

Management of Recurrent or Metastatic Cervical Cancer

Presented by Nadeem R. Abu-Rustum, MD

ABSTRACT

Cervical cancer often affects individuals aged <50 years, with the main cause being a long-lasting infection with certain types of human papillomavirus (HPV). Prevention of cervical cancer includes screening tests and the HPV vaccine and, if found early, it can be treatable. Metastatic disease, however, is more lethal and is a significant problem worldwide due to screening and treatment limitations. Clinicians should discuss early detection options and treatment modalities with patients with cervical cancer for informed decision-making.

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Despite the availability of the human papillomavirus (HPV) vaccine, cervical cancer remains a significant problem in the United States and worldwide.¹ Furthermore, the treatment of recurrent or metastatic disease continues to pose even more of a challenge to clinicians. At the NCCN 2023 Annual Conference, Nadeem R. Abu-Rustum, MD, Chief, Gynecology Service; Avon Chair in Gynecologic Oncology Research, Memorial Sloan Kettering Cancer Center; Professor, Weill Cornell Medical College; and Chair of the NCCN Guidelines Panel for Cervical Cancer discussed significant advances in surgery, radiation therapy (RT), and chemotherapy for cervical cancer, as well as treatment limitations for this disease.

Initial Treatment of Recurrent Cervical Cancer

Identifying the location of recurrence, whether localized to the pelvis or a distant site, is a crucial first step in the treatment of recurrent cervical cancer. The nature of primary therapy is then established. In most cases, when surgery was the first treatment, RT or chemotherapy can be used as therapy for recurrence. However, initial treatment with RT warrants the use of chemotherapy or surgery in the second line. According to Dr. Abu-Rustum, it is important to note that although chemotherapy can be applied more broadly and used repeatedly, reapplication of definitive RT to the same field is frequently not possible or is unsuccessful.¹ Therefore, surgery is often the best treatment option for these patients.

There are other considerations to determining the treatment modality, such as location of the recurrence, whether it is in the central or pelvic side wall, and whether the recurrence affects the iliac blood vessels, nodal basins, or even related muscular structures. “That would make a big difference in our ability to control this

disease,” he mentioned. “Of course, most importantly, it’s also the patient’s preferences, as well as the patient’s overall medical comorbidities to which these therapies should be tailored, because all of these therapies carry high morbidity and toxicity. And again, key components... are the availability of these modalities, [surgical] expertise, and resources.”

Limitations of Current Treatments

Surgery for recurrent cervical cancer is complex and ultra-radical, requiring surgical expertise and excellent anesthesia, nurses, and recovery facilities such as intensive care units due to the morbidity and extensiveness of these procedures, explained Dr. Abu-Rustum. Treatment with radiation also requires technical skills with external-beam RT, as well as interstitial brachytherapy, which is a sophisticated technology for the treatment of central pelvic recurrences.

Use of modern chemotherapy regimens containing a combination of platinum and paclitaxel with drugs such as bevacizumab and pembrolizumab is difficult in this patient population, because bevacizumab and pembrolizumab are not widely available, are expensive, and require specific expertise to be delivered. Despite their improved activity over traditional chemotherapy such as platinum and paclitaxel alone, their availability worldwide remains limited.

“As much as we would like to see the incidence of cervical cancer decrease and become an extremely rare disease, unfortunately the burden remains very high, particularly in countries with less access to healthcare, screening, and vaccinations,” stated Dr. Abu-Rustum.

Pelvic Exenteration

Due to constraints involving radiation tolerance of the bowel and other pelvic structures, patients with

local recurrence after primary radiation are not eligible for further RT. Additionally, patients who underwent prior RT and have recurrence in the radiation field, the response rate to chemotherapy is approximately 10%,² leaving surgery as the only potential curative option, according to Dr. Abu-Rustum.

“Surgery after radiation for central pelvic recurrence or pelvic recurrent disease was pioneered by Dr. Alexander Brunschwig in the 1940s. Prior to 1948, most patients who failed [to respond to] RT had a very hopeless prognosis,” Dr. Abu-Rustum commented. The surgery was performed as a one-stage abdominoperineal resection requiring a colostomy and urinary diversion. Although the original intent of these surgeries involved more of a palliative resection to remove infected tumors that developed fistulas from RT, they ultimately demonstrated long-term outcomes and even cures, he added.

Approximately 75 years later, the complete excision of the pelvic viscera is now referred to as pelvic exenteration, and remains a realistic treatment option for select patients with recurrent cervical cancer (Figure 1). Unfortunately, just 20% of potential candidates are eligible because the disease must be localized to the central pelvis. Due to the fact that many recurrences are distant, the potential for this surgery remains limited.

Distant Recurrence and Detection

The anatomic location, volume of disease—whether isolated or multisite—and patient symptoms should be considered when selecting treatments for distant disease. “Again, like with any other situation, patient preferences take priority,” added Dr. Abu-Rustum. “In the setting of distant disease, the availability of therapeutic modalities

and resources also remains paramount.” RT, chemotherapy, immunotherapy, and surgery all require significant resources, which are expensive and not available in all parts of the world.

The preferred imaging modality to detect local disease recurrence is a pelvic MRI with contrast because it displays the best resolution of pelvic structures, aids in outlining surgical resection planes, and provides an appropriate localization of tumor for possible radiation. An FDG-PET/CT scan of the neck, chest, abdomen, pelvis, and groin is the preferred modality for detecting regional and distant recurrence, according to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Cervical Cancer. However, if those modalities are not available, a CT scan of the chest, abdomen, and pelvis with contrast is acceptable, noted Dr. Abu-Rustum.³

Pathologic confirmation of a recurrence is important for the management of recurrent disease, and a biopsy of the tumor is required before proceeding to pelvic exenteration or RT. The NCCN Guidelines recommend PD-L1 testing for patients with recurrent, progressive disease, or metastatic disease; DNA mismatch repair (dMMR), microsatellite instability (MSI), and tumor mutational burden (TMB) testing are also recommended. *NTRK* and *RET* gene fusion testing can be considered for patients with cervical sarcoma and select cases of locally advanced or metastatic cervix cancer, respectively.³

Systemic Therapies

Based on available clinical trials, first-line therapy options for patients with PD-L1–positive recurrent disease include pembrolizumab + cisplatin/paclitaxel ± bevacizumab. However, despite its effectiveness, this regimen

	Comparison of Infralevator Exenteration Types			Comparison of Supralevator Exenteration Types	
	Anterior	Posterior	Total	Posterior	Total
Indication	Central pelvic recurrence Primary therapy for select FIGO stage IVA when primary radiation not feasible				
Intent	Curative				
Uterus, tubes, ovaries	Removed if still present	Removed if still present	Removed if still present	Removed if still present	Removed if still present
Vagina	Removed	Removed	Removed	Removed	Removed
Bladder and urethra	Removed	Preserved	Removed	Preserved	Removed
Rectum	Preserved	Removed	Removed	Removed	Removed
Anal sphincter	Preserved	Removed	Removed	Preserved, colonic anastomosis possible	Preserved, colonic anastomosis possible
Reconstruction options Urinary system	Ileal conduit or continent diversion	N/A	Double barrel wet colostomy, ⁿ ileal conduit, or continent diversion	N/A	Double barrel wet colostomy, ⁿ ileal conduit, or continent diversion
Reconstruction options GI system	N/A	End colostomy	Double barrel wet colostomy ⁿ or end colostomy	End colostomy or anastomosis with temporary ileostomy	Double barrel wet colostomy, ⁿ end colostomy, or anastomosis with temporary ileostomy
Neovaginal reconstruction options	Myocutaneous flap (rectus, gracilis, etc.), or split-thickness skin graft with omental J-flap				

Figure 1. Resection of locally recurrent cervical cancer with no distant metastasis (post radiation). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Cervical Cancer, Version 1.2023 [CERV-C, 6 of 7].

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is complex, potentially cost-prohibitive, and may not be available in countries with limited resources.⁴ Other first-line options may include cisplatin/paclitaxel + bevacizumab or carboplatin/paclitaxel + bevacizumab.

The KEYNOTE-826 study assessed the relative benefit of adding pembrolizumab to chemotherapy ± bevacizumab in patients with PD-L1–positive, advanced cervical cancer. Results of this trial demonstrated significantly longer progression-free and overall survival with pembrolizumab versus placebo in this patient population ($P < .001$).⁴ Dr. Abu-Rustum noted that “This trial moved this combination of pembrolizumab and platinum paclitaxel ± bevacizumab into the first choice for patients with recurrent/advanced disease, if the regimen is available.”

Other Recommended Regimens

More widely available first-line regimens include cisplatin/paclitaxel, as well as carboplatin/paclitaxel for patients who have received prior cisplatin, have had radical hysterectomy, or have multiple risk factors. RT may be added to these regimens, noted Dr. Abu-Rustum. Other combination therapies include topotecan/paclitaxel/bevacizumab, topotecan/paclitaxel, and cisplatin/topotecan.

“For second-line or subsequent therapy, preferred regimens would include pembrolizumab for TMB-high tumors or PD-L1–positive or MSI-high/dMMR tumors. Again, this would require specific pathologic evaluation that may not be available worldwide, and would allow for the consideration of pembrolizumab in that setting,” stated Dr. Abu-Rustum. Other subsequent regimens not previously listed include docetaxel, fluorouracil, gemcitabine, pemetrexed, vinorelbine, and irinotecan. In rare cases of tumors harboring *RET* gene fusions or *NTRK* gene fusions, approved drugs such as seliprecatinib and larotrectinib or entrectinib can be used, respectively.

Recurrent or Metastatic Disease	
First-line Therapy ^c	Second-line or Subsequent Therapy
Preferred Regimens <ul style="list-style-type: none"> • Cisplatin/etoposide • Carboplatin/etoposide 	Other Recommended Regimens <ul style="list-style-type: none"> • Bevacizumab^d • Albumin-bound paclitaxel • Docetaxel • Topotecan • Topotecan/paclitaxel • Cisplatin/topotecan • Cisplatin • Carboplatin • Paclitaxel • Irinotecan (category 2B)
Other Recommended Regimens <ul style="list-style-type: none"> • Cisplatin/etoposide + atezolizumab (or durvalumab)^{16,17} • Carboplatin/etoposide + atezolizumab (or durvalumab)^{16,17} • Topotecan/paclitaxel/bevacizumab^{d,18} • Cisplatin/paclitaxel • Carboplatin/paclitaxel (for patients who have received prior cisplatin therapy) 	

Figure 2. Small cell neuroendocrine recurrent or metastatic cervical cancer.

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Small Cell Neuroendocrine Cervical Cancer

Small cell neuroendocrine cervical cancer is an aggressive type of cervical cancer. Most data on treatment regimens for this disease have been adapted from lung and pulmonary disease-management guidelines, given that small cell disease is commonplace in those fields. Because this condition is rare in the gynecologic realm and few data are available on small cell cervical cancer, high-level randomized trials are difficult to achieve. However, NCCN Guidelines have outlined specific regimens that may be useful in this setting (Figure 2).³

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