

The impact of HIV infection on women receiving radiation for cervical cancer

Mapule Mangena,¹ Leon Snyman,¹ Greta Dreyer,^{1*} Sheynaz Bassa,² Piet Becker³

¹Gynaecological Oncology Unit, Department of Obstetrics and Gynaecology, University of Pretoria

²Department of Radiation Oncology, University of Pretoria

³Research Office, Faculty of Health Sciences, University of Pretoria

*Correspondence to: Greta Dreyer, email: gretadreyer@mweb.co.za

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Abstract

Background: The objective of the study was to compare patient characteristics, treatment toxicity and interruptions, and survival in human immunodeficiency virus (HIV)-positive and HIV-negative cervical cancer patients receiving radiation as primary or adjuvant treatment.

Method: Demographics, clinical and tumour characteristics, and the outcomes of 51 HIV-positive and 47-HIV negative consecutive cervical cancer patients were assessed and compared, including co-morbidities, performance status, treatment type and toxicities, and survival.

Results: HIV-positive women were 13 years younger ($p < 0.001$), more often had anaemia ($p 0.021$) and needed pretreatment blood transfusion ($p 0.037$) more often than HIV-negative women. Performance status, kidney function, International Federation of Gynecology and Obstetrics stage, histology types and treatment intent and planning did not differ between the two groups. Treatment interruptions ($p 0.004$), transfusion during treatment ($p 0.012$), treatment toxicities ($p 0.040$) and average deficit ($p 0.021$) occurred significantly more in HIV-positive patients. Survival was significantly worse in HIV-positive women ($p 0.029$) and was associated with insufficient radiation ($p < 0.001$) and treatment interruptions ($p 0.051$).

Conclusion: In spite of being younger, the pretreatment correction of anaemia and the prescription of sufficient radiation dosages, HIV-infected cervical cancer patients experienced poorer survival. Treatment interruption and incomplete radiation contributed to poor outcomes.

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Introduction

Worldwide, cervical cancer is the second most common cancer in women.¹ Approximately 8 000 new cases are diagnosed per year in South Africa, and the World Health Organization estimates the age-standardised incidence rate for South Africa to be 31.7 per 100 000 women.² On the basis of very incomplete national cancer data, the disease was estimated to account for 17-22% of all cancers in women in South Africa, with an age-standardised incidence rate of 30 per 100 000 women-years and reported to be the leading cause of cancer-related mortality.³ The high case mortality rate is attributed, among other factors, to poor access to medical facilities, poor nutrition and the late presentation of cervical cancer. Local data also demonstrate that black women are more affected than other races,^{3,4} and co-morbidities, including infection with human

immunodeficiency virus (HIV), are also common in black women.

HIV infection emerged as an infectious disease epidemic in the last decade of the 20th century. It was estimated that over six million people in South Africa were living with this disease in 2012, and more women were affected than men. Antenatal HIV surveillance data showed an increase in prevalence from less than 1% in 1990 to 29.5% in 2012.⁵ The influence of the acquired immune deficiency syndrome (AIDS) epidemic on the prevalence and mortality rate of cervical cancer is difficult to estimate. Cervical cancer was accepted as an AIDS-defining disease by the Centres for Disease Control and Prevention in 1993,⁶ but the impact of HIV infection and AIDS on the natural course and treatment of the disease is not fully known.

The association between HIV infection and cervical cancer, both, in part, sexually transmitted infections, is complex. Unlike other AIDS-defining cancers, cervical cancer cannot be explained on the basis of immune suppression only. HIV-positive patients are at increased risk of persistent human papillomavirus infection, precancerous lesions and cervical cancer, compared to HIV-uninfected women.⁷⁻⁹ On the other hand, a dramatic increase in the incidence of cervical cancer coinciding with the emergence of the epidemic has not been reported in South Africa.¹⁰ HIV infection initiates an ongoing decrease in cell-mediated immunity by the destruction of T-helper lymphocytes, and this propagates cervical cancer growth. This may account for the more aggressive tumour behaviour, poor response to treatment and poorer prognosis, as demonstrated by several authors in HIV-positive patients, and which seems to relate to the degree of immune depletion.¹¹⁻¹³

Radiation and concomitant chemotherapy are common treatment modalities for patients with cervical cancer. These modalities can be used as primary treatment, adjuvant therapy after surgery, or therapy with palliative intent. The acute toxicity due to concomitant chemoradiation is higher than the toxicity of radiation only.¹⁴ Treatment toxicity, response and outcome depend upon many variables, and differ between patient populations.¹⁵ Many of these factors relate to tumour biology and general health, and are potentially influenced by HIV status.

The difference in treatment toxicity between HIV-negative and HIV-positive patients is still largely unknown. A paucity of data describe the outcome of comparable groups of HIV-positive and -negative patients treated for cervical cancer with contemporary optimal radiation treatment. It has been suggested in several case series of HIV-positive patients treated for cervical and anal cancer that therapy is tolerable, but toxicity may be increased.^{11,16,17}

The current study compares the short-term outcome of HIV-positive patients who received radiation therapy and/or chemoradiation for cervical cancer, with that of HIV-negative patients. This retrospective study was performed in a public health facility which serves uninsured patients referred to the tertiary hospital following a diagnosis of invasive cervical cancer. Access to resources was probably representative of conditions in most South African university hospitals at the time of the audit, with limitations to medication availability, service, maintenance and the replacement of equipment, as well as budget constraints. The study also aimed to compare known poor prognostic factors between the two groups.

Method

One hundred patients diagnosed with cervical cancer and treated with radiation or chemoradiation between 1 January 2007 and 31 January 2008 were included in this retrospective descriptive study. A convenience sample was selected, with patients selected consecutively. On the basis of the first available HIV serology test in the records, 50 consecutive HIV-positive and 50 consecutive HIV-negative

patients were selected for inclusion in the analysis. All data were obtained from the records of the Radiation Oncology Department at Steve Biko Academic Hospital, Faculty of HealthSciences at the University of Pretoria. Demographic data included age and parity, while clinical data included the performance status,¹⁸ International Federation of Gynecology and Obstetrics (FIGO) stage, kidney function and hydronephrosis, information about co-morbid disease, initial haemoglobin (Hb) levels, as well as immune status. Tumour data were recorded on histology type, grade and maximum diameter.

All HIV-positive patients with a CD4 count of > 200 cells/mm³, and those on antiretroviral therapy (ART), received cervical cancer treatment according to the standard treatment protocol used in the departments of Gynaecologic Oncology and Radiation Oncology. According to these treatment protocols, operable patients with FIGO stages I and IIA were treated with primary surgery. The need for, and type of, postoperative adjuvant therapy, was discussed, and decided at a combined interdisciplinary meeting.

Patients with stage IIB and higher were treated with primary radiotherapy or concomitant chemoradiation. The addition of chemotherapy and the dosage relied mostly on general health, performance status and kidney function. Cisplatin was the drug of choice, administered weekly at a usual dosage of 30 mg/m², provided that the CD4 count was at least 200 cells/mm³.

Primary radiation treatment intent was either radical or palliative, depending on the FIGO stage and medical condition. The total dose of radical radiation given in 2 Gy fractions, without any planned breaks, was usually 46 Gy for stage IIB, and 50 Gy for stages III and IV, followed by high-dose-rate therapy of 26 Gy in four fractions, and 24 Gy in three fractions, respectively. Adjuvant postoperative radiation consisted of 45 Gy in 25 fractions, with the addition of high-dose-rate treatment (20 Gy in four fractions) and chemotherapy, depending on the pathological risk factors. Palliative doses varied from 8-30 Gy, administered between one and 10 fractions.

Highly active antiretroviral therapy was available during the period of study for all HIV-positive women with invasive cervical cancer. Many patients were first diagnosed with HIV infection at the time of cervical cancer diagnosis, and therapy for both diseases was initiated at the same time. During the study period, the Hb target was 12 g/dl before radiation, and the transfusion trigger during radiation was 10 g/dl, tested weekly.

Treatment data on HIV and cancer treatment type, dosage and intent, treatment interruptions, blood transfusion and overall treatment time were collected. Treatment intent could be palliative, radical or adjuvant. Treatment deficit was calculated as the difference between prescribed and actual received dosage. If this was 10 Gy or more, it was defined as incomplete treatment. Reasons for treatment interruptions were classified as either hospital or patient

related, and detailed data on the exact reasons were collected and analysed. Data were collected on treatment toxicity and grade, according to the criteria of the Radiation Therapy Oncology Group,¹⁹ but the availability of detailed information in the files did not permit further analysis. Survival data were obtained from the national register of deaths at the Department of Home Affairs, and last updated in June 2012, between 24 and 30 months from the onset of radiation.

Data were analysed using SPSS[®] version 17. Descriptive statistics were used to describe the population (frequency and percentage), and a comparison between the two groups was made using a two-sided chi-square test. Where the expected values were less than 5, Fisher's exact tests were used. *P*-values less than 0.05 were considered to be statistically significant. Survival analysis was performed using Kaplan-Meier survival estimates.

The study received ethics approval from the Research Ethics Committee, Faculty of Health Sciences, University of Pretoria (176/2008).

Results

Two patients were excluded from further analysis because of unconfirmed HIV status. One patient was initially recorded as being HIV negative, but her status was subsequently confirmed as HIV positive. The final groups consisted of 47 HIV-negative and 51 HIV-positive women. A CD4 count of more than 200 cells/mm³ was recorded in 39 patients (78%) in the HIV-positive group.

The median age in the HIV-negative group was 56 years [standard deviation (SD) 8.78], and 43 years (SD 11.58) in the HIV-positive group. This difference was statistically significant (*p* < 0.001). An initial pretreatment performance status of 0 and 1 was attributed to 87% of patients in the HIV-negative group, and the corresponding percentage was 90% in the HIV-positive group. The HIV-negative group was comparable to the HIV-positive group in terms of FIGO stage, histological type and kidney function. There was a trend towards more co-morbidities in older, HIV-negative women, but this was not statistically significant.

Pretreatment anaemia was more common in HIV-positive women, as was the need for blood transfusion. Both these parameters reached statistical significance (Table 1). The mean Hb level was 11.4 g/dl for HIV-negative women and 11.1 g/dl for HIV-positive patients (*p* 0.82).

Treatment intent was similar for the two groups; palliative for 11 patients and curative or radical for 87 patients, of whom 11 received adjuvant postoperative therapy (three HIV positive and eight HIV negative). Although planned treatment was comparable for the two groups, HIV-positive patients experienced more treatment interruptions. Common medical reasons for interruptions included the need for blood transfusion and non-specified co-morbidities. Patients needing blood transfusion required

hospitalisation, and the limited availability of beds and time lost to order, receive and transfuse blood led to interruptions to the provision of radiation. Thirteen (25%) HIV-negative women required blood transfusion during treatment, compared to 25 (50%) HIV-infected women. This difference was statistically significant (*p* 0.012). Radiation treatment deficit and incomplete treatment occurred significantly more in HIV-positive women (*p* 0.06). The mean prescribed radiation dosage not received in the HIV-negative group was 2.8 Gy, and 6.7 Gy in the HIV-positive group (*p* 0.021). HIV-infected women experienced more treatment toxicity than HIV-negative women; mainly skin and bladder complications (Table 2).

Table 1: The study demographics

Characteristics	HIV negative n = 47 (%)	HIV positive n = 51 (%)	<i>p</i> -value
Age distribution (years)			
< 36	0	15	< 0.0001
36–45	5	17	
46–55	18	13	
56–65	15	5	
> 65	9	1	
FIGO stage			
Localised disease (I–IIA)	5 (11)	5 (10)	0.610
Advanced central disease (IIB–IIIA)	15 (32)	21 (41)	
Advanced sidewall disease (IIIB–IVA)	27 (57)	25 (49)	
Tumour type			
Squamous	43	49	
Non-squamous	4	2	
Kidney function			
Normal	38 (84)	42 (89)	0.340
Impaired	3 (7)	4 (9)	
Severely impaired	4 (9)	1 (2)	
Hydronephrosis			
Present	9 (19)	10 (20)	0.960
Co-morbidities			
Hypertension	18 (38)	9 (18)	0.160
Diabetes mellitus	2 (4)	3 (6)	
Pretreatment haemoglobin (g/dl)			
< 10	13 (27)	22 (43)	0.043
10–12	17 (35)	21 (41)	
> 12	18 (38)	8 (16)	
Anaemic	30 (63)	43 (84)	0.021
Red cell concentrate transfused (units)			
0	34	26	0.037
2–3	11	15	
4–5	2	5	
6+	0	5	

FIGO: International Federation of Gynecology and Obstetrics

Using univariate analysis, survival was associated with a positive HIV status (p 0.071), incomplete treatment (p 0.029) and treatment interruption (p 0.049). Pretreatment anaemia, kidney function and the requirement for blood transfusion did not influence survival.

Treatment deficit was the most significant predictor of overall survival, followed by HIV status in the multivariate survival analysis.

The overall survival of HIV-negative patients was significantly better than that for HIV-positive women (Figure 1). Median survival was 21 months for the total group of HIV-positive patients, and 32 months for the HIV-negative women. When survival was adjusted for age, this difference was more pronounced (p 0.05) (Figure 2). Overall survival was also significantly worse in patients who experienced treatment interruptions (p 0.051), and in those who received incomplete

treatment (p < 0.001). The latter was most significantly negatively associated with overall survival (Figures 3 and 4). Patients who did not complete their treatment had a median survival of only eight months in comparison to 30 months for those who did.

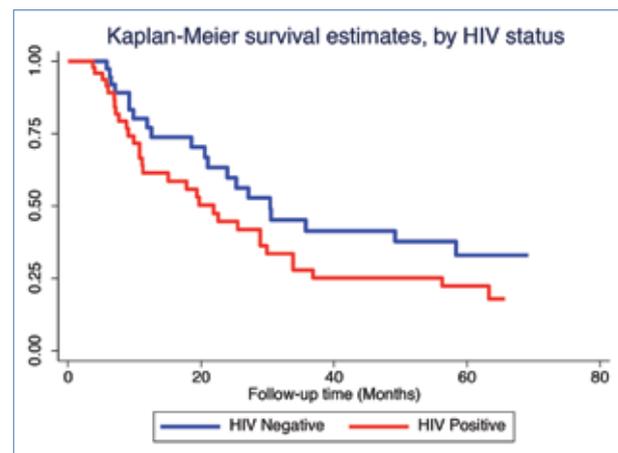
Discussion

The observation that the HIV-positive patients were significantly younger than the HIV-negative patients was consistent with previously published South African data.^{9,10,20,21} This is most probably owing to a shorter pre-cancer phase and more rapid progression to invasive disease.²⁰ Based on these findings, screening in HIV-infected women should be initiated at the time of diagnosis of HIV infection, and should not be determined by age.

Pretreatment performance status, FIGO stage, tumour size and type, kidney function and the prevalence of hydronephrosis were comparable for the two groups, indicating similar healthcare exposure and late diagnosis. The trend towards increased diabetes and hypertension in the HIV-negative group was probably owing to the age difference between the two groups. Pretreatment anaemia

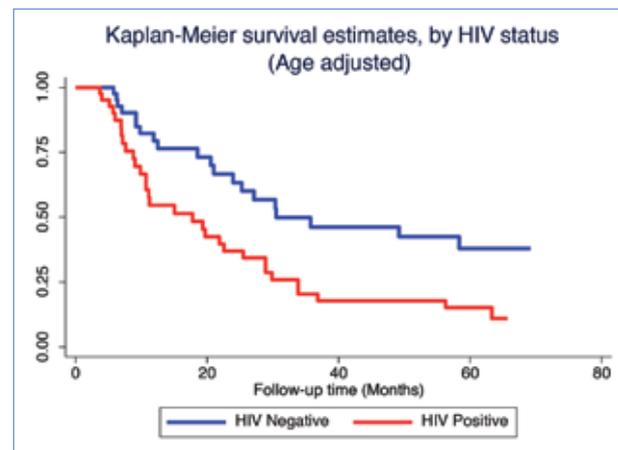
Table 2: Treatment intent and outcomes

Treatment intent and outcomes	HIV negative n = 47 (%)	HIV positive n = 51 (%)	p-value
Treatment intent			
Palliative	4	7	0.530
Radical	43	44	
Planned treatment			
External beam radiotherapy	47	51	
External boost	6	8	
Brachytherapy	32	29	
Concurrent chemotherapy	34	38	
Treatment interruptions			
Patient defaulted	6 (13)	6 (12)	0.004
Hospital related	11 (24)	11 (22)	
Blood transfusion	2 (4)	8 (16)	
Co-morbidity	7 (15)	14 (28)	
Total interruptions	24 (53)	41 (82)	
Radiation treatment deficit (Gy)			
Total treatment deficit	131	340	0.120
Patients with treatment deficits	5 (11)	12 (24)	
Average deficit of total group	2.8	6.7	0.021
Average deficit of incompletely treated	26.2	28.3	
Treatment completion	42 (89)	39 (76)	0.060
Blood transfusion during treatment	13 (25)	25 (50)	0.012
Treatment toxicity			
Skin	4	12	0.040
Bladder	3	6	0.290
Gastrointestinal	1	0	0.480
Haematological	1	1	0.730
Total	9	19	0.040



HIV: human immunodeficiency virus

Figure 1: Overall survival by human immunodeficiency virus status



HIV: human immunodeficiency virus

Figure 2: Overall survival by human immunodeficiency virus status, age adjusted

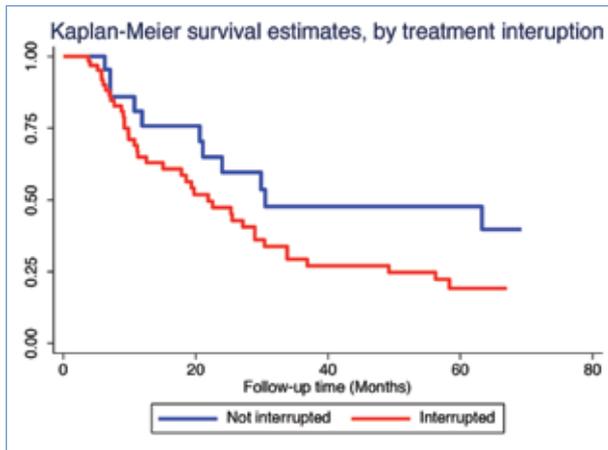


Figure 3: Overall survival by treatment interruption

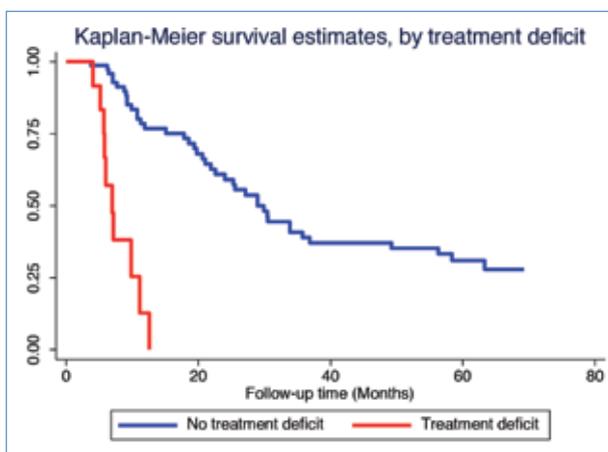


Figure 4: Overall survival by treatment deficit

was more common in HIV-positive women. This finding is consistent with other published data.¹¹ Many factors contribute to anaemia, including HIV-induced bone marrow suppression, anaemia of chronic disease and blood loss from advanced-stage cervical carcinoma.²² Anaemia is an important predictor of locoregional tumour control and survival, probably because of chronic and transient hypoxia, resulting in radioresistance.²³ Anaemia (defined as Hb < 10 g/dl) in HIV-infected patients without malignancy is associated with more rapid disease progression to AIDS, and an increased risk of death.²⁴

Although pretreatment haemoglobin values were comparable for the two groups, more HIV-infected women started treatment with a level < 11 g/dl. This, combined with underlying bone marrow disease and increased bone marrow susceptibility to radiation toxicity, probably explains the increased need for blood transfusion during treatment in HIV-positive patients. Anaemia, and the need for blood transfusion during treatment, also emerged as important reasons for treatment interruption in this study.

Treatment interruptions were significantly more common in HIV-positive patients, with 82% of this group experiencing this problem. As it is known that extended treatment duration negatively affects prognosis,^{11,25} it is important to investigate the underlying contributors, and to examine

potential preventative interventions. We were only able to identify general poor health or anaemia as medical reasons for treatment interruption. Other reasons included technical problems relating to hospital management and machine maintenance, and patients who defaulted on treatment for undisclosed reasons.

Although there was a trend towards more co-morbid diseases in the HIV-negative group at the start of treatment, and this group was significantly older, medical conditions in this group contributed less to reported treatment interruptions than medical conditions in the HIV-positive women. Almost all HIV-infected patients in this study received ART, but many started it late, and often simultaneously with antineoplastic therapy. The contribution of ART to antineoplastic treatment tolerance is unknown.

Data on toxicity were scanty, and the reported differences should be interpreted with caution. HIV infection was found to predispose patients to acute radiation toxicity in studies reporting on other forms of cancer.²⁵

This study reports on the survival of HIV-negative and -positive women who received similar radiation treatment for cervical cancer. The significant age-adjusted survival difference favouring HIV-negative women was an important finding. This difference occurred both when data were centred around 50 years, and when analysed in age categories. Therefore, HIV infection is an independent poor prognostic factor in women treated for cervical cancer with radiation therapy, and significantly compromises survival. Treatment interruptions, as well as failure to complete the prescribed therapeutic dosage, are both independent poor prognostic factors with regard to overall survival.

Limitations of the study included poor documentation and the high number of patients who were lost to follow-up during and after treatment.

Conclusion

HIV-infected women are more likely to require blood transfusion during radiation, and are at higher risk of unplanned treatment interruptions owing to medical conditions, in spite of being significantly younger. They are less likely to receive the full prescribed radiation dosage, and may experience more treatment-related toxicity than HIV-negative women.

All these factors play a role in explaining the main finding of this study, namely significantly poorer survival in HIV-infected women with cervical cancer, than that in HIV-negative women, in spite of similar treatment prescriptions.

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Conflict of interest: The authors have no commercial or other affiliation which might have caused a conflict of interest when conducting this study.

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