

# A Primer on Cervical Cancer and Current Standards of Care

**CERVICAL CANCER IS** the fourth most common cancer in women in the United States. As of 2011, the estimated annual medical cost of care is approximately \$1.6 billion.<sup>1-4</sup> For individual patients during their last year of life, these costs can be as high as \$79,000 for those older than 65 years and \$118,000 for younger patients.<sup>3,4</sup>

Most cases of cervical cancer can be prevented by human papillomavirus (HPV) vaccination, routine screening, and treatment of precancerous lesions.<sup>1,5,6</sup> In fact, incidence rates are higher in areas where there is less access to screening. During the COVID-19 pandemic, there was a considerable decline in screening rates for cervical cancer. This decline was seen everywhere in the country and ranged from 77% in urban areas to 82% in metropolitan areas and 85% in rural areas. The most affected ethnic groups were Asian/Pacific Islander women (92%) and Black women (82%).<sup>7</sup>

Survival rates vary depending on how advanced the disease is; localized and early-stage disease have high survival rates, whereas patients with advanced and recurring disease have much poorer outcomes with the available therapies, highlighting the necessity for the expansion of treatment options.<sup>8</sup> This article provides an overview of the incidence, pathogenesis, and treatment of cervical cancer, including the current standard of care (SOC) for patients with advanced or recurring disease.

## Incidence and Risk Factors

In the United States, there has been a 50% decrease in incidence and mortality rates of cervical cancer that began in the 1970s when cervical cancer screening became widespread.<sup>3,5,6,9,10</sup> The trend of decreased rates continued following the availability and uptake of the first HPV vaccine in 2006.<sup>3,5,6,9-11</sup>

However, the pace of this decline has slowed during the past decade.<sup>3,9,10</sup> In 2018, the CDC reported 12,733 new cases of cervical cancer and about 4000 deaths. It is estimated that in 2021, these numbers will increase to 14,480 new cases and 4290 deaths.<sup>3,9,12,13</sup>

Although infections with HPV are common and rarely cause cancer, nearly all cervical cancers are caused by persistent infection with certain types of the virus.<sup>9-15</sup> In addition to persistent infection with HPV, other risk factors include tobacco smoking, long-term use of oral contraceptives, immunosuppression, HIV infection, young age at first sexual encounter, high number of sexual partners, exposure to diethylstilbestrol in utero, chlamydia infection, and multiple full-term pregnancies beginning at a young age.<sup>10,14,16-25</sup>

## Pathogenesis, Staging, and Prognosis

There are 2 main types of cervical cancers: squamous cell carcinoma (SCC) and adenocarcinoma (ADC).<sup>16,26</sup> About 80% to 90% of cervical cancers are SCCs that develop from cells in the exocervix, and 10% to 20% are ADCs that develop from the mucus-producing gland cells of the endocervix. Some tumors can also present features of both types and are called adenosquamous or mixed carcinomas.

Most cervical cancers develop in the transformation zone, which is the junction between the ectocervix and the endocervical canal.<sup>16</sup> Precancerous lesions present as intraepithelial neoplasia and are named either cervical intraepithelial neoplasia or ADC in situ. If left untreated, these lesions eventually progress

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**TABLE.** SOC Treatment Options for Cervical Cancer by FIGO Stage<sup>27</sup>

Stage (FIGO Staging Criteria)	Standard Treatment Options
Stage 0 (In situ carcinoma of the cervix) <sup>a</sup>	Conization
	Hysterectomy for postreproductive patients
	Internal radiation therapy for medically inoperable patients
<b>Early Stages</b>	
Stage IA	Conization
	Total hysterectomy
	Modified radical hysterectomy with lymphadenectomy
	Radical trachelectomy
	Intracavitary radiation therapy
Stage IB	Radiation therapy with concomitant chemotherapy
	Radical hysterectomy and bilateral pelvic lymphadenectomy
	Radical trachelectomy
	Neoadjuvant chemotherapy
	Radiation therapy alone
	IMRT
<b>Advanced Stages</b>	
Stage IIA	Radiation therapy with concomitant chemotherapy
	Radical hysterectomy and bilateral pelvic lymphadenectomy
	Radical trachelectomy
	Neoadjuvant chemotherapy
	Radiation therapy alone
	IMRT
Stages IIB, III, and IVA	Radiation therapy with concomitant chemotherapy
	Interstitial brachytherapy
	Neoadjuvant chemotherapy
Stage IVB	Palliative radiation therapy
	Palliative chemotherapy and other systemic therapy
Recurrent	Radiation therapy and chemotherapy
	Palliative chemotherapy and other systemic therapy
	Pelvic exenteration

FIGO, International Federation of Gynecology and Obstetrics; IMRT, intensity-modulated radiation therapy; SOC, standard of care.

<sup>a</sup>This stage is not recognized by FIGO.

to invasive cancer.<sup>10,16</sup> This progression is typically slow (10-12 years) for most patients (30%-70%). However, for about 10% of patients (30%-70%). However, for about 10% of patients, some lesions can progress in less than a year.<sup>27</sup>

As mentioned above, HPV infection is the main causal factor for cervical cancer, and 90% of cervical cancers are positive for HPV DNA.<sup>10,28</sup> HPV mainly targets squamous epithelium and is linked to cutaneous and mucosal infections.<sup>17</sup> There are 14 high-risk HPV types that are associated with a higher risk of cervical cancer development, and most HPV-related cancers are caused by HPV-16 and HPV-18.<sup>29,30</sup>

The immune system is often able to fight off HPV infections before they cause serious cell damage and harm, but sometimes, HPV can evade detection by the immune system. Persistent HPV infections may cause normal cells on the surface of the cervix to transform into malignant cells, which could result in cervical cancer.<sup>17,31</sup>

Cervical cancer may not initially present with any signs or symptoms.<sup>1,17,32</sup> Screening for cervical cancer involves a complete medical history, a physical and pelvic exam, and cervical cytology (Papanicolaou test). Abnormal findings can be further investigated with colposcopy, endocervical curettage, or biopsy.<sup>17,32</sup>

Based on the results from the diagnostic tests, which include the physical exam, biopsies, and imaging tests, the clinical stage of the disease can be determined.<sup>33</sup> Cervical cancer is classified according to the International Federation of Gynecology and Obstetrics (FIGO) staging system as either stage I (confined to the cervix), stage II (extended beyond the uterus but not up to the pelvic wall), stage III (extended up to the pelvic wall and/or involving the pelvic and/or para-aortic lymph nodes), or stage IV (extended beyond the pelvis).<sup>34,35</sup>

The prognosis depends on several factors, which include the clinical stage of the disease at the time of diagnosis and pelvic lymph node status.<sup>36</sup> Other factors that are associated with poor outcomes include positive HIV status, c-MYC overexpression, and HPV-18 infection.<sup>36-40</sup>

According to data from the Surveillance, Epidemiology, and End Results database, the average 5-year relative survival rate among all patients with cervical cancer (based on diagnoses between 2011 and 2017) is 66%. The relative survival rate is 92% for patients with localized disease (cancer has not spread outside the cervix or uterus), 58% for patients with regional disease (cancer has spread to nearby lymph nodes), and 18% for patients with distal disease (cancer has spread outside the cervix and uterus to nearby or distant organs).<sup>41</sup>

### Considerations for Treatment Decision-Making

The current SOC treatments for cervical cancer are summarized in the **Table**.<sup>27</sup> The most important factor

when choosing a treatment for cervical cancer is the FIGO stage. Other factors that may also influence this decision include the type of cancer (SCC or ADC), the exact location of the tumor, the age of the patient and their overall health, and the patient's wish to preserve their fertility.<sup>1,42</sup>

Typically, early-stage disease (stages IA, IB1, and IB2) can be treated with surgery.<sup>42</sup> Fertility preservation options (conization and trachelectomy) are available for patients with up to stage IB2 cervical cancer.<sup>27,42</sup> There is disagreement about whether adjuvant hysterectomy following primary chemoradiation should be recommended for stage IB or IIA tumors, as there is limited evidence of benefits and some evidence of increased morbidity associated with the procedure.<sup>27,42-45</sup> If pathologic risk factors, such as large primary tumors, deep stromal invasion, lymphovascular space invasion, positive lymph nodes, surgical margins, or parametrium, are discovered following radical hysterectomy, adjuvant treatment with radiotherapy alone or chemoradiotherapy is recommended.<sup>27,42</sup>

Radiation therapy is another appropriate option for early-stage disease.<sup>46</sup> Typically, external beam radiation therapy (EBRT) is administered to the pelvis (45-50 Gy) together with low-dose brachytherapy, if necessary. The traditional radiation therapy dose is 70 Gy for smaller tumors and up to 90 Gy for larger ones.<sup>27</sup>

Concurrent chemoradiation, a combination of platinum-containing chemotherapy and radiation therapy, is recommended for advanced-stage cervical cancer (stages IB3 through IVA), but can also be used for patients with earlier stages of the disease who are not candidates for hysterectomy.<sup>42</sup> Chemoradiation is superior to radiation alone in terms of overall and disease-free survival.<sup>47,48</sup> Cisplatin as a single agent is the preferred chemotherapy regimen and can be substituted with carboplatin if the patient is cisplatin intolerant.<sup>27,42,49-51</sup> Cisplatin/fluorouracil is an alternative first-line regimen, although it may have higher toxicity.<sup>51,52</sup> There is evidence that cisplatin/gemcitabine used concurrently with EBRT, followed by 2 additional cycles of chemotherapy after radiation therapy, may improve survival compared with survival after cisplatin therapy alone.<sup>53</sup> However, this regimen also has increased toxicity. Finally, there are nonplatinum-based options such as fluorouracil and/or mitomycin for patients who are unable to tolerate platinum-based therapy.<sup>54</sup>

Neoadjuvant chemotherapy followed by surgery can be used for stages IB through IVA. There have been several studies investigating the role of neoadjuvant chemotherapy, and the largest randomized trial showed an improvement in survival for patients with stages IB, IIA, and IIB cervical cancer. However, the results are not reflective of current practice, and the control arm used radiation therapy alone.<sup>27</sup>

Finally, in the past few years, targeted agents and biologics have been developed for the treatment of various cancers, including cervical cancer. Two of these agents, bevacizumab and pembrolizumab, are indicated for the treatment of cervical cancer.<sup>55,56</sup>

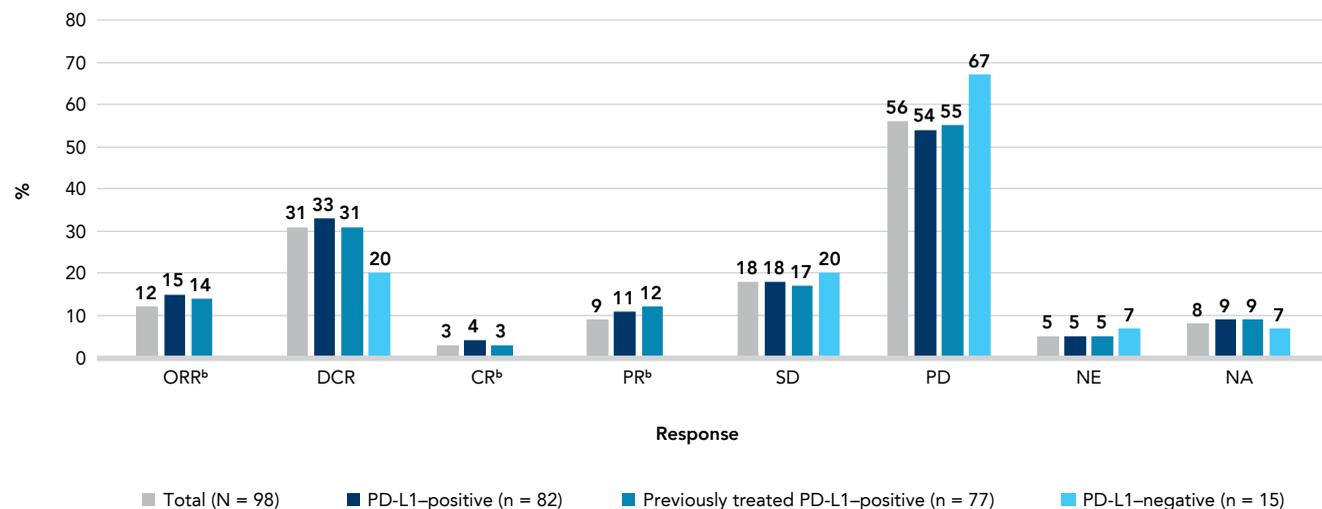
### Advanced and Recurrent Cervical Cancer

Response rates of various SOC regimens for recurrent cervical cancer range from 11% with bevacizumab monotherapy to 46% with cisplatin/paclitaxel combination.<sup>27</sup> Because the survival rate for patients with distal disease is 18%, there is a need for therapies that can adequately treat advanced and recurrent cervical cancer.<sup>41</sup> Treatment for recurrent disease depends on whether the recurrence is localized or distant.<sup>42</sup>

In general, patients with localized recurrences may be candidates for radical retreatment with radiation therapy and/or chemotherapy or with surgery, depending on the nature of the original treatment and where the recurrent tumor presents. If surgery is feasible, it should be considered; radiation therapy with or without chemotherapy is also an option.<sup>27,42</sup> The preferred chemotherapy regimens are single-agent cisplatin, carboplatin, paclitaxel, or topotecan. Other agents include docetaxel, ifosfamide, 5-fluorouracil, irinotecan, gemcitabine, and mitomycin, and drug combinations are often used.<sup>42</sup>

The prognosis for patients who experience recurrence and for those who develop distant metastases is poor.<sup>27,42</sup> The recommended treatment for patients with metastases typically includes platinum-based chemotherapy (cisplatin or carboplatin) combined with other agents such as paclitaxel and topotecan. Bevacizumab in combination with paclitaxel and cisplatin or paclitaxel and topotecan is also indicated for patients with persistent, recurrent, or metastatic cervical cancer, and its addition provides a survival benefit.<sup>27,55</sup> While cisplatin-based chemoradiotherapy treatments for early-stage disease are effective, the response rates in patients with advanced or recurrent disease range from 18% for single-agent use to 46% when combined with paclitaxel.<sup>57,58</sup> Finally, there are clinical trials available for patients with metastatic or recurrent disease.<sup>27,42</sup>

Bevacizumab is a monoclonal antibody that targets the vascular endothelial growth factor, which promotes angiogenesis and is a key mediator of cancer progression.<sup>59,60</sup> In 2014, the Gynecologic Oncology Group (GOG) 240 phase 3 clinical trial (NCT00803062) assessed the efficacy and safety of adding bevacizumab to combination chemotherapy for advanced or recurrent cervical cancer. The study enrolled 452 patients with metastatic, persistent, or recurrent cervical carcinoma, who were randomized to receive cisplatin plus paclitaxel with or without bevacizumab or topotecan plus paclitaxel

**FIGURE.** Responses to Pembrolizumab Monotherapy in Patients with Advanced PD-L1–Positive Cervical Cancer in KEYNOTE-158<sup>65,a</sup>

CR, complete response; DCR, disease control rate; NA, not able to be assessed; NE, not evaluable; ORR, objective response rate; PR, partial response; SD, stable disease.

<sup>a</sup>Assessed by an independent central review committee according to Response Evaluation Criteria in Solid Tumors v.1.1 criteria.

<sup>b</sup>The ORR, CR, and PR for patients with PD-L1–negative cervical cancer was 0.0.

with or without bevacizumab. All patients had to have a GOG performance status of 0 or 1; adequate renal, hepatic, and bone marrow function; and measurable disease. Ineligibility criteria included patients who were candidates for curative therapy by pelvic exenteration, those receiving chemotherapy for recurrence, and those with nonhealing wounds, active bleeding conditions, or inadequately anticoagulated thromboembolism. The primary end points for this study were overall survival (OS) and frequency and severity of adverse events (AEs); the secondary end points were progression-free survival (PFS) and response rate.<sup>61</sup>

At the 20.8-month follow-up, the median OS was 3.7 months longer (17.0 vs 13.3 months) for the groups that incorporated bevacizumab (HR for death, 0.71; 98% CI, 0.54–0.95). There was also improvement in PFS (8.2 vs 5.9 months), and the response rate was higher (48% vs 36%) in the bevacizumab groups.<sup>61</sup>

The main AEs of concern that were higher in the bevacizumab groups were grade 3 or higher gastrointestinal or genitourinary fistulas (6% vs 0%), thromboembolic events (8% vs 1%), and grade 2 hypertension (25% vs 2%).<sup>61</sup> Based on these results, bevacizumab combined with paclitaxel and cisplatin or paclitaxel and topotecan received FDA approval to treat patients with persistent, recurrent, or metastatic cervical cancer.<sup>55</sup>

In 2018, pembrolizumab, a monoclonal antibody against PD-1, received approval by the FDA for the treatment of recurrent or metastatic cervical cancer on or after chemotherapy whose tumors express PD-L1 (combined

positive score [CPS]  $\geq 1$ ).<sup>62,63</sup> PD-1 is a receptor expressed on the surface of T cells that acts in an immunoregulatory capacity and can contribute to carcinogenesis by allowing tumors to evade immunosurveillance.<sup>63–65</sup>

One of the pivotal trials leading to the approval of pembrolizumab as a treatment for cervical cancer was KEYNOTE-158 (NCT02628067), a phase 2 basket study that investigated the efficacy and safety of pembrolizumab in adult patients with previously treated advanced solid tumors.<sup>62,65</sup> Patients in the cervical cancer cohort (N = 38) had measurable disease confirmed histologically or cytologically, progression during or intolerance to standard therapies, an ECOG performance status of 0 or 1, and adequate organ function. PD-L1 expression was assessed from a new or archived nonirradiated tumor sample; PD-L1 positivity was defined as CPS  $\geq 1$ . Exclusion criteria included active central nervous system metastases; active autoimmune disease; history of noninfectious pneumonitis; prior targeted therapy against PD-1, PD-L1, PD-L2, or another coinhibitory T-cell receptor; therapy with an antineoplastic antibody in the previous 4 weeks; other antineoplastic therapy in the previous 2 weeks; or unresolved AEs from previous therapies. The primary end point was the objective response rate (ORR) and the proportion of patients with a complete response (CR) or partial response (PR). DOR was one of the secondary end points.<sup>65</sup>

Responses to pembrolizumab monotherapy in the KEYNOTE-158 trial are shown in the **Figure**.<sup>65</sup> The ORR

among all patients in the cervical cancer cohort was 12%, which included CR of 3%, PR of 9%, and stable disease (SD) of 18%. DOR was not reached.

Patients with PD-L1–negative tumors (n = 15) did not obtain CR or PR with pembrolizumab, but 20% obtained SD. Conversely, among patients in the cervical cancer cohort with PD-L1–positive tumors (n = 82) the ORR was 15% (CR, 4%; PR, 11%; SD, 18%); of these, the ORR among patients whose disease was previously treated (n = 77) was 14% (CR, 3%; PR 12%; SD, 17%).<sup>65</sup>

Disease progressed in 56% of patients in the cervical cancer cohort, which included 54% of patients with PD-L1–positive tumors and 67% of patients with PD-L1–negative tumors.

Among patients in the cervical cancer cohort, no treatment-related mortality was observed, and 4 patients discontinued treatment because of AEs.<sup>65</sup>

## Conclusion

Advanced and recurring cervical cancer is associated with a considerable economic and health care burden. Increased rates of screening and the introduction of the HPV vaccine have led to a decline in the incidence rates of cervical cancer in the past decades.<sup>1-4</sup> However, the drastic decrease in routine screening and preventive procedures during the COVID-19 pandemic may increase the risk of late detection of the disease.<sup>7</sup> This risk is particularly concerning, because 5-year survival rates for patients with recurrent and advanced disease are drastically lower than for those with early-stage and/or localized cervical cancer.<sup>8</sup> Consequently, more treatment options are needed for patients with advanced disease.

Immunotherapies, including PD-1/PD-L1 inhibitors, have shown improved responses in patients with recurring or advanced cervical cancer, supporting the development of these agents to expand therapeutic options.<sup>62-65</sup> The next article will discuss these and other therapeutic approaches currently in clinical trials. ♦

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