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Treatment of cervical cancer: overcoming challenges in access to brachytherapy

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Abstract

Introduction: Brachytherapy is an essential component of the cervical cancer treatment paradigm as it contributes to improved clinical outcomes and overall survival. Yet brachytherapy remains globally underutilized, with disparities in access at both national and international levels.

Areas covered: The review explores current brachytherapy utilization practices and efforts being undertaken to address barriers to implementation in low-, middle-, and high-income

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countries, and how these efforts are projected to impact future brachytherapy access. The content presented is based on a review of published literature and the authors' collective clinical experiences.

Expert opinion: There exists a tremendous opportunity to expand access to essential brachytherapy services for women with cervical cancer. Many national and international brachytherapy efforts exist; yet it remains imperative that such focused efforts continue to grow and provide further access to this critical treatment modality for women in need worldwide.

Keywords

Brachytherapy; Cervix Cancer; global health; global oncology; health disparities; gynecologic cancer; medication education; radiotherapy; radiation oncology

1. Introduction

In 2018, cervical cancer was the fourth most common cause of cancer, with approximately 570,000 cases diagnosed and an estimated 311,000 cervical cancer-related deaths globally [1,2]. Approximately 88% of all cervical cancer-related deaths occurred in low- and middle-income countries (LMICs), with highest rates of incidence observed in Western, Eastern, and Southern African countries [2].

Curative treatment of locally advanced cervical cancer involves external beam radiation therapy (EBRT) with concurrent cisplatin-based chemotherapy, followed by brachytherapy [3]. The addition of brachytherapy to the cervical cancer treatment paradigm has been found to improve clinical outcomes, including overall survival [4–8]. As such, national and international guidelines for cervical cancer treatment recommend brachytherapy as an integral part of curative treatment [3,9].

Unfortunately, brachytherapy has been underutilized both in the United States (U.S.) and internationally due to several factors: limited exposure to the procedure during residency training, difficulty in maintenance of skills, lack of supportive infrastructure, low-volume treatment centers, alternative boost practices, limitations in advanced imaging techniques, preference for noninvasive techniques, and financial restraints and disincentives [4,10–14]. Graduating residents report lack of confidence and comfort in performing brachytherapy procedures independently, and specialized training, such as a fellowship in brachytherapy, is sometimes required [15]. Between 1988 and 2011, it is estimated that brachytherapy utilization for patients with cervical cancer in the U.S. has decreased by 11–25% [4,16]. Additionally, significant disparity among brachytherapy utilization for cervical cancer exists within different socioeconomic and ethnoracial groups within the same country [17]. In this review, we aim to explore current brachytherapy utilization practices and future initiative to improve brachytherapy access from the perspective of both low- and middle-income countries and high-income countries.

1.1. Access to brachytherapy in low- and middle-income countries

In developed nations, widespread adoption of the Papanicolaou smear heralded a decrease in cervical cancer as earlier detection prevented cervical intraepithelial neoplasia (CIN)

from progressing to invasive disease. However, in many LMICs, these screening techniques are not readily accessible to their general populations, and as such, cervical cancer disproportionally impacts LMICs.

Additionally, mortality from cervical disease is expected to persist in the coming decades, with the highest rates of the disease expected in Central and South America, East Africa, South and Southeast Asia, and the Western Pacific, where limited access and awareness to appropriate screening, lower rates of HPV vaccination, and co-infection with viruses predisposing to HPV persistence (e.g. human immunodeficiency virus (HIV)) drive disparities [9,18].

As previously discussed, brachytherapy has an integral role in cervical cancer care, for both curative [3–5] and palliative treatments [19]. In LMICs, cervical cancer alone accounts for 7% of all patients with a need for radiation [20]. Challenges to implementation of brachytherapy programs include both geographic and economic barriers. Inadequate funding for equipment and maintenance, poor infrastructure, inconsistent referral processes, and a shortage of trained health professionals contribute to the challenge.

The demand for brachytherapy is highest in LMICs as 60% of cervical cancer cases present with locally advanced disease [20]. Analysis by Zubizarreta et al [20], of over 400,000 cervical cancer patients in LMICs estimated that approximately 295,000 of the cases would require brachytherapy. However, the distribution of HDR afterloaders across LMICs is sparse and not uniform [20,21]. A patterns-of-care study in 2011 surveyed 17 radiotherapy centers across Latin America and found just over half reported use of brachytherapy [22]. Among those who reported using brachytherapy, 95% of the procedures were for gynecologic cancer. Barriers to brachytherapy use included lack of patient referrals, patient capacity to pay for treatment, infrastructure issues related to exchanging radioactive sources, and access to reliable power sources.

In 2018, 21.7% of all cancer deaths in sub-Saharan African (SSA) women were due to cervical cancer; whereas cervical cancer deaths account for less than 1% of cancer-related deaths in the United States [23]. Across African countries, brachytherapy is known to be offered in 20 out of 52 nations with a capacity to treat an estimated 24,300 patients a year; however, the incidence of cervical cancer in Africa was 119,314 in 2018 (up from 72,000 in 2008), highlighting a stark disparity in access assuming the majority present with advanced disease [24].

In Asia-Pacific, there are 450 radiation centers with the majority concentrated in India and China, but few offer brachytherapy. In India, most brachytherapy units are concentrated in the south despite large population centers in the north. In a recent state-specific analysis, Chopra et al. estimated that 14 Indian states had a deficit of brachytherapy units and estimated that 127 additional brachytherapy units are needed to treat patients with cervical cancer [25]. In Thailand, one HDR brachytherapy unit in one hospital has treated 1,000 cases of cervical cancer in one year [26]. The current distribution of HDR brachytherapy units across LMICs in Asia does not currently match the needs of the population.

Recent global efforts have focused on publishing recommendations for brachytherapy in LMICs. In 2016, the American Brachytherapy Society (ABS) published guidelines for brachytherapy delivery to treat locally advanced cervical disease in resource-limited settings [27]. Similarly, the American Society of Clinical Oncology convened a multidisciplinary, multinational panel of cancer control professionals to produce recommendations reflecting resource-tiered settings [28]. Both guidelines provide resource-stratified clinical practice guidelines. Additionally, LaVigne et al. published strategic approaches to common barriers for use of radiotherapy for cervical cancer in LMICs, including consideration of the use of brachytherapy alone in contexts where extensive external beam radiotherapy support is lacking [10].

The ability for staff to deliver brachytherapy safely and effectively requires appropriate training. A variety of skilled professionals are required, including a trained radiation oncologist, medical physicist, radiation therapists, and radiation oncology nurses. Training programs focused on brachytherapy technique and radiation safety are limited in LMICs but there exists a growing number of efforts.

Imaging is also an essential component of cervical brachytherapy. Plain X-ray films are a basic requirement for cervical brachytherapy, but 3D imaging (CT, ultrasound, and/or MRI) can often provide information on the precise location of targets and organs at risk [6,29,30]. MRI is considered the gold standard for image-guided cervical brachytherapy and its use is associated with improved clinical outcomes and reduced toxicities [31–33]. However, MR and 3D imaging and treatment techniques are limited by their availability, required training, and cost. As such, international organizations (IBS-GEC ESTRO-ABS) have published approaches for alternative treatment planning including use of CT guided adaptive therapy [34].

The International Cancer Expert Corps (ICEC) and ABS have come together with a joint focus of training competent brachytherapy teams. The ABS International Committee, has been in dialog with the Bugando Medical Center (BMC) in Tanzania providing support as the team continues to develop their brachytherapy practice. The partnership includes education resource sharing and opportunities for ABS members to review and provide guidance on cases. The goal is to continue to establish and foster long-term mutual mentoring relationships between ABS members and international centers. Additionally in 2018, Rayos Contra Cancer, a nonprofit organization that seeks to provide tele-education and training to providers in LMICs, launched a HDR brachytherapy training course for clinics in Africa, the Middle East, and Eastern Asia with participants demonstrating improved brachytherapy confidence across several assessed domains [35]. Lastly, the Elekta BrachyAcademy has conducted over 65 brachytherapy workshops since 2013 training over 1,000 participants at locations including Tata Memorial Center (Mumbai, India), Chulalongkorn University Hospital (Bangkok, Thailand) [36]. The two-day workshops are open to radiation oncologists and medical physicists and include needs assessments, lectures, contouring and treatment planning education, and observed patient cases in the operating room [37]. Expanding brachytherapy-focused training opportunities in LMICs is an essential component to increasing access to high-quality cervical cancer care.

1.2. Access to brachytherapy in high-income countries

The Directory of Radiotherapy Centers (DIRAC) has recorded an estimated 3,318 brachytherapy units distributed around the world (n.b. there are an estimated 14,875 megavolt therapy machines used to deliver external beam radiation) [21]. Brachytherapy machines are concentrated in high-income regions, which have almost twice the number of units than LMICs. Radiation resources, including brachytherapy, tend to be located in populated, urban regions which results in limited access for patients in rural regions.

National and international guidelines highlight brachytherapy as an integral part of and a key quality-of-care indicator for the curative management of locally advanced cervical cancer [38]. However, brachytherapy experienced a precipitous decline in usage for cervical cancer patients in the U.S. throughout the 2000s despite inferior clinical outcomes. A large database analysis in the U.S. demonstrated a decrease in the brachytherapy utilization rate from 83% in 1988 to 58% in 2009 [16]. A similar database analysis of cervical cancer patients from 2004 to 2012 found 54% patients received EBRT and brachytherapy. Of the cases treated with EBRT alone, 52% received an EBRT boost and the remainder received no boost of any form [16]. Yet another survey of U.S. patients treated from 2004 to 2011 showed declining brachytherapy use from 96.7% in 2004 to 86.1% in 2011 [4]. This study also demonstrated a significant parallel increase in intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT) use from 3.3% to 13.9%, despite EBRT boost techniques resulting in inferior overall survival compared to those who received brachytherapy.

This decline in brachytherapy in some countries may have been influenced by financial considerations. The U.S. primarily employs a fee-for-service payment model for both private insurance as well as Medicare and Medicaid [39]. Compared to EBRT techniques (IMRT, VMAT, and SBRT ‘boost’), brachytherapy is more invasive and resource intensive, requiring more physician time, infrastructure costs, and attendant malpractice insurance [40]. Data suggest that Medicare reimbursements do not always sufficiently cover operating costs [41]. A new payment model by the Center for Medicare and Medicaid Services, the Radiation Oncology Alternative Payment Model (RO Model), has proposed bundled payments based on the disease site [42]. National organizations have used these proposed changes to highlight concerns regarding the reimbursement rate of brachytherapy procedures, stating that reimbursement not commensurate with the time and effort required to perform brachytherapy procedures will likely result in inferior outcomes for women who do not receive brachytherapy as a part of their cervical cancer care [43]. Indeed, some suggest that it should conversely be incentivized [44]. However, recent analysis of the RO Model by Thacker et al [14] found that monotherapy brachytherapy episodes for cervical cancer will in fact have an average positive reimbursement payment from the model (+$533), while combination modality episodes will receive lower payments. Due to these concerns over the RO Model de-incentivizing best care practices with combined modality, brachytherapy services have been removed from the final rule for 2022 [45].

Declining utilization of brachytherapy within the U.S. is not mirrored in other high-income countries. In fact, Europe has long-standing history of providing brachytherapy since 1902 when Dominici treated a cervical cancer patient in Paris with the first intracavitary intrauterine application [46]. Since then, there have been numerous efforts to strengthen the

impact of brachytherapy in Europe. In the 1960s the Groupe Européen de Curiethérapie (GEC) was established and later merged in 1990's with the European Society for Therapeutic Radiology and Oncology (ESTRO) creating the GEC-ESTRO group. The administration and GEC-ESTRO GYN Working Group have strengthened and improved aspects of brachytherapy research, education, and collaboration across Europe [46–48]. A European survey published in 2010 found that 60% of healthcare centers from 41 European countries had brachytherapy services and treated an average of 138 patients per year, an increase of 18% from 2002 [49]. Among the centers surveyed, brachytherapy was most commonly (59%) used for gynecological tumors. The survey also noted computed tomography (CT) guided planning was utilized by 61% of centers compared 33% in 2002 [49]. Furthermore, a survey of centers in Australia and New Zealand found that although availability of brachytherapy units was unchanged from 2005 to 2009, there was a three-fold increase in the utilization of CT and magnetic resonance imaging (MRI) guidance for brachytherapy as compared to two-dimensional (2D) X-ray techniques [50]. Additionally, data from a small cohort of patients from 2003 to 2007 treated in New Zealand revealed that 74% of patients treated with definitive radiation received brachytherapy in addition to EBRT.

Brachytherapy access and volume also varies across centers. In the mid-2000s, a U.S.-based survey found that only 8% of facilities treated on average more than three eligible patients per year. Furthermore, 65% of patients began treatment at a facility that treated three or fewer eligible patients per year. A survey of Canadian oncology centers found that despite the availability of brachytherapy at 93% of centers, only 49% of providers treated gynecologic cancers [51]. Among the centers, the median number of patients treated per year with brachytherapy was 30 patients, of which, approximately 50% were uterine and/or cervical cancer. Previous studies have demonstrated that high brachytherapy procedure volume is positively correlated with likelihood of receiving guideline-recommended care, which in turn is associated with improved survival [51]. Similar results have been shown in Taiwan, where high-volume hospitals demonstrate higher brachytherapy utilization and superior survival outcomes [4]. To address such issues of disproportionate volume, many regions have adopted new models of care. For example, GYN-CoP (Cancer Care Ontario Gynecology Community of Practice) works to ensure that all cervical cancer patients in the province have access to appropriate brachytherapy services, if needed, through new models of care in which patients receive ERBT at a local facility and then are referred to a high-volume center for brachytherapy [52].

Despite the relative abundance of high-quality care in HICs, disparities in treatment and outcomes remain prevalent. A U.S. National Cancer Database study reaffirmed that receipt of a brachytherapy boost was associated with superior cervical cancer survival compared to EBRT boost or no boost [53]. Importantly, they also demonstrated that Black patients were less likely to be treated with brachytherapy as compared to Caucasian and Hispanic patients, likely contributing to the finding that they also had worse survival rates. Patient populations at risk of receiving no boost at all included those with Medicaid, no insurance, income <$48,000/year, and treated at low-volume, non-academic, non-comprehensive community cancer centers. Other studies similarly have found that Black patients as well as those on Medicaid, Medicare, or without insurance have lower rates of receipt of brachytherapy, with commensurate impact on survival in these groups [17,54–56]. Several of these studies

have demonstrated that racial survival disparities did not persist when comparing outcomes between racial groups that had all received brachytherapy as part of their treatment [17,54].

Given that brachytherapy is a limited resource usually concentrated in urban areas, it would be simple to assume that distance from a treatment center would be inversely correlated to receipt or completion of treatment. However, studies at the city and the state level have shown that patients in close proximity to a brachytherapy facility are less likely to receive treatment [57,58,58]. A state-wide study in North Carolina found that rural residents living <5 miles from a treatment facility were less likely to receive brachytherapy, although this association was not seen with urban residents [57]. A small cohort study at the University of Maryland found that patients living close to the treatment center were significantly less likely to complete their prescribed treatment within eight weeks [59]. Similarly, a survey of oncology care delivery in Virginia was conducted to better identify barriers to care given the prevalence of both urban centers and far-outlying populations in mountainous Appalachia [58]. The authors found that while increased proximity to any equipped facility resulted in higher rate of brachytherapy receipt and that high-volume centers more often delivered guideline-concordant care, patients living less than 3.5 miles from high-volume centers were less likely to receive all recommended treatment [60]. Taken together, these studies suggest that while distance may be a barrier to access for some, psychosocial factors for patients living in the heavily urbanized, inner-city locations where academic, high-volume centers are often located may also play a role in the delivery of brachytherapy. However, given that this trend has also been observed in rural geographies, there are likely complex factors at play that warrant further study. The rise of patient navigation programs in the breast cancer population and the subsequent increase in treatment and patient survival may provide lessons for institutions delivering brachytherapy [61].

Brachytherapy is a specialized, technical skill requiring adequate exposure and patient-volume for trainees and providers to incorporate into their practice safely and effectively. Unfortunately, the availability of training has declined over time. In the U.S., the mean number of interstitial brachytherapy procedures performed per resident declined recently by 25% [62]. According to Marcrom et al. only 54% of residents reported feeling a ‘high’ or ‘somewhat high’ level of confidence in their final year of training in starting a brachytherapy practice after residency [63]. Similarly, a survey of French trainees revealed that 82% felt they had not received sufficient brachytherapy teaching. While 71% had seen at least one gynecological brachytherapy, only 12% felt knowledgeable enough to perform the procedure [64]. Among Canadian trainees, only 54% reported having formal, written institutional objectives outlining the knowledge, skills, and attitudes required for resident competency in brachytherapy [15]. In reaction to this, the U.S. based Accreditation Council for Graduate Medical Education (ACGME) has recently increased the number of intracavitary and interstitial implants required during a Radiation Oncology residency, and mandated that five of these implants are ‘tandem based’ [65]. However, even with this change, five cases are unlikely to reach the necessary experience for independent brachytherapy practice. The Canadian Royal College has established a formal brachytherapy curriculum and fellowship program. The program provides training for brachytherapists in practice who apply for accreditation through the Practice Eligibility Route (PER), and graduating residents who can undergo a one-year training fellowship to receive at brachytherapy diploma known

as the AFC (Area of Focused Competence) [66]. Additionally, the University of Toronto fellowship program has attracted providers from around the world and to date have trained 42 brachytherapists since its establishment in 2014.

Since less than 2% of U.S. residents have reported interest in a one-year brachytherapy fellowship [63], some novel efforts are being implemented to increase trainees' comfort-level with performing brachytherapy. For example, a U.S. training program implemented a cadaver-based simulation module. Trainees who completed the program reported feeling significantly more comfortable performing the procedure independently [67]. Further development of such brachytherapy education and training is essential to help preserve and disseminate brachytherapy skills for radiation oncologists and patients.

The need for ongoing education and mentorship outside of formal training programs or fellowships has been recognized since the 1990s, when the American Brachytherapy Society established its first brachytherapy school [68]. These workshops have historically drawn physicians from across the U.S. and Europe and provide hands-on education in all aspects of brachytherapy (gynecology, prostate, low-dose rate, high-dose rate, image-guidance, contouring, etc.). Given the relatively small number of brachytherapy-focused fellowships, these workshops are critical for early and mid-career physicians who may find a change in practice patterns require new skills. Notably, according to a Canadian survey, 71% of physicians currently practicing brachytherapy reported receiving additional training after residency [51]. These schools have become keepers of critical knowledge as brachytherapy popularity has waxed and waned.

The ABS schools naturally progressed to the ABS '300 in 10' initiative which has a goal of training 300 brachytherapists over the next ten years. The initiative includes six areas of programming efforts: 1) development of a national brachytherapy curriculum; 2) simulation-based medical education; 3) two-month training fellowships at designated ABS certified centers; 4) competency-based evaluation by an ABS certified expert or proctor; 5) an ABS brachytherapy certification; and 6) an ABS maintenance of certification. Mentorship is a cornerstone of the 300 in 10 initiative, with development of a new ABS mentorship program: NextGen Brachy. The mentorship program pairs early-career radiation oncologists with experienced ABS brachytherapists and physicists for a one-year mentorship program. A pilot study was recently completed with encouraging results demonstrating increased confidence in starting a brachytherapy practice [69].

2. Conclusion

It is critical to outcomes that cervical cancer patients have access to evidence-based care including high-quality brachytherapy. Barriers to both patient access and provider implementation of brachytherapy exist across high-income and LMICs, including appropriate training, continued education, physical resources, infrastructure, and funding. It is vital to consider how attitudes toward brachytherapy will influence adoption and it is the responsibility of oncologists to educate healthcare providers, patients, insurers, and policymakers about the important role brachytherapy can play in improving patient outcomes.

3. Expert opinion

Brachytherapy remains an indispensable component of cervical cancer care. It is estimated that of the 9.4 million women in LMICs requiring treatment with EBRT, 7 million will require treatment with brachytherapy. Despite this, multiple studies have reported suboptimal use of brachytherapy in cervical cancer treatment across high-income and LMICs – secondary to lack of equipment or trained personnel [4,10–13,15,18,64]. Unfortunately, brachytherapy usage in cervical cancer is at risk for decline in some high-income countries due to the requirement for a specialized inter-disciplinary team, preferential use of noninvasive boost techniques such as IMRT and SBRT, financial disincentives for cervical cancer brachytherapy, inadequate training, and maintenance of skills [13,62]. Moreover, international radiotherapy access initiatives have historically prioritized access to EBRT rather than brachytherapy [70–72].

Although brachytherapy is indeed underutilized for cervical cancer treatment in high-income countries, and declines in usage have often been reported in lower-income patients with government insurance [73–75], a 2020 U.S.-based study reports a recent reversal in this downward trend, with the most pronounced improvements in Medicare and Medicaid patients as compared to privately insured patients [44]. This recent positive trend of brachytherapy use Medicare and Medicaid patients with cervical cancer may be influenced by awareness of declining brachytherapy utilization rates raised by researchers and the implementation of the Affordable Care Act [44]. It is unclear that this change will be sustained over the next five years; however, the recent advocacy and eventual removal of brachytherapy from the RO Model is promising [45].

In LMICs, it is expected that the overall number of brachytherapy afterloaders available for cervical cancer treatment will increase over the next five years due to concerted international efforts to bring radiotherapy to lower-resource settings and shifting international and national priorities [24,76]. Moreover, access to brachytherapy is increasing due to resource sharing between geographically close institutions in different countries [25]. But also due to increased global knowledge share as telehealth education and innovative training opportunities expand allowing centers to implement and hone brachytherapy skills. However, it is unclear whether this increase in number of brachytherapy afterloaders will keep pace with rapid population changes in lower resource countries, which has not been the case in recent history. It is also important to consider the World Health Organization’s launch of the global strategy to accelerate the elimination of cervical cancer, which may result in an increase in HPV vaccination rates and a declining need for brachytherapy over time [77]. The WHO Cervical Cancer Elimination Modeling Consortium estimates that high HPV vaccination coverage of girls and cervical cancer screening can lead to cervical cancer elimination in most LMICs by the end of the century [77]. However, it is unclear how the recent uptick in vaccine hesitancy will impact HPV vaccination coverage rates, especially in the COVID-19 era [78]. Regardless, as there is an anticipated lag in the reduction in the absolute burden of cervical cancer, even if vaccination rates increase to goal levels, access to brachytherapy will remain a critical component of global strategy to ensure the best care for all women with this disease.

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Article highlights

- Brachytherapy is an essential component of the cervical cancer care treatment paradigm.
- - Suboptimal use of brachytherapy for cervical cancer exists globally across both high-income and low- and middle-income countries.
- Barriers to brachytherapy implementation are multifactorial and differ between countries and regions.
- Numerous promising efforts exist to increase rates access to brachytherapy care worldwide.
- Today there exists a tremendous opportunity to expand access to essential brachytherapy services for women with cervical cancer.