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Current Management of Locally Advanced and Metastatic Cervical Cancer in the United States

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abstract

Despite decreases in incidence in the twentieth century, cervical cancer continues to be a highly morbid disease in the United States. For those diagnosed with locally advanced disease, single-agent cisplatin-based chemotherapy concurrent with radiation remains the mainstay of treatment. For patients with metastatic, progressive, and recurrent disease, treatment typically consists of combination chemotherapy and incorporation of bevacizumab, and recent data show benefits with the addition of upfront immunotherapy in women whose cancer expresses programmed death ligand-1. The physical sequelae of locally advanced cervical cancer treatments stem largely from irradiation of the pelvis, and treatment of these is aimed at identifying reversible or treatable causes of symptoms and palliating those with irreversible causes. From a psychologic standpoint, patients with cervical cancer face the stigma of having a preventable cancer caused by a sexually transmitted infection and the ramifications of sexual dysfunction. Clinicians must invite honest dialogue to be able to address specific survivorship issues.

JCO Oncol Pract 18:417-422. © 2022 by American Society of Clinical Oncology

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INTRODUCTION

An estimated 14,480 new cases of cervical cancer are expected in the United States in 2021.[1] For those diagnosed with invasive cervical cancer, the treatment options in 2021 are largely unchanged from the previous decade, and although more attention has been paid to survivorship issues in the 21st century, invasive cervical cancer remains a disease with high physical and psychologic morbidity. In this review, we discuss the epidemiology, treatment, and survivorship issues related to locally advanced and advanced cervical cancer.

EPIDEMIOLOGY

In 1930, cervical cancer was the leading cause of cancer death in American women. The Papanicolaou smear was developed in the 1940s, and wide-scale public screening was put in place in the United States in the 1960s. By 2007, the overall incidence of invasive cervical cancer decreased by more than 50% in the United States, with steeper decreases in African-American women, who traditionally suffered significantly higher incidence of cervical cancer.[1] Although the incidence gap is closing, mortality still remains higher for African-American women than for White American women. In 2006, the first recombinant human papillomavirus (HPV) vaccine became available in the United States. Although its full effect on invasive cervical cancer incidence will likely not be fully seen for decades, the 2020 American Cancer Society guideline has changed the recommended age of cervical cancer screening initiation from 21 to 25 years, because of the first generation of vaccinated women now coming into this age group.[2] However, the decrease in incidence of cervical cancer in the United States has slowed in the 2000s and plateaued during the 2012-2017 period.[3] A 2016 geospatial study of cervical cancer prevention posits that this is driven by the fact that minorities and those who live in low socioeconomic communities continue to be underserved.[4] Finally, although this article focuses on the United States, it should be noted that the incidence and mortality of cervical cancer remain high worldwide.[5]

Ninety-five percent (95%) of invasive cervical cancers in the prescreening era were squamous cell carcinoma, but there has been a disproportionate decrease in squamous cell carcinoma since the implementation of the Pap test for screening. By 2007, squamous cell carcinoma accounted for about 75% of invasive cervical cancer, with adenocarcinoma and adenosquamous carcinoma accounting for most of the additional 25% and a wide range of rare histologies including neuroendocrine tumors, adenoid cystic carcinoma, and mixed epithelial and mesenchymal tumors making up < 2% of all histologies.[6]

PRESENTATION

Just more than half of invasive cervical cancer cases involve regional or distant metastases at diagnosis.[7]

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Accepted on February 20, 2022 and published at ascopubs.org/journal/op on March 14, 2022: DOI https://doi.org/10.1200/OP.21.00795

Although early disease is often asymptomatic and discovered through routine screening, patients with locally advanced cervical cancer are more likely to present with symptoms such as irregular vaginal bleeding, postcoital bleeding, and vaginal discharge. Pelvic pain, bone pain, back pain because of hydronephrosis, and other urinary or bowel symptoms at presentation are associated with advanced and metastatic disease.

STAGING

As the burden of disease lies more heavily in resource-poor settings worldwide, cervical cancer staging has historically relied heavily on physical examination and low-cost imaging modalities, as reflected by previous staging methods. Although fairly effective at detecting very early-stage and very late-stage disease, these modalities are not sensitive or specific in determining lymph node involvement, which has important prognostic and treatment implications. Clinicians in resource-rich settings have used advanced imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scans to guide treatment decisions regardless of formal staging. The 2018 International Federation of Gynecology and Obstetrics staging system (summarized in Table 1), while remaining a clinical staging system, has incorporated precise measurements of tumor size and specific information about lymph node involvement to allow for more clinically relevant staging when this information can be obtained.[9]

In general, evaluation of invasive cervical cancer is made of the tumor size, parametrial spread, lymph node involvement, and distant metastasis. In a multicenter clinical trial comparing clinical examination, CT, and MRI, MRI is found to be superior in the measurement of tumor size and determination of uterine body involvement.[10] Ultrasound imaging is comparable and can be used where MRI is not available.[11] As for lymph node involvement, noninvasive evaluation with CT, MRI, and fluorodeoxyglucose-PET/CT all plays a role with good specificity. However, sensitivity is relatively poor, and tumor involvement of para-aortic nodes may be found on surgical lymph node evaluation without suspicion on imaging. Evaluation for distant metastasis should be performed with full-body PET/CT or, if not available, contrasted CT imaging of the chest, abdomen, and pelvis.

TABLE 1. Summary of FIGO Staging

Categorization	FIGO 2018 Stages	Description
Early-stage	IA, IB1, IB2	Invasive cervix-only disease < 5 mm deep and deeply invasive cervix-only disease smaller than 4 cm in the greatest dimensions
Locally advanced	IB3, II, III, IVA	Deeply invasive cervix-only disease larger than 4 cm, disease that invades beyond the uterus, into regional lymph nodes, and into adjacent organs
Metastatic	IVB	Cancer that extends beyond the pelvis into distant organs

NOTE. For full staging details, see Revised FIGO staging for carcinoma of the cervix uteri.[8]

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics.

PRIMARY TREATMENT FOR LOCALLY ADVANCED DISEASE

In resource-rich settings, the backbone of primary treatment for locally advanced cervical cancer is concurrent chemoradiation. As more than 90% of all cervical cancer are squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma by histology, the below discussion pertains to these types.

All patients with locally advanced cervical cancer are potential candidates for primary chemoradiation. Weekly cisplatin concurrent with radiation therapy is the primary treatment of choice. For stage IIA1 disease, surgical management with lymphadenectomy can be considered instead of primary chemoradiation. In stage IIB through IVA disease, surgery alone is unlikely to be curative and surgery followed by radiation has shown higher rates of complications compared with primary chemoradiation.[12]

Cisplatin-based doublet therapies concurrent with radiation are no longer prescribed in routine practice. For example, cisplatin and fluorouracil (FU) with concurrent radiation, when compared with single-agent cisplatin with radiation, showed no benefit in complete response rate, progression-free survival (PFS), or 4-year survival, while having increased morbidity.[13]

For patients who are suboptimal candidates for cisplatin, such as those with pre-existing chronic renal failure or significant baseline neuropathy, weekly carboplatin dosed by area under the curve two should be considered. In patients with renal dysfunction caused by malignant ureteral obstruction, re-establishment of urinary flow with ureteral stenting should be pursued before treatment, as normalization of renal function may restore candidacy for cisplatin. A study of 51 patients who received carboplatin with concurrent radiotherapy showed similar response and toxicity profiles when compared with historical controls who had been chosen to receive cisplatin and concurrent radiation.[14] Furthermore, an observational, noninferiority study of patients with locally advanced cervical cancer assigned to cisplatin or carboplatin and concurrent radiotherapy showed no significant difference in terms of local control, disease-free survival, and 3-year overall survival (OS) although the study was underpowered.[15] Aside from carboplatin, there is scarce evidence for other agents to be used first line in primary chemoradiation. A promising study of single-agent gemcitabine has raised the need for further investigation,[16] and others involving single-agent FU and paclitaxel, also agents used in the setting of recurrence, have not shown appropriate benefit profiles in primary treatment to warrant recommendation.

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The nuances of radiation therapy are beyond the scope of this article. For the medical oncologist, however, it is important to note that the recommended regimen for locally advanced cervical cancer is external beam radiotherapy (EBRT) plus brachytherapy boost. EBRT dedicated to the pelvis is the most common initial therapy and should cover sites of disease. Extended field radiation to include the para-aortic lymph nodes should be considered and is routinely used for those with high common iliac and para-aortic nodal involvement although it comes at the cost of significant morbidity.[17] During this period, brachytherapy is recommended to begin for all patients when appropriate shrinkage of the tumor occurs, usually between the third and fifth weeks of EBRT or after its completion. Brachytherapy utilization has declined since the 1980s although it saw some recovery in the early 2010s.[18] Regardless of the trend, brachytherapy, although resource-intensive and not available in all settings, should be considered an essential component of the standard of care for patients, and recent advances in image-guided brachytherapy should make new options available to patients. All radiotherapy should be completed within 8 weeks, and treatment holidays are discouraged because of the negative impact on the rate of cure.

There is no evidence that adjuvant chemotherapy has benefit after completion of primary chemoradiation, as demonstrated in the recent OUTBACK study.[19]

TREATMENT FOR METASTATIC, PROGRESSIVE, AND RECURRENT DISEASE

Stage IVB disease makes up around 15% of cervical cancer cases in the United States.[1] Metastasis generally occurs via lymphatic spread to the pelvic and para-aortic nodes or hematogenous spread to the lungs, bones, liver, and other distant organs.[20] Oligometastatic disease amenable to local treatment may be treated with definitive radiotherapy to or resection of metastases and systemic therapy.[21] For patients with recurrent or persistent disease confined to the pelvis after prior radiation treatments, cure may still be possible with pelvic exenteration. This surgery should be performed only at a center with expertise in gynecologic oncologic surgery. In the same population but with no history of previous radiation, radiation or systemic therapy with site-directed radiation may be considered for palliation.

For those with stage IVB disease or recurrent disease with multiple sites of metastases, metastases not covered in a single radiation field, or metastatic disease otherwise not amenable to local treatment, treatment is palliative in intent and long-term survival is rare. Palliative care should be provided in conjunction with, or sometimes in place of, primary systemic therapy.

For those receiving primary systemic treatment for metastatic disease or for those who have previously received single-agent platinum therapy and now has recurrent disease, combination chemotherapy is recommended, along with bevacizumab where available, as its addition has been shown to significantly increase OS, PFS, and objective response rate compared with chemotherapy alone (See Table 2).[22] Preferred combination therapy consists of cisplatin and paclitaxel with bevacizumab, with carboplatin in place of cisplatin for contraindication or intolerance or in women who previously received cisplatin as part of their initial therapy. Alternative chemotherapy regimens of cisplatin and vinorelbine, cisplatin and topotecan, and cisplatin and gemcitabine have been found to be nonsuperior to cisplatin and paclitaxel.[23] All these platinum-based combination therapies have significant toxicities.[24]

Recently, a phase III study of 617 patients with persistent, progressive, or metastatic cervical cancer found that the addition of pembrolizumab to a first-line platinum-based regimen with or without bevacizumab provides OS and PFS benefits in patients whose tumor expresses programmed death ligand-1.[25] Although immunotherapy is generally well tolerated, toxicities may involve any organ system and can lead to interruptions in care or discontinuation. Guidelines for diagnosis and management of immunotherapy-related toxicities can be found at National Comprehensive Cancer Network's website.[26]

With regard to second-line therapies, the newcomer to the list is tisotumab vedotin-tftv, a tissue factor–directed antibody and microtubule inhibitor drug conjugate specifically for use in metastatic cervical cancer that has progressed on chemotherapy.[27] Tisotumab vedotin was granted accelerated approval by the US Food and Drug Administration in September 2021 on the basis of a single-arm trial of 101 patients, and studies are ongoing. Other active agents include paclitaxel, topotecan, and carboplatin. If pembrolizumab has not been previously used, it may be used as a single agent for patients with tumor programmed death ligand-1 expression

TABLE 2. Summary of Treatment Options for Locally Advanced and Metastatic Cervical Cancer

Stage	Treatment Options
IB3	Chemoradiation
IIA1	Chemoradiation Surgical management
IIA2	Chemoradiation
IIB	Chemoradiation
III	Chemoradiation
IVA	Chemoradiation
IVB	Systemic therapy with or without radiation to metastatic sites for cancers with oligometastasis Systemic therapy using chemotherapy plus bevacizumab Systemic therapy using chemotherapy plus pembrolizumab with or without bevacizumab for PD-L1–expressing tumors Supportive care for all

Abbreviation: PD-L1, programmed death ligand-1.

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or high microsatellite instability/mismatch repair deficiency.[28] Otherwise, agents such as albumin-bound paclitaxel, docetaxel, FU, gemcitabine, ifosfamide, irinotecan, mitomycin, pemetrexed, and vinorelbine may play a role. However, as objective response rate for these therapies ranges from 15-22% at best and may come with significant toxicities, palliative care should be considered as a viable alternative.

POST-TREATMENT SURVEILLANCE

Patients with locally advanced or metastatic disease are at high risk for recurrence, with a majority of recurrences happening in the first 2 years, and should be followed every 3 months in the first 2 years, every 6 months for 3 years, and annually thereafter.[29] There is no consensus on the modality of surveillance at these intervals except for a careful physical examination, especially of the pelvic organs. Imaging can be used to augment physical examination when clinically indicated.

SURVIVORSHIP

As of January 1, 2018, there were 293,394 people alive with cervical cancer in the United States.[1] Patients living with cervical cancer or the sequelae of cervical cancer treatment deal with a host of physical, emotional, and social issues unique to the disease, and younger age at diagnosis leads to more survivorship issues over time.

The physical sequelae of locally advanced cervical cancer treatments stem largely from irradiation of the pelvis and include dysfunction of the bowel, bladder, and sexual organs. Treatment for these symptoms is aimed at identifying reversible or treatable causes of symptoms and palliating those with irreversible causes.

Dysfunction of the bowel is very common after pelvic irradiation, and incidence is higher than that in patients who receive surgery alone, with up to half of patients reporting decreased quality of life from bowel issues over a 20-year period.[30] Bowel dysfunction in patients who have received radiation can arise from more than one cause at a time, leading to symptoms including nausea, vomiting, diarrhea, constipation, and fecal urge or incontinence. Bowel symptoms, especially fecal urge and incontinence, are particularly linked to social isolation and depression. Bladder dysfunction is another potential long-term effect of radiation therapy, and urinary problems such as urgency or neurogenic bladder may be chronic for years after treatment has ended.[31] Those treated with surgery, and especially lymph node dissection, often report chronic lymphedema, which can negatively affect the quality of life. In addition, cancer-related fatigue can be chronic in some patients.

Sexual dysfunction in survivors is prevalent, more pronounced in younger patients, and is often related to treatment-related menopause and direct treatment effects on sexual organs.[32] Patients may suffer in silence, and it is important for oncologists to destigmatize discussion about issues of sexuality. For common post-treatment sequelae that lead to increased sexual dissatisfaction such as decreased vaginal lubrication, dyspareunia, shortened vaginal canal, and decreased vaginal elasticity, there exist a variety of interventions, such as vaginal lubricants and moisturizers, topical anesthetics, vaginal dilators, participation in pelvic physical therapy, and referral to urogynecology. Postmenopausal symptoms can also be addressed pharmacologically. Oncologists should be cognizant of psychologic barriers to sexual well-being, such as decreased sexual interest, anxiety about sexual activity, and body image issues, and provide appropriate support. For two excellent resources on ways to address sexual health problems in patients with cancer, see the clinical practice guides from the studies by Carter et al and Bober et al.[33,34]

Aside from the psychologic implications related to sexual well-being, patients are also at risk for mood disturbances such as dysphoria and anxiety. Scanxiety is a well-described phenomenon in oncology, and patients with cervical cancer are not immune, especially given the risk for recurrence and frequent post-treatment surveillance in locally advanced cervical cancer. Furthermore, patients with cervical cancer face the stigma of having a preventable cancer caused by a sexually transmitted disease. The stigma of cervical cancer is tragically elucidated in a 2013 study, where participants read case descriptions of patients with cancer caused by family history or by HPV and then rated patients with HPV-caused cancer as more dirty, dishonest, and unwise and felt more moral disgust for these patients.[35] Patients may blame themselves for undergoing infrequent cervical cancer screening, for not having received the HPV vaccine, and for having contracted HPV. Besides exploring conscious and unconscious biases and leaving these outside the examination room, clinicians can help patients by inviting honest dialogue about difficult topics, and cervical cancer support and advocacy groups may provide a safe setting where patients can talk about disease-specific issues without fear of judgment.

SPECIAL CONSIDERATIONS FOR NONTRADITIONALLY GENDERED PATIENTS

Although cisgender women with cervical cancer face many challenges, nontraditionally gendered patients with cervical cancer are a unique and underserved demographic. Transgender men and nonbinary individuals assigned female at birth who have not had gender confirmation procedures and/or retain their uterine cervix are at risk for cervical cancer at rates comparable with cisgender women, but have lower rates of cervical cancer screening and therefore at higher risk for invasive cancer at diagnosis. The causes for decreased screening are multifactorial. A 2020 scoping review found high levels of knowledge regarding cervical cancer risk among transgender male survey participants, but barriers to care included triggering of gender dysphoria, physical pain on speculum examination

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because of hormone-related vaginal changes, perception of provider insensitivity and lack of knowledge, deficiency of health care system accommodations, and health insurance coverage issues.[36] In addition, androgen use and clinician's lack of experience with the anatomy in question appear to result in higher rates of inadequate Pap test samples in transgender male patients.[37] Fortunately, recent studies have seen a rise in screening rates using self-collected HPV swabs instead of the traditional Pap test.[38] Once diagnosed, invasive cervical cancer is treated similarly in transgender male patients as in cisgender female patients. In addition to the above physical and psychosocial considerations during and after treatment, transgender male patients also face issues such as gender dysphoria when dealing with a gynecologic disease.

In conclusion, although significant strides have been made in prevention of cervical cancer, progress has stalled recently in the United States. The first-line treatment for patients with locally advanced cervical cancer remains cisplatin with radiotherapy, whereas the treatment of metastatic and recurrent disease has seen more change, with the addition of bevacizumab and pembrolizumab, respectively. Patients experience significant disease and treatment-related morbidity, and oncologists should address treatment-related issues. In 2018, the WHO announced a global initiative to eliminate cervical cancer within the next century.[39] Until that happens, additional work needs to be performed to improve therapeutics and supportive care for patients with cervical cancer.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/OP.21.00795.

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Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Current Management of Locally Advanced and Metastatic Cervical Cancer in the United States

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Research Funding: Aduro Biotech (Inst), Lilly (Inst), Tesaro (Inst), Novartis (Inst), VBL Therapeutics (Inst), AstraZeneca (Inst), Merck (Inst)
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No other potential conflicts of interest were reported.

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