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 radiation 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.

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.

Radiotherapy 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 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.

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.3 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 600 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 al4 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...
radiation (EBRT) 45–50 Gy in 25 fractions, weekly concomitant cisplatin. Treatment for Stage Iib–IIIb disease includes pelvic external beam therapy for patients with inoperable disease, including those of this author’s institution. 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–IIIb 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 hydronephrosis 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, hydronephrosis 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 treatment 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 very well provide the answer to the use of platinum-based chemotherapy in Stage III cervix carcinoma, the most common stage of presentation of women in the developing world. However, 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 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
further African studies looking at conventional fractionation radiotherapy alone outside of the setting of HIV-positive patients.

Kigula-Mugumbe et al.11 focused on the outcomes for HIV-positive patients undergoing radiotherapy. A small audit of 36 patients was undertaken. All patients received between 50–60 Gy opposing fields with Cobalt-60 and after a month delay 22 patients received a single brachytherapy treatment with 28–30 Gy Caesium-137. Radiotherapy was effective in the HIV-negative group with survival at four years being 64%; further conclusions drawn regarding survival in the HIV-positive group are questionable considering only 7 patients were included in the study. A second study by Gichangi et al.12 from Nairobi also examined the outcome for HIV-positive and negative patients who received EBRT alone. This group consisted of 208 patients who received EBRT in a similar regimen to the Kampala group; no patients received brachytherapy. Twenty per cent of patients enrolled were HIV-positive. There was a high percentage of grade III to IV toxicity in both groups with 24.5% having a significant treatment interruption due to grade IV toxicity. This high percentage of grade III to IV toxicity has been criticised by McArdle et al.13 as being unexpectedly high and this is not a trend that is seen in their institution. The only statistically significantly increased toxicity in the HIV-positive group was genito-urinary. There was no difference in the received dose or duration of treatment for the HIV-positive group. Evidence of residual disease was higher in the HIV-positive group, 41% vs 16%. Conclusions can be drawn that when treated with EBRT alone, treatment regimens need not differ in relation to toxicity though the outcomes may be poorer for the HIV-positive patients, highlighting that improvements need to be made to ensure improved survival in this group.

There are no further published data on radiotherapy with curative intent published by African clinicians since 1999 in the international literature referenced by Pubmed. As a surrogate one can look to publications from other developing world settings to evaluate the role of radiotherapy; a number of these arise from India. Two examples from the literature follow. Jain et al.14 examined a cohort of 214 patients who completed EBRT and high-dose rate (HDR) brachytherapy treatment. 47.1% of these patients were Stage III. The overall survival for this group was 33% (95% CI 24–35%). This was lower than predicted but this may have been due to prolonged treatment time, as brachytherapy was delayed until after completion of EBRT and two fractions were given a week apart. Total brachytherapy dose was also low at 7.5 Gy per fraction (15 Gy total dose). A retrospective analysis by Sahibshikumar et al.15 showed that treating with an external beam boost rather than brachytherapy showed a very poor outcome for patients with overall five year survival only at 15.1% (median of nine months). Of note these patients were found ‘not suitable’ for brachytherapy. It is unclear what these criteria are. Both these retrospective reviews had lower survival than would be expected overall in cervix carcinoma, even for those who are in the more advanced stages, but it re-iterates the point that treatment with brachytherapy is an essential part of therapy and the lack of access to this in many developing countries undoubtedly contributes to poorer outcomes with radiotherapy.

Altered fractionation

Though EBRT to a dose between 45–50 Gy is the ideal, this is obviously labour intensive as treatment will be over five weeks. With long waiting lists and demands for machine time, particularly in centres and countries with only one treatment unit, it is important that other options are considered. Hypofractionation or the delivery of radiotherapy in larger doses per fraction and fewer fractions is an option that needs further study. Campbell et al.16 from Nairobi examined this concept randomising 480 patients to either hypofractionation (treatment over three weeks) or conventional fractionation. Five year survival rates of Stage III patients for the hypofractionated group leading the authors to recommend caution in the use of this regimen. Muckaden et al.17 from Mumbai retrospectively reviewed patients with IIIB cervix carcinoma in who received 39 Gy in 13 fractions followed by a single intracavitary treatment of 25 Gy (low dose rate). Of the 62 patients treated, 48 completed the regimen. Six patients had acute grade III or IV toxicity and five patients had late grade III rectal toxicity. Most importantly the overall survival at three years was 50%. The role that hypofractionated radiotherapy plays in treatment of cervix carcinoma has not been defined and it is vital that further randomised studies are designed to address this extremely important question. Maximising survival and resource use, whilst limiting toxicities, should be a goal for African radiotherapists.

Conclusions

Health care resources are scarce and we are often forced to make choices. However, the lives of women with cervix carcinoma are 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.

References:

3. Natural communication. Dr Leon Gouws GVI Oncology.