



Cervical cancer in low and middle income countries: Addressing barriers to radiotherapy delivery



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ABSTRACT

The global cervical cancer burden falls disproportionately upon women in low and middle-income countries. Insufficient infrastructure, lack of access to preventive HPV vaccines, screening, and treatment, as well as limited trained personnel and training opportunities, continue to impede efforts to reduce incidence and mortality in these nations. These hurdles have been substantial challenges to radiation delivery in particular, preventing treatment for a disease in which radiation is a cornerstone of curative therapy. In this review, we discuss the breadth of these barriers, while illustrating the need for adaptive approaches by proposing the use of brachytherapy alone in the absence of available external beam radiotherapy. Such modifications to current guidelines are essential to maximize radiation treatment for cervical cancer in limited resource settings.

1. Introduction

With over 528,000 new cases and more than 266,000 deaths in 2012 alone, cervical cancer is the fourth most common cancer in women worldwide, and second for women ages 15 to 44 (Bailey et al., 2016). Roughly 740 deaths per day occur due to cervical cancer (Small et al., 2017), making it the second most common cause of cancer death in women (Chabra, 2016). This statistic is predicted to only rise, with an estimated 443,000 annual deaths by 2030—a 67% increase and double the expected maternal mortality from pregnancy complications (Cervical Cancer Action, 2011).

The discrepancy in cervical cancer incidence and mortality between developed and developing nations has become increasingly apparent. 85% of cases and cervical cancer deaths occur in low and middle income countries (LMIC) (Randall and Ghebre, 2016) (Chuang et al., 2016), where the death rate is 18 times higher (Small et al., n.d.). Importantly, low income countries (LIC) differ from middle income countries (MIC) in terms of resources available. LIC in general have no radiation, no access to skilled gynecologic oncologists, minimal imaging and pathologic expertise and little to no access to chemotherapy, while in MIC there may be basic infrastructure supporting all of these,

but the healthcare system may be overwhelmed by large patient numbers. In addition, in MIC, rural care can be drastically different from care provided in larger urban centers, rendering it more equivalent to oncologic care in LIC.

Collectively, LMIC are expected to account for more than 95% of deaths by 2030 (Cervical Cancer Action, 2011). The rate of cervical cancer has fallen in developed nations such as the US, which observed a 70% decrease from 1955 to 1992 (Cervical Cancer Action, 2011). Yet, the rate has remained unchanged or even risen in many LMIC (Organization, 2016). In East Africa and South Asia, cervical cancer remains the most common cancer in women, and the number one cause of death (Chabra, 2016). Moreover, it is important to consider these statistics in the context of local and national tumor registries. Infrastructural constraints frequently hinder accurate and extensive recording in LMIC, while patients in rural areas in particular, who are unable to access care, go unreported. These factors can contribute to gross underestimation of incidence, suggesting that the global cervical cancer burden may be greater than currently reported.

Potential contributors to this persistent and growing discrepancy comprise a complex, multifaceted collection of factors. A paucity of trained health professionals, lack of essential equipment, proper

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facilities and infrastructure, and financial limitations of not only nations, but also patients themselves, have all been cited as key drivers. A study in rural Bangladesh showed that 9.8% of households requiring emergency hysterectomy subsequently became impoverished (Meara et al., 2015). LMIC face high rates of delayed presentation due to limited patient education and disease awareness, fear, conflicting religious and cultural beliefs, and transportation scarcity (Randall and Ghebre, 2016) (Meara et al., 2015).

In this report, we seek to address the status of cervical cancer care in LMIC by highlighting key aspects of and barriers to prevention and treatment. Moreover, in discussing the efficacy of brachytherapy only therapy, we advocate for adaptive treatment approaches in order to enhance disease management in limited resource settings.

2. Cervical cancer prevention in LMIC

Cervical cancer is now known to develop from persistent high risk Human Papilloma Virus (HPV) infection (Bosch et al., 2013). Effective cervical cancer control in high income countries (HIC) has been largely associated with secondary prevention. In addition, primary prevention through HPV vaccination is more easily utilized in HIC than it is in LMIC.

Worldwide, while nearly 81% of countries have cervical cancer policies and strategies, only 48% have an operational plan that includes funding (Cervical Cancer Action, 2011). Cervical cancer screening is a fundamental component of these plans, along with HPV vaccination. LMIC are frequently constrained by the complex infrastructure that successful application of cytology necessitates. Visual inspection with acetic acid (VIA) has therefore been proposed as a more achievable option in limited resource settings. As of 2015, 26 countries had incorporated VIA into national policy, while an additional 35 have initiated pilot programs (Cervical Cancer Action, 2011). Screening is an essential component in comprehensively approaching cervical cancer, but its ethical implications in regards to treatment must also be considered. A minimal level of treatment infrastructure must be in place to support any programs or policies, in order to avoid identifying patients with disease without the ability to offer therapy.

HPV is considered a necessary but insufficient cause of cervical cancer, with HPV 16 and 18 alone accounting for 70% (Bailey et al., 2016). Significant attention and efforts have thus been directed toward establishing widespread HPV vaccination and testing. These initiatives have proved variably successful in developed nations, and implementation in LMIC has faced greater challenges. Nevertheless, over the past decade, promising advances have been made in HPV vaccination coverage in LMIC. From 2007 to 2016, the number of LMIC with vaccine experience grew from just several to 46 (Watson-Jones and LaMontagne, 2016). As of 2015, 84 countries had established national HPV programs and 38 had started pilot programs, representing a 60% increase from 2012 (Bailey et al., 2016).

3. Cervical cancer treatment in LMIC

Efforts to control cervical cancer in LIC have often largely focused on prevention, yet treatment of invasive disease is critical to cervical cancer control. Many women with invasive cancer can be either cured or effectively palliated with even limited resources. Any screening program will identify women with invasive cancer; the availability of and linkage to care is therefore a critical component of secondary prevention.

The current standard of care in the US for cervical cancer ranges from single to multimodality therapy, depending on the stage of disease. While early stage 1 disease can potentially be treated with surgery alone, consideration of radiotherapy and systemic treatment becomes increasingly important for more advanced malignancies. External beam radiation therapy (EBRT) in combination with brachytherapy has become a well-established and clinically validated approach, along with

chemotherapy.

In addition to preventative care, gaps in cervical cancer morbidity and mortality are also tied to global treatment distribution. Although stage-based standards of care are well-established for cervical cancer, in much of the world lack of access to adequate surgical care, radiation therapy, and systemic therapies often preclude delivery of potentially curative therapy.

3.1. Surgery

Approximately 70% of the global population currently lacks access to key surgical services and are vulnerable to crippling out of pocket expenses if emergent surgery were needed (Meara et al., 2015). This unmet surgical need is undeniable in the context of cervical cancer, where LMIC account for close to 50% of the global population, but are home to only 29% of the world's obstetricians (Holmer et al., 2015) (Meara et al., 2015). Provider density, including general surgeons, anesthesiologists, and obstetricians, averages 0.7 per 100,000 people in low-income countries and 5.5 per 100,000 in LMIC, compared to 56.9 per 100,000 in high-income countries (Holmer et al., 2015). The density of obstetricians in particular in LMIC ranges from 0.042 to 12.5 per 100,000 people (Hoyler et al., 2014). In 2012, Uganda was estimated to have 124 obstetrician-gynecologists within the entire country (Hoyler et al., 2014). In several countries, such as Rwanda where two international obstetrician-gynecologists are present, few if any trained obstetrician-gynecologists are available to evaluate and treat patients.

Difficulty in retaining practitioners in country is but one contributing factor to these provider density differences. In high-income nations, an average of 12% of surgeons, anesthesiologists and obstetricians trained outside the country in which they currently practice. Up to 70% of these medical migrants come from LMIC (Meara et al., 2015). Moreover, scarcity in available education and training opportunities continues to perpetuate this void. Coupled with delays in patient presentation, this disparity in surgical distribution remains a significant barrier to reducing preventable cervical cancer morbidity and mortality—a fact that has begun to garner increased attention. In 2014, the *Lancet* created the Commission on Global Surgery, comprised of an international, multidisciplinary team representative of 110 countries. The working groups proposed that core surgery and anesthesia care packages should include an obstetric and gynecological component specifically to provide treatment for pre-cancerous cervical lesions and hysterectomies for invasive cervical cancer, highlighting such services as a basic necessity (Meara et al., 2015).

3.2. Radiotherapy: external beam

The lack of global access to radiation therapy for cervical cancer parallels, if not rivals, that of surgical treatment. The belief that Africa “is functioning at 25% of its potential treatable capacity for cervical cancer alone,” illustrates the need for broader consideration of global radiation delivery (Chuang et al., 2016) (Abdel-Wahab et al., 2013) (Fisher et al., 2014). Roughly 56.4% of the world's cancer patients are able to access only 31.7% of the world's current teletherapy units. The recommended ratio of units to individuals is 1 to 120,000–250,000 people. While high income countries average 1 unit to 130,000 people, this ratio is approximately 1 unit to 1.4 million people in LMIC (Datta et al., 2014).

In 2014, Datta et al. reported on the status of radiotherapy in 139 countries defined as low- and middle-income by the World Bank criteria (Datta et al., 2014). Only 4 of these countries were meeting their current radiotherapy needs. Eighty nations had an average of 36.7% access to radiotherapy, while 55 nations had no radiation therapy at all. Thirty of these 55 countries were in Africa (Datta et al., 2014), where 60% of teletherapy units are in South Africa and Egypt (Grover et al., 2015). Approximately 4221 teletherapy units are present in LMIC—an amount believed to be 38 to 49% of the total number needed (Zubizarreta et al.,

2015).

In 2012, Nigeria alone accounted for 8.3% of cancer cases (Irabor et al., 2016). Yet, a 2015 radiotherapy needs assessment found that only two out of the country's 9 radiation centers were operating at full capacity (Irabor et al., 2016). A level of equipment less than that of one established US center is therefore providing radiotherapy for the entire country. Nigeria has roughly 1 radiation unit per 19.4 million people, in comparison to the recommended ratio of 1 to 120,000–250,000 people. Moreover, two of the linear accelerator radiotherapy units that Nigeria acquired in 2010 were out of service within one year (Irabor et al., 2016). This result highlights the concern that even when machines are available, access to appropriate radiotherapy technology in LMIC may vary from day to day or month to month, in part due to the difficulty of maintaining proper equipment servicing.

This scarcity of radiation treatment in Nigeria results from a complex web of barriers to radiotherapy delivery, which are widely shared among LMIC. Similar to the multifaceted challenges contributing to disparities in cervical cancer incidence and mortality, infrastructural, educational and financial hurdles continue to drive this unmet radiotherapy need. With only one trained linear accelerator engineer within the country, Nigeria has been able to achieve only limited investment in machine maintenance and quality assurance. The immense demand placed on each unit serves to only hasten machine wear and tear. Moreover, only 40% of the population has access to electricity, which is unreliable 60% of the time. Radiation centers are currently operating on diesel generators that themselves, can be an unreliable power source (Datta et al., 2014). Together, these factors work to delay and ultimately reduce access to treatment. Specific challenges to radiotherapy include initial cost of installation and equipment, having appropriately trained personnel, having steady electrical supply for non-cobalt linear accelerators, and the availability of imaging for treatment planning, among others (Table 1).

3.3. Radiotherapy: brachytherapy

Brachytherapy is a key component of radiotherapy treatment for cervical cancer stages IB and greater. This category of disease represents 60% of cervical cancer cases in developing countries—twice as many as the 30% seen in developed nations (IAEA, 2011). Thus, having access to high quality brachytherapy is essential for effective disease management. Given the widespread unmet surgical need, disproportionately in LMIC, the therapeutic potential of brachytherapy highlighted in Cetina et al.'s recent work is of particular significance. Comparing EBRT followed by radical hysterectomy or standard brachytherapy in stage IB2 to IIB cervical cancer patients, this study failed to show superiority of radical hysterectomy over brachytherapy in regards to progression free survival and overall survival (Cetina et al.,

2013).

In the case of LMIC, cervical cancer alone counts for 7% of the patients with indications for radiotherapy (Zubizarreta et al., 2015). Small et al. recently commented on the lack of radiotherapy equipment to meet the cervical burden in LMIC. A high-dose rate (HDR) brachytherapy unit is capable of treating roughly 10–12 cases per day—Ethiopia uses one HDR machine for the entire country (Small et al., 2017). In Africa as a whole, there are 20 countries that are currently able to deliver brachytherapy; however, 75% of these services lie in the northern part of the continent and in the country of South Africa (Bvochara-Nsingo et al., 2014). Transportation and housing costs alone pose a daunting challenge to individuals who do not live near such concentrated areas of radiation therapy, and too often prevent patients from accessing treatment. This unmet need extends beyond Africa to nations such as Thailand, which has been using one machine to treat 1000 cases of cervical cancer per year, and to Honduras which, like many other LMIC, currently has no access to brachytherapy (Small et al., 2017).

Strategies to combat the growing cervical cancer burden in LMIC must include context-specific consideration of radiotherapy delivery in limited resource environments. As Suneja et al. have demonstrated, cervical cancer standards of care need to be adapted to accommodate the unique circumstances of individual countries in order to maximize efficacy (Suneja et al., 2017). In their recent publication, Suneja et al. adapted the American Brachytherapy Society guidelines to address brachytherapy delivery in minimal resource settings (Suneja et al., 2017). A significant challenge that many LMIC face is the lack of access to advanced imaging technology. Such is the case in Rwanda, where the majority of stage IB to III cervical cancer patients are unable to undergo staging CT scans, due to the small number of scanners, expense and lengthy turnaround time. Importantly, Suneja et al. take note of this barrier, advocating that effective planning and treatment administration can be accomplished with such constraints. The paper includes extensive recommendations for how to approach aspects such as treatment fields, planning and applicator placement without this imaging, such as using bony landmarks, prescribing to points of interest and using fixed applicator configurations with a plan library or radio-opaque applicators (Suneja et al., 2017).

This adaptive approach has previously shown success in Senegal, where, prior to 2012, a single cobalt-60 radiotherapy unit serviced the country's population of 13 million people. The machine was treating between 30 and 40 patients per day for a total of 100 cervical cancer patients per year (Einck et al., 2014). From January 2008 to December 2012, 48% of the country's cervical cancer patients presented with Stage III to IVA disease. Their treatment was solely neoadjuvant or palliative, as without brachytherapy, the facility was unable to offer definitive treatment (Einck et al., 2014).

Table 1
Proposed strategic approaches to radiotherapy delivery barriers.

Barriers to radiotherapy	Strategic approaches
No external beam radiotherapy No linear accelerator unit Radiotherapy unit servicing	Consider treatment with brachytherapy alone - Consider Cobalt-60 - Inclusion of maintenance and servicing plans in radiotherapy strategic development and implementation - Technological support and educational exchange from international organizations and industry
Difficult transport of radiation units through customs No imaging capacity 2D imaging capacity Minimal education and training	- Consider Cobalt-60 vs. iridium-192 (shorter half-life, more frequent source exchange required) - Fixed applicator configurations, library-based treatment plans - Radio-opaque applicators, prescription to points of interest - Collaboration with national and international organizations, and industry to create workshops, courses and educational exchange - International Atomic Energy Agency training guides and resources
Insufficient finances	- National engagement in dedicated resource allocation - Financial engagement from international organizations and industry
Patient transport/treatment center inaccessibility	- National commitment to infrastructure - Enhanced geographical distribution of radiotherapy resources - Infrastructural support from international organizations and industry

In 2012, Radiating Hope, a non-profit organization focused on providing radiation therapy resources to developing countries, brought an HDR afterloader to Senegal and developed delivery modifications in order to surmount key challenges in implementing treatment (Einck et al., 2014). The available treatment planning system did not have the ability to perform real-time planning. To address this issue, the group created a pre-planned treatment technique. Using fixed geometry applicators, they developed a plan library with pre-planned dosimetry, and created transparent isodose overlays that could be used with orthogonal images to assess rectal and bladder dosage. The use of an aluminum ring during imaging enabled the team to match the scale of the overlays. Although further work is needed to collect sufficient data on efficacy and toxicity, these techniques ultimately resulted in “efficient, accurate, and simple HDR treatment system.” (Einck et al., 2014).

3.4. Brachytherapy alone in limited resource settings

In 1915, Kelly and Burnham published a study of 213 cervical and vaginal cancer patients treated with surgery and brachytherapy, or with brachytherapy alone (Kelly and Burnham, 1915). Of the 203 patients treated with brachytherapy alone, 4 were considered operable and 199 were considered inoperable. All 4 operable patients, and 53 of the inoperable patients were considered cured following treatment, with no evidence of disease on palpation or curettage. Follow up intervals ranged from 6 years to 6 months, with 29 patients without disease at 1 year. Moreover, 109 patients experienced improvement of symptom management and reduction in tumor burden (Kelly and Burnham, 1915). Kelly and Burnham concluded that this improvement alone, regardless of cure, justified this application of radiotherapy in cervical and vaginal cancer.

Hamberger et al. reported results from a study of 151 cervical cancer patients treated with brachytherapy alone. 5 year overall survival rates of 100%, 96% and 86% were achieved for patients with stage IA, IB small volume and IB disease respectively (Hamberger et al., 1978). Regional recurrences occurred in 7 patients, while only one distant metastasis was observed. Hamberger et al. proposed that brachytherapy alone was capable of covering an anatomical area equivalent to radical hysterectomy, and that the addition of EBRT would only increase the irradiated region and subsequent risk of fibrosis (Hamberger et al., 1978). They argued that given the low rates of failure observed, brachytherapy alone was justified in Stage I disease.

Volterrani and Lombardi published the largest study to assess cervical cancer outcomes with the treatment of brachytherapy alone (Volterrani and Lombardi, 1980). 649 patients with stage IB “occ” (histological stromatic invasion > 0.3 cm but not evident on clinical exam) to stage III disease were included. 5 year overall survival rates ranged from 82.6%, 64.8%, 50.3% and 29.8% in stage IB “occ”, IB, II and III disease respectively (Volterrani and Lombardi, 1980). Moreover, the local regional recurrence rate was 25.8% for the entire cohort, and 5% and 20.1% specifically in stage IB “occ” and IB disease. The overall rate of distant metastasis was 3.6%. The 5 year overall survival rate and low rate of lymph node metastasis observed, particularly in stage IB “occ” patients, seemed to further support the use of brachytherapy alone in early stage disease (Volterrani and Lombardi, 1980).

Reporting of adverse events in the aforementioned studies revealed tolerable rates of treatment related toxicity. In Volterrani and Lombardi’s study, 4 treatment related deaths occurred, while rates of proctitis/proctosigmoiditis and rectal ulceration remained less than 4%, and that of cystitis and fistula less than 1% (Volterrani and Lombardi, 1980).

Discussion of radiotherapy delivery in LMIC has primarily focused on settings with some EBRT access but minimal to no brachytherapy capacity. However, “little evidence” exists to guide treatment decisions in scenarios where EBRT is nonexistent (Chuang et al., 2016). In Rwanda, limited EBRT availability has resulted in reliance on neoadjuvant chemotherapy and surgery alone to treat the majority of stage IB

to IIA cervical cancer patients. Although a referral connection for radiotherapy treatment in Nairobi, Kenya has been established, few if any patients can ultimately be referred, forcing providers to consider only the highest-risk cases. Moreover, in order to receive treatment in Nairobi, patients without insurance must pay out of pocket. This financial burden is one that few patients can manage, highlighting the significant barrier that treatment costs create for successful therapy delivery. Few LMIC have national health insurance systems, while even those with health insurance may not receive adequate coverage through their plans. In Uganda, the demise of the country’s sole cobalt-60 unit in the spring of 2016 has similarly threatened the therapeutic course of the nearly 33,000 cancer patients it has been treating annually (Byaruhanga, 2016). Many of these patients are women with cervical cancer.

According to the American Society of Clinical Oncology’s 2016 resource stratified clinical practice guidelines, areas with brachytherapy but no EBRT should be classified as equivalent to a “Basic” level of radiotherapy, defined as unavailable radiation treatment (Chuang et al., 2016). Machine wear and tear, financial constraints and infrastructural capacity are all potent drivers of such a scenario and are not infrequent in LMIC. Brachytherapy alone, with low dose platinum chemotherapy followed by radical hysterectomy, remains as only a low evidence, weak recommendation for IB2 and IIA2 disease (Chuang et al., 2016).

The body of research that has contributed to the development of current cervical cancer radiotherapy guidelines has primarily considered comparisons such as surgery versus radiotherapy, EBRT versus EBRT with brachytherapy, LDR versus HDR brachytherapy, and treatment with or without chemotherapy, along with further refinement of dosing and treatment fields. Assessment of EBRT versus brachytherapy alone has been far less prominent of an investigation. Yet, these historical studies have validated the efficacy of brachytherapy alone in cervical cancer, supporting its application to resource limited settings.

The implementation of brachytherapy is not without limitations. The technology requires significant safety and maintenance considerations. As decaying radioactive sources, brachytherapy units must not only be stored appropriately, but also replaced over time. Operators must therefore be extensively trained in both operation and upkeep of units in order to ensure treatment efficacy and safety. The International Atomic Energy Agency maintains strict regulations for radioactive sources worldwide that guide such education and instruction. Moreover, the potential unintended use of radioactive units as a form of weaponry remains an ongoing fear for their consideration in more politically unstable environments. In 2013, a radioactive cobalt-60 unit was stolen while en route to a storage facility. While the unit was ultimately recovered, its theft fueled concern for the incorporation of radioactive sources into “dirty” bombs (Martinez and Partlow, 2013). As a result of these safety issues, iridium-192 sources or other sources with a short half-life may be held at customs and not released in a timely manner preventing routine source swaps and impacting clinical care. In a study comparing the dosimetry of cobalt-60 to iridium-192 in HDR brachytherapy, Nandwana et al. demonstrated the ability of cobalt-60 to meet the necessary qualifications as an intracavitary radiotherapy source under the International Commission on Radiation Units guidelines (Nandwana et al., 2015). Thus, cobalt-60 could be considered as an alternative to iridium-192 in limited resource settings in order to decrease the frequency of source exchange and potential customs complications.

Assurance of adequate equipment maintenance and safety must come in tandem with comprehensive training and regional engagement in infrastructural provisions. As Grover et al. advocate, education for critical team members as defined in the American Association of Physicists in Medicine Radiation Therapy Committee Task Group-59 Report—a radiation oncologist, medical physicist and a treatment-unit operator—is essential in enabling the necessary coordination and implementation for successful treatment delivery (Grover et al., 2017). Industry partnerships and collaboration between local and

international organizations are optimally positioned to provide support through educational exchanges, workshops and the creation of replicable training and treatment models (Grover et al., 2017).

4. Conclusion

Developing countries continue to bear a disproportionate percentage of the global cervical cancer burden. Investigations into the growing gap in incidence and mortality between developed nations and LMIC have cited persistent financial, infrastructural and educational limitations as key drivers. Pervasive lack of access to both preventative and definitive care has left a substantial portion of cervical cancer patients with minimal options for disease management.

For countries with little to no radiotherapy capacity, few evidence based recommendations exist to guide therapeutic decision making. Settings with brachytherapy but not EBRT are currently considered equivalent to those without any radiotherapy units, according to the most recent ASCO guidelines. Here, we argue that historical data supports the use of brachytherapy alone in cervical cancer.

Brachytherapy is a complex treatment approach with extensive safety regulations—factors that often render it prohibitive in limited resource settings. Yet, given its therapeutic potential for cervical cancer, it must be made more accessible to the global community. Insufficient training opportunities and specialized staff remains a significant barrier to radiation delivery in LMIC. In highlighting this research, our intent is not to suggest that brachytherapy alone should be a replacement for the current standard of care. Rather, we argue that it should be considered for cases in which patients would otherwise be left without any radiotherapy management. In such settings, brachytherapy may ultimately serve as a potential bridge to future treatment or, as historically observed, a potentially curative option for early stage disease.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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