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ASCO Resource Stratified Guidelines Primary Prevention of Cervical Cancer Secondary Prevention of Cervical Cancer Management of Women with Invasive Cervical Cancer

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Primary Prevention of Cervical Cancer: American Society of Clinical Oncology Resource-Stratified Guideline

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Introduction

- Approximately 85% of incident cervical cancers occur in less developed regions, often overlapping with low- and middle-income countries (LMICs) around the world, and represent 12% of cancers among women in those regions.

- HPV causes virtually all cervical cancer and its immediate precursors everywhere in the world. The HPV 16 and HPV 18 subtypes are most associated with cervical cancer.

- The purpose of this guideline is to provide expert guidance on primary prevention, the reduction in human papillomavirus (HPV) infection by HPV vaccine administration, of cervical cancer to clinicians, public health leaders, and policymakers in all resource settings.

ASCO Guideline Development Methodology

The ASCO Clinical Practice Guidelines Committee 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-primary-prev-guideline

Clinical Questions

This clinical practice guideline addresses the overarching clinical question, What is the optimal method for primary prevention of cervical cancer in each resource stratum?

- For which cohorts is routine vaccination recommended?
- What number of doses and intervals are recommended?
- Should catch-up to subjects outside the priority age groups for vaccination be offered for the prevention of HPV infection?
- Should HPV vaccination of boys be recommended to reduce HPV infection?
- What vaccination strategy is recommended for special populations?

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Summary of Recommendations

In Maximal and Enhanced Resource Settings:

- For which cohorts is routine vaccination recommended?
  - *Recommendation A1a.* Public health authorities, ministries of health, and primary care providers should routinely vaccinate girls with the target age range being as early as possible starting at 9 years through 14 years of age
  - *Recommendation A1b.* Public health authorities may set the upper end of the target population higher than 14 years of age, depending on local policies and resources

Summary of Recommendations

- What number of doses and intervals are recommended?
  - *Recommendation A2a.* For girls 9 to 14 years of age who are immune competent, a two-dose regimen is recommended
  - *Recommendation A2b.*The interval between two doses should be at least 6 months and may be up to 12 to 15 months
  - *Recommendation A2c.*Girls 15 years of age or older at the time of the first dose/initiation (outside of target population) who receive vaccine should receive three doses

Summary of Recommendations

- Should catch-up to subjects outside the priority age groups for vaccination be offered for prevention of HPV infection?
  - *Recommendation A3.* For females who have received one dose and are more than 14 years of age, public health authorities may provide additional doses/complete the series up to 26 years of

- Should HPV vaccination of boys be recommended to reduce HPV infection?*
  - *Recommendation A4.* For prevention of cervical cancer, if there is low vaccine coverage of the priority female target population (< 50%) in maximal or enhanced resource settings, then vaccination may be extended to boys
  - For prevention of cervical cancer in maximal or enhanced resource settings where vaccine coverage of girls is ≥50%, there are insufficient data to recommend for or against vaccination of boys

Special Commentary

In vaccinated cohorts, what is recommended for secondary prevention in terms of cost-effectiveness ratios for the combined strategies?

- Vaccination does not replace screening.
- Until further data are gathered, vaccinated cohorts will need to be screened.
- Screening after vaccination is discussed in detail in the ASCO Screening Resource Stratified Guideline (www.asco.org/rs-cervical-cancer-secondary-prev-guideline)

Special Commentary

Is there a need to have a registration system (i.e., enrollment, refusal, surveillance of potential adverse effects) to evaluate the impact and coverage of the strategies?

- There is a need for monitoring the implementation of vaccines in terms of coverage and outcomes detected by screening and cancer registries.

- Strengthened systems for monitoring immunization adverse events are essential for tracking potential adverse effects, especially rare or late-occurring events.

- The rationale for screening and cancer registries is the need for data over time in order to track longer-term outcomes, especially cervical cancer outcomes, and the duration of immunity/protection.

Special Commentary

Safety

- The safety profile of HPV vaccines has been assessed extensively in RCTs and by robust pharmacovigilance in the postlicensure setting using both passive and active vaccine surveillance.

- As with all serious vaccine adverse events, it is important that appropriate investigations be carried out promptly to determine whether the event is caused by the vaccine and whether any remedial action is needed.

- The key challenge faced in pharmacovigilance is to distinguish real adverse events from background conditions that would occur regardless of vaccination.

- Population-based data on incidence of potential adverse events prior to vaccination allow analysis of observed/expected rates in vaccinated populations.[2,3]

Special Commentary

- International Papillomavirus Society assessed reviews by WHO, FDA, CDC, EMA, International Federation of Gynecology and Obstetrics, UK Medicines & Healthcare Products Regulatory Agency, TGA, and other publications and concluded that there is no evidence that neurologic disease, autoimmune diseases, or deaths are vaccine-attributable and emphasized there have been no deaths associated with HPV vaccines.[4]

- This guideline agrees with the International Papillomavirus Society policy statement on the safety of HPV vaccines.

Uptake

- Primary care providers and pediatricians are in a unique position to promote HPV vaccination given their longstanding relationship with their child and adolescent patients and their parents.

- Once informed and educated about the importance of HPV vaccination by a trusted source (usually their children's health care provider) parents are more likely to vaccinate their children.

- Therefore, at all levels (basic through maximal), education of primary care physicians and pediatricians about the cancer-preventive properties of HPV vaccination and its safety could provide the highest return on investment in cervical cancer primary prevention.

Cost Implications

- In low-resource settings, cost remains the primary barrier to HPV vaccination.
- Vaccination is usually second in line of cost effectiveness after routine screening, but this needs high coverage of the female population.
- Cost-effectiveness analyses support this guideline's recommendations for, at minimum, vaccination of girls ages 9 to 14. In the near future, screening will have to accompany vaccination.

Secondary Prevention of Cervical Cancer: American Society of Clinical Oncology Resource-Stratified Clinical Practice Guideline

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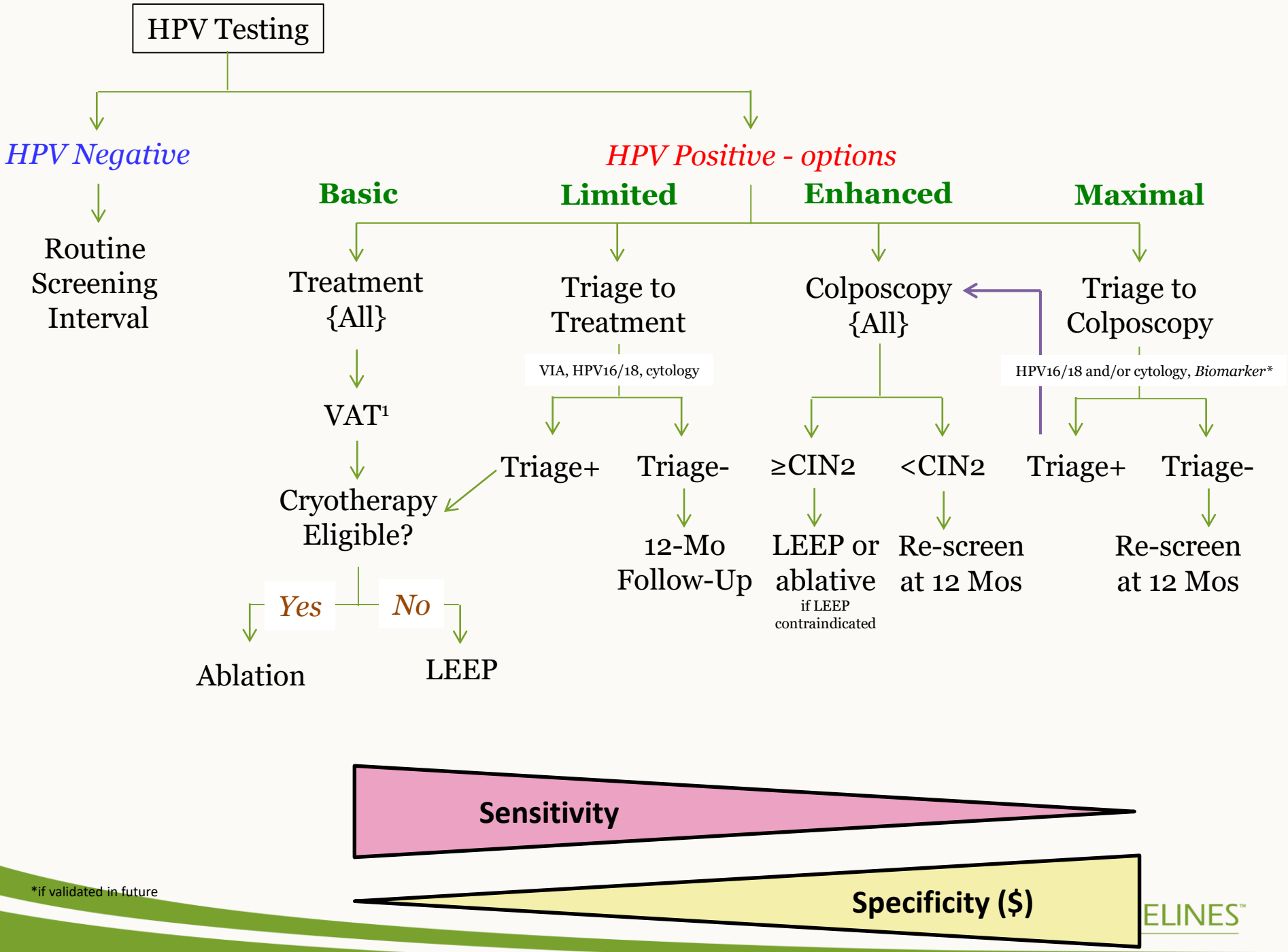
HPV Testing
HPV Negative
Routine Screening Interval
HPV Positive - options
Basic
Limited
Enhanced
Maximal
Treatment {All}
VAT1
Cryotherapy Eligible?
Yes
No
Ablation
LEEP
Triage to Treatment
VIA, HPV16/18, cytology
Triage+
Triage-
12-Mo Follow-Up
Colposcopy {All}
≥CIN2
<CIN2
LEEP or ablative
if LEEP contraindicated
Re-screen at 12 Mos
Triage to Colposcopy
HPV16/18 and/or cytology, Biomarker*
Triage+
Triage-
Re-screen at 12 Mos
Sensitivity
Specificity ($)
*if validated in future

Summary of Recommendations

Maximal resource setting

- In maximal resource settings, cervical cancer screening with HPV DNA testing should be offered every 5 years from ages 25 to 65 years. On an individual basis, women may elect to receive screening until 70 years of age.

- Women who are ≥ 65 years of age who have had consistently negative screening results during past ≥ 15 years may cease screening.

Summary of Recommendations

Enhanced Resource Setting

- In enhanced resource settings, cervical cancer screening with HPV DNA testing should be offered to women 30 to 65 years of age, every 5 years.

- If there are two consecutive negative screening test results, subsequent screening should be extended to every 10 years

- Women who are ≥ 65 years of age who have had consistently negative screening results during past ≥ 15 years may cease screening

Summary of Recommendations

Basic Resource Setting

- If HPV DNA testing for cervical cancer screening is not available, then VIA should be offered with the goal of developing health systems and moving to population-based screening with HPV testing at the earliest opportunity. Screening should be offered to women 30 to 49 years of age, at least once per lifetime, but not more than three times per lifetime.

- If the results of available HPV testing are positive, clinicians should then perform VAT followed by treatment with cryotherapy and/or LEEP, depending on the size and location of the lesion.

Cost and Policy Implications

- The secondary prevention of cervical cancer is a cost-effective strategy to reduce the incidence and mortality of cervical cancer.
- Cost-effectiveness analyses discussed in this guideline support the introduction of HPV DNA tests in maximal-, enhanced-, and limited-resource settings and the introduction of VIA in basic-resource settings.
- However, there are specific implementation issues regarding providing screening and treatment in limited and basic settings in primary care, outside of research studies.
- Targeting screening to women in their 30s reduces the number of women needing screening, thereby reducing burden on the health care system and costs, and decreases the number of screen-detected cancers, the latter of which typically peaks in women in their 40s and 50s.
- Additional strategies to further implementation of mass screening include buy-in from policymakers, which affects the provision of resources, including physical infrastructure; prioritizing cancer prevention; sponsorship of screening; and quality control.

Future Directions

In addition to addressing research limitations, future research is needed in other areas, e.g., self-collection, biomarkers, needs and preferences of women, low cost technology, and the impact of vaccination on screening.

Addressing policy/health system barriers may include:

- Education of medical and public health communities to change practices and incorporate new technologies
- Participation and sponsorship from policymakers
- Partnerships with institutions/regions/countries with treatment facilities
- Coordinated, volume purchasing and procurement of HPV testing
- Improvement of health information systems in order to have better follow-up and treatment of women with positive screening results
- Quality control
- Monitoring and evaluation

Management and Care of Women with Invasive Cervical Cancer: American Society of Clinical Oncology Resource-Stratified Clinical Practice Guideline

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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 conization, hysterectomy or radical hysterectomy, radiation therapy, and/or chemotherapy.

- 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.

Clinical Questions

This clinical practice guideline addresses 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 in

  (1) Workup

  (2) Treatment

  (3) Follow-up and post-treatment surveillance

  (4) Palliative care

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.

Treatment Capacity

Treatment	Setting			
	Basic	Limited	Enhanced	Maximal
Surgery	Simple (extrafascial) hysterectomy or more extensive hysterectomy can be performed*	**Modified radical and radical hysterectomy**	**Capable of performing most major surgeries,** including radical hysterectomy, **radical trachelectomy,† pelvic and para-aortic LN sampling, and pelvic exenteration†** Following are not available: PET scan, interventional radiology, sentinel node biopsy/IORT, and bevacizumab	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**
Chemotherapy	Availability of chemotherapy drugs is unpredictable	**Chemotherapy may be available**	**Chemotherapy available**; bevacizumab not available	Chemotherapy available; **bevacizumab is available**
Radiation therapy	No radiation therapy available	**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	**RT including external beam and brachytherapy available;** interventional radiology not available	RT including external beam and brachytherapy available; interventional radiology available

Treatment Capacity

Treatment	Setting			
	Basic	Limited	Enhanced	Maximal
Pathology	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.)	**Pathology services in development** (There are basic pathology and **frozen section** services. Consultations are not readily available.)	Pathology services in development or not always available (Pathology services including frozen sections are available. Tumor registry and regular multidisciplinary conferences are not consistently available in the region.)	**Pathology available** **(Full pathology services including diagnosis, consultation, tumor registry, and multidisciplinary conferences are available.)**
Palliative care	Palliative care service is in development; basic palliative care, including pain and symptom management, should be provided‡	**Pain and symptom management available**; palliative care service is in development	Palliative care service not always available	**Palliative care service available**

*Where medical facilities exist to take care of women who are at high risk for postoperative complications
†Can be performed in some enhanced levels
‡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.

Work Up

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

NOTE. Bold indicates addition of a recommended action over a previous resource level (eg, 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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Summary of Recommendations

Type of Disease	Setting			
	Basic	Limited	Enhanced	Maximal
IA1, LVSI negative, FS	1A1 (negative margins): cone biopsy[1] (with scalpel) Repeat cone biopsy or extrafascial hysterectomy for positive margins Type of recommendation: evidence-based Evidence: high Recommendation: strong	1A1 (negative margins): cone biopsy Repeat cone biopsy or extrafascial hysterectomy for positive margins Type of recommendation: evidence-based Evidence: high Recommendation: strong	1A1 (negative margins): cone biopsy Repeat cone biopsy, or extrafascial hysterectomy for positive margins. Type of recommendation: evidence-based Evidence: high Recommendation: strong	1A1 (negative margins): cone biopsy Repeat cone biopsy or extrafascial hysterectomy for positive margins Type of recommendation: evidence-based Evidence: high Recommendation: strong
IA1, LVSI positive, FS	Cone biopsy in selected cases, if follow-up possible Type of recommendation: consensus-based Evidence: intermediate Recommendation: weak	Cone biopsy Type of recommendation: consensus-based Evidence: intermediate Recommendation: weak	Cone biopsy **plus PLND** (see Discussion regarding current evidence on FS sparing for women desiring fertility preservation) Type of recommendation: evidence and consensus-based Evidence: high Recommendation: strong	Cone biopsy plus PLND Type of recommendation: evidence and consensus-based Evidence: high Recommendation: strong
			OR **radical trachelectomy plus pelvic LND** Type of recommendation: evidence and consensus-based Evidence: intermediate Recommendation: moderate	OR radical trachelectomy plus PLND **(may offer ± SLN)** Type of recommendation: evidence and consensus-based Evidence: intermediate Recommendation: moderate

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Summary of Recommendations

Type of Disease	Setting			
	Basic	Limited	Enhanced	Maximal
IB2 and IIA2	If chemotherapy is available, use NACT followed by extrafascial hysterectomy; if chemotherapy is not available, extrafascial hysterectomy (modification as deemed necessary) may be performed if the surgical capacity is present Type of recommendation: consensus-based Evidence: low Recommendation: weak	If chemotherapy is available, NACT **followed by radical hysterectomy (see Note) plus PLND ± para-aortic LN sampling may be an option**[4,6] Type of recommendation: evidence-based Evidence: intermediate Recommendation: moderate	**Pelvic RT plus concurrent low-dose platinum-based chemotherapy plus brachytherapy** Type of recommendation: evidence-based Evidence: high Recommendation: strong	Pelvic RT plus concurrent low-dose platinum-based chemotherapy plus brachytherapy Type of recommendation: evidence-based Evidence: high Recommendation: strong
		If EBRT is available, but not brachytherapy, then chemoRT followed by extrafascial hysterectomy or RT (if chemotherapy not available) followed by extrafascial hysterectomy (see Note) Type of recommendation: consensus-based Evidence: low Recommendation: weak	**Pelvic RT plus** concurrent low-dose platinum-based chemotherapy **plus brachytherapy plus adjuvant hysterectomy**; adjuvant hysterectomy is not recommended except if evidence of presence of residual disease Type of recommendation: evidence-based Evidence: intermediate Recommendation: weak	Pelvic RT plus concurrent low-dose platinum-based chemotherapy plus brachytherapy plus adjuvant hysterectomy; adjuvant hysterectomy is not recommended except if evidence of presence of residual disease Type of recommendation: evidence-based Evidence: intermediate Recommendation: weak

Summary of Recommendations

Type of Disease	Setting			
	Basic	Limited	Enhanced	Maximal
IIIB to IVA	Palliative care Type of recommendation: evidence-based Evidence: intermediate Recommendation: strong	**ChemoRT or RT[6] followed by extrafascial or radical hysterectomy (see Note) ± PLND[7] ± PANB** **NACT (followed by radical hysterectomy plus PLND[7] ± PANB may be an option] and/or palliative care** Type of recommendation: consensus-based Evidence: low/intermediate Recommendation: weak/moderate	**Pelvic RT plus brachytherapy plus** concurrent low-dose platinum-based chemotherapy **(in some cases extended-field RT)** AND/OR palliative care Type of recommendation: evidence-based Evidence: high Recommendation: strong	Pelvic RT plus brachytherapy plus concurrent low-dose platinum-based chemotherapy (in some cases extended-field RT) AND/OR palliative care (Options before palliative care alone include: **RT boost, salvage surgery,** or chemotherapy) Type of recommendation: evidence and consensus-based Evidence: high Recommendation: strong
	NACT followed by extrafascial hysterectomy Type of recommendation: consensus-based Evidence: insufficient Recommendation: weak	**RT ± concurrent low-dose platinum-based chemotherapy (may offer systemic adjuvant chemotherapy)** Type of recommendation: evidence-based Evidence: intermediate Recommendation: moderate	RT + **brachytherapy** ± concurrent low-dose platinum-based chemotherapy (may offer systemic adjuvant chemotherapy) Type of recommendation: evidence-based Evidence: intermediate Recommendation: weak	RT + brachytherapy ± concurrent low-dose platinum-based chemotherapy (may offer systemic adjuvant chemotherapy) Type of recommendation: evidence-based Evidence: intermediate Recommendation: weak
Note		Wherever radical hysterectomy with concurrent chemoRT listed as a surgical option above, **extrafascial hysterectomy is preferred if there is residual disease or initial tumor > 6 cm** Type of recommendation: consensus-based Evidence: intermediate Recommendation: weak		

Chemotherapy Regimens for Stage IV or Recurrent Disease

Setting			
Basic	Limited	Enhanced	Maximal
Single-agent platinum-based therapy (cisplatin or carboplatin)	Cisplatin or carboplatin, **cisplatin plus paclitaxel, or carboplatin plus paclitaxel**	Cisplatin plus paclitaxel or Carboplatin plus paclitaxel (highest-level evidence for cisplatin: CCO)	Cisplatin plus paclitaxel **plus bevacizumab** or carboplatin plus paclitaxel **plus bevacizumab**

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Special Commentary

Palliative Care for Women with Advanced Cervical Cancer

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

- Pain control is a vital component of palliative care; it is a basic human right often neglected in cancer control programs.

- 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

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.

- 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.

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.

Additional Resources

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

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

Patient information is available at www.cancer.net