Clinical Expert Series

New Paradigms in the Treatment of Cervical Cancer

Teresa K. L. Boitano, MD, Tavonna Kako, MD, and Charles A. Leath III, MD, MSPH

Despite effective screening strategies and the development and implementation of prophylactic high-risk human papillomavirus vaccination, cervical cancer remains a significant public health burden. This burden is most pronounced in under-resourced countries without fully developed screening and vaccination programs, although the disease remains present worldwide, including in industrialized countries. To that end, the World Health Organization (WHO) has an active focus on the elimination of cervical cancer, with objective metrics to be achieved by countries by the year 2030. Although increased vaccination and screening will be needed to approach potential eradication of cervical cancer, as recognized by the WHO initiative, treatment will need to continue to not only be effective in the near term, but to improve outcomes as well. Accordingly, assessments to improve primary treatment options, including surgery for women with early-stage disease, modification of chemoradiation for those with locally advanced cervical cancer, and systemic therapy for those with recurrent or metastatic presentations, are ongoing. Accordingly, we highlight important areas of both recent and ongoing focus as they relate to improving cervical cancer outcomes.

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Cervical cancer is one of the most common gynecologic cancers worldwide. In 2020, there were an estimated 604,127 cervical cancer cases and 341,831 deaths globally.\(^1\) Approximately 85–90% of these new cases and deaths occurred in less developed countries.\(^2\)

From the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, and the Department of Obstetrics and Gynecology, University of Alabama at Birmingham School of Medicine, Birmingham, Alabama.

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SCREENING, PREVENTION, AND DIAGNOSIS

Most cervical cancers are the outcome of a persistent human papillomavirus (HPV) infection.\(^3\) Of the estimated 604,000 new cervical cancers cases annually,
HPV 16 and 18 account for 71%; HPV 31, 33, 45, 52, and 58 account for another 19%. Knowledge of the etiologic agent has led to a focus on both early detection and primary prevention. Over the years, there has been implementation of organized screening programs as well as the promotion of the HPV vaccine. Standard Pap testing every 3–5 years is effective at the population level in reducing both cervical cancer incidence and mortality. Nonetheless, much of the success of screening has been limited to higher-income countries; the adoption and implementation of similar approaches in both low- and middle-income countries has been hindered by lack of insurance coverage, organization of programs, and quality assurance and test review. A recent systematic review on cervical cancer screening in low- and middle-income countries identified several barriers, including cultural or traditional and religious, societal, and health system or structure barriers, as well as lack of knowledge and awareness of cervical cancer in general.

The HPV vaccine has been shown to be effective against anogenital warts and high-grade cervical lesions. A study published in 2020 that included more than 1 million women in Sweden found that the quadrivalent HPV vaccine demonstrated a substantially reduced risk of invasive cervical cancer. Furthermore, a modeling study based on data from Australia demonstrated that, with their extremely robust vaccination and screening rates, cervical cancer could be eliminated as a public health risk over the next 20 years. Despite the promising data, as with screening, there remain barriers to receiving the HPV vaccine.

Traditionally, cervical cancer has been staged clinically given its high rates and limited resources in low- and middle-income countries. However, as part of the updated International Federation of Gynecology and Obstetrics’ guidelines in 2018, surgical and radiologic evaluation are now included (if available) when assigning a stage. The notation of “r” is included for imaging and “p” for pathology when indicating stage assignment (ie, IIB1r for a women with radiographic evidence of pelvic lymph node metastasis). Other significant changes included no longer considering the horizontal dimension in microinvasive lesions, stratifying stage IB from two subgroups into three subgroups (IB1: smaller than 2 cm; IB2: 2–4 cm; IB3 larger than 4 cm), and pelvic nodes being classified as IIA1c and para-aortic nodes being classified IIA2 (Table 1).

Likely driven by the effects of the development of cervical cancer on women and their communities worldwide and the fact that both screening and, perhaps more importantly, prevention are available, the World Health Organization (WHO) published guidelines and metrics that focused on the goal of global cervical cancer eradication. The three objective metrics focus on HPV vaccination, cervical cancer screening, and active treatment of women with both preinvasive cervical disease and cervical cancer. Specifically, for a country to be considered to be on track for eradication, three metrics need to be achieved by 2030. In terms of vaccination, 90% of girls need to be fully vaccinated by age 15 years. Second, from a screening standpoint, 70% of women need to have undergone an effective or high-performing screening test (a test that allows for early detection, is cost effective, and has high sensitivity and specificity) both by age 35 years and again by age 45 years. Finally, 90% of women with either preinvasive disease or invasive cervical cancer will need to undergo treatment. Taken together, if countries are able to achieve these stated metrics, mathematical modeling has predicted that the incidence of cervical cancer will decrease by nearly one-half as soon as 2045 and by nearly 97% by 2120. As projected by the WHO model, as soon as 2030, 300,000 cervical cancer deaths would be averted, with up to 14 million deaths prevented by 2070.

There have been significant advances in the realm of cervical cancer over the past several years. This includes changes in primary surgical management for early-stage disease, both in terms of the scope of radicality and nodal evaluation. Furthermore, continued attempts to improve outcomes of chemoradiation for locally advanced cervical cancer have led to new therapies for persistent, metastatic, and recurrent disease.

CERVICAL CANCER SURGICAL PARADIGMS
The Role of Less Radical Surgery
Patients diagnosed with early-stage cervical cancer (those lesions confined to the cervix and generally less than 4 cm) are most commonly treated with surgery. The size of the lesion dictates the specific type of surgical management. Patients diagnosed with a stage IA1 lesions have a number of treatment options, including uterine preservation after either a cold knife cone or loop electrosurgical excision procedure or simple extra-fascial hysterectomy. Those with stage IA1 tumors and lymphovascular space invasion are at increased risk and may be treated with modified radical hysterectomy with lymphadenectomy or sentinel lymph node mapping and dissection. More recently, fertility-preserving surgical therapy has been explored for women with stage IA2 or IB1 tumors, who were historically treated with definitive radical surgery. In
those wishing to preserve fertility, radical trachelectomy with lymphadenectomy has been suggested as an option for managing these relatively small tumors.\textsuperscript{21,22}

In addition, the need for radical pelvic dissection has been questioned in patients with small, early-stage tumors. Schmeler and colleagues published results from the ConCerv trial, a single-arm prospective trial of 100 women with stage IA2-IB1 cervical cancer without lymphovascular space invasion (33\% IA2 and 67\% IB1) who were managed with one of two non-radical surgical approaches, namely a conization with lymph node dissection, including the option for sentinel lymph node (SLN) dissection, or the same procedures combined with a subsequent simple hysterectomy when fertility was not desired\textsuperscript{23} (Table 2). The study demonstrated a low rate of both recurrence (3.5\%) and nodal involvement (5\%). Results from two other important clinical trials prospectively evaluating the role of less radical surgery are eagerly awaited and will likely further inform decisions on less radical procedures. The SHAPE trial (Radical Versus Simple Hysterectomy and Pelvic Node Dissection With Low-risk Early Stage Cervical Cancer) (NCT01658930),\textsuperscript{24} with up to 700 participants, from the Canadian Cancer Trials Group, is randomly assigning women to either radical hysterectomy with pelvic lymph node dissection or simple hysterectomy with lymph node dissection. Preliminary results show that, in early-stage, low-risk patients, the 3-year pelvic recurrence rate is not inferior with simple hysterectomy compared with radical hysterectomy.\textsuperscript{25}

There were also fewer associated urologic complications with simple hysterectomy in this patient population. Furthermore, GOG 278 (NCT 01649089),\textsuperscript{26} whose primary objectives are to assess the effects of either cold knife conization or simple hysterectomy, both in combination with pelvic lymphadenectomy, on lymphedema as well as bladder, bowel, and sexual function and clinical outcomes, will provide both quality-of-life and survival data. Hopefully these trials, combined with ConCerv, will further inform clinical care for patients with early-stage cervical cancer.

### Abdominal Compared With Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer

Radical hysterectomy with bilateral pelvic lymphadenectomy has been considered the primary treatment for most patients with early-stage, operable cervical cancer.\textsuperscript{20} Over the past two decades, minimally invasive surgery has progressively emerged as the primary method of surgical management for cervical cancer. Compared with open surgery, minimally invasive

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Carcinoma is strictly confined to the cervix</td>
</tr>
<tr>
<td>1A</td>
<td>Invasive carcinoma that can be diagnosed with microscopy, maximum depth of invasion is &lt; 5 mm</td>
</tr>
<tr>
<td>1A1</td>
<td>Stromal invasion &lt; 3 mm in depth</td>
</tr>
<tr>
<td>1A2</td>
<td>Stromal invasion ≥ 3 mm and &lt; 5 mm in depth</td>
</tr>
<tr>
<td>1B</td>
<td>Invasive carcinoma confined to the cervix; deepest measured invasion must be ≥ 5 mm</td>
</tr>
<tr>
<td>1B1</td>
<td>Tumor measures &lt; 2 cm in greatest dimension</td>
</tr>
<tr>
<td>1B2</td>
<td>Tumor measures ≥ 2 and &lt; 4 cm in greatest dimension</td>
</tr>
<tr>
<td>1B3</td>
<td>Tumor measure ≥ 4 cm in greatest dimension</td>
</tr>
<tr>
<td>2</td>
<td>Carcinoma invades beyond the uterus, but not into the lower third of the vagina or to the pelvic wall</td>
</tr>
<tr>
<td>2A</td>
<td>Limited to the upper two-thirds of the vagina without parametrial involvement</td>
</tr>
<tr>
<td>2A1</td>
<td>Tumor measures &lt; 4 cm in greatest dimension</td>
</tr>
<tr>
<td>2A2</td>
<td>Tumor measures ≥ 4 cm in greatest dimension</td>
</tr>
<tr>
<td>2B</td>
<td>With parametrial involvement but does not involve the pelvic wall</td>
</tr>
<tr>
<td>3</td>
<td>Carcinoma involves the lower third of the vagina, and/or extends to the pelvic wall (can cause hydrenephrosis or affect kidney function), and/or involves the pelvic and/or para-aortic lymph nodes</td>
</tr>
<tr>
<td>3A</td>
<td>Involves the lower third of the vagina, no extension to the pelvic wall</td>
</tr>
<tr>
<td>3B</td>
<td>Extension to the pelvic wall and/or hydrenephrosis or nonfunctioning kidney from tumor</td>
</tr>
<tr>
<td>3C</td>
<td>Involvement of pelvic and para-aortic lymph nodes</td>
</tr>
<tr>
<td>3C1</td>
<td>Pelvic lymph node metastasis only</td>
</tr>
<tr>
<td>3C2</td>
<td>Para-aortic lymph node metastasis</td>
</tr>
<tr>
<td>4</td>
<td>Carcinoma has extended beyond the true pelvis or has biopsy-proven bladder or rectal involvement</td>
</tr>
<tr>
<td>4A</td>
<td>Spread to adjacent pelvic organs</td>
</tr>
<tr>
<td>4B</td>
<td>Spread to distant organs</td>
</tr>
</tbody>
</table>

Modified from Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. Int J Gynaecol Obstet 2018;143 Suppl 2:22–36. doi: 10.1002/ijgo.12611. This is an open access article distributed under the terms of the Creative Commons CC BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
surgery is associated with shorter length of hospital stay, decreased complication rates, and lower operative morbidity.\textsuperscript{27} Based on small, retrospective studies that demonstrated no difference in oncologic outcomes between open and laparoscopic radical hysterectomy, minimally invasive surgical approaches were widely incorporated into practice for early-stage cervical cancer\textsuperscript{28,29} (Table 3). However, in 2018, two trials were published demonstrating a concern with minimally invasive surgery for early-stage cervical cancer. The phase III, randomized controlled LACC trial (Laparoscopic Approach to Carcinoma of the Cervix) by Ramirez and colleagues\textsuperscript{30} demonstrated that patients undergoing minimally invasive radical hysterectomy had lower rates of disease-free survival (DFS) and overall survival (OS) when compared with those undergoing open abdominal radical hysterectomy. A total of 631 patients were included in the trial, with most patients having stage IB1 disease (92%); the 4.5-year DFS rate was 96.5% in the open radical hysterectomy group compared with 86.0% in the minimally invasive surgery group. The 3-year OS rate was 93.8% in patients who underwent minimally invasive surgery compared with 99.0% in those who underwent open surgery. Possible mechanisms for the increased recurrence risk for minimally invasive surgery include the use of a uterine manipulator, which may lead to tumor spillage; the effect of CO\textsubscript{2} insufflation on tumor cell spread; and the previous retrospective studies being sequential comparisons instead of concurrent.

The second trial, by Melamed et al, was an observational cohort study using the National Cancer Database that included 2,461 women. The risk of death was higher in women undergoing minimally invasive radical surgery compared with open surgery (9.1% vs 5.3%; hazard ratio [HR] 1.65; 95% CI 1.22–2.22; \( P < .002 \)).\textsuperscript{18} These data led to a practice-change in surgical approach for radical hysterectomy, with the National Comprehensive Cancer Network, the Society of Gynecologic Oncology, and the European Society of Gynaecological Oncology all recommending

### Table 2. Tumor Eligibility Criteria and Patient Groups From the ConCerv Clinical Trial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FIGO 2009 stage</th>
<th>Histology</th>
<th>Tumor size</th>
<th>Lymphovascular space invasion</th>
<th>Depth of invasion</th>
<th>Imaging</th>
<th>Conization margins</th>
<th>Surgical group by procedure</th>
<th>Data are n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open abdominal surgery</td>
<td>IA2–IB1</td>
<td>All squamous cell carcinomas</td>
<td>2 cm or less</td>
<td>Absent</td>
<td>10 mm or less</td>
<td>Negative</td>
<td>Negative</td>
<td>Conization and lymph node assessment only</td>
<td>44 (44)</td>
</tr>
<tr>
<td>No unplanned minimally invasive surgery</td>
<td></td>
<td>Grade 1 or 2 adenocarcinomas only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Conization followed by simple hysterectomy and lymph node assessment</td>
<td>40 (40)</td>
</tr>
<tr>
<td>Unintentionally performed hysterectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>“Unplanned/inadvertent” simple hysterectomy and lymph node assessment</td>
<td>16 (16)</td>
</tr>
</tbody>
</table>

### Table 3. Differences in Overall Survival in Minimally Invasive Compared With Open Surgery for Early-Stage Cervical Cancer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LACC Trial</th>
<th>Melamed et al\textsuperscript{18}</th>
<th>Wang et al\textsuperscript{29}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>RCT</td>
<td>Cohort (NCDB)</td>
<td>Matched cohort</td>
</tr>
<tr>
<td>No. of patients</td>
<td>633</td>
<td>2,461</td>
<td>203</td>
</tr>
<tr>
<td>OS (y)</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>MIS (%)</td>
<td>93.8</td>
<td>90.0</td>
<td>93.2</td>
</tr>
<tr>
<td>Open surgery (%)</td>
<td>99.0 (HR 6; 95% 1.8–20.3)</td>
<td>94.7 (HR 1.7; 95% CI 1.2–2.2; ( P &lt; .001 ))</td>
<td>92.1 (( P = .94 ))</td>
</tr>
<tr>
<td>Time (y)</td>
<td>4.5</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Measurement</td>
<td>DFS</td>
<td>RFS</td>
<td>91.3</td>
</tr>
<tr>
<td>MIS (%)</td>
<td>86.0</td>
<td></td>
<td>90.4 (( P = .8 ))</td>
</tr>
<tr>
<td>Open surgery (%)</td>
<td>96.5 (95% CI −16.4 to −4.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LACC, Laparoscopic Approach to Carcinoma of the Cervix; National Cancer Database; OS, overall survival; MIS, minimally invasive surgery; HR, hazard ratio; NR, not reported; DFS, disease-free survival; RFS, recurrence-free survival.

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laparotomy over a minimally invasive surgical approach.\textsuperscript{31,32} Although the LACC trial resulted in a fairly rapid discontinuation of minimally invasive radical hysterectomy, ongoing studies, including ROCC (A Trial of Robotic versus Open Hysterectomy Surgery in Cervix Cancer) (NCT 04831580), are attempting to determine whether there remains a role for minimally invasive radical surgery for patients with early-stage cervical cancer.\textsuperscript{33} Importantly, in addition to strict safety assessments, novel surgical modifications including specimen manipulation as well as tumor-containment systems are being used.

**Sentinel Lymph Node Dissection**

Lymph node metastasis or positivity is one of the most important prognostic factors for survival and recurrence for patients with early-stage cervical cancer. Currently, the standard of care is full pelvic lymphadenectomy for nodal staging. However, there are known significant side effects associated with the procedure, including lymphocele formation, lymphedema, and infection.\textsuperscript{34} Other gynecologic cancers have moved toward SLN dissection, which has a high sensitivity and specificity and decreased morbidity for both uterine and vulvar cancer.\textsuperscript{35,36} Similarly, early data demonstrated promising results for SLN dissection for cervical cancer.\textsuperscript{37} More recently, a prospective study that evaluated 245 women found that SLN dissection was associated with a high sensitivity (96%; 95% CI 81–100%) and negative predictive value (99%; 95% CI 93–100%) when the protocol-specified SLN approach was used.\textsuperscript{38} Sentinel lymph node dissection has been included as a surgical consideration by the National Comprehensive Cancer Network and can be considered in patients with cervical tumors smaller than 4 cm, no suspicious lymph nodes on preoperative imaging, bilateral SLN detection, and ultrastaging on pathology.\textsuperscript{39}

**MANAGEMENT OF LOCALLY ADVANCED CERVICAL CANCER—CHEMORADIATION**

**Attempts to Modify the Chemoradiation Backbone**

After the National Cancer Institute’s clinical alert in 1999 regarding the importance of the addition of cisplatin to radiation for women undergoing treatment for locally advanced cervical cancer, subsequent clinical trials over nearly 25 years have failed to show improved survival compared with the standard treatment of weekly cisplatin 40 mg/m\textsuperscript{2} with external beam radiation followed by brachytherapy. During this time period, prolonged venous infusion 5-FU as compared with weekly cisplatin, the use of recombinant human erythropoietin to prevent anemia, and the addition of the hypoxic cell sensitizer tirapazamine all failed to demonstrate improved outcomes.\textsuperscript{40–42}

On the contrary, a multinational open-label clinical trial that enrolled women with stage IIB–IVA locally advanced cervical cancer compared the standard-of-care arm with cisplatin-based chemoradiation with an experimental arm that included the addition of both weekly gemcitabine and adjuvant cisplatin and gemcitabine after chemoradiation.\textsuperscript{43} This trial included 515 women and noted an improvement in progression-free survival (PFS) at 3 years (74.4% of patients in the experimental arm vs 65.0% in the control arm; \(P = .29\)). Nonetheless, this improvement was associated with nearly a doubling of grade 3 and 4 toxicities (86.5% vs 46.3%, \(P < .001\)) for those in the experimental arm, including two potentially treatment-related deaths.

Although certainly more toxic, the potential benefit of the addition of chemotherapy to the chemoradiation backbone helped inform the design of another large trial for locally advanced cervical cancer (stage IB1 node positive–stage IVA), the OUTBACK trial. In OUTBACK, 919 eligible women were randomized to receive either standard chemoradiation or chemoradiation followed by four cycles of adjuvant paclitaxel 155 mg/m\textsuperscript{2} and carboplatin AUC 5.\textsuperscript{44} After a median follow-up of 60 months, the addition of adjuvant chemotherapy did not improve OS, with 72% (95% CI 67–76%) of patients alive in the experimental arm compared with 71% (95% CI 66–75%) in the control arm (HR 0.90, 95% CI 0.70–1.17, \(P = .81\)). In addition, adjuvant chemotherapy was noted to have a negative effect on quality of life for up to 6 months after therapy.

Based on phase I and II clinical trial data,\textsuperscript{45,46} the ribonucleotide reductase inhibitor triapine was added to standard chemoradiation in NRG-GY006, a recently completed phase III, open-label, randomized controlled trial (NCT 02466971).\textsuperscript{47} Compared with previous trials, GY006 allowed the use of intensity-modulated radiation therapy, which is becoming the standard of care at most institutions; incorporated a rapid, near real-time review of intensity-modulated radiation therapy plans; and allowed enrollment of women with vaginal cancer. This trial enrolled 450 women with locally advanced cervical cancer, and, although the addition of triapine did not improve OS, both arms had approximately 70% survival at 5 years, suggesting continued improvement in more modern chemoradiation therapy.\textsuperscript{48} In addition, oral triapine is also being evaluated in similar groups of patients with both locally advanced cervical and vaginal cancers (NCT 02595879).\textsuperscript{49}
The Role of Immunotherapy in Combination with Chemoradiation

Although the addition of novel agents to the chemoradiation backbone generally has been disappointing, alternative approaches to modify this therapy continue to be investigated. After the observations that immunotherapy has activity in women with recurrent cervical cancer and considering the nature of persistent HPV infection and neoplastic development, there has been interest in the integration of immunotherapy with chemoradiation. Multiple immunotherapy agents, including both anti–programmed cell death receptor-1 (anti–PD-1) and anti–programmed cell death ligand 1 (anti–PD-L1) antibodies as well as CTLA4 inhibitors, have been evaluated. Mayadev and colleagues, in GOG 9929, on behalf of the Gynecologic Oncology Group, evaluated the use of sequential immunotherapy with the CTLA-4 inhibitor ipilimumab after standard chemoradiation therapy for women with node-positive locally advanced cervical cancer. In this single-arm phase 1 trial, 32 participants received up to four infusions of ipilimumab at one of two doses (3 mg/kg or 10 mg/kg); it was ultimately noted that the maximal tolerated dose was 10 mg/kg, with 81% of patients tolerating progression free at 12 months and 90% alive at the same timepoint. This important proof-of-principle study suggested that the addition of immunotherapy to the chemoradiation backbone, albeit after completion of chemoradiation, was tolerable and safe and warranted additional study.

Although GOG 9929 evaluated sequential therapy, subsequent clinical trials have evaluated the use of immunotherapy in combination with chemoradiation, either concurrently or, in one trial, as an induction therapy. Details of these important clinical trials are shown in Table 4, with all studies evaluating similar but different combination strategies. Duska and colleagues designed and implemented an eight-site, open label, phase 2 randomized clinical trial that used pembrolizumab in combination with chemoradiation therapy for women with locally advanced cervical cancer. Patients in this open-label study were randomized in a 1:1 fashion to either the addition of three cycles of maintenance pembrolizumab at a dose of 200 mg intravenously every 3 weeks or three cycles of pembrolizumab 200 mg intravenously added concurrently to chemoradiation, with administration preferred to be on days of cisplatin and before radiation therapy. Preliminary results on nearly 60% of the planned trial population noted that pembrolizumab with chemoradiation appeared to be safe and did not affect the ability to complete standard chemoradiation. More recent data demonstrated similar DFS at 3 years of 78% (90% CI 64.2–86.8%) for the maintenance therapy group compared with 75% (90% CI 60.0–84.9%) for the concurrent group. Considering data from this trial, a much larger phase 3 trial with an enrollment of nearly 1,000 women with high-risk, locally advanced cervical cancer is evaluating both the addition of pembrolizumab to chemoradiation and maintenance therapy for up to 15 additional cycles (KEYNOTE A-18, NCT 04221945); the trial has completed accrual.

A similarly designed international study of women with node-negative as well as node-positive locally advanced cervical cancer, the CALLA trial, used the anti PD-L1 antibody durvalumab in combination with chemoradiation as well as for maintenance therapy after chemoradiation. In this blinded, placebo-controlled trial of 770 women randomized in a 1:1 fashion, the addition of durvalumab to chemoradiation did not improve either PFS or OS.

Atezolizumab, another anti–PD-L1 antibody, has also been evaluated as an adjunct to standard chemoradiation therapy in women with node-positive locally advanced cervical cancer. Building on previous experience of the GOG, NRG-GY017 was designed as a randomized phase 1 trial to determine the potential effects of two distinct approaches of atezolizumab use with chemoradiation. Forty women were randomly assigned to receive either a single priming dose of atezolizumab followed by two cycles concurrently with chemoradiation therapy or all three cycles during chemoradiation therapy. Of 36 evaluable patients, including 14 with para-aortic nodal metastasis, the median PFS had not been reached in either group after a median follow-up of 25.8 months. Moreover, the use of atezolizumab as a priming or neoadjuvant therapy was associated with an expansion of T cell receptor clonality clones. Although not designed to compare strategies from an efficacy standpoint, superior pathologic responses (complete responses plus partial responses) were noted in the priming approach (69% vs 40%, *P*=.13) midway through therapy at day 28.

ADVANCES IN PERSISTENT, METASTATIC, AND RECURRENT DISEASE

There are limited effective second-line treatments for women with metastatic or recurrent cervical cancer. After a series of clinical trials, platinum-based doublet chemotherapy with paclitaxel was most commonly used as first-line therapy, but a randomized controlled trial published in 2014 demonstrated that the addition of bevacizumab led to an improvement of 3.7 months in median OS. For many years, monotherapy with a
cytotoxic agent was the most commonly used second-line therapy, and, in general, the overall objective response rate was less than 15%. Newer studies have continued to evaluate additional therapies with improvements in outcomes, including the addition of pembrolizumab to platinum-based chemotherapy with or without bevacizumab, cemiplimab as an alternative to chemotherapy,\textsuperscript{61} and antibody drug conjugate monotherapy with tisotumab vedotin-tftv. In 2019, a phase 2 trial was published demonstrating that pembrolizumab, an anti–PD-1 monoclonal antibody, had activity in tumors that have high microsatellite instability or are deficient in DNA mismatch repair, with an objective response rate of 14.6%.\textsuperscript{62} This study then led to the evaluation of pembrolizumab in combination with a platinum-based doublet therapy (plus or minus bevacizumab, cemiplimab as an alternative to chemotherapy),\textsuperscript{61} and antibody drug conjugate monotherapy with tisotumab vedotin-tftv.

In 2019, a phase 2 trial was published demonstrating that pembrolizumab, an anti–PD-1 monoclonal antibody, had activity in tumors that have high microsatellite instability or are deficient in DNA mismatch repair, with an objective response rate of 14.6%.\textsuperscript{62} This study then led to the evaluation of pembrolizumab in combination with a platinum-based doublet therapy (plus or minus bevacizumab) in recurrent, metastatic, and persistent cervical cancer. The randomized controlled trial by Colombo et al demonstrated that women with PD-L1 scores of 1 or higher had PFS of 10.4 months, compared with 8.2 months in the placebo group.\textsuperscript{51} Furthermore, OS at 24 months was 53% in the pembrolizumab group compared with 42% in the placebo group. This is now considered the standard of care for patients with PD-L1 scores of at least 1 and persistent, metastatic, or recurrent disease.\textsuperscript{53,64}

In 2022, Tewari and colleagues\textsuperscript{61} reported results for another anti–PD-L1 agent, cemiplimab. In a phase 3 trial, they evaluated the use of cemiplimab alone compared with investigator’s choice of single-agent chemotherapy in patients with recurrent cervical cancer who previously received first-line platinum chemotherapy. The study included 608 women and demonstrated a significant improvement in median OS in the cemiplimab group of 12.0 months, compared with 8.5 months in the single-agent chemotherapy group (HR 0.69; 95% CI 0.56–0.84; \textit{P} = .001). They also noted an objective response rate of 18% in women with PD-L1 expression of 1 or greater.

Finally, in a multi-center, single-arm, phase II study, tisotumab vedotin-tftv, which is a tissue factor–directed antibody–drug conjugate, was evaluated as a second-line treatment for recurrent or metastatic cervical cancer. More than 100 women were enrolled, with an objective response rate of 24% and with seven women having a complete response.\textsuperscript{65} The median duration of response was 8.3 months, with a median OS of 12.1 months. Most patients in the study also experienced a rapid response, with decreasing tumor sizes noted within the first two treatments. This offers a treatment option for patients with a higher response rate than previous single-agent regimens. A confirmatory randomized phase 3 clinical trial comparing tisotumab vedotin-tftv with physician’s choice of chemotherapy is ongoing (NCT 04697628).\textsuperscript{66}

### Future Directions—Working Toward Eradication

Consistent with the WHO cervical cancer metrics, treatment of both preinvasive and invasive lesions is critically important to ultimately prevent cervical...
cancer. However, we are likely decades away from seeing the widespread effects of HPV vaccination and appropriate screening interventions in clinical practice. Recent clinical trial results not only have dramatically affected current management of women across the cervical cancer spectrum, these results importantly have demonstrated the activity of novel agents, often leading to drug approval. Although cervical cancer is uniquely positioned as a cancer that essentially can be eradicated, it will take both willpower and a serious national commitment to reach the goals from the WHO.

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PEER REVIEW HISTORY
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