THE PROFILE OF HUMAN IMMUNODEFICIENCY VIRUS-INFECTED PATIENTS WITH INVASIVE CERVICAL CANCER IN THE POLOKWANE/MANKWENG COMPLEX HOSPITAL

By

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MINI-DISSERTATION

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DEDICATION

To my beautiful mother, who gave me strength when I thought of giving up and who continually provides her spiritual support.

And to my late father, A.M. Dzivhani. May his soul rest in eternal peace.

DECLARATION

I declare that the mini-dissertation hereby submitted to the University of Limpopo, for the degree of Master of Medicine in Radiation Oncology has not been submitted by me for a degree at this or any other university; and that it is my work in design and in execution, and that all material contained herein has been duly acknowledged.

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Date

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ABSTRACT

Introduction

Invasive cervical cancer (ICC) constitutes almost 50% of all cancer conditions diagnosed and treated at the Polokwane/Mankweng Hospital Complex (PMHC). HIV infection is also a very common condition. There is no consensus on the relationship between the two clinical conditions among patients treated at PMHC. There is a need to describe the simultaneous occurrence of the two clinical conditions among these patients to define a rational approach to these conditions' clinical management.

Methodology

This was a retrospective review of medical records of patients diagnosed with ICC who were treated at PMHC in Limpopo Province, South Africa in 2013.

Results

Three hundred and twenty-nine medical records were reviewed in this study; 64% of the patients were HIV-negative, and only 35% were HIV-positive. Thirty-five percent of the patients were younger than 50 years of age, followed by those aged 50–59 years (23%). Among women in the age group 30–59 years, the most common ICC stages were IIB and IIIB. In women older than 60 years, stages IIB, IIIA, IIIB and IVA were the most common. In the HIV-positive women, 18% had a CD4 cell count of less than 200/μL, compared to 2% in the HIV-negative women ($p < 0.05$). Among the HIV-negative women, stages IIIB (49.8%) and IIB (24.6%) were the most common, where as among those who were HIV-positive, stages IIIB (55.6%) and IIB (22.6%) dominated.

Conclusion

This retrospective study did not find any relationship between HIV infection and ICC in patients treated at PMHC. However, it indicated that a significant proportion of HIV-positive women with ICC had lower CD4 cell counts compared to those of HIV-negative women.

KEY CONCEPTS: Invasive cervical cancer, Human immunodeficiency virus, Stage, Prevalence, CD4 cell count, Age, Polokwane/Makweng Hospital Complex

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DEFINITIONS OF CONCEPTS

Abdominal ultrasound: This is a type of radiological imaging technique. It uses sound waves to create images of structures and blood flow in the abdomen. Ultrasound images are a useful way of examining organs, tissues, blood vessels, and other structures within the abdomen (NCI, 2020). In this study, abdominal ultrasound means an ultrasound study performed in the abdomen to investigate the extent of cancer in the cervix, uterus, kidneys and other stuctures of the pelvis.

Acquired immunodeficiency syndrome (AIDS): AIDS is a syndrome caused by infection with the human immunodeficiency virus (HIV), with ensuing compromise of the body's immune system (Castro, Ward, Slutsker, Buehler, Jaffe, Berkelman, & Curran, 1993). In this study, AIDS means the syndrome of reduced body immunity to resist infections accompanied by any opportunistic infection and associated neoplasms such as cervical cancer.

Biospy: Biopsy is the process of removing tissue from a living body to determine the presence, cause, or extent of a disease (NCI, 2020). In this study, cervical biopsy means the removal of a tissue sample from the cervix to analyse it for the presence of a neoplasm.

Cancer stage: A cancer stage is the process of determining the extent to which a cancer has developed by growing and spreading within an organ or to other organs of the body (NCI, 2020). In this study, cervical cancer stage means the extent of the cancer according to the International Federation of Gynaecology and Obstetrics (FIGO) classification system (Gichangi, Bwayo, Estambale, De Vuyst, Ojwang, Rogo, Abwao, & Temmerman, 2003).

CD4 cells: CD4 cells, also known as CD4+ T cells, are white blood cells that form a critical component of the immune system, typically used to monitor the immunity status of the body (Ding, Zheng, Song, Fu, Xu, Jiang, Shang, & Zhang, 2020).

Colposcopy: Colposcopy is a medical diagnostic procedure used to examine an illuminated, magnified view of the cervix and the vagina and vulva (Kim, Cho, Kim, Kim, & Park, 2020). In this study, colposcopy means the procedure by which a gynaecologist visually examines the cervix for the purpose of making a diagnosis.

Cystoscopy: Cystoscopy is the endoscopic examination of the urinary bladder through the urethra (Kim *et al.*, 2020). In this study, cystoscopy means a part of the endoscopic examination used for staging cancer of the cervix to assess if the bladder is affected.

Histology: Histology is the study of the microscopic structure of tissues to determine its characteristics (NCI, 2020). In this study, histology means microscopic examination of a cervical biopsy tissue to determine the type of abnormal cells, for example squamous cell carcinoma.

Human immunodeficiency virus (HIV) infection: HIV infection is an infection caused by a virus thought to have originated in Central Africa that may have been transmitted from primates to humans (Patel, Raizes & Broyles, 2020). In this study, HIV infection means presence of the infection diagnosed using a patient's blood test.

Prevalence: Prevalence is defined as the proportion of a population with a disease of a particular condition at a specific point in time or over a specified period of time (Noordzij, Dekker, Zoccali & Jager, 2010). In this study, prevalence means the proportion of patients diagnosed with cervical cancer and HIV amongst the patients treated for cervical cancer within the study period.

Proctoscopy: Proctoscopy is a medical procedure in which an instrument called a proctoscope is used to examine the anal cavity, rectum, or sigmoid colon (Kim *et al.*, 2020). In this study, proctoscopy is the endoscopic procedure performed to determine whether cancer of the cervix has infiltrated the rectum.

LIST OF ABBREVIATIONS

AIDS: Acquired immune deficiency syndrome

ART: Anti-retroviral therapy

ASIR: Age-standardised incidence rate

ASCUS: Atypical squamous cells of undetermined significance

CD4: Cluster destination-4

CI: Confidence interval

CIN: Cervical intraepithelial neoplasia

ELISA: Enzyme-linked immunosorbent assay

FIGO: International Federation of Gynaecology and Obstetrics

HAART: Highly active anti-retroviral therapy

Hb: Haemoglobin

HIV: Human immunodeficiency virus

HIV+ve: HIV-positive

HIV-ve: HIV-negative

HPV: Human papillomavirus

HSIL: High-grade squamous intraepithelial lesion

IARC: International agency for research on cancer

ICC: Invasive cervical cancer

LFT: Liver function test

LMICs: Low and middle income countries

LSIL: Low-grade squamous intraepithelial lesion

OR: Odds ratio

PLT: Platelet

PMHC: Polokwane/Mankweng Hospital Complex

SASOG: The South African society of obstetrics and gynaecologists

SEER: Surveillance, epidemiology, and end results

UNAIDS: The Joint United Nations Programme on HIV/AIDS

WCC: White cell count

WHO: World health organization

WIHS: Women’s interagency HIV study

CHAPTER 1: INTRODUCTION

1.1 Introduction

Cervical cancer is the fourth most common frequent cancer globally, with an estimated 570 000 new cases in 2018, representing approximately 6.6% of all female cancers (Arbyn, Weiderpass, Bruni, de Sanjosé, Saraiya, Ferlay, & Bray, 2020). It's estimated global age-standardised incidence rate (ASIR) is 13.1 per 100 000 women, ranging widely from less than 2 in developed countries to 57 in low and middle income countries (LMICs) (Arbyn *et al.*, 2020). In the LMICs, it is the second most common cancer in incidence in women, with the majority of new cases occurring among people from the lower socioeconomic status in the society (Bhatla, Aoki, Sharma, & Sankaranarayanan, 2018). Globally, the average age at diagnosis was 53 years, ranging from 45 to 68 (Arbyn *et al.*, 2020). Invasive cervical cancer (ICC) remains the most common cancer in South Africa; affecting 1 in 41 South African women with an ASIR of 24.17 (Incidence and Worldwide, 2000).

In 2012, there were approximately 266 000 deaths from cervical cancer worldwide, accounting for 75% of all female cancer deaths (IARC, 2012). The average age at death from cervical cancer globally is 59 years (Arbyn *et al.*, 2020). Almost 9 out of 10 (87%) cervical cancer deaths occur in less developed countries (IARC, 2012). In 2018, in South Africa, cervical cancer ranked second for both incidence (12 983, 12.1%) and cancer deaths (5595, 9.8%) (Bray, Ferlay, Soerjomataram, Siegel, Torre, & Jemal, 2018).

ICC is staged according to FIGO staging classification, which divides it into early-stage (IA to IB1), locally advanced stage (IB2 to IVA) and advanced or metastatic stage (IVB) (Pecorelli & Odicino, 2009). Over 90% of cervical tumours are classified histologically as squamous cell carcinoma; approximately 7% to 10%, as adenocarcinoma; and 1% to 2%, as clear cell or mesonephric carcinoma (Perez & Kavanagh, 2008).

Invasive cervical cancer has long been recognised as an acquired immunodeficiency syndrome (AIDS)-defining illness (Maiman, Frutcher, & Clark, 1997). A human immunodeficiency virus (HIV)-infected person with concurrent carcinoma of the cervix is, therefore, considered to have AIDS. Worldwide, approximately 37 million people were living with HIV in 2016 (UNAIDS, 2019). In 2013, it was estimated that 24.7 million people were living with HIV infection in sub-Saharan Africa, which is nearly 70% of the global total (UNAIDS, 2013). The majority of people living with HIV in sub-Saharan Africa are women (58%) (UNAIDS, 2013). Infection with HIV, places the women at a higher risk of acquiring a persistent or repeated infection with human papilloma virus (HPV). HIV and HPV have a common risk factor: transmission through sexual intercourse and having multiple sex partners. Cervical abnormalities such as cervical intraepithelial neoplasia (CIN) are reported to be more severe and aggressive in the presence of HIV infection and consequent HPV co-infection, which both expose the women to a higher risk of developing ICC.

Persistent human papillomavirus (HPV) infection is associated with cervical intraepithelial neoplasia (CIN) grade 2 or 3, and cervical cancer in HIV-positive women (Clifford, Gonclaves, & Francesschi, 2006; De Vuyst, Lillo, & Smith, 2008). CIN is a pre-malignant condition. Multiple infections of HPV can cause the cervical epithelium to develop CIN, which then progresses to CIN grades 2 and 3, and ICC.

Currently, there are no specific treatment guidelines for ICC in HIV-positive women (Ntekim, Campbell, & Rothenbacher, 2015). The internationally recommended standard treatment is surgery for early-stage ICC, and cisplatin-based chemoradiotherapy in locally advanced stages regardless of whether the patient is HIV-positive or not (Ferreira, Coghill, Chaves, Bergmann, Thuler, Soares, Pfeiffer, Engels, & Soares, 2017). However, there are concerns over using the standard regimen in HIV-positive women because of their low immunity, which is often associated with poor general condition of the patient, the presence of opportunistic infections, low CD4 cell count levels, and the patient's highly active anti-retroviral therapy (HAART) status.

The present study evaluated the profile of all patients diagnosed with ICC who were treated in the Polokwane/Mankweng Hospital Complex (PMHC), a combination of Pietersburg and Mankweng tertiary hospitals in Limpopo Province, South Africa.

1.2 Research Problem

ICC and HIV infection are significant public health problems that are prevalent in LMICs and are a cause of mortality and morbidity among women. Both ICC and HIV share a common transmission factor by being mainly sexually transmitted illnesses. Presence of HIV is believed to deteriorate the outcome of treatment of ICC. There is no consensus on the prevalence of HIV infection among patients with ICC treated at PMHC. There is a need to describe the simultaneous occurrence of the two clinical conditions among these patients to define a rational approach to clinical management of ICC to improve treatment outcomes.

1.3 Research question

What is the profile of HIV-infected patients with ICC treated in PMHC?

1.4 Purpose of the study

1.4.1 Aim

The aim of this study was to describe the profile of HIV-infected patients with ICC in PMHC.

1.4.2 Objectives

The specific objectives of the study were:

1.4.2.1 To determine the proportion of patients with ICC who are HIV-positive.

1.4.2.2 To describe age of patients with ICC at diagnosis.

1.4.2.3 To determine the CD4 cell count of patients with ICC.

1.4.2.4 To evaluate the relationship between HIV status and ICC stage among these patients.

1.5 Outline of the study

This study report consists of five chapters. Chapter 1 addresses the basic background, research problem, purpose and the approach to the study. Chapter 2 provides a context for the research by reviewing relevant literature that supports and critiques the association between the CD4 cell count and HIV status of patients with ICC, and the relationship between HIV status and ICC among these patients. This chapter also examines the literature regarding the proportion of patients with ICC who are HIV-positive, as well as the stage and age of patients with ICC. Chapter 3 discusses the research methodology which outlines the method, design, reliability and validity of the study. Chapter 4 presents the data based on the objectives of this study and the overview of the research findings. In Chapter 5, the findings of the study are discussed relative to the existing literature report. It also presents the conclusion of the study in relation to the objectives, outlines the limitations, and proposes recommendations arising from the findings.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

This chapter provides the context for the research by reviewing relevant literature on the association between HIV-infected patients and ICC. First, the proportion of HIV-positivity among women diagnosed with ICC is discussed. Secondly, the distribution by the age of women with ICC and HIV status is demonstrated. Thirdly, the association between CD4 cell count level and ICC stage is explored. Fourthly, the relationship between HIV status and ICC stage is evaluated.

2.2 The proportion of HIV-positive patients with ICC

ICC is classified as one of the AIDS-defining illnesses. The link between HIV infection and cancers was established as far back as in the 1980s when Kaposi's sarcoma and Non-Hodgkin's lymphoma were recognised as hallmarks of AIDS (Ghebre, Grover, Xu, Chuang, & Simonds, 2017). The increased incidence of ICC in HIV-positive women only gradually became evident with time until in 1993 when the Centers for Disease Control and Prevention (CDC) classified it as an AIDS-defining illness (Ghebre *et al.*, 2017).

Most studies have revealed an increased risk for both HIV and ICC in women. In a pre-HAART era retrospective analysis of records over a 10-year period (1987–1995), Maiman, Frutcher, & Clark (1997) found cervical cancer to be the most common malignancy in the study population representing 55% of cases, followed by non-Hodgkin's lymphoma (29%) and Kaposi's sarcoma at 16%. In another study investigating trends in cancer risk among people with AIDS in the United States of America (USA) between 1980 and 2002, the risk of cervical cancer had a significant standardised incidence rate (SIR) of 5.3, remaining fairly constant during the pre-HAART period (1980–1995) and after the introduction of HAART

from 1996 to 2002 (Engels, Pfeiffer, Goedert, Virgo, McNeel, Scoppa, & Biggar, 2006). A study by Chaturvedi, Madeleine, Biggar, & Engels, (2009) investigating the risk of HPV-associated cancers among HIV-negative and HIV-positive patients found an increased risk for cervical cancer in HIV-positive women with an SIR of 68.6, at a 95% confidence interval (CI) of 59.7 to 78.4. Another study that supported this trend was a multi-cohort study conducted in North America, investigating invasive cervical cancer risk, that revealed that HIV-positive women had an elevated incidence of ICC (26 per 100000 person-years) compared with HIV-negative women (6 per 100000 person-years) and that the risk of ICC increased significantly with increasing immunosuppression (Abraham, Strickler, Jing, Gange, Sterling, Silverberg, Saag, Rourke, Rachlis, Napravnik, & Moore, 2013). These studies, conducted mainly in North America, used data from a large number of patients.

Contrary to the results in the studies above, other studies concluded that the incidence of ICC in HIV-positive women remained constant or even decreased compared to the general population. Ferreira et al. (2017) assessed the outcomes of cervical cancer among HIV-positive and HIV-negative women treated at the Brazilian National Cancer Institute and found that 336 (74.1%) were HIV-negative, and only 87 (25.9%) were HIV-positive and had cervical cancer. However, in the present retrospective study, which covered 8 744 hospital records for cervical cancer patients from 2001 to 2013, HIV serology was only performed in 62% of patients, from which 82 were found to be sero-positive. An additional five patients were diagnosed by their CD4 cell counts and viral load without serology. A significant number of patients classified as HIV-negative (3322 or 38%) did not undergo serology testing. Additionally, the sample size of 338 HIV-negative patients was selected based on matching one HIV-positive patient to four HIV-negative patients (Ferreira *et al.*, 2017).

In a study conducted in Tanzania by Kahesa, Mwaiselage, Wabinga, Ngoma, Kalyango, & Karamagi (2008), 29 of 138 patients (21%) with ICC were HIV-positive, and 79% (109/138) were HIV-negative. The limitation of this study was that the data were hospital-based and depended on patients who could attend a

single oncology centre in Tanzania. The study does not include some patients who may have been treated in other hospitals or those who were not referred to this centre.

In a prospective cohort study conducted in Uganda from August 2013 to August 2015, Wu, Urban, Krantz, Mugisha, Nakisige, Schwartz, Gray, & Casper (2020) enrolled 96 cervical cancer patients who were HIV-negative and 53 who were HIV-positive. Even though the stated purpose of this study was to compare the cervical cancer stages at diagnosis in HIV-positive and HIV-negative patients and to characterize the relationship between HIV disease and cervical cancer survival in Uganda, the inclusion criteria were very restrictive as only those who committed to continually attend the institution were recruited. The study is silent on those patients who may have been diagnosed but were unable to continue to attend. However, a significant proportion of this cohort (35%) were HIV-positive.

A prospective study conducted in KwaZulu-Natal, South Africa, comparing the prevalence and presentation of cervical cancer in HIV-positive and HIV-negative women, revealed that out of a total of 672 patients reviewed, only 21% (138) were HIV-positive, and 79% (522) were HIV-negative (Moodley, Moodley, & Kleinschmidt, 2001).

Moodley (2006) conducted another study in KwaZulu-Natal, South Africa, in which he compared the trends of prevalence of ICC and HIV infection in 1999 and 2003. It was found that the prevalence of HIV infection among women with ICC remained constant over the two time periods at 21% and 21.1%, respectively, and that there was a significant reduction in the number of women presenting with ICC (Moodley, 2006). This was supported by a study conducted in Kenya from 1989 to 1998, where no significant change in the incidence of ICC among HIV-positive women was found ($p > 0.05$) (Gichangi, Bwayo, Estambale, De Vuyst, Ojwang, Rogo, Abwao, & Temmerman, 2002).

In Limpopo, South Africa, it was reported that HIV-infected women were at an increased risk of pre-cancerous cervical lesions (CIN 1 and CIN 2; $p=0.02$ and $p=0.01$, respectively) but not ICC ($p=0.015$) (Van Bogaert and Correspondence,

2013). These findings were supported by Moodley (2006), who found that the adjusted odds ratio associated with HIV infection was 4.4 (95% CI:2.3–8.4) for atypical squamous cells of undetermined significance (ASCUS), 7.4 (3.5–15.7) for low-grade squamous intraepithelial lesions (LSILs), 5.8 (2.4–13.6) for high-grade squamous intraepithelial lesions (HSILs), and 1.17 (0.75-1.85) for ICC. Moodley (2006) suggested that the low incidence could have been attributed to competing risks of mortality from other associated infections, particularly in areas where HAART was not yet available.

Most of the African and South African studies analysed above were mainly hospital-based and included small samples of patients who were treated at the different institutions . The findings are mainly in contradiction to the mostly North American studies in the earlier paragraphs of this section that demonstrated increased risk of ICC in HIV-positive patients. The only South African study that concurs with the North American studies was an investigation of the trends in the age-standardized and age-specific incidence rates of cervical cancer in rural South Africa covered by a population-based cancer registry (Somdyala, Bradshaw, Dhansay, & Stefan, 2020). In this study conducted in the Eastern Cape Province of South Africa for the period 1998–2012, the investigators demonstrated an almost 2-fold increase of annual ASIRs per 100 000 women from 24.0 (95% CI:21.1–27) in 1998–2002 to 39 (95% CI:35.6–42.5) in 2008–2012 (Somdyala *et al.*, 2020).

2.3 Age of patients with ICC at diagnosis

Age at diagnosis of patients with ICC was similar among HIV-positive and HIV-negative women in a study conducted by Ferreira et al. (2017). It was found that approximately 60% of women regardless of their HIV status were between 35 and 49 years of age (Ferreira *et al.*, 2017).

Wu et al. (2020) investigated the association between HIV infection and cervical cancer presentation and survival in Uganda and reported that the median age at

diagnosis of women with ICC was 44 years and 54 years for HIV-positive and HIV-negative women, respectively.

Gichangi, Bwayo, Estambale, De Vuyst, Ojwang, Rogo, Abwao, & Temmerman (2003) conducted a study to determine the association between ICC and HIV infection in Kenyan women. They concluded that HIV-positive women with ICC were diagnosed when they were on average 10 years younger than HIV-negative patients were. They also found that HIV infection was associated with poor histological differentiation of the tumours, which could suggest an increased rate of progression of pre-malignant cervical lesions to ICC. It was also reported that the average age at diagnosis of cervical cancer in HIV-positive women (40 years) was a decade lower than that in HIV-negative women (52 years) (Ntekim, Campbell, & Rothenbacher, 2015). This finding is similar to that of the Ugandan study by Wu et al. (2020).

Similarly, in Tanzania and South Africa, the mean age of HIV-positive women with ICC was lower (44.3 and 39.8 years, respectively), whereas the mean age of HIV-negative women was 54 and 55.2, respectively (Moodley, Moodley & Kleinschmidt, 2001; Kahesa *et al.*, 2008). The possible reason for these observations was postulated to be as a result of cellular genetic changes due to HPV and HIV (Van Bogaert, 2011).

Van Bogaert (2011) conducted a prospective study in South Africa in which he evaluated age at diagnosis of pre-invasive and invasive cervical cancer in HIV-positive versus that in HIV-negative women. The outcome indicated that HIV-positive women were diagnosed with ICC at a significantly younger age (18 years younger) than that of HIV-negative women (Van Bogaert, 2011). This study also revealed that there is a longer lag of approximately 20 years between the pre-invasive and invasive stages in HIV-negative women compared to those in HIV-positive women (Van Bogaert, 2011).

2.4 CD4 cell count of patients with ICC

Epidemiological studies on cancer trends have demonstrated a decline in the incidence of the main AIDS-defining cancers such as Kaposi's sarcoma and non-Hodgkin's lymphoma, but not cervical cancer (Engels *et al.*, 2006; Chaturvedi *et al.*, 2009; Shiels & Engels, 2017). The decline has been achieved mainly through the introduction of HAART since 1996. Human papilloma virus is the main etiological factor in cervical carcinoma. The increased risk of cancer among individuals with HIV or AIDS is consistent with a high incidence and persistent HPV infections whereby HIV immunosuppression plays a significant role in the etiology of cervical cancer (Chaturvedi *et al.*, 2009). The HIV attacks the T-cells in the immune system, leading to progressive impairment of the immune response (Castro, Ward, Slutsker, Buehler, Jaffe, Berkelman, & Curran, 1993). AIDS is defined as HIV infection associated with an absolute CD4 cell count of less than 200/μL and/or an AIDS-defining opportunistic infection or AIDS-defining cancers such as Kaposi's sarcoma, non-Hodgkin's lymphoma and cervical cancer (Anampa, Barta, Haigentz, & Sparano, 2020). Therefore, HIV infection is typically associated with clinical conditions that occur when the body's immunity is impaired, such as opportunistic infections and faster malignant transformations from pre-malignant conditions.

CD4 cells (also known as CD4+ T cells) are white blood cells that form a critical component of the immune system typically used to monitor the immune status of the body (Ding, Zheng, Song, Fu, Xu, Jiang, Shang, & Zhang, 2020). These are the cells that HIV kills. The CD4 cell count is the best direct measure of a patient's immune status and remains an important test with regard to key clinical decision-making, including when to start HAART and whether to screen for or provide prophylaxis against opportunistic infections (Ford, Meintjes, Vitoria, Greene, & Chiller, 2017)**.**

Biggar, Chaturvedi, Goedert, & Engels, (2007) conducted a study investigating the association between cancer risk and CD4 cell count among persons with

AIDS from 1990 to1995 before HAART became available and then from 1996 to 2002. They found that the incidence of ICC was higher between 1996 and 2002 (86.5 per 100000 person-years) than that between 1990 and 1995 (64.2 per 100000 person-years) with no statistical significance in the difference of incidence, however, they found no strong association between CD4 counts and risk of ICC (Biggar, Chaturvedi, Goedert, & Engels, 2007) . They suggested that immunosuppression could promote early-stage cervical dysplasia due to persistent HPV infection.

In Brazil, Ferreira et al. (2017) reported that among the 47 HIV-positive patients in their series, CD4 cell counts were available in 23 (49%) who had a CD4 cell count of 263 (range:137–368) cells/mm³. Wu et al. (2020) reported a median CD4 cell count of 373 (range: 300–502) cells/mm³ for HIV-positive women versus 926 (range: 639–1045) cells/mm³ for HIV-negative women. They concluded that even though the CD4 cell counts were above the level considered as high risk for opportunistic infections (200 cells/mm³) in HIV-positive patients, it was still much lower than that in HIV-negative women with a median CD4 cell count of 926 cells/mm³.

However, a retrospective study conducted by Lomalisa, Smith & Guidozzi (2000) revealed that only HIV-positive women with a CD4 cell count below 200/mm³ were diagnosed with the advanced-stage ICC as compared to HIV-positive women with normal level of CD4 count above 500/mm^3. Another study conducted in South Africa found the risk of ICC to be higher in HIV-positive women with a CD4 cell count below 200/mm³ compared with that in women with a CD4 cell count above 500/mm³ (Firnhaber, Van Le, Pettifor, Schulze, Michelow, Sanne, Lewis, Williamson, Allan, Williams, & Rinas, 2010).

2.5 HIV status and ICC stage

In the studies conducted in Brazil and Côte d'Ivoire, it was concluded that the majority (40% and 50%, respectively) of the patients presented with advanced stage disease (stages III and IV, respectively) irrespective of their HIV status (Adjorlolo-Johnson, Unger, Boni-Ouattara, Touré-Coulibaly, Maurice, Vernon, Sissoko, Greenberg, Wiktor, & Chorba, 2010; Ferreira *et al.*, 2017). These findings are similar to the findings of a study conducted in Nigeria that demonstrated that there is no difference in the proportion of patients with the early-stage disease (stage I-IIA) from the late-stage disease (IIB-IVA) between HIV-positive and HIV-negative (early stage: 11% vs 59%;late stage 89% vs 91%) (Ntekim, Campbell, & Rothenbacher, 2015).

In KwaZulu-Natal, South Africa, Moodley (2006) performed a retrospective study to determine the trends of prevalence of ICC and HIV infection among such women in 1999 and 2003. He found that the majority of women regardless of their HIV status in the 1999 period (92%) presented with the late-stage disease compared to 70% in the 2003 period (Moodley, 2006).

Wu et al. (2020) reported that 32% of HIV-positive women presented with the advanced-stage disease (III-IV) compared to 39% of HIV-negative women. This finding is contrary to those of the studies above.

Moodley et al. (2001) compared the prevalence and presentation of cervical cancer in King Edward Hospital, South Africa. They stratified patients by age groups for analysis of age versus stage status versus HIV status and reported that there was no evidence of a significant association between stage and HIV status (Mantel–Haenszel odds ratio: 0.86, P=0.68).

Retrospective data collection conducted by Pelkofski, Stine, Wages, Gehrig, Kim, & Cantrell (2016), assessing cervical cancer in women younger than 35 years, concluded that the majority (96 of 114, 84%) had either early-stage IA (31 of 144, 27%) or IB (65 of 114, 57%) ICC. In the study above, patients older than

35 years were excluded, and HIV status of the patients was not mentioned. This is the only study that I reviewed regarding cancer stage and ICC and found that the majority of the patients presented with early-stage disease.

2.6 Conclusion

The majority of the studies concluded that the incidence of ICC in HIV-positive women had either remained constant or had decreased. The outcome of the studies was that HIV-positive women were diagnosed with ICC at a younger age than that of HIV-negative women. Some studies reported that women with ICC presented with advanced-stage disease, irrespective of their HIV status, where as others reported that only HIV-positive women with a CD4 cell count below 200/mm³ presented with advanced-stage disease compared to HIV-positive women with CD4 counts above 500/mm^3.

This study will address the possible association between HIV infection and ICC at PMHC in Limpopo, South Africa, by determining the following: the ICC stage at presentation among HIV-positive women compared to HIV-negative women; the correlation between the absolute CD4 cell count level and the extent of disease; and the age of presentation with ICC in HIV-positive patients compared to that in HIV-negative patients.

CHAPTER 3: RESEARCH METHODOLOGY

3.1 Study design

This is a retrospective review of medical records of patients diagnosed with ICC and treated at PMHC in the Limpopo Province, South Africa in 2013.

3.2 Study setting

PMHC is a combination of Pietersburg Hospital and Mankweng Hospital campuses. It provides tertiary services to all the district and regional hospitals in the Limpopo Province. The Radiation and Clinical Oncology Department has chemotherapy facilities and two radiation oncology specialists. The Pietersburg Hospital campus provided all the patients for the study as radiation oncology facilities are only available there.

3.3 Sampling

3.3.1 Study population

The medical records of all patients diagnosed with ICC who presented for management at the Radiation Oncology Department in Pietersburg Hospital campus from January 2013 to December 2013 were reviewed.

3.3.2 Sampling method

Records of patients who consecutively met the inclusion criteria were included in the study.

3.3.2.1 Inclusion criteria

The inclusion criteria were as follows:

i. all patients with histologically confirmed ICC,
ii. all patients who were clinically staged by a gynaecologist or trained medical officer using FIGO staging (Pecorelli and Odicino, 2009),
iii. Patients with known HIV status,
iv. patients who had absolute CD4 cell count results recorded before they started treatment, and
v. patients whose age was recorded.

3.3.2.2 Exclusion criteria

Medical records of all patients diagnosed with ICC in 2013 were included as all of them met the inclusion criteria.

3.3.2.3 Analysis of disease characteristics

FIGO staging was performed by the gynaecologist or trained medical officer at the Mankweng Hospital campus. Patients were examined under general anaesthesia. The following diagnostic tests were used to determine the disease stage: palpation (of lymph node regions, the abdomen and the pelvis), inspection (ulcers or obvious perineal tumours), colposcopy (to assess the vagina and the cervix), hysteroscopy (to assess the uterus), cystoscopy (to assess bladder wall involvement), proctoscopy (to assess rectal wall involvement), intravenous urography or pelvic/renal ultrasound (to assess for hydronephrosis and hydroureter) and a chest X-ray image for lung metastasis (Pecorelli and Odicino, 2009).

HIV testing was done by means of the HIV Rapid Test and, if positive, confirmed by ELISA using Beckman Coulter DXi 800. If ELISA results happened to come back as inconclusive or positive from Beckman Coulter DXi 800, then blood samples were analysed using Roche, Cobas e411 to confirm the results. HIV pre-test counselling and testing were conducted by a trained HIV counsellor or medical doctor, and the patient was required to give consent before the test could

be conducted. Both HIV-positive and HIV-negative patients received post-test counselling, but HIV-positive patients were also referred to HIV/AIDS clinics for further management.

The CD4 cell count was taken after HIV testing, irrespective of the patient's HIV status. A Beckman Coulter FC 500 was used to analyse blood samples for the CD4 cell count.

3.3.2.4 Data on patient demographics

Patients' demographic information, including age, was extracted from the radiation oncology database.

3.3.2.5 Ethical issues relating to sampling

HIV counselling and testing was conducted by a trained HIV counsellor or medical doctor, and the patient was required to give consent before the test could be conducted. Consent was obtained using the Department of Health and Social Development HIV testing consent form (Appendix F). HIV-positive patients received post-test counselling and were also referred to Hope clinic for further management of HIV. Hope Clinic is a clinic attached to each of the tertiary hospitals where patients diagnosed with HIV infection received counselling and HAART. Regular follow-up are made and other associated physical symptoms of illnesses and social problems are adressed.

3.3.3 Sample size

A total of 329 medical records of patients with ICC were reviewed.

In this retrospective study, the sample size was determined using the formula below based on the study conducted by Lomalisa, Smith & Guidozzi (2000), and Abdus-Salam, Ogunnorin & Abdus-Salam (2008).

$$N = \frac{z^2 p(1-p)}{e^2},$$

Where N= sample size, z = 95% confidence interval, p = 7% prevalence of HIV-positive women (Lomalisa, Smith, & Guidozzi, 2000), and e = 5% sampling error or marginal error.

The required minimum sample size was estimated to be 102 patients. However, a total of 329 medical records were reviewed. There were no negative ethical implications for including all the records more than the calculated minimum sample size required for the study as retrospective data were used and not that of living participants who would have been interviewed unnecessarily.

3.4 Data collection

Data were collected from the Radiation Oncology Department's database at the Pietersburg Hospital campus after ethical clearance had been obtained. Data were captured into a customised data extraction sheet (Appendix G) designed for this study. The following characteristics were included in the data collection sheet (Appendix G): age, FIGO stage, HIV status, histological subtypes and CD4 cell count. Data were then entered into a spread sheet (Table 4). The data were checked and approved by the supervisor of the project.

3.5 Data analysis

The data analysis was performed with the assistance of a biostatistician at PMHC. Data were entered and analysed using Epi Info™ statistical software. Where data were missing, an unknown variable was created. Continuous data (for example, age and demographic information) were analysed using measures of central tendency (mean or median), which were appropriate for characterising

the variables. The chi-squared test was used to assess differences between categorical variables. A p-value less than 0.05 was considered statistically significant.

3.6 Validity and reliability

Validity refers to the degree to which a measurement represents a true value and indicates whether the conclusions of the study design are justified, based on the design and interpretation (Polit & Beck, 2012). To avoid a statistical conclusion or inferential validity, an appropriate statistical technique (the chi-squared test) was used to assess the association between categorical variables, and the Epi Info™ statistical software was used for data analysis.

Reliability refers to how consistently a method measures something. If the same result can be achieved consistently by using the same method under the same circumstances, then the measure is considered reliable (Burns, Nancy, & Grove, 2005). To ensure reliability, a data extraction sheet was designed for this study.

3.7 Bias

Bias is defined as any influence that produces a distortion or misrepresentation of an outcome of a particular finding of a study (Wasserbauer & Abraham, 1995). Sampling bias is limited in this study because the medical records of all patients diagnosed with ICC in 2013 were used.

3.8 Ethical considerations

Permission to conduct the study was obtained from the Chief Executive Officer (CEO) of PMHC (Appendix E) and the Head of the Radiation Oncology

Department. Ethical clearance was obtained from the Sefako Makgatho Health Sciences University Research Ethics Committee (SMUREC) (Appendix C), and the Limpopo Department of Health and Social Development (Appendix D).

The anonymity of the patients was ensured by assigning a computer number to each patient record. No patient was identified by name during the study or will be in any written article that may arise from this work. Confidentiality was observed by ensuring that patients' medical records were handled by authorised staff only. Paper-based patient records were locked away when not in use by the researcher and authorised staff. Electronic records, including raw data, were protected by a password.

HIV counselling and testing was done by a trained HIV counsellor or medical doctor, and a patient was required to give consent before the test could be done. Consent was obtained using the Department of Health and Social Development HIV testing consent form (Appendix F). HIV-positive patients received post-test counselling and were also referred to HIV/AIDS clinics for further management.

CHAPTER 4: RESULTS

4.1 Introduction

The methodology used in this study was outlined in the previous chapter. The objectives of the study were as follows:

- to determine the proportion of HIV-positive patients with ICC,

- to describe ages of patients with ICC at diagnosis,

- to determine the CD4 cell count and HIV status of patients with ICC,and

- to evaluate the relationship between HIV status and ICC stage among these patients.

In this chapter, the findings of the study are presented and interpreted.

4.2 Demographic information of the participants

A total of 329 records of cervical cancer patients were reviewed. Of these, 35% were younger than 50 years, followed by those aged 50–59 years, at 23% (Figure 1). The mean age of the patients was 56.2±14.5 (range: 25–90 years).

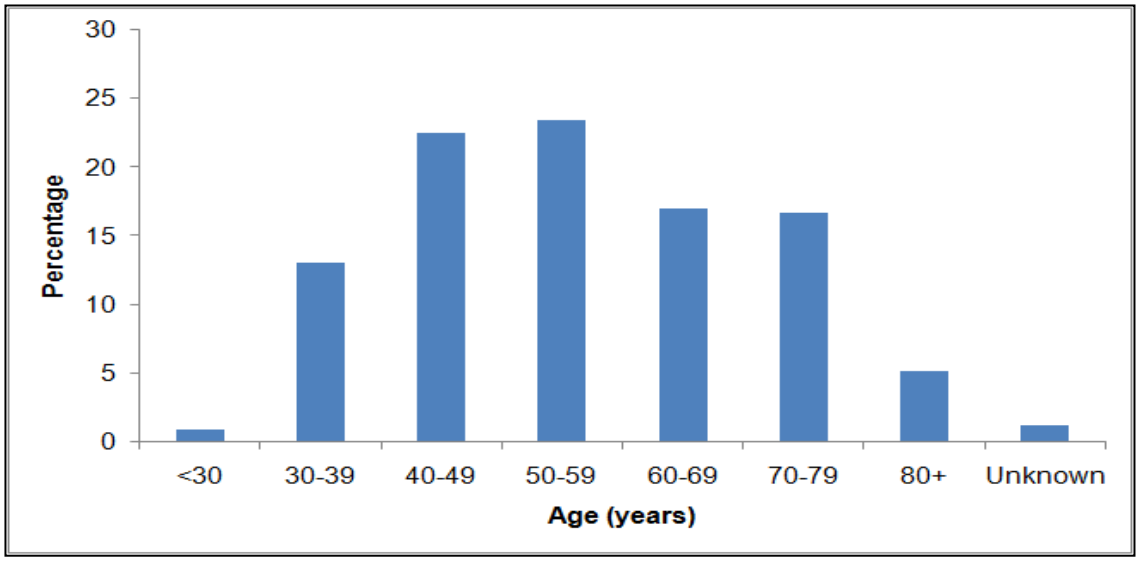

Figure 1: Age distribution

The findings of this study indicated that the majority (92%) of the women had squamous cell carcinomas (Figure 2).

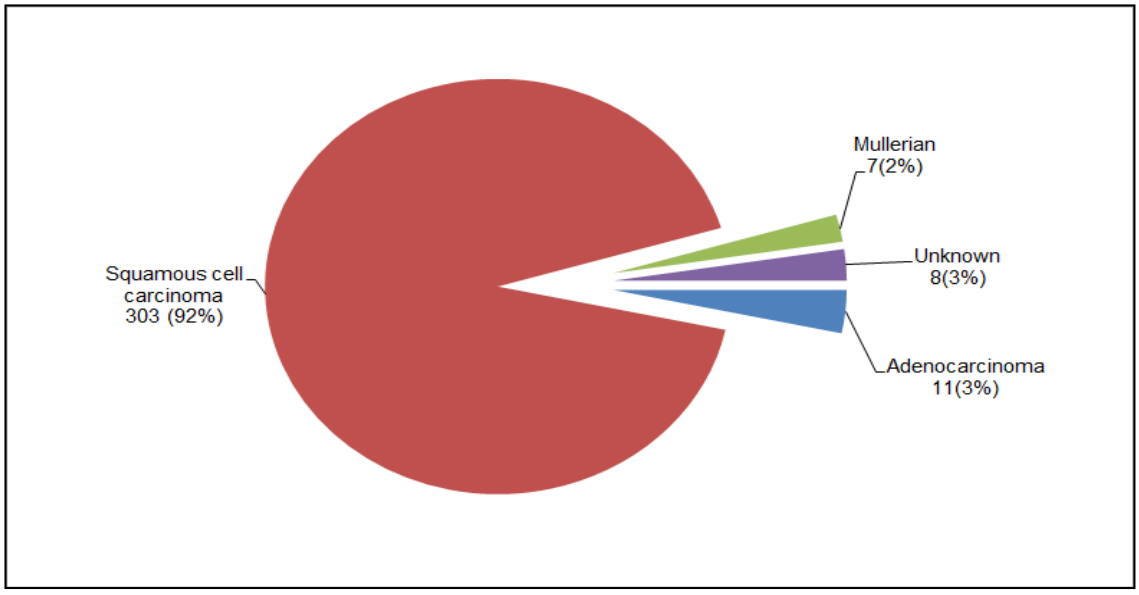

Figure 2: Histology

4.3 Proportion of HIV-positive patients with ICC

Figure 3 depicts the HIV status of the participants. A large proportion (65%) of the patients in this study was HIV-negative, and only 35% of them were HIV-positive. HIV status was unknown in two (1%) of the patients.

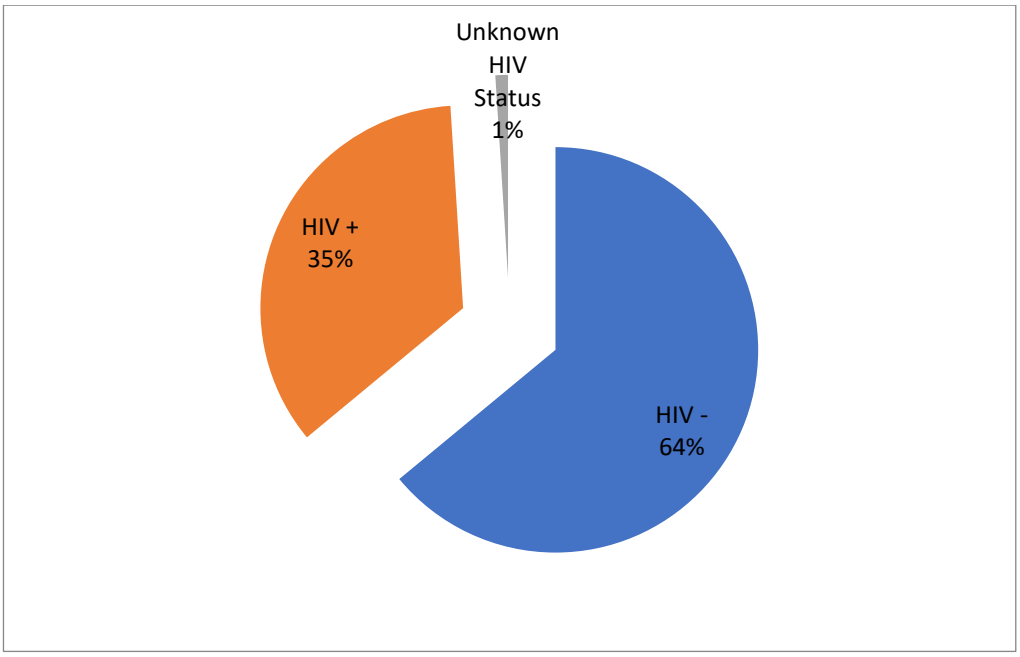

Figure 3: Distribution of HIV status of the participants

4.4 Age of patients with ICC at diagnosis

Table 1 illustrates the distribution of ages of women by stage of cancer. Among women in the age group 30–59 years, the most common stages were IIB and IIIB. In women aged 60 years and older, stages IIB, IIIA, IIIB, and IVA were common.

Table 1: Age of the participants by cancer stage

Stage	<30 yrs		30–39 yrs		40–49 yrs		50–59 yrs		60+ yrs	
	No	%	No	%	No	%	No	%	No	%
IA1									1	0.8
IB			1	2	2	1	1	1		
IIA			1	2	3	4	4	5	5	3.9
IIB			15	35	18	24	19	25	26	20.3
IIIA	1	33	4	9	5	7	9	12	14	10.9
IIIB	2	67	20	47	42	57	38	50	66	51.5
IVA			1	2	2	3	4	5	12	9.4
IVB			1	2	2	3	1	1	2	1.6
Recurrent									1	0.8
Total	**3**	**100**	**43**	**100**	**74**	**100**	**76**	**100**	**128**	**100**

4.5 CD4 cell count and HIV status of patients with ICC

The association between CD4 cell count and HIV status is illustrated in Table 2. Overall, a greater proportion (92.4%) of the women had CD4 cell count below 200/μL. Of the HIV-positive women, 18% had a CD4 cell count below 200/μL compared to 2% in HIV-negative women ($p < 0.05$).

Table 2: HIV status by CD4 cell count

CD4 cell count (/μL)	HIV-negative		HIV-positive		Total	
	No	%	No	%	No	%
<100	1	0.5	6	5.3	7	2.2
100–200	3	1.5	14	12.3	17	5.4
>200	199	98.0	94	82.5	293	92.4
Total	203	100.0	114	100	317	100.0

Chi-squared test, $p<0.001$

4.6 Relationship between HIV status and ICC stage among these patients

Overall, the majority (51.8%) of the women were stage IIIB, followed by stage IIB (23.9%) and stage IIIA (10.4%). Table 3 illustrates the distribution of cervical cancer stage by HIV status. Among the HIV-negative patients, stages IIIB (49.8%) and IIB (24.6%) were the most common; similarly, among those who were HIV-positive, stages IIIB (55.6%) and IIB (22.6%) dominated.

Table 3: Distribution of cervical cancer stage by HIV status

Stage	HIV-negative		HIV-positive		Total	
	No	**%**	**No**	**%**	**No**	**%**
IA1	1	0.5	0	0.0	1	0.3
IB	3	1.4	2	1.8	5	1.5
IIA	7	3.3	6	5.2	13	4.0
IIB	52	24.6	26	22.6	78	23.9
IIIA	23	10.9	11	9.6	34	10.4
IIIB	105	49.8	64	55.6	169	51.8
IVA	14	6.6	5	4.3	19	5.8
IVB	5	2.4	1	0.9	6	1.8
Recurrent	1	0.5	0	0.0	1	0.3
Total	**211**	**100.0**	**115**	**100.0**	**326**	**100.0**

4.7 Conclusion

Three hundred twenty nine medical records were reviewed. The majority of the patients were HIV-negative women. Women in the age group 30–59 years presented with locally advanced-stage ICC, which is similar to the stage presented in women older than 60 years. Both HIV-positive and HIV-negative women presented with locally advanced-stage ICC. Of the HIV-positive women, 18% had CD4 cell count below 200/µl compared to 2% in the HIV-negative women. In chapter 5, the results of the study are discussed and compared with those of other studies.

CHAPTER 5: DISCUSSION AND RECOMMENDATIONS

In this chapter, the findings of the present study are explained indepth. The agreement or disagreement with other similar studies are considered and commented on. The limitations of the study are outlined, and the recommendations arising from the findings in view of the current published literature are made.

5.1 Discussion

Globally, the incidence of new HIV infections was estimated to be 37.9 million in 2018 (UNAIDS, 2016). In South Africa, the prevalence of people living with HIV infection among adults (15–49 years) was 20.4% in 2018 (UNAIDS, 2016). There were 240 000 people newly infected with HIV in 2018 in South Africa (UNAIDS, 2016). These figures demonstrate a reduction in the number of new HIV infections from 390 000 in 2010 to 240 000 in 2018 in South Africa (UNAIDS, 2016).

In 2012, it was estimated that 12.2% of the South African population (6.4 million individuals) were HIV-positive, with demographic variability suggesting that the prevelance differed significantly by province (Shisana, Rehle, Simbayi, Zuma, Jooste, Zungu, Labadarios, & Onoya, 2015). The prevalence of HIV infection among people of reproductive age (15–49 years) in South Africa was 18.8% (Shisana *et al.*, 2015). Prevalence is the proportion of a population with a disease or condition at a specific period in time (Noordzij, Dekker, Zoccali, & Jager, 2010). HIV prevalence was highest among females aged 30–34 and males aged 35–49, with the females in this age group being at a higher risk of HIV infection and reported to be 1.6 times more likely to be HIV-positive compared to males (Shisana *et al.*, 2012).

In the same year (2012), 5 785 women were diagnosed with ICC, representing 15.4% of all histologically diagnosed neoplasms in females in South Africa (IARC, 2012). Five percent of the cervical cancer was diagnosed in the age group 30–34 years, and the largest proportion (13%) was diagnosed in the age group 45–49 years. Given the high prevalence of cervical cancer and HIV infection, especially in females of reproductive age, the two are considered as a significant public health problem in South Africa. Globally, the average age at diagnosis of ICC was 53 years regardless of HIV status (Arbyn *et al.*, 2020).

5.1.1 The proportion of HIV positive patients with ICC

In the PMHC series, it was found that 35% of women with ICC were HIV-positive, compared to 64% of those who were HIV-negative. The PMHC series was a retrospective study of all patients with cancer of the cervix who were treated in a particular year. Cancer was positively diagnosed by histology, and HIV serology was confirmed by an ELISA test in all patients. The Ugandan study by Wu et al. (2020), in which a similar cohort of hospital patients was positively diagnosed for cervical cancer and HIV, also found a 35.5% prevalence of HIV infection. In a South African study involving 672 patients with cervical cancer, of which 660 were tested, 138 were HIV-positive, giving a prevalence rate of 21% (Moodley, Moodley and Kleinschmidt, 2001). In these three reports, all patients were diagnosed with ICC, and nearly all had HIV tests performed.

Other investigators conducted case control studies using a control group of patients that were not diagnosed with ICC. Gichangi et al. (2002) in Kenya found an HIV seropositivity rate of 15% among women with ICC, compared to 12% among controls who were diagnosed with fibroids. However, after controlling for confounding factors such as age, marital status, life-time sex partners and past sexually transmitted illnesses, the odds of HIV infection were twice as high among the cases as those among controls (OR = 2.0; 95% CI:1.1–3.5; *P*=0.016) (Gichangi *et al.*, 2002). The Tanzanian study by Kahesa *et al*. (2008) was also a case control study in which the participants were 138 women with, and 138

without ICC who consented to have an HIV test. There searchers found HIV-positive rates of 21% among the cases and 11.6% among the controls, and that HIV positivity was associated with cervical cancer (OR = 2; 95% CI: 1.1–3.9) (Kahesa *et al.*, 2008).

In developed countries, the incidence of ICC among HIV-positive women is still high compared to that among their HIV-negative counterparts, even though to a less extent compared to those found in LMICs, as demonstrated earlier. A study by Abraham et al. (2013) in North America demonstrated this fact. In this study, 13 690 HIV-positive women and 12 021 HIV-negative women who did not initially have ICC were followed up for a period of between 1.5 and 10 years and assessed for the development of cancer. The HIV-positive women were followed up for a median time of 4.5 (interquartile range: 1.5 to 8.3) years, and the HIV-negative women were followed up for a median duration of 5.0 (interquartile range: 2.3 to 10) years. An elevated incidence of ICC was found in HIV-positive women, whereby 17 developed ICC compared to 4 in the HIV-negative cohort, with incidence rates of 26 and 6 per 100 000 person-years, respectively (Abraham *et al.*, 2013).

However, some studies did not demonstrate the elevated incidence of ICC in HIV-positive women relative to HIV-negative women. In the USA, it was reported that the incidence of ICC among HIV-positive women remained statistically indistinguishable from HIV-negative women in the Women's Interagency HIV Study (WIHS), an ICC prevention program (Massad, Hessol, Darragh, Minkoff, Colie, Wright, Cohen, & Seaberg, 2017). The WIHS enrolled 2 295 women who were tested for HIV by a western blot serology test and subsequently followed up for a mean duration of 11.8 years (median: 12.3 years; interquartile range: 4.4 to 20.1 years) with a 6-monthly Papanicolau (Pap) smear. The HIV-negative and HIV-positive cohort was followed up for a median duration of 17 years (interquartile range: 6.9–20.5 years) and 10,6 years (interquartile range: 3.9–19.0 years), respectively. Out of 488 seronegative women with a 6 615 person-years follow-up and 1 807 seropositive women with 20 561 follow-up years, no ICC was found in the former group, whereas four ICC cases were confirmed in

the latter group. There was no statistically significant difference (p=0.53) of ICC with an incidence rate of 19.5 cases per 100 000 person-years in the seropositive group, compared to no incidence in the seronegative group (Massad *et al.*, 2017). The investigators, however, noted that HIV-positive women exited the study earlier because of death from HIV associated illnesses as some were not on HIV treatment.

Overall, most investigators found that ICC incidence in an HIV-positive group was higher than that in an HIV-negative group.

5.1.2 Age of patients with ICC at diagnosis

The PMHC data revealed that the majority (35%, 115 of 329) of patients with ICC were younger than 50 years of age, followed by 23% (76 of 329) who were between 50 and 59 years of age, regardless of their HIV status. In South Africa, HIV infection was found to be higher in patients of childbearing age (15–49 years) than in patients older than 50 years (Shisana *et al.*, 2012). Analysis of HIV infection and ICC occurrence by age was beyond the scope of the current study and is, therefore, not discussed.

However, most studies reported that HIV-positive patients with ICC were relatively younger by an average of 10 years than HIV-negative ICC patients (Ntekim, Campbell & Rothenbacher, 2015). Gichangi *et al*. (2002) in their study in Kenya found that even though ICC patients were generally older than their controls with fibriods, the cases of women younger than 35 years were 2.6 times more likely to be HIV-positive than controls of similar age. They also reported that among the cases with ICC, HIV-positive patients were on average 10 years younger than HIV-negative patients (40 years versus 50 years; $P<0.001$). Wu *et al*. (2020) reported that the median age at diagnosis for ICC was 44 years (range: 39–48) for HIV-positive and 54 years (range: 47–62) for HIV-negative women. Lomalisa *et al*. (2000), in Johannesburg, South Africa, found that 73% of HIV-positive patients and 42% of negative patients were below 50 years of age at presentation ($P<0.001$), with a median age of 44±9.8 and 53±12.7 years, respectively. Kahesa *et al*. (2008) also reported that the mean age for HIV-

positive (44.3 years) was lower than that for HIV-negative (54 years; *P*=0.0001) women with ICC.

5.1.3 CD4 cell counts of patients with ICC

The present study found that overall, 92.4% of the women with ICC, whether HIV positive or negative, had CD4 cell counts more than 200/μL. However, sub-group analyses revealed that 18% of HIV-positive women had CD4 cell count below 200/μL, compared to 2% of HIV-negative women ($p<0.05$). Even though Wu *et al*. (2000) in Uganda did not observe a CD4 cell count level below 200/μL in their series, they however demonstrated that the median CD4 cell count levels were lower in HIV-positive patients (373; interquartile range: 300-500) as compared to HIV-negative patients (926; interquartile range: 639-1045) with ICC. The higher percentage of HIV-positive women who presented with CD4 cell counts below 200/μL in this study is supported by the observations in the study conducted by Gichangi *at al*.(2002), who found that a relatively high percentage (17%) of HIV-positive patients had CD4 cell counts below 200/μL compared to the low percentage (0.9%) of HIV-negative women with ICC.

Prior to 2013, the World Health Organization (WHO) ARV guidelines recommended that HIV-positive patients commence ARV when CD4 cell count was less than or equal to 350/μL, irrespective of HIV clinical stage (UNAIDS, 2016). It also recommended that HIV-positive patients with opportunistic infections or AIDS-defining cancers initiate ARV, regardless of CD4 cell count level (UNAIDS, 2016). After 2013, WHO ARV guidelines were updated recommending that HIV-positive patients with CD4 cell count less than or equal to 500/μL commence ARV, regardless of opportunistic infections or AIDS-defining cancers (UNAIDS, 2016).

In South Africa, the life expectancy of a 20-year-old HIV-positive female is 43.1 years when HAART is initiated at a baseline CD4 cell count above 200/μL (Johnson, Mossong, Dorrington, Schomaker, Hoffmann, Keiser, Fox, Wood, Prozesky, Giddy, & Garone, 2013). Anti-retroviral therapy (ART) is one of the

reasons for the decreasing incidence of ICC in HIV-positive patients due to the prolonged progression of HGSIL to ICC (Firnhaber *et al.*, 2010).

This study also revealed that 92% of the patients with ICC were diagnosed with squamous cell carcinoma (SCC) histology, followed by 3% of patients presenting with adenocarcinoma. Pelkofski, Stine, Wages, Gehrig, Kim & Cantrell (2016) working in Virginia, United States of America (USA) found that squamous histology was predominant compared to adenocarcinoma and other histological types. In a restrospective review of data from 114 patients with ICC between 1990 to 2012, they found that squamous histology dominated overall (77/114; 67.5%), followed by adenocarcinoma (30/114; 26.3%), small cell carcinoma (5/114: 4.4%) and adenosquamous (2/114; 1.7%) (Pelkofski, Stine, Wages, Gehrig, Kim & Cantrell, 2016). The histological pattern in the Virginia study was similar to the the Surveillance, Epidemiology, and End Results (SEER) report for 1975 to 2012 in USA that the predominating histology was SCC (68%), followed by adenocarcinoma (26%) (SEER, 2015).

5.1.4 HIV status and ICC stage

In this study, the majority of patients with ICC had advanced-stage disease from IIB (23.9%) to IIIB (51.8%), irrespective of their HIV status. This is similar to the observation reported in Nigeria, where more than 80% of the women with ICC presented with advanced-stage disease (Abdus-Salam, Ogunnorin & Abdus-Salam, 2008). In the Nigerian study, where records of 221 patients with ICC were analyzed to assess the prevalence of HIV infection, only 6 out of 221 were HIV-positive, of which 2 were in stage IIB, and the remaining 4 were in stages IIA, IIIA, IIIB and IVB. Fruchter, Maiman, Arrastia, Matthews, Gates, & Holcomb (1998), in an earlier study compared the predictors of advanced disease in HIV-positive and HIV-negative women and found that although major predictors of advanced cervical cancer stage are similar in HIV-positive and negative women, HIV infection was associated with a 3-fold increase in advanced stage cancer (odd ratio = 3.1; p=0.03). Lomalisa *et al*. (2000) observed no difference in the

stage of cancer at presentation between HIV-positive and HIV-negative patients with 65% of the former and 55.4% of the latter presenting with stage III and IV, respectively (p=0.177) . Ferreira *et al*. (2017) found that the majority (40%) of women with ICC presented with advanced-stage disease (stage III) irrespective of their HIV status. Other studies also reported that patients in LMICs presented with advanced-stage ICC regardless of their HIV status (Gichangi *et al.*, 2003; Wu *et al.*, 2020).

Ntekim *et al*. (2015) conducted a systematic review of the literature on the optimal treatment of cervical cancer in the presence of HIV infection. Among other things, they found no difference in the distribution of patients with early-stage disease or late-stage diease between HIV-positive and HIV-negative women. They postulated that late-stage of ICC at diagnosis may be due to lack of access to healthcare facilities (Ntekim, *et al*. 2015).

By contrast, a study conducted in Kenya found that patients with ICC diagnosed through cervical cancer screening programmes presented with early-stage disease (Mungo, Cohen, Maloba, Bukusi, & Huchko, 2013). Cervical cancer screening programmes have been implemented in South Africa with HIV-positive patients recommended to undergo screening every 3 years, and HIV-negative patients, every 5 years (Support, HPV & Primary, 2015).

5.2 Limitations

Selection bias may have been a factor because only the patients who attended Pietersburg Hospital were included in the study, as other patients from Limpopo province with ICC might not have reached the hospital or were treated in other hospitals in or outside the province during this period.

5.3 Conclusion

This retrospective study did not indicate any difference in the occurrence of ICC in HIV-positive compared to HIV-negative patients, despite a high prevalence of HIV infection in South Africa. The majority of the patients with ICC were younger than 50 years of age, regardless of their HIV status. There was no difference in the stage at which patients were diagnosed with ICC among the HIV-positive and HIV-negative women, as both groups presented with advanced-stage disease (IIB–IIIB). However, HIV-positive patients were more likely to present with CD4 cell counts below 200/μL than HIV-negative patients with ICC ($p < 0.05$).

5.4 Recommendations

This study highlights the need for improving and strengthening cervical cancer screening programmes by educating the public and commencing early and regular Papanicolaou (Pap) smears, especially among women at risk, regardless of their HIV status, to achieve early-stage diagnosis and reduce the number of women presenting with advanced stage invasive cervical cancer (ICC) .

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7. APPENDICES

7.1 Appendix A: Timeframes

ACTIVITY	TIMEFRAME
CEO permission	20 August 2014
SMU SREC approval	19 September 2014
SMUREC	9 April 2016
Provincial permission obtained	30 July 2015
Data collection	August 2015 to November 2015
Data capturing	January 2016 to April 2016
Data analysis	July 2016 to December 2016
Report writing	January 2018 to December 2018
First draft of the report	October 2019
Reviews by supervisor	November 2019
Corrections	January 2020 to March 2020
Corrected report	March 2020
Final report	April 2020

7.2 Appendix B: Sefako Makgatho Health Sciences University School Research Ethics Committee

School of Medicine
Administration Office

P O Box 210
Medunsa Campus

☎ (012) 521 4307
Fax: (012) 521 5811
e-mail: Magda.Henrico@ul.ac.za

UNIVERSITY OF LIMPOPO

INTERNAL MEMO

TO : Dr Dzivani
Department: Radiation Oncology
Box 210
Bendor
Polokwane, 0713

FROM : Prof S Mda
Chairperson: SREC
Box 168
University of Limpopo
Medunsa Campus
0204

DATE : 17/09/2014

SUBJECT: **Title:** **Prevalence of HIV infection among patients with invasive cervical cancer in Polokwane/Mankweng Hospital complex**

With reference to the SREC meeting held 17 September 2014.

Your research protocol with the title noted above was reviewed by School Research Ethics Committee (SREC) dated 17 September 2014.

NB: **The revised protocol to reach Mrs Henrico's office within 3 months (SREC closing dates to be kept in mind within this period). (Room S014A, School of Medicine, Ground Floor, Clinpath Building.)**

Protocols not received within the above specified period will be withdrawn from SREC. Researchers will then have to submit new submissions to SREC.

When compiling revised protocols please ensure to address revisions/recommendations as requested by SREC, point by point in a **covering letter** (according to the protocol).

The Committee **DID NOT** recommend the protocol. The protocol to be **re-submitted to SREC again**.

The Committee recommended the following revisions:

Title:
Amended to read as "**The profile of HIV infected patients with invasive Cervical Cancer in Polokwane/ Mankweng complex".**

Literature Review: Correct grammatical errors. Relate the findings/outcomes e.g. the 1st two sentences in pg. 5 are unnecessary. The same with subsequent references.

Finding solutions for Africa

Purpose of Study: Delete "in 2013" from the sentence starting with "The aim of this study……..".

Study Design: Add cross-sectional study to "retrospective"

Study Population:
Sample: Complete sample of patients presenting for management of ICC during 2013.
Remove any other information and put under eligibility/selection criteria.

Setting: Clarify if both hospitals will provide patients.

Reliability, Validity & Objectivity: The researcher does not specify how the factors that affect these themes will be mitigated.

Bias: The researcher needs to indicate the type of bias anticipated and how he/she deal with it.

NB: Your corrected protocol must be co-signed by your supervisor as an indication of his/her approval of the updated version.

We are looking forward to your response.

Yours sincerely

PROF S MDA
CHAIRPERSON: SREC

SUPERVISOR'S APPROVAL OF REVISIONS DONE:

I, _____ as the Supervisor of the protocol with the title:

_____

_____

_____

of _____(Student Number) _____

have studied and hereby approve the submission of the revised protocol to SREC.

SUPERVISOR: _____ SIGNATURE: _____

DATE: _____

School of Medicine
Molotlegi Street, Ga-Rankuwa, 0208
Telephone: 012 521 4321 **Fax:** 012 521 5811
Email: nazeema.ebrahim@smu.ac.za
PO BOX 210, MEDUNSA, 0204

INTERNAL MEMO

TO : Dr Ndivhuwo Dzivhani
Department: Radiation Oncology
Box 210
Bendor
Polokwane, 0713

FROM : Prof S Mda
Chairperson: SREC
Sefako Makgato Health Sciences University
PO Box 210
Medunsa, 0204

DATE : **27th February 2015**

SUBJECT : Title: **The profile of Human Immunodeficiency Virus-infected patients with invasive cervical cancer in Polokwane/Mankweng Complex Hospital**

Your research protocol with the title noted above was reviewed by School Research Ethics Committee (SREC) dated **15th January 2015.**

NB: **The revised protocol to reach Mrs Henrico's office within 3 months (SREC closing dates to be kept in mind within this period). (Room S014A, School of Medicine, Ground Floor, Clinpath Building.)**

Protocols not received within the above specified period will be withdrawn from SREC. Researchers will then have to submit new submissions to SREC.

When compiling revised protocols please ensure to address revisions/recommendations as requested by SREC, in a **covering letter** point by point in **tabular format** (according to the protocol).

The Committee **provisionally approved** the protocol subject to the following revisions:

1. **Study Problem**:
The researcher should avoid using the word "our", as in "our population" and "our patients"; the patients (and population) don't belong to "them", but they are rather treated at the hospital complex.

2. **Literature review**
This should come after study problem, but before Aim and Objectives of the study and Research Questions. Literature Review will thus remain as point 2, but point 3 will be Purpose of study, with 3.1 as Aim and 3.2 as Objectives. Research Question will then be point 4, and Study Methods point 5, etc.

3. **Objectives**
The researcher should add a fourth objective where (s)he will assess whether there is a correlation between HIV status and clinical and laboratory features of patients with ICC and with stage of ICC.

4. **Study population**
What is the estimated number of patients with ICC that were treated at the hospital complex in 2013?

5. **Data Analysis**
The researcher needs to state the statistical package that will be used for analysis.

6. **Data Collection Form**
The researcher should remove patient identifiers from the Data Collection Form, e.g. Name and telephone number.

We are looking forward to your response.

Yours sincerely

PROF S MDA
CHAIRPERSON: SREC

SUPERVISOR'S APPROVAL OF REVISIONS DONE:

I, _____ as the Supervisor of the protocol with the title:

_____

_____

_____

of _____(Student Number) _____

have studied and hereby approve the submission of the revised protocol to SREC.

SUPERVISOR: _____ SIGNATURE: _____

DATE: _____

7.3 Appendix C: Sefako Makgatho Health Sciences University Research Ethics Committee certificate

Sefako Makgatho Health Sciences University
Research & Postgraduate Studies Directorate
Sefako Makgatho University Research Ethics Committee
(SMUREC)

Motlotlegi Street, Ga-Rankuwa 0208
Tel: (012) 521 5617/3698 | fax: (012) 521 3749
Email: lorato.phiri@smu.ac.za
P.O. Box 163 Medunsa 0204

APPROVAL NOTICE - NEW APPLICATION

09 April 2015

Dr N Dzivhani
Department of Radiation Oncology
University of Limpopo, Turfloop Campus

MEETING:	**03/2015**
SMUREC Ethics Reference Number:	**SMUREC/M/65/2015: PG**

The New Application received on **19 March 2015**, was reviewed by members of Sefako Makgatho University Research Ethics Committee on **09 April 2015** and was approved on **09 April 2015.**

Title:	The profile of human immunodeficiency virus infected patients with invasive cervical cancer in Polokwane/Mankweng Complex Hospital
Researcher:	Dr N Dzivhani
Supervisor:	Dr F Ooko
Hospital Superintendent:	Dr S Maweya (Pietersburg Hospital)
Department:	Radiation Oncology
School:	Medicine
Degree:	Fellowship in Radiation Oncology

Please note the following information about your approved research protocol:

Protocol Approval Period:	**09 April 2015 – 09 April 2016**

Please remember to use your protocol number (**SMUREC/M/65/2015: PG)** on any documents or correspondence with the REC concerning your research protocol. Please note that the REC has the prerogative and authority to ask further questions, seek additional information, require further modification, or monitor the conduct of your research and the consent process.

After Ethical Review: Please note a template of the progress report is obtainable in the Research Office and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit. Translation of the consent document in the language applicable to the study participants should be submitted.

International Organisation **(IORG0004319),** Institutional Review Board **(IRB00005122),** Federal Wide Assurance **(FWA00009419)** **Expiry date: 11 October 2016** and **NHREC No: REC 210408-003**

Sincerely

DR C BAKER
DEPUTY CHAIRPERSON SMUREC

SEFAKO MAKGATHO
HEALTH SCIENCES UNIVERSITY
SMU Research Ethics Committee
Chairperson
Date: 09/04/2015

Sefako Makgatho Health Sciences University
Research & Postgraduate Studies Directorate
Sefako Makgatho University Research Ethics Committee
(SMUREC)

Motlotlegi Street, Ga-Rankuwa 0208
Tel: (012) 521 5617/3698 | fax: (012) 521 3749
Email: lorato.phiri@smu.ac.za
P.O. Box 163 Medunsa 0204

APPROVAL NOTICE – CONTINUATION OF STUDY

07 April 2016

Dr N Dzivhani
Department of Radiation Oncology
University of Limpopo, Turfloop Campus

MEETING:	**03/2015** **03/2016**
SMUREC Reference Number:	**SMUREC/M/65/2015: PG**
Title:	The profile of human immunodeficiency virus infected patients with invasive cervical cancer in Polokwane/Mankweng Complex Hospital
Researcher:	Dr N Dzivhani
Supervisor:	Dr F Ooko
Hospital Superintendent:	Dr S Maweya (Pietersburg Hospital)
Department:	Radiation Oncology
School:	Medicine
Degree:	Fellowship in Radiation Oncology

The New Application received on **19 March 2015**, was reviewed by members of Sefako Makgatho University Research Ethics Committee on **09 April 2015** and was approved on **09 April 2015.**

On the **07 April 2016** SMUREC **approved** continuation of this study.

Please note the following information about your approved research protocol:

Protocol Approval Period: **09 April 2016 – 09 April 2017**

Please remember to use your protocol number (**SMUREC/M/65/2015: PG)** on any documents or correspondence with the REC concerning your research protocol. Please note that the REC has the prerogative and authority to ask further questions, seek additional information, require further modification, or monitor the conduct of your research and the consent process.

After Ethical Review: Please note a template of the progress report is obtainable in the Research Office and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit. Translation of the consent document in the language applicable to the study participants should be submitted.

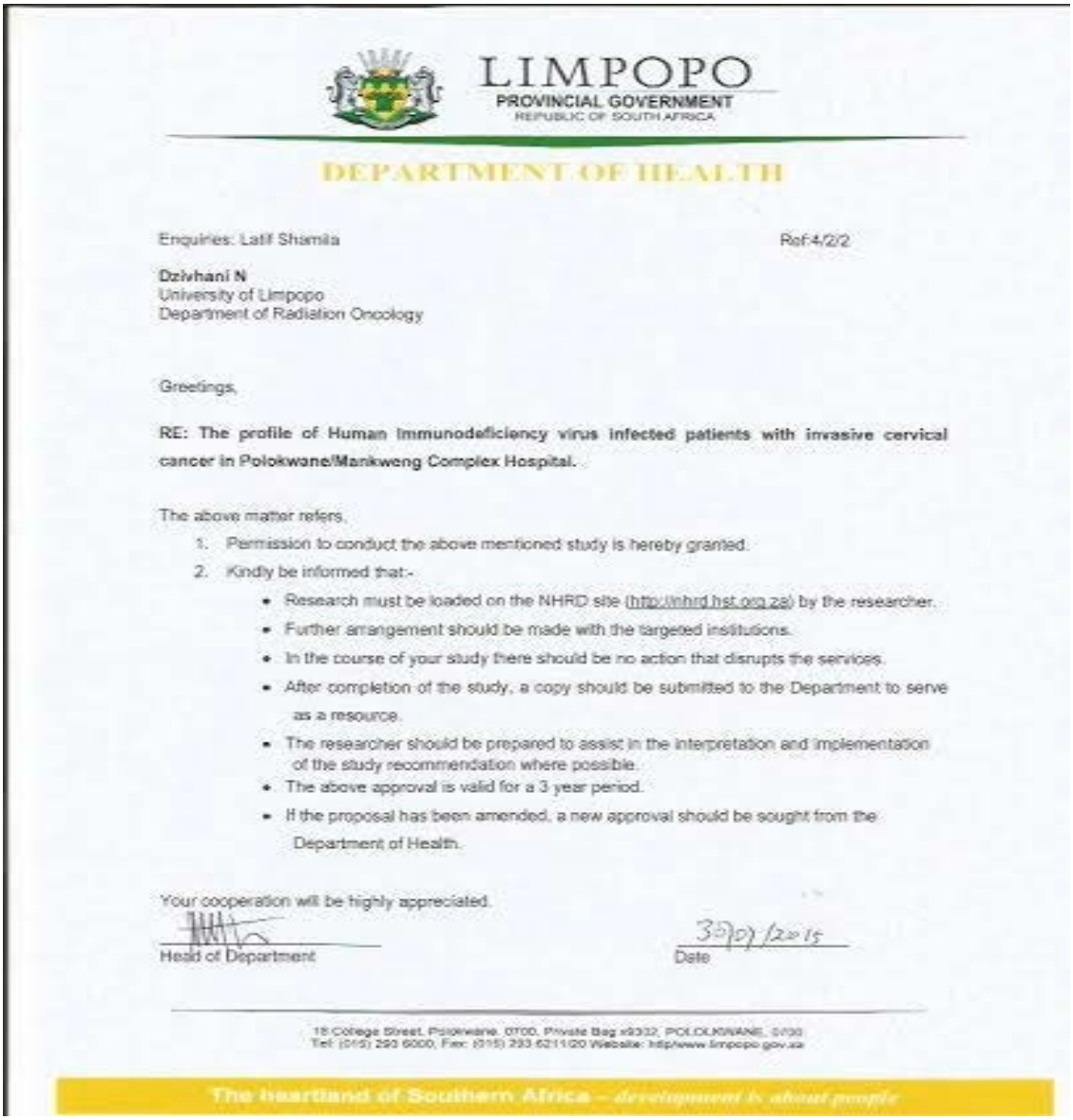
International Organisation (IORG0008691), **Institutional Review Board** (IRB000010386) Expiry date: 09 December 2018, **Federal Wide Assurance** (FWA000023943) Expiry date: 31 August 2017 and **NHREC No: REC 210408-003**

Sincerely

DR C BAKER
DEPUTY CHAIRPERSON SMUREC

SEFAKO MAKGATHO
HEALTH SCIENCES UNIVERSITY
SMU Research Ethics Committee
Chairperson
Date: 07/04/2016

7.4 Appendix D: Limpopo Department of Health and Social Development certificate



LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF HEALTH

Enquiries: Latif Shamila Ref:4/2/2

Dzivhani N
University of Limpopo
Department of Radiation Oncology

Greetings,

RE: The profile of Human Immunodeficiency virus infected patients with invasive cervical cancer in Polokwane/Manikweng Complex Hospital.

The above matter refers.

1. Permission to conduct the above mentioned study is hereby granted.
2. Kindly be informed that:-
   - Research must be loaded on the NHRD site (http://nhrd.hst.org.za) by the researcher.
   - Further arrangement should be made with the targeted institutions.
   - In the course of your study there should be no action that disrupts the services.
   - After completion of the study, a copy should be submitted to the Department to serve as a resource.
   - The researcher should be prepared to assist in the interpretation and implementation of the study recommendation where possible.
   - The above approval is valid for a 3 year period.
   - If the proposal has been amended, a new approval should be sought from the Department of Health.

Your cooperation will be highly appreciated.

Head of Department

30/01/2015
Date

15 College Street, Polokwane, 0700, Private Bag x9302, POLOKWANE, 0700
Tel: (015) 293 6000, Fax: (015) 293 6211/20 Website: http://www.limpopo.gov.za

7.5 Appendix E: Permission to conduct the study from the Pietersburg Hospital campus

LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF
HEALTH & SOCIAL DEVELOPMENT
PIETERSBURG / MANKWENG HOSPITAL COMPLEX

CAMPUS: [X] PIETERSBURG [ ] MANKWENG
ENQUIRIES:..... EXTENSION:.....
REFERENCE NO:.....

The Acting Clinical Manager
Clinical Services
Pietersburg Hospital

Subject: Permission to carry out a clinical study at Pietersburg Hospital.

I am a final year post-graduate student in the department of radiation oncology at Pietersburg Hospital and would like to carry out a study for part fulfillment of the requirement for fellowship of the College of Radiation Oncologists of South Africa [FC RadOnc (SA)].

The study topic is: The profile of Human Immunodeficiency Virus infected patients with Invasive Cervical Cancer in Polokwane/Mankweng Complex Hospital in 2013. This is a retrospective study utilizing patients' data obtained in radiation oncology. Patients' identity and sensitive information will be kept confidential and may be revealed only to authorized personell. Ethics approval is being sought from University of Limpopo MREC.

Thank you for your assistance.

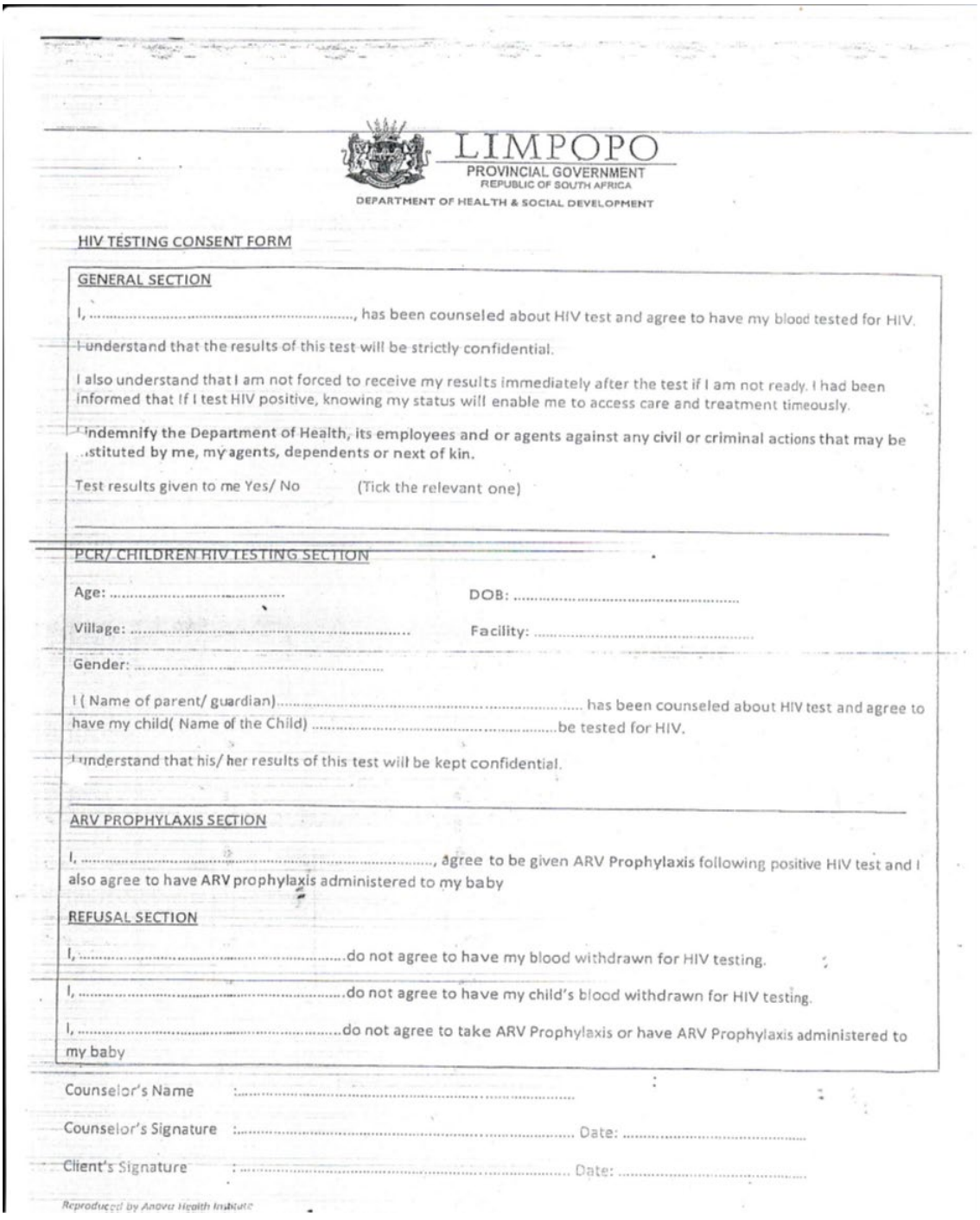
PERMISSION AND APPROVAL.

1. Recommended / ~~Not Recommended~~
   Comments:.....
   Head of Joint Department: Dr F. Ooko
   Signature:..... Date: 2015/02/24
2. Approved / ~~Not Approved~~
   Comments:.....
   Hospital Acting Clinical Manager: Dr C.T Ntsoane
   Signature: ..... Date: 2015/02/24

PIETERSBURG / MANKWENG HOSPITAL COMPLEX
PIETERSBURG CAMPUS
DEPARTMENT OF HEALTH AND WELFARE
COR HOSPITAL & DORP STREET
Private Bag X 9316
POLOKWANE 0700

PIETERSBURG / MANKWENG HOSPITAL COMPLEX
MANKWENG CAMPUS
DEPARTMENT OF HEALTH AND WELFARE
Private Bag X 1117
SOVENGA
0727

7.6 Appendix F: HIV testing consent form



LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA
DEPARTMENT OF HEALTH & SOCIAL DEVELOPMENT

HIV TESTING CONSENT FORM

GENERAL SECTION

I, ..., has been counseled about HIV test and agree to have my blood tested for HIV.

I understand that the results of this test will be strictly confidential.

I also understand that I am not forced to receive my results immediately after the test if I am not ready. I had been informed that If I test HIV positive, knowing my status will enable me to access care and treatment timeously.

Indemnify the Department of Health, its employees and or agents against any civil or criminal actions that may be ..stituted by me, my agents, dependents or next of kin.

Test results given to me Yes/ No (Tick the relevant one)

PCR/ CHILDREN HIV TESTING SECTION

Age: ..... DOB: .....

Village: ..... Facility: .....

Gender: .....

I (Name of parent/ guardian)..... has been counseled about HIV test and agree to have my child(Name of the Child) .....be tested for HIV.

I understand that his/ her results of this test will be kept confidential.

ARV PROPHYLAXIS SECTION

I, ..., agree to be given ARV Prophylaxis following positive HIV test and I also agree to have ARV prophylaxis administered to my baby

REFUSAL SECTION

I, ...do not agree to have my blood withdrawn for HIV testing.

I, ...do not agree to have my child's blood withdrawn for HIV testing.

I, ...do not agree to take ARV Prophylaxis or have ARV Prophylaxis administered to my baby

Counselor's Name :.....

Counselor's Signature :..... Date: .....

Client's Signature :..... Date: .....

Reproduced by Anova Health Institute

7.7 Appendix G: Data collection form

Study No:
Age :
LP No: **Computer No:**
Diagnosis:
Histology Ref. No.:
Histology type: **Grade:**
IVP:Hydronephrosis :N / Y
Chest X-ray: (Lung metastasis) : N / Y

Recent Blood Results:							
HIV Status	**Absolute CD4 COUNT**	**Total WCC**	**PLT**	**Hb**	**Urea**	**Creatinine**	**LFT**

Gynaecology Exam:	**Primary Assessment: N / Y Date:**
Vulva:	**Lymph nodes: N/ Y (Where ?)**
Vagina:	**Metastasis: N / Y (Where ?)**
Cervix:	**Tumour with parametrial invasion: N / Y**
Uterus:	**Tumour extends to pelvic wall: N / Y**
Rectum:	**Tumour extends to lower 1/3 of the vagina: N/Y**
Bladder:	**TInvades mucosa of bladder or rectum: N / Y**

FIGO Stage:		
Doctor:	**Signature:**	**Date:**

Table 4: Data collection sheet

Computer number	Age	HIV status	Stage	CD4 count	Histology subtype