THE IMPACT OF HIV STATUS ON STAGING, TREATMENT AND OUTCOMES IN LOCALLY ADVANCED CERVICAL CARCINOMA

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"DECLARATION

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification."

This dissertation includes 4 original first-author papers published in peer-reviewed journals. The development and writing of the papers were the principal responsibility of myself.

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Abstract

Cervical carcinoma is one of the most frequently diagnosed malignancies in women in many countries in sub-Saharan Africa, including South Africa. In sub-Saharan Africa, among women without HIV the age-standardised cervical cancer incidence rate is greater than 40 per 100 000. However, women infected with both the human-immunodeficiency virus (HIV) and the human papilloma virus (HPV) have a higher risk of developing cervical carcinoma than women infected with HPV alone.

Published studies of the ideal staging methods, treatment algorithms, and outcomes for women with comorbid locally advanced cervical carcinoma and HIV are scarce. The aim of this body of work is to fill some of these gaps.

We conducted four cohort studies of patients with locally advanced cervical carcinoma with or without HIV, recording demographic data, staging information and treatment delivered. Additional information gathered for individual studies included treatment response and survival outcomes. We evaluated the statistical significance of differences between HIV-positive and negative patients. Logistic regression models were utilised to evaluate risk for toxicity, treatment response, and survival outcomes.

In the first of three retrospective cohort studies, among 383 patients, early response to chemoradiation was found to be related to advanced stage [OR 2.39, 95% CI 1.45-3.96] and completion of brachytherapy [OR 3.14; 95% CI 1.24-7.94] but not HIV status. In the second retrospective study, among 213 patients undergoing radical radiotherapy, acute Grade 3 / 4 toxicity was associated with receiving chemotherapy [OR4.41; 95%CI 1.76-11.1; p 0.023] and having HIV [OR 2.16; 95% CI0.98-4.8; p 0.05]. In a prospective study of 492 patients, OS at 5 years was 49.5% (95%CI; 44.6% - 54.4%) among HIV-negative patients but only 35.9% (95% CI; 23.9% - 48.0%) among HIV-positive patients (p=0.002).

In our Cox models, factors affecting outcome were HIV infection, stage IIIB disease, hydronephrosis, and delivery of concurrent chemotherapy. In the fourth cohort study, among 273 patients with locally advanced cervical carcinoma who underwent a radiotherapy planning PET-CT scan, overall 235 (84.5%) were upstaged. Upstaging was not associated with HIV status (HIV-negative 83.9% vs HIV-positive 87.2%; p=0.47). Following the PET-CT scan, among the 263 patients who attended for radiotherapy treatment, intent changed for 124 patients (46.3%): 53.6% of HIV-positive patients and 42.9% of HIV-negative patients (p=0.11).

This body of work demonstrated that in HIV-positive patients, integration of PET-CT into staging algorithms for cervical carcinoma is a viable option. During treatment HIV-positive patients experienced increased toxicity, but most were able to complete treatment, and their 5-year overall survival was nearly 40%. Among women with locally advanced cervical cancer, those with HIV infection should be treated with the best standard of care. Future research should focus on factors that improve outcomes for these women.

Abstrak

Servikale karsinoom is een van die mees gediagnoseerde kwaadaardige gewasse in vroue in baie lande in sub-Sahara Afrika, insluitende Suid-Afrika. Die voorkoms van servikale kanker is meer as 40 per 100 000 (ouderdom-gestandaardiseerde koers) in sub- Sahara Afrika, selfs onder vroue sonder menslike immuniteitsgebrek virus (MIV). Vroue met beide MIV en menslike papilloom virus (MPV) infeksies het 'n hoër risiko vir die ontwikkeling van servikale karsinoom as vroue wat slegs MPV infeksie het.

Daar is 'n tekort aan gepubliseerde werk oor die ideale stadiërings ondersoeke, behandeling algoritmes en uitkomste vir vroue met lokaal gevorderde servikale karsinoom en MIV infeksie. Verder dit is onduidelik wat die impak van MIV-positiwiteit mag hê op hierdie parameters. Die doel van hierdie navorsing is om sommige van hierdie vrae te antwoord.

Pasiënte, met of sonder MIV en lokaal gevorderde servikale karsinoom is in vier kohort studies bestudeer. In al die studies is inligting versamel oor demografie, stadiëring en die behandeling ontvang. Bykomende inligting vir individuele studies het respons op behandeling en oorlewing-uitkomste ingesluit. Die statistiese betekenisvolheid van verskille tussen MIV-positiewe en negatiewe pasiënte is bereken. Logistiese regressie modelle is gebruik om die risiko vir newe-effekte, behandelingsuitkoms en oorlewing te evalueer.

In die eerste van die drie terugskouende kohort studies op 383 pasiënte, is bevind dat vroeë reaksie op chemo- bestraling betekenisvol verband hou met gevorderde stadium van karsinoom [KV 2.39, 95% VI 1.45- 3.96] en voltooiing van bragiterapie [KV 3.14; 95% VI 1.24-7.94] maar nie met MIV status nie. In die tweede terugskouende studie, wat 213 pasiënte

ingesluit het wat radikale radioterapie ondergaan het, was akute graad 3 / 4 toksisiteit betekenisvol geassosieer met byvoeging van chemoterapie [KV4.41; 95% VI 1.76-11.1; p 0.023] en MIV positiwiteit [KV 2.16; 95% VI 0.98-4.8; p 0.05]. Vyf jaar algehele oorlewing is in 'n prospektiewe studie van 492 pasiënte geëvalueer. Die algehele oorlewing van MIV-negatiewe pasiënte was 49.5% (95% VI 44.6% – 54.4%) teen 5 jaar. Die algehele oorlewing van MIV-positiewe pasiënte was aansienlik laer, 35.9% (95% VI 23.9% – 48.0%) teen 5 jaar (p = 0.002). In die Cox modelle was die faktore wat uitkoms beïnvloed het, MIV-infeksie, stadium IIIB siekte, die teenwoordigheid van hidronefrose en toediening van gelyktydige chemoterapie. In die vierde kohort studie van 273 pasiënte met lokaal gevorderde servikale karsinoom, het pasiënte vir radioterapie beplanning 'n Pet-RT (rekenaar tomografie) skandering ontvang. In totaal is 235 pasiënte (84.5%) se stadiëring verhoog weens die bykomende inligting verkry van Pet-RT skandering. Verhoging in stadium het nie verband gehou met MIV-status nie (MIV-negatiewe 83.9% teenoor MIV- positiewe 87.2%; p = 0.47). Van die 263 pasiënte wat wel radioterapie behandeling ontvang het, is die plan verander vir 124 pasiënte as gevolg van die Pet-RT skandering (46.3%), 53.6% van MIV-positiewe pasiënte en 42.9% van MIV-negatiewe pasiënte (p = 0.11).

Hierdie navorsing het getoon dat integrasie van Pet-RT in stadiëring algoritmes vir servikale karsinoom 'n redelike opsie is vir MIV-positiewe pasiënte. Verder is aangetoon MIV-positiewe pasiënte meer newe-effekte ervaar tydens behandeling, maar in staat is om behandeling in die meerderheid van gevalle te voltooi met 'n 5-jaar algehele oorlewing van bykans 40%. In vroue met lokaal gevorderde servikale kanker moet diegene met MIV-infeksie met die beste standaard van sorg behandel word. Toekomstige navorsing moet fokus op faktore wat uitkomste verbeter vir hierdie vroue.

Acknowledgements

<u>Dedication</u>

Hennie and Haynes – without whom none of this would be possible. For more than a decade we have cared for the women in these pages together; it is inspiring to work alongside both of you.

Judith and Al – thank you for the encouragement and support.

Raymond Dusabe – I hope these findings answer some of your questions, Ray. We miss you.

My family and friends, who have waited for this day to arrive.

The women who participated in these studies.

THE IMPACT OF HIV STATUS ON STAGING, TREATMENT AND OUTCOMES IN LOCALLY ADVANCED CERVICAL CARCINOMA

Table of Contents

1. Chapter 1 - Introduction

1.1 Background

Cervical carcinoma is one of the most frequently diagnosed malignancies in women in many countries of sub-Saharan Africa, including South Africa[1]. In 2018 in South Africa, nearly 12 000 women were diagnosed with invasive cervical cancer (ICC), and 5000 succumbed to it[2]. Among women in the general population of sub-Saharan Africa, the age-standardised cervical cancer incidence rate is greater than 40 per 100 000[2]. In addition, cervical cancer has been considered an AIDS-defining cancer as women infected with both the human papilloma virus (HPV), which causes most cervical cancer, and the human-immunodeficiency virus (HIV) have a higher risk of developing cervical carcinoma than women infected with HPV alone.

In high-income countries (HICs), the HPV vaccine has been relatively well received; its availability is likely to reduce already low cervical cancer incidence rates over time. However, in sub-Saharan Africa, due to the high prevalence of high risk HPV subtypes and of HIV, incidence rates are higher and the lack of healthcare funding has been a barrier to implementation of population vaccination programmes[3]. Even if all eligible (pre-sexual debut) young girls in sub-Saharan Africa were vaccinated tomorrow, cervical cancer incidence would remain high for at least the next decade. Meanwhile, we need to study and try to meet the care needs of women with cervical carcinoma with or without comorbid HIV, in our resource-limited setting.

Where available, a chest X-ray or abdominal ultrasound may aid clinical staging to establish the extent of disease. In HICs, magnetic resonance imaging (MRI) and positron emission tomography–computed tomography (PET-CT) scanning are widely available to facilitate accurate staging; PET-CT in particular appears to be effective in detecting

involved lymph nodes and small volume metastatic disease, enabling clinicians to make the best use of oncological interventions[4]. PET-CT is now increasingly available in low- and middle-income countries (LMICs), including South Africa. A cohort study in this institution showed that more than 35% of patients' treatment plans were amended after PET-CT, either by conversion to palliative regimens or by the addition of extended field irradiation for involved para-aortic nodes[5]. In HIV-infected patients, PET-CT imaging may reveal additional fludeoxyglucose F-18 (FDG)-avid pathology, including reactive lymphadenopathy, or co-existent infectious disease, such as tuberculosis; these abnormal findings are difficult to interpret[6]. Prior to the commencement of this study, no further data were available regarding the utility of PET-CT in HIV-positive women with cervical carcinoma.

Once a patient with cervical carcinoma has been confirmed as suitable for curative treatment, the standard of care includes radical radiotherapy, brachytherapy and concurrent chemotherapy. International standards have been set for treatment planning and dose fractionation[7,8]. However, little is known about the efficacy and safety of these treatment algorithms for HIV-positive patients. For patients with both advanced cervical carcinoma and HIV, anti-retroviral toxicity and immunodeficiency complicate the administration of chemoradiation, which would otherwise be the treatment of choice. Published studies from LMICs describe small subsets of patients treated with low energy cobalt-60 machines using large open fields[9,10,11]. These studies report that HIV-positive patients have higher risks than uninfected patients of skin and gastrointestinal toxicity as well as more frequent withdrawal from treatment or subsequent inferior doses. Reviews of the management of HIV-positive cervical carcinoma patients in European and American populations have not drawn on retrospective or prospective data to compare their outcomes to those of HIV-negative patients; in the absence of such data, they have

generally concluded that HIV-infected patients should receive the same treatment as other patients[12,13].

The results of a randomised trial of chemoradiation vs radiation alone in HIV-positive cervical carcinoma patients in South Africa unfortunately remain unpublished. Prior to the commencement of this body of research, data on the efficacy and safety of chemoradiation for patients with HIV were lacking, and data on the survival outcomes of HIV-infected cervical carcinoma patients were limited. Two small cohort studies from India and Kenya did not include survival data due to loss to follow-up[9,10]. Few studies reported on outcomes of cervical carcinoma patients in sub-Saharan Africa treated with internationally accepted protocols, and most of those studies involved patients who were treated on Cobalt-60 low energy machines. Whether, given treatment with advanced chemoradiation techniques on high energy linear accelerators (LINAC), patients from our local population have comparable outcomes to participants in international studies in HICs has been unknown.

Although continuous antiretroviral therapy (cART) is prolonging the life expectancy of women with HIV, it is not reducing their risk of developing cervical cancer. This research attempts to determine the ideal diagnostic pathway and management of the growing numbers of HIV-positive women with cervical carcinoma.

1.2 Problem Statement

The ideal staging techniques and treatment regimens for HIV-positive cervical carcinoma patients needs to be identified to ensure optimal outcomes in this vulnerable and growing cohort of patients.

1.3 Central Research Theme and Objectives

The central research theme is the impact of HIV status on staging and on clinical outcomes following curative chemoradiation in women with locally advanced cervical carcinoma from the Western Cape, South Africa.

Acute response and toxicity of chemoradiation:

Study 1:

Patients treated for cervical carcinoma with primary radiotherapy with radical intent from July 2007 through December 2010, to compare those who are HIV-infected with those who are uninfected, regarding:

Objective 1: Clinical response to treatment

Objective 2: Completion of treatment

Study 2:

Patients treated for cervical carcinoma with primary radiotherapy with radical intent from November 2009 through December 2011, to compare those who are HIV-infected with those who are uninfected, regarding:

 Objective 1: Acute treatment toxicities

Overall survival:

Study 3:

Patients who received primary radiotherapy for cervical carcinoma from July 2007 through December 2011, to compare those who are HIV-infected with those who are uninfected, regarding:

Objective 1: 5-year overall survival (OS).

PET-CT as a staging tool:

Study 4:

Patients who underwent PET-CT imaging for cervical carcinoma from January 2015 through December 2018, to compare those who are HIV-infected with those who are uninfected, regarding:

Objective 1: Change in clinical stage

Objective 2: Additional radiological-pathological findings

Objective 3: Subsequent change in treatment decision

1.4 Research Methodology

The research consists of four studies.

Study 1:

Place of research: Tygerberg Hospital, Radiation Oncology Division

Study design: Cohort study

Selection of participants: 461 consecutive cervical carcinoma patients treated with primary radiotherapy with radical intent from July 2007 through December 2010. Primary radiotherapy includes all patients who received the equivalent of 45 Gray (Gy) external beam radiation, a minimum of 18 Gy high-dose-rate brachytherapy and concurrent weekly cisplatin chemotherapy where renal function was sufficient (glomerular filtration rate > 50ml/min). HIV patients included were immunocompetent with a CD4 count >150.

Viral load was untested in this cohort. All patients were prescribed anti-retroviral therapy (ART) prior to cervical cancer treatment.

Exclusion criteria: Patients who were treated only with palliative intent or who previously received surgery for cervical carcinoma

Methodology: Retrospective patient record analysis

Data analysis: The statistical significance of differences in demographic factors, clinical parameters, and toxicity between HIV-positive and negative patients was evaluated by means of t-tests for continuous variables and chi-squared tests for categorical variables. Multivariable logistic regression models were developed to evaluate the association of HIV status with adverse outcomes controlling for confounding variables. Data were analysed using SPSS (version 18.0; SPSS, Inc., Chicago, Ill).

Study 2:

Place of research: Tygerberg Hospital, Radiation Oncology Division

Study design: Cohort study

Selection of participants: 213 consecutive cervical carcinoma patients treated with primary radiotherapy with radical intent from November 2009 through December 2011 with completed toxicity data. Treatment protocol as per Study 1.

Exclusion criteria: Patients who were treated only with palliative intent or who previously received surgery for cervical carcinoma

Methodology: Retrospective patient record analysis

Statistical analysis: The statistical significance of differences in demographic factors, clinical parameters, and toxicity between HIV-positive and negative patients was evaluated by means of t-tests for continuous variables and chi-squared tests for categorical variables. Multivariable logistic regression models were developed to analyse the association of HIV status with risk of developing a grade 3-4 toxicity, controlling for

confounding variables. Data were analysed using SPSS (version 21.0; SPSS, Inc, Chicago, IL).

Study 3:

Place of research: Tygerberg Hospital, Radiation Oncology Division

Study design: Cohort study

Selection of participants: 492 consecutive patients treated for cervical carcinoma with primary radiotherapy with radical intent from July 2007 through December 2011. Treatment protocol as per Study 1. Active cohort on clinical follow-up.

Exclusion criteria: Patients who were treated only with palliative intent or who previously received surgery for cervical carcinoma

Methodology:

Patient record analysis of active cohort on clinical follow-up. Record demographic and disease characteristics. Define treatment parameters. Document overall survival at 5 years; the starting point is defined as first day of treatment.

Survival data were acquired from patient records; patients lost to follow-up were tracked and traced by means of national person linkage database.

Data analysis: statistical significance of differences in demographic factors, clinical parameters, and toxicity between HIV-positive and -negative patients was evaluated by means of t-tests for continuous variables and chi-squared tests for categorical variables. The Kaplan-Meier method was used to determine OS and to compare OS of HIV-positive and -negative patients. Cox proportional hazards regression models were developed to analyse the associations of HIV status with mortality, controlling for confounding variables.

Study 4:

Place of research: Tygerberg Hospital, Radiation Oncology Division and Nuclear Medicine Division

Study design: Cohort study

Selection of participants:

- Retrospective/Prospective: 278 consecutive HIV-positive and -negative patients diagnosed with locally advanced cervical carcinoma who underwent a staging PET-CT scan from January 2015 to end December 2018 (all patients referred in this time period by the principal investigator).

- *Exclusion criteria*: Scan not performed. Small cell and neuroendocrine carcinomas.

Retrospective methodology:

Original data were extracted from patients' folders

Reports and images were retrieved from the Nuclear Medicine Hermes database.

Prospective methodology: Patients were identified and consented in the combined gynaecology oncology clinic and referred as per routine clinical practice. Patients found to have equivocal or ill-defined lesions on the PET-CT were referred for the appropriate investigations, including biopsy, to determine the nature of the lesion if technically possible.

PET-CT protocol – all patients with inoperable cervical carcinoma who were fit for primary radiotherapy. HIV-positive patients who are immunocompetent with a CD4>150. All HIV-positive patients were included irrespective of ARV therapy; viral load was measured. All patients diagnosed with HIV were informed and referred routinely to infectious diseases. PET-CT was performed as part of routine staging. PET-CT imaging was performed on an outpatient basis. The imaging protocol included a whole-body low dose CT, acquisition of PET images and a contrast-enhanced pelvic planning scan.

Data capture and analysis (retrospective and prospective): Descriptive statistics for demographic and staging factors. Determination of the percentage of HIV-infected and -uninfected patients upstaged and management changed, by the PET-CT findings relative to conventional imaging. Determination of the percentage of equivocal or unrelated clinical findings. Statistical significance of differences in demographic factors, clinical parameters, and imaging findings between HIV-positive and -negative patients was evaluated by means of t-tests for continuous variables and chi-squared tests for categorical variables.

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Chapter 2

Published manuscript: Completion of and Early Response to Chemoradiation Among Human Immunodeficiency Virus (HIV)-Positive and HIV-Negative Patients With Locally Advanced Cervical Carcinoma in South Africa

Chapter 3

Published manuscript: HIV Status and Acute Hematologic Toxicity Among Patients With Cervix Cancer Undergoing Radical Chemoradiation

Chapter 4

Published manuscript: Five-year overall survival following chemoradiation among HIV-positive and HIV-negative patients with locally advanced cervical carcinoma in a South African cohort

Chapter 5

Accepted manuscript: HIV status does not impact PET-CT findings or radiotherapy treatment recommendation in patients with locally advanced cervical cancer

Original Article

Completion of and Early Response to Chemoradiation Among Human Immunodeficiency Virus (HIV)-Positive and HIV-Negative Patients With Locally Advanced Cervical Carcinoma in South Africa

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BACKGROUND: Very few published studies have dealt with the management of locally advanced cervix carcinoma among human immunodeficiency virus (HIV)-positive patients. The objective of this study was to compare the clinical characteristics, radiation and chemotherapy treatments, and outcomes in a cohort of HIV-positive and HIV-negative women with cervical cancer. **METHODS:** The authors reviewed the charts of 59 HIV-positive patients and 324 HIV-negative patients who had stage IB1 to IIIB cervical carcinoma and who received radiation therapy. Demographic and clinical characteristics were compared at the time of diagnosis; and radiation doses, chemotherapy cycles, and responses were compared at the time of brachytherapy and at 6-week follow-up. Logistic regression models of response to treatment were developed. **RESULTS:** Forty-nine HIV-positive patients (88.1%) but only 213 HIV-negative patients (65.7%) presented with stage IIIB disease ($P = .009$). Forty-seven HIV-positive patients (79.7%) and 291 HIV-negative patients (89.8%) completed the equivalent dose of 68 Grays (Gy) external-beam radiation and high-dose-rate brachytherapy. ($P = .03$). Of the 333 patients who commenced concurrent chemotherapy, 26 HIV-positive patients (53.1%) and 212 HIV-negative patients (74.6%) completed ≥ 4 weekly cycles of platinum-based treatment. Follow-up was censured at 6 weeks. In models that included age, disease stage, HIV status, and treatment, a poor response at 6 weeks was associated only with stage IIIB disease (odds ratio, 2.39; 95% confidence interval, 1.45-3.96) and receiving an equivalent radiation dose in 2-Gy fractions of <68 Gy (OR, 3.14; 95% CI, 1.24-7.94). **CONCLUSIONS:** HIV-positive patients fared worse than HIV-negative patients because of later presentation and a decreased likelihood of completing treatment. The current findings emphasize the importance of completing irradiation therapy. Further studies will address the association of these variables with survival. *Cancer* 2012;118:2971-9. © *2011 American Cancer Society.*

KEYWORDS: cervical cancer, human immunodeficiency virus-positive, acquired immunodeficiency syndrome-defining malignancy, radiation, chemoradiation.

INTRODUCTION

Cervical cancer is the second most common cancer in women worldwide and the most common malignancy in young women in sub-Saharan Africa. In South Africa, women have a 4% lifetime risk of developing the disease.[1] One in 6 women of reproductive age in the Western Cape in South Africa is living with human immunodeficiency virus (HIV).[2] HIV-positive patients have a greater persistence of the human papillomavirus (HPV), a greater likelihood of developing

high-grade cervical intraepithelial neoplasia, and ultimately a more rapid progression to invasive cervical carcinoma than women without HIV.[3] Highly effective antiretroviral therapy (HAART) prolongs survival among women with HIV but does not appear to prevent them from developing cervical carcinoma; therefore, the increasing availability of HAART, paradoxically, is likely to lead to a rise in the incidence of cervical carcinoma.[4]

Most women with cervical carcinoma in South Africa present at an advanced stage, precluding the use of surgery. In 1999, several studies reported that chemoradiation was superior to radiation alone (the prior standard of care for women with locally advanced cervical carcinoma).[5-8] A meta-analysis confirmed that the combination of chemotherapy and radiation therapy was associated with improved survival for patients with stage IB2 through IVA cervical cancer.[9] Chemoradiation is now the standard of care, where resource constraints allow, in South Africa.

However, to our knowledge, no published studies have focused on the management of HIV-positive patients who receive chemoradiation for locally advanced cervical carcinoma. The randomized trials of chemoradiation reported to date have excluded women with HIV. Randomized studies currently under way are intended to address this question. The potential risks of treating HIV-positive patients with chemoradiation include the additional risk of infectious morbidity because of immunosuppression and drug interactions between HAART and chemotherapy, including gastrointestinal (GIT) toxicities and severe skin reactions.

Although data regarding the tolerance of chemoradiation are lacking for HIV-positive women with cervical cancer, chemotherapy has now been incorporated into their treatment. The objective of our current study was to compare the clinical characteristics, treatments, and outcomes of HIV-positive and HIV-negative women with advanced cervical cancer.

MATERIALS AND METHODS

Tygerberg Hospital is a state-funded public hospital in the Western Cape of South Africa. It provides state oncology services to patients from the remote and rural areas of the province, urban Cape Town, and the suburban area close to the hospital. Most patients who attend the hospital have little education, limited incomes, difficulties accessing care, and comorbidities. The hospital's oncology resources for patients with cervical carcinoma are compa-

rable to those of many tertiary care facilities in Europe and the United States; they include a full Surgical Gynecologic Oncology Unit, access to chemotherapy, and modern radiation machines with computed tomography planning and conformal techniques. Since 2007, HAART has been widely available in the province, and HIV-positive patients have access to medication and expertise from the Infectious Diseases Department.

Patient Records

We performed a retrospective study of all women diagnosed with invasive cervical cancer between June 2007 and December 2010. Patients included in the study were those who were diagnosed with histologically confirmed cervical cancer (International Federation of Gynecology and Obstetrics [FIGO] stage IB1 to IIIB) and were treated with curative intent. Patients with early stage disease who underwent primary surgery were excluded. Approval for the study was obtained from the Stellenbosch University ethics committee.

Patients were stratified into 2 cohorts based on HIV status: HIV-positive and HIV-negative. Clinical and demographic characteristics were extracted from institutional databases. Among HIV-positive patients, prior receipt of HAART and CD4 cell counts at the start of treatment were documented. Disease characteristics included tumor histology, evidence of hydronephrosis, lymph node involvement (detected by abdominal ultrasound or computed tomography studies), disease stage, and chemoradiation treatment regimen. Treatment variables included external-beam radiation therapy (EBRT) dose and fractionation, the number of chemotherapy cycles, high-dose-rate brachytherapy (HDR) or external-beam boost dose and fractionation, and overall treatment time for those who completed prescribed EBRT and HDR radiation. The total dose of EBRT and HDR radiation received was calculated by using equations for the equivalent dose in 2-gray (Gy) fractions (EQD_2).[10] Reasons for incomplete radiation and/or chemotherapy were noted when available. Response data were collected at time of examination under anesthetic (EUA) for brachytherapy planning and on clinical examination at 6-week follow-up in the clinic.

Treatment

The standard treatment protocol at our institution for patients with locally advanced stage IB2 to IIIB cervical carcinoma is 46 to 50 Gy in 23 to 25 fractions of EBRT delivered to the pelvis with concurrent weekly cisplatin

chemotherapy at a dose of 40 mg/m^2 for 4 to 6 cycles and HDR brachytherapy at 20 to 26 Gy in 4 to 5 fractions starting in week 5 of EBRT.[11] The cervix, uterus, parametrium, and pelvic lymph nodes up to and including the common iliacs are delineated on a planning computed tomography scan following the guidelines of Taylor et al.[12] The para-aortic lymph nodes (PAN) are delineated up to the renal hilum if the common iliacs or lower PANs are involved on imaging. This volume is then conformally planned on the XiO Radiation Treatment Planning System (Computerized Medical Systems, Inc., Maryland Heights, Mo). The department protocol is EBRT at 2 Gy per fraction 5 days a week or, alternatively, at 1.8 Gy per fraction if the patient has a history of abdominal surgery, is HIV-positive, or has a PAN field. The PAN field receives 45 Gy, and the pelvic field receives 50.4 Gy. Patients who have a poor performance status or very advanced local disease with bilateral hydronephrosis or renal compromise are prescribed 40.05 Gy in 15 fractions at 2.67 Gy per fraction. Treatment is delivered on an 18-megavolt linear accelerator with multileaf shielding capabilities. During or after the fifth week of EBRT, each patient is EUA, and her response is categorized as either complete or partial. A smit sleeve is then placed in the cervical os, and HDR brachytherapy is planned with a standard plan, straight source to a total dose of 20 to 26 Gy in 4 to 5 fractions.[13] The dose is delivered on a Varian GammaMed machine (Varian Medical Systems, Palo Alto, Calif). Overall treatment time recommended is 55 days or less as per the American Brachytherapy Society.[11]

Chemotherapy is prescribed based on an evaluation of renal function before treatment. The creatinine clearance/glomerular filtration rate (cGFR) is calculated using the Cockroft-Gault formula or, when available, an ethylene diamine tetracetic acid (EDTA)-GFR. If the cGFR or the EDTA-GFR is ≥60 mL/minute, then weekly cisplatin 40 mg/m^2 for a minimum of 4 cycles is prescribed; if the rate is 50 to 60 mL/minute, then the dose is reduced by 25% per cycle; and, if the rate is <50 mL/minute, then cisplatin is not given. If the GFR is 30 to 50 mL/minute, then carboplatin is given weekly by calculating a dose based on the area under the curve equals 2 as an alternative. The regimen consists of prechemotherapy antiemetics, cisplatin diluted in 250 mL normal saline given over 15 minutes, followed by 1000 mL of normal saline over 2 hours, and 20 mg of oral furosemide. In 2009, an additional 1000 mL prehydration was added to the regimen. Chemotherapy is delayed if the neutrophil count falls below 1000/μL if the platelet count falls below 75,000/

μL, or if the patient develops grade 3 GIT toxicity. Chemotherapy is discontinued if the cGFR falls below 50mL/minute or decreases by >50%, if the neutrophil or platelet count does not recover, or if the patient develops persistent grade 3 GIT toxicity. Patients on hypofractionated radiation schedules and patients who have serious medical comorbidities (eg, active tuberculosis) do not receive chemotherapy.

At the time of diagnosis, patients who have never been tested for HIV or who have not been tested recently are referred for testing and counseling. HIV-positive patients are referred expeditiously for infectious disease consultation so that they can begin prophylaxis with cotrimoxazole, and those not already receiving it can commence antiretroviral therapy. Before April 2010, the standard HAART protocol included stavudine, lamivudine, and efavirenz. Thereafter, tenofovir was substituted for stavudine at the discretion of the infectious disease specialist.

HIV-positive patients receive the same treatment for their cervical cancer as HIV-negative patients, but the dose per fraction is reduced to 1.8 Gy; and, if the CD4 count is <200 cells/μL, then chemotherapy is omitted. Patients whose CD4 count is <150 cells/μL may not tolerate a long course of radiation; some are treated on a shortened regimen dependent on performance status.

Statistics

The outcome variables were total dose of EBRT (≥45 Gy vs <45 Gy), total dose of HDR (≥18 Gy vs <18 Gy), total radiation dose expressed as EQD$_2$ (≥68 Gy vs <68 Gy; equivalent to 45 Gy in 25 fractions EBRT and 18 Gy in 3 fractions HDR), total overall treatment time (≤55 days vs >55 days), the number of cycles of chemotherapy (≥4 cycles vs <4 cycles), and clinical response (complete vs partial) at EUA during or after the fifth week of chemoradiation and 6 weeks post-treatment. We compared the demographic and clinical characteristics of HIV-positive and HIV-negative patients using t tests for normally distributed continuous variables and chi-square tests for categorical variables. Then, we developed multivariable logistic regression models to analyze the risk of adverse outcomes, controlling for HIV status, age, disease stage, and completion of treatment. Results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). All tests were 2-sided, and P values < .05 were considered statistically significant. We used the SPSS Statistics software program (version 18.0; SPSS, Inc., Chicago, Ill).

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RESULTS

Patient Characteristics

In total, 461 patients with stage IB1 to IIIB cervical carcinoma who met inclusion criteria were identified. Twenty-four patients were lost to follow-up or declined treatment. An additional 41 patients (9.7%) received palliative EBRT alone at doses ranging from 8 Gy to 40.05 Gy
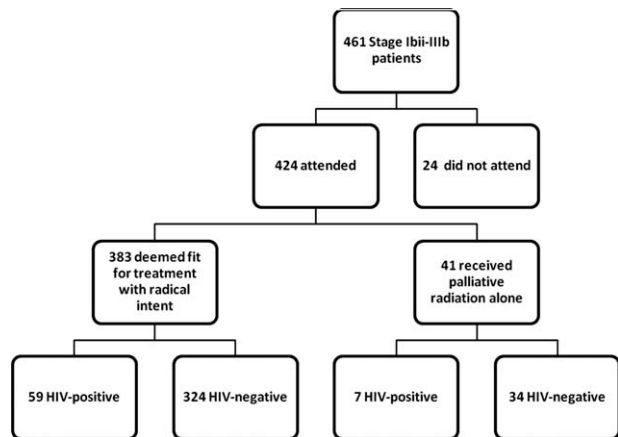

Figure 1. This is a flow chart of the study population. HIV indicates human immunodeficiency virus.

because of either poor performance status or comorbidities. These patients also were excluded from the analysis.

In all, 383 patients initiated curative-intent treatment and were included in the analysis (Fig. 1). These included 59 HIV-positive patients (15.4%), 19 (32.2%) of whom who were receiving HAART at the time of their initial evaluation. The median CD4 count of the HIV-positive patients was 354 cells/µL (range, 33-1249 cells/µL), and 88.1% of all HIV-positive patients had a CD4 count >200 cells/µL. The HIV-positive patients were younger than the HIV-negative patients (median age, 41 years vs 50 years; $P < .001$).

In total, 49 HIV-positive patients (88.1%) but only 213 of 324 HIV-negative patients (65.7%) presented with stage IIIB disease ($P = .009$). HIV status was not associated with histologic subtype (>90% of both HIV-positive and HIV-negative patients had squamous cell carcinoma), hydronephrosis, or lymph node disease (Table 1).

Treatment

Radical radiotherapy

In total, 291 HIV-negative patients (89.8%) and 47 HIV-positive patients (79.7%) received radiation doses

Table 1. Demographic and Clinical Characteristics According to Human Immunodeficiency Virus Status

			HIV Status				
	Positive		Negative		Total		
Characteristic	No.	%	No.	%	No.	%	P
Entire cohort	59	15.4	324	84.6	383	100	
Median age, y	41		50				<.001[a]
Age group, y							<.001[a]
<40	27	45.8	55	17	82	21.4	
40-49	20	33.9	100	30.9	120	31.3	
50-59	11	18.6	105	32.4	116	30.3	
≥60	1	1.7	64	19.8	65	17	
Histology							.57
Squamous	56	94.9	300	92.6	356	93	
Adenocarcinoma	1	1.7	15	4.6	16	4.2	
Other	2	3.4	9	2.8	11	2.9	
FIGO stage							.009[a]
IB1	0	0	3	0.9	3	0.8	
IB2	0	0	3	0.9	3	0.8	
IIA	0	0	4	1.2	4	1	
IIB	10	16.9	99	30.6	109	28.5	
IIIA	0	0	2	0.6	2	0.5	
IIIB	49	83.1	213	65.7	262	68.4	
Hydronephrosis (IIIB only)	9	15.3	31	9.6	40	10.4	.51
Lymph nodes present	15	25.4	61	18.8	76	19.8	.28
Para-aortic/common iliac lymph nodes	4	6.8	23	7.1	27	7	1.0

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; HIV, human immunodeficiency virus; SD, standard deviation.
[a] Significant ($P < .05$).

Table 2. Completion of Radiotherapy According to Human Immunodeficiency Virus Status

| | HIV Status | | | | | | |
| Radiotherapy Variable | Positive | | Negative | | Total | | P |
	No.	%	No.	%	No.	%	
Entire cohort	59	15.4	324	84.6	383	100	
EBRT dose: Mean±SD, Gy	47.7±4.6		49.1±6.7				.05[a]
≥45 Gy EBRT	50	84.7	309	95.4	359	93.7	.05[a]
≥18 Gy HDR	47	79.7	293	90.4	340	88.8	.051
≥45 Gy EBRT plus 18 Gy HDR	45	76.3	284	87.7	329	85.9	.026[a]
≥68 Gy EQD$_2$	47	79.7	291	89.8	338	88.3	.026[a]
EQD$_2$ dose: Mean±SD, Gy	72.4±13.7		75.1±10.9				.094
Overall treatment time: Mean±SD, d[b]	44±3.60		40±3.83				<.01[a]
Reasons for incomplete EBRT <45Gy							
Entire cohort	9	37.5	15	62.5	24	100	
Patient refused to complete	2	25	3	21.4	5	22.7	
Developed metastatic disease	2	25	—	—	2	9.1	
Infection	2	25	—	—	2	9.1	
Renal failure	1	12.5	2	14.3	3	13.6	
Poor attendance	—	—	2	14.3	2	9.1	
Persistent neutropenia	—	—	1	7.1	1	4.5	
GI toxicity grade3/4	—	—	2	14.3	2	9.1	
Hypofractionated RT	2	12.5	5	28.6	7	22.7	

Abbreviations: EBRT, external-beam radiotherapy; EQD$_2$, equivalent dose in 2-Gy fractions; GI, gastrointestinal; Gy, grays; HDR, high-dose-rate brachytherapy; HIV, human immunodeficiency virus; RT, radiotherapy; SD, standard deviation
[a] Significant ($P < .05$).
[b] For those who completed treatment with ≥45 Gy EBRT plus 18 Gy HDR.

≥68 Gy EQD$_2$ ($P = .03$). Table 2 provides details of the radiation received. Of note, 6 of 7 patients who had CD4 counts <200 cells/μL completed ≥68 Gy EQD$_2$. Of 27 patients who received extended-field radiotherapy, 25 completed 45 Gy. The 2 patients who did not complete the intended PAN treatment were HIV positive. Two HIV-negative patients had data missing on treatment time. The overall treatment time for those who completed both the EBRT component and the HDR component was ≤55 days for all HIV-positive patients, and only 1 patient in the HIV-negative group was treated for >55 days. The mean overall treatment time for HIV-positive patients was 44 days compared with 41 days in the HIV-negative group ($P < .01$) (Table 2). Reasons for incomplete EBRT (<45 Gy) included hypofractionated regimens, poor attendance, refusal to complete, renal failure, neutropenia, grade 3 GIT toxicities, and development of metastatic disease (Table 2).

Concurrent chemotherapy

Of 284 HIV-negative patients who began platinum-based chemotherapy, 212 (74.6%) completed ≥4 cycles. Of the 49 HIV-positive patients who commenced chemotherapy, only 26 (53.1%) completed ≥4 cycles of platinum-based chemotherapy ($P = .01$) (Table 3). Eight of 19 patients who were receiving HAART (42.1%) and 18

of 40 patients who were not receiving HAART (45%) managed to complete adequate chemotherapy. Those who completed chemotherapy had higher median CD4 counts than those who did not (416 cells/μL vs 311 cells/μL; $P = .02$).

Fifty patients (40 HIV-negative patients and 10 HIV-positive patients) received no chemotherapy because of poor renal function, poor performance status, a CD4 count <200 cells/μL, active pulmonary tuberculosis, or hypofractionated radiotherapy. Renal dysfunction was the most common reason why chemotherapy was not completed. Other contributing factors were poor compliance, incomplete EBRT, discovery of active pulmonary tuberculosis, discovery of a positive HIV test and subsequent low CD4 count, hematologic toxicity, persistent grade 3 GIT toxicity, and, in 1 patient, a diagnosis of small cell carcinoma (that patient received a different regimen) (see Table 4).

Completion of ≥45 Gy external-beam radiotherapy/≥18 Gy high-dose-rate brachytherapy/4 cycles of chemotherapy

Among the 49 HIV-positive patients and 284 HIV-negative patients who initiated curative-intent chemoradiation, 22 HIV-positive patients (44.9%) and 199 HIV-

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Table 3. Completion of Chemotherapy According to Human Immunodeficiency Virus Status

Chemotherapy Variable	Positive No.	Positive %	Negative No.	Negative %	Total No.	Total %	P
Entire cohort	59		324		383	100	
Commenced chemotherapy	49	83	284	87.3	333	86.9	
Received ≥4 cycles cisplatin or carboplatin	26	53.1	212	74.6	238	71.5	.002[a]
Received ≥4 cycles of cisplatin	23	46.9	191	67.2	214	57.3)	
No. of cycles							
0	10	16.9	40	12.7	50	13.1	
1	6	10.2	15	4.6	21	5.5	
2	11	18.6	26	8.3	37	9.7	
3	6	10.2	31	9.6	37	9.7	
Received ≥4 cycles of chemotherapy with 45 Gy EBRT plus 18 Gy HDR	22	44.9	199	70.9	221	66.4	.001[a]
Reasons for incomplete platinum-based chemotherapy							
Entire cohort	23		72[b]		95	100	
Renal dysfunction	15	65.2	54	75	69	72.6	
Incomplete EBRT	3	13	5	6.9	8	8.4	
Active PTB[c]	1	4.3	—	—	1	1.1	
CD4 count <200 cells/μL[d]	1	4.3	—	—	1	1.1	
Poor compliance	—	—	2	2.8	2	2.1	
Hematologic toxicity	2	8.7	4	5.5	6	6.3	
Gastrointestinal toxicity	—	—	4	5.5	4	4.2	
Alternate chemotherapy (small cell)	—	—	1	1.4	1	1.1	
Infection	1	4.3	2	2.8	3	3.2	

Abbreviations: EBRT, external-beam radiotherapy; Gy, grays; HDR, high-dose-rate brachytherapy; HIV, human immunodeficiency virus; PTB, pulmonary tuberculosis.
[a] Significant ($P < .05$).
[b] Complete data were available on 72 of 73 HIV-negative patients.
[c] PTB was diagnosed after treatment commenced.
[d] HIV status was established only after treatment commenced.

negative patients (70.4%) completed treatment ($P = .001$) (Table 3).

Response to Treatment
At the time of EUA and at the 6-week follow-up visit, the numbers of patients available for evaluation were reduced because of incomplete treatment, loss to follow-up, referral back to distant medical centers, and death. Of the 383 patients analyzed, 370 patients (309 HIV-negative patients and 51 HIV-positive patients) had EUA before the initiation of brachytherapy; 108 HIV-negative patients (35%) but only 10 HIV-positive patients (19.6%) had a complete response ($P = .008$) (Table 4).

At 6 weeks, only 326 patients (279 HIV-negative patients and 47 HIV-positive patients) presented for follow-up. Of those, 160 HIV-negative patients (57.3%) but only 18 HIV-positive patients (38.3%) had a documented complete response ($P = .02$) (Table 4). In logistic regression models that were adjusted for age, HIV status, disease stage, and completion of treatment, the factors associated with an incomplete response were stage IIIB disease (OR,

2.39; 95% CI, 1.45-3.96) and receiving <68 Gy EQD_2 (OR, 3.14; 95% CI, 1.24-7.94). Table 5 provides the details of each component of treatment. The CD4 count was not included in the model, because 52 of 59 HIV-positive patients had CD4 counts >200 cells/μL.

DISCUSSION
Among the women with cervical cancer in our study, those who were HIV-positive presented at a younger age and with more advanced stage disease than their HIV-negative counterparts. Most patients were able to complete adequate EBRT and HDR brachytherapy; however, although the HIV-positive patients received less radiation and substantially less chemotherapy than the HIV-negative patients, disease stage and completing radiation were the only independent predictors of response. In particular, the completion of brachytherapy was a vital component of treatment.

The demographic and clinical differences we observed between HIV-positive patients and HIV-

Table 4. Response at Examination Under Anesthesia and at 6 Weeks According to Human Immunodeficiency Status

| | HIV Status | | | | | | |
| | Positive | | Negative | | Total | | |
Response	No.	%	No.	%	No.	%	P
Entire cohort	59		324		383	100	
Underwent EUA	51	86.4	309	95.4	360	94	
Complete response at EUA	10	19.6	108	35	118	32.8	.036[a]
Attendance at 6 wk	47	79.7	279	86.1	326	85.1	
Complete response at 6 wk	18	38.3	160	57.3	178	54.6	.018[a]

Abbreviations: EUA, examination under anesthesia; HIV, human immunodeficiency virus.
[a] Significant ($P < .05$).

Table 5. Factors Associated With Partial Response Versus Complete Response at Six Weeks

Variable	OR	95% CI	P
HIV status			
Negative	1.00	Referent	
Positive	1.71	0.85-3.36	.135
FIGO stage			
IB1-IIIA	1.00	Referent	
IIIB	2.41	1.45-4.00[a]	.001[a]
Age group, y			
<40	1.00	Referent	
40-49	0.87	0.44-1.69	.67
50-59	0.68	0.35-1.33	.26
≥60	0.51	0.22-1.17	.11
Completion of EBRT, Gy			
≥45	1.00	Referent	
<45	1.18	0.36-3.89	.78
Completion of HDR, Gy			
≥18	1.00	Referent	
<18	3.13	1.28-7.61	.012[a]
Completion of chemotherapy			
≥4 Cycles	1.00	Referent	
<4 Cycles	0.62	0.36-1.06	.08

Abbreviations: CI, confidence interval, EBRT, external-beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; Gy, grays; HDR, high-dose-rate brachytherapy; HIV, human immunodeficiency virus; OR, odds ratio.
[a] Significant ($P < .05$).

negative patients with cervical carcinoma (eg, younger age and more advanced disease at presentation) have been reported previously.[14] Few of our HIV-positive patients knew their HIV status before their cancer diagnosis, and few had commenced HAART before their first oncology visit. Because the median CD4 count among the HIV-positive patients was 354 cells/μL, and the majority had counts >200 cells/μL, immunocompetence did not appear to reduce the risk of cervical carcinoma as it does

the risks of Kaposi sarcoma and non-Hodgkin lymphoma.[15]

Our findings are similar to those reported from studies of tolerance for chemoradiation among HIV-positive patients with anal cancer.[16,17] Oehler-Janne et al reported that significantly fewer HIV-positive patients (30%) than HIV-negative patients (64.2%) received the prescribed chemotherapy. Hammad et al also observed that 89% of HIV-negative patients but only 45% of HIV-positive patients completed chemotherapy at the planned dose. What is clear is that the chemotherapy component is the most difficult aspect of chemoradiation therapy for HIV-positive patients to complete. In our study, we noted that patients who failed to complete chemotherapy had lower median CD4 counts than those who completed chemotherapy. We were surprised to note that renal dysfunction, and not myelosuppression or GIT toxicity, was the most common reason for HIV-positive patients to discontinue therapy. We simply may have a conservative and cautious approach to chemotherapy in choosing 50 mL/minute as the cutoff GFR for giving cisplatin. If cisplatin is commenced and renal function deteriorates, then we do attempt to reduce the dose to either 25% or 50% of the planned dose in an attempt to continue with weekly dosing. Some institutions use a lower standard dose of cisplatin up front, but the benefit of this approach has yet to be confirmed in prospective efficacy studies.[18]

The benefit of chemotherapy in patients with stage IIIB cervical cancer also is less than clear. The most recent meta-analysis of treatment for cervical cancer noted that, among patients with stage IIIB disease, the incremental benefit of chemoradiation over radiation alone was only 3%.[9] The numbers of patients with stage IIIB disease in those studies were small, however; and further studies of such patients are awaited. In our cohort, completion of

chemoradiation had no greater impact on response at 6 weeks than radiation alone. Because most of our HIV-positive and HIV-negative patients had stage IIIB disease, it may be reasonable to omit chemotherapy; doing so may enable us to deliver a full dose of radiation in a timely manner.

The few studies of treatment and outcomes for HIV-positive patients receiving radiotherapy for cervical carcinoma have reported variable results. Shrivastava et al described a cohort of 42 HIV-positive patients who received treatment at the Tata Memorial Hospital in India.[19] In that study, only 22 patients completed EBRT, and only 50% had a complete response at 6 weeks. Moodley and Mould from KwaZulu/Natal, South Africa, reported that only 53% of HIV-positive patients were able to complete treatment (including surgery or radiotherapy),[20] in part because of resource constraints in the region. Gichangi et al in Nairobi, Kenya, observed that HIV-positive patients did not differ from HIV-negative patients in dose received but had significantly poorer outcomes at 4 months and 7 months.[21] In their final analysis, 9 of 24 patients had residual disease at follow-up (adjusted risk ratio, 6.2; 95% CI 1.4-28.1). In our data, HIV-positive patients had worse responses than HIV-negative patients; however, in logistic regression models that adjusted for age, HIV status, disease stage, and completion of treatment, the only significant factors were advanced stage and completion of radiation. The model conveyed that the HIV-positive patients had poorer responses only because they were more likely to present with advanced disease and less likely to complete treatment than the HIV-negative patients.

Although our study is 1 of the largest to compare cervical cancer outcomes among HIV-positive and HIV-negative women, it has several important limitations. It included all women with HIV from a region where the disease is endemic; however, its HIV-positive sample consisted of only 59 women. Therefore, the study may have been underpowered to detect differences in some characteristics and outcomes. Another limitation is that the data were collected retrospectively from the medical charts. However, all patients were treated according to the same treatment principles and guidelines.

Currently, we are conducting further analyses of treatment-associated toxicity and temporal trends in toxicity in our cohort. In addition, the goal of the current study was to report on completion of and short-term response to treatment. Data on overall survival are maturing and will be reported in future publications.

In conclusion, despite the small numbers, our findings suggest that good medical care of HIV-positive patients can enable patients to complete treatment for locally advanced cervical cancer. The current results also highlight the importance of radiation therapy. Thus, as we await the publication of results from the randomized chemoradiation trials in progress among both patients with FIGO stage IIIB disease and patients with HIV, we will concentrate on enabling our patients to complete their radiation therapy.

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ORIGINAL STUDY

HIV Status and Acute Hematologic Toxicity Among Patients With Cervix Cancer Undergoing Radical Chemoradiation

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Introduction: Women infected with the human immunodeficiency virus (HIV) have a higher risk of developing cervix carcinoma than do other women who are thought to be more vulnerable to acute toxicities during chemoradiation. We compared HIV-positive/HIV-negative patients with cervix carcinoma at a single institution with respect to cancer treatment toxicities.

Methods and Materials: Among patients with stage Ib1-IIIb invasive cervical carcinoma who received radiation or chemoradiation with curative intent, we evaluated demographic and clinical characteristics of HIV-positive and HIV-negative patients. Treatment regimens were documented and toxicities scored as per Radiation Therapy Oncology Group guidelines. We developed logistic regression models for the associations of grade 3/4 toxicities with HIV status.

Results: Complete data were available on 213 patients, including 36 (16.8%) who were HIV positive. More than 85% of both HIV-positive and HIV-negative patients received a minimum of 68-Gy equivalent dose in 2-Gy-fraction external beam and high-dose-rate brachytherapy. More HIV-positive than HIV-negative patients were prescribed radiation alone (38.9% vs 24.29%, $P = 0.01$), experienced at least 1 grade 3/4 toxicity (38.9% vs 26.6%), or developed grade 3/4 leucopenia (30.6% vs 10.2%, $P = 0.003$).

In a multivariable model, patients who developed a grade 3/4 toxicity were 4 times as likely to have received chemotherapy (odds ratio, 4.41 [95% confidence interval, 1.76–11.1]; $P = 0.023$) and twice as likely to be HIV positive (odds ratio 2.16 [95% confidence interval, 0.98–4.8]; $P = 0.05$) as women who did not experience such toxicities.

Conclusions: HIV-positive patients with cervical carcinoma received adequate radiotherapy but were less likely than HIV-negative patients to complete chemotherapy. Few HIV-positive or HIV-negative patients who received radiotherapy *without chemotherapy* experienced grade 3/4 toxicity. However, among patients who received chemotherapy, those who were HIV positive were more likely than others to experience hematologic toxicity.

Key Words: Cervical cancer, Human immunodeficiency virus, AIDS-defining malignancy, Radiation, Chemoradiation, Toxicity

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1

Cervical carcinoma remains one of the leading causes of cancer and cancer mortality among women in the developing world, including women infected concurrently with human papillomavirus (HPV) and human immunodeficiency virus (HIV).[1] Most research on the co-occurrence of the 2 conditions has focused on incidence. Recent studies suggest that by prolonging the life expectancy of HIV-positive women, antiretroviral therapy (ART) may have actually contributed to rising incidence rates of cervix carcinoma.[2]

Treating patients with the 2 conditions challenges the oncology and infectious disease teams. Treatment involves balancing oncological therapy, concomitant ART, and antimicrobials, and trying to cure the underlying malignancy, to control HIV-related opportunistic infections, and to minimize treatment toxicities. However, very little research has dealt with the effects of HIV status on cervix carcinoma treatment and its outcomes. In a previous study of patients with cervix cancer treated between 2007 and 2010, we found that 79.7% of HIV-positive patients and 89.8% of HIV-negative patients received adequate radiation and that 44.9% of HIV-positive patients vs 70.9% of HIV-negative patients completed both radiation and 4 or more cycles of platinum-based chemotherapy.[3] Poor response at 6 weeks was found to be related to stage IIIb disease and inadequate radiation. The aim of the current study was to compare treatment toxicities in another cohort (overlapping the first) of HIV-positive and HIV-negative patients whose treatment toxicity data were collected prospectively.

METHODS AND MATERIALS

Patient Records

For this prospective cohort study, we reviewed the charts of all patients diagnosed as having stage Ib1 to IIIb invasive cervical carcinoma who were categorized as HIV positive or HIV negative, received radiation or chemoradiation with curative intent, and had complete toxicity data between November 2009 and December 2011 at the Division of Radiation Oncology, Tygerberg Hospital. Patients who underwent primary surgery were excluded. Ethical approval was obtained from the University of Stellenbosch human ethics committee.

In late 2009, our oncology clinic consultant introduced clinic residents to the use of a modified Radiation Therapy Oncology Group toxicity score sheet that included hematologic, renal, gastrointestinal, urinary, skin, and weight parameters.[4] The team then began reviewing charts, recording demographic and clinical characteristics of the patients, and collecting toxicity data at the time of treatment. The consultant reviewed the completed sheets weekly. We determined whether or not the HIV-positive patients had commenced ART before treatment of cervix cancer and recorded their initial CD4 cell count. Treatment regimens, including external beam radiation therapy (EBRT) dose, high-dose-rate (HDR) brachytherapy dose, and chemotherapy cycles, were documented. The total doses of EBRT and HDR were calculated using equivalent dose in 2-Gy (EQD$_2$) fraction formulas.[5]

Treatment

The radiotherapy protocols used for the study participants have been previously reported.[3] Patients without contraindications received 46- to 50-Gy external beam radiation in 23 to 25 fractions, using conformal 3-dimensional planning and 18-MV energy, 4-field arrangement. This was followed by 20- to 25-Gy HDR intracavitary brachytherapy in 4 to 5 fractions. A straight intrauterine source and standard plans for the appropriate intracavitary length were used. At the time of the study, no image-guided brachytherapy was available. For patients who had a history of extensive abdominal surgery or were HIV positive, the daily dose per fraction was dropped to 1.8 Gy. The absolute minimum total dose considered adequate was 68-Gy EQD$_2$ (45-Gy external beam radiotherapy and 18 Gy in 3-fraction HDR brachytherapy).

If renal function was allowed, 40 mg/m^2 cisplatin was given weekly; if calculated glomerular filtration rate or ethylenediaminetetraacetic acid glomerular filtration rate was less than 50 mL/min, carboplatin area under the curve^2 weekly was given. No dose modifications were made for CD4 cell count unless it fell below 200, in which case chemotherapy was omitted. Because of pressure on the radiotherapy waiting list, in some cases of stage IIIB disease, chemotherapy was omitted and a hypofractionated regimen of 40.05 Gy in 15 fractions, or 42.72 Gy in 16 fractions, was used with standard HDR brachytherapy. The same fractionation was also used for patients with poor renal function or poor performance status.

At our institution, patients with locally advanced cervix carcinoma are routinely tested for HIV at first presentation. All HIV-positive patients are scheduled for HPV screening annually; thus, very few develop locally advanced disease. Almost all of the patients in this cohort were diagnosed as having HIV at the time of the cervix cancer diagnosis. Patients with cervix carcinoma who test positive start receiving ART either just before or as soon as possible after commencing radiation treatment. Antiretroviral therapy at the time of the study included triple therapy with lamivudine, efavirenz, and tenofivir, unless the creatinine clearance was low, in which case the patient received stavudine instead of tenofivir. Every HIV-positive patient commencing radiation or chemoradiation receives concurrent cotrimoxazole. Because HIV infection is a large burden for tertiary centers, many of our patients receive their HIV care at community health centers, and we were unable

to obtain data on viral load, compliance, medication changes, and ART toxicities for this study.

Statistics

The statistical significance of differences in demographic factors, clinical parameters, and toxicity between HIV-positive and HIV-negative patients was evaluated by means of t tests for continuous variables and χ^2 tests for categorical variables. Multivariable logistic regression models were developed to analyze the risk of developing a grade 3/4 toxicity controlling for HIV status, total dose of radiation, and prescription of chemotherapy. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). All tests were 2 sided, and P values of 0.05 or less were considered significant. Data were analyzed using the SPSS Statistics software program (version 21.0; SPSS, Inc, Chicago, IL)

RESULTS

Patient Characteristics

A total of 259 patients with cervical carcinoma stages IB to IIIB commenced radical radiotherapy during the study period; 46 patients had no toxicity data. Of the patients with no toxicity scores, 36 were HIV negative and all completed their prescribed radiotherapy; of the 10 patients who were HIV positive, 6 completed radiotherapy.

Complete toxicity data were available on 213 patients; 36 (16.8%) were HIV positive. The HIV-positive patients were younger than the HIV-negative patients but did not differ from them with respect to the prevalence of either squamous cell carcinoma or stage IIIB disease (see Table 1). The median CD4 cell count of the HIV-positive patients was 341 (range, 33–790); 30 patients had a CD4 greater than 200. Sixteen patients began ART before the commencement of radiotherapy. All others commenced ART either during or after radiotherapy.

Chemoradiation

More than 85% of both HIV-positive and HIV-negative patients received external beam and HDR brachytherapy, totaling more than 68-Gy EQD2. Significantly more HIV-positive than HIV-negative patients were prescribed radiation alone (38.9% vs 24.3%, $P = 0.01$; see Table 2). The reasons for not commencing chemotherapy in the HIV-positive group included active pulmonary tuberculosis (n = 2), a CD4 cell count less than 200 (n = 6), and prescription of a hypofractionated radiation regimen (n = 5). A similar proportion of the HIV-negative patients (n = 33) also received the hypofractionated radiotherapy regimen without chemotherapy.

Of the 22 (61.1%) HIV-positive patients who were prescribed chemoradiation, 15 (68.9%) completed 4 or more cycles of chemotherapy and received adequate radiotherapy (see Table 2). Of the 177 HIV-negative patients, 137 (75.7%) commenced chemoradiation and 129 (94.2%) completed it ($P = 0.05$).

Among *both* HIV-negative and HIV-positive patients, 62% who received 4 or more cycles of chemotherapy had a reduction in dose to either 30 or 20 mg/m^2 cisplatin because their creatinine clearance had fallen by 10% or below 50 mL/min. These criteria are strictly adhered to in the clinic to minimize risk of renal toxicity.

Toxicity

Fourteen HIV-positive patients (38.9%) and 47 HIV-negative patients (26.6%) had at least 1 grade 3–4 toxicity ($P = 0.16$; Table 3). Eleven HIV-positive patients (30.6%) but only 18 HIV-negative patients (10.2%) developed grade 3–4 leukopenia ($P = 0.003$). All patients whose white cell count dropped substantially had received chemotherapy.

Looking only at hematologic toxicity, the HIV-positive patients were also more likely to develop grade 2 anemia and neutropenia (Table 4). HIV status was not associated with increased gastrointestinal, renal, skin, or weight toxicities.

TABLE 1. Demographic and clinical characteristics of patients with cervix carcinoma, by HIV status

| Characteristic | HIV Status | | | P |
	Positive	Negative	Total	
No. of patients (%)	36 (16.9)	177 (83.1)	213 (100)	
Age, y				<0.001*
Median	41	50	49	
Range	26–62	23–79	23–79	
Histology, n (%)				0.27
Squamous	34 (94.4)	163 (91.6)	197 (92.1)	
Adenocarcinoma	1 (2.8)	5 (2.8)	6 (2.8)	
Other	1 (2.8)	9 (5.6)	10 (5.1)	
FIGO stage, n (%)				0.55
Ib1-IIIa	9 (25)	56 (31.6)	65 (30.5)	
IIIb	27 (75)	121 (68.4)	148 (69.5)	

*$P \leq 0.05$ considered significant.
FIGO, International Federation of Gynecology and Obstetrics.

TABLE 2. Completion of treatment by HIV status

| | HIV Status | | | | | | |
| | Positive | | Negative | | Total | | |
Treatment	n	%	n	%	n	%	*P*
No. of patients	36	16.9	177	83.1	213	100	
Completed >EQD2 68 Gy (all patients)	31	86.1	160	89.8	191	89.2	0.55
Prescribed EBRT alone	14	38.89	43	24.29	57	26.76	0.01*
Completed >EQD2 68 Gy	10	71.4	32	74.42	42	73.68	1.0
Prescribed chemoradiation	22	61.1	134	75.7	157		0.10
>EQD2 68 Gy + 4 cycles of weekly platinum	15	68.18	117	87.31	132		0.05*

*$P \le 0.05$.

Fifty-seven patients were prescribed radiation alone; they were prescribed either 1.8- or 2-Gy fractionated EBRT, or hypofractionated EBRT, and brachytherapy. Overall, only 8 (14.0%) of these patients had a recorded grade 3–4 toxicity compared with 54 patients of the 159 (34.0%) who received any chemotherapy ($P = 0.03$). Four HIV-negative patients had grade 3–4 anemia and 2 had grade 3–4 creatinine toxicity. Two HIV-positive patients had grade 3 anemia.

In a multivariable model that included HIV status, total dose of radiotherapy received, and prescription of chemotherapy, patients who developed a grade 3–4 toxicity were 4 times as likely to have received chemotherapy as patients without such a toxicity (OR, 4.41 [95% CI, 1.76–11.1]; $P = 0.002$). In the same model, patients who developed a grade 3–4 toxicity were twice as likely to be HIV positive as patients who did not

(OR, 2.16 [95% CI, 0.98–4.8]; $P = 0.057$). As expected, those who received less than 68-Gy EQD_2 showed a lower risk of toxicity, although this was not significant (Table 5).

DISCUSSION

Among 213 patients with cervical carcinoma in this study, HIV-positive patients generally received adequate radiotherapy but were less likely than HIV-negative patients to complete chemotherapy. These results are similar to those of our previously reported study.[2] Nearly 40% of HIV-positive patients in the current study either were not prescribed concurrent chemotherapy at the outset of treatment because of low CD4 counts or were prescribed a hypofractionated regimen. Very few HIV-positive or HIV-negative patients who

TABLE 3. Grade 3-4 toxicities by HIV status

| | HIV Status | | | | | | |
| | Positive | | Negative | | Total | | |
Toxicities	n	%	n	%	n	%	*P*
No. of patients	36	16.9	177	83.1	213	100	
Overall	14	38.9	47	26.6	61	28.6	0.157
Leucopenia	11	30.6	18	10.2	29	14.0	0.003*
Thrombocytopenia	1	2.8	0	0	1	0.5	0.169
Anemia	3	8.3	12	6.8	15	7.0	0.723
Neutropenia	3	8.3	7	4.0	10	4.7	0.378
Creatinine	0	0	4	2.3	4	1.9	1.0
Nausea	1	2.8	14	8.0	15	7.0	0.476
Vomiting	1	2.8	4	2.3	5	2.3	1.0
Diarrhea	1	2.8	5	2.8	6	2.8	1.0
Cystitis	0	0.0	1	0.6	1	0.5	1.0
Skin	1	2.8	2	1.1	3	1.4	1.0
Weight	0	0.0	0	0.0	0	0.0	1.0

*$P \le 0.05$ considered significant.

TABLE 4. Grade 2 hematologic toxicities by HIV status

	HIV Status						
	Positive		Negative		Total		
Toxicity	n	%	n	%	n	%	P
Leucopenia	10	27.7	47	26.6	57	26.8	0.839
Thrombocytopenia	2	5.5	3	1.7	5	2.35	0.199
Anemia	23	63.8	71	40.1	94	44.1	0.01*
Neutropenia	7	19.4	15	8.5	22	10.3	0.02*

*$P \leq 0.05$ considered significant.

received EBRT (whether hypofractionated or prescribed in conventional 1.8- or 2-Gy fractions) and HDR brachytherapy *without chemotherapy* experienced a grade 3–4 toxicity.

Unfortunately, in the developing countries where cervical cancer and HIV are common, many patients have no access to radiation therapy or have access only to low-energy machines, such as Co^{60}, which lack the skin-sparing benefits of the 18-MV treatment prescribed in this study. They also lack access to 3-dimensional conformal planning with computed tomography–based techniques, which allow beam shaping with multileaf collimators, thereby decreasing dose to normal tissues.

The literature regarding radiotherapy toxicity in HIV-positive patients with cervical carcinoma is very limited. Gichangi et al[6] found that more than 50% of both HIV-positive and HIV-negative patients in Kenya who received radiation therapy experienced grade 3–4 toxicity. However, those patients were treated with large parallel-opposed fields with low-energy Co^{60}. In a survey in Uganda, 12% of patients experienced skin, 7% gastrointestinal, and 3% genitourinary toxicity.[7] A study at Tata Memorial Medical Centre in India retrospectively examined radiotherapy toxicity among HIV-positive patients.[8] Of 32 patients who commenced radical EBRT, 22 completed treatment; grade 3–4 gastrointestinal toxicity occurred in 14% of patients and 27% had a grade 3–4 toxicity leading to treatment delays. These reports did not

include enough details about the patient population and the treatment to permit direct or full comparisons with our own cohort. Although those of our patients who received radiation alone had very few toxicities, the overall grade 3–4 toxicity rate approached 30%, and nearly 40% of HIV-positive patients who received chemoradiation experienced such toxicities, most of them hematologic. It should probably not be surprising that HIV-positive patients who receive chemotherapy on top of pelvic radiation develop leukopenia. An ongoing prospective randomized study sponsored by the International Atomic Energy Agency is currently comparing outcomes among HIV-positive patients with cervical cancer receiving either chemoradiation or radiation alone. If completed, this study would be the first randomized trial of the 2 treatment modalities in HIV-positive patients; however, it is uncertain if data collection will be completed (Charlotte Maxeke Johannesburg Academic Hospital, personal communication).

The literature on chemoradiation toxicity among HIV-positive patients with pelvic malignancies is sparse. Most reports focus on anal carcinoma. Although patients with anal carcinoma are not comparable to patients with cervix carcinoma and have different chemotherapy regimens, HIV-positive patients are less likely to complete chemoradiation for either cancer than HIV-negative patients.[9–11]

We were unable to evaluate the effects of ART on patients receiving chemoradiation because most of our patients

TABLE 5. Factors associated with grade 3/4 toxicity

	OR	95% CI Lower	95% CI Higher	P
HIV status				
Negative	1.0 Referent			
Positive	2.16	.98	4.8	0.05*
Total EQD$_2$				
≥68 Gy	1.0 Referent			
<68 Gy	0.44	0.15	1.33	0.15
Concurrent chemotherapy				
No	1.00 Referent			
Yes	4.41	1.76	11.1	0.023*

*$P \leq 0.05$ considered significant.

commenced ART either just before or during their cancer treatment. Some studies have shown an association of ART with adverse changes in hematologic parameters. However, we are unable to draw conclusions regarding the role of ART in leucopenia in the few HIV-positive patients in our cohort.

Of the HIV-negative patients in our cohort, nearly 95% completed chemoradiation, and more than 25% had a recorded grade 3–4 toxicity. These proportions are comparable to those in international studies of chemoradiation vs radiation alone. In a study by Keys et al,[12] 90% of patients receiving weekly cisplatin completed their prescribed treatment and 35% developed grade 3–4 toxicity. In the study published by Rose et al,[13] 93% of patients completed 4 or more cycles of weekly cisplatin and received adequate radiation. The patients in our study cohort achieved comparably high rates of completion of radiation due, in part, to the use of high-energy megavoltage radiation, multileaf collimation, and conformal volumes. However, many of our patients required a chemotherapy dose reduction, probably because they were in poorer overall health than patients in developed countries. In a phase 1 study by Nyongesa et al[14] in a patient population similar to ours, the maximum tolerated dose of cisplatin was found to be $25 \, \text{mg/m}^2$. Further in-depth study of toxicities and dose reductions in limited resource settings is urgently needed.

A limitation of this study is the relatively small number of HIV-positive patients in our sample; however, we included consecutive patients who met the eligibility criteria on our analysis, and ours is one of the largest HIV-positive cohorts in the published literature. Ten patients who were HIV positive did not have toxicity data recorded, which may introduce bias into the statistical results. Another limitation is that several different clinicians assessed and recorded the toxicities; they may not have used consistent criteria, but their use of a detailed standard toxicity sheet may have helped to minimize inconsistencies. A strength of the study is that both HIV-positive and HIV-negative patients adhered to our radiation treatment protocols.

The challenge is to find ways to help patients with cervical cancer, with and without HIV, in the many parts of the developing world where aging equipment or no equipment for radiation therapy is available. Unless screening becomes sufficiently widespread to downstage detected disease, or until HPV vaccination eliminates the carcinogenic strains of HPV, how to provide better treatment for the patients who need it most will remain a conundrum for health policy.

CONCLUSIONS

This study found that HIV-positive patients undergoing curative chemoradiation for cervical cancer had a higher risk of developing acute hematologic toxicity than did patients treated with radiation alone. Oncologists should exercise caution in the use of chemotherapy for such patients, in particular in the developing world setting where patients overall have poorer health and limited access to health care services. The data do not definitively support omitting chemotherapy from the treatment protocol for HIV-positive patients because only 36 of our 213 patients were HIV positive. Overall, this cohort of HIV-positive and HIV-negative patients

tolerated radiation alone very well, most likely because they were treated with state-of-the-art equipment and radiation planning techniques. In the developed world setting, use of advanced techniques such as intensity-modulated radiation therapy may be beneficial in further reducing dose to normal tissue. However, we have as yet no information about long-term treatment effects, recurrence, or survival in our patients, and studies of those end points among patients with cervical cancer with and without HIV in the developing world are much needed. Recurrence and survival data will be reported on a larger cohort from this institution. Randomized trials will hopefully provide data on how to maximize efficacy while minimizing adverse effects.

ACKNOWLEDGMENTS

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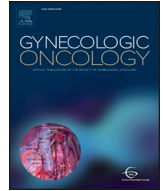
Five-year overall survival following chemoradiation among HIV-positive and HIV-negative patients with locally advanced cervical carcinoma in a South African cohort

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HIGHLIGHTS

- HIV-positive patients with locally-advanced cervical carcinoma were less likely to complete chemoradiation.
- Outcomes showed comparatively lower 5-year overall survival in HIV-positive patients.
- Total dose of radiation was not found to affect overall survival.
- Factors linked to poor outcomes included HIV status and inability to receive chemotherapy

ARTICLE INFO

ABSTRACT

Objectives. In South Africa, where HIV prevalence among adults is 18.9%, cervical carcinoma is the second most common malignancy in women. However, oncology services are considerably more accessible in South Africa than in many neighbouring countries.
This study reports five-year overall survival in a cohort of HIV-positive and -negative cervix carcinoma patients undergoing primary radiotherapy at a single institution in South Africa.

Methods. Prospective cohort study of all locally advanced cervix carcinoma patients referred for radiotherapy (EBRT) from July 2007 to November 2011. Overall survival (OS) was the primary end-point.

Results. A total of 492 patients commenced treatment with radical intent, including 71 HIV-positive patients (14.4%) and 421 HIV-negative patients (85.6%). Of the 433 who were prescribed standard fractionation EBRT, 384 were prescribed concurrent platinum-based chemotherapy (88.7%). Fewer HIV-positive than HIV-negative patients (58.5% *vs.* 76.1%; p = 0.007) completed ≥4 cycles. The OS of HIV-negative patients was 49.5% (95%CI; 44.6%–54.4%) at 5 years. The OS of HIV-positive patients was significantly lower, 35.9% (95% CI; 23.9%–48.0%) at 5 years (p = 0.002). In our Cox models, factors affecting outcome were HIV infection, stage IIIB disease, presence of hydronephrosis, and delivery of concurrent chemotherapy.

Conclusion. In our large cohort, HIV-positive patients had poorer survival than HIV-negative patients, however nearly 40% survived 5 years, justifying provision of the best standard of care to HIV-positive patients with cervical carcinoma.

1. Introduction

Cervical carcinoma is the second most common malignancy among women in South Africa; the overall age-standardised incidence rate (ASR) is 22.06/100,000, and among black women it is 25.90/100,000 [1]. Rates are similar in most sub-Saharan African countries and other low- or middle-income countries (LMICs), but no high-income country (HIC) has an ASR above 10/100,000. The LMICs also have higher cervical carcinoma mortality rates, due in part to inadequate healthcare.

Infection with the human papilloma virus (HPV), which causes cervical carcinoma, is highly prevalent in sub-Saharan Africa, and human

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immunodeficiency virus infection (HIV) is also highly prevalent [2]. Women with HIV and HPV infections are more likely than women with HPV alone to develop persistent HPV infections, high grade cervical intra-epithelial lesions, and ultimately cancer [3].

Since 2004, national guidelines regarding antiretroviral therapy (ART) for HIV have been available in South Africa [4]. Until 2011, only those patients with a CD4 < 200 cells/μl or WHO stage 4 were eligible for ART, but current local guidelines now support commencement of cART at a CD4 cell count <500 cells/μl [5]. In 2014, South Africa introduced a school-based national HPV vaccination program for girls aged 9–10 years [6]. However, this program has yet to influence the prevalence of HPV in the South African population at risk for cervical cancer.

Unlike many of its neighbors, South Africa is an upper middle-income country with large academic medical centres that can provide cervical cancer treatment on a par with the best practice in many HIC facilities. South Africa's public tertiary care hospitals have multidisciplinary gynaecological oncology units and can offer LINAC (linear accelerator) based 3-dimensional radiotherapy, high-dose rate brachytherapy, and chemotherapy agents.

The management of cervical cancer in HIV-positive women has, thus far, been based on best practice for HIV-negative women, while seeking to optimize combination antiretroviral therapy (cART) so as to maintain adequate CD4 counts and to suppress the viral load [7]. Little is known about the long-term survival of patients with cervical cancer and HIV [8–10].

We therefore analyzed overall five-year survival in a prospective cohort of HIV-positive and -negative cervix carcinoma patients undergoing radiotherapy, from a single institution in South Africa providing access to high quality oncology services.

2. Methods

2.1. Patient records

For this prospective cohort study, we collected a patient registry for all cervix carcinoma patients attending for primary radiotherapy during the time period July 2007 to November 2011 in the Division of Radiation Oncology, Tygerberg Hospital. Patients were entered into the registry at the start of treatment. The patients included in this analysis had stage IB1 to stage IIIB cancers and commenced external beam radiotherapy (EBRT) prescribed to a minimum of 40 Gray (Gy) with radical intent. Patients who were excluded from the analysis were those who did not start radiotherapy as planned and those who had undergone a hysterectomy, or had radical surgery for cervical cancer.

Ethical approval was obtained from the University of Stellenbosch Human Research Ethics Committee and Tygerberg Academic Hospital.

Data collected included demographic and clinical characteristics of the patients. For HIV-positive patients, we determined whether they had commenced cART before, or during, treatment of cervix cancer, and we recorded their initial CD4 cell count. During the time period of this study, viral load was not routinely tested in the oncology clinic. Cervical cancer treatment details, including EBRT dose, high-dose-rate (HDR) brachytherapy dose, and chemotherapy cycles, were documented. The total doses of EBRT and HDR brachytherapy were calculated using equivalent dose in 2Gy fraction (EQD_2) formulas [11].

2.2. Treatment

At our institution, patients with cervix carcinoma are routinely tested for HIV during diagnostic work-up. Many patients were diagnosed as HIV-positive incidentally during their work-up for suspected cervix carcinoma. Patients who tested HIV-positive started receiving cART either just before, or as soon as possible after commencing radiation treatment. At the time of the study, cART included triple therapy with lamivudine, efavirenz, and tenofovir, unless the creatinine clearance was low, in which case the patient received stavudine instead of tenofovir. Every HIV-positive patient commencing radiation or chemoradiation received concurrent cotrimoxazole prophylaxis. Because many patients receive their routine HIV care in local clinics, we have limited access to information on their adherence to cART therapy.

Diagnostic work-up included laboratory investigations, chest X-ray and abdominal ultrasound. In our institution, PET-CT was not available for the assessment of nodal and distant metastases until 2012. In addition, the evaluation of nodal cancer is challenging because HIV-positive patients often have reactive nodes.

Patients with IB1 cancers who were not fit for surgery or locally advanced IB2-IIIB disease received 45 to 52.5 Gy external beam radiation (EBRT) in 23 to 28 fractions, 1.8–2 Gy per fraction. Patients with anaemia and hydronephrosis were included if they were medically fit and had adequate renal function. During the study period, the lower dose per fraction was prescribed for HIV-positive patients or patients with previous abdominal surgery, due to theoretical concerns regarding gastrointestinal toxicities. Due to pressure on the radiotherapy waiting list, some patients with stage IIIB disease, including the elderly and those with severe medical co-morbidities, poor performance status, or poor renal function, received a hypofractionated regimen of 40.05 Gy in 15 fractions, or 42.72 Gy in 16 fractions, and no chemotherapy.

Table 1
Demographic and clinical characteristics of patients with cervical carcinoma, by HIV status.

Variable	HIV-negative	HIV-positive	Total	p-Value
	n = 421 (85.6%)	n = 71 (14.4%)	n = 492	
Median age years (interquartile range)	50 (43–58)	40 (35–49)	49 (41–57)	0.001[*]
Age groups				
39 years or less	65 (15.4%)	33 (46.5%)	98 (19.9%)	<0.001[*]
40–59 years	266 (63.2%)	37 (52.1%)	303 (61.6%)	
60 years or more	90 (21.4%)	1 (1.4%)	91 (18.5%)	
Histology				
Squamous cell carcinoma	391 (92.9%)	67 (94.4%)	458 (93.1%)	0.65
Adenocarcinoma	15 (3.6%)	2 (2.8%)	17 (3.5%)	
Other	15 (3.6%)	2 (2.8%)	17 (3.5%)	
Stage				
Stage IB1-IIA	12 (2.9)	0	12 (2.4%)	
IIB	120 (28.5%)	15 (21.1%)	135 (27.4%)	
IIIA	3 (0.7%)	0	3 (0.7%)	
IIIB	286 (67.9%)	56 (78.9%)	342 (69.5%)	0.06
Hydronephrosis present (stage IIIB)	58 (20.3%)	14 (25.0%)	72 (21.1%)	0.43
Node positive (ultrasound)	67 (15.9%)	14 (19.7%)	81 (16.5%)	0.42

[*] p < 0.05 regarded as significant.

Table 2
Treatment characteristics by HIV status.

Variable	HIV-negative	HIV-positive	Total	p-Value
	n = 421	n = 71	n = 492	
Standard fractionation	369 (87.6%)	64 (90.1%)	433 (88.0%)	0.55
Hypofractionation	52 (12.4%)	7 (9.9%)	59 (12.0%)	
Median EQD2 Gy (interquartile range)	77.7 Gy	76.3 Gy	77.7 Gy	0.94
	(75.0–80.8)	(69.3–81.5)	(75.0–80.9)	
≥69.25 Gy EQD$_2$ total dose	356 (84.6%)	54 (74.1%)	410 (83.3%)	0.08
≥20 Gy HDR[a]	333 (90.3%)	51 (79.7%)	384 (88.5%)	0.02[*]
Chemo 4 or more cycles[b]	252 (76.1%)	31 (58.5%)	283 (73.7%)	0.007[*]
1–3 cycles	79 (23.9%)	22 (41.5%)	101 (26.4%)	
Transfusion given[c]	173 (42.3%)	45 (66.2%)	218 (45.7%)	<0.001[*]

[a] If prescribed 1.8–2 Gy per fraction (n = 433).
[b] If prescribed 1.8–2 Gy per fraction and chemotherapy (n = 384).
[c] Missing data 15 patients.
[*] p < 0.05 significant.

Full treatment details have been described in our previous paper [12]. We used conformal 3-dimensional planning and a 6–18 MV (megavoltage) energy, 4-field arrangement. We then delivered 20 to 26 Gy Ir^{193} HDR intracavitary brachytherapy in 4 to 5 fractions. During the time period of this study, no image-guided brachytherapy was available. The absolute minimum total dose considered adequate for the purpose of this study was 69.25 Gy EQD$_2$ (45 Gy EBRT and 20 Gy in 4 fractions HDR brachytherapy). After 2009, we increased the brachytherapy dose to 25Gy in 5 fractions in keeping with international recommendations that total dose EQD$_2$ should be >80 Gy [13] (Higher doses per fraction are not suitable for the straight source HDR technique). Treatment is scheduled to be completed within 55 days.

Most patients also received cisplatin 40 mg/m^2 weekly, but if their calculated glomerular filtration rate or ethylenediaminetetraacetic acid (EDTA) glomerular filtration rate was <50 ml/min, they received carboplatin area-under-the-curve 2 (AUC2) weekly. We did not modify the dose for patients with a low CD4 cell count unless it fell below 200, in which case chemotherapy was omitted. Patients whose haemaglobin (Hb) fell below 10 g/dl received a red cell concentrate transfusion (resource constraints limit the use of blood transfusions).

2.3. Follow-up

Follow-up is scheduled routinely at 6 weeks post treatment, every three months in year 1, every six months in years 2 to 5, and annually to 10 years. Due to the poor socio-economic situation of many patients, and the distance they must travel from home to the cancer centre, many do not adhere to the follow-up program. Consequently, we could not determine local recurrence rates and progression- or disease-free survival at five years. Therefore, the primary end-point of this study was overall survival, measured from the start of EBRT to date of death or last recorded visit. Patient data were censored on 1 December 2016, 5 years after the last patient commenced EBRT in the cohort. We obtained mortality data from the South African Medical Research Council's national population register (NPR), which can provide a date of death for those patients who have a national identity number. We right-censored those without a national identity number at their last recorded date of follow-up. For most patients, we could not establish cause of death because we lacked access to death certificate information; we had in-patient records of pre-terminal events for only a few patients. For the purposes of this study, therefore, we analyzed all-cause mortality or overall survival.

2.4. Statistics

We evaluated the statistical significance of differences in demographic factors and clinical parameters between HIV-positive and HIV-negative patients by means of *t*-tests for continuous variables and χ^2 tests for categorical variables. Overall survival was computed using the Kaplan-Meier method. We developed Cox multivariable logistic regression models for the associations of HIV status, stage, total dose of radiation, and prescription of chemotherapy with mortality, expressing results as hazard ratios (HRs) with 95% confidence intervals (CIs). All tests were 2-sided, and p values of 0.05 or less were considered
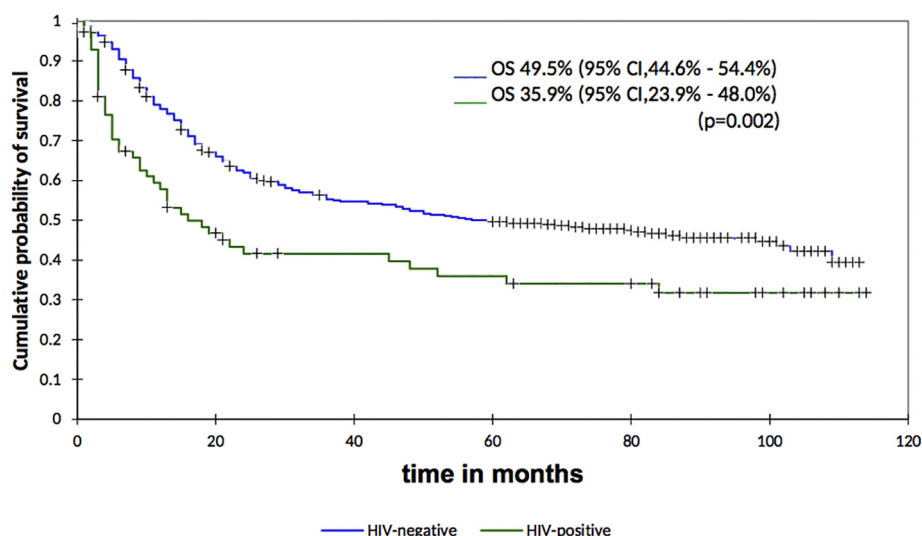

Fig. 1. 5-Year overall survival by HIV status.

Table 3
Predictors of all-cause mortality.

Variable	Hazard ratio	95% CI	p-Value
HIV status			
Negative	Referent		
Positive	1.45	1.01–2.08	0.04*
Stage			
IB1-IIIA	Referent		
IIIB	1.50	1.10–2.05	0.01*
Hydronephrosis			
Absent	Referent		
Present	1.70	1.12–2.59	0.01*
Total EQD$_2$ dose			
>69.25 Gy	Referent		
<69.25	1.01	0.65–1.57	0.96
Chemotherapy			
≥4 cycles	Referent		
1–3	1.18	0.84–1.65	0.34
0	1.86	1.26–2.76	0.02*

  * $p < 0.05$

significant. Data were analyzed using the SPSS Statistics software program (version 25.0; SPSS, Inc., Chicago, IL).

3. Results

From May 2007 to November 2011, 525 cervical carcinoma patients stage IB1 to IIIB commenced primary radiotherapy treatment. Of these, 33 patients received palliative treatment of 8–30 Gy and were excluded from this analysis. The remaining 492 patients were prescribed >40 Gy EBRT and were included.

3.1. Demographic and clinical characteristics

The cohort included 71 HIV-positive patients (14.4%) and 421 HIV-negative patients (85.6%) (Table 1). Their median age was 49 years, but the HIV positive group was younger at 40 years than the HIV-negative group at 50 years (p = 0.001). Most of the patients (69.5%) were diagnosed in stage IIIB, 78.9% of the HIV group and 67.9% of the un-infected group (p = 0.06). The vast majority of cases were pathologically defined as squamous cell carcinoma (93.1%).

Among the HIV infected patients, the median CD4 count was 386 cells/μl (iQR 256–450); 43 (60.6%) of the HIV-infected patients were on cART at the time of cervical cancer diagnosis, with a median CD4 of 366 cells/μl (iQR 276–458). The remaining 28 patients commenced treatment before or during EBRT, with a median CD4 of 324 cells/μl (iQR 209–407). Eleven patients had a recorded CD4 < 200, 7 of whom were not on cART.

3.2. Treatment parameters

Overall, 433 (88.0%) patients (87.6% of HIV-positive and 90.1% of HIV-negative patients) were prescribed standard fractionation EBRT (Table 2).

The median EQD$_2$ to point A was 77.7 Gy (iQR 75.0–80.9), for both groups. A large proportion of the cohort received a minimum of 69.25 Gy (83.3%); more of the HIV-negative patients (84.6%) than the HIV-positive patients (74.1%) completed the total prescribed radiotherapy (p = 0.08). Of those who were prescribed 1.8–2 Gy per fraction, 90% of the HIV-negative patients but only 80% of the HIV-positive patients completed brachytherapy (p = 0.012).

Of the 433 patients in the standard fractionation group, 384 (88.7%) were prescribed platinum-based chemotherapy. Fewer HIV-positive than -negative patients were able to complete 4 or more cycles. In addition, more HIV-positive than -negative patients required a red blood cell transfusion to maintain a hemoglobin over 10 g/dl, 66.2% (p < 0.001).

3.3. Survival

The median follow-up for the 492-patient cohort was 30.5 months (0–114 months) and 22,367 person-months. Two-year and five-year survival data were not available for 35 (7.1%) and 44 (8.9%) of the total cohort, respectively. The overall survival for the whole cohort was 59.1% (median not reached) at 2 years and 47.6% (median, 4.2 years; 95%CI, 27.1–72.9 months) at 5 years. Among patients who were prescribed chemoradiation and completed at least one cycle, the OS was 51.8% at 5 years.

HIV-negative patients had an OS of 62.0% (95%CI; 57.2%–66.7%) at 2 years and 49.2% (95%CI; 44.6%–54.4%) at 5 years. HIV-positive patients had poorer OS, 41.6% (95% CI; 29.5%–53.7%) at 2 years and 35.9% (95%CI; 23.9%–48.0%), at 5 years (p = 0.002) (Fig. 1). Within two years, 38 HIV-positive patients had died; only three more patients died in the next three years. The difference in survival remained significant when patients with a CD4 cell count of 200 or less were excluded from the analysis. Within the HIV-positive cohort, 5-year OS of those established on cART was similar to that of patients newly diagnosed with HIV, 38.4% vs. 31.4% (p = 0.322). The difference between the 5-year survival of the HIV negative group and that of HIV-positive patients established on cART was not quite statistically significant, 49.5% vs. 38.4% (p = 0.063).

The two- and five-year survival for Stage IB1-IIIA patients was 74.3% and 61.5% overall. For the Stage IIIB patients, 2- and 5-year OS was 52.2% and 41.3% overall. Survival was significantly lower for HIV-positive patients (Supplementary Table 1, S1).

In bivariate analysis, survival was not influenced by age, nodal status, histological subtype or transfusion status. The presence of hydronephrosis did, however, impact survival significantly.

With respect to total radiotherapy dose delivered, those who received 69.25 Gy EQD$_2$ or more fared better, with a 5-year OS of 50% vs. 36.9% (p = 0.002). HIV-status again conferred a lower OS even on those receiving adequate radiation (Supplementary Table 1).

In the standard fractionation cohort, survival was strongly associated with chemotherapy but was adversely affected by HIV-positivity. Among patients who received 4 or more cycles of platinum chemotherapy and complete radiotherapy >69.25 GY, 5-year OS was significantly better in the HIV-negative patients at 57.0% [Stage IB1-IIIA 71.9%; IIIb 48.2%] than at 35.2% in the HIV-positive patients [Stage IB1-IIIA 66.8%; IIIB 25.2%] (p = 0.009).

Those who received no chemotherapy, due to their comorbidities and poor performance status, fared worst of all; 5-year OS was 36.2% and 20.2% in the HIV-negative and -positive patients, respectively.

We developed Cox regression models for the 433 patients who had been deemed fit for radical standard fractionation radiotherapy, with or without chemotherapy (Table 3). The models included all factors found to be significant on bivariate analysis: stage at diagnosis, HIV status, presence of hydronephrosis, completion of EQD$_2$ 69.25 Gy radiotherapy and any chemotherapy. Red cell transfusion status was not associated with poor survival. Factors that were significantly associated with poor overall survival were HIV infection, Stage IIIB disease, the presence of hydronephrosis and ineligibility for chemotherapy.

4. Discussion

This study is one of the first to report the 5-year overall survival of a prospective cohort of HIV-positive cervical carcinoma patients. The overall 5-year survival of the 492 patients in the cohort, including patients with risk factors that are frequently reasons for exclusion from clinical trials, such as HIV infection and hydronephrosis, was 47.8%. Demographic and clinical factors adversely affecting outcome in the 433 patients treated with standard fractionation external beam radiotherapy were HIV positivity, advanced stage (stage IIIB) disease, and, in particular, hydronephrosis. Those who were unfit to receive chemotherapy fared worse.

The adherence of the cohort to prescribed external beam radiotherapy and brachytherapy was high; >80% received the prescribed minimum dose. In addition, 76% of the HIV-negative patients were able to tolerate at least 4 cycles of the prescribed concomitant platinum-based chemotherapy.

HIV-positive patients were less likely than HIV-negative patients to complete prescribed radiotherapy and even less likely to complete chemotherapy. However, approximately 75% of HIV-positive patients received adequate radiotherapy, and 58% completed the prescribed minimum cycles of chemotherapy.

In this observational study, patients who were not prescribed chemotherapy or were prescribed hypofractionated regimens were more likely than others to have a poor performance status, inadequate renal function, or other co-morbidities, such as active tuberculosis, which is common in the Western Cape Province of South Africa.

In a subset of HIV-negative patients without hydronephrosis, who completed chemoradiation, the 5-year overall survival was 58.4% (stage IIB 71.9% and stage IIIB 49.7%). These results are similar to those of a recent chemoradiation trial from Tata Memorial Hospital in India, with arguably a comparable, though highly selected, treatment population [14]. The 1243-patient United Kingdom audit of outcomes for chemoradiation reported a 5-year OS of 55% for the chemoradiation group, 61% for stage IIB and 44% for the stage IIIB patients [15]. Overall survival among our HIV-negative patients who were prescribed chemoradiation was therefore consistent with both developing and developed world data.

We could find no other prospective cohort study reporting 5-year survival for an HIV-positive cohort with an HIV-negative comparison group and complete demographic and treatment data. Coghill et al. reported on associations between HIV status and cancer deaths based on cancer registry data in the United States [8]. Among cervix carcinoma patients in the period 1996–2010, those who were HIV-positive had an all-cause mortality hazard ratio of 2.50, but a cancer-specific hazard ratio of 1.27 that was not statistically significant. In our sample, we could not tell whether the deaths we identified were AIDS-related or cancer-specific because we receive only limited death notice information. Most of the HIV-positive patients who died in our study did so within the first 2 years after diagnosis. We can speculate that HIV makes cervical carcinoma more biologically aggressive than it would otherwise be, or that cancer therapy adversely affects HIV control. With inadequate clinical follow-up, it is unclear which scenario is more likely.

Two HIV-positive cohort studies from Botswana, Dryden-Petersen et al. and Grover et al., presented conflicting results at their 2-year follow-up point [16,17]. In the former, HIV infection nearly doubled the risk of death (HR 1.95, 95% CI 1.2–3.17; p = 0.007), and median overall survival was 21.7 months. In the latter, the HR 1.12 was not statistically significant, the median OS was not reported, and the 2-year OS was 66% among HIV-positive patients, >20% higher than that of our HIV-positive patients. The differences between the two Botswana studies, noted by Grover et al., were partially explained by the inclusion of patients who were prescribed only palliative care in the Dryden-Petersen cohort, a lower CD4 cell count, and missing treatment data. In our unit, unlike that in the two Botswana studies, very few patients with early-stage disease are treated with chemoradiation. At our institution, gynaecological oncology surgeons manage active screen-and-treat programs and provide radical surgery for all early-stage disease. The patient population in our unit probably consists mainly of women who did not access the screening program. As a result, most of them present with locally advanced disease; nearly 80% of the HIV-positive patients in our study sample were stage IIIB, potentially accounting for the low survival of the cohort as a whole. In addition, our HIV-positive patients had a lower median CD4 cell count than those in the Grover study, probably because many of them were referred in the era prior to universal cART coverage.

Ferreira et al. performed a matched retrospective cohort study of all cervix cancer patients treated at a single institution in Brazil over a 12-year period [9]. The cohort included 87 HIV-positive patients. Of the subset who underwent radiotherapy, the HIV-positive patients were more likely to relapse within 2 years.

In a study of outcomes among 228 stage IIB patients, 13 of whom were HIV-positive, in South Africa, Jemu et al. found that HIV infection did not affect survival [18]. In Ethiopia, a cohort study of 1655 cervix cancer patients, of whom 139 were HIV-positive, also found that HIV status did not impact survival [10]. However, 789 patients were listed as HIV status unknown, and the study did not categorize patients by therapy received, although it noted that 71% of patients who received radiotherapy were treated with palliative intent. Finally a small matched cohort study of 50 HIV-positive patients undergoing adjuvant, radical and palliative radiotherapy in South Africa found that HIV infection adversely affected the ability to complete treatment and led to poor overall survival [19].

The strengths of our study include the prospective collection of demographic and treatment data. Although a number of patients were lost to clinical follow-up, access to the national registry ensured that vital status was available for over 90% of the cohort at 5 years. All patients were managed within a multi-disciplinary team environment, and high quality oncological and infectious disease interventions were available at no or minimal cost to the patients. Our sample included only patients treated with primary radiotherapy with curative intent. Adherence to planned radiotherapy was 98%, as we noted in our previous paper [12]. Most patients who failed to complete radiotherapy did so because of medical complications.

Limitations of the study include the use of paper records prior to the introduction of an electronic patient management system in radiotherapy; as a result, some subjects may have been missed. Information on acute toxicity was not reported in this study because it was available only for a subset of the cohort and had been previous reported [20]. Lack of data on late toxicity, local recurrence, distant metastases and cause of death is a limitation but one that is common among survival studies conducted in low resource settings, where many patients find it difficult to attend for frequent follow-up. The proportion of HIV-positive patients in our sample was 14.4%, relatively low compared to that of other centres in sub-Saharan Africa, but consistent with HIV prevalence in our institution's catchment area. The HIV-positive patients in our sample had a moderately low median CD4 count, probably because many of our patients were diagnosed and treated prior to the full cART rollout. A new cohort study in the 'modern' era is needed to see if cervical cancer patients whose HIV is well controlled have better survival than the HIV-positive patients in this study. Finally, our cohort included both patients who were deemed fit for radical therapy and patients who had co-morbidities that limited prescription of chemotherapy.

5. Conclusions

This cohort study of nearly 500 patients with locally advanced cervical cancer found that among women eligible for curative treatment for cervical cancer, HIV-positive patients had poorer overall survival than HIV-negative patients. Additional factors affecting outcome were cervical cancer stage and concurrent chemotherapy. A number of HIV-infected patients were able to tolerate adequate chemoradiation (58.5%), or radiation alone (74.1%), and nearly 40% were alive at 5 years. The outcomes of the HIV-negative cohort were comparable to data from the developed world. Despite their lower survival, we conclude that HIV-positive patients should be provided access to antiretroviral therapy, an effective screening program, and the best standard of care both in surgical and non-surgical oncology therapy in order to optimize outcomes. In addition, including HIV-positive patients in clinical trials will assist in answering questions that cohort studies cannot.

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Author contributions

Hannah M Simonds - conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, writing - original draft, and writing - review and editing.

Matthys H Botha - conceptualization, funding acquisition, methodology, supervision, validation, visualization, writing - review and editing.

Alfred I Neugut - conceptualization, supervision, visualization, writing - review and editing.

Frederick H Van der Merwe - conceptualization, investigation, visualization, writing - review and editing.

Judith S Jacobson - conceptualization, formal analysis, methodology, supervision, validation, visualization, writing - review and editing.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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HIV status does not have an impact on positron emission tomography-computed tomography (PET-CT) findings or radiotherapy treatment recommendations in patients with locally advanced cervical cancer

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Highlights
- More than 80% of patients had pelvic nodal involvement, and more than 40% had uptake in common iliac and/or para-aortic nodes.
- Overall, 84.5% were upstaged after PET-CT scan and it was not associated with HIV status.
- HIV status did not have an impact on PET-CT findings or oncology treatment decisions.

ABSTRACT

Introduction Positron emission tomography-computed tomography (PET-CT) imaging is commonly used to identify nodal involvement in locally advanced cervical carcinoma, but its appropriateness for that purpose among HIV-positive patients has rarely been studied. We analyzed PET-CT findings and subsequent treatment prescribed in patients with locally advanced cervical carcinoma in Cape Town, South Africa.
Methods We identified a cohort of consecutive cervical carcinoma patients International Federation of Gynecology and Obstetrics (FIGO) stage IIB to IIIB at our cancer center who underwent a planning 18-fluorodeoxyglucose (^{18}FDG) PET-CT scan from January 2015 through December 2018. Demographics, PET-CT findings, and subsequent treatment prescribed were recorded. Patients were selected for PET-CT only if they had no signs of distant disease on staging chest X-ray or abdominal ultrasound; were deemed suitable for radical chemoradiation by the multidisciplinary team; and had normal renal function. HIV-positive patients ideally had to have been established on continuous antiviral therapy for more than 3 months and to have a CD4 cell count above 150 cells/µL. Small cell and neuroendocrine carcinoma cases were excluded from the study. Differences in demographic and clinical measures between HIV-positive and HIV-negative patients were evaluated by means of t-tests for continuous variables and χ^2 tests for categorical variables.
Results Over a 4 year period, 278 patients—192 HIV-negative (69.1%) and 86 HIV-positive (30.9%)—met the inclusion criteria. HIV-positive patients had a median CD4 count of 475 cells/µL (IQR 307–612 cells/µL). More than 80% of patients had pelvic nodal involvement, and more than 40% had uptake in common iliac and/or para-aortic nodes. Nodal involvement was not associated with HIV status. Fifty-four patients (19.4%) had at least one site of distant metastatic disease. Overall, 235 patients (84.5%) were upstaged following PET-CT staging scan. Upstaging was not associated with HIV status (HIV-negative 83.9% vs HIV-positive 87.2%; p=0.47). Ten patients who did not return for radiotherapy were excluded from the analysis. Following their PET-CT scan, treatment intent changed for 124 patients (46.3%): 53.6% of HIV-positive patients and 42.9% of HIV-negative patients (p=0.11).
Conclusion We found no differences between HIV-positive or HIV-negative patients in nodal involvement or occult metastases, and PET-CT imaging did not lead to, or justify, treatment differences between the two groups. Future studies will evaluate survival and correlation of upstaging with outcome.

INTRODUCTION

Cervical carcinoma is one of the most frequently diagnosed malignancies in women throughout sub-Saharan Africa. In South Africa, its age-standardized incidence rate is >40 per 100 000 women; in 2018, more than 12 000 women were diagnosed with invasive cervical cancer.[1 2] In addition, cervical carcinoma is associated with HIV, and in South Africa HIV prevalence is 26.3% among women aged 15–49 years.[3] Various imaging modalities (eg, chest X-ray, abdominal ultrasound) are used to determine the extent of disease in cancer patients. In higher-income countries, newer technologies, such as magnetic resonance imaging and positron emission tomography-computed tomography (PET-CT) scanning, are often used for this purpose. The latter has proved to be highly effective in identifying poor prognostic features of cervical carcinoma, such as positive pelvic lymph nodes, and in accurately defining targeted treatment by radiation.[4 5] The addition of PET-CT to the staging algorithm has changed treatment intent and enhanced the accuracy of radiotherapy planning.

Original Article

PET-CT is now increasingly available in middle-income countries, including South Africa. A small study found that PET-CT led to conversion to palliative regimens or the addition of extended field irradiation for involved para-aortic nodes in more than 35% of patients.[6]

The 2018 update to the International Federation of Gynecology and Obstetrics (FIGO) staging of cervical cancer has highlighted the need for accurate imaging of nodal involvement.[7] Patients with evidence of nodal disease must be upstaged to IIIC1r for pelvic or IIIC2r for para-aortic nodal disease. HIV-positive patients who undergo PET-CT imaging may have fluorine-18 fluorodeoxyglucose ([18]FDG)-avid benign pathology, such as reactive lymphadenopathy or co-existent tuberculosis. This limitation in specificity may lead to some uncertainty in interpretation of abnormal findings and thus raises questions about the suitability of [18]FDG PET-CT staging for HIV-infected patients with cervical carcinoma. We therefore conducted a study of the contribution of PET-CT to staging and stratification for treatment in HIV-negative and HIV-positive women in a large cohort of patients with cervical cancer. Our hypothesis was that nodal involvement, as determined on PET-CT, would be more prevalent in HIV-positive than in HIV-negative patients due to a greater proportion of false positives in the former group; and that PET-CT findings among HIV-positive patients would lead to inappropriate changes in radiotherapy fields or treatment intent.

METHODS

This retrospective/prospective cohort study was undertaken at Tygerberg Academic Hospital, in Cape Town, South Africa. Study participants were consecutive HIV-positive and HIV-negative patients diagnosed with locally advanced cervical carcinoma (FIGO stage IIB-IIIB) who underwent a staging PET-CT scan from January 2015 through December 2018. Ethical approval was obtained from the University of Stellenbosch Human Research Ethics Committee (S17/01/016). For the retrospective cohort (January 2015 through February 2017) patients were identified through the Nuclear Medicine booking system. For the prospective cohort (March 2017 through December 2018), patients were consented at their new-patient visit to Radiation Oncology and referred to Nuclear Medicine as per routine clinical practice.

For the 12 gynecology oncology patients scheduled per week for radiotherapy, only 3–5 PET-CT planning scan appointments were available. Patients were selected for PET-CT only if they had advanced stage IIB, IIIA or IIIB disease with no signs of distant disease on staging chest X-ray or abdominal ultrasound; were deemed suitable for radical chemoradiation by the multi-disciplinary team; and had normal renal function. HIV-positive patients ideally had to have been established on continuous antiviral therapy for more than 3 months and to have a CD4 cell count above 150 cell/μL. Small cell and neuroendocrine carcinoma cases were excluded from the study.

Patients fasted for at least 4 hours before administration of the radiopharmaceutical. The PET-CT scans were performed using a Phillips Gemini Big Bore time-of-flight 16-slice PET/CT camera (Philips Medical Systems, Best, The Netherlands) with a flat couch top suitable for radiotherapy planning. The systems were calibrated according to the European Association of Nuclear Medicine Research Ltd standards. Patients were imaged from base of skull to mid-thigh in the supine position with a low-dose CT and PET scan. A second, contrast-enhanced planning CT scan from the pelvic area up to T10 was exported to the radiation oncology planning system for volume delineation. The PET and low-dose CT images were evaluated and reported jointly by an experienced team that included a nuclear medicine physician and a radiologist. Lymph nodes were interpreted as inflammatory when located in nodal basins not draining the primary tumor (directly or indirectly), and when the nodes appeared symmetrical in distribution and were sub-centimeter with only mild uptake. Lymph nodes were interpreted as malignant when enlarged and demonstrating moderate or intense uptake well above the degree of uptake in presumed inflammatory nodes. Avidity in nodes similar to the primary lesion was reported as malignant. Complex cases were discussed with the radiation oncologist when clarification was needed. Equivocal or ill-defined lesions on the PET-CT were highlighted as suspicious, and further investigations were left to the clinician's discretion (capacity to biopsy suspicious lesions was limited because of long surgical and diagnostic radiology waiting lists).

Table 1 Patient demographics and clinical characteristics by HIV status

	HIV-positive	HIV-negative	Whole cohort	P value
	86 (30.9%)	192 (69.1%)	278	
Age (median)	41 years (26–67 years) SD 8.75	50 years (26–79 years) SD 11.77	47 years (26–79 years)	**0.00***
Histology†				0.65
Squamous cell	81 (96.4%)	178 (92.7%)	259 (93.8%)	
Other	3 (3.6%)	14 (6.3%)	17 (6.2%)	
FIGO stage				0.46
IIB	15 (17.4%)	29 (15.1%)	44 (15.8%)	
IIIA	0	3 (1.6%)	3 (1.1%)	
IIIB	71 (82.6%)	160 (83.3%)	231 (83.1%)	

*P<0.05 considered significant.
†Complete data for 84 out of 86 HIV-positive patients.
FIGO, International Federation of Gynecology and Obstetrics.

Original data, including demographic and clinical characteristics, were extracted from the patients' folders. Reports and images were retrieved from the Nuclear Medicine database (Hermes Medical Solutions, Stockholm, Sweden). Radiotherapy data were retrieved from the MOSAIQ patient management system. PET-CT reports were coded for involved pelvic nodes, common iliac nodes, para-aortic nodes, distant nodal disease, and metastases to lung, liver, bone, and other sites. Equivocal or unrelated clinical findings were noted. Following introduction of the revised FIGO 2018 staging system, patients were allocated to stage IIB, IIIA, IIIB, IIIC1r, IIIC2r, or IVB based on clinical examination and the PET-CT findings.

All locally advanced cervical carcinomas deemed fit for treatment received 46–50.4 Gy in 23–28 fractions external beam radiotherapy (EBRT) to primary disease, parametria, upper vagina, and pelvic node groups up to and including the common iliac nodes. Forty-five Gray (45 Gy) in 25 fractions to a para-aortic node field extending to the renal hilum was prescribed for involved para-aortic node or upper common iliac nodes at the clinician's discretion. Prophylactic para-aortic node radiotherapy was not performed for positive nodes if all were below the common iliac vessels. EBRT was delivered concurrently with cisplatin 40 mg/m^2 up to five cycles, if renal function allowed, and was followed by high dose-rate brachytherapy 22–25 Gy in 4–5 fractions. During the period of this cohort, intensity-modulated radiotherapy to boost involved nodes was not in use; EBRT was delivered using 3D conformal techniques. Patients unsuited for radical radiotherapy were prescribed hypofractionated EBRT 40.05 Gy in 15 fractions with or without brachytherapy. Palliative patients received 10 Gy in a single fraction, repeated monthly to three fractions in selected cases, and/or palliative chemotherapy. Additional factors considered before starting treatment included deterioration in performance status and new-onset renal dysfunction.

Differences in demographic and clinical measures between HIV-positive and HIV-negative patients were evaluated by means of t-tests for continuous variables and χ^2 tests for categorical variables. All tests were two-sided, and values of $p \leq 0.05$ were considered significant. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) statistics software program (version 25.0; SPSS, Inc, Chicago, IL).

RESULTS

In the 4 year study period, 1093 patients with cervical carcinoma, including all radical, adjuvant, and palliative patients registered on MOSAIQ, were referred for radiation therapy. Of these patients, 278 met the inclusion criteria and were included in the final analysis (Table 1). The study included 192 HIV-negative patients (69.1%) and 86 HIV-positive patients (30.9%) (Table 1). The median age was 47 years (range 26–79). The HIV-positive patients were significantly younger than the HIV-negative patients (p<0.001) with a median CD4 count of 475 cells/µL (IQR 307–612 cells/µL). Viral load was available for 79 of 86 patients with a median of 0 copies/mL (IQR 0–100 copies/mL); 91.1% (n=72) had <1000 copies/mL as per WHO guidelines for viral suppression.[8] Most patients had squamous cell carcinomas and were clinically staged FIGO IIIB before their PET-CT imaging.

PET-CT findings

More than 80% of patients had pelvic nodal involvement, and more than 40% had uptake in common iliac and/or para-aortic nodes (Table 2). Nodal involvement was not associated with HIV status. Fifty-four patients had at least one site of distant metastatic disease, including lung (n=34), nodes (n=30), bone (n=7), liver (n=3), and sacral nerve (n=3) (Figure 1). Overall, 235 patients (84.5%) were upstaged to FIGO (2018) IIIC1r (37.4%), IIIC2r (27.7%) or IVB (19.4%) after PET-CT staging scan (Table 3). Upstaging was not associated with HIV status (HIV-negative 83.9% vs HIV-positive 87.2%; p=0.47). More than two-thirds of the patients also had benign or unrelated pathology (n=191; 68.7%), mainly post-inflammatory lung nodules. Other findings included active respiratory infections, bone marrow hyperplasia secondary to anemia, and undiagnosed breast cancer. These findings were unrelated to HIV status (HIV-negative 67% vs HIV-positive 73.3%; p=0.27). HIV-related lymphadenopathy was identified in 20 patients.

Treatment intent after PET-CT

Among the 268 patients who returned for treatment after the PET-CT planning scan, the intent of treatment changed from radical chemoradiation to hypofractionated EBRT in 27 (10.1%) patients, and to palliative EBRT in 32 (11.9%) (Table 4). Radical radiation was altered to include extended field para-aortic node EBRT in 65 cases

Table 2 PET-CT findings by HIV status

	HIV-positive N=86	HIV-negative N=192	All N=278	P value
Positive nodes (any)	75 (87.2%)	159 (82.8%)	234 (84.2%)	0.35
Pelvic	73 (84.9%)	150 (78.1%)	223 (80.2%)	
Common iliac	45 (52.3%)	85 (44.3%)	130 (46.8%)	
Para-aortic	38 (44.2%)	74 (38.5%)	112 (40.3%)	
Distant	12 (14%)	18 (9.4%)	30 (10.8%)	
Lung	12 (14%)	22 (11.5%)	34 (12.2%)	0.56
Liver	0	3 (1.6%)	3 (1.1%)	0.24
Bone	1 (1.2%)	6 (3.1%)	7 (2.5%)	0.33
Other	1 (1.2%)	2 (1.0%)	3 (1.1%)	0.93

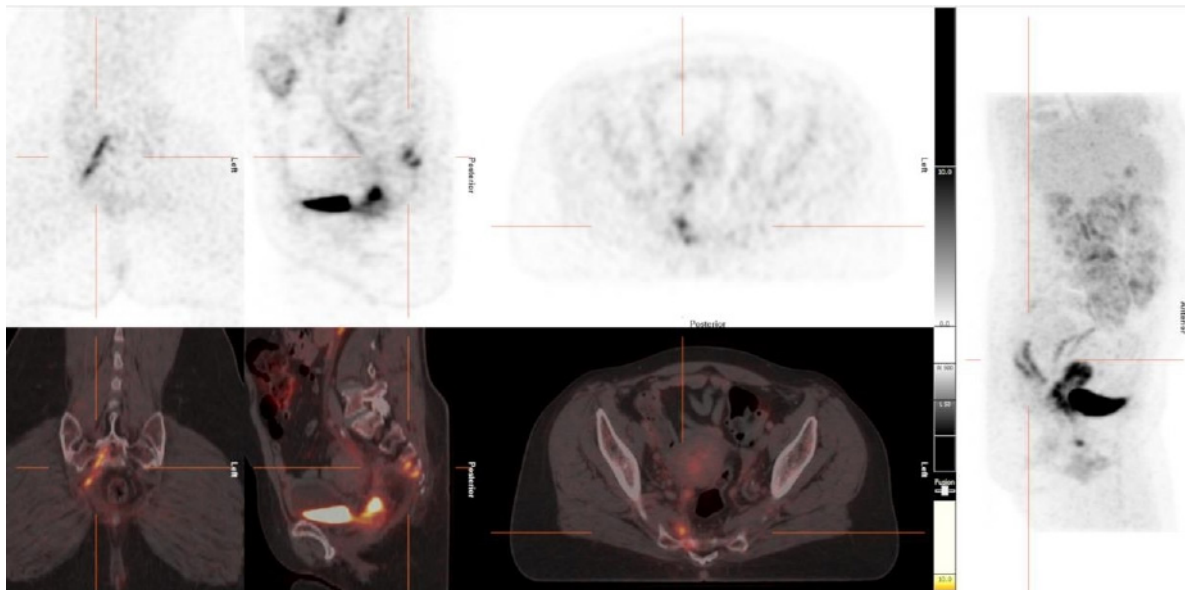CT, computed tomography; PET, positron emission tomography.

Figure 1 PET-CT images of a 63-year-old woman, initial stage IIIB squamous cell carcinoma of the cervix, HIV negative. Imaging findings included nodal uptake, lung metastases, and infiltration of the right sacral nerve. The patient received palliative pelvic radiotherapy and was started on palliative chemotherapy. CT, computed tomography; PET, positron emission tomography.

(24.3%). Following the PET-CT, overall treatment intent changed in 124 patients (46.3%), 53.6% in HIV-positive patients and 42.9% in the HIV-negative patients (p=0.11) (online supplementary figure 1). Of the 104 patients upstaged to IIIC1r, 95 (91.3%) proceeded to standard fractionation radiotherapy. Of the 77 patients upstaged to IIIC2r, 67 (87.0%) underwent EBRT. Para-aortic nodal extended-field radiotherapy was prescribed to 31.1% (n=65) of cases, including 75% (n=48) of the IIIC2r patients and 11.8% (n=11) of the IIIC1r patients, all of whom had common iliac nodal uptake on PET-CT. None of the patients staged IIB, IIIA or IIIB on PET-CT received extended field EBRT. Of the 54 patients upstaged to IVB disease, 13 were still prescribed radical EBRT (including six who received extended-field EBRT) after multi-disciplinary review of the images by the oncologist and nuclear medicine team.

DISCUSSION

Most of the 278 patients in our study had nodal disease, and nearly half had a change in treatment after PET-CT. Integrating PET-CT into the staging algorithm upstaged 85% of patients overall, including

65.1% upstaged to the current FIGO 2018 groups of IIIC1r or IIIC2r following findings of pelvic and/or para-aortic nodal involvement. The remaining 20% were diagnosed with distant metastatic disease, which in some cases was isolated (oligometastatic). The HIV-positive patients included in this cohort were immune-competent, with a high median CD4 count, and more than 90% were virally suppressed. Baseline clinical stage (before PET-CT) was not associated with HIV status. HIV status was not associated with differing PET-CT findings for either nodal disease or distant metastases.

In a recent study in South Africa, Id et al found that 36.4% of 126 patients with cervical carcinoma (including 74 with HIV and 88 with stage IIb or IIIB disease) had positive nodal involvement on PET-CT.[9] Stage was not associated with HIV status. In our cohort, more patients had positive nodes, most probably due to more advanced disease. Because the HIV-positive patients included in our cohort were immune-competent, our findings may not be generalizable to patients with a high HIV viral load.[10] Other recent studies have found no difference in stage distribution between HIV-negative and HIV-positive patients with malignancy. Mhlanga et al compared HIV-positive lymphoma patients to a control group without malignancy and found that the best way of distinguishing them was through asymmetry and quantitative measures of intensity of [18]FDG uptake (higher scores in malignant nodes)—methods similar to those used in our institution.[11] In a South African retrospective cohort of patients with Hodgkin's lymphoma, Lawal et al found no significant difference between those with and those without HIV in PET-CT findings and metabolic indicators.[12]

The accuracy of PET-CT in detecting nodal metastases in patients with locally advanced disease is difficult to determine with absolute certainty; in most clinical settings, such nodes are unlikely to be sampled to confirm involvement. The prevalence of pelvic and/or para-aortic node positivity on PET-CT was higher among our patients (both HIV-positive and HIV-negative) than has been reported in international data on HIV-negative populations. In the

	HIV-positive N=86	HIV-negative N=192	All N=278	P value
IIB	2 (2.3%)	7 (3.6%)	9 (3.2%)	0.34
IIIA	0	2 (1.0%)	2 (0.7%)	
IIIB	10 (11.6%)	22 (11.5%)	32 (11.5%)	
IIIC1r	28 (32.6%)	76 (39.6%)	104 (37.4%)	
IIIC2r	25 (29.1%)	52 (27.1%)	77 (27.7%)	
IVB	21 (24.4%)	33 (17.2%)	54 (19.4%)	

Table 3 Final FIGO stage (2018) by HIV status

FIGO, International Federation of Gynecology and Obstetrics.

Table 4 Treatment intent by HIV status

	HIV-positive N=84	HIV-negative N=184	All N=268*	P value
Standard fractionation EBRT	39 (46.4%)	105 (57.1%)	144 (53.7%)	0.11
Extended field EBRT	24 (28.6%)	41 (22.3%)	65 (24.3%)	
Hypofractionated EBRT	12 (14.3%)	15 (8.2%)	27 (10.1%)	
Palliative EBRT	9 (10.7%)	23 (12.5%)	32 (11.9%)	

*Exclusion of 10 patients who did not return for treatment.
EBRT, external beam radiotherapy.

recent EMBRACE trial, of more than 1000 cervical cancer patients, 52% had positive nodes on imaging.[13] That study included patients with earlier-stage disease and thus lower risk of nodal metastases. Similarly, a large PET-CT study undertaken by Kidd et al found positive nodal uptake in 58% of squamous cell carcinomas, a smaller proportion than in our cohort.[14] In a second study by Kidd et al, only 32% of patients with stage IIIB disease had positive nodes.[15] Our study population was a selected high-risk group in that most had stage III disease, most likely due to more delayed access to healthcare than is common in more developed countries.

The main purpose of integrating PET-CT into the staging algorithm in our cohort was to identify patients who needed a change in the planned radiation fields or in treatment intent. Nearly half of our patients were allocated to palliative treatment, hypofractionated radiotherapy, or extended field radiotherapy. In our previous cohort study, PET-CT findings imparted a 40% change in treatment intent.[6] In the future, in our institution, affected nodal areas may receive intensity-modulated radiotherapy boosts; if so, the value and importance of including PET-CT in our staging algorithms will increase. A randomized Canadian trial comparing imaging with CT to that with PET-CT was performed to determine whether PET-CT would find more distant disease than CT, and whether or not patients would receive more extensive EBRT due to increased detection of para-aortic nodes.[16] The two groups proved not to differ in terms of distant disease, but only eight out of 171 patients had such disease. More patients in the PET-CT group than in the CT group received extended field EBRT; some of the patients did not have positive para-aortic nodes and were treated off protocol.

The limitations of our study include the factors that influenced patient selection in the first 2 years of the cohort. In those years, we formed the cohort as a selected population of advanced disease patients who were deemed suitable for radical treatment and referred from the multi-disciplinary clinic. That sample is not representative of the entire cohort of cervical cancer patients at our institution. Due to limited surgical and diagnostic radiology resources, we were unable to biopsy equivocal pelvic or para-aortic nodes. The differential diagnoses of nodal uptake in this population would include HIV-reactive adenopathy, and infectious processes, including local tumor infection and tuberculosis. Diagnosis relies on pattern recognition; our nuclear medicine physicians have extensive experience in reporting PET-CT findings in patients with tuberculosis, an endemic disease in the hospital's catchment area. A number of patients had evidence of post-inflammatory lung lesions that may have represented metastatic disease in a small number of patients. Although the differences in age of our two study groups was significant, the evidence for an age effect (in the reported age ranges of our samples) on the prevalence of either

metastases or reactive lymphadenopathy is lacking, and we did not consider it to be a limitation.

The strengths of our study include its sample size; our cohort of 278 patients, of whom 84 were HIV-positive, is one of the largest in which HIV status and PET-CT findings have been described in any malignancy. Furthermore, consecutive patients were included; all patients referred in the study time period were evaluated. A multi-disciplinary team consisting of gynecological oncologists, a clinical oncologist, radiologists, and nuclear medicine physicians contributed to the treatment decisions and clinical care in our setting. Imaging findings were discussed when needed and a collective decision was made on interpreting equivocal findings. A single oncology team was responsible for all final treatment decisions providing consistent management for this patient cohort.

CONCLUSION

We found no differences between HIV-positive and HIV-negative patients in nodal involvement or occult metastases, and PET-CT did not lead to, or justify, treatment differences between the groups. We will continue to follow this cohort for survival outcomes, and correlation of upstaging with outcome.

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Chapter 6

Conclusions

The primary overarching objective of these four cohort studies was to evaluate the impact of HIV infection on outcomes in locally advanced cervical carcinoma in a South African patient population.

6.1 Summary of literature to date

Prior to the commencement of this study very little available data was published in relation to the management of HIV-positive patients with radiotherapy. From 2012-2019 outcomes were reported in cohort studies from Botswana, Brazil, Ethiopia, South Africa and the United States as detailed in Chapter 4.

Additional publications include a systematic review by Ntekim *et al* from 2015[1]. The authors found only 8 suitable studies – 5 retrospective and 3 prospective. Chapter 2 from this PhD was included in the review and was the only one assessed as having low bias in study methods and data analysis in the retrospective group. Additional studies included in this review were the cohorts from Kenya and India as discussed and two unpublished student dissertations from Johannesburg, South Africa. The overall conclusions of the review included mild increased toxicity in the HIV positive patients and higher adherence to completion of radiotherapy in those who commenced anti-retroviral therapy early.

A study from the United States looking at those who did, or did not, receive treatment amongst HIV positive patients examined a cohort of cervical cancer patients and found that 11.7% (n=196) of HIV positive patients did not receive treatment compared to 3.7% (3.7%) in the HIV negative group [OR 2.81 (CI 1.77-4.45)][2]. This re-iterates the challenges of access to care in this vulnerable group of women.

More recently Einstein *et al* from the AIDS Malignancy Consortium published the outcomes of Phase II study which enrolled HIV positive women with locally advanced

cervical cancer Stage IB2-IVA to receive standard of care chemoradiation[3]. Of the 38 women treated - 31 completed prescribed therapy. The treatment had comparable tolerability to published outcomes in the HIV negative population and 76.3% one year PFS.

The updated NCCN guidelines of cancer patients living with HIV suggest that cervical cancer patients should be treated as per routine SOC with the additional care of an HIV specialist and HIV pharmacists to evaluate drug-drug interactions[4].

With the update of the FIGO staging of cervical cancer in 2018 the need for accurate staging is now essential[5]. The use of PET-CT as a staging tool in HIV positive cervical cancer patients is rarely reported in the literature as described in Chapter 5. Since publication no new data is available.

Overall the number of studies published on advanced imaging and radiotherapy management of HIV positive women with cervical cancer remains limited to date, all of these are restricted to cohort studies.

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6.3 Summary of findings

 "*Completion of and Early Response to Chemoradiation Among Human Immunodeficiency Virus (HIV)-Positive and HIV-Negative Patients With Locally Advanced Cervical Carcinoma in South Africa*" was the first publication to report early outcomes for HIV-infected and uninfected patients treated with advanced 3-D conformal chemoradiation for cervical carcinoma in an LMIC. It was the largest cohort study of cervical carcinoma patients with and without HIV published. Adherence to treatment was high as the patients received managed oncology care in a multi-disciplinary setting with adequate resources and the sample included only patients deemed fit for therapy. The conclusions emphasised the importance of completion of radiotherapy, and in particular brachytherapy, to ensure good clinical outcomes among both HIV-positive and -negative patients with cervical carcinoma.

"*HIV Status and Acute Hematologic Toxicity Among Patients With Cervix Cancer Undergoing Radical Chemoradiation*" examined the question of potential increased toxicity of oncological therapy in the vulnerable HIV-positive population. It was one of the largest cohort studies to compare HIV-positive and -negative patients from a single cohort with respect to treatment toxicity. It demonstrated that HIV-infected patients experienced more toxicities related to their scheduled chemotherapy than uninfected patients. Haematological toxicity appeared to be the most significant

toxicity; gastro-intestinal toxicity (GIT) was limited due to the use of advanced 3-D radiotherapy techniques. Previous published work showing increases in GIT toxicity was not confirmed in this cohort. The findings of increased haematological toxicity were not unexpected considering the additional effects of immunosuppression and concurrent antiretroviral therapy.

"*Five-year overall survival following chemoradiation among HIV-positive and HIV-negative patients with locally advanced cervical carcinoma in a South African cohort"* was the first publication demonstrating long-term outcomes in HIV-positive cervical carcinoma. Outcomes among HIV-positive cervical carcinoma patients had previously been reported only for small cohorts (< 40 patients) living in low-income countries and treated with 2-D radiotherapy techniques. This study examined survival among patients with and without HIV treated with advanced techniques. In our large cohort, HIV-positive patients had poorer survival than HIV-negative patients; however, nearly 40% survived 5 years. The results inform practice for the radiation oncology community; in both HICs and LMICs, HIV-positive patients should receive the best standard of care, just as HIV-negative patients should.

"*HIV status does not impact PET-CT findings or radiotherapy treatment recommendation in patients with locally advanced cervical cancer"* was one of the first studies to evaluate the role of PET-CT in the staging of cervical carcinoma in HIV-positive women, it is the largest cohort published to date. Notably, a high percentage these patients proved to have nodal involvement. This study revealed no difference in the findings on PET-CT between HIV-negative and HIV-positive patients with cervical carcinoma. In addition, subsequent treatment decisions, although influenced by the PET-CT results, were not associated with HIV status.

6.4 Summary of contributions

Overall these studies aimed to answer questions regarding the effect of concurrent HIV infection and locally advanced cervical carcinoma. The common outcome is that HIV infection should not hinder the use of advanced imaging techniques or the best standard of care with chemoradiation. Patients must be established on cART, and support from infectious disease colleagues is essential to ensure that patients have a suppressed viral load and are compliant on therapy. Thereafter, the use of PET-CT for accurate staging is suitable for this population of patients and necessary to ensure that the treatment plan is correct. During treatment, due efforts must be made to maintain compliance on cART, prophylaxis with appropriate antibiotic cover, and pro-active management of haematological toxicities. Survival outcomes, although poorer in HIV-positive than HIV-negative patients, confirm that all patients with locally advanced cervical carcinoma should have equal access to appropriate oncological therapy.

6.5 Future Research

The questions that remain unanswered are many. The overall survival among HIV-positive patients was poorer than among those who were HIV-negative. The possible reasons include: HIV-related illness; potential interplay in toxicity of chemotherapy and cART preventing completion of adequate therapy; persistence of high-risk HPV leading to early recurrence. Future work will include investigation of drug-drug interactions between Cisplatin and cART; and testing for persistent HPV. Although no difference was demonstrated in PET-CT findings between the cohorts, many patients had nodal lesions that were not confirmed via cytology or histology; hence, the false positive rate in this population is unconfirmed. The outcomes in terms of recurrence and survival for the

patients with PET-positive nodal disease also need to be confirmed. Long-term follow-up of the nearly 300 patients who underwent PET-CT scanning will be undertaken.

This body of work has established that women with locally advanced cervical cancer and HIV infection should be treated with the best standard of care. The many patients who participated in these cohort studies have helped to ensure that future patients with and without HIV will have equal access to health care resources in oncology in our institution.