinicians to perform or offer urogenital-specific interventions. See the Special Commentary section.

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Key Points

• If follow-up is available, the expert panel recommends cone biopsy for stage IA2 disease in basic settings. In enhanced and maximal settings, radical trachelectomy is recommended for patients with stage IB1 disease with tumor size up to 2 cm in those patients who disease fertility-sparing surgery.

• In basic settings in patients who cannot be treated with radiation therapy, extrafascial hysterectomy, either alone or after chemotherapy, may be an option for patients with stage IA1 to IVA cervical cancer.
Key Points

• In basic settings, in women with larger tumors or advanced-stage cervical cancer, neoadjuvant chemotherapy is recommended whenever chemotherapy is available for the purpose of shrinking the tumor before hysterectomy.

• Concurrent radiotherapy and chemotherapy is standard in enhanced and maximal settings in women with stage IB to IBA disease.

• The panel stresses the addition of low-dose chemotherapy to radiotherapy, but not at the cost of delaying radiation therapy if chemotherapy is not available.
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• With the lack of surgeons and radiation treatment, basic extrafascial hysterectomy or its modifications or neoadjuvant chemotherapy followed by surgery is recommended for women with early stage disease.

• The Panel stated that these recommendations are based on weak evidence but chose to make recommendations rather than not offering these women any opportunities for disease control and survival.

• For more women with advanced stage disease in the basic setting, neoadjuvant chemotherapy followed by radical surgery when feasible becomes the only viable option.
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- In settings where surgeons are able to perform radical surgery but there is a general lack of radiation machines, the Guideline recommended the option of shorter radiation fractionation schemes with curative intent.

- The Panel specifically addressed the setting where there is a lack of brachytherapy— an option to deliver an additional radiation boost of 18-20 Gy following a 50 Gy external radiation was presented. To compensate for the lack of brachytherapy, extrafascial hysterectomy or its modification may be performed if there is limited residual tumor in the cervix.

- The Panel reviewed and adopted the WHO chapter of palliative care for its cervical cancer guideline.
The Bottom Line

• If the resources are available and the patient cannot receive treatment with curative intent, the patient should receive palliative radiation therapy to relieve symptoms of pain and bleeding.

• Where resources are constrained, single or short-course radiotherapy schemes can be used with retreatments if feasible for persistent or recurrent symptoms.
Qualifying Statements

• Palliative care and pain management are part of the treatment of cancers, including cervical cancer, to avoid unnecessary suffering during the final stages of the disease.

• Pain control is a vital component of palliative care, a basic human right often neglected in cancer control programs.
Palliative Care & Pain Management

• Pain is often a disabling symptom of advanced or recurrent cervical cancer. Narcotic analgesics may be prepared for oral, rectal, vaginal, sublingual, intravenous, intramuscular, epidural, or topical administration.

• When pain is directly attributable to specific foci of disease a brief course of palliative radiation therapy yields substantial pain reduction in a high percentage of patients. However, pain relief may not be maximally achieved until weeks after the palliative radiation therapy ends.
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References

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- Journal of Global Oncology published May 2016
- Journal of Clinical Oncology published July 2016
- Journal of Oncology Practice published June 2016
# ASCO Guideline Panel Members

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<thead>
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</thead>
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<td>Sunnybrook Odette Cancer Centre and University of Toronto, Toronto, Ontario, Canada</td>
</tr>
<tr>
<td>Vandana Gupta, Patient Representative</td>
<td>VCare, Mumbai, India</td>
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• Thank you!
Special Commentary

• In limited resource settings where radiation therapy is limited, providers may have to prioritize its use to treat selective patients with advanced-stage disease and to palliate symptoms in other patients who normally receive antitumor treatment in maximal-level settings.

• Interventions to control vaginal bleeding include radiation therapy or brachytherapy, embolization of the uterine arteries, surgical resection, and arterial ligation. Vaginal packing is usually a temporary measure.
The Bottom Line

• In limited resource settings where there is no brachytherapy, the ASCO expert panel recommends extrafascial hysterectomy or its modification for women who have residual tumor 2-3 months after concurrent chemoradiation therapy and an additional boost.

• For patients with stage IV or recurrent cervical cancer, single agent chemotherapy, carboplatin or cisplatin, is recommended in basic settings.
Summary of Recommendations

Workup
The purpose of workup is to assess the patient’s overall health status and gather data to inform treatment. Modalities include history and physical examination, biopsies, blood tests, and imaging. Tests available in maximal settings, such as magnetic resonance imaging or positron emission tomography (PET) – computed are optional.

Treatment
The treatment for invasive cervical cancer consists of surgery, chemotherapy, and radiation therapy, sometimes in combination.

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Target Population and Audience

Target Population
Women at all levels of resource settings diagnosed with invasive cervical cancer.

Target Audience
This clinical practice guideline globally targets health care providers (including gynecologic oncologists, medical oncologists, radiation oncologists, obstetricians and gynecologists, surgeons, nurses, and palliative care clinicians), policymakers, patients, and caregivers.
Summary

• The Panel encourages leaders and other health care policymakers to consider the toll of invasive disease in terms of mortality, morbidity, loss of working age women in the workforce, and opportunity costs to families and societies.

• Cervical cancer is a major public health problem that requires priority attention and funding similar to that addressing other common problems in low resource settings, e.g., clean water, malaria, and tuberculosis.

• The Panel recognizes the enormous gaps and disparities in access to care, especially radiation therapy, and endorses the efforts of groups working to address these critical issues, increase education in basic resource settings, and encourages participation in international advocacy efforts.
Options for Follow-Up for All Settings

• Follow-up should be based on each individual’s risk of cervical cancer recurrence; high-quality evidence is lacking on the best methods of post-treatment surveillance; some guidance is offered in other guidelines and is provided here as guidance rather than as recommendations:
  • After 1 to 2 years, every 3 to 6 months
  • After 3 to 5 years: every 6 to 12 months
  • After ≥ 5 years, every year based on risk of recurrence
• Pelvic and physical examination
• Imaging and laboratory tests based on symptoms or suspicion
• Patient education
• Cytology may be offered, if available, every 3 years after cone biopsy, radical hysterectomy, or trachelectomy; cytology should not be performed after RT
• In patients at high risk for locoregional failure, PET-CT 3 months after therapy is optional

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Palliative Care & Pain Management for Women with Advanced Cervical Cancer

• Patients with advanced or recurrent cervical cancer may have any of the following symptoms

  – Vaginal bleeding or discharge
  – Pelvic or back pain
  – Urinary or bowel fistulas
  – Lower-extremity edema
  – Deep-venous thrombosis
  – Dyspnea resulting from anemia or pulmonary involvement or
  – Uremia from ureteral obstruction
Limitations of Research

- There were several areas where evidence was lacking to make strong recommendations.
  - Using squamous cell carcinoma antigen and/or high-sensitivity C-reactive protein
  - Optimal dose fractionation of brachytherapy
  - Optimal treatment for women with stage IA2 or IB1 disease with tumors smaller than 2 cm in size and 1 cm in depth in the non–fertility-sparing setting and patients with stage IB1 cervical cancer with tumor size between 2 and 4 cm
  - Optimal fertility-sparing procedures for women with stage IA1 or IA2 disease
  - Treatment of women in basic settings, including regarding chemotherapy and radiation therapy

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Additional Resources

More information, including a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at

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Patient information is available at www.cancer.net