HHS Public Access

Author manuscript

Am Soc Clin Oncol Educ Book. Author manuscript; available in PMC 2016 June 24.

Published in final edited form as:

Am Soc Clin Oncol Educ Book. 2015 ; : e299–e309. doi:10.14694/EdBook_AM.2015.35.e299.

Nonsurgical Management of Cervical Cancer: Locally Advanced, Recurrent, and Metastatic Disease, Survivorship, and Beyond

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Overview

Despite the declining incidence of cervical cancer as a result of the introduction of screening programs, globally it remains a leading cause of cancer-related death in women. Outcomes for patients who are diagnosed with anything but early-stage disease remain poor. Here we examine emerging strategies to improve the treatment of locally advanced disease. We discuss emerging biologic data, which are informing our investigation of new therapeutic interventions in persistent, recurrent, and metastatic cervical cancer. We recognize the importance of interventions to improve quality of life and to prevent long-term sequelae in women undergoing treatment. Finally, and perhaps most importantly, we recognize the need for global collaboration and advocacy to improve the outcome for all women at risk of and diagnosed with this disease.

Cervical cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide and is the fourth leading cause of cancer death in women.[1] Human papillomavirus (HPV), particularly types 16 and 18, is associated with subsequent development of cervical cancer, with an increased risk also seen among smokers.[2] The incidence and mortality rates of cervical cancer are substantially higher in resource-poor regions of the world; the age standardized incidence of cervical cancer being 1.6 times higher in less developed countries. These regional discrepancies are attributable to reductions made in the incidence of cervical cancer in resource-rich countries with the introduction of widely accessed screening programs.[3] This decline is expected to continue as a result of the implementation and increased availability of vaccination against HPV.[4] These gains, however, remain challenging to replicate in resource-poor regions, which lack the infrastructure and funding to implement screening and vaccination programs, and where access to treatment remains an important problem. Within the United States, over 12,000

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Disclosures of Potential Conflicts of Interest

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Institutional relationships are marked “Inst.” Relationships marked “U” are uncompensated. **Employment:** None. **Leadership Position:** None. **Stock or Other Ownership Interests:** None. **Honoraria:** None. **Consulting or Advisory Role:** None. **Speakers’ Bureau:** None. **Research Funding:** None. **Patents, Royalties, or Other Intellectual Property:** None. **Expert Testimony:** None. **Travel, Accommodations, Expenses:** Helen Mackay, AstraZeneca. **Other Relationships:** None.

women will be diagnosed with cervical cancer in 2015 with approximately 4,000 women expected to die from their disease. Cervical cancer is disproportionately more common in women of African American or Hispanic ethnicity and in patients with limited access to health care.[3] Despite the advances in cervical cancer prevention and diagnosis, the outcome for patients diagnosed with later-stage and recurrent disease remains poor.

NONSURGICAL MANAGEMENT OF LOCALLY ADVANCED CERVICAL CANCER

The use of low-dose chemotherapy concurrent with pelvic radiation has been proven to improve survival, and became the established standard of care for locally advanced cervical cancer after the National Cancer Institute issued a clinical alert in 1999 about the benefit of chemoradiation compared with radiation alone as observed in five randomized clinical trials.[5] The Medical Research Council (MRC) individual patient data meta-analysis found that the addition of concurrent chemotherapy to radiation increased the 5-year overall survival (OS) rate by 6% (hazard ratio [HR], 0.81; 60% vs. 66%).[6] On the basis of the studies in this analysis, weekly cisplatin at a dose of 40 mg/m^2 during pelvic radiation has been adopted as the standard of care for the treatment of locally-advanced disease. However, the 5-year disease-free survival rate was only 58% in the chemoradiation group, which although superior to 50% with radiation alone, still leaves substantial room for improvement.

Identifying Patients Most at Risk of Recurrent Disease

The main prognostic factor for outcome in cervical cancer has traditionally been the International Federation of Gyne-cology and Obstetrics (FIGO) staging system, which is based on clinical examination alone. In those with FIGO stage 1B2 or higher, treatment with primary chemoradiation in the recommended approach.[7] In the meta-analysis, the additional benefit of chemotherapy was seen regardless of age, tumor histology, or grade. However, there appeared to be a lesser degree of benefit in higher staged tumors, with an absolute 5-year survival benefit of 10% for women with stages Ib to IIa cervical cancer, 7% for those with stage IIb, and 3% for women with stage III to IVa disease.[6]

In the meta-analysis, a benefit of adding chemotherapy was also seen regardless of nodal involvement, although it was only possible to look at this in five of the 18 included trials. However, Narayan et al and others have highlighted the important prognostic role of both nodal and uterine corpus involvement as detected by imaging, with MRI and PET now accepted modalities for noninvasively determining these features.[8–10] Nodal involvement has been documented to predict disease relapse in multiple studies, but is not part of the current FIGO staging system.[8,11–14] Uterine corpus invasion tends to be associated with tumors that grow endophytically rather than exophytically, and has also been shown to predict worse outcomes, in part because it predicts nodal metastasis (Fig. 1).[15–20] The relapse rate in those with PET-positive node disease has been reported to be approximately 50% after standard chemoradiation.[17,21,22] Some suggest that a follow-up fludeoxyglucose (FDG)-PET scan done 3 to 4 months postchemoradiation can predict patient outcome and may help to determine the intensity of follow-up needed.[23]

Optimizing Local Therapy

Although the development of distant disease after chemoradiation is the predominant cause of mortality, local relapse may also be a problem that causes substantial morbidity. Although the patterns of treatment failure have not been well described in all studies, in the meta-analysis, locoregional treatment failure was responsible for 35%of the failure events across trials.[6]

Standard radiation treatment involves 40 to 50.4 Gy of external beam radiation therapy (EBRT) delivered in fractions of 1.8 to 2 Gy to the pelvis. The upper border for treatment is usually L4-S1, unless an extended field is required to cover involved node disease. Parametrial or nodal boost may also be given if these areas are involved. In addition to EBRT, brachytherapy direct to the primary tumor is considered to be an essential component of therapy. It is recommended that the overall treatment time for chemoradiation should not exceed 8 weeks. The role for intensity modulated radiation therapy (IMRT) is controversial and an area of active research because of the recognition that the cervix moves as a result of changes in bladder and bowel filling, and uterine movement.

There is also ongoing controversy about the best approach to delivery of brachytherapy. Traditionally, brachytherapy has been planned to give a recommended cumulative dose of 80 to 90 Gy EBRT and brachytherapy to “point A,” which is an anatomic landmark 2 cm lateral to the central canal of the uterus and 2 cm up from the mucous membrane of the lateral fornix in the axis of the uterus.[24] There has also been increased interest in the value of using conformal brachytherapy, in which the dose is prescribed to the residual tumor volume at the end of EBRT rather than to point A. Proponents report that this approach may increase the effectiveness of local treatment and also reduce toxicity.[25] It is also recommended that image-guidance using either MRI or ultrasound is used to ensure that the tandem and ovoids used for the delivery of brachytherapy are correctly positioned within the uterus (Fig. 2).

A variety of approaches to intensifying the concurrent chemotherapy component of chemoradiation have been tested including the addition of cytotoxic agents. To date, no chemotherapy regimen has been found to be superior to 40 mg/m^2 (for most of the GOG studies, the does was capped at a maximum of 70 mg) of cisplatin weekly. However, the meta-analysis does suggest that substituting other agents that have demonstrated efficacy such as carboplatin or 5-flurouracil (5-FU) should be considered for women with a contraindication to cisplatin.[6] Addition of biologic agents to chemoradiotherapy is an active area of research. Despite success in head and neck cancers, the combination of the epidermal growth factor receptor (EGFR) inhibitor cetuximab, cisplatin, and radiotherapy proved toxic in patients with cervical cancer.[26] RTOG 0417 investigated 10 mg/kg of intravenous bevacizumab every 2 weeks (for three doses only) in combination with chemoradiation in 47 patients.[27] Results were promising and the toxicity profile was acceptable with no perforations or fistulas observed; further investigation is warranted.[28]

Multidisciplinary care is essential during chemoradiation for cervical cancer. In addition to monitoring side effects such as diarrhea and nausea, given the nature of the disease and the patient demographic, financial and psychosocial concerns are common. Early involvement of social work and psychology may assist women to cope with these issues. Younger women

may require referral to discuss options for fertility preservation and hormone-replacement therapy. Smoking cessation is highly encouraged as ongoing smoking during chemoradiation may reduce the effectiveness of treatment, as well as increase the risk for the development of a second malignancy.[29] Treatment of anemia may also be required and it is generally recommended that the hemoglobin is maintained at 10 g/dL or higher during treatment.[30] Eryth-ropoietin during chemoradiation, however, is not recommended because of an increased risk of thromboembolic events.[31]

Adjuvant Chemotherapy

Although chemoradiation is effective treatment for the primary disease, relapsed disease most commonly develops as distant metastatic disease.[32] It is therefore reasonable to predict that the addition of further cycles of adjuvant chemotherapy following completion of chemoradiation may decrease the development of distant metastases and thus improve survival. GOG109 was a U.S. study that randomly assigned patients who had been initially treated with radical hysterectomy and pelvic lymphadenectomy, and subsequently found to have positive pelvic nodes and/or positive margins and/or microscopic parametrial involvement, to receive adjuvant radiation alone or adjuvant chemoradiation. The chemotherapy consisted of four cycles of cisplatin and 5-FU, given as two cycles concurrent with radiation and two cycles post radiation. Progression-free survival (PFS) and OS rates were substantially improved for patients who received the additional chemotherapy. Although only 60% completed all planned chemotherapy, a higher number of chemotherapy courses was positively associated with improved survival rates.[33] This trial was one of two trials considered in a subset analysis of the MRC meta-analysis that considered the potential value of giving additional adjuvant chemotherapy. In this subset, there was an impressive absolute improvement of 19% in 5-year survival (from 60% to 79%) compared with radiation alone.[33,34]

More recently, Duenes-Gonzalez et al demonstrated a benefit of adding concurrent gemcitabine to the standard regimen of weekly cisplatin during radiation, followed by two further cycles of adjuvant cisplatin/gemcitabine. This multicenter, randomized, phase III trial showed a significant 9% improvement in the primary outcome of PFS at 3 years (65% to 74%; $p = 0.029$).[35] Toxicity, however, was a concern with two deaths in the experimental arm and a doubling of grade 3 to 4 adverse events (86.5% vs. 46.3%). In addition, prior investigators had been unable to safely deliver similar doses of drugs combined with radiotherapy in a North American population. Furthermore, it remains unclear how much of the benefit observed in this trial was a result of the additional chemotherapy given following the chemoradiation. Finally, follow-up data were truncated at 1 year, and as a result, an accurate measure of the effect on OS or rate of serious late complications cannot be properly assessed.[36]

Although not practice changing, these studies do raise important and unresolved questions regarding the potential value of adjuvant chemotherapy for women with locally advanced cervical cancer.

Current Clinical Trials

The Gynecologic Cancer InterGroup (GCIG) has an ongoing series of international, randomized, phase III trials aiming to test the effect of different chemotherapy strategies during chemoradiation on OS rates. The OUTBACK trial, led by the Australia New Zealand Gynaecological Oncology Group (ANZGOG) in collaboration with NRG Oncology, is testing the value of administering additional adjuvant chemotherapy after standard cisplatin-based chemoradiation compared with chemoradiation alone (ACTRN12610000732088). The primary aim is to determine if the addition of four cycles of adjuvant carboplatin and paclitaxel to standard cisplatin-based chemoradiation can improve OS.

The TACO trial, led by the Korean Gynecologic Oncology Group (KGOG) and Thai Cooperative Group, is comparing standard treatment with weekly cisplatin during chemoradiation to 3-weekly cisplatin (NCT01561586). This is based on a prior phase II trial from the KGOG, which suggested that the triweekly cisplatin maybe more effective and feasible to deliver.[37] It may also be an attractive regimen to use in low-resource countries because of the reduced number of chemotherapy treatments required.

Finally, INTERLACE, a trial led by the National Cancer Research Institute in the United Kingdom, is testing the value of administering additional neoadjuvant chemotherapy before chemoradiation compared with chemoradiation alone (NCT01566240). Although a previous meta-analysis suggested no improvement in OS with neoadjuvant chemotherapy in locally advanced cervical cancer, there was a suggestion of improved outcomes in those trials with a shorter cycle length of 14 days or less or higher dose intensity of cisplatin.[38] The regimen being tested of six doses of weekly carboplatin and paclitaxel before standard chemoradiation has been shown to be feasible to deliver in a prior phase II study[39]

QUALITY OF LIFE FOR PATIENTS WITH CERVICAL CANCER AFTER TREATMENT

Cervical cancer survivors often experience substantial quality of life (QOL) disruptions associated with the disease and treatment, many of which persist long into survivorship.[40–45] A recent analysis of health-related QOL data among U.S. cancer survivors indicates that cancer survivors are more likely to have poor physical and mental health–related QOL (25% and 10%, respectively > 1 standard deviation above the U.S. population mean) compared with adults with no cancer history (10% and 5%, respectively). Furthermore, cervical cancer survivors and short-survival cancer survivors report the worst mental health–related QOL.[46]

Persistent sequelae include pain, bladder and bowel dysfunction,[47–51] sexual dysfunction,[52–56] lymphedema, and menopausal symptoms,[57] as well as reproductive concerns among women of childbearing age.[45,58–62] Adverse psychologic consequences are shared with women diagnosed with other gynecologic tumors, and include depression and anxiety,[63] sleep disturbance, and concentration difficulties to a greater magnitude than many other populations of patients with cancer.[41,42,64–68] Despite challenges inherent in this cancer survivor population, supportive interventions may assist in substantially improving

QOL, with potential to also improve stress-related biomarkers.[69] This could, in turn, improve disease outcomes.[70–72]

A recent study indicated that of patients with cervical cancer diagnosed 9 to 30 months earlier, patients who reported the worst QOL also reported more gynecologic problems and less social support.[73] Gynecologic problems were substantially worse in patients treated with radiation with or without chemotherapy compared with those treated with surgery only, with a moderate-to-large effect size which is both statistically significant and clinically relevant (FACT-Cx, $p = 0.014$; FACT-TOI,$p = 0.006$). Treatment with radiation with or without chemotherapy also contributed to substantially poorer QOL, higher perceived stress, and greater depression, with modest-to-moderate effect sizes. Further, patients with three or more comorbidities before cancer diagnosis have also been reported to have substantially worse QOL, higher perceived stress, more depression and anxiety, and lower social support. In identifying subpopulations who are likely to benefit from supportive care interventions, it appears that a brief screening of type and number of premorbid medical problems, including mood disorders, could target the patients who have the greatest need for more immediate care and attention, as well as future cancer control studies. Therefore, further study of supportive care interventions to improve distress and decrease gynecologic problems in this vulnerable population appear warranted, particularly for women whose cancer treatment extends beyond surgery.

A recent supportive care study examined the effect of a psychosocial telephone counseling (PTC) intervention on QOL domains and associations with biomarkers. In this randomized clinical trial, after adjusting for age and baseline scores, participants receiving PTC had significantly improved depression and improved gynecologic and cancer-specific concerns at 4 months compared with usual care participants (all $p < 0.05$); significant differences in gynecologic and cancer-specific concerns ($p < 0.05$) were sustained at 9 months. Participants with decreasing interleukins-4, −5,−10, and −13 had substantially greater improvement in QOL than patients with increasing cytokine levels. This trial confirms that PTC benefits mood, QOL regarding cancer-specific and gynecologic concerns, for a multiethnic underserved cancer survivor population. The improvement in patient-reported outcomes with decreases in T-helper type 2, and counter-regulatory cytokines support a potential bio-behavioral pathway relevant to cancer survivorship.[74] Providing supportive care during treatment, and evaluating the effects of supportive care, may reduce the prevalence and magnitude of long-term sequelae of cervical cancer, which will in turn improve QOL and quality of care.

TREATMENT OF METASTATIC OR RECURRENT CERVICAL CANCER

Patients with distant metastases and/or with recurrent disease not suitable for local control have a very poor prognosis, with 5-year survival rates between 5% and 15%.[75] In this setting, any treatment is palliative, aiming to prolong survival but also to maintain or improve QOL. Platinum-based combinations have shown the most promising response rates with the combination of cisplatin (or carboplatin) with paclitaxel considered the standard of care. Responses to platinum-based chemotherapy are short-lived; median OS is around 12 months[76] and can be less than 6 months for those women who have poor prognostic

features.[77] Response to chemotherapy is influenced by site of recurrence in relation to previous treatment, with progressive disease within a previously irradiated field being particularly resistant to cytotoxic agents.[78] Receipt of prior platinum-based chemoradiation and a short time to relapse after primary treatment are also important negative prognostic factors. There are no effective second-line chemotherapy options for women whose disease progresses.

Targeting Angiogenesis

Persistent HPV infection leads to neovascularization and tumor growth promotion, with many studies having demon-strated a prognostic role for vascular endothelial growth factor (VEGF) and other markers of increased angiogenesis in cervical cancer (Fig. 3).[79–89] Targeting angiogenesis has therefore emerged as a rational therapeutic strategy in the treatment of cervical cancer. Early phase clinical studies with the anti-VEGF antibody bevacizumab, either alone or in combination with chemotherapy, suggested promising activity. Toxicity was acceptable and responses seen even in previously irradiated sites of disease.[89–91] As a result, a four-arm prospective, randomized clinical trial, GOG 240, was conducted. Over 400 patients were randomly assigned to receive treatment with one of two chemotherapy regimens: cisplatin plus paclitaxel versus paclitaxel plus topotecan with or without bevacizumab. Although there was no difference in outcome noted between the two chemotherapy regimens, the addition of bevacizumab led to a significant improvement in median OS, 17 months compared with 13.3 months in the chemotherapy alone arms (HR 0.71; 98% CI, 0.54 to 0.95; p = 0.004). Response rates were also higher for bevacizumab-containing arms (48% vs. 36%; p = 0.008). The benefit from bevacizumab was maintained in women with prior platinum exposure, recurrent/persistent disease, and responses were seen in previously irradiated fields. Toxicity, however, was increased by the addition of bevacizumab with an increased risk of fistula formation in gastrointestinal and genitourinary tracts (10.9% vs. 1%), grade 2 hypertension (25% vs. 2%), neutropenia (35% vs. 26%), and thromboembolism (8% vs. 1%). As a result of this study bevacizumab received a U.S. Food and Drug Administration label for the treatment of cervical cancer in combination with chemotherapy. This has become a new standard of care for women with cervical cancer in resource-rich populations, but expense precludes its use in most parts of the world.[70] A better understanding of the risk factors for fistulae development and identification of predictive biomarkers for response would help us to further refine the use of this drug by identifying the subgroups of women who may derive benefit while minimizing toxicity risk.

Antiangiogenic agents targeting other parts of the pathway have also been investigated in cervical cancer. Single agent, orally administered, multitargeted receptor tyrosine kinases inhibitors pazopanib (VEGFR 1, 2, and 3; PDGFR-α and β; and c-KIT) and sunitinib (VEGFR 1,2 and 3; PDGFR, c-KIT, and FLT3) were studied in phase II trials. Sunitinib did not display sufficient activity to warrant further investigation and was associated with an unacceptably high (26%) rate of fistula formation.[92] In the second, larger study, 230 patients were randomly assigned to one of three arms: pazopanib alone, lapatinib (a tyrosine kinase targeting EGFR and HER2/neu) alone, or a combination of the two agents. Pazopanib improved PFS (HR 0.66; 90% CI, 0.48 to 0.91; p = 0.013) and OS (HR 0.67; 90% CI, 0.46 to 0.99; p = 0.045) compared with lapatinib alone. Median OS was 50.7 weeks compared

with 39.1 week for pazopanib and lapatinib, respectively. Pazopanib alone was well tolerated, but the combination of the two drugs lacked efficacy and was associated with more serious adverse events.[93]

Clearly, targeting angiogenesis in cervical cancer has benefits in terms of efficacy, but patient selection is key and consideration of maintenance of QOL essential when considering future investigation of this therapeutic approach.

Targeting the EGFR

EGFR is expressed at moderate to high levels in cervical carcinoma. However, activating mutations are rare and studies evaluating the association of EGFR protein expression and prognosis in cervical cancer have yielded conflicting results.[95–96] Trials investigating the monoclonal antibody cetuximab, either alone or in combination with chemotherapy, failed to demonstrate sufficient clinical activity to warrant further investigation and reports of increased toxicity in combination with chemotherapy are concerning.[97–99] Clinical studies with the EGFR tyrosine kinase inhibitors gefitinib, erlotinib, and lapatinib were also disappointing.[100,101]

Molecular Profiling and Potential Therapeutic Targets

Our understanding of cervical cancer biology has focused around the role of HPV infection in the development of this disease.[102] The HPV oncoproteins E5, E6, and E7 are the primary viral factors responsible for initiation and progression of cervical cancer, and act largely by overcoming negative growth regulation by host cell proteins, including downstream effects that increase angiogenesis (Fig. 3).

Recent emerging data, however, are helping us to understand more about the genomic profile of cervical cancer. These data are helping to identify potentially “drugable targets” and thus new therapeutic approaches for investigation. Activating mutations and amplification of *PIK3CA* (the gene encoding phosphoinositol-3-kinase) have been reported for some time, occurring in 23% to 36% of cervical cancer cases. Reports of somatic mutations in other genes including *PTEN, TP53, STK11*, and *KRAS* were also reported.[103–105] A more comprehensive analysis was published in 2014, which included whole-exome sequencing. Previously unknown somatic mutations were identified in 79 primary squamous cell cervical carcinomas (SCC), including recurrent substitutions in *MAPK* and inactivating mutations in *HLA-A*, *-B* and *B2M*, suggesting a role for immune evasion in cervical cancer (Table 1). HPV integration appeared to be a common mechanism for gene overexpression, including *ERBB2*, which also appears to occur as a result of somatic mutation and amplification.[106] A further paper from Wright et al focused on the differences between adenocarcinoma, which account for 10% to 20% of cervical cancers but have a worse prognosis, and SCC.[107] Although *PIK3CA* mutations and *PTEN* loss were observed in both histologic subtypes, *KRAS* mutations were detected only in adeno-carcinomas (17.5% vs. 0%), and *EGFR* mutations only in SCC (0% vs. 7.5%).[108]

The prevalence of mutations within the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway, regardless of histologic subtype, make this an attractive therapeutic target in cervical cancer. An initial phase II study of the mTOR inhibitor temsirolimus for the

treatment of women with metastatic or recurrent cervical cancer demonstrated limited activity.[109] However, further investigation of newer agents (such as PI3K inhibitors) alone or in combination are warranted, potentially in patient populations enriched for *PIK3CA* mutations. Other potential therapeutic directions include exploring MAPK1 inhibition or ERBB2 inhibition in patients with activating mutations and mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK) inhibitors in patients with *KRAS* mutations (extrapolating from the experience in low-grade serous ovarian cancer).

Immunotherapy

There is a strong rationale for investigating immunotherapy in cervical cancer given the host/HPV-induced immune evasion, which leads to persistent infection and carcinogenesis. Regulatory T cells are known to modulate the maintenance of an immunologically tolerant environment to HPV-associated preinvasive and malignant lesions.[110,111] Furthermore, the presence of tumor-infiltrating lymphocytes (TiLs) in tumor specimens has been associated with improved outcomes.[112,113] Currently, investigation of immu-nomodulating agents and strategies which either enhance the innate immune response to cervical cancer or repress immune-protective pathways are a very active area of cervical cancer research (Table 1). Upregulation of cytotoxic T lymphocyte-associated molecule-4 (CTLA-4) receptor on T lymphocytes is a negative regulator of T-cell activation. Ipilimumab is a fully human immunoglobulin (IgG1 kappa) that blocks CTLA-4. CTLA-4 blockade results in the expansion of activated T-cell clones directed at tumor epitopes, theoretically increasing immunovigilance and eradication of tumor cells.[114–116] Ipilimumab has demonstrated substantial clinical activity in patients with metastatic melanoma and is currently being investigated in two clinical trials enrolling women with advanced cervical cancer with results expected soon. (GOG 9929/NCT01711515; NCT01693783). A second attractive immunomodulatory strategy under investigation utilizes antibodies directed against another coinhibitory pathway on activated T-cells, the inhibitory receptor programmed cell death 1 (PD-1) and its ligand PD-L1. It remains to be seen if this approach will yield results in cervical cancer.[117] The use of bacterial vectors directed against E7 has been shown to induce tumor regression in preclinical models, and a phase II trial conducted in India with a live-attenuated *Listeria* monocytogenes vaccine suggests that this approach may be successful with further studies ongoing (GOG 265/NCT01266460).[118] Finally, patients with cervical cancer are being included in adoptive immunotherapy programs exploring the potential of TiLs harvested from patient tumor samples and then reinfused after immunodepletion (NCT01266460).

Targeting DNA Repair

Repair of DNA damage occurring in cells is essential for their survival. Therefore, inhibition of DNA repair following radio-therapy is a potentially interesting strategy in cervical cancer. Furthermore, there are reports that a subgroup of cervical cancers may have defective homologous recombination as a result of epigenetic modification of the Fanconi anemia (FA) complementation group F (*FANCF*).[119,120] As a result, investigation of the poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors, which block base excision repair of single stranded DNA breaks, in cervical cancer a potentially interesting idea.[121] Other proposed strategies inhibiting the repair of DNA damage include inhibition of

ribonucleotide reductase (RNR)[122,123] and agents which abrogate the G2/M arrest induced by radiation or chemotherapy, such as the Wee1 inhibitor MK1774 (NCT01076400).[124]

CHALLENGES IN CERVICAL CANCER RESEARCH

The majority of women affected globally by cervical cancer are unlikely to have access to trials or be able to afford new biologic therapies. Conducting clinical trials in patients with cervical cancer in the developed world is becoming increasingly challenging. Ironically, the falling incidence of cervical cancer in the developed world not only results in fewer women who are eligible for clinical trials, but may also result in a lack of interest by pharmaceutical companies to explore new agents in this patient population, despite the major mortality the disease causes worldwide. International collaboration is increasingly required to complete studies in a timely fashion, which, despite efforts in harmonization by organizations such as the GCIG, continue to pose substantial logistical barriers between countries. Within the United States, the patient demographic makes trial enrollment challenging.[125] The participation of ethnic minorities and medically underserved populations in clinical trials is critical to making progress. However, multiple well-documented factors account for disproportionally low enrollment rates among minority patients in clinical trials.[126–128] These include patients and their families being unaware of clinical trials, a fear of being "treated like a guinea pig,"[129–131] and the presence of mistrust of medical research and researchers among certain ethnic groups including American Indian, Asian American, and African American communities.[126,132,133] Furthermore, patients with cancer who are immigrants, live in rural areas, have a poor socioeconomic status, and work frequently cite practical concerns, including issues with transportation, family responsibilities, and out-of-pocket expenses as factors that inhibit their ability to participate in research.[126,134,135] It is imperative that clinical researchers of cervical cancer acknowledge these issues and reach out to our most vulnerable patients to provide assistance in helping them to become aware of all of their treatment options.

Given the relatively small numbers of patients available to enroll in clinical trials, it is essential that studies are rationally designed and based on biologically sound hypotheses. To limit the administrative burden and maximize participation, creative trial design is essential. Trial designs such as multiarm (or umbrella) or rolling phase II studies are essential if we are to investigate multiple agents in a time- and resource-efficient manner. Incorporation of translational substudies and functional imaging studies will allow us to gain the maximum information from each trial. Commonality with other HPV-induced malignancies, such as cancers of the oropharynx and anal canal, suggest there might be underdeveloped routes of collaboration. Patients with cervical cancer may be eligible for studies requiring the presence of specific mutational profiles which are not limited to a particular cancer type.[125]

FINAL REMARKS

Much progress is still needed in the treatment of cervical cancer. It is important that we remember that the majority of women affected globally by cervical cancer are unlikely to be able to access new biologic therapies or have access to clinical trials. If we are to achieve maximum benefit for women with this disease, we need to reach out and form partnerships

that allow us to raise the standards for all women. Costs must be considered in the development of new agents so that our results may be globally relevant, and advocacy is essential. Data from randomized trials exploring the role of adjuvant chemotherapy are expected soon that may change our approach to the front-line management of women with locally-advanced cervical cancer. However, the key to ensuring truly improved quality of care for patients is to recognize and identify patients who require supportive interventions both during and following therapy.

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KEY POINTS

- Cervical cancer remains one of the leading causes of cancer-related morbidity and mortality in women worldwide.
- A number of ongoing clinical trials are examining the role of adjuvant chemotherapy in addition to the standard-of-care treatment, low-dose chemotherapy (cisplatin) concurrent with pelvic radiotherapy for locally advanced cervical cancer.
- Women undergoing treatment for locally advanced cervical cancer experience significant psychosocial distress. Multidisciplinary supportive care may reduce the magnitude of long-term sequelae and improve quality of life.
- Outcome for women diagnosed with metastatic or recurrent cervical cancer remains poor; there are a number of potential therapeutic targets actively under investigation. The first biologic agent, in combination with chemotherapy, to show a survival benefit was bevacizumab.
- International collaboration and engagement of medically underserved communities are essential to making progress in the treatment of cervical cancer.

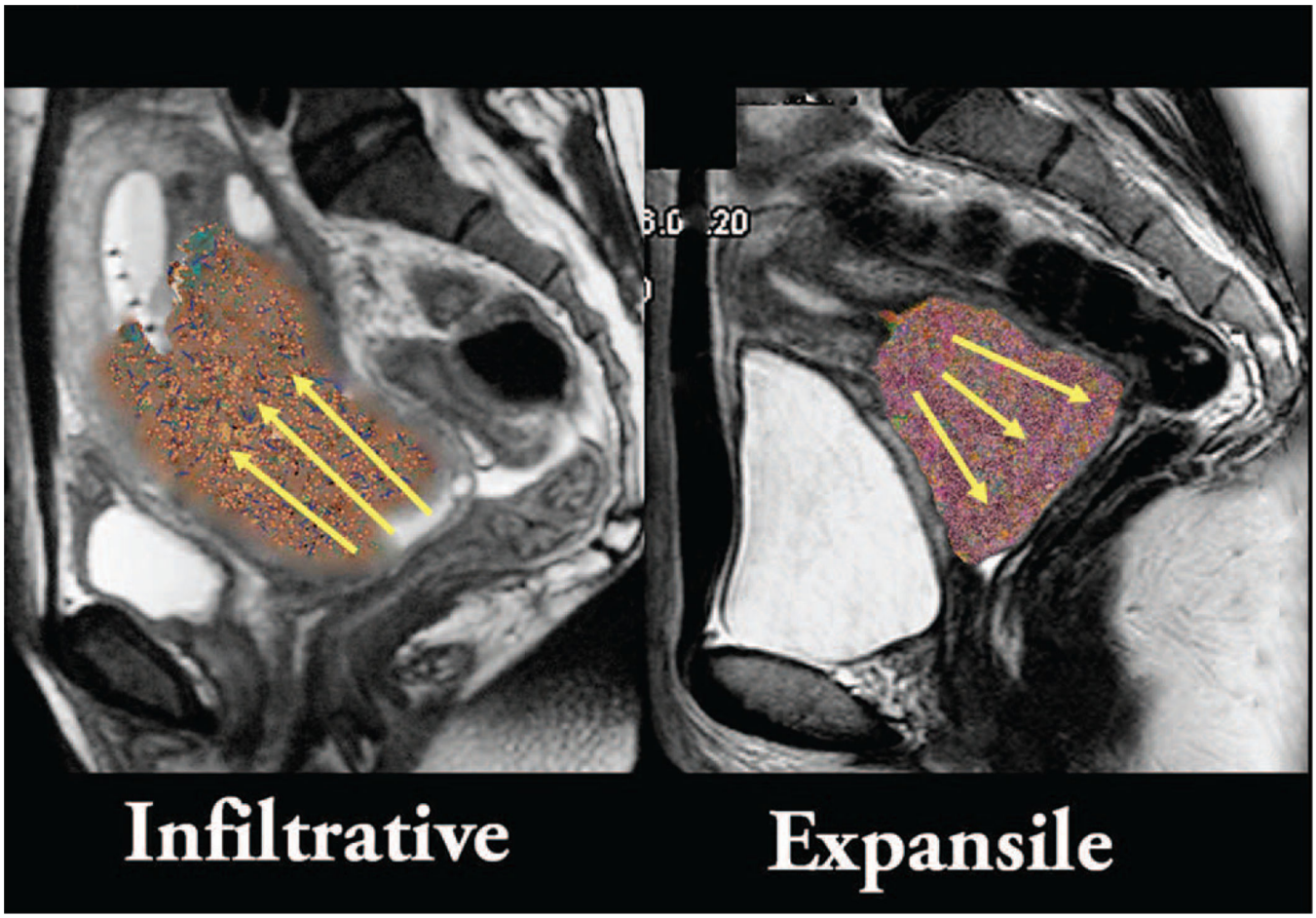

FIGURE 1. Infiltrative versus Expansile Cervical Cancer

Infiltrative corpus invasive cervix cancer has higher local failure rates, increased frequency of nodal metastases at presentation, and poor survival compared with exophytic tumor of similar volume.

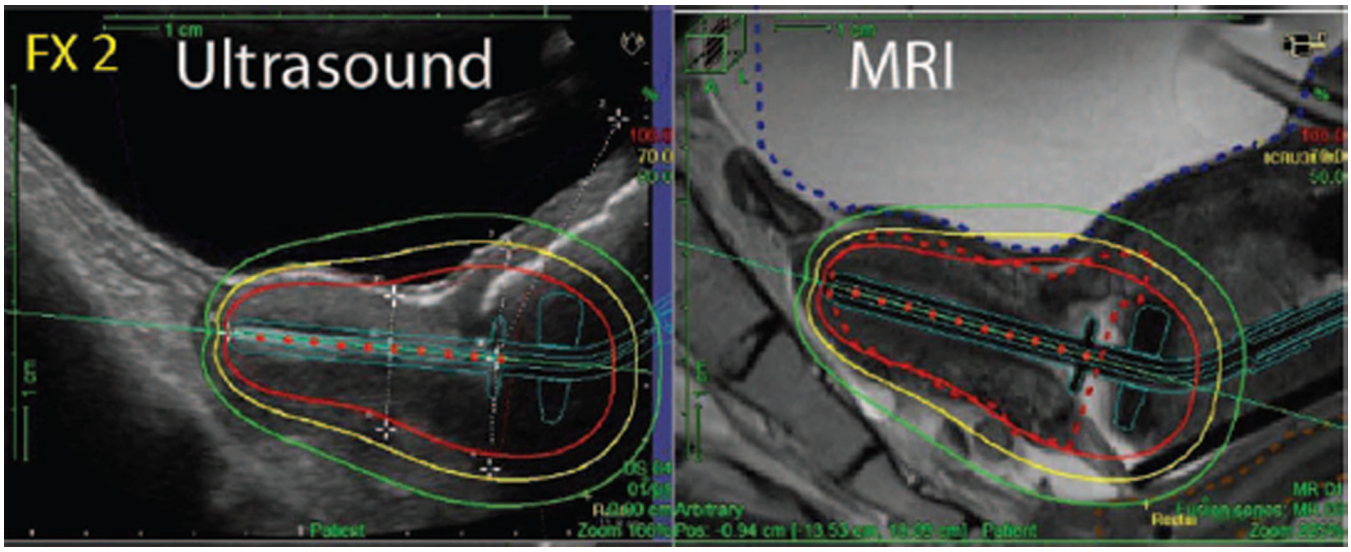

FIGURE 2. Ultrasound and MRI Images for Delivery of Brachytherapy

The left ultrasound image shows the tandem position and superimposed isodoses in the treatment position. The ultrasound images correlates very well with the corresponding MRI image.

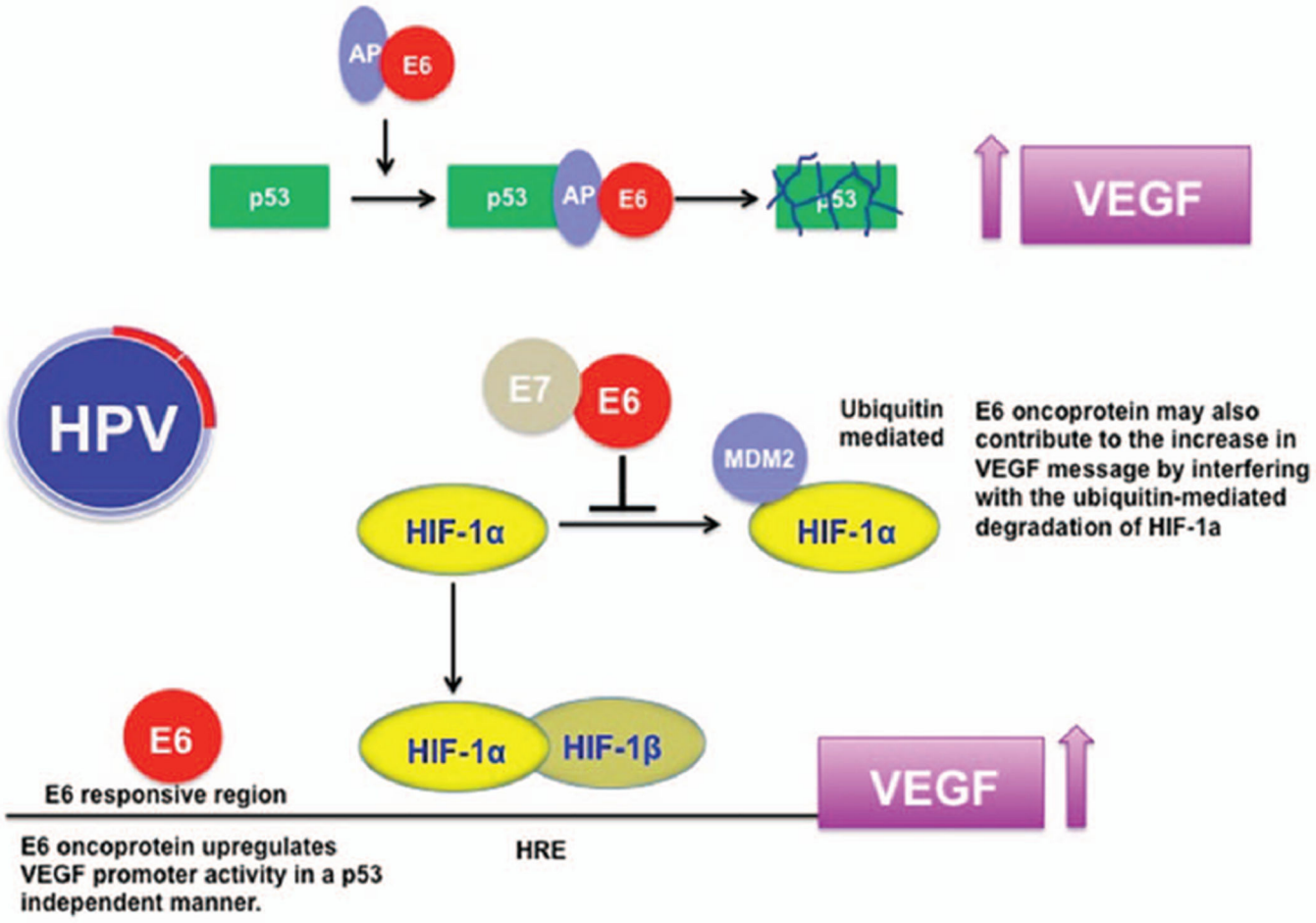

FIGURE 3. Rationale for Targeting Angiogenesis in Cervical Cancer

Abbreviations: TSP-1, thrombospondin-1; VEGF, vascular endothelial growth factor; HIF1α, hypoxia inducible factor 1α.

TABLE 1

Agents Currently under Investigation for the Treatment of Recurrent, Persistent, and Metastatic Cervical Cancer

Target	Phase of Study	Agent(s)	Clinical Trials No.
Immunotherapy			
CTLA	II	Ipilumimab	NCT01693783
PD-1	II	Nivolomab	NCT02257528
TiLs		TiLs	NCT01585428
T-cell immunotherapy	HPV16 only	T cells	NCT02280811
Pathway-Targeted Therapy			
RAS/ERK/PI3K/AKT/MTOR	II	Trametanib (MEK inhibitor)/GSK2141795 (AKT inhibitor)	NCT01958112
PI3K	II	BKM120	NCT01613677
RTK/Angiogenesis	II	Pazopanib/topotecan	NCT02348398
RTK/Angiogenesis	II	Carboplatin/paclitaxel ± nintedanib or placebo followed by maintenance	NCT02009579
HPV-Related Therapy			
HPV 16 and 18-positive cancer	II	VGX-3100 (plasmids encoding E6 and E7 protein)/ INO-9012 (plasmid encoding interleukin 2) delivered via electroporation	NCT01693783
Therapeutic vaccine	I-II	ADXS11-001 high dose (therapeutic vaccine)	NCT02164461
	I-II		
	HPV 16 only	ISA101 (HPV 16 E6/E7 long peptides vaccine) with or without interferon alpha with carboplatin paclitaxel	NCT02128126
Cytotoxic Agents	II	Albumin-bound paclitaxel/nedaplatin	NCT01667211
	II	Eribulin mesylate	NCT0167818
Other			
Chromosome Region 1 Maintenance Protein	II	Selinexor	NCT02025985

Abbreviations: TiLs, tumor-infiltrating lymphocytes; HPV, human papillomavirus.
Studies are single arm unless otherwise indicated.