REVIEW ARTICLE

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Cervical Cancer

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An interactive graphic is available at NEJM.org

In 2020, an estimated 604,127 new cases of cervical cancer were reported worldwide, with 341,831 related deaths.[1] Low-resource regions of Latin America, sub-Saharan Africa, and Southeast Asia, including India, have a high disease burden (Fig. 1A; and see the interactive graphic). There is a clear correlation between socioeconomic status and the incidence of cervical cancer and mortality rates, with progressively lower rates of both incidence and mortality as the mean national Human Development Index increases. In 2024, a total of 13,820 new cases and 4360 related deaths were expected to occur in the United States[2]; in the European Union, 58,169 cases were anticipated (56% from central and eastern Europe), with 22,989 related deaths.[1] The median age at diagnosis is 50 years.[3]

Risks factors for cervical cancer are linked to sexual behavior.[3] An early age at first intercourse, multiple sex partners, partners with multiple partners, a lack of access to screening, and a history of abnormal Papanicolaou smears, human papillomavirus (HPV) infection, cervical dysplasia, or sexually transmitted infection (or a combination of these) increase the risk. Tobacco use and oral contraceptives have also been implicated as factors that increase risk.

HPV is a double-stranded DNA virus that replicates as an episome. Low-risk subtypes of HPV (most often types 6 and 11) may cause anogenital warts. High-risk subtypes of HPV (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) carry oncogenes that are repressed by the E2 regulatory protein (Fig. 1B). Viral integration into the host genome occurs within the *E2* reading frame, leading to *E6* and *E7* transcription. E6 and E7 degrade and inactivate cellular tumor suppressor gene products p53 and pRb, respectively.[3,4]

Screening and Prevention

HPV is ubiquitous. Sexually active persons may have transient infection. In women infected with high-risk HPV that has not cleared by 30 years of age, cervical intraepithelial neoplasia (CIN), or dysplasia, may occur. This condition is a precursor to invasive disease, which may take 10 to 15 years to develop.[3] Prophylactic vaccination is effective when administered before HPV exposure (Table 1).[5-8]

The sensitivity and specificity of Papanicolaou testing for detecting moderate-to-severe cervical dysplasia (CIN 2 or CIN 3) (Fig. 1C) is 55.4% and 96.8%, respectively, and the sensitivity and specificity of testing for high-risk HPV is 94.6% and 94.1%, respectively.[9] In rural India, HPV testing in 34,126 healthy women reduced the rate of death from cervical cancer, as compared with standard care (i.e., no screening) (hazard ratio, 0.52; 95% confidence interval [CI], 0.33 to 0.83).[10] Primary screening with HPV testing is supported by the ATHENA (Addressing the Need for Advanced HPV Diagnostics)[11] and HPV FOCAL (Human Papillomavirus Testing for Cervical Cancer Screening)[12] trials, with current guidelines provided by the U.S. Preventive Services Task Force (Table 1).[13]

KEY POINTS

CERVICAL CANCER

- Cervical cancer is preventable through vaccination and treatment of dysplasia identified on screening (cytologic screening, DNA testing for high-risk human papillomavirus subtypes, or both).
- Early-stage cervical cancer is treated with open radical hysterectomy and pelvic lymphadenectomy; small lesions can be treated with extrafascial hysterectomy or more conservative fertility-preserving operations.
- Locally advanced cervical cancer is treated with chemoradiation therapy plus brachytherapy; incorporation of immunotherapy for International Federation of Gynecology and Obstetrics (FIGO) stage III through IVA disease is associated with a survival benefit.
- Isolated, centrally recurrent cervical cancer may be managed by means of pelvic exenteration with urinary diversion; however, owing to an increased incidence of distant or concomitant pelvic and extrapelvic relapse after widespread adoption of chemoradiation for locally advanced disease, fewer patients are candidates for this operation than in previous years.
- Patients with newly diagnosed recurrent or metastatic disease may benefit from chemotherapy plus immunotherapy, with or without bevacizumab.
- Antibody–drug conjugates may be an option for patients with disease progression after treatment with chemotherapy plus immunotherapy.

Colposcopic magnification with acetic acid staining of the cervical transformation zone (the area where squamous epithelium transitions to columnar epithelium) and squamocolumnar junction may reveal thickened "acetowhite" epithelium and vascular markings (e.g., mosaicism, punctation, and atypical vessels), which are findings suggestive of dysplasia or microinvasion (Fig. 1D).[3]

Biopsy establishes the diagnosis. Preinvasive disease is treated with the use of ablative techniques (carbon dioxide laser or cryotherapy) or excisional techniques (large loop excision of the transformation zone or conization). Management algorithms developed by the American Society of Colposcopy and Cervical Pathology are available at https://app.asccp.org.[14] Visual inspection with acetic acid and immediate cryotherapy was endorsed by the World Health Organization for low-resource settings after a National Cancer Institute–funded trial in India showed a 30% reduction in mortality from cervical cancer with this approach.[15] Spontaneous regression occurs in approximately 50 to 75% of patients with CIN 1 or CIN 2, allowing for conservative management with follow-up in some patients.

STAGING OF CERVICAL CANCER

Staging and management of cervical cancer are performed according to the International Federation of Gynecology and Obstetrics (FIGO) criteria (Fig. 2A), which were updated in 2018 and now include pathological or radiographic assessment of lymph nodes (Table 2).[16] Patients with severe dysplasia (CIN 3) and microinvasion (FIGO stage IA_1 or IA_2) may be asymptomatic; those with stage IB_1 or IB_2 disease may have abnormal bleeding or pelvic pain and pressure. Cervical cancer spreads through local extension and locoregional lymphatics in the parametria to the pelvic nodes.[3] In cases of locally advanced disease (stages IB_3 through IVA), pelvic sidewall extension with hydronephrosis may cause flank pain, lower-extremity edema, and deep-vein thrombosis (DVT); hematuria, rectal bleeding, or both may also occur. Supraclavicular adenopathy and hemoptysis indicate metastatic disease (stage IVB).

A review of systems, general physical examination, and speculum and rectovaginal examinations are appropriate, along with serum analyses (complete blood count and electrolyte and creatinine levels), urinalysis, and imaging studies. Positron-emission tomography combined with noncontrast axial computed tomography (CT) increases the sensitivity for detecting paraaortic nodal metastases that are 1 cm in diameter or larger.[17] Bulky tumors may warrant cystoscopic examination while the patient is under anesthesia. Magnetic resonance imaging (MRI) can be used to evaluate loss of the fat plane between the vagina and the bladder and rectum. Lymph nodes with radiographic features consistent with the presence of metastases can be surgically staged by means of laparoscopy or CT-guided biopsy.

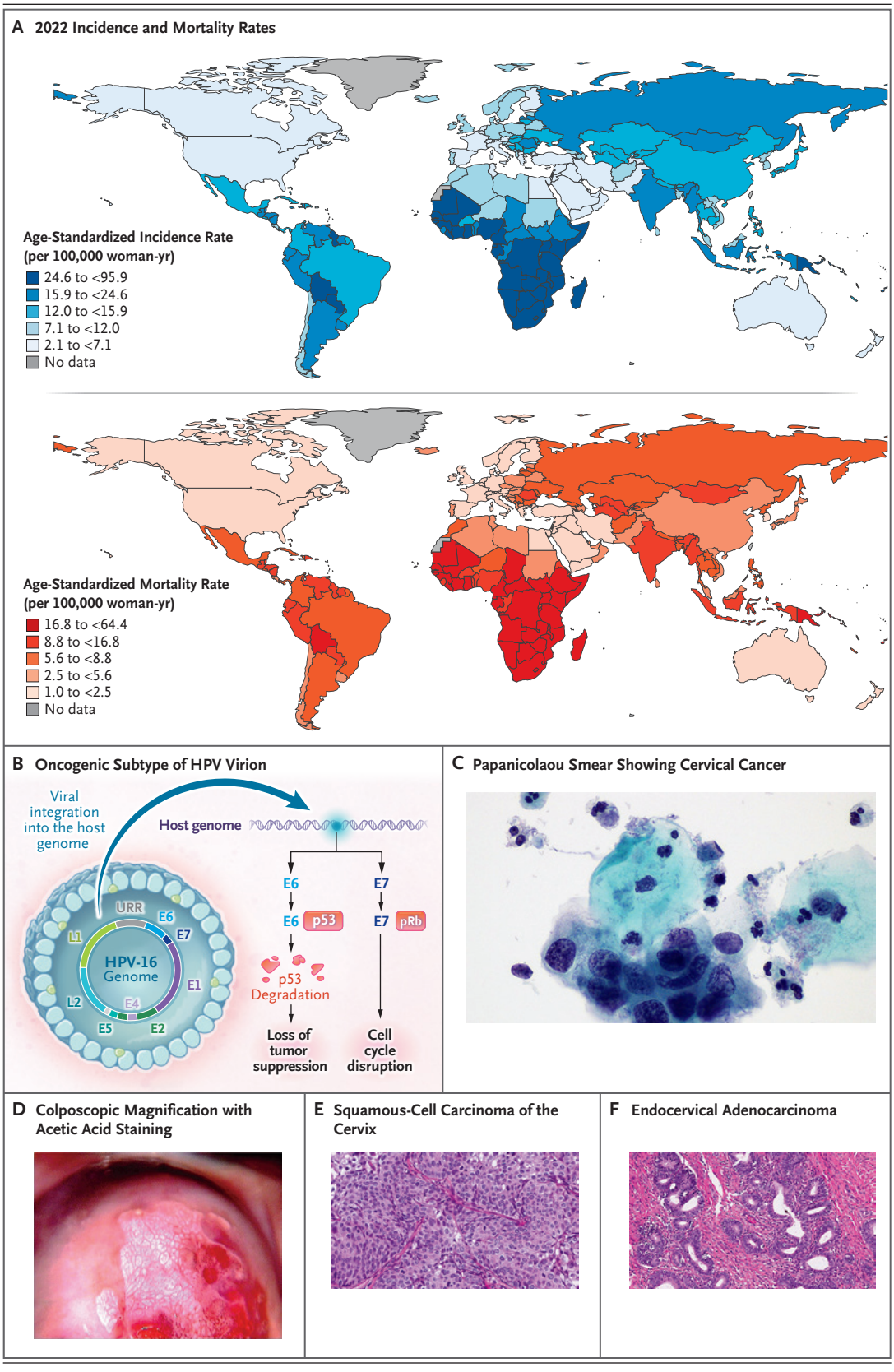


Figure 1 (facing page). Epidemiologic, Genetic, Cytologic, and Pathological Features of Cervical Cancer.

Panel A shows worldwide age-standardized incidence and mortality rates for cervical cancer in 2022. Data are from the GLOBOCAN database and were collated by the International Agency for Research on Cancer and hosted by the Global Cancer Observatory. Panel B shows the oncogenic subtype of the human papillomavirus type 16 (HPV-16) virion, with representation of L1 and L2 capsid proteins, as well as E2 (gene-expression regulator) and the viral oncogene products E6 and E7. A complementary DNA (cDNA) of the antigenic L1 is used in HPV vaccine development involving viruslike particle technology. The E2 product prevents oncogene expression when HPV exists in episomal form as double-stranded, circular DNA, but integration into the host genome occurs in the E2 reading frame, allowing transcription of E6 and E7. The protein products degrade and inactivate the cellular tumor-suppressor gene products p53 and pRb (retinoblastoma), respectively, ultimately resulting in increased vascular endothelial growth factor expression and tumor angiogenesis. URR denotes upstream regulatory region. The Papanicolaou smear of the cervix in Panel C shows a high-grade squamous intraepithelial lesion, with metaplastic cytoplasm, a high nuclear-to-cytoplasmic ratio, hyperchromatic nuclei, and nuclear envelope irregularities. Panel D shows the cervix under colposcopic magnification after the application of acetic acid. Abnormal vascular markings, such as the mosaicism seen in this example, along with punctation, irregular vessels, or both, represent harbors of angiogenesis, findings that are consistent with high-grade dysplasia or cervical intraepithelial neoplasia grade 2 or 3. Panel E shows squamous-cell carcinoma of the cervix with koilocytotic atypia, abundant eosinophilic cytoplasm, and keratinization (hematoxylin and eosin staining). Cervical squamous-cell carcinoma is often associated with HPV-16 infection. Panel F shows endocervical adenocarcinoma with columnar-shaped cells and elongated, hyperchromatic nuclei with coarse chromatin; loss of polarity and brisk mitotic activity are evident (hematoxylin and eosin staining). Adenocarcinoma often occurs with HPV-18 infection.

Squamous-cell carcinomas arise on the ectocervix, are often associated with HPV-16, and account for 75% of cases of cervical cancer (Fig. 1E).[3] Adenocarcinomas, which may develop in the endocervical canal, account for 20 to 25% of cases; the precursor, adenocarcinoma in situ, which may be missed with cytologic analysis alone, has been associated with skip lesions (neoplastic areas separated by intervening normal tissue) and HPV-18 infection (Fig. 1F).[3] The stage-for-stage prognosis for squamous-cell carcinomas is not dissimilar to that for adenocarcinomas. Adenosquamous carcinomas are uncommon (3% of cases), and small-cell neuroendocrine tumors are rare (<1%).

SURGERY FOR EARLY-STAGE DISEASE

The National Comprehensive Cancer Network (NCCN) guidelines for the treatment of cervical cancer have recently been updated.[18] Hysterectomy or radiotherapy is an option for early-stage disease (stages IA through IB_2),[19] although surgery allows for the endogenous hormonal benefit of ovarian preservation, and oocyte retrieval allows for in vitro fertilization and surrogacy. Unlike extrafascial hysterectomy for nononcologic indications, radical hysterectomy with pelvic lymphadenectomy involves developing bilateral paravesical and pararectal spaces and ligating the uterine arteries at their origin along the internal iliac arteries.[3] Dissection of the ureters from the pelvic brim to the bladder insertion facilitates the removal of parametria and 2 to 3 cm of the upper vagina to obtain clear surgical margins (Fig. 2B). Hypogastric nerve sparing may minimize postoperative bladder dysfunction. Complications, which include perioperative hemorrhage, constipation, DVT, pulmonary embolus, lymphocyst, lymphedema, ureteral injury, and stricture, occur in less than 5% of patients.[3] After radical hysterectomy, the risk of disease recurrence can be reduced with the use of adjuvant pelvic radiotherapy[20] or adjuvant chemoradiation therapy,[21] which are selected on the basis of surgicopathological risk factors (Table 2). Consolidation chemotherapy after adjuvant chemoradiation therapy does not improve survival.[22]

The randomized Laparoscopic Approach to Cervical Cancer (LACC) trial evaluated radical hysterectomy by means of minimally invasive surgery as compared with laparotomy. The rate of disease recurrence was higher and 3-year disease-free survival was lower (91.2% vs. 97.1%) with minimally invasive surgery (hazard ratio for disease recurrence or death from cervical cancer, 3.74; 95% CI, 1.63 to 8.58).[23] Steep Trendelenburg positioning and vaginal colpotomy in the high intraperitoneal pressure environment due to laparoscopic insufflation may have led to disseminated disease. The Food and Drug Administration (FDA) prohibition against radical hysterectomy performed with minimally invasive surgery is supported by the NCCN. The ongoing

Table 1. Vaccination and Screening Recommendations for the Prevention of Cervical Cancer.

Guideline and Patient Characteristic	Recommendation
CDC recommendations for HPV vaccination (female and male patients)*	
Age 11–14 yr	Administer two doses of HPV vaccine before 15th birthday for most persons, with the second dose given 6–12 mo after the first dose
Age 15–26 yr	Administer three doses of HPV vaccine, with the second dose 1–2 mo after the first dose, and the third dose 6 mo after the first dose
Age 27–45 yr	Vaccination may be considered if patient was not fully vaccinated when younger
U.S. Preventive Services Task Force screening guidelines (2018)†	
Age <21 yr	No screening necessary
Age 21–29 yr	Perform cytologic testing alone every 3 yr
Age 30–65 yr	Perform cytologic testing alone every 3 yr, cotesting (high-risk HPV testing and cytologic testing) every 5 yr, or primary HPV testing every 5 yr
Age >65 yr	No screening necessary after adequate negative results on previous screening
Previous total hysterectomy	No screening necessary in persons without history of high-grade cervical dysplasia or cervical cancer
Previous HPV vaccination	Follow age-specific recommendations

* The Advisory Committee on Immunization Practices provides advice and guidance to the director of the Centers for Disease Control and Prevention (CDC). Three licensed human papillomavirus (HPV) vaccines are available in the United States: HPV bivalent (types 16 and 18), quadrivalent (types 6, 11, 16, and 18), and nine-valent (types 6, 11, 16, 18, 31, 33, 45, 52, and 58). Vaccination may begin at the age of 9 years. Persons with immunocompromise (including those with human immunodeficiency virus infection) between the ages of 9 and 26 years should receive three doses of HPV vaccine. Vaccination of male patients reduces rates of transmission to female patients.

† The U.S. Preventive Services Task Force (USPTF) screening guidelines have been endorsed by the American College of Obstetricians and Gynecologists, the American Society of Colposcopy and Cervical Pathology (ASCCP), and the Society of Gynecologic Oncology. The ASCCP supports the American Cancer Society (ACS) screening guidelines issued in 2020. The ACS guidelines are consistent with the USPSTF guidelines, with the following exceptions: no screening is recommended for persons who are 21 to 25 years of age; the preferred screening for persons who are 25 to 65 years of age is primary HPV testing every 5 years, with cotesting every 5 years or cytologic testing alone every 3 years as acceptable alternatives; and no screening is recommended for persons older than 65 years of age who do not have a history of cervical intraepithelial neoplasia grade 2 or 3, a more severe diagnosis in the past 25 years, or a history of cervical cancer.

Randomized Controlled Trial of Robotic versus Open Surgery for Early Stage Cervical Cancer (ROCC; ClinicalTrials.gov number, NCT04831580) is evaluating radical hysterectomy with the use of robotics and vaginal stapling before colpotomy.

Radical trachelectomy (removal of the cervix, upper vagina, and parametria) with cerclage placement and laparoscopic lymphadenectomy initially emerged as an option to preserve fertility in women with stage IB_1 disease. Less than 5% of patients had recurrent disease, and more than 60% who attempted pregnancy were successful, although 30% delivered preterm.[24]

Recently, the SHAPE (Simple Hysterectomy and Pelvic Node Assessment) trial changed the management of early-stage disease, allowing for more conservative surgery (e.g., extrafascial hysterectomy and lymphadenectomy) for tumors smaller than 2 cm in diameter with clear margins on preoperative conization or limited stromal invasion on MRI evaluation (Table 2). Conization alone is likely to be sufficient for the treatment of stage IA_1 disease. In addition, the results from the SHAPE trial now obviate the need for radical trachelectomy.[25]

The Sentinel Lymph Node Biopsy in Cervical Cancer (SENTICOL-2) trial showed that sentinel lymph-node mapping with the use of blue dye,

technetium-99, or indocyanine green was associated with fewer complications than full lymphadenectomy in patients with cervical cancer.[26] Adoption of this technique cannot be recommended until survival data from the ongoing SENTICOL-III trial (NCT03386734) are reported.

Pregnancy provides an opportunity to screen for cervical cancer. Dysplasia complicates 1 in 1000 pregnancies, and although cervical biopsy during the first trimester or early in the second trimester to rule out invasive disease is safe, endocervical sampling should be avoided. Surveillance in each trimester by a colposcopist who is familiar with physiologic cervical changes in pregnancy is warranted, with definitive therapy pursued after delivery. Some data suggest that vaginal delivery may induce regression of dysplasia.

Patients who are pregnant and have stage IA through IB_1 disease (confirmed by means of ultrasonography and MRI, neither of which exposes the fetus to ionizing radiation) without clinically significant bleeding may also be monitored conservatively.[3] Glucocorticoids administered in the third trimester accelerate fetal lung maturation.[3] Cesarean section with extrafascial hysterectomy, bilateral salpingectomy, and lymphadenectomy performed at approximately 34 weeks' gestation avoids the onset of labor.[3] Vaginal delivery is contraindicated in order to avoid hemorrhage, obstructed labor, tumor dissemination through regional lymphatics or the bloodstream, and metastases at the episiotomy site. Locally advanced disease in early pregnancy has been controlled with neoadjuvant chemotherapy after first-trimester organogenesis to permit gestational advancement.[27,28]

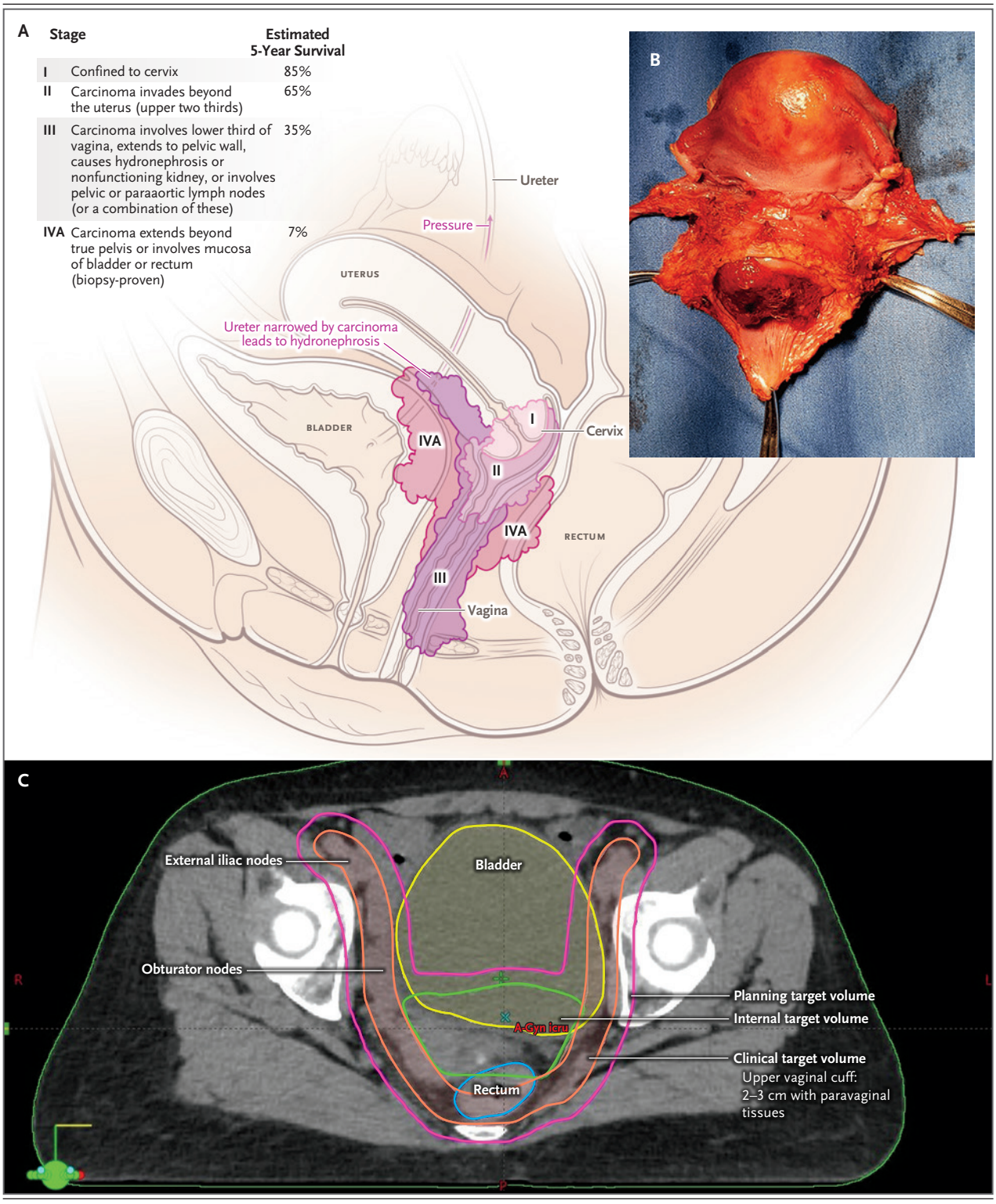
CHEMORADIATION THERAPY FOR LOCALLY ADVANCED DISEASE

Patients with stage IB_3 or IIA disease who undergo radical hysterectomy have an increased likelihood of requiring adjuvant chemoradiation therapy,[3] and it is not possible to obtain clear surgical margins in patients with disease in more advanced stages (IIB through IVA) without removing the bladder, rectum, or pelvic sidewall structures. External-beam radiotherapy alone fails to prevent disease progression in 35 to 90% of patients.[3] The rationale for administering chemotherapy to enhance radiosensitivity and reduce the risk of distant failure is supported by models showing that DNA–platinum adduct formation inhibits sublethal damage repair, alters cellular kinetics, and decreases tumor volume, thereby improving blood supply and tissue oxygenation.[3]

Five randomized trials evaluated concurrent chemoradiation therapy in patients with bulky tumors, locoregional spread, or high-risk features after hysterectomy.[21,29-32] Although chemoradiation therapy increased self-limited grade 3 or 4 hematologic and gastrointestinal adverse effects, the magnitude of the benefit was consistent across trials, with a reduction in disease recurrence of approximately 50%. The administration of weekly cisplatin (at a dose of 40 mg per square meter of body-surface area) with daily pelvic radiotherapy (1.8 to 2.0 Gy per day for a total dose of 45.0 to 50.4 Gy), followed by high-dose-rate intracavitary brachytherapy, has been adopted at most centers (Table 2). The NCCN recommends a volume of external-beam radiotherapy that provides a vaginal margin of 3 cm around the area of gross disease and that includes parametria and nodal chains at risk.

Traditional radiation planning with the use of anatomical bony landmarks has been replaced by CT-guided conformal three-dimensional techniques that integrate soft-tissue and anatomical data to account for variations in tumor size and position, thereby sparing organs at risk. The dose distribution is enhanced with intensity-modulated radiation therapy, as shown in a meta-analysis involving more than 1000 patients (odds ratio for grade 3 or 4 gastrointestinal toxic effects and genitourinary toxic effects, 0.55 and 0.31, respectively, with no decrement in overall survival at 3 years). CT-based treatment planning and conformal blocking are now standard.[33] Gross tumor volume, clinical target volume, and planning target volume are defined by reports 50 and 62 of the International Commission on Radiation Units and Measurements (ICRU) (Fig. 2C). One or more parametrial boosts of 8 to 10 Gy may be considered in selected cases.

The Manchester two-dimensional brachytherapy technique for delivering a cumulative radiation dose of 80 to 85 Gy to point A (defined as a point 2 cm superior to the external cervical os where the uterine artery crosses over the ureter in the parametria) has evolved into three-dimensional CT-guided or MRI-guided brachytherapy approaches (Table 2). The EMBRACE-I (MRI-Guided Brachytherapy in Locally Advanced Cervical Cancer)



trial showed that the efficacy of three-dimensional brachytherapy was superior to that of two-dimensional techniques and was associated with a lower cumulative incidence of grade 3 or 4 adverse events at 5 years (gastrointestinal events, 8.5%; genitourinary events, 6.8%; vaginal events,

Figure 2 (facing page). Primary Therapy for Localized Carcinoma of the Cervix.

Panel A shows early-stage and locally advanced cervical cancer according to the International Federation of Gynecology and Obstetrics (FIGO) staging classification. Panel B shows the surgical specimen from a radical hysterectomy with bilateral salpingectomy in a premenopausal patient with FIGO stage IB_2 cervical cancer who wished to retain her ovaries. The upper vagina and the parametria on both sides are removed en bloc with the uterus, cervix, and fallopian tubes. The operation is indicated for stage IA_2 through IB_2 disease and is performed by means of a laparotomy in conjunction with bilateral pelvic lymphadenectomy. Patients with stage IA_2 through IB_1 disease who have clear surgical margins on cervical conization or limited stromal invasion on preoperative magnetic resonance imaging may be offered extrafascial hysterectomy with lymphadenectomy. Panel C shows three-dimensional conformal pelvic radiotherapy with the planning target volume and clinical target volume depicted to provide coverage of the upper vagina, bilateral parametria, and nodal chains at risk. The doses are distributed in a way that will spare organs at risk (i.e., the bladder and rectum). The ongoing EMBRACE-II trial (NCT03617133) aims to increase local, nodal, and systemic control and limit morbidity with the use of an advanced target-volume selection and contouring protocol for intensity-modulated radiation therapy and image-guided brachytherapy. Panel C image provided by Tanuja A. Bhandari, M.D.

5.7%; and fistulae, 3.2%). Interstitial brachytherapy may be considered for tumors with complex geometry.[34,35]

The OUTBACK trial, which involved 926 patients with stage IB_1 through IVA disease, showed that four cycles of consolidation therapy with carboplatin plus paclitaxel after chemoradiation therapy did not lead to longer overall survival than chemoradiation therapy alone (hazard ratio for death from any cause, 0.90; 95% CI, 0.70 to 1.17; P=0.81).[36] Although adherence to chemoradiation therapy was similar in the two treatment groups, 22% of patients assigned to adjuvant chemotherapy did not receive it, with the most common reason being the patient's preference. The lack of a placebo group may have contributed to some patients withdrawing from the trial prematurely.

Neoadjuvant chemotherapy is used to downsize bulky disease so that radical hysterectomy can be performed in regions where sophisticated brachytherapy is unavailable.[37] However, the European Organisation for Research and Treatment of Cancer 55994 trial, in which 626 patients with stage IB_2 through IIB disease were randomly assigned to receive either neoadjuvant chemotherapy followed by radical hysterectomy or chemoradiation therapy, did not show a significant difference in survival at 5 years between the two treatment groups (76% with chemoradiation therapy and 72% with neoadjuvant chemotherapy and radical hysterectomy; hazard ratio for death from any cause, 0.84).[38]

The INTERLACE (Induction Chemotherapy plus Chemoradiation as First Line Treatment for Locally Advanced Cervical Cancer) trial evaluated induction chemotherapy before chemoradiation therapy.[39] From 2012 through 2022, a total of 500 patients were randomly assigned to receive chemoradiation therapy alone or six weekly cycles of carboplatin (area under the concentration–time curve, 2 mg per milliliter per minute) and paclitaxel (80 mg per square meter of body-surface area) before chemoradiation therapy. The median overall treatment time was 45 days for patients who received chemoradiation therapy alone and those who received induction chemotherapy before chemoradiation therapy; grade 3 or 4 adverse events were reported in 48% and 59% of the patients in the two groups, respectively. Induction therapy before chemoradiation therapy was associated with significantly improved 5-year progression-free survival (hazard ratio for disease progression or death, 0.65; 95% CI, 0.46 to 0.91; P=0.013) and 5-year overall survival (hazard ratio for death, 0.62; 95% CI, 0.40 to 0.91; P=0.04). However, it is unclear how to interpret these findings, since the trial population comprised patients with relatively low-risk disease, with stage III through IVA disease in only 14% of patients and negative lymph nodes in 58% of patients. Although chemoradiation therapy was started on schedule in all the patients who received induction chemotherapy (median interval, 7 days), concern has been expressed about delaying potentially curative chemoradiation therapy if clinically significant hematologic toxic effects occur. In addition, over the 10-year recruitment period, advances in radiotherapy techniques were made.

IMMUNOTHERAPY FOR LOCALLY ADVANCED DISEASE

On January 12, 2024, the FDA approved the programmed death 1 (PD-1) inhibitor pembrolizumab in combination with chemoradiation therapy

Table 2. Management of Invasive Cervical Cancer, According to the 2018 International Federation of Gynecology and Obstetrics (FIGO) Stage.

FIGO Stage	Description	Management
Stage I	Carcinoma confined to the cervix	
IA	Invasion diagnosed only with microscopy; maximum depth of invasion <5 mm	
IA_1	Stromal invasion <3 mm	Conization or extrafascial hysterectomy*
IA_2	Stromal invasion ≥3 mm and <5 mm	Conization or extrafascial hysterectomy with lymphadenectomy
IB	Visible lesion or depth of invasion ≥5 mm	
IB_1	Tumor diameter <2 cm	Conization or extrafascial hysterectomy with lymphadenectomy
IB_2	Tumor diameter ≥2 cm and <4 cm	Radical hysterectomy with lymphadenectomy†
IB_3	Tumor diameter ≥4 cm	Chemoradiation therapy
Stage II	Carcinoma invades beyond uterus but not to lower third of vagina or to pelvic wall	
IIA	Upper two thirds of vagina without parametrial involvement	
IIA_1	Tumor diameter <4 cm	Chemoradiation therapy‡
IIA_2	Tumor diameter ≥4 cm	Chemoradiation therapy
IIB	Parametrial involvement (on one side or both sides)	Chemoradiation therapy
Stage III	Carcinoma involves lower third of vagina, extends to pelvic wall, causes hydronephrosis or nonfunctioning kidney, or involves pelvic or paraaortic lymph nodes (or a combination of these)	
IIIA	Lower third of vagina	Chemoradiation therapy plus pembrolizumab§
IIIB	Extension to pelvic wall, hydronephrosis, or nonfunctioning kidney	Chemoradiation therapy plus pembrolizumab
IIIC	Involvement of pelvic or paraaortic lymph nodes, irrespective of tumor size and extent	Chemoradiation therapy
$IIIC_1$	Pelvic lymph-node metastasis only	
$IIIC_2$	Paraaortic lymph node metastasis with or without pelvic lymph-node metastasis	
Stage IV	Carcinoma has spread beyond the true pelvis or involves mucosa of bladder or rectum (biopsy-proven) or has spread beyond the true pelvis	
IVA	Spread to adjacent pelvic organs, including bladder or rectum	Chemoradiation therapy plus pembrolizumab
IVB	Spread to distant organs	CPS <1: chemotherapy plus bevacizumab CPS ≥1: chemotherapy plus pembrolizumab, with or without bevacizumab¶

* Conization of the cervix alone (with clear margins) is acceptable for patients with stage IA_1 through IB_1 disease who are of child-bearing potential and wish to preserve fertility. Surveillance should include visual inspection and palpation of the cervix with serial cytologic testing with or without HPV testing and endocervical curettage. Patients with lesions larger than 2 cm in diameter and less than 4 cm in diameter who wish to preserve fertility may be considered for radical trachelectomy with lymphadenectomy and immediate cerclage placement. Patients should be informed that the oncologic safety of trachelectomy for tumors larger than 2 cm in diameter has not been established.

† Radical hysterectomy can be avoided in patients with stage IA_2 or IB_1 disease, provided preoperative magnetic resonance imaging shows limited stromal invasion or clear surgical margins are obtained on cervical conization. For premenopausal patients undergoing extrafascial or radical hysterectomy, the ovaries may be left in situ if they appear grossly normal intraoperatively. To reduce the risk of high-grade serous ovarian cancer, it is advisable to remove the fallopian tubes at the time of hysterectomy, irrespective of the decision to leave or remove the ovaries. Lateral ovarian transposition to the ipsilateral paracolic gutter may be considered if adjuvant radiotherapy is required on the basis of preoperative or intraoperative findings. Radical hysterectomy should be performed by means of laparotomy rather than laparoscopic or robotic-assisted laparoscopic techniques. Sentinel lymph-node mapping is currently under investigation and should not be considered standard care at this time. Adjuvant pelvic irradiation after hysterectomy is administered if two or more high- or intermediate-risk factors are present: large tumor diameter, deep stromal invasion, or lymphovascular space invasion (GOG-092 Sedlis criteria). Adjuvant chemoradiation therapy is administered if one or more of the following high-risk features are identified: invasive disease at the vaginal margin, parametria, or pelvic lymph nodes (GOG-0109 Peters Criteria).

Table 2. (Continued.)

‡ Chemoradiation therapy consists of weekly cisplatin (40 mg per square meter of body-surface area) and external-beam radiation therapy (1.8 Gy per day), administered as three-dimensional conformal or intensity-regulated radiation therapy and followed by high-dose intracavitary or image-guided brachytherapy, bringing a total dose of 80 to 85 Gy to point A (defined as a point 2 cm superior to the external cervical os where the uterine artery crosses over the ureter in the parametria), with a boost of 8 to 10 Gy applied to the parametrium on one or both sides in selected cases. Interstitial brachytherapy may be suitable for tumors with complex geometry.

§ Incorporation of pembrolizumab with chemoradiation (200 mg every 21 days during chemoradiation and every 21 days for 15 cycles after completion of chemoradiation) for stage III through IVA disease is not biomarker-restricted.

¶ The combined positive score (CPS), which quantifies PD-L1 expression, is derived by adding together the total number of PD-L1–positive tumor cells, PD-L1–positive lymphocytes, and PD-L1–positive macrophages, dividing by the total number of viable tumor cells, and multiplying the result by 100. Consider adding bevacizumab for patients with stage IVB disease and a CPS greater than 1 if there are no contraindications (e.g., severe hypertension, healing wounds, increased bleeding risk, clinically significant proteinuria or nephrotic syndrome, a high risk of fistula due to tumor location, or signs or symptoms of small-bowel obstruction).

for FIGO 2014 stage III through IVA disease on the basis of findings in the KEYNOTE-A18 trial (Table 2).[40] This indication is not biomarker-restricted, and although the trial included patients with stage IB_2 through IIB disease, the reason for restricting the treatment to patients with more advanced disease is unclear. The NCCN also stipulates that pembrolizumab may be added to chemoradiation therapy only for patients with stage III through IVA disease.[18]

A role for immunotherapy in cervical cancer is supported by the infectious cause and by the survival benefits observed in patients with recurrent or metastatic disease (discussed below). Viral integration into the host genome is necessary for tumorigenesis and leads to amplification of immune checkpoints, including programmed death ligands 1 and 2 (PD-L1 and PD-L2).[41,42] PD-L1 is not expressed in normal cervical tissues but is reported in squamous carcinomas (in up to 88% of cases) and adenocarcinomas (in 14% of cases). Expression of other immune inhibitory molecules (cytotoxic T-lymphocyte antigen 4 [CTLA-4]) and increased tumor mutational burden (5 to 6 mutations per megabase) have also been reported. Increased numbers of tumor-infiltrating lymphocytes, mature M1 macrophages, and CD8+ and CD4+ regulatory T cells in the tumor microenvironment are correlated with prolonged survival.[3]

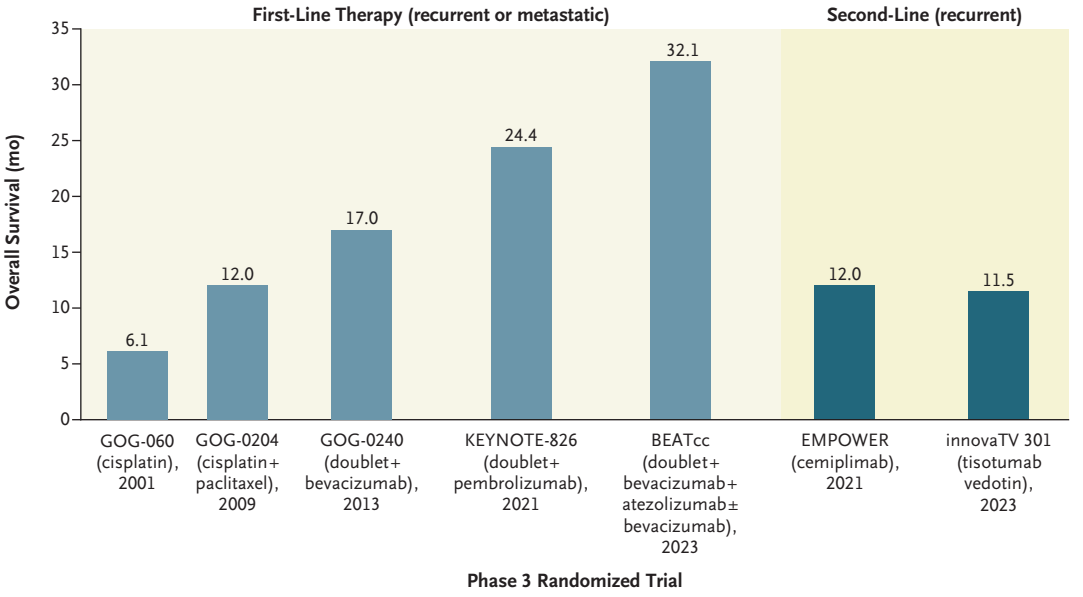
In the CALLA (Durvalumab with Chemoradiotherapy for Women with Locally Advanced Cervical Cancer) trial, the PD-L1 inhibitor durvalumab plus chemoradiation therapy was investigated as treatment for locally advanced disease; however, the results for progression-free survival, the primary end point in the trial, were not significant (hazard ratio for disease progression or death, 0.84; 95% CI, 0.65 to 1.08; P=0.17).[43] In the KEYNOTE-A18 trial, 1060 patents with stage IB_2 through IIB disease and nodal metastases or with stage III through IVA disease regardless of nodal status were randomly assigned to receive chemoradiation therapy with or without pembrolizumab (at a dose of 200 mg every 21 days, followed by a 400-mg maintenance dose every 42 days for 15 cycles). At a median follow-up of 17.9 months, an interim analysis showed that pembrolizumab significantly prolonged progression-free survival (hazard ratio for progression or death, 0.70; 95% CI, 0.55 to 0.89; P=0.002).[40] Results for patients with PD-L1–positive tumors (defined by a combined positive score of >1) mirrored the result in the primary analysis (hazard ratio, 0.72). Toxic effects were manageable, with no new safety signals. At a median follow-up of 29.9 months, pembrolizumab plus chemoradiation therapy was associated with significantly improved overall survival (hazard ratio for death from any cause, 0.67; 95% CI, 0.50 to 0.90; P=0.004).[44] The conflicting outcomes in CALLA and KEYNOTE-A18 have led to speculation about potential differences in efficacy between PD-L1 and PD-1 inhibitors, as well as the enrollment of a higher-risk population in KEYNOTE-A18 (more than two pelvic lymph nodes with a size >1.5 cm in the short axis vs. more than one node with a size >1.0 cm in the short axis).[45]

PELVIC EXENTERATION FOR ISOLATED, CENTRAL RECURRENCE

Total pelvic exenteration after radiotherapy may be curative for selected patients who have isolated, central pelvic disease relapse and undergo thorough psychosocial counseling. The uterus, cervix, parametria, bladder, rectum, vagina, and

(occasionally) vulva are removed en bloc after confirmation of negative paraaortic nodes on assessment of an intraoperative frozen section. Urinary diversion is accomplished through an ileal conduit, a continent pouch, or neobladder creation. A temporary ileostomy is made, and a neovagina is developed with the use of full-thickness skin grafts. In a National Cancer Database study involving 517 patients who underwent pelvic exenteration between 1998 and 2011, the median overall survival was 73.2 months among patients with node-negative disease.[46] Intraoperative and 30-day mortality approaches 0% in most series, probably reflecting improved perioperative care.

Indications for exenteration have declined since the adoption of chemoradiation therapy. Disease often recurs outside the radiation field



Hazard Ratio for Death			0.71 (98% CI, 0.54–0.95)	0.64 (95% CI, 0.50–0.81)	0.68 (95% CI, 0.52–0.88)	0.69 (95% CI, 0.56–0.84)	0.70 (95% CI, 0.54–0.89)
Objective Response Rate — %	31.4	29.1	48.0	68.1 in PD-L1+	84.0	18.0 in PD-L1+	17.8

Figure 3. Phase 3 Randomized Trials for Treatment of Recurrent or Metastatic Cervical Carcinoma.

Although total pelvic exenteration with urinary diversion is a potentially curative option for patients who have isolated, central pelvic recurrence after primary treatment of locally advanced disease with chemoradiation therapy, patients with relapse at distant sites, with or without pelvic recurrence, are not candidates for this operation. Initial trials by the Gynecologic Oncology Group (GOG) focused on platinum analogues and dose schedules, with the cisplatin–paclitaxel doublet established as the palliative standard in the GOG-0204 trial in 2009. The rationale for studying antiangiogenesis therapy in GOG-0240 was based on clinical features (colposcopically identified vascular aberrations associated with abnormal cervical cytologic features), pathological findings (the prognostic affect of microvessel density according to endothelial CD31 expression among patients treated with radical hysterectomy), molecular features (degradation or inactivation of the cellular tumor-suppressor gene products p53 and pRb by viral oncoproteins E6 and E7, triggering hypoxia-inducible factor 1α expression and, ultimately, vascular endothelial growth factor production), and therapeutic observations (notable activity of the angioinhibitory drugs TNP-470, pazopanib, and bevacizumab in phase 1 and 2 cervical cancer studies). The rationale for studying immunotherapy with the use of anti–programmed cell death 1 (anti–PD-1) agents (pembrolizumab and cemiplimab) and an anti–programmed death ligand 1 (anti–PD-L1) agent (atezolizumab) in KEYNOTE-826, BEATcc, and EMPOWER was predicated on the infectious (i.e., HPV-mediated) cause of cervical cancer, along with notable PD-L1 expression in squamous-cell carcinoma and adenocarcinoma (as compared with no PD-L1 expression in normal cervical tissue), the amplification of the immunologic checkpoints PD-L1 and PD-L2 that occurs with viral integration into the host genome, the prognostic effect of tumor-infiltrating lymphocytes in the cervical cancer microenvironment, and promising results of immune checkpoint blockade in squamous-cell carcinoma of the head and neck (which in many cases is induced by HPV). Although the median overall survival (OS) in BEATcc was numerically higher than that reported in KEYNOTE-826 (32.1 months vs. 24.4 months), the hazard ratios (HRs) for death from any cause were similar.

or concurrently at local and distant sites.[3] Recent reports on case series focus on functional outcomes when exenteration is performed for palliation.

FIRST-LINE THERAPY FOR METASTATIC OR RECURRENT DISEASE

Cisplatin (50 mg per square meter) plus paclitaxel (135 mg per square meter, administered over a 24-hour period) emerged as the palliative standard in the Gynecologic Oncology Group (GOG) 0204 trial, with a median overall survival of 12.87 months and an objective response (complete or partial response) occurring in 29.1% of participants.[47] In the GOG-0240 trial, cisplatin plus paclitaxel and bevacizumab (15 mg per kilogram of body weight) prolonged median overall survival (17 months; hazard ratio for death from any cause, 0.71; 98% CI, 0.54 to 0.95) without deterioration in the quality of life (Fig. 3).[48-54] Fistulae (grade 3 or 4) occurred in 6% of patients treated with bevacizumab, all of whom had previously undergone irradiation.[48] The Japanese Clinical Oncology Group 0505 trial substituted carboplatin (area under the curve, 5 mg per milliliter per minute) for cisplatin and showed significant noninferiority for overall survival, provided that patients had previous exposure to cisplatin (e.g., chemoradiation therapy before relapse).[55]

In the KEYNOTE-158 trial, monotherapy with pembrolizumab was shown to have antitumor activity among 77 patients with PD-L1–positive tumors who had had disease progression after treatment for recurrent or metastatic disease (objective response, 14.3%).[56] In the KEYNOTE-826 trial, 617 untreated patients with recurrent or metastatic disease were randomly assigned to receive chemotherapy with or without pembrolizumab.[57] The decision to use bevacizumab and carboplatin was left to the trial investigators. The median progression-free survival favored pembrolizumab over placebo (10.4 months vs. 8.2 months; hazard ratio for progression or death, 0.62; 95% CI, 0.50 to 0.77; P<0.001), as did overall survival at 24 months (53.0% vs. 41.7%; hazard ratio for death from any cause, 0.64; 95% CI, 0.50 to 0.81, P<0.001).[57,58] Subgroup analyses suggested that pembrolizumab improved overall survival irrespective of the decision regarding the use of bevacizumab, which 63% of the patients received.[59] The most common grade 3 or 4 adverse events were anemia (in 30.3% of patients who received pembrolizumab and 26.9% of those who did not) and neutropenia (12.4% and 9.7%, respectively). No negative effects on quality of life were observed in the pembrolizumab group.[60] The efficacy of immunotherapy is also supported by the BEATcc (Platinum Chemotherapy plus Paclitaxel with Bevacizumab and Atezolizumab in Metastatic Carcinoma of the Cervix) trial, which evaluated the PD-L1 inhibitor atezolizumab combined with chemotherapy and bevacizumab, as compared with standard therapy, in 410 patients (hazard ratio for death from any cause, 0.68; 95% CI, 0.52 to 0.88; P=0.005) (Fig. 3).[61]

On October 13, 2021, the FDA approved pembrolizumab plus chemotherapy, with or without bevacizumab, for patients with PD-L1–positive metastatic (stage IVB) or recurrent disease who are not candidates for curative therapy (Table 2 and Fig. 3). PD-L1–negative tumors are treated with chemotherapy plus bevacizumab. Both options are included in the NCCN category 1 recommendations.[18]

The COMPASSION-16 trial, a phase 3, randomized, double-blind, placebo-controlled trial conducted in China, evaluated the bispecific antibody cadonilimab (inhibiting PD-1 and CTLA-4).[62] When combined with platinum-based chemotherapy, with or without bevacizumab, first-line treatment with cadonilimab was associated with significantly longer median overall survival than placebo (hazard ratio for death from any cause, 0.64; 95% CI, 0.48 to 0.86; P=0.001).

SECOND-LINE THERAPY FOR RECURRENT DISEASE

Antibody–drug conjugates are active second-line options. Tissue factor is highly expressed in cervical cancer tissues, including nodal and distant metastases.[63] Tisotumab vedotin is a tissue factor–directed human monoclonal antibody covalently linked to the microtubule-disrupting agent monomethyl auristatin E.[64] The Innovate Tisotumab

Vedotin 301 (innovaTV 301) trial recently established the efficacy and side-effect profile of tisotumab vedotin (2.0 mg per kilogram) as compared with the physician's choice of chemotherapy in 502 patients (median overall survival, 11.5 months vs. 9.5 months; hazard ratio for death from any cause, 0.70; 95% CI, 0.54 to 0.89; P=0.004),[65] which led to FDA approval on April 29, 2024 (Fig. 3). The effectiveness of the drug did not depend on tissue factor expression by the tumor. Grade 3 or 4 ocular adverse events have been reported in 3.2% of patients receiving tisotumab vedotin, and a mitigation strategy for ocular adverse events, required by the FDA, stipulates ongoing examinations by an eye specialist and the use of vasoconstricting, glucocorticoid, and lubricating eyedrops.

Trastuzumab deruxtecan, an antibody–drug conjugate comprising human epidermal growth factor receptor 2 (HER2) linked to trastuzumab (5.4 mg per kilogram), received accelerated approval by the FDA on April 5, 2024, for HER2-expressing solid tumors of any type (a score of 3+ on immunohistochemical assessment), on the basis of the phase 2 DESTINY–PanTumor02 trial. An objective response occurred in 6 of the 8 women in the cervical cancer cohort.[66] *HER2* mutations occur in at least 5% of cervical cancers.[67]

The anti–PD-1 agents cemiplimab and nivolumab were evaluated as second-line treatment in the phase 3 EMPOWER trial[68] and the phase 2 CheckMate 358 trial,[69] respectively. Because cemiplimab showed a survival benefit over the physician's choice of chemotherapy (12.0 months vs. 8.5 months; hazard ratio for death from any cause, 0.69; 95% CI, 0.56 to 0.84; P<0.001)[68] (Fig. 3), NCCN guidelines recommend cemiplimab (350 mg) as a preferred second-line treatment option. Nivolumab or pembrolizumab may be used for PD-L1–positive tumors.[18] However, since many patients receive pembrolizumab plus chemotherapy as first-line treatment, anti–PD-1 retreatment may not be effective. In addition, by introducing pembrolizumab earlier in the life cycle of the disease, according to the KEYNOTE-A18 protocol, the KEYNOTE-826 regimen may have diminished efficacy at the time of recurrence. Immune checkpoint combinations have also been evaluated. Although atezolizumab plus tiragolumab, an agent that inhibits TIGIT (T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains), was not active in the SKYSCRAPER-04 trial,[70] an anti–PD-1 agent combined with an anti–CTLA-4 agent (nivolumab plus ipilimumab or balstilimab plus zalifrelimab) as second-line treatment has been shown to produce an objective response in more than 20% of patients.[71,72]

ON THE HORIZON

The tools exist for global eradication of cervical cancer. The World Health Organization's Global Strategy for the Elimination of Cervical Cancer has set targets to eliminate this disease as a public health problem by 2030 (https://cervicalcanceraction.org/cervical-cancer-elimination). However, without public health policy prioritization and substantial funding, mass vaccination campaigns and the provision of adequate screening of women worldwide will not occur. For this reason, drug development continues. Overexpression of trophoblastic cell-surface antigen 2 (Trop-2) is associated with increased tumor-infiltrating lymphocytes in the tumor microenvironment in cervical cancer.[73,74] Antibody–drug conjugates with a Trop-2 inhibitor (sacituzumab govitecan and sacituzumab tirumotecan) are being studied in ongoing phase 2 and phase 3 randomized trials (NCT05838521 and NCT06459180, respectively). Autologous T-cell therapy requires biopsies of viable tumor to isolate and expand tumor-infiltrating lymphocytes before reinfusion. This strategy led to sustained complete responses in two of nine heavily pretreated women with cervical cancer (response duration, >15 months in one woman and >22 months in the other),[75] a "breakthrough therapy" designation by the FDA, and the ongoing phase 2 LN-145 trial (NCT03108495).

A National Institutes of Health Cancer Moonshot grant is funding the study of exceptional and poor responses in banked tissue from GOG-0240 with the use of next-generation sequencing platforms. In contrast to the cervical cancer samples in the Cancer Genome Atlas, which are predominantly cervical dysplasia and early-stage carcinoma, the GOG-0240 samples are higher risk. The recent report of novel AT-rich interaction domain 1A (*ARID1A*) and phosphatidylinositol-4,5-biophosphonate 3-kinase catalytic subunit alpha (*PIK3CA*) mutations suggest a path forward.[76]

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

REFERENCES

1. Singh D, Vignat J, Lorenzoni V, et al. Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. Lancet Glob Health 2023;11(2):e197-e206.
2. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024;74:12-49.
3. Tewari KS, Monk BJ. Invasive cervical cancer. Creasman WT, Mutch DG, Mannel RS, Tewari KS, eds. In: DiSaia and Creasman clinical gynecologic oncology, 10th ed. Philadelphia: Elsevier, 2023;40-103.
4. Tewari KS, Taylor JA, Liao SY, et al. Development and assessment of a general theory of cervical carcinogenesis utilizing a severe combined immunodeficiency murine-human xenograft model. Gynecol Oncol 2000;77:137-48.
5. Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2019;68:698-702.
6. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-27.
7. Paavonen J, Naud P, Salmerón J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet 2009;374:301-14.
8. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015;372:711-23.
9. Mayrand M-H, Duarte-Franco E, Rodrigues I, et al. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. N Engl J Med 2007;357:1579-88.
10. Sankaranarayanan R, Nene BM, Shastri SS, et al. HPV screening for cervical cancer in rural India. N Engl J Med 2009;360:1385-94.
11. Wright TC, Stoler MH, Behrens CM, Sharma A, Zhang G, Wright TL. Primary cervical cancer screening with human papillomavirus: end of study results from the ATHENA study using HPV as the first-line screening test. Gynecol Oncol 2015;136:189-97.
12. Ogilvie GS, van Niekerk D, Krajden M, et al. Effect of screening with primary cervical HPV testing vs cytology testing on high-grade cervical intraepithelial neoplasia at 48 months: the HPV FOCAL Randomized Clinical Trial. JAMA 2018;320:43-52.
13. Marcus JZ, Cason P, Downs LS Jr, Einstein MH, Flowers L. The ASCCP Cervical Cancer Screening Task Force endorsement and opinion on the American Cancer Society updated cervical cancer screening guidelines. J Low Genit Tract Dis 2021;25:187-91.
14. Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP risk-based management consensus guidelines: updates through 2023. J Low Genit Tract Dis 2024;28:3-6.
15. Shastri SS, Mittra I, Mishra GA, et al. Effect of VIA screening by primary health workers: randomized controlled study in Mumbai, India. J Natl Cancer Inst 2014;106(3):dju009.
16. Bhatla N, Berek JS, Cuello Fredes M, et al. Revised FIGO staging for carcinoma of the cervix uteri. Int J Gynaecol Obstet 2019;145:129-35.
17. Atri M, Zhang Z, Dehdashti F, et al. Utility of PET-CT to evaluate retroperitoneal lymph node metastasis in advanced cervical cancer: Results of ACRIN6671/GOG0233 trial. Gynecol Oncol 2016;142:413-9.
18. National Comprehensive Cancer Network. NCCN clinical practice guidelines (https://www.nccn.org/guidelines/category_1).
19. Landoni F, Maneo A, Colombo A, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet 1997;350:535-40.
20. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group Study. Gynecol Oncol 1999;73:177-83.
21. Peters WA III, Liu PY, Barrett RJ II, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000;18:1606-13.
22. Jhingran A. Adjuvant chemotherapy following concurrent chemoradiation (CRT) in patients with high-risk early-stage cervical carcinoma following radical hysterectomy: results of NRG oncology/RTOG 0724/GOG-0724. J Clin Oncol 2024;42:Suppl:5504 (https://ascopubs.org/doi/10.1200/JCO.2024.42.16_suppl.5504).
23. Ramirez PT, Frumovitz M, Pareja R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med 2018;379:1895-904.
24. Smith ES, Moon AS, O'Hanlon R, et al. Radical trachelectomy for the treatment of early-stage cervical cancer: a systematic review. Obstet Gynecol 2020;136:533-42.
25. Plante M, Kwon JS, Ferguson S, et al. Simple versus radical hysterectomy in women with low-risk cervical cancer. N Engl J Med 2024;390:819-29.
26. Mathevet P, Lécuru F, Uzan C, et al. Sentinel lymph node biopsy and morbidity outcomes in early cervical cancer: results of a multicentre randomised trial (SENTICOL-2). Eur J Cancer 2021;148:307-15.
27. Tewari K, Cappuccini F, Gambino A, Kohler MF, Pecorelli S, DiSaia PJ. Neoadjuvant chemotherapy in the treatment of locally advanced cervical carcinoma in pregnancy: a report of two cases and review of issues specific to the management of cervical carcinoma in pregnancy including planned delay of therapy. Cancer 1998;82:1529-34.
28. Fruscio R, Villa A, Chiari S, et al. Delivery delay with neoadjuvant chemotherapy for cervical cancer patients during pregnancy: a series of nine cases and literature review. Gynecol Oncol 2012;126:192-7.
29. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 1999;340:1137-43.
30. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999;340:1144-53.
31. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 1999;340:1154-61.
32. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol 1999;17:1339-48.
33. Lin Y, Chen K, Lu Z, et al. Intensity-modulated radiation therapy for definitive treatment of cervical cancer: a meta-analysis. Radiat Oncol 2018;13:177.
34. Pötter R, Tanderup K, Schmid MP, et al. MRI-guided adaptive brachytherapy in locally advanced cervical cancer (EMBRACE-I): a multicentre prospective cohort study. Lancet Oncol 2021;22:538-47.
35. Vittrup AS, Kirchheiner K, Pötter R, et al. Overall severe morbidity after chemoradiation therapy and magnetic resonance imaging-guided adaptive brachytherapy in locally advanced cervical cancer: Results from the EMBRACE-1 study. Int J Radiat Oncol Biol Phys 2023;116:807-24.
36. Mileshkin LR, Moore KN, Barnes EH, et al. Adjuvant chemotherapy following chemoradiotherapy as primary treatment for locally advanced cervical cancer versus chemoradiotherapy alone (OUTBACK): an

international, open-label, randomised, phase 3 trial. Lancet Oncol 2023;24:468-82.
37. Sardi JE, Giaroli A, Sananes C, et al. Long-term follow-up of the first randomized trial using neoadjuvant chemotherapy in stage Ib squamous carcinoma of the cervix: the final results. Gynecol Oncol 1997;67:61-9.
38. Kenter GG, Greggi S, Vergote I, et al. Randomized phase III study comparing neoadjuvant chemotherapy followed by surgery versus chemo radiation in stage IB2-IIB cervical cancer: EORTC-55994. J Clin Oncol 2023;41:5035-43.
39. McCormack M, Rincon DG, Eminowicz G, et al. A randomized phase III trial of induction chemotherapy followed by chemoradiation compared with chemoradiation alone in locally advanced cervical cancer: the GCIG INTERLACE trial. In: Proceedings and abstracts of the 2023 European Society for Medical Oncology Congress, October 20–24, 2023. Madrid: European Society for Medical Oncology, 2023.
40. Lorusso D, Xiang Y, Hasegawa K, et al. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): a randomised, double-blind, phase 3 clinical trial. Lancet 2024;403:1341-50.
41. Cancer Genome Atlas Research Network. Integrated genomic and molecular characterization of cervical cancer. Nature 2017;543:378-84.
42. Ojesina AI, Lichtenstein L, Freeman SS, et al. Landscape of genomic alterations in cervical carcinomas. Nature 2014;506:371-5.
43. Monk BJ, Toita T, Wu X, et al. Durvalumab versus placebo with chemoradiotherapy for locally advanced cervical cancer (CALLA): a randomised, double-blind, phase 3 trial. Lancet Oncol 2023;24:1334-48.
44. Lorusso D, Xiang Y, Hasegawa K, et al. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2024;404:1321-32.
45. Tewari KS, Monk BJ. Immunotherapy plus chemoradiotherapy in cervical cancer management. Lancet 2024;403:1310-1.
46. Graves S, Seagle B-LL, Strohl AE, Shahabi S, Nieves-Neira W. Survival after pelvic exenteration for cervical cancer: a National Cancer Database study. Int J Gynecol Cancer 2017;27:390-5.
47. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 2009;27:4649-55.
48. Obermair A, Wanner C, Bilgi S, et al. Tumor angiogenesis in stage IB cervical cancer: correlation of microvessel density with survival. Am J Obstet Gynecol 1998;178:314-9.
49. Kudelka AP, Verschraegen CF, Loyer E. Complete remission of metastatic cervical cancer with the angiogenesis inhibitor TNP-470. N Engl J Med 1998;338:991-2.
50. Monk BJ, Sill MW, Burger RA, Gray HJ, Buekers TE, Roman LD. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol 2009;27:1069-74.
51. Monk BJ, Mas Lopez L, Zarba JJ, et al. Phase II, open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer. J Clin Oncol 2010;28:3562-9.
52. Tewari KS, Sill MW, Long HJ III, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med 2014;370:734-43.
53. Penson RT, Huang HQ, Wenzel LB, et al. Bevacizumab for advanced cervical cancer: patient-reported outcomes of a randomised, phase 3 trial (NRG Oncology-Gynecologic Oncology Group protocol 240). Lancet Oncol 2015;16:301-11.
54. Tewari KS, Sill MW, Penson RT, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). Lancet 2017;390:1654-63.
55. Kitagawa R, Katsumata N, Shibata T, et al. Paclitaxel plus carboplatin versus paclitaxel plus cisplatin in metastatic or recurrent cervical cancer: the open-label randomized phase III trial JCOG0505. J Clin Oncol 2015;33:2129-35.
56. Chung HC, Ros W, Delord J-P, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol 2019;37:1470-8.
57. Colombo N, Dubot C, Lorusso D, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. N Engl J Med 2021;385:1856-67.
58. Tewari KS, Colombo N, Monk BJ, et al. Pembrolizumab or placebo plus chemotherapy with or without bevacizumab for persistent, recurrent, or metastatic cervical cancer: subgroup analyses from the KEYNOTE-826 randomized clinical trial. JAMA Oncol 2024;10:185-92.
59. Monk BJ, Tewari KS, Dubot C, et al. Health-related quality of life with pembrolizumab or placebo plus chemotherapy with or without bevacizumab for persistent, recurrent, or metastatic cervical cancer (KEYNOTE-826): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2023;24:392-402.
60. Monk BJ, Colombo N, Tewari KS, et al. First-line pembrolizumab + chemotherapy versus placebo + chemotherapy for persistent, recurrent, or metastatic cervical cancer: final overall survival results of Keynote-826. J Clin Oncol 2023;41:5505-11.
61. Oaknin A, Gladieff L, Martínez-García J, et al. Atezolizumab plus bevacizumab and chemotherapy for metastatic, persistent, or recurrent cervical cancer (BEATcc): a randomised, open-label, phase 3 trial. Lancet 2024;403:31-43.
62. Wu X, Sun Y, Yang H, et al. Cadonilimab plus platinum-based chemotherapy with or without bevacizumab as first-line treatment for persistent, recurrent, or metastatic cervical cancer (COMPASSION-16): a randomised, double-blind, placebo-controlled phase 3 trial in China. Lancet 2024;404:1668-76.
63. Zhao X, Cheng C, Gou J, et al. Expression of tissue factor in human cervical carcinoma tissue. Exp Ther Med 2018;16:4075-81.
64. Coleman RL, Lorusso D, Gennigens C, et al. Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol 2021;22:609-19.
65. Vergote I, González-Martín A, Fujiwara K, et al. Tisotumab vedotin as second- or third-line therapy for recurrent cervical cancer. N Engl J Med 2024;391:44-55.
66. Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 phase II trial. J Clin Oncol 2024;42:47-58.
67. Oaknin A, Friedman CF, Roman LD, et al. Neratinib in patients with HER2-mutant, metastatic cervical cancer: findings from the phase 2 SUMMIT basket trial. Gynecol Oncol 2020;159:150-6.
68. Tewari KS, Monk BJ, Vergote I, et al. Survival with cemiplimab in recurrent cervical cancer. N Engl J Med 2022;386:544-55.
69. Naumann RW, Hollebecque A, Meyer T, et al. Safety and efficacy of nivolumab monotherapy in recurrent or metastatic cervical, vaginal, or vulvar carcinoma: results from the phase I/II CheckMate 358 trial. J Clin Oncol 2019;37:2825-34.
70. Salani R, McCormack M, Kim Y-M, et al. A non-comparative, randomized, phase II trial of atezolizumab or atezolizumab plus tiragolumab for programmed death-ligand 1-positive recurrent cervical cancer (SKYSCRAPER-04). Int J Gynecol Cancer 2024;34:1140-8.

71. Oaknin A, Moore K, Meyer T, et al. Nivolumab with or without ipilimumab in patients with recurrent or metastatic cervical cancer (CheckMate 358): a phase 1-2, open-label, multicohort trial. Lancet Oncol 2024;25:588-602.
72. O'Malley DM, Neffa M, Monk BJ, et al. Dual PD-1 and CTLA-4 checkpoint blockade using balstilimab and zalifrelimab combination as second-line treatment for advanced cervical cancer: an open-label phase II study. J Clin Oncol 2022;40:762-71.
73. Chiba Y, Kojima Y, Yazaki S, et al. Trop-2 expression and the tumor immune microenvironment in cervical cancer. Gynecol Oncol 2024;187:51-7.
74. Zeybek B, Manzano A, Bianchi A, et al. Cervical carcinomas that overexpress human trophoblast cell-surface marker (Trop-2) are highly sensitive to the antibody-drug conjugate sacituzumab govitecan. Sci Rep 2020;10:973.
75. Stevanović S, Draper LM, Langhan MM, et al. Complete regression of metastatic cervical cancer after treatment with human papillomavirus-targeted tumor-infiltrating T cells. J Clin Oncol 2015;33:1543-50.
76. Hari AY, Sill MW, Monk BJ, et al. PIK3CA and ARID1A mutations in recurrent/metastatic cervical cancer: the NRG Oncology/Gynecologic Oncology Group-0240 National Institutes of Health Beau Biden Cancer Moonshot. In: Proceedings and abstracts of the 2023 Society of Gynecologic Oncology Annual Meeting on Women's Cancer, March 24–28, 2023, Tampa, FL: Society of Gynecologic Oncology, 2023.

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