Opinion: Radiation therapy for cervix carcinoma: the benefits and constraints in sub-Saharan Africa

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ABSTRACT
Cervix carcinoma is one of the most prevalent cancers in women in Africa. Primary and secondary prevention measures in place are currently not sufficient to prevent further cases. Radiotherapy is the main therapeutic option as most cases present at a locally advanced stage. Unfortunately radiotherapy resources are scarce and literature considering outcomes for radiation treatment in Africa is limited. This review will highlight the difficulties in access to treatment, examine international meta-analyses and African literature related to radiation treatment, and discusses the special considerations needed when adapting international treatment standards to the developing world.

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Keywords: cervix; cancer; resources; radiation; radiotherapy; Africa

Introduction
Cervix carcinoma is one of the most prevalent causes of oncological mortality and morbidity in sub-Saharan Africa. In Eastern Africa the age-standardised incidence rate is 42.7/100 000 and in Southern Africa 38.2/100 000.1 There are many publications on primary and secondary prevention in Africa and the gynaecological communities’ attempts to reduce the number of cases of cervix carcinoma. In particular, there has been a greatly increased global advocacy for implementation of the Human Papillomavirus (HPV) vaccine. However, the reality is that many women will miss the opportunity for these preventative measures due to poor health services and socio-economic factors. Cervix carcinoma thus frequently presents in the locally advanced stages of disease where surgery is no longer an option for treatment. The mainstay of therapy and the only real hope for cure remains radiotherapy.

The purpose of this review is to highlight the limited availability of radiotherapy resources in Africa and its implications on access to treatment. Furthermore a review will be made of the literature published by radiotherapy centres in Africa in the last 10 years, specifically considering radiotherapy treatment in cervix carcinoma, including publications on the treatment of HIV-positive patients. Also considered will be examples of international data from other developing world centres on the outcomes of radiation in cervix carcinoma. Conclusions will be drawn on the appropriateness of international recommendations for treatment with radiotherapy, and chemotherapy, in the sub-Saharan setting.

Radiation therapy resources and access to treatment
Radiotherapy services are sporadic in Africa either due to lack of equipment, personnel or geographic access to treatment centres. Many countries have no service at all. The recommendation by the International Atomic Energy Agency (IAEA) is that a radiotherapy machine should treat between 350–400 patients a year.2 Data by Barton et al3 shows that there were a total of 155 units in Africa in 1999, falling significantly short of the estimated need for 842 machines in 2002 to achieve the recommendations by the IAEA. Developments have been made since this time; recent support by the IAEA has lead to the establishment of centres in both Tanzania and Zambia.

In South Africa, the situation in the public health sector is more encouraging; there are six national academic radiation centres with a small number of additional satellite units. In total there are 29 machines currently available to treat public sector patients.4 These services far exceed those available to other populations in Africa. Despite this, radiation services are still very limited for large numbers of cervix carcinoma patients, which may be more than 800 cases a year in some centres. Waiting lists are long and some centres have no option of chemotherapy due to resource constraints. Geographic access to treatment centres may be difficult for patients who live in remote areas. Even in the relatively developed oncology services in South Africa we are faced with the same problems of inequitable access for those most in need of radiation treatment.

Health systems in most African countries are run on some form of user fee payment and even if radiotherapy centres can be accessed, financial difficulties lead to many being turned away. Obi et al5 from the University of Nigeria demonstrated in a small sample of 95 patients with cervix carcinoma that 81% did not receive treatment as they could not afford the medical bills. The impact of this can be far reaching; the women who suffer from this disease are often young mothers who may be working...
and providing for families. The unnecessary loss of life will have a detrimental socio-economic impact. Improving access to treatment has to be high on the agenda of health policy makers to redress this situation.

International and African literature on chemoradiation treatment for cervix carcinoma

In 1999 the National Cancer Institute published an alert that the addition of chemotherapy to radiotherapy in cervix carcinoma improved overall survival, and its use in combination was recommended. A meta-analysis in 2001 found the absolute survival benefit to be 12% (hazard ratio [HR] = 0.71, p < 0.0001) at five years. These guidelines have been adopted worldwide and are recommended in many department protocols for all patients with inoperable disease, including those of this author’s institution. Treatment for Stage Iib – IIb3 disease includes pelvic external beam radiation (EBRT) 45–50 Gy in 25 fractions, weekly concomitant cisplatin chemotherapy 40mg/m² and intracavitary brachytherapy (ICT) 15 to 28 Gy in two to four fractions.

A recent meta-analysis of individual patient data, published in 2008, looked again at the addition of chemotherapy to radiotherapy. This has raised some interesting points. Firstly, the initial overall survival is less than the 2001 meta-analysis and is now stated as 6% (hazard ratio [HR] = 0.81, p < 0.001). In addition, the trend in overall survival benefit for Stage III–IVa is a mere 3% (p = 0.017). Of note, the number of Stage III patients in these international studies is very small, reflecting the difference in the disease in the developed world vs the developing world. As regards overall survival, the benefit did not differ between using platinum vs non-platinum chemotherapy which would be relevant to the African situation where hydrenephrosis and medical co-morbidities limit the use of platinum-based regimens.

The data published in Africa regarding the use of concurrent cisplatin consists firstly of a phase I study by Nyongesa et al from Johannesburg. A dose escalation study was performed comparing the dose of cisplatin between three groups 20 mg/m², 25 mg/m² and 30 mg/m². Only at a dose level of 30 mg/m² was renal dysfunction evident. Reasons for reduced tolerance in the study population were postulated: inherent renal dysfunction, advanced stage of malignancy, chronic infections, dehydration, concomitant medication and limited medical facilities. The authors recommended a dose reduction to 25–30 mg/m² for patients treated in the developing world setting. Though this appears to be a valuable suggestion, the dose used in the international studies was 40 mg/m², and these lower doses have unproven efficacy. A second study by McArdle et al in Kampala demonstrated that only 15.1% of patients referred for radiotherapy were eligible for chemoradiation with cisplatin due to frequent occurrence of exclusion factors such as HIV-positivity, hydrenephrosis and anaemia. In the African setting such problems are difficult to correct due to poor access to antiretrovirals, nephrostomies and a transfusion service.

From the limited African studies one can already deduce that international guidelines on chemoradiation are not necessarily adaptable to the African situation. An IAEA study comparing chemoradiation vs radiation alone in Stage III cervix carcinoma is still ongoing with participation by local African departments. A second study is underway on the Indian continent asking a similar research question. The outcome of these studies may further research needs to be performed on non-platinum drug regimens and less nephrotoxic drugs such as carboplatinum in combination with radiotherapy.

Further concern about the use of chemotherapy is related to the co-existence of cervix carcinoma and HIV. The exact incidence of HIV-positivity in this group of patients has not been formally defined and varies between approximately 10 and 20%. Prevalence of HIV was found to be 11.6% in this group of patients has not been formally defined and varies between approximately 10 and 20%. Prevalence of HIV was found to be 11.6% in the McArdle study and 19.4% in a study by Kigula-Mugambe both from Kampala. Kahesa et al performed a matched control study of cervix cancer patients in Dar-es-Salaam and found the prevalence of HIV to be 21% in patients, and 11.6% in the control group. In this author’s institution in the Western Cape, it stands at 12% from statistics gathered from 2007 to 2008. The combination of chemotherapy and underlying HIV may exacerbate risks of neutropenia, skin and gastrointestinal toxicity. In truth this has yet to be established and again is a focus of an ongoing study in a South African academic institution.

Conventional radiotherapy alone as a modality

With very few countries in Africa having access to chemotherapy one needs to look at radiotherapy as a single modality for the treatment of cervix carcinoma. Data from both Uganda and Zimbabwe shows that radiotherapy was not used very frequently in the 1990s. The Kampala group found that only 24% of patients received radiotherapy. The advantage of radiotherapy over no treatment was not evident beyond one year. The Harare data from the same time period showed that 49% received radiotherapy and that the survival advantage was lost by the fourth year of follow-up. What is absent from both studies are the number in the non-radiotherapy group who received surgery, and those treated with best supportive care. These are also both observational studies and it is not appropriate to draw conclusions about the benefit, or lack thereof, in the use of radiotherapy. There are no
was also low at 7.5 Gy per fraction (15 Gy total dose). A retrospective EBRT and two fractions were given a week apart. Total brachytherapy dose treatment time, as brachytherapy was delayed until after completion of high-dose rate (HDR) brachytherapy treatment. 47.1% of these patients study. Campbell et al18 from Nairobi examined this concept randomising doses per fraction and fewer fractions is an option that needs further considered. Hypofractionation or the delivery of radiotherapy in larger lists and demands for machine time, particularly in centres and countries Though EBRT to a dose between 45–50 Gy is the ideal, this is obviously highly valued and we must do all we can to improve access and outcomes of treatment. Though the action to promote primary and secondary prevention has my unwavering support, I strongly urge the gynaecological oncology community not to forget that we must continue to advocate for better treatment resources, and not lose out to funding drives for vaccination. Without radiotherapy resources we may not be able to treat this generation of women and we will face the consequences of their loss. This is not an ethical option, and, as a radiotherapist, I find lack of access to treatment unacceptable. As a radiotherapy community we must focus on how we can act responsibly with our resources in Africa. We must be motivated to increase research in treatment outcomes, and we must be more innovative and question international standards. Is chemoradiation better than radiation alone in Stage IIb disease? Until it has been proven so, those with limited resources must focus on delivering radiotherapy and ensuring access to brachytherapy services. Are the prolonged radiation courses appropriate to waiting list constrained departments? We must focus on novel hypofractionated regimens and establishing their safe and effective use in Africa. In conclusion, we must develop our own standards of care and push forward in answering the questions that are relevant to our own situation through pioneering African research.

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