Review Article

Cervical Cancer: A Global Health Crisis

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Cervical cancer is the fourth most common malignancy diagnosed in women worldwide. Nearly all cases of cervical cancer result from infection with the human papillomavirus, and the prevention of cervical cancer includes screening and vaccination. Primary treatment options for patients with cervical cancer may include surgery or a concurrent chemoradiotherapy regimen consisting of cisplatin-based chemotherapy with external beam radiotherapy and brachytherapy. Cervical cancer causes more than one quarter of a million deaths per year as a result of grossly deficient treatments in many developing countries. This warrants a concerted global effort to counter the shocking loss of life and suffering that largely goes unreported. This article provides a review of the biology, prevention, and treatment of cervical cancer, and discusses the global cervical cancer crisis and efforts to improve the prevention and treatment of the disease in underdeveloped countries. ***Cancer* 2017;123:2404-12**. © *2017 American Cancer Society.*

KEYWORDS: activism, brachytherapy, cervical cancer, Cervix Cancer Research Network (CCRN), chemotherapy, developing world, Gynecological Cancer InterGroup (GCIG), human papillomavirus (HPV), vaccination.

INTRODUCTION

Cervical cancer is one of the leading causes of cancer death among women.[1] Worldwide, cervical cancer is the fourth most frequently occurring malignancy in women, and results in an estimated 530,000 new cases annually with 270,000 deaths. Approximately 85% of the worldwide deaths from cervical cancer occur in underdeveloped or developing countries, and the death rate is 18 times higher in low-income and middle-income countries compared with wealthier countries.[2] The highest incidence rates occur in Central and South America, the Caribbean, Sub-Saharan Africa, and Southern Asia.[3] In the United States in 2016, there were an estimated 12,990 cases and 4120 deaths from cervical cancer,[4] and the median age at the time of diagnosis is 47 years.

The standard management of patients with early-stage (FIGO stage IA-IB1) cervical cancer is radical hysterectomy and lymph node dissection and/or radiation with or without chemotherapy.[5-7] The standard management of individuals with locally advanced cervical cancer includes external beam radiotherapy with concurrent cisplatin-based chemotherapy with brachytherapy.[8-16] Brachytherapy is critical for curative-intent treatment of cervical cancer, and when it is replaced with external beam radiotherapy, the results are clearly inferior.[17-20] With state-of-the-art staging and treatment, the 3-year local control rate for patients with early-stage and advanced stage cervical cancer is 87% to 95% and 74% to 85%, respectively.[15,16] For all stages combined, the 3-year to 5-year survival rate from cervical cancer for many underdeveloped countries is $<50\%$.[21] Death from cervical cancer often involves local disease progression, resulting in significant suffering, including ureteral obstruction, pain, and fistulas. The purpose of this article was to thoroughly review the biology, prevention strategies, treatment, and activism regarding cervical cancer, with an emphasis on the global impact of these complex issues.

Biology of Cervical Cancer

The cervix is lined by stratified squamous epithelium that covers the exocervix and mucus-secreting columnar epithelium characteristic of the endocervical canal. The transition between these 2 populations of cells is called the squamocolumnar junction, and it is this area that is believed to be at greatest risk of viral neoplastic transformation. Tumors arising in the

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ectocervix are most often squamous cell carcinomas, which account for approximately 75% of invasive cervical carcinoma cases. In contrast, tumors arising from the endocervix are more likely to be adenocarcinomas. Adenosquamous, small cell or neuroendocrine, serous papillary, and clear cell carcinomas of the cervix are less common histological subtypes.

The majority of cases of cervical cancer result from infection with the human papillomavirus (HPV), with HPV DNA identified in approximately 95% of malignant cervical lesions.[22] The majority of HPV infections are transient and will be cleared spontaneously. However, in some cases, persistent infection will result in the development of the premalignant conditions of cervical intraepithelial neoplasia or adenocarcinoma in situ. Without treatment, the transition from dysplasia to invasive carcinoma may take years to decades to develop in most women. However, in approximately 10% of patients, this transition can occur in <1 year.[23] In addition, adenocarcinoma in situ appears to be more difficult to detect on Papanicolaou testing, and this is thought to be one of the reasons for the increasing incidence of this subtype of cervical cancer.[24]

Various factors have been suggested to increase the likelihood of the development of persistent infection and subsequent malignant transformation, including cigarette smoking, long-term oral contraceptive use, high parity, and coinfection with type 2 herpes simplex virus or the human immunodeficiency virus. HPV serotypes 16 and 18 are reported to account for approximately 70% of cases, with the most common serotypes of HPV in women with cervical cancer, in descending order of frequency, being 16, 18, 45, 31, 33, 52, 58, and 35.[22,25]

Perhaps due to the relative rarity of locally advanced or metastatic cervical cancer in the developed world, to our knowledge there have been only a few published reports of profiling of cervical tumors to search for actionable driver mutations. The most common finding has been of abnormalities in the phosphatidylinositide 3-kinases (PI3K) pathway, as reported by Wright et al,[26] who used the OncoMap platform (Dana-Farber Cancer Institute, Boston, Mass) to examine 80 cervical tumors for 1250 mutations in 139 genes. They identified *PIK3CA* mutations in 31% of cases, with shorter survival times observed in those patients with a mutation.[26] However, targeting this pathway therapeutically has proven difficult. Wright et al also identified *KRAS* mutations in 17.5% of the adenocarcinomas but none of the squamous cell carcinomas, suggesting that these tumor subtypes will need different kinds of targeted therapies. Ojesina et al[27] recently published the findings of deep sequencing of 115 cervical cancers to search for somatic mutations. They identified several novel somatic mutations in the squamous cell carcinomas profiled, including E322K substitutions in the *MAPK1* gene (8%); inactivating mutations in the *HLA-B* gene (9%); and mutations in *EP300* (16%), *FBXW7* (15%), *TP53* (5%), and *ERBB2* (6%). Somatic mutations in *ELF3* (13%) and *CBFB* (8%) were found in 24 adenocarcinomas.[27]

Prevention of Cervical Cancer

Recognition that cervical neoplasia begins as an intraepithelial change, which usually takes many years to develop into invasive disease, led to the use of cervical exfoliative cytology to detect cervical intraepithelial neoplasia that can be treated to prevent the development of cervical cancer. With the discovery that cervical cancer is caused by high-risk HPV infection and the development of prophylactic vaccination in the 1990s, there now is the means with which to achieve a more global approach to prevention through prophylactic vaccination. Vaccination can be viewed as primary prevention, with screening as secondary prevention.

The pivotal role of HPV in cervical carcinogenesis means that screening with HPV testing can achieve a more accurate risk-based approach. Randomized trials[28-31] have demonstrated that HPV testing is more sensitive than cytology, and that for HPV-negative women, screening intervals can be safely extended.[32] HPV testing lacks specificity, which means that cytology is required to triage women for referral to colposcopy. Based on limited data, triage of high-risk HPV (hrHPV)-positive women using a combination of genotyping for HPV types 16 and 18 and reflex cytology for women who are positive for the 12 other hrHPV genotypes appears to be a reasonable approach to managing patients who are hrHPV positive.[33] A challenge for primary HPV screening is the management of women with negative cytology, but various risk-based strategies are being developed based on HPV type and persistence. Screening programs around the world currently are in the process of switching from primary cytology aided by visual inspection with acetic acid to primary HPV testing.

Prophylactic Vaccination Against HPV

HPV infection of the cervix, believed to occur in the majority of women at some time in their life, is most prevalent after the onset of sexual activity. In the majority of cases, the infection is cleared by the immune system. However, in a significant minority of individuals,

infection is persistent and the viral genome becomes integrated into host DNA, resulting in genomic dysregulation caused largely by the HPV oncogenes E6 and E7. The concept behind prophylactic vaccination is to achieve a high level of type-specific neutralizing antibodies directed against HPV that are capable of preventing cervical infection. The critical discovery that led to the vaccines we have today is that the major capsid protein of HPV, L1, could self-assemble into so-called virus-like particles,[34] which were shown to be highly immunogenic. Two vaccines, both based on virus-like particles made from HPV types 16 and 18, were produced, with each using a different adjuvant. One was bivalent (types 16 and 18) and the other vaccine was quadrivalent to include the types responsible for genital warts (types 6 and 11). Both these vaccines have been rigorously tested, initially in phase 1 and phase 2 trials and then in pivotal phase 3 trials.[35,36] These trials were performed among patient cohorts aged 15 to 26 years, and they demonstrated very high levels of type-specific antibody, which achieved very high efficacy (>95%) in preventing HPV infection and similar efficacy in preventing type-specific cervical intraepithelial neoplasia as well as vaginal and vulvar lesions. However, the data from these trials demonstrated that the vaccines were ineffective in females who already had an established HPV infection. In addition, the vaccination of boys before sexual activity at ages 11 to 12 years is recommended by the American Academy of Pediatrics to prevent HPV-induced cancers of the oropharynx, anus, and penis.[37] Vaccination of both sexes will have a large impact on herd immunity.

Most developed countries have introduced vaccination programs for prepubescent girls, and there has been early evidence of a public health benefit with a reduction in the incidence of high-risk infection, a reduced incidence of cervical abnormalities, and even a reduction in genital warts in males who have not been vaccinated. This provides clear evidence of herd protection achieved by vaccination.

Recent Developments in Prophylactic Vaccination

The original vaccination regimens were based on 3 doses, given at time 0, 2 months, and 6 months. Recently, 2 doses have been shown to be as effective as 3 doses,[38] provided the second dose is given 6 months to 12 months after the initial dose. For example, in the United Kingdom, a 2-dose regimen has replaced the 3-dose regimen in the publicly funded schools-based program, which is achieving coverage rates of 85% to 90%. Another development has been the production of a nonavalent vaccine that adds types 31, 33, 45, 52, and 58 to the vaccine containing types 6, 11, 16, and 18. This vaccine has been demonstrated in phase 3 trials to achieve similar efficacy against types 6, 11, 16, and 18 in addition to achieving high efficacy against the new types.[39,40] The nonavalent vaccine has been licensed in some countries, including the United States and the United Kingdom,[41,42] and may well replace the bivalent and quadrivalent vaccines over the next few years.[43,44] Prophylactic vaccination has the means to save hundreds of thousands of lives, but this will require the political will to ensure that vaccination is implemented in resource-poor countries.

There also is increasing interest and research into the possibility of treating established cervical cancer using immunotherapy approaches. The 2 main oncogenes associated with HPV-driven cancers, E6 and E7, are considered to be excellent targets for immunotherapy. Promising results have been observed with clinical trials involving therapeutic HPV vaccines, adoptive T-cell therapy, and checkpoint inhibitors, with currently ongoing trials examining various combination immunotherapy approaches with standard treatments such as radiotherapy.[45]

Gynecological Cancer Intergroup and the Cervix Cancer Research Network

The Gynecologic Cancer InterGroup (GCIG), formalized in 1997, aims to promote and facilitate high-quality clinical trials to improve outcomes for women with gynecological cancer. Currently, there are 29 member groups, including representation from North America, Europe, Asia, and Australia. The GCIG has several standing committees including the Ovarian Cancer, Endometrial Cancer, Cervix Cancer, Translational Research, Harmonization (operations and statistics), Rare Tumors, Symptom Benefit, Phase 2, and Membership committees.

The GCIG also has developed a Cervix Cancer Research Network (CCRN) whose aim is to promote high-quality clinical research for cancer of the cervix diagnosed in women in developing countries. The purpose of the CCRN is to bring research in cervical cancer to the countries where the burden is the highest and there is a lack of GCIG cooperative groups (Fig. 1).[46] Interested sites complete a prequalifying set of capability questions followed by a radiologic/physics check (questionnaire courtesy of IROC, Houston, Tex). Site visits then are performed by a review team from GCIG to assess clinical activity, site resources, clinical trial operations, radiotherapy facilities/quality assurance and treatment record, and

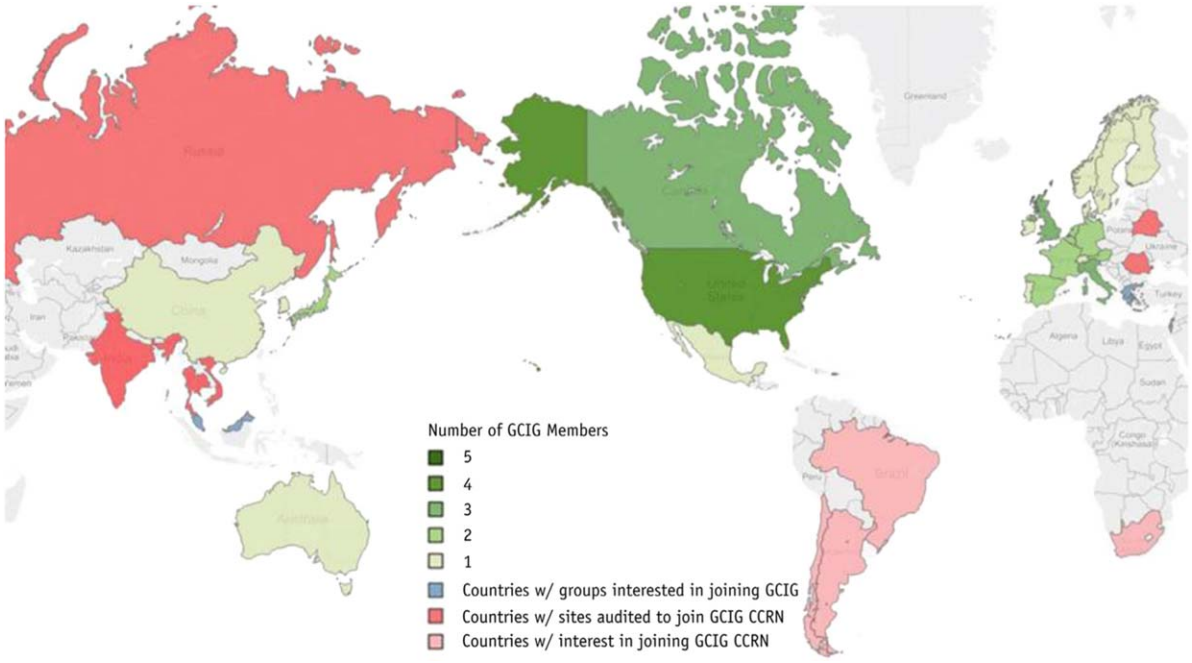

Figure 1. Countries around the world have many Gynecological Cancer InterGroup (GCIG) members or are interested in joining the GCIG or the Cervix Cancer Research Network (CCRN). Reproduced with permission from Gaffney DK, Suneja G, Ryu SY, et al. The Cervix Cancer Research Network: a global outreach effort on behalf of the Gynecologic Cancer InterGroup. *Int J Radiat Oncol Biol Phys*. 2015;92:506-508.[46]

clinical trials management information. Participation in a beam measurement program (thermoluminescence dosimeters/optically stimulated luminescence dosimeters) every 2 years is a requirement. Ongoing quality assurance and quality control is performed according to the lead group trial protocols. CCRN currently has 4 active cervical cancer trials, as described below.

The success of the GCIG relates to pooled intellectual resources and collaboration, rapid and large accrual, evidence-based medicine and application of the results, and the opportunity for substantial translational research. GCIG is unique in the world of cancer research and has been intensively productive in collaborative trials, intellectual exchanges and learning, brainstorming, and consensus conferences.

Modern Treatment of Cervical Cancer

The treatment of cervical cancer is dictated by International Federation of Gynecology and Obstetrics (FIGO) stage, which is a clinical staging system.[47] For patients with early cervical cancers, surgery is recommended. A cone biopsy is adequate treatment for patients with stage IA1 disease, whereas for patients with stage IA1 disease with lymphovascular space invasion or stage IA2 disease, a cone biopsy with negative surgical margins and pelvic lymph node dissection are recommended. Fertility-sparing surgery is an option for patients with early-stage cervical cancers. For patients with high-risk stage IA1 through stage IB1 disease, a radical trachelectomy and pelvic lymph node dissection can be considered. An additional option for some patients would be pelvic radiotherapy and brachytherapy. There currently are ongoing trials evaluating reduced-intensity surgery for patients with early-stage lesions. The **S**imple **H**ysterectomy **A**nd **P**elvic node dissection in **E**arly cervix cancer (SHAPE) trial is evaluating simple versus radical hysterectomy for patients with cervical tumors measuring <2 cm in size. SHAPE is a CCRN trial that has immediate application to underresourced countries. A randomized trial of surgery versus radiotherapy for patients with stage IB1 to stage IIA cervical cancer demonstrated no difference in survival.[5] It is interesting to note that patients in this trial did not receive chemotherapy, and 84% of patients in the surgical arm with tumors measuring >4 cm required postoperative radiotherapy. Morbidity was noted to be greater in patients who received both modalities, and therefore current recommendations are to try to use a single modality.

Advanced imaging such as computed tomography, magnetic resonance imaging, and positron emission

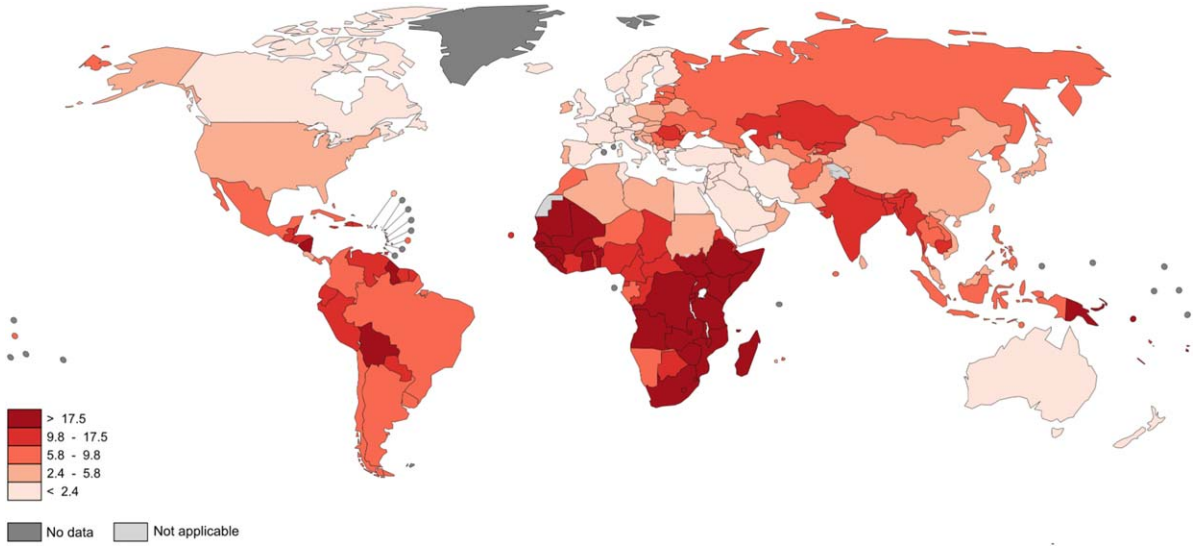

Figure 2. Estimated age-standardized world rates of deaths, females, and cervical cancer worldwide in 2012. Reproduced with permission from Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0: Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. Lyon, France: International Agency for Research on Cancer; 2013. http://globocan.iarc.fr. Accessed December 21, 2016.[67]

tomography are not permissible in FIGO staging; however, imaging (if available) should be used to appropriately guide treatment. Positron emission tomography scans are helpful for delineating the extent of disease. Magnetic resonance imaging is superior at demonstrating soft tissue resolution for the extent of cervical cancer within the pelvis. This can be critical for brachytherapy treatment planning or conformal radiotherapy techniques.

A National Cancer Institute Alert in 1999 demonstrated the superiority of cisplatin-containing concurrent chemoradiotherapy for women with advanced cervical cancer. The hazard rate for reduction and death was approximately 0.52.[11] Consequently, this technique was rapidly adopted worldwide, and weekly cisplatin became the worldwide standard.[48] The optimization of chemotherapy is unclear, and the CCRN has 3 trials testing the optimal combination of chemotherapy and radiotherapy.[49] Extended adjuvant chemotherapy in patients with locally advanced disease currently is being tested in the OUTBACK (A Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone) trial. The Radiation Therapy Oncology Group (RTOG) 0724 trial also is evaluating extended adjuvant chemotherapy for patients treated with a radical hysterectomy who have positive lymph nodes or positive parametria, although this currently is not a CCRN trial. Dose-intense neoadjuvant chemotherapy is being tested in the phase 3 INTERLACE (A phase III multicentre trial of weekly induction chemotherapy followed by standard chemoradiation versus standard chemoradiation alone in patients with locally advanced cervical cancer) trial. In addition, a phase 2 trial showed promising results with a higher dose of cisplatin administered every 3 weeks.[50] This finding now is being compared with weekly cisplatin in the **T**ri-weekly **A**dministration of **C**isplatin in L**O**cally Advanced Cervical Cancer (TACO) trial. The TACO trial has been the most successful CCRN trial, with significant accrual from Vietnam and Thailand.

In patients with advanced disease who are receiving curative radiotherapy, an important quality metric is to keep the total treatment course duration within 8 weeks. In multiple studies, prolonged treatment after 8 weeks has been shown to have an approximate 1% loss in local control for every day of treatment beyond 8 weeks. Adherence to a few quality metrics such as receipt of concurrent chemoradiotherapy, brachytherapy, and completion of treatment within 8 weeks will markedly improve survival worldwide.

Brachytherapy

Brachytherapy is an integral component of the treatment of patients with advanced cervical cancer and is the standard of care in combination with external beam radiotherapy in all-national guidelines.[51-53] The advantage of brachytherapy comes from its dosimetric benefits,

TABLE 1. Treatment Capacity for Different Modalities Based on Setting

Treatment	Setting			
	Basic	Limited	Enhanced	Maximal
Surgery	Simple (extrafascial) hysterectomy or more extensive hysterectomy can be performed[a]	**Modified radical or radical hysterectomy**	**Capable of performing most major surgeries**, including radical hysterectomy, **radical trachelectomy,**[b] **pelvic and para-aortic LN sampling, and pelvic exenteration**[b] Following are not available: PET scan, interventional radiology, sentinel node biopsy/IORT, or bevacizumab	Radical hysterectomy, radical trachelectomy, pelvic and para-aortic LN sampling, **sentinel node biopsy**, and pelvic exenteration; RT, **chemotherapy, interventional radiology, palliative care service, and bevacizumab are all available**
Chemotherapy	Availability of chemotherapy drugs is unpredictable	**Chemotherapy may be available**	**Chemotherapy available**; bevacizumab not available	Chemotherapy available; **bevacizumab is available**
RT	No RT available	**Limited external RT with no brachytherapy available**; in some areas where there is only brachytherapy and no external RT, this will be considered as basic level	**RT including external beam and brachytherapy available**; interventional radiology not available	RT including external beam and brachytherapy available; **interventional radiology available**
Pathology	Pathology services are not available; if there is a way to send pathology for review when needed, that should occur (Basic pathology may be available, but diagnosis is often delayed for more than 1 month; there are no frozen sections or pathology consultations in the region)	**Pathology services in development** (There are basic pathology and **frozen section** services; consultations are not readily available)	Pathology services in development or not always available (Pathology services including frozen sections are available; tumor registry and regular multidisciplinary conferences are not consistently available in the region)	**Pathology available (Full pathology services including diagnosis, consultation, tumor registry, and multidisciplinary conferences are available)**
Palliative care	Palliative care service is in development; basic palliative care, including pain and symptom management, should be provided[c]	**Pain and symptom management available**; palliative care service is in development	Palliative care service not always available	**Palliative care service available**

Abbreviations: IORT, intraoperative radiation therapy; LN, lymph node; PET, positron emission tomography; RT, radiotherapy.
NOTE. It is the view of the American Society of Clinical Oncology that health care providers and health care system decision makers should be guided by the recommendations for the highest stratum of resources available. This guideline is intended to complement but not replace local guidelines. Bold font indicates addition of a recommended action over a previous resource level (eg, in limited setting, a bold action is one that was not recommended in basic).
[a] Where medical facilities exist to take care of women who are at high risk for postoperative complications.
[b] Can be performed at some enhanced levels.
[c] Palliative care is multifaceted and in some contexts can be provided concurrently with tumor-directed therapy. Pain management and best supportive care are necessary but insufficient parts of palliative care in all settings. Women with advanced cervical cancer with or without access to tumor-directed therapy may have specific late-stage symptoms that require clinicians to perform or offer urogenital-specific interventions.
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including the ability to deliver a locally high and conformal dose to the site of disease with a rapid dose fall-off, thereby sparing adjacent structures such as the bladder, rectum, sigmoid, and small bowel.[54] Brachytherapy remains unavailable in many countries. Even in countries in which brachytherapy is easily accessible, its use is declining.[55-65] An analysis of the Surveillance, Epidemiology, and End Results (SEER) database found a decline in the use of brachytherapy from 83% in 1988 to 58% in 2009 ($P<.001$), although brachytherapy was found to be independently associated with better cause-specific survival (hazard ratio, 0.64; 95% confidence interval, 0.57-0.71) and overall survival (hazard ratio, 0.66; 95% confidence interval, 0.60-0.74).[54] A similar study of the National Cancer Data Base found brachytherapy use decreased from 97% in 2004 to 86% in 2011.[65,66] In one

of these studies, the impact of the use of brachytherapy was greater than that noted for the use of concurrent chemotherapy.[65] Brachytherapy is a complex procedure that necessitates significant resources and infrastructure, which is particularly challenging in resource-limited countries. Only 20 of the 52 African countries had brachytherapy in 2010.[54,66] Of 12 centers in Latin America, 3 do not perform gynecological brachytherapy.[54]

One high-dose rate brachytherapy machine can treat approximately 10 to 12 patients per day. In Ethiopia, a country of 94.1 million individuals with 60,000 new cancer cases each year, there is 1 afterloader for the entire country. In Thailand, in 1 hospital, a total of 1000 brachytherapy procedures are performed in 1 year by 1 afterloader. In Honduras, where 1000 new cases of cervical cancer are diagnosed annually, there is no brachytherapy facility in the entire country. Increasing the worldwide availability of brachytherapy should be a global health priority.

Treatment of Cervical Cancer in the Developing World

The majority of patients with cervical cancer in the developing world present with an advanced stage of disease, with limited access to adequate treatment. As a result, the mortality rates are high for these women (Fig. 2).[67] Because of the unpredictable availability of resources, the guidelines that are used to treat patients with cervical cancer in high-income countries are not applicable to many of the developing countries.

Two resource-stratified guidelines were recently published by the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology.[47] The NCCN guidelines provided evidence-based recommendations by the representatives from NCCN member institutions. The American Society of Clinical Oncology established a process including mixed methods of guideline development, adaptation of the clinical practice guidelines of other organizations, and formal consensus by the international expert panels. Recommendations were made regarding the management of patients with cervical cancer based on 4 different resource stratifications (Table 1).[68] Included in Table 1 are the 4 resource settings, which included a basic setting, in which bare essential services are available to provide gynecologic cancer care. The other 3 settings-limited, enhanced, and maximal-offer additional capacities that are essential in providing care and improving survival for patients with cervical cancer. Both guidelines stressed that the highest level of care be provided to women whenever available.

A Global Call to Action

It is no exaggeration to state that cancer represents an imminent and severe crisis for developing countries, with cervical cancer as the one of the most prevalent. A resounding call to action for this crisis is building; advocates are needed to save lives. For example, a recent report from the *Lancet Oncology* presented a body of evidence that quantifies the worldwide shortage of radiotherapy services by country. By scaling up radiotherapy departments in lower-income and middle-income countries, we could potentially observe >26.9 million life-years saved in these countries over the lifetime of the patients who received treatment.[69]

A global call to action against cancer in low-income and middle-income countries is desperately needed.[70] Although there are organizations attempting to make a difference,[71,72] much needs to be accomplished to stem this global crisis. A total of 740 women die each day of cervical cancer. The majority of these deaths occur among relatively young women, and the deaths result in unmeasurable pain and suffering. The World Health Organization has made safer motherhood a priority,[73] and now the same urgency needs to be directed toward cervical cancer. Vaccination programs are important, but we cannot ignore women who already are infected with HPV. We, and others, implore the global women's health movement to make the treatment of cervical cancer a priority.[74]

Conclusions/Summary

Cervical cancer is one of the leading causes of cancer death among women,[1] representing the fourth most common malignancy diagnosed in women worldwide.[3] To tackle this complex problem, there needs to be action taken on multiple fronts, including primary and secondary prevention, improvements in treatment, and access to care. The treatment of cervical cancer is a global health crisis that needs to be a call to action for the world health community. The GCIG through the CCRN is bringing relevant and important trials to low-income and middle-income countries. Our hope is that new attention can be brought to cervical cancer, especially among governmental and philanthropic agencies.

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William Small Jr has acted as a paid member of the Speakers Bureau for Zeiss and as a member of the Advisory Board for Varian for work performed outside of the current study.

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