Treatment responses in HIV-positive and HIV-negative patients treated for uterine cervix cancer with radical intent at Universitas Annexe hospital

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TREATMENT RESPONSES IN HIV-POSITIVE AND HIV-NEGATIVE PATIENTS TREATED FOR UTERINE CERVIX CANCER WITH RADICAL INTENT AT UNIVERSITAS ANNEXE HOSPITAL

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DECLARATION OF INDEPENDENT WORK

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I SYDNEY GLADSTONE MASALLA - student number: 8733005 – do hereby declare that this project, submitted for the degree MAGISTER TECHNOLOGIAE: RADIOGRAPHY (THERAPY) in the SCHOOL OF HEALTH TECHNOLOGY, FACULTY OF HEALTH AND ENVIRONMENTAL SCIENCES, is my own independent work that has not been submitted before, to any institution by me or anyone else as part of any qualification.

Signature of student

2009 – 11 – 24

Date

Dedicated to my mom:

Sarah Masalla,

who passed on during the final writing phase

of this thesis.

She always inspired me with the words of

Benjamin Franklin:

"If a man empties his purse into his head,

no man can take it away from him.

An investment in knowledge always

pays the best interest."

Although she is no longer with us, she is forever

remembered.

I am sure she shares my joy and happiness

in her place of quiet rest.

To my wife, Jennie

And our children:

Nigel, Nicole and Neilen –

Your constant reference to:

"...daddy's working on the computer..."

Had me feeling like a

"Wannabe IT technologist"

<u>Many thanks</u>

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your role in this process.

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an enriching learning experience, and

Your joie de vivre made the experience fun!

And my co-supervisor

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D. SUMMARY

A retrospective study was conducted to analyse the treatment responses in HIV+ and HIV- patients that were treated with the same standard of radical treatment for FIGO stage II and III Ca Cx, at DROUAH. The main objective of the study was to determine how the HIV+ patients tolerated their treatment. The secondary objective was to retrospectively analyse the overall outcomes and therapeutic benefits of the treatment in terms of quality of life and tumour responses amongst the HIV+ patients. General condition of patients, adverse responses to treatment, and tumour responses were used as indicators of overall outcomes and therapeutic benefits of the treatment. The HIV- patients were included in the study to benchmark the therapeutic benefits in terms of quality of life and tumour response.

Ninety six (96) patients who were treated with radical intent for FIGO stage II and III Ca Cx at DROUAH were included in the study. The patients that were included in the study received treatment between January 2002 and August 2006. All the patients that were included in the study were treated using a combination of EBRT, HDR-ICBT and concurrent chemotherapy. The EBRT was given in daily fractions of 2 Gy to a total of 50 Gy. The HDR-ICBT was given in 4 to 6 weekly fractions varying between 2.0 Gy and 2.5 Gy per fraction, to a minimum total dose of 15 Gy to point A. Five weekly cycles of Cisplatin were given as the chemotherapeutic agent.

The data that was used for the current study constituted oncologists' and other medical staff reports in the patients' treatment files. An electronic Excel® data source form was used as the research tool to collect data from the eligible patients' treatment files. The data was processed and analysed by statisticians at the department of Biostatistics at the UFS. The Fisher's exact- and the Chi-squared tests were used to analyse the data.

Although the focus of the current study was not to compare the HIV+ and HIV- patients, parallel analyses of the two groups were conducted. From the 96 patients

that were included in the data sub-analysis, there were 19 reported deaths, representing an 18-month overall survival rate of 80.2%. Twelve of the 19 reported deaths were HIV+ patients, whilst the remaining seven were HIV-. This implies a 67.6% 18-month overall survival rate for HIV+ patients, and an 88.1% rate for HIV- patients in the study.

From this retrospective analysis it can be concluded that HIV+ patients treated at DROUAH for FIGO stage II and III Ca Cx with radical intent do not tolerate their treatment as well as their HIV- counterparts. The tumour responses of HIV+ patients were analysed, with HIV- patients used to benchmark the therapeutic benefits in terms of quality of life and tumour response. The study results suggest that the overall quality of life of HIV+ patients was more adversely affected than that of HIV- patients, in terms of both general condition and the adverse responses that were reported.

1. CHAPTER 1: INTRODUCTION AND BACKGROUND

1.1 INTRODUCTION

The successful treatment and management of cancer continue to pose challenges to both researchers and oncologists (Symonds 2001:1107). The success of cancer treatment is determined by the extent to which local tumour control is accomplished, while damage to surrounding normal tissue and quality of life are simultaneously limited to a minimum (International Commission on Radiation Units and Measurements, ICRU 1985). Medical scientists continue to engage in research aimed at improving the available treatment for cancer in order to enhance cancer cure rates (Jemal 2002:23). Such improvements in the treatment and management of cancer will lead to enhanced local tumour control, improved survival rates and a higher quality of life for patients (Symonds 2001:1107).

According to the December 2006 AIDS Epidemic Update released by the United Nations Joint Programme on HIV/AIDS (UNAIDS), more than 15 million Africans have died from conditions related to the Human Immunodeficiency Virus (HIV) and the Acquired Immune Deficiency Syndrome (AIDS) [HIV/AIDS] over the past three decades. It is expected that the impact of HIV/AIDS will remain severe for many years to come (UNAIDS 2006). This expectation poses challenges to the health sector [World Health Organisation (WHO) 2008], which relate to physical, financial and human resources (WHO 2008). HIV/AIDS also has important effects on society, the economy and politics (Barnett and Whiteside 2002:6). The negative impact of the HIV/AIDS epidemic is not only experienced by those countries severely and directly affected by the epidemic, but by the entire international community (UNAIDS 2006).

Marco (1999:2) states that cancer has been around forever, but the conditions related to the Human Immunodeficiency Virus and the Acquired Immune

Deficiency Syndrome (HIV/AIDS) are relatively new. Most of the attitudes expressed in the face of HIV/AIDS and cancer relate to fear and hopelessness. Whether they are based on perceptions or facts, these attitudes are largely influenced by the morbidity and high death rates commonly associated with these conditions. The treatment and management of cancer pose challenges to patients and the team involved in treating such patients. Thus, it would seem that patients who are diagnosed as having both cancer and HIV/AIDS are confronted with complex health challenges.

This study investigates the treatment responses of patients who were treated with curative or radical intent for cancer of the uterine cervix (Ca Cx) at the Department of Radiation Oncology at the Universitas Annexe Hospital in Bloemfontein. (For the purposes of this study the Department of Radiation Oncology at the Universitas Annexe hospital in Bloemfontein will be denoted by the following acronym: DROUAH.) The study focuses on the effect HIV infection has on the patients' tolerance of the radical treatment approach.

Chapter 1 provides background on key aspects relating to the study, which include Ca Cx, DROUAH and HIV/AIDS. The chapter concludes with the rationale, aims and objectives of the study, as well as the motivation and significance of the study. Background to Ca Cx is dealt with first.

1.2 BACKGROUND TO CA CX

Uterine cervical carcinoma, better known as cervix cancer (Ca Cx), develops in the lining of the cervix, which is the lower part of the uterus that enters the vagina (Graham, Sotto, and Paoloucek 1988:19). Ca Cx usually develops over time, with normal cervical cells gradually mutating or undergoing changes; and then it grows out of control to become pre-cancerous and then cancerous (Piver 1996:79).

Cervical intra-epithelial neoplasia (CIN) is the term used to describe the abnormal changes that take place in cervical cells (Graham *et al.* 1988:19). Graham, Sotto and Paoloucek (1988:42) classify CIN according to the degree of cell abnormality, with low-grade CIN indicating a minimal change in the cells and high-grade CIN indicating a greater degree of abnormality. CIN may progress to a squamous intra-epithelial lesion (SIL) or to carcinoma-in-situ (Beahrs, Henson, Hutter, and Kennedy 1992:156). SIL is a condition that precedes Ca Cx, while carcinoma-in-situ is a condition where the carcinoma does not extend beyond the epithelial membrane. SIL and carcinoma-in-situ may progress to invasive cervical carcinoma, in cases where the carcinoma has spread to healthy tissue.

There are three commonly known types of Ca Cx, namely Squamous cell carcinoma, Adenocarcinoma and Adeno-Squamous carcinoma (Chang, Ganz, Hayes, Kinsella, Pass, Schiller, Stone and Stretcher 2006:874). Squamous cell carcinomas originate from cells that lie on the surface of the cervical lining and are the most common cervix cancers, constituting approximately 80% of all Ca Cx (Chang *et al.* 2006:874). Adeno-carcinomas originate from cells in the glandular surface of the cervix, and constitute approximately 10-12% of all Ca Cx (Chang *et al.* 2006:874). Adeno-Squamous carcinomas make up about 3-5% of Ca Cx, and they have characteristics of both Squamous- and Adeno-carcinomas (Chang *et al.* 2006:874).

1.3 EPIDEMIOLOGY OF CA CX

The origin and development of Ca Cx are unclear (Abraham and Allegra 2001:212). However, Abraham and Allegra suggest that sexually transmitted infection with the human papilloma virus (HPV) is strongly associated with cervical and vulvar cancer, and is the most important risk factor for Ca Cx. They further state that evidence of HPV is found in nearly 80% of cervical carcinomas. HPV is a common sexually transmitted disease, and according to a study published in the United States of America (USA) in 2000, 43% of women of “college age” were infected in a 3-year period (Bosch, 2002:248). Factors that

raise the risk of being infected with HPV include becoming sexually active at an early age, having many sexual partners (or having sex with a man who has had many partners), and/or having sex with a man who has penile warts (Bosch 2002:248).

Infection with HIV reduces the immune system's ability to fight infection, including HPV infection (Bosch 2002:249). This increases the likelihood that precancerous cells will progress to cancer. Because infection with a sexually transmitted disease (STD) is a risk factor for Ca Cx, any risk factors for developing STD's are also risk factors for developing Ca Cx (Ellerbrock, Chiasson and Bush 2000:1033). Sexual activity that increases the risk for infection with HPV and HIV and for Ca Cx includes the following: having multiple sexual partners or having sex with a promiscuous partner; a history of STD; and sexual intercourse at a young age (De Vita, Hellman, and Rosenberg 2004:887).

Infection with HIV, the virus that causes AIDS, is a risk factor for Ca Cx (De Vita, *et al*. 2004:887). These authors state that when a woman is infected with HIV, her immune system is less able to fight off early cancers. Women whose immune systems have been suppressed by corticosteroid medications, kidney transplants or treatments for other types of cancers or AIDS are also at greater risk.

1.4 INCIDENCE OF CA CX

Ca Cx is the sixth most common cancer in women in the world, after carcinoma of the breast, lung, colorectum, endometrium and ovary (Perez and Kavanagh 2004:1800). More than 80% of cases of Ca Cx are reported in underdeveloped countries (Stewart and Kleihues 2003:215). Jemal (2002:23) claims that approximately 500 000 cases of Ca Cx are diagnosed across the world each year, and approximately half (50%) of these cases lead to death. In 2001, the American Cancer Society estimated that there were approximately 12 900 new cases of Ca Cx in the United States of America (USA), with 4 400 deaths resulting from the disease in addition to over 50 000 cases of carcinoma in situ

(Perez and Kavanagh 2004:1800).

There is a strong relationship between the incidence of Ca Cx and the standard of living in societies (Parkin, Bray and Devesa 2001:554). The disease is more common among women of poor socio-economic status, who have a lower probability of receiving regular screening and early treatment, (Chang *et al.* 2006:874). Ca Cx is more common in middle-aged and older women (Chang *et al.* 2006:874), with an increased incidence among African American, Hispanic and Native American women. In 2002, it was reported that there had been a 75% decrease in incidence and mortality from Ca Cx in developed nations over the past 50 years (Parkin *et al*. 2001:554). This decrease is mainly due to the effective institution of Ca Cx screening programs in wealthier countries (Parkin *et al*. 2001:554).

Whereas developed countries have a low incidence of the disease with high cure rates, the patients in underdeveloped countries have a high rate of locally advanced disease (Duenas-Gonzalez, Cetina, Sánchez, Gomez, Rivera, Hinojosa, López-Graniel, Gonzalez-Enciso and de la Garza 2003:390). These locally advanced conditions require a much more aggressive treatment approach, with generally poor prospects for survival. Developing countries with a high incidence of Ca Cx are Zimbabwe, Uganda, South Africa, Gambia and Algeria (Mqoqi, Kellet, Sitas and Jula 2004:22).

1.5 STAGING OF CA CX

Cancer staging represents a core aspect of understanding a patient's clinical condition and planning the most appropriate therapy for each patient (Odicino, Miscioscia, Giancarlo, Rampinelli, Sartori and Pecorelli 2007:8). Staging a tumour is one of the most important steps in the process of determining the prognosis and outcome of a disease (Odicino *et al.* 2007:8).

The issue of Ca Cx staging dates back to 1928, when the Health Organisation of

the League of Nations asked the Radiological Sub-commission of the Cancer Commission to explore the possibility of having a uniform statistical report on radio-therapeutic results for Ca Cx (Greene, Page, Fleming, Fritz, Balch and Haller 2002:47). The Sub-commission reported that this could be accomplished if various institutions produce their results in a uniform and consistent manner. Accordingly, a group of experts was given the task of producing an appropriate classification framework, and subsequently, the first staging system for Ca Cx was published in 1929. These recommendations became known as the League of Nations Classification for Ca Cx. Since then, eight changes to the staging classification have been made, with the International Federation of Gynaecology and Obstetrics (FIGO) becoming the main sponsor about 50 years ago (Odicino *et al.* 2007:8).

The FIGO system, a clinical staging system, stages the cancer based on findings from clinical examination and evaluation, and basic radiographic studies (Chang *et al.* 2006:877). The examinations include inspection, palpatation, colposcopy with biopsy and endocervical curettage, cervical conisation, hysteroscopy, intravenous pyelogram and plain films of the chest and bones. The FIGO staging system is appropriate for invasive Ca Cx, but not for precancerous lesions (Chang *et al*. 2006:878). Appendix 1 contains a summary of the 2002 FIGO staging system as provided by the American Joint Committee on Cancer (AJCC) in the AJCC Cancer Staging Manual (De Vita *et al.* 2004:887). The next section presents an overview of the demographics of the DROUAH.

1.6 UNIVERSITAS ANNEXE HOSPITAL

This research study was conducted retrospectively to analyse the treatment responses of HIV-positive (HIV+) and HIV-negative (HIV-) patients who received treatment for Ca Cx with radical intent at DROUAH. Bloemfontein is the capital of the Free State province, one of nine provinces in the Republic of South Africa. The Free State is surrounded by the Northern Cape, Eastern Cape, North West and Gauteng provinces, as well as the

Kingdom of Lesotho. DROUAH is one of two oncology departments that serve the entire Free State and Northern Cape provinces, parts of the Eastern Cape and North West provinces, and the Kingdom of Lesotho. The second oncology department is privately owned and primarily caters for patients with medical insurance, and was not included in this study.

The regions served by the Bloemfontein oncology facilities constitute a vast geographical area, with a predominantly rural population. The population of the Free State province alone is estimated at approximately 2.9 million people, with 85% of these people dependent on public health services (Statistics South Africa, 2008). The overwhelming dependence (85%) of the population on public health services was further justification for exclusion of the private practice from this study. The Goldfields region of the Free State, which is well known for its gold mining activities, also forms part of the Department's service area. The population of the hospital's service area includes people with different levels of knowledge, experience, beliefs and perceptions regarding cancer and healthcare. An already complex situation is further compounded by factors such as migrant labour, high levels of illiteracy, lack of information and lack of knowledge about the importance of healthy living and general healthcare.

Figures released by the Centre for the Study of AIDS suggest that 30% of women who report for antenatal care at the province's public healthcare facilities are HIV+ (Hargreaves, Morison, Kim, Bonell, Porter, Watts, Busza, Phetla and Pronyk 2008:114). The socio-economic conditions associated with the mining activities in the Goldfields region have been linked to the increasing prevalence of HIV/AIDS in the Free State province (Hargreaves *et al.* 2008:114). The Goldfields region accounts for approximately 40% of the HIV+ antenatal cases in the Free State (Hargreaves *et al.* 2008:114). The emergence of HIV/AIDS as an epidemic inevitably has an impact on healthcare in the region. The issue of HIV/AIDS and its impact on the treatment and management of Ca Cx at DROUAH are discussed later on in this chapter. The next section deals with the incidence of Ca Cx at DROUAH

1.7 INCIDENCE OF CA CX AT THE UNIVERSITAS ANNEXE HOSPITAL

The figures received from the departmental statistician show a high incidence of Ca Cx at DROUAH. According to the Department's statistics, there were 1603 patients who were registered with a diagnosis of Ca Cx upon admission to the Department between January 2002 and August 2006 (Doman 2007). The statistics, as received from the departmental statistician for the aforementioned period, are summarized in table 1.1.

Table 1.1 Incidence of Ca Cx at the Department of Radiation Oncology, Universitas Annexe Hospital, Bloemfontein, January 2002 to August 2006 (Doman, 2007)

Year	No. of patients	White	Black
2002	388	36	352
2003	304	24	280
2004	350	34	316
2005	338	36	302
2006	223	19	204
Total	**1603**	**149**	**1454**
Average (%)		**9.3**	**90.7**

The proportion of black patients to white patients, as reflected in the departmental statistics, seems to concur with the assertions of the authors cited in section 1.4 about the following: the relationship between the incidence of Ca Cx and the standard of living in societies; the disease being more common among women of low socio-economic status; and South Africa being among the developing countries with a higher incidence of Ca Cx.

1.8 TREATMENT OF CA CX AT UNIVERSITAS ANNEXE HOSPITAL

Ca Cx patients at DROUAH are either treated with curative (radical) or palliative intent. Patients are treated with radical intent if they are diagnosed with Ca Cx, FIGO stages I to III. Ca Cx Patients are further required to be in a good or fair general condition upon referral for treatment. Patients are classified in accordance with the index provided in appendix 2. If patients are diagnosed with progressive disease such as FIGO stage IV or metastatic disease, or if radical treatment options are considered by the oncologists to be ineffective, then such patients are treated with palliative intent. If patients are HIV+, they need to have a CD4 count of more than 200 CD4 cells per mm of blood, and they also need to be in a good general condition. However, HIV+ patients are also considered for radical treatment if they are in a fair general condition, with a CD4 count of more than 400 CD4 cells per mm of blood.

The radical approach to treatment at DROUAH entails the combined use of chemotherapy and radiotherapy as a modality of treatment. The combined use of chemotherapy and radiotherapy is often referred to as chemo-radiotherapy, and involves aggressive methods of treatment, often subjecting patients to severe adverse effects (Rubatt, Boardman, Segreti, Kavanagh and Wheelock 2007:5). These include nausea, vomiting, infection of the urinary tract, metabolic derangements, uraemia, haematological and gastro-intestinal toxicities, and skin rash (De Vita *et al.* 2004:887). The radical treatment protocol used at DROUAH is outlined in chapter 2 of this research report.

The palliative approach to treatment at DROUAH is determined by the symptoms and the extent of the disease in every individual case. The symptoms of advanced disease and the extent of progression of the disease vary widely from patient to patient (Rubatt *et al.* 2007:5). The symptoms include vaginal bleeding or discharge, localised pain, skeletal pain, fistulas of the bladder or rectum, oedema of the lower extremities, deep venous thrombosis, dyspnoea from anaemia or pulmonary involvement, uraemia from urethral obstruction and

distant metastasis (Rubatt *et al.* 2007:5). External beam radiotherapy (EBRT), using high fraction doses, is widely used in the treatment of advanced disease in the Department.

1.9 BACKGROUND TO HIV/AIDS

The Human Immunodeficiency Virus (HIV) attacks the body's immune system (Buehler and Ward 1993:118). At first, the immune system fights back by producing new T-helper cells, which are better known as CD4 cells (McMichael and Dorrell 2005:5). The virus then multiplies and spreads from one cell to another at an incredibly high speed, damaging and destroying cells. HIV eventually causes so much damage to the immune system that it fails to keep up with the production of new CD4 cells to replace the destroyed cells (Baillieres 2000:217). When this happens the CD4 cell count drops below 200 cells per mm of blood and AIDS develops (Palefsky and Holly 2003:41). Patients in this condition are said to be immune suppressed or immune compromised (McMichael and Dorrell 2005:5).

Immune compromised patients are vulnerable to infections and other conditions that characterise AIDS (Marco 1999:2). Conditions that characterise AIDS are referred to as AIDS-defining conditions, and include tuberculosis (TB), pneumocystic carini pneumonia, Ca Cx, Kaposi sarcoma, and non-Hodgkin’s lymphoma (McMichael and Dorrell 2005:5).

According to the Centres for Disease Control, a CD4 cell count below 200 per mm of blood under normal circumstances is a criterion for AIDS (Palefsky and Holly 2003:43). This means that in the absence of AIDS-defining conditions, patients with a CD4 cell count below 200 per mm of blood are regarded as having AIDS. If patients are diagnosed with any AIDS-defining condition, such patients are said to have AIDS, regardless of their CD4 cell count (McMichael and Dorrell 2005:5).

1.10 INCIDENCE AND PREVALENCE OF HIV/AIDS

Statistics on HIV/AIDS published by the “Until There’s A Cure Foundation” for the awareness and prevention of HIV/AIDS, suggest that at the beginning of 2008 there were 42 million people worldwide living with HIV/AIDS, with over 22 million recorded AIDS-related deaths (Kemppainen, Kim-Godwin, Reynolds and Spencer 2008:127). The foundation believes that approximately 74% of the people diagnosed with HIV/AIDS live in sub-Saharan Africa. The foundation also estimates that about 14,000 new infections occur each day, of which more than 95% occur in poor, developing countries in sub-Saharan Africa and Asia (Kemppainen *et al.* 2008:127).

Walensky and Fofana (2007:1) state that even the best strategic plans would not succeed in preventing about one million HIV/AIDS-related deaths in South Africa between 2007 and 2010. This prediction is based on projections by the Massachusetts General Hospital presented at the HIV Implementers’ Meeting in Kigali, Rwanda in 2007. The South African National Strategic Plan on AIDS for 2008-2011, presents 3 scenarios about the availability of treatment and HIV/AIDS-related deaths between 2007 and 2010. The worst-case scenario predicts that if there is no growth in the rate of expansion of treatment programmes, there will be approximately 2.19 million HIV/AIDS-related deaths in South Africa by the end of 2010. The best-case scenario suggests that if treatment programmes are expanded so rapidly that 90-100% of those in need are reached, there would still be approximately 1.16 million HIV/AIDS-related deaths by the end of 2010. The third scenario suggests that if treatment programmes are constantly expanded at the required rate, there will be approximately 300 000 HIV/AIDS-related deaths in 2010 alone.

1.11 PHYSIOLOGICAL CHANGES CAUSED BY HIV/AIDS

The most significant physiological changes associated with HIV infection relate to suppression of the immune system (McMichael and Dorrell 2005:5). Suppression

of the immune system results in weakened defences against infections, making persons infected with HIV vulnerable to secondary or opportunistic infections and other conditions that characterise AIDS (McMichael and Dorrell 2005:6). Conditions that characterise AIDS are referred to as AIDS-defining conditions, and include tuberculosis (TB), pneumocystic carini pneumonia, Ca Cx, Kaposi sarcoma, and non-Hodgkin's lymphoma (Marco 1999:2).

Gallagher (2007:11) lists chronic fatigue and anaemia as some of the more common effects related to the physiological changes caused by HIV infection. Baillieres (2000:217) lists anaemia as the most common complication, seen in up to 95% of HIV/AIDS patients. Anaemia occurs when the body does not have enough blood cells to carry and transport oxygen to various parts of the body (Belperio and Rhew 2004:27). All 3 types of blood cells, i.e. red blood cells, white blood cells and platelets, are reduced in number in anaemic patients, with an increased risk of iron overload (Baillieres 2000:217).

Oxygen is required by the body to produce energy and maintain regular metabolism of every organ (Belperio and Rhew 2004:27). A reduction in the red blood cell count in particular, decreases the oxygen supply to the tissues in the body. Reduced oxygen supplies to the tissues result in a reduction in the body's capacity to produce energy and maintain regular metabolism of the organs (Belperio and Rhew 2004:27). This helps to explain why anaemia may result in fatigue, loss of energy, general weakness, light-headedness and pallor.

Chronic fatigue is one of the most frequent and distressing symptoms of people suffering from HIV-infection (Voss, Dodd, Portillo and Holzemer 2006:38). Chronic fatigue is listed as a primary indicator of malfunctions of endocrine organs, muscles and the brain, and has been correlated with decreased quality of life and functional status (Voss *et al.* 2006:38).

1.12 HIV AND CA CX

In 1993, the United States Centres for Disease Control (CDC) recorded 16 784 cases of women with AIDS (CDC 1993:11). Among this population of AIDS patients, Ca Cx was the most common (1.3%) type of cancer diagnosed (CDC 1993:11). Subsequently, the CDC added invasive Ca Cx to its list of AIDS-defining conditions (Clarke and Chetty 2002:19).

Hawes, Critchlow and Niang (2003:557) suggest that women infected with HIV have a higher prevalence of infection with HPV, resulting in a higher incidence and prevalence of cervical intraepithelial neoplasia (CIN) lesions and a more likely rapid progression to invasive Ca Cx. Data published by the Sentinel Hospital Surveillance System for HIV infection suggest that the prevalence of invasive Ca Cx was higher for HIV-infected women than for uninfected women. There were 10.4 cases per 1000 women reported for HIV+ women, and 6.2 cases per 1000 women reported for HIV- women, representing a relative risk or odds ratio (OR) of 1.7; CI 1.1–2.5 (Chin, Sidhu, Janssen and Weber 1998:84). In South Africa, the OR of HIV with Ca Cx was found to be 1.6; CI 1.1–2.3 (Sitas, Pacella-Norman, Carrara, Patel, Ruff, Sur, Jentsch, Hale, Rowji, Saffer, Connor, Bull, Newton and Beral 2000:490). Chirenje (2005:271) states that it is difficult to ascertain the actual incidence of Ca Cx in HIV-infected women in HIV-endemic countries, where the burden of Ca Cx is the heaviest, but cancer registries are still very scanty.

Results based on a study conducted by Abraham and Allegra (2001:219) indicate that HIV+ women with Ca Cx have more aggressive and more advanced Ca Cx disease than patients who are HIV-. The authors also report that the HIV+ patients had a poorer prognosis than those who were HIV-. The authors of the study (Abraham and Allegra 2001:221) conclude that there could be a correlation between the presence or absence of HIV infection and the responses of patients to the same standard of therapy, with the response to therapy expected to be worse in HIV+ patients than in HIV- patients.

1.13 RATIONALE OF THE STUDY

Oncologists at DROUAH observed that when patients were given the same standard of curative or radical chemo-radiotherapy treatment for Ca Cx, the HIV+ patients did not tolerate their treatment as well as their HIV-counterparts. The oncologists suspected that the HIV+ patients were more prone to the adverse effects of the radical chemo-radiotherapy treatment for Ca Cx due to their compromised physiological state caused by the HIV infection. This, they thought, resulted in the HIV+ patients showing a poorer tolerance of the radical treatment than their HIV- counterparts.

The assumptions of the oncologists in the Department seem to be consistent with the conclusion drawn by Abraham and Allegra (2001:221). They believe there could be a correlation between the presence or absence of HIV infection and the responses of patients to the same standard of therapy, with the response to therapy expected to be worse in HIV+ patients than in HIV- patients.

The toxic effects of chemo-radiotherapy are expected to induce adverse effects in patients who are treated for Ca Cx. Based on the information in the preceding sections, it is reasonable to deduce that people with HIV/AIDS have an increased predisposition to react negatively to the radical chemo-radiotherapy treatment of Ca Cx at DROUAH. In order to test this expectation, it might be useful to address the question: *What are the responses of HIV positive and HIV negative Ca Cx patients, respectively, to radical therapy at the Universitas Annex Hospital?*

1.14 AIM AND OBJECTIVES OF THE STUDY

The aim of this study was to analyse the responses of patients who received the same standard of radical treatment protocol for FIGO stage II and III Ca Cx at DROUAH. The main objective of the study was to determine how the HIV+ patients tolerated their treatment. Patients' treatment tolerance was determined by retrospectively analysing their general condition and adverse responses to

treatment throughout the treatment schedule and for a period of 18 months after conclusion of treatment.

The secondary objective of the study was to retrospectively analyse the overall outcomes and therapeutic benefits of the treatment in terms of quality of life and tumour responses among the HIV+ patients. The general condition of patients, adverse responses to treatment and tumour responses were used to determine overall outcomes and therapeutic benefits of the treatment. The HIV- patients were included in the study to benchmark the therapeutic benefits in terms of quality of life and tumour response.

1.14.1 Adverse responses

Adverse responses to chemo-radiotherapy are generally accepted as the result of dose-related toxicities that patients incur from administration of the chemo-radiotherapy in the treatment of cancer (Davey, Chaitt, Albert, Piscitelli, Kovacs and Walker 1999:851). These toxicities include temporary symptoms that could interfere with the activities of the patients' daily lives (Davey *et al*. 1999:851). The frequency and severity of these responses may vary from patient to patient, and from one treatment protocol to another (Grady, Anderson and Chase 1998:230). Adverse effects to chemo-radiotherapy may be classified into two groups, namely acute and chronic adverse effects (Losso, Belloso, Emery, Benetucci, Cahn and Lasala 2000:1616).

According to Losso *et al.* (2000:1616) the common acute adverse effects reported by patients when they receive chemo-radiotherapy for cancers in the pelvic area include: diarrhoea; fatigue and tiredness; irritable bladder, commonly known as radiation cystitis; feeling sick, bleeding from the vagina after insertion of brachytherapy sources; and pain and redness of the vulva and skin. Losso *et al.* (2000:1616) suggest that it is fairly common for the short-term side-effects to continue to get worse for a couple of weeks after the treatment, before they get better.

Long-term adverse effects to chemo-radiotherapy may include reduction or loss of function of the bladder and bowel; changes to the vaginal area, such as stenosis and fibrosis; early menopause; and infertility (Grady *et al.* 1998:230). The treatment may also have a negative impact on the emotions of patients in the long-term. Appendix 2 provides an index with the list and the classification of the adverse responses as they were used in this study.

1.15 MOTIVATION AND SIGNIFICANCE OF THE RESEARCH STUDY

The treatment of cancer has always been directed by the principles of maximum tumour control and minimum damage to surrounding normal tissue (Bentzen 2003:77). The overall outcome or efficacy of cancer treatment is measured by the extent to which local tumour control and overall and progression-free survival are improved, the reduction in side-effects, and the enhancement of quality of life (Novetsky, Einstein, Goldberg, Hailpern, Landau, Fields, Mutyala, Kalnicki and Garg 2007:637). Medical scientists are always researching new methods and exploring technological developments that seek to improve the efficacy of cancer treatment (De Vita *et al.* 2004:7).

The negative impact of HIV/AIDS on the survival rates of cancer patients poses a dilemma for the approach of oncologists to the treatment and care of such patients. The perception that HIV compromises patients' response to treatment, as well as such patients' reduced life expectancy, may easily prejudice the way oncologists treat these patients.

On the other hand, the advent of more effective highly active anti retroviral therapy (HAART) and the availability of other treatment modalities have improved survival times for HIV+ patients (Chirenje 2005:276). The treatment and management of cancer patients affected by HIV thus demands that oncologists remain objective. The objectivity of oncologists is critical in guiding their decisions in their choice of the appropriate approach to treatment for the patient and the overall therapeutic benefits of such treatment. This study will present objective

results regarding HIV+ patients' tolerance of the radical treatment of Ca Cx at DROUAH. The results will help oncologists to confirm or reject their observations and/or perceptions about HIV+ patients' reactions to the radical treatment of Ca Cx.

There are two documented studies about patients with Ca Cx at DROUAH. The first study was conducted by Friedrich (1996) and the second by Long (2008). The focus of Friedrich's study is a clinical radiobiological analysis of the treatment of Ca Cx in Bloemfontein between 1967 and 1990. Long's study analyses the effectiveness of dose and the incidence of late rectal complications where high dose-rate brachytherapy was used in the treatment of FIGO stage I – III Ca Cx. This study is unique in the sense that it analyses the way in which a specific group of (HIV+) patients tolerated their treatment. The results of the current study will guide oncologists in making objective judgements about the efficacy of radical cancer treatment and its impact on patients' quality of life.

1.16 STRUCTURE OF THE DISSERTATION

Chapter 1: Introduction and Background

Chapter 1 constitutes the introduction to the study and provides background information on Ca Cx and the treatment and management of the disease. HIV and its possible role in and influence on the treatment and management of Ca Cx, as well as its relevance to the study, are also discussed. The chapter concludes with the rationale, aims and objectives of the study, as well as the motivation for and significance of the study.

Chapter 2: Literature Review

The literature review presents information on the application of chemo-radiotherapy in the treatment and management of FIGO stage II and III (invasive) Ca Cx. The uses of external beam radiotherapy (EBRT), intra-cavitary brachytherapy (ICBT) and chemotherapy in the treatment of Ca Cx, with Cisplatin as a chemotherapeutic agent, are also investigated. The chapter looks at the

radical approach to the treatment of Ca Cx in the Department, as well as cases from the applicable literature.

Chapter 3: Materials and Methodology

In chapter 3, a description is given of the selection of patients for the study, the research tools, the methods and materials used during the study, and the way in which data was collected and analysed. A brief account is also given of the procedures that were used to acquire the necessary consent to conduct the study and to access information and data from patient files. In complying with the proposal of the research study, a pilot study was conducted. Information on the pilot study is also provided in this chapter.

Chapter 4: Results

Chapter 4 presents the results of the study. The chapter also provides information on patient inclusion procedures, analysis of the patients' clinical information and status at referral for treatment in the Department, as well as analysis of the responses of each group of patients with regard to specific variables at specific intervals.

Chapter 5: Discussion and Conclusion

This chapter discusses the responses of FIGO stage II and III Ca Cx patients to the radical treatment protocol at DROUAH. The HIV+ patients' tolerance of the radical treatment, the overall outcomes and the therapeutic benefits of the treatment are also discussed. The challenges and shortcomings of the study, as well as recommendations, are also shared.

1.17 CONCLUSION

The approach to the treatment and management of patients with a dual diagnosis of Ca Cx and HIV/AIDS can be easily influenced by the attitudes and perceptions outlined in section 1.1, relating to fear and hopelessness. The treatment and management of patients require healthcare practitioners to be objective and

balanced at all times, with regard to their judgement and the treatment options they offer their patients. Despite the possible risks posed by the impact and implications of the dual diagnosis of Ca Cx and HIV/AIDS, the objective and balanced judgement of healthcare practitioners and the treatment options that they offer their patients should not be influenced by these possible risks. Until there is factual proof that HIV+ patients with Ca Cx tolerate their treatment less well than their HIV- counterparts, the approach to patients' treatment should be based on the premise that the treatment responses and tolerance levels are the same in HIV- and HIV+ patients treated for the same standard of therapy. The current study aims to shed more light on HIV+ patients' tolerance of treatment. Chapter 2 outlines the literature review conducted for the purposes of the current study.

2. CHAPTER 2: LITERATURE REVIEW

2.1 INTRODUCTION

Radiotherapy and chemotherapy are both widely used in the management of gynaecological malignancy (Symonds and Foweraker 2006:100). Thomas (1999:1198) suggests that several clinical trials have demonstrated the value of adding chemotherapy to radiotherapy to decrease mortality rates from cancer. However, the toxicity of chemotherapeutic agents is always a primary concern when used in the treatment of cancer (Thomas 1999:1198).

The current study was motivated by the nagging suspicion of oncologists that HIV+ patients do not tolerate the chemo-radiotherapy treatment for Ca Cx at DROUAH as well as their HIV- counterparts. This belief was based on observations in the clinical setting. The current study aims to test the validity of this feeling among oncologists.

This literature review investigates the use of chemo-radiotherapy as a modality for the treatment and management of FIGO stage II and III (invasive) Ca Cx. The literature review offers some background information on EBRT, ICBT and chemotherapy, and their use in the treatment and management of Ca Cx. Cisplatin is discussed as a chemotherapeutic agent. The chapter provides information on the radical approach to the treatment of Ca Cx at DROUAH. The literature review also looks at other approaches to the treatment of stage II and III Ca Cx, obtained from the studies consulted for this project.

The findings collected in the literature served as a benchmark for the findings of this study. The next section outlines the approach and methods that were used to access relevant studies.

2.2 SEARCH STRATEGY AND CRITERIA

The literature review process entailed the exploration of publications such as books and journals, as well as the investigation of Internet resources. Especially helpful were publications that focused on the treatment of stage II and III Ca Cx where chemo-radiotherapy was used, or studies that involved stage II and III Ca Cx patients that were HIV+. Studies about chemo-radiotherapy included those referring to the use of EBRT or high-dose (HDR) ICBT. EBRT and HDR-ICBT were used either in combination or separately. During the literature review care was taken to include studies published during the past two decades (i.e. from the 1980s to the present time) in order to get a perspective on the advances and developments in the treatment and management of Ca Cx, FIGO stage II and III, especially in the areas of chemo-radiotherapy and HIV/AIDS.

For Internet searches, keywords were used to search the Science Direct, PubMed/MEDLINE, Ebsco and Google search engines. Keywords included, *inter alia*, the following: concurrent chemotherapy and radiotherapy for Ca Cx; chemo-radiotherapy in carcinoma of the uterine cervix; impact of HIV/AIDS on Ca Cx; toxicity of cancer treatment; and trends in Ca Cx treatment. The website of the Central University of Technology, Free State, South Africa (www.cut.ac.za) also provided valuable links through the EbscoHost, SpringerLink and ISI Web of Science links. The website of the National Cancer Institute of the United States of America, better known as the NCI, was also accessed for announcements, press releases and information about publications relevant to this study. Only English books and publications were considered for the literature review.

The findings in the literature will be used to compare the benefits of the radical chemo-radiotherapy treatment approach at DROUAH with the adverse effects of the approach, particularly on HIV+ patients. The next section gives a description of radiotherapy and its uses in the treatment and management of Ca Cx, FIGO stage II and III.

2.3 RADIOTHERAPY FOR STAGE II AND III CA CX

Radiation therapy, commonly referred to as radiotherapy, plays an important role in the treatment of Ca Cx, and has proven to be a very effective mode of therapy for the treatment of stage II and III Ca Cx (Graham, Sotto and Paoloucek 1988:56). Radiotherapy can be employed alone, or in combination with other therapies, such as chemotherapy and, in rare cases, surgery (De Vita *et al*. 2004:277). Radiotherapy for Ca Cx is available in two modalities, namely external beam radiation therapy (EBRT) and intracavitary brachytherapy (ICBT). EBRT uses an external source of radiation whilst ICBT refers to a source that is implanted in the relevant anatomical area.

The choice of radiotherapy modality in the treatment of Ca Cx is influenced by factors such as efficacy, availability of equipment, duration of treatment, expertise, and safety considerations (Nag, Dally, De la Torre, Tatsuzaki, Kizilbash, Kurusun, Pinilos, Pokrajac, Sur and Levin 2002:298). The choice between the use of EBRT and ICBT in combination or as separate modalities is determined by the availability of these modalities in the treatment facility (Nag *et al*. 2002:298).

The curative potential of radiotherapy in the treatment of Ca Cx is enhanced by using ICBT. This means that EBRT is used as the primary treatment source to spread the radiation dose throughout the treatment volume, while ICBT is given to supplement or “boost” the EBRT dose. (Patel, Rai, Malick and Sharma 2005:125). Thomas (2000:46) suggests that the standard approach to radiotherapy for any Ca Cx that has advanced beyond FIGO stage I should be the use of EBRT in combination with ICBT. This has an added impact on the tumour, while sparing the normal surrounding tissues.

2.3.1 External beam radiotherapy (EBRT) for stage II and III Ca Cx

The American Brachytherapy Society (ABS) acknowledges that the EBRT dose given to the whole pelvis varies from one institution to another, with the fraction sizes being determined by the envisaged total EBRT dose and overall treatment time (Nag, Erickson, Thomadsen, Orton, Demanes and Petereit 2000:203). Some institutions give a limited dose to the whole pelvis in patients with early stage disease, with the first fraction of ICBT being given after an EBRT dose of 20 Gy to the whole pelvis. In such cases, the ABS recommends that the size and number of ICBT fractions should be increased, whilst care is taken that individual fraction sizes are kept below 7.5 Gy to keep rectal dose levels in check.

DROUAH uses a total EBRT dose of 50 Gy, using daily fractions of 2 Gy. This dosage is in line with those of other centres across the world, where EBRT doses to the whole pelvis range from 40 – 50 Gy, with doses varying between 1.5 Gy to 2 Gy per fraction. Unlike the case where EBRT doses of 20 Gy are given to the whole pelvis, with 7.5 Gy ICBT fractions, centres using the 40 – 50 Gy whole pelvis EBRT dose approach, including DROUAH, should use smaller ICBT fractions – about 2 – 2.5 Gy (Nag *et al.* 2000:203).

2.3.2 Intracavitary brachytherapy (ICBT) for stage II and III Ca Cx

There are two approaches to the use of ICBT in the treatment of Ca Cx. One approach is to use low-dose-rate ICBT (LDR-ICBT), and the other is to use high-dose-rate ICBT (HDR-ICBT). LDR is defined as a dose of 0.4 – 2 Gray per hour (Gy/h), and HDR is defined as a dose of more than 12 Gy/h (International Commission on Radiation Units and Measurements (ICRU) 1985). LDR-ICBT has been in use for the treatment of Ca Cx for more than a century, and has undergone continuous refinement during this period (Ferrigno, Nishimoto, Dos Santos-Novaes, Pellizzon, Maia, Fogarolli and Salvajoli 2005:1108). HDR-ICBT for Ca Cx has been in use for over 30 years, and is widely applied throughout Asia and Europe, and its use is steadily increasing in North and South America (Nag, Orton and Young 1999:111).

The Patterns of Care Studies show that, in the United States, the use of HDR for the treatment of Ca Cx increased from 9% during 1992–1994 to 16% during 1996–1999, although this increase did not reach significance (Eifel, Moughan, Erickson, Larocci, Grant and Owen 2004:1145). LDR techniques were developed in an era when remote afterloading technology was unavailable. Remote afterloading techniques were developed due to concerns about health care workers' exposure to radiation.

The use of HDR-ICBT is the result of technological development in the manufacturing of high-intensity radioactive sources, sophisticated computerised remote afterloading devices and treatment planning software (Martinez, Stitt and Speiser 1997:569). Some advantages of HDR-ICBT include the following: shorter treatment times; the prospect of improved immobilisation; patients can receive their treatment on an outpatient basis; accuracy of the source and applicator positioning; and individualised treatment with source optimisation. These advantages offer the benefit of reduced hospitalisation costs, less disruption in patients' daily routines, reduced risk of applicator movement during treatment, higher rate of patient throughput in busy departments and improved radiation protection for personnel and the general public (Wright, Jones and Whelan 1994:188).

Sarkaria, Petereit, Stitt, Hartman, Chappell, Thomadsen, Buchler, Fowler and Kinsella (1994:75) reported on a study they conducted to compare the efficacy and complication rates of LDR-ICBT versus HDR-ICBT in the treatment of FIGO stage IB to IIIB Ca Cx, with curative intent. A combination of EBRT and LDR-ICBT was used for one group, and a combination of EBRT and HDR-ICBT was used for another group. Sarkaria *et al.* (1994:79) observed that the treatment results for LDR-ICBT and HDR-ICBT were similar with respect to survival rates, pelvic control and late complications in the treatment of Ca Cx. They concluded that HDR brachytherapy appears to be a safe and effective alternative to LDR therapy in the treatment of Ca Cx. The effectiveness of treatment relates to local tumour control and the incidence of radiation effects. However, the authors

(Sakaria *et al.* 1994:80) mention that HDR-ICBT has more advantages, such as improved convenience for patients and less exposure to radiation for healthcare workers.

Ferrigno *et al.* (2005:1115) applied a retrospective analysis to gain insight into the comparative outcome of FIGO stage I to III Ca Cx patients treated with LDR-ICBT and HDR-ICBT, respectively. The authors concluded that there were similar outcomes for LDR-ICBT and HDR-ICBT in the treatment of FIGO stages I and II. In FIGO stage III, lower overall and disease-free survival rates and marginally lower local control were observed when HDR-ICBT was used. Fewer late rectal complications were also observed in the patients who received HDR-ICBT. The authors attribute these findings to the relatively low dose of HDR-ICBT delivered at Point A. Point A is defined as a geometric point in relation to the cervical os and the uterine axis (Perez 1998:1751). The rectal dose and the total number of fractions given are influenced by the anatomical layout in the surrounding area (Perez 1998:1751). HDR-ICBT has the potential of improving the optimisation of dose distribution (Nag 2004:620). Optimisation of dose distribution is useful in addressing the challenges presented by rectal tolerance doses in brachytherapy (Nag 2004:620).

Technical advances in HDR-ICBT and its advantages over LDR-ICBT has made this modality of radiotherapy, in combination with EBRT, a key role-player in the treatment and management of invasive Ca Cx (Nag *et al.* 2002:299). The high incidence of Ca Cx in developing countries is the most common justification for the choice of HDR-ICBT for gynaecological cancers (Nag *et al.* 2002:299). The justification for the choice of HDR-ICBT for gynaecological cancers, as postulated by Nag and co-workers, is accordingly also applicable in the South African context.

The use of HDR-ICBT in the treatment of Ca Cx is relevant to the current study because HDR-ICBT is used as a modality of radiotherapy in the radical treatment of invasive Ca Cx at DROUAH. HDR-ICBT is used to “boost” EBRT, which is

given as the primary course of radiotherapy. Chemotherapy and its uses in the treatment and management of Ca Cx, FIGO stage II and III are discussed next.

2.4 CHEMOTHERAPY FOR STAGE II AND III CA CX

Chemotherapeutic agents currently in use are cytotoxic radiosensitisers that affect both normal and malignant cells (Steel 2002:224). Practically all patients who are in good medical condition and receiving radiation for invasive Ca Cx are offered chemotherapy in addition to their radiation (Perez 1998:1760). It may even be offered for earlier stage patients, at the discretion of the oncologists. Chemotherapy is not known to be very effective when used alone as a primary treatment modality (Thomas 1999:1199).

Several clinical trials have demonstrated the usefulness of adding chemotherapy to radiation in terms of decreasing mortality rates from Ca Cx (Thomas 1999:1199). Evidence suggests that giving chemotherapy and radiotherapy together improves overall survival in patients treated for invasive Ca Cx (Green, Kirwan, Tierney, Symonds, Fresco, Collingwood and Williams 2001:782). There is also evidence that combined chemo-radiotherapy delays tumour recurrence and reduces the risk of recurrence and distant metastasis. An increase in side-effects has been noted when chemotherapy is used in the treatment of invasive Ca Cx. Haematological and gastro-intestinal toxicities are among the most common side-effects of chemotherapy (Green *et al.* 2001:782).

Various chemotherapeutic agents are available, and they are often given in combinations for a series of months (Steel 2002:224). The chemotherapy regimen given to patients is normally at the discretion of the oncologists, and this is influenced by various factors, such as financial considerations, availability, politics and even personal preference (Thomas 1999:1199). Cisplatin is among the most commonly used chemotherapeutic agents (Green *et al.* 2001:781). Cisplatin is of interest to the current study since it is the chemotherapeutic agent that forms part of the chemo-radiotherapy protocol for patients treated for Ca Cx

with radical intent at DROUAH. The radical chemo-radiotherapy protocol for Ca Cx forms part of this study. The next section discusses Cisplatin as a chemotherapeutic agent.

2.4.1 Cisplatin as a chemotherapeutic agent

Cisplatin is a chemotherapeutic agent and is classified as an alkylating drug in terms of the American Chemical Abstract Registry (Bentzen 2003:81). Cisplatin is a platinum-based radiosensitiser with cytotoxic characteristics that affect normal and malignant cells, and was the first medicine developed in that drug class (Peters, Liu, Barrett, Stock, Monk, Berek, Souhami, Grigsby, Gordon and Alberts 2000:1613). Ca Cx and various other cancers, including testicular, ovarian, bladder, head and neck, oesophageal, small and non-small cell lung, breast, cervical and stomach cancers can be successfully treated with Cisplatin (Bentzen 2003:81).

Like other chemotherapeutic agents, Cisplatin induces side-effects when used in the treatment of Ca Cx (Perez 1998:1760). However, Cisplatin does offer several benefits that have proven to outweigh the side-effects that it may cause (Classe, Morice and Rodier 2002:61). The side-effects of Cisplatin and their severity depend on the dosage that is administered, with higher doses more likely to produce more severe side-effects. The presence or severity of side-effects of Cisplatin has no known relationship with the efficacy of the drug. Despite the possible gains in overall survival ratios when Cisplatin is combined with radiotherapy in the treatment of Ca Cx, the acute adverse effects of treatment can be aggravated by the side-effects of Cisplatin (McArdle and Kigula-Mugambe 2007:96).

Some common side-effects of Cisplatin, occurring in more than 30% of patients who receive the drug, are nausea and vomiting, kidney toxicity and abnormalities in blood tests (Thomas 1999:1199). Kidney toxicity includes nephritis and nephrotoxicity, and can lead to elevations in serum creatinine levels. Abnormalities in blood tests include decreased magnesium, calcium and

potassium levels, low white blood counts and low red blood cell counts (anaemia). Low white blood cell counts can increase the risk of infections in patients. Cisplatin may be inadvisable for patients who have a history of severe allergic reaction to platinum-containing formulations, and is not recommended for patients receiving any kind of immunisation or vaccination (Peters *et al.* 2000:1613).

The overall outcome or efficacy of cancer treatment is measured by the extent to which local tumour control and overall and progression-free survival rates are improved, the reduction in side-effects and the enhancement of quality of life (Novetsky *et al*. 2007:637). Medical scientists are always trying to improve the efficacy of cancer treatment through research and technological development (De Vita *et al.* 2004:7).

The aforementioned information on the characteristics, uses and effects of radiotherapy and chemotherapy in the treatment of Ca Cx, as well as the side-effects of Cisplatin as a chemotherapeutic agent, are critical factors in understanding the relevance of this study. In order to contextualise this information, the radical approach to the treatment and management of FIGO stage II and III Ca Cx at DROUAH is described next.

2.5 TREATMENT FOR STAGE II AND III CA CX AT UNIVERSITAS ANNEXE HOSPITAL

The treatment approach for Ca Cx, FIGO stage II and III at DROUAH involves radical chemo-radiotherapy. To be considered for the radical treatment protocol, patients are required to be in a good or fair general condition in the opinion of the oncologists upon referral for treatment. Patients are classified in accordance with the index provided in appendix 2. HIV- and HIV+ patients are considered for inclusion in the radical treatment protocol. If patients are HIV+, they need to have a CD4 count of more than 200 CD4 cells per mm of blood, and they need to be in a good general condition. However, HIV+ patients are also considered for radical

treatment if they are in a fair general condition with a CD4 count of more than 400 CD4 cells per mm of blood.

The radical chemo-radiotherapy protocol consists of a combination of EBRT, HDR-ICBT and weekly cycles of chemotherapy given concurrently. EBRT in this protocol involves administering a total dose of 50 Gy in daily fractions of 2 Gy (2 Gy / fraction), for a total of 25 fractions. The HDR-ICBT is administered weekly, using the Nucletron Microselectron® (1994) Afterloading unit. The Microselectron Afterloading unit is loaded with an Ir-^{192} source, using a central uterine applicator and a ring applicator. The first HDR-ICBT fraction is administered in the third week of the treatment schedule, with consecutive weekly fractions in the subsequent weeks of treatment. The HDR-ICBT is given on days when patients do not receive EBRT. The weekly dosage varies between 2.0 Gy and 2.5 Gy per fraction, given in 4-6 fractions. The HDR-ICBT is normalised to the highest rectum dose point, to achieve a minimum total dose of 15 Gy to point A.

Cisplatin is given concurrently as the preferred chemotherapeutic agent. The Cisplatin is administered weekly, using doses of 25 mg/m^2 per week for 5 weeks (5 cycles). The chemotherapy is given on days when patients do not receive HDR-ICBT. The total time required for the administration of the radical treatment protocol, or rather, the overall treatment time (OTT), extends over a period of approximately 7 weeks. Throughout the treatment schedule, the patients have to undergo prescribed clinical care and management procedures. These procedures are outlined in the next section.

2.5.1 Clinical care and management of patients during treatment in the department

Oncologists have weekly routine consultations with patients who are on the treatment protocol in the Department. In this way, patients are monitored and provided with whatever clinical or medical support or interventions they might need. Monitoring involves examining the patients and analysing available clinical reports and data. Reports of adverse responses to treatment are also recorded

and treated appropriately. Adverse effects range from minor to severe responses to treatment. Adverse responses are classified and recorded in accordance with the index contained in appendix 2.

Blood samples for haematology studies are drawn on a weekly basis. Haematology studies provide oncologists with additional information on a patient's general condition and the effects of treatment on the patient. Haematological tests monitor, among other things, the levels of haemoglobin, leucocytes, platelets, urea and electrolytes (U+E), and creatinine. Chemo-radiotherapy has potentially toxic effects, which place a huge strain on the body's energy resources (De Vita *et al*. 2004:887). Monitoring the blood levels of patients who are receiving chemo-radiotherapy helps physicians to predict the ability of patients to endure the vigorous demands and possible adverse effects of the treatment they receive (De Vita *et al*. 2004:887).

Haemoglobin levels give an indication of the blood-oxygen levels, which relate to the enhancement of the radiobiological effects of radiation therapy (Steel 2002:225). Testing for leukocytes gives a good indication of the body's ability to fight or overcome any disease or infection. Patients are considered for chemotherapy if they have a minimum leukocyte count of 1500/mm^3. Platelets, on the other hand, are useful in helping the blood to clot, especially when there is a possibility of uncontrolled bleeding in the body.

U+E is a measure of kidney function, which is important in maintaining the electrolyte balance of the body (Steel 2002:225). This is particularly important in cases where dehydration or toxicity may occur. Creatinine is a molecule of major importance for energy production in muscles and a good indicator of kidney function. Abnormally high levels of creatinine thus warn of possible malfunction or failure of the kidneys, sometimes even before a patient reports any symptoms.

The aim of the current study was to determine how HIV+ patients tolerated their chemo-radiotherapy regimen and to analyse the overall outcomes and

therapeutic benefits of the treatment. General condition of patients, adverse responses to treatment and tumour responses were the variables used as a yardstick to determine overall outcomes and therapeutic benefits. An exploration of the relevant literature was chosen as the most appropriate tool to acquire data on the experiences and evidence from other treatment centres, using similar or related treatment techniques. Applicable evidence and experiences related to chemo-radiotherapy regimens are presented in the next section.

2.6 CHEMO-RADIOTHERAPY FOR STAGE II AND III CA CX

The current study focused on the responses of HIV+ and HIV- patients treated for Ca Cx with chemo-radiotherapy with radical intent, in order to determine how HIV+ patients tolerated their treatment. Chang *et al.* (2006:879) assert that chemo-radiotherapy, using a combination of EBRT and ICBT, is the treatment of choice for FIGO stage II to IVA invasive Ca Cx. The assertions of Chang *et al*. (2006:879) are supported by the results of a retrospective analysis conducted by Ferrigno, Dos Santos-Novaes, Pellizzon, Maia, Fogarolli, Gentil and Salvajoli (2001:1123)

The analysis conducted by Ferrigno *et al.* (2001:1123) is based on dose effectiveness and late radiation complications in 138 patients with Ca Cx, FIGO stages II and III. The patients were given 25 fractions of EBRT, which amounted to a total dose of 45 Gy to the whole pelvis. HDR-ICBT was given in four weekly fractions of 6 Gy to point A, which amounted to a total of 24 Gy. The results suggest overall survival, disease-free survival and local control rates of 53.7%, 52.7%, and 62% at 5 years, respectively. The incidence of rectal, bladder and small bowel late complications was 16%, 11% and 14%, respectively. Although this is an analysis of late complications, the results do offer insight into the long-term effectiveness of the treatment approach in terms of improved prospects of survival and limited late treatment complications.

Green *et al.* (2001:783) published the findings of their multi-centre trials conducted on patients treated for Ca Cx, FIGO stage IB to IVA. The trials involved 4580 randomised patients treated at six centres in the United Kingdom between 1981 and 2000. The results from these trials indicate that the overall survival rate of patients on chemo-radiotherapy regimens improved by 12%. These improved survival rates were observed even in cases where agents other than Cisplatin were used. Progression-free survival among patients on the chemo-radiotherapy regimens improved by 16% (Green *et al.* 2001:783).

Green *et al.* (2001:783) ascribe significant benefits concerning local and distant recurrence to the use of chemo-radiotherapy. Odds ratios of 0.61, p<0·0001, and 0.57, p<0·0001, were recorded for local recurrence and distant metastasis, respectively. The authors believe that concomitant chemo-radiotherapy appears to improve overall and progression-free survival rates and reduces local and distant recurrence in patients with Ca Cx. The authors suggest that such concomitant chemotherapy may afford the radiosensitisation and systemic cytotoxic effects (Green *et al.* 2001:783).

Despite the gains in overall and progression-free survival rates, and the reduced probability of local recurrence and distant metastasis, there was evidence of an increase in side-effects when chemotherapy was used in combination with radiotherapy. Most of the recorded side-effects were related to haematological and gastrointestinal toxicities. Even though chemotherapeutic agents other than Cisplatin were used in the trials reported by Green *et al.* (2001:783), the occurrence of haematological and gastrointestinal toxicities seems to correlate with the side-effects of Cisplatin described in section 2.4 above.

Morris and associates reported their findings of studies conducted in Texas, between 1990 and 1997 (Chang *et al.* 2006:881). These studies included 403 women with Ca Cx, FIGO stages IIB to IVA. The study compared the effect of radiotherapy (EBRT combined with ICBT) with the effect of chemo-radiotherapy. In the chemo-radiotherapy approach, Cisplatin was used as the

chemotherapeutic agent. Morris and associates reported that even though a larger number of rectal complications were observed in the chemo-radiotherapy group, the treatment yielded improved local tumour control and overall disease-free survival rates (Chang *et al.* 2006:885).

Toita, Moromizato, Ogawa, Kakinohana, Maehama, Kanazawa and Murayama (2005:665) conducted a retrospective study on 52 patients to assess the feasibility and efficacy of concurrent chemo-radiotherapy in the treatment of patients with invasive Ca Cx, FIGO stage IB-IVA. All patients were treated with a combination of EBRT and HDR-ICBT, using Ir-^{192}. Cisplatin was used as the chemotherapeutic agent in the treatment protocol. The results indicate that the actuarial 3-year pelvic control rate, disease-free survival rate and overall survival rate were 91%, 67% and 79%, respectively. Acute toxicity was also reported in most patients, with haematological toxicity being the most prevalent, with 83% of patients showing effects in their leukocyte counts. Other forms of acute toxicity reported were nausea and vomiting (28%), and diarrhoea (15%). Thirty-two percent (32%) suffered late radiation complications. One (1) patient suffered enterocolitis, while seven patients incurred pelvic infection that required treatment.

Toita *et al.* (2005:670) is of the opinion that concurrent chemo-radiotherapy with HDR-ICBT is feasible and efficacious for patients with Ca Cx. The authors further state that despite the limited number of patients and limited follow-up period, the retrospective study demonstrated a high rate of pelvic control and survival, with an acceptable level of acute and late toxicities for patients with loco-regionally advanced Ca Cx. The reports by Toita and associates do not provide specifics about dosage and fractionation schedules, and the nature and extent of late radiation complications. However, the use of EBRT, Ir-^{192} HDR-ICBT and Cisplatin as treatment modalities for invasive Ca Cx makes their results and observations relevant to the current study.

The South Koreans Lee, Wu, Kim, Ha, Kim, Kim and Lee (2007:95) conducted a

study involving 33 patients who were treated between March 2000 and January 2004 to evaluate the toxicity and efficacy of chemo-radiotherapy as a definitive treatment for FIGO stage IB to IVB squamous Ca Cx. The patients were treated with concurrent chemo-radiotherapy, using EBRT and ICBT, with a chemotherapy combination of Paclitaxel and Carboplatin given concurrently. Lee *et al.* (2007:98) report that there were three interruptions in patients' treatment secondary to toxicity. The toxicities were graded according to the NCI Common Toxicity Criteria (2006, v. 3.0). All three of these patients developed grade 4 neutropenia. Chemo-radiotherapy was delayed a week for two patients, and the second cycle of chemotherapy was delayed three weeks for one patient.

Lee *et al.* (2007:98) also report that patients incurred haematological toxicity, with leucopenia being the most common form of this type of toxicity. Grade 3 leucopenia was observed in 17 patients, representing 52% of the study population, while three patients (9%) incurred grade 4 leucopenia. Grade 3 nausea was observed in one patient. Vesicovaginal fistulas occurred in two patients (6%) as a late complication. Seventy percent (70%) of patients showed a complete response (CR) and 30% showed a partial response (PR) for Ca Cx. The authors claim that the overall survival rate in this study was superior to that of the historical control group of their institute, in which all patients were treated with radiotherapy alone. The authors conclude that this regimen was tolerated well and showed excellent local control rates.

The literature consulted for this study suggests that concurrent chemo-radiotherapy regimens can be accepted as an effective approach to the treatment and management of Ca Cx. Based on data from five randomised trials, the National Cancer Institute (NCI) released a consensus statement in February 1999, declaring that concurrent chemo-radiotherapy should be considered as the new standard of care for all patients with Ca Cx (Kim, Cho, Keum, Lee, Seong, Suh and Kim 2007:58). Evidence collected from the literature consulted for this study and discussed in preceding sections underscores the importance of the NCI campaign. The support for the use of chemo-radiotherapy as the treatment

of choice for FIGO stage II and III Ca Cx is based on the effectiveness of these treatment modalities in terms of local tumour control, overall and progression-free survival, incidence of side-effects and quality of life (Ferrigno *et al*. 2001:1132). The effectiveness of treatment in improving local tumour control, increasing overall and progression-free survival and enhancing quality of life seems to outweigh the adverse effects incurred from the treatment given (Ferrigno *et al*. 2001:1132).

The prevalence of HIV/AIDS among patients reporting for treatment of Ca Cx at DROUAH poses the challenge of influencing the outcome of treatment. The potential challenges arise from the physiological changes caused by HIV/AIDS, such as anaemia and chronic fatigue (Gallagher 2007:11). Fatigue is associated with decreased quality of life and functional status (Voss *et al.* 2006:38).

Other potential challenges arise from evidence that suggests the following: HIV+ women have more aggressive and more advanced Ca Cx disease than HIV- patients; HIV+ patients with Ca Cx have a poorer prognosis than their HIV- counterparts; and there seems to be a correlation between the presence or absence of HIV and the responses of patients to the same standard of therapy, with the HIV+ patients expected to do worse than the HIV- patients (Abraham and Allegra 2001:222). The next section offers brief background information on chemo-radiotherapy approaches to the treatment of invasive Ca Cx in HIV+ patients.

2.7 CHEMO-RADIOTHERAPY TREATMENT OF CA CX IN HIV+ PATIENTS

The treatment of invasive Ca Cx in HIV-positive women depends on local guidelines and the availability of resources (Chirenje 2005:6). HIV-infected women are observed to present with disease at a more advanced stage than HIV-negative women, particularly when their CD4 cell counts are below 200/mm^3 (Fruchter, Maiman, Arrastia, Matthews, Gates and Holcomb 1998:244). Treatment outcomes for invasive Ca Cx are observed to be poorer in HIV+

women than in HIV-negative women, with recurrence rates of up to 88%, as observed in a study of HIV-infected women with Ca Cx in New York City (Maiman, Fruchter, Clark, Arrastia, Matthews and Gates 1997:79).

McArdie and Kigula-Mugambe (2007:94) conducted an important prospective study in Uganda. The study assessed the eligibility of patients living in the developing world and suffering from Ca Cx for concomitant chemo-radiotherapy. The chemo-radiotherapy protocol involved the use of EBRT and ICBT, with concomitant Cisplatin administered weekly. The study by McArdie and Kigula-Mugambe (2007:94) was based on concerns that the highest incidence of Ca Cx occurs among women in the developing world, who are faced with multiple challenges. These challenges include economic, social and geographical factors, which are further exacerbated by co-existing HIV and poor nutritional status (McArdie and Kigula-Mugambe 2007:94).

The study by McArdie and Kigula-Mugambe (2007:96) was based on a sample size of 314 patients (n = 314), with histologically confirmed FIGO stage II and III Ca Cx. Fifty percent (50%) of the patients in the study were HIV+, whilst 11.6% of the patients were confirmed to be HIV+. HIV status was not confirmed in 38.4% of the patients. The results indicated that of the 314 patients who were referred for chemo-radiotherapy treatment, 47 patients (15.1%) were eligible for combined modality treatment and 190 (60.5%) were not eligible on the basis of the exclusion criteria for the study. Eligibility could not be established in 77 cases (24.4%). McArdie and Kigula-Mugambe (2007:96) state that patients were excluded from the chemo-radiotherapy treatment in the following cases: FIGO stage IA and IV; haemoglobin (Hb) count of less than 8 g/dL; leucocyte count of less than 2000/μL; platelet count of less than 100,000/μL; and creatinine count of more than 97 μmol/L.

Based on their results, McArdie and Kigula-Mugambe (2007:97) conclude that a small proportion of patients with Ca Cx are likely to benefit from the chemo-radiotherapy treatment using concomitant weekly Cisplatin. These results concur

with the findings of Green, Kirwan, Tierney, Vale, Symonds, Fresco, Williams and Collingwood (2005:25), and the results published by Lukka, Hirte, Fyles, Thomas, Elit, Johnston, Fung and Browman (2002:210). The results from the two aforementioned studies suggest that the contribution of concomitant chemo-radiotherapy to overall survival advantage in the treatment of Ca Cx ranges between 10% and 16%. Even though overall survival rate is not the focus of the current study, the information obtained from the aforementioned studies throws more light on the assessment of the therapeutic benefits of the chemo-radiotherapy protocol for HIV+ patients.

Treatment options for invasive Ca Cx in HIV+ patients are determined by the stage of the Ca Cx, as well as careful assessment of the general medical condition of each patient (Chirenje 2005:6). Radical radiotherapy is useful for large lesions (FIGO stages IB2, and stages II_B–IV_A), those who are medically unfit for surgery, and situations where surgical expertise is unavailable. Concurrent chemo-radiotherapy seems to provide a survival advantage compared with radiotherapy alone. This was demonstrated by the randomised controlled trials that informed the NCI's recommendation to apply concurrent Cisplatin-based chemotherapy with radiotherapy in women who require radiotherapy for treatment of invasive Ca Cx (NCI 1999).

2.8 CONCLUSION

The evidence in the literature consulted for this study supports the combined use of EBRT and ICBT, with HDR-ICBT as an effective treatment modality for FIGO stage II and III Ca Cx, as used at DROUAH. The extent to which Cisplatin is used as a chemotherapeutic agent in the above-mentioned studies offers a useful reference for the current study in terms of efficacy and side-effects. This makes possible the benchmarking of the overall outcomes of treatment in terms of the general condition of patients, adverse responses to treatment, tumour response rates, and quality of life.

During the literature review for the current study, which was a continuous process, gaps were identified with regard to the availability of studies similar or relevant to the current one. This also applies to studies done in the local or regional context. The previously conducted studies by Friedrich (1996) and Long (2008) at DROUAH are not relevant to the current study. The studies by Friedrich (1996) and Long (2008) were conducted to address specific needs that were identified in the Department. Similarly, the current study was also inspired by a need identified by oncologists at DROUAH.

Studies involving women with Ca Cx and HIV/AIDS continue to be conducted throughout the region and the world. The evidence on the adverse effects of curative concurrent chemo-radiotherapy treatment for Ca Cx, coupled with the compromised defences of HIV+ patients, reinforces local oncologists' concerns about HIV+ patients' tolerance of the concurrent chemo-radiotherapy protocol for Ca Cx at DROUAH. Unfortunately, no evidence of a study exactly similar to this one could be found. Although this research gap presents a challenge to the objective interpretation of the results of the current study, they do justify the need for and purpose of this study. The methodology used in conducting this study is discussed in chapter 3.

3. CHAPTER 3: MATERIALS AND METHODOLOGY

3.1 INTRODUCTION

The current study was conducted retrospectively at DROUAH, using the records of patients treated with radical intent for stage II and III Ca Cx. An analysis of patients' recorded acute and chronic treatment reactions and patients' general health status was done.

This chapter provides background information on the methods and procedures followed in conducting the study. The main objective of the study was to determine how the HIV+ patients tolerated their treatment. Patients' treatment tolerance was determined by retrospectively analysing their general condition and adverse responses to treatment throughout the treatment schedule and for a period of 18 months after conclusion of treatment.

The secondary objective was to retrospectively analyse the overall outcomes and therapeutic benefits of the treatment in terms of quality of life and tumour responses amongst the HIV+ patients. General condition of patients, adverse responses to treatment, and tumour responses to treatment were used as indicators of overall outcomes and therapeutic benefits of the treatment.

A description is given of the selection of patients, the research tools and methods that were applied, and the way in which data was collected and analysed. A brief account is also given of the procedures that were involved in acquiring consent to conduct the study and to access data contained in patients' files. In compliance with the proposal of the research study, a pilot study was conducted. Details of the pilot study are presented in this chapter.

3.2 STUDY DESIGN

This project represents an observational study (Schulz and Grimes 2002:616), which means that inferences can be drawn about the effect of a specific treatment protocol on a selected group of patients, with two different types of clinical classification (HIV+ and HIV-). The study was conducted retrospectively, using descriptive statistics to describe qualitative data collected from patients' treatment records. Lachin, Matts and Wei (1998:369) define descriptive statistics as statistical methods used to summarise or describe a collection of data. The data was collected from the patients' treatment files and captured electronically with the aid of a data source sheet. This implies an *ex post facto* design, because previously reported data were analysed (Manion, Cohen and Morrison 2000:205).

The plan was to offer insight into the effects of a prescribed treatment protocol on a selected group of patients (Ca Cx, FIGO stage II and III), treated at DROUAH between January 2002 and August 2006. The findings of the current study could then be used to review the current approach to treatment of HIV+ patients with FIGO stage II and III Ca Cx at DROUAH. Based on the aforementioned characteristics, the study can also be classified as exploratory and developmental research (Lues, 2009:46). The results of this study are presented in chapter 4.

3.3 TREATMENT PROTOCOL

The treatment protocol applicable to this study consisted of a combination of EBRT, HDR-ICBT and weekly cycles of chemotherapy given concurrently. EBRT in this protocol involved administering 25 daily fractions of 2 Gy (2 Gy / fraction), to a total dose of 50 Gy to the whole pelvis. The HDR-ICBT was given weekly on days when patients did not receive EBRT. The HDR-ICBT commenced in the third week of the treatment schedule, with consecutive weekly fractions in the subsequent weeks of treatment. The weekly dosage varied between 2.0 Gy and

2.5 Gy per fraction, given in 4-6 fractions. The HDR-ICBT was normalised to the highest rectum dose point, to achieve a minimum total dose of 15 Gy to point A. Cisplatin was given concurrently as the preferred chemotherapeutic agent. The Cisplatin was administered weekly, using doses of 25 mg/m^2 per week for 5 weeks (5 cycles). Patients that were treated using the protocol described in this section were patients with FIGO stages II and III, and hence their inclusion in the current study.

3.4 ELIGIBILITY

The study was conducted retrospectively, using data recorded in the patients' treatment files. Patients at DROUAH are registered according to their unique departmental identification numbers, referred to as the RT-numbers. When a patient is registered for the first time at DROUAH, such a patient receives an RT-number, which serves as the patient's unique identification number for any subsequent visits to the Department.

Before commencing with the study, the departmental statistician at DROUAH provided the researcher with a list of patients who were registered in the Department with a diagnosis of Ca Cx during the period January 2002 to August 2006. This list contained the names and RT numbers of 1603 patients. These patients' files had to be accessed and analysed to determine whether they were eligible for use in the current study. The inclusion and exclusion criteria are set out below.

3.4.1 Inclusion criteria

1. Patients who received the entire treatment protocol at DROUAH, as set out in section 3.3.
2. Patients with a histologically confirmed diagnosis of Ca Cx, FIGO stage II or III.
3. Histology types: Squamous, Adenocarcinoma, and Adeno-Squamous carcinoma of the cervix.

4. HIV+ and HIV- patients were eligible for inclusion, and their HIV status had to be confirmed and recorded in the files before the commencement of treatment.
5. The follow-up data in patients' files were reviewed for a maximum follow-up period of 18 months, subsequent to conclusion of treatment.
6. The information in the patients' files and follow-up records had to be available, clear and compliant with the needs of the data source form.
7. Patients who were registered and recorded as deceased within the 18-month follow-up period. These records were used to determine mortality rates and to establish if any deaths were a consequence of the treatment.

3.4.2 Exclusion criteria

1. Patients who did not have histological confirmation of Ca Cx, FIGO stage II or III.
2. Patients with a histology type other than Squamous, Adenocarcinoma, or Adeno-Squamous carcinoma of the cervix.
3. Patients with Ca Cx, FIGO stage I or IV.
4. Patients who were not treated under the protocol set out in section 3.3 above, or if there was any uncertainty about a patient's treatment protocol.
5. Patients whose treatment and follow-up details were missing, unclear, incomprehensive, or lacked the information required on the data source form.

3.5 RESEARCH TOOL

A preliminary patient data source form (appendix 3) was designed for use as a research tool to capture all the necessary data from the patients' treatment files. This form was designed by the researcher after consultations with senior oncologists at DROUAH. The questions on the data source form were formulated to address the needs identified by oncologists at DROUAH. The preliminary data source form was included as part of the research proposal and also served as part of the application for ethical approval of the research project. The data

source form contained questionnaires to collect information from individual patient files. This information can be divided into two main categories, namely clinical data and treatment data, based on the needs identified by the researcher and the oncologists in the Department.

The clinical data included information on diagnosis, FIGO staging, HIV status, CD4 counts, blood counts, and the general condition of the patients. All the parameters of patients' clinical data were presented as options on the data source form, which the researcher could select by marking the appropriate option.

The treatment data on the data source form included information on the various parameters of the treatment the patients received. These parameters included patients' responses to treatment, such as general and physical responses, and tumour responses. The information on the treatment the patients received included specific details on EBRT, HDR-ICBT and the concurrent chemotherapy the patients received, with reference to dose, frequency and overall time.

The researcher could also capture data about patients' responses to treatment by selecting the appropriate options provided on the data source form. This selection process would be completed for each parameter of the patient's treatment data on the data source form. Other information that the data source form sought related to the acute, early, intermediate and late effects of treatment, as well as information recorded during the patients' follow-up visits, subsequent to completion of treatment. If patients received any interventional treatment for adverse treatment responses, this was also indicated on the data form.

3.6 PILOT STUDY

A pilot study was conducted to test the data source form for completeness and for effectiveness in capturing data logically from the patients' treatment files. The pilot study was executed after ethical approval was granted by the Ethics

Committee of the University of the Free State (UFS). As mentioned in section 3.5, the preliminary data source form was used to capture data from the patients' files. The patients' files were accessed with the aid of the patient list received from the departmental statistician at DROUAH. The researcher retrieved listed files from the patient file archive in the department. Patients were selected using the criteria outlined in section 3.4.

Twelve patient files deemed eligible in accordance with the inclusion criteria were selected for the pilot study. Data from the patients' files were captured electronically on the data source form, using Microsoft Excel®. Each patient's data was captured on a separate Excel worksheet under the headings listed on the worksheet, and in accordance with the procedure outlined in section 3.5.

Upon conclusion of the data collection process for the pilot study, the researcher had a consultative meeting with a representative from the Department of Bio-Statistics at the UFS. The purpose of the meeting was to discuss some of the challenges identified during the pilot study. Two key challenges were identified during the pilot study. The challenges related to the scanty clinical data in the treatment files and the practical uses of the preliminary data source form. The scanty clinical data in the patients' treatment files were a consequence of the oncologists' methods of recording data in the patients' treatment files.

During the pilot study, it was evident that the oncologists did not have a standard method of reporting such as the Eastern Cooperative Oncology Group (ECOG) performance status system, the European Organisation for Research and Treatment of Cancer (EORTC) quality of life module, and the NCI Common Toxicity Criteria. The ECOG performance status provides scales and criteria that oncologists can use to assess and report on the progress of a patient's disease, how the disease affects the daily life of the patient, and the appropriate treatment and prognosis (Oken, Creech, Tormey, Horton, Davis, McFadden and Carbone 1982:649). The EORTC quality of life module provides oncologists with guidelines to report on patients' quality of life (Jayasekara, Rajapaksa, and

Greimel 2008:1053). Oncologists can use the NCI Common Toxicity Criteria to report on toxicities that patients incur from treatment they receive (Saibishkumar, Patel, Sharma, Karunanidhi, Sankar and Mallick 2005:76).

Discrepancies in the different reports of oncologists were particularly evident in the terminology they used and the comprehensiveness of the records. Even though the oncologists seemed to have a common understanding of the terminology used in the patients' files, the information was vague, and, in some instances, open to interpretation. Some examples of vague and unspecified terms are *"…patient is doing well…tolerating treatment well…severe diarrhoea…weight loss…nausea…blood count too low…swelling…vaginal infection…offensive discharge…no tumour…weak…enlarged mass…requires hospitalisation…deteriorating…"*

Capturing of data on the data source form entailed the selection of options that were relevant to the clinical parameters used for the current study. The options that could be selected were limited only to the options provided on the data source form. These limitations had the potential of placing constraints on data collection and analysis. The other challenge was that each patient's data had to be captured on an individual data source form, which was in the form of an MS Word® document file. Each document file consisted of at least eight pages, which made it difficult for the statistician to capture and manage the large volumes of data and information.

Based on the discussions between the researcher and the statistician, a collective decision was taken to revise the data source form to create a simpler, more practical, more efficient data source form. Several literature sources were explored to assist in the compilation of such a data source form. These sources included a study conducted by Kim *et al.* (2007:61), as well as a study conducted by Saibishkumar et al. (2005:77). The changes that were made to the data source form are discussed in section 3.6.1 below.

3.6.1 Revision of the data source form

Revision of the data source form was intended to address the challenges identified in section 3.6 above. The first part of the revision process concerned the availability of data in the treatment files. The scanty data in the treatment files required the researcher to formulate a reference sheet that could be used for the collection of data. The terminology in the patients' treatment files was used to generate an index for the various relevant clinical parameters. These parameters were: the general condition of the patient; adverse responses to treatment; and tumour responses. Appendix 2 provides an index that was generated for use in the collection and analysis of data. The terminology that was commonly used to record the oncologists' reports is also included in the index.

The second part of the revision process concerned the practicality of the form. Whereas the original data source form consisted of a detailed questionnaire for each patient's data, the revised data source form (appendix 4) consisted of a single data source sheet for all the patients included in the study. The single data source sheet was in the form of an Excel® file document, which consisted of two worksheets, namely the data-capturing sheet and the index sheet. The data-capturing sheet was used to capture all the patients' data from their files and transfer it onto the worksheet, with each category of data being captured in the designated area provided on the worksheet. The index sheet contained descriptions of the codes that were used on the first worksheet. Whereas the original data source form contained a textual representation of the required clinical and treatment parameters, the revised form was based on a numerical coding system.

By means of the coding system, the patients' treatment and clinical data were grouped under various categories, and each category was further grouped into clearly defined subcategories. Each subcategory was represented on the data source form by a numerical code. Take the example of a patient diagnosed with Squamous cell carcinoma. In this case, the data would be recorded under the category "diagnosis", and the "sub-category" would be represented by the

numerical code 1, where 1 = Squamous cell carcinoma, 2 = Adeno-carcinoma, and 3 = Adeno-squamous cell carcinoma.

Take another example: a patient who completed a full course of chemotherapy. In this case, the data would be recorded under the category “chemotherapy”, and the “sub-category” would be represented by the numerical code 1, where 1 = patient completed the whole prescribed course, and 2 = there were interruptions in the administration of chemotherapy during the course of treatment.

The revised data source form was analysed by the researcher and a representative from the Department of Bio-Statistics, UFS, to determine whether the revised data source form efficiently addressed the previously identified challenges. The data that was collected from the pilot study was used to assess the revised data source form. The form was accepted and the researcher, therefore, could proceed with the data collection process for the main study.

3.7 DATA COLLECTION

The data used for the current study were based on information in patients’ files, as recorded by oncologists. Using the list of Ca Cx patients provided by the departmental statistician at DROUAH, the RT numbers of patients were used to access data.

Once a file was deemed fit for selection in accordance with the inclusion criteria, the data were extracted from the file with the aid of the data source form. The patients’ clinical and treatment data were captured electronically and presented as codes under the different categories and sub-categories provided on the data source form, as described in section 3.6.

Through this process, all the files could be accessed, and where there was compliance with the inclusion criteria, the data were captured on the data source form. The data from all the eligible files were captured on a single worksheet in

the Excel® file document that was used as the research tool to collect the data. This single Excel® file document was then submitted to the statisticians at the Department of Biostatistics at the UFS for processing and analysis.

3.8 STATISTICAL ANALYSIS

All the information and data given to the statisticians at the Department of Biostatistics at the UFS were processed and analysed. A sub-analysis of the data was also conducted. Based on these analyses, the variables used were projected quantitatively in the form of numbers and frequencies. Fisher's exact test and the Chi-squared test were used to analyse the data. The results obtained by the statisticians were presented to the researcher for final analysis and interpretation, in order to formulate inferences and conclusions.

The researcher kept hard copies of all the data that was captured from the patients' files and submitted for analysis. This enabled the researcher to validate and verify the analysed data that was received from the statisticians. The researcher was also able to refer to the data at any time. The analysis and interpretation of these results are discussed in chapter 4.

3.9 ETHICS

The study adhered to all legal and ethical requirements throughout. Consent to conduct the study was granted by the Hospital Manager: Clinical Services (appendix 5). Consent to conduct the study was granted on condition that no patient information was published without the consent of the Chief Executive Officer (CEO) of the hospital, Consent to conduct the study was granted on the further understanding that the protocol of the study was approved by the Ethics Committee of the UFS.

In granting approval for research studies, the Ethics Committee of the UFS observes ethical and statutory guidelines that ensure that researchers practice

within an established framework of ethical rules and practice. The research protocol for this study was submitted to the Ethics Committee of the UFS for approval, The study was duly approved on 15 August 2007, ETOVS number 133/07 (appendix 6).

In addition to the conditions set out for the approval of the current study the researcher also sought the advice of colleagues from the Department of Biostatistics at the UFS, relating to the disclosure of information relating to the HIV status of individuals. The advice from the colleagues from the Department of Biostatistics at the UFS led to a decision by the researcher not to include the patients' personal and demographic data on the data source form for this study.

3.10 CONCLUSION

The primary objective of the study was to determine how HIV+ CA Cx patients tolerated the radical treatment protocol at DROUAH, with HIV- patients used to benchmark the therapeutic benefits in terms of quality of life and tumour response. The methods and processes described above were used to conduct an analysis of patients' acute and chronic treatment reactions, as well as their general health status during and after treatment. Chapter 4 presents the results of radical chemo-radiotherapy in the treatment of Ca Cx at DROUAH.

4. CHAPTER 4: RESULTS

4.1 INTRODUCTION

The current study focused on how HIV+ patients tolerated the radical treatment protocol for Ca Cx at DROUAH by assessing overall quality of life throughout the treatment schedule, and for a maximum period of 18 months after conclusion of treatment. Quality of life was assessed by analysing the patients' general condition, and the rate of adverse responses reported. Tumour response was a secondary objective, with HIV- patients being used to benchmark the therapeutic benefits.

This chapter presents the results of the study. The chapter also presents information on patient inclusion procedures, analysis of the patients' clinical information and status at referral for treatment in the Department, as well as analysis of the responses of each group of patients for specific variables at specific intervals. The variables were the general condition of patients while receiving treatment, adverse responses and tumour responses of the patients reported during follow-up consultations at specified intervals, after conclusion of the treatment protocol.

4.2 STUDY POPULATION

During the planning phase of the current study, a list of all patients registered with a diagnosis of Ca Cx for the period 2002 to 2006 was obtained from the departmental statistician. This list contained the details of 1603 patients. Patients were selected for inclusion in the current study according to the criteria set out in sections 3.4.1 and 3.4.2. Accordingly, 111 patients (n = 111) were entered into the study.

Table 4.1 presents information on the clinical characteristics of the initial study population, reflecting the clinical status of patients upon referral for treatment in the Department. Aspects of the patients' clinical status that were analysed include diagnosis, FIGO staging and CD4.

Table 4.1 Demographics of the clinical status of the initial study population

	HIV Negative n = 72 (64.9%)	**HIV Positive n = 39 (35.1%)**	**Total (n=111)**
Diagnosis (Ca Cx type):			
Squamous Cell	57 (79.2%)	33 (84.6%)	90
Adenocarcinoma	12 (16.7%)	6 (15.4%)	18
Adenosquamous	3 (4.1%)	0 (0%)	3
FIGO Stage:			
II	13 (18.1%)	11 (28.2%)	24
III	59 (81.9%)	28 (71.8%)	87
CD4 Count:			
< 100	0 (0.00%)	0 (0.00%)	0
100 - 200	0 (0.00%)	0 (0.00%)	0
200 - 400	0 (0.00%)	12 (30.8%)	12
> 400	72 (100.00%)	27 (69.2%)	99

Although 1603 patients were registered for treatment for Ca Cx at DROUAH from January 2002 to August 2006, 647 (40%) patients were treated with radical intent for FIGO stage II and III Ca Cx during the aforementioned period. The number of patients that were included in the study was 111, representing 7% of the total population of Ca Cx patients in the department, and 17% of the total number (n=647) of patients treated for Ca Cx with radical intent.

The follow-up data in 339 (52%) of the 647 patients treated with radical intent during the period of interest to this study, did not comply with the inclusion criteria

for the study. Of the 647 patients treated with radical intent, 77 (12%) patients were from the Northern Cape Province. Due to bureaucratic reasons, the follow-ups for patients from the Northern Cape Province were conducted in Kimberley, and these patients' records could not be used for this study. Sixty-three (10%) of the 647 patients treated with radical intent were treated using a different protocol to the one of interest in this study, whilst 57 (9%) files were unaccounted for during data collection.

4.2.1 Diagnosis

It is evident that the majority of patients [n = 90 (81.0%)] were diagnosed with squamous cell carcinoma. Adenocarcinoma and adenosquamous carcinoma were diagnosed in a smaller number of patients [n = 18 (16.2%) and n = 3 (1.8%), respectively].

4.2.2 FIGO Staging

In line with the inclusion criteria, only patients with FIGO stage II or III Ca Cx were eligible for enrolment in the study. Based on the analysis, it is clear that patients were predominantly diagnosed with FIGO stage III [n = 87 (78.3%)].

4.2.3 CD4 Count

The distribution of patients according to CD4 cell counts made clear that 89.1% of patients (n = 99) had a CD4 cell count in excess of 400 CD4 cells per mm of blood. The rest [n = 12 (10.9%)] presented with a CD4 count between 200 and 400 CD4 cells per mm of blood at the commencement of treatment for Ca Cx.

4.3 DATA ANALYSIS

Based on the collected data, the statistician observed that patient data became more difficult to come by as patients' treatment follow-up sessions progressed. The decline in data was a consequence of patients who did not honour their follow-up appointments as scheduled by the oncologists. The patients' records indicated that patients defaulted on their follow-up appointments at various

intervals after completion of the treatment protocol. This tendency was more prevalent at longer intervals (12 to 18 months) after completion of treatment. Fisher's exact test was used as the method of choice for the analysis of data, with the Chi-squared test being employed in cases where the statistician considered data sparse.

A preliminary data analysis conducted by the statistician suggested that there was a discrepancy in the composition of HIV+ and HIV- patients in the current study. It was evident that some patients commenced with treatment in a good general condition while others commenced in a fair general condition. A potential consequence was that patients' general condition at the commencement of treatment would be a variable in the analysis of data.

A collective decision was taken by the statistician and the researcher to conduct a sub-analysis only on the patients who were in a good general condition at the commencement of treatment. The motivation for the decision was to ensure that all participants would commence treatment in the same general condition, thus eliminating the patients' general condition as a variable during data analysis. This meant that the study population was reduced by 13.5% (from n = 111 to n = 96). The number of HIV- patients was reduced by 18% (from n = 72 to n = 59), and the number of HIV+ patients by 5% (from n = 39 to n = 37).

The results presented by the statistician were subjected to manual verification by the researcher and a senior oncologist. The raw data were collated with the analysed data to check that they correlated. The intention of the verification process was to make sure that the results were a true reflection of the data submitted and to ensure that the results were pure, authentic and valid.

All the results in this chapter reflect the analysis of a total study population of n = 96. Table 4.2 contains information on the clinical characteristics of the study population included in the data sub-analysis. The table represents the patient data in the form of numbers, with their percentages in brackets. The number of

patients excluded from the initial study population during the sub-analysis is presented in brackets as negative numbers in italic font.

Table 4.2 Demographics of the clinical status of the study population included in the data sub-analysis

	HIV Negative n = 59 (61.5%) *(-13)*	**HIV Positive n = 37 (38.5%) *(-2)***	**Total (n = 96) *(-15)***
Diagnosis:			
Squamous Cell Ca	46 (77.9%) *(-11)*	32 (86.5%) *(-1)*	78 *(-12)*
Adenocarcinoma	10 (17.0%) *(-2)*	5 (13.5%) *(-1)*	15 *(-3)*
Adenosquamous Ca	3 (5.1%) *(-3)*	0 (0%)	3
FIGO Stage:			
II	12 (20.3%) *(-1)*	10 (27%) *(-1)*	22 *(-2)*
III	47 (79.7%) *(-12)*	27 (73%) *(-1)*	74 *(-13)*
CD4 Count:			
< 100	0 (0%)	0 (0%)	0
100 - 200	0 (0%)	0(0%)	0
200 - 400	0 (0%)	12 (32.4%)	12
> 400	59 (100%) *(-13)*	25 (67.6%) *(-2)*	84 *(-15)*

4.4 TREATMENT RESPONSES

The key objective of the current study was to assess how HIV+ patients tolerated the treatment protocol, with the HIV- patients used to benchmark the therapeutic benefits in terms of tumour response and general patient condition. Analysis of the treatment responses of patients during treatment and shortly thereafter was seen as a good indicator of how patients tolerated their treatment.

The study used a maximum follow-up time of 18 months after conclusion of

treatment. The 18-month follow-up interval was motivated by information obtained from two studies reported in the literature. The first was a retrospective analysis of the treatment results of patients with invasive Ca Cx, conducted by Saibishkumar *et al.* (2005:75) in India. The mean follow-up time for overall results of treatment was 16.5 months. The second study was conducted by Soeters, Bloch, Levin, Dehaeck, and Goldberg (1989:44) and constituted an analysis of results obtained by treating patients with chemo-radiotherapy, using Cisplatin, Bleomycin and Vinblastine. Fifty-five percent (55.5%) of the patients in this study had a median survival time of 20 months. The use of these two studies as a benchmark was based on similarities in social, economic, political and cultural circumstances that could affect the overall responses of patients.

The sections below provide a summary of the data analysis of patients' responses. Responses throughout the duration of treatment up to a period of 18 months subsequent to conclusion of the treatment were analysed. The analysis focused on the general condition of patients, adverse responses and tumour responses. The analysis of general condition, adverse responses and tumour responses was related to the chemo-radiotherapy treatment protocol. The weekly responses during treatment are dealt with first.

4.4.1 General condition during treatment

Patients were examined by oncologists on a weekly basis for the duration of their treatment schedule. Records of the weekly consultations were kept in the patients' files. For the purposes of the current study, the data obtained from patients' records focused mainly on their general condition during consultation. The researcher grouped the patients' general condition into five main categories, namely good, fair, bad, poor and pre-terminal. The categories for general condition are summarised in appendix 2.

Figure 4.1 presents a graphic distribution of the general condition categories for the study population of HIV+ and HIV- patients during their seven-week treatment schedule.

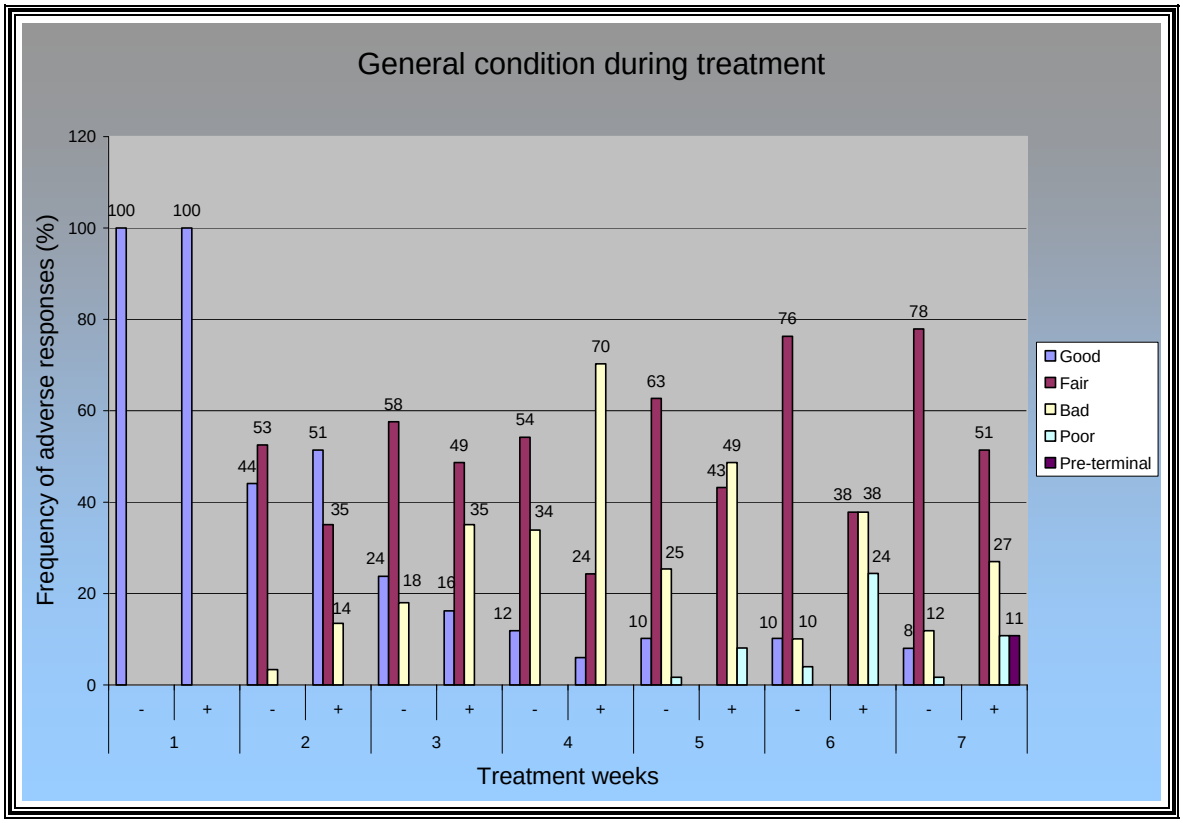

Figure 4.1 General condition during treatment

In the next section, a detailed report, followed by a summary of patient responses to treatment during each weekly consultation are presented (see Tables 4.3 to 4.9).

Week 1:

All the patients (100%) in the current study were in visibly good general condition during the first weekly consultations. Table 4.3 presents the distribution of general condition categories for the two groups of patients during the first week of treatment. There was no statistically significant difference between HIV+ and HIV- patients in terms of general condition in week 1 of treatment ($p = 0.057$).

Table 4.3 General condition of patients during week 1 of treatment

Week 1		
HIV status	**-**	**+**
Good	100%	100%
Fair	0	0
Bad	0	0
Poor	0	0
Pre-terminal	0	0
p-value	0.0572	

Week 2:

Almost half (51%) of the HIV+ patients were in good general condition during the second week of treatment. Approximately half (53%) of the patients in the HIV- group were in fair condition. There was no statistically significant difference between HIV+ and HIV- patients in terms of general condition in week 2 of treatment (p = 0.096). Table 4.4 presents the distribution of general condition categories for the two groups of patients during the second week of treatment.

Table 4.4 General condition of patients during week 2 of treatment

Week 2		
HIV status	**- (%)**	**+ (%)**
Good	44	51
Fair	53	35
Bad	3	14
Poor	0	0
Pre-terminal	0	0
p-value	0.0961	

Week 3:

Approximately half (49%) of the HIV+ patients were in fair general condition during week 3 of treatment. More than half (58%) of the HIV- patients were in fair general condition at the same stage of treatment. There was no statistically significant difference between HIV+ and HIV- patients in terms of general condition in week 3 of treatment (p = 0.1801). Table 4.5 presents the distribution of general condition categories for the two groups of patients during the third week of treatment.

Table 4.5 General condition of patients during week 3 of treatment

Week 3		
HIV status	**- (%)**	**+ (%)**
Good	24	16
Fair	58	49
Bad	18	35
Poor	0	0
Pre-terminal	0	0
p-value	0.1801	

Week 4:

During the fourth week of treatment, more than two-thirds (70%) of the HIV+ group were in bad general condition. Approximately one-quarter (24%) of the group were in fair general condition. More than half (54%) of the HIV- group of patients were in fair condition during the fourth week of treatment, whilst approximately one-third (34%) were in bad general condition. There was no statistically significant difference between HIV+ and HIV- patients in terms of general condition in week 4 of treatment (p = 0.0024). Table 4.6 presents the distribution of general condition categories for the two groups of patients during the fourth week of treatment.

Table 4.6 General condition of patients during week 4 of treatment

Week 4		
HIV status	**- (%)**	**+ (%)**
Good	12	6
Fair	54	24
Bad	34	70
Poor	0	0
Pre-terminal	0	0
p-value	0.0024	

Week 5:

There was an almost equal distribution of reports denoting fair (43%) and bad (49%) general condition for HIV+ patients during the fifth week of treatment. Just under two-thirds (63%) of HIV- patients were in fair general condition, whilst one-quarter (25%) were in bad general condition during the fifth week of treatment. There was a statistically significant difference between HIV+ and HIV- patients in terms of general condition in week 5 of treatment ($p = 0.0072$). Table 4.7 presents the distribution of general condition categories for the two groups of patients during the fifth week of treatment.

Table 4.7 General condition of patients during week 5 of treatment

Week 5		
HIV status	**- (%)**	**+ (%)**
Good	10	0
Fair	63	43
Bad	25	49
Poor	2	8
Pre-terminal	0	0
p-value	0.0072	

Week 6:

There was an equal distribution of reports denoting fair (38%) and bad (38%) general condition for HIV+ patients during the sixth week of treatment. Approximately one-quarter (24%) of HIV+ patients were in poor general condition during the sixth week of treatment. At the same stage of treatment, approximately three-quarters (76%) of HIV- patients were in fair general condition. There was a statistically significant difference between HIV+ and HIV- patients in terms of general condition in week 6 of treatment ($p = 0.0001$). Table 4.8 presents the distribution of general condition categories for the two groups of patients during the sixth week of treatment.

Table 4.8 General condition of patients during week 6 of treatment

Week 6		
HIV status	**- (%)**	**+ (%)**
Good	10	0
Fair	76	38
Bad	10	38
Poor	4	24
Pre-terminal	0	0
p-value	<0.0001	

Week 7:

During the seventh week of treatment, approximately half (51%) of HIV+ patients were in fair general condition, whilst approximately one-quarter (27%) were in bad general condition. At the same stage of treatment, approximately three-quarters (78%) of HIV- patients were in fair general condition. There was a statistically significant difference between HIV+ and HIV- patients in terms of general condition in week 7 of treatment ($p = 0.0004$). Table 4.9 presents the distribution of general condition categories for the two groups of patients during the seventh week of treatment.

Table 4.9 General condition of patients during week 7 of treatment

Week 7		
HIV status	**- (%)**	**+ (%)**
Good	8	0
Fair	78	51
Bad	12	27
Poor	2	11
Pre-terminal	0	11
p-value	<0.0004	

Summary: General condition of patients during treatment

The results show that the majority of HIV+ and HIV- patients were in fair general condition throughout the treatment schedule. During the first four weeks of treatment, there were no statistically significant differences between HIV+ and HIV- patients. However, in weeks 5, 6 and 7 there were statistically significant differences between HIV+ and HIV- patients in terms of general condition

4.4.2 Follow-up consultations

Once the patients had completed the entire treatment schedule, they were given an appointment date for their first follow-up consultation. The date for the first follow-up consultation was scheduled three months after completion of the treatment protocol. Subsequent follow-up consultations were scheduled at 3-month intervals for a period of 1 year, following the treatment protocol. After a year, the follow-up consultations were scheduled at 6-month intervals. Patients were expected to visit the oncologists on the scheduled dates.

During follow-up consultations, the oncologists conducted routine examinations of patients, based on clinical examinations, cervical Papanicolaou smears (Pap smears), and the information the patients conveyed to them during consultation. If the oncologists suspected central or parametrial recurrence during the clinical

examination or Pap smears, a biopsy was taken for histological confirmation. The information that patients conveyed to the oncologists concerned their general well-being, how they felt, and their general health subsequent to treatment.

For the purposes of the current study, the data sought from the patients' files primarily focused on their general condition, tumour responses and adverse responses experienced or reported during follow-up consultations. The variables, i.e. general condition, adverse responses and tumour response, that were of interest during follow-up consultations, are summarised in appendix 2.

During the collection of data, it was observed that in some instances patients did not report for their follow-up consultations as scheduled. Some of these patients came at a later stage within the scheduled 18-month follow-up period, whilst others never came again. In the former case, the records were only used for the current study if the follow-up schedule coincided with the schedules prescribed for the study. The next section provides information on missing frequency in the data analysis.

4.4.2.1 Missing frequency

In terms of the selection criteria for the study, the follow-up records in the patients' files had to be available, clear and compliant with the needs of the data source form. In cases where this criterion was not met these patients were excluded from the study. However, there were instances where patients' data for specific follow-up schedules were not available in the files. The data for each follow-up schedule was recorded on the data source form as "missing frequency". Two categories of missing frequency were identified and included in the study.

The first category included patients who reported for their follow-up consultations in line with the prescribed follow-up schedule, but according to the oncologists, however, their condition did not justify any further examinations related to tumour and/or adverse responses. These patients were, according to the judgement of

the oncologists, either pre-terminally ill or had proven progression and were just seen for symptomatic interventions or follow-up. The follow-up records of these patients were available and up-to-date, except that they did not contain information on tumour and/or adverse responses.

The second category included patients who turned up for their follow-up consultations, but were outside the schedule prescribed for the study. After considering the socio-economic and logistical challenges that patients have to contend with, an allowance of 2 weeks on either side of the scheduled follow-up date was given for patients to turn up. If patients did not come within the given period, their data could not be used for the particular follow-up interval. Patients were included in the study because their previous and/or subsequent visits were on schedule, and their treatment records were available, clear and compliant with the data source form.

The missing frequency categories on all tables and graphs in the current study are presented as “no follow-up”; they represent the number of patients for whom no data were available at the specific follow-up interval. The “no follow-up” data were recorded as a percentage of n = 96, because there was no way to determine in what condition the patient would have been at the specified follow-up interval.

Analysis of the data showed that there was a higher incidence of “no follow-up” data amongst the HIV+ patients compared to the HIV- patients. The incidence of “no follow-up” data for the HIV+ and HIV- patients, over the 18-month follow-up interval were 18% and 12% respectively. The majority of “no follow-up” cases were reported in the second half of the 18-month follow-up period, with incidences of 73% and 61% for the HIV+ and HIV- patients, respectively.

4.4.2.2 General condition of patients at follow-up

The general condition of patients during follow-up consultations was recorded and categorised as good, fair, bad, poor or pre-terminal. The categories for general condition during follow-up are summarised in appendix 2. Figure 4.2 presents a graphic distribution of the general condition of HIV+ and HIV- patients during their follow-up visits. The calculation of percentages was based on the total number of patients in each group who reported for the scheduled follow-up consultations.

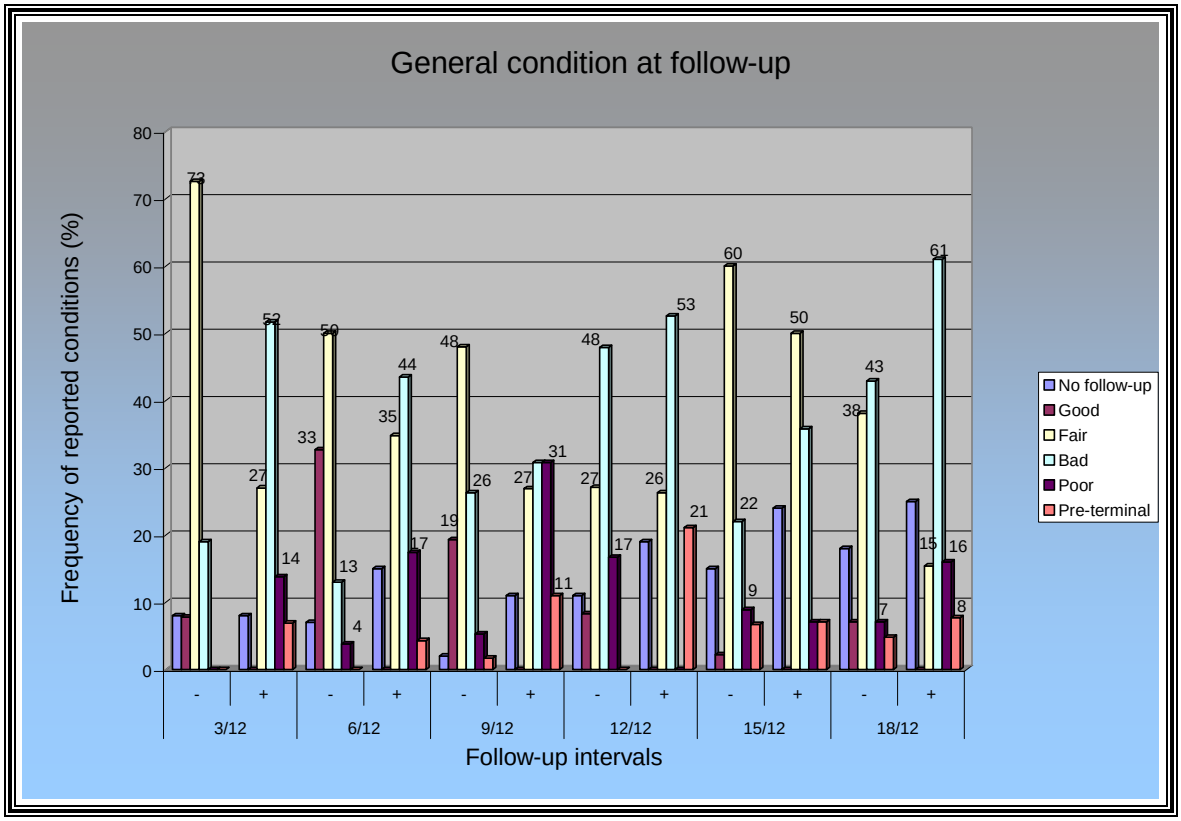

Figure 4.2 General condition at follow-up

Follow-up 1: 3 Months after conclusion of treatment

A relatively large number (52%) of patients from the HIV+ group were in bad general condition, while 27% and 14% of the group were in fair and poor general condition, respectively. Most (73%) HIV- patients were in fair general condition. There was a statistically significant difference ($p < 0.0001$) between HIV+ and HIV- patients in terms of general condition during this period.

Follow-up 2: 6 Months after conclusion of treatment

Seventy-nine percent (79%) of HIV+ patients were in fair (35%) or bad (44%) general condition. Half the HIV- patients were in fair general condition, while one-third were in good general condition. There was a statistically significant difference ($p < 0.0001$) between HIV+ and HIV- patients in terms of general condition for this period.

Follow-up 3: 9 Months after conclusion of treatment

There was an even distribution of HIV+ patients who were either in bad (31%) or poor (31%) general condition, while 27% of patients were in fair general condition. Almost half (48%) of the HIV- patients were in fair general condition. There was a statistically significant difference ($p = 0.0004$) between HIV+ and HIV- patients in terms of general condition nine months after treatment.

Follow-up 4: 12 Months after conclusion of treatment

Just over half (53%) of HIV+ patients who turned up for follow-up 12 months after treatment were in bad general condition, while just over a quarter (26%) of the group were in fair condition. Slightly less than half (48%) of HIV- patients were in bad general condition, while just over a quarter (27%) of the group were in fair general condition. Twelve months after conclusion of treatment, there was no statistically significant difference ($p = 0.0064$) between HIV+ and HIV- patients in terms of general condition.

Follow-up 5: 15 Months after conclusion of treatment

Half the HIV+ patients were in fair general condition, while just over one-third (36%) were in bad general condition. Almost two-thirds (60%) of the HIV- patients were in fair general condition. There was no statistically significant difference ($p = 0.8751$) between HIV+ and HIV- patients in terms of general condition during this period.

Follow-up 6: 18 Months after conclusion of treatment

Most HIV+ patients were in bad general condition (61%), while smaller numbers were in fair (15%) or poor (16%) general condition. Most HIV- patients were in bad (43%) or fair (38%) general condition. There was no statistically significant difference ($p = 0.3561$) between HIV+ and HIV- patients in terms of general condition 18 months after treatment.

Summary: General condition of patients at follow-up

The results provide evidence of a specific relationship between HIV+ and HIV- patients in terms of general condition. The data related to the general condition of patients at follow-up over the designated 18-month period could be interpreted with reference to two 9-month periods. During the first 9 months after conclusion of treatment, there were statistically significant differences between the two groups. Throughout the first 9-month period, most HIV+ patients were in bad general condition during their follow-up consultations. Most HIV- patients were in fair general condition in the same 9-month period subsequent to conclusion of treatment.

During the second 9-month period subsequent to conclusion of treatment, there were no statistically significant differences between HIV+ and HIV- patients. At each follow-up interval, the highest frequencies of reports for general condition were concentrated in the same categories, namely bad and fair, for both HIV+ and HIV- patients.

4.4.2.3 Adverse responses at follow-up

The adverse responses of patients recorded during follow-up consultations were categorised into six groups, namely none, moderate, severe, life-threatening and death-related. A summary of the categories and a description of adverse responses are provided in appendix 2. Figure 4.3 presents a graphic distribution of the adverse responses of HIV+ and HIV- patients during follow-up consultations.

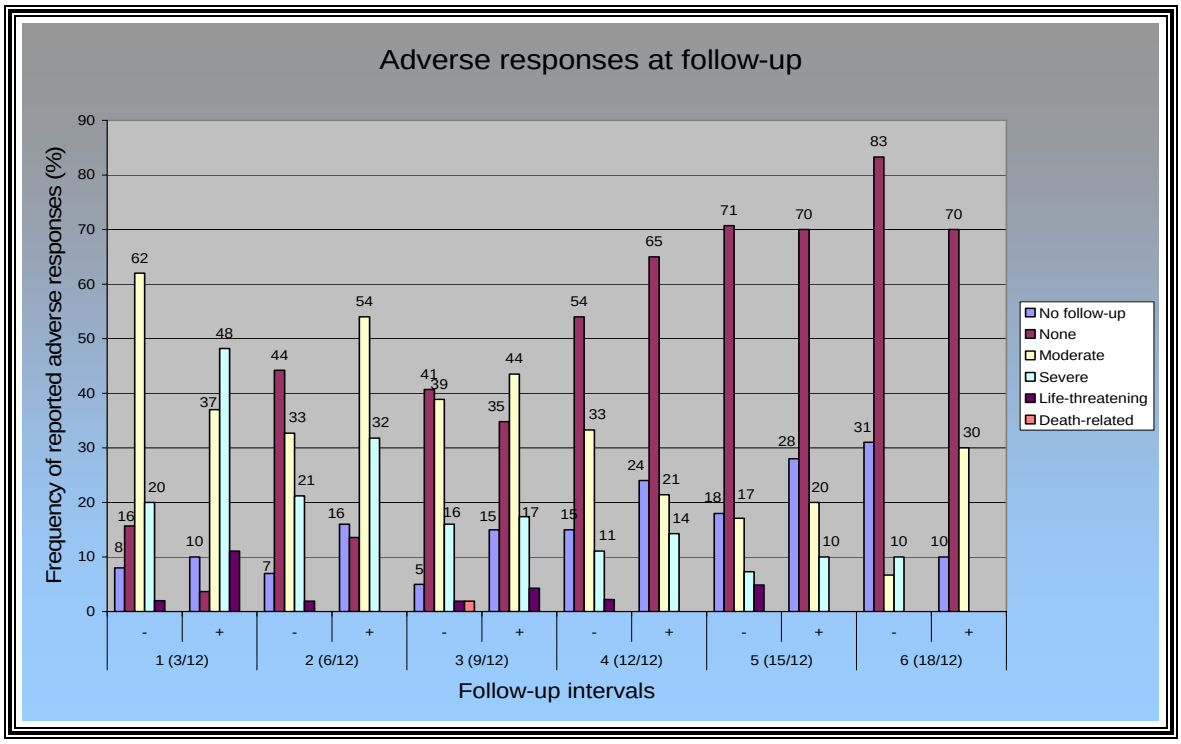

Figure 4.3 Adverse responses at follow-up

Follow-up 1: 3 Months after conclusion of treatment

Almost half (48%) of the HIV+ patients reported severe adverse responses. The majority of HIV- patients (62%) reported moderate adverse responses. There was no statistically significant difference (p = 0.0115) between HIV+ and HIV- patients in terms of adverse responses for this period.

Follow-up 2: 6 Months after conclusion of treatment

More than half (54%) the number of HIV+ patients reported moderate adverse responses, with one-third (32%) reporting severe adverse responses six months after conclusion of treatment. Most HIV- patients reported no (44%) adverse responses or moderate (33%) adverse responses. There was no statistically significant difference (p = 0.0384) between HIV+ and HIV- patients in terms of adverse responses six months after conclusion of treatment.

Follow-up 3: 9 Months after conclusion of treatment

The majority (79%) of HIV+ patients reported no (35%) adverse responses or

moderate (44%) adverse responses nine months after conclusion of treatment. The majority (80%) of HIV- patients reported no (41%) adverse responses or moderate (39%) adverse responses. There was no statistically significant difference ($p = 0.8488$) between HIV+ and HIV- patients in terms of adverse responses nine months after conclusion of treatment.

Follow-up 4: 12 Months after conclusion of treatment

The majority (86%) of HIV+ patients reported no (65%) adverse responses or moderate (21%) adverse responses 12 months after conclusion of treatment. Eighty-seven percent (87%) of HIV- patients reported no (54%) adverse responses or moderate (33%) adverse responses 12 months after conclusion of treatment. There was no statistically significant difference ($p = 0.7503$) between HIV+ and HIV- patients in terms of adverse responses 12 months after conclusion of treatment.

Follow-up 5: 15 Months after conclusion of treatment

Seventy percent (70%) of HIV+ patients reported no adverse responses 15 months after conclusion of treatment. The majority (71%) of HIV- patients reported no adverse responses 15 months after conclusion of treatment. The remaining 5% reported life-threatening responses. There was no statistically significant difference ($p = 0.8982$) between HIV+ and HIV- patients in terms of adverse responses 15 months after conclusion of treatment.

Follow-up 6: 18 Months after conclusion of treatment

At the follow-up interval scheduled 18 months after conclusion of treatment, HIV+ patients reported no (70%) adverse responses or moderate (30%) responses. The majority of HIV- patients reported no (83%) adverse responses, while 7% reported moderate adverse responses and 10% reported severe adverse responses 18 months after conclusion of treatment. The difference between HIV+ and HIV- patients 18 months after conclusion of treatment was not statistically significant ($p = 0.224$).

Summary: Adverse responses at follow-up

Throughout the 18-month follow-up period, there were no statistically significant differences between the reports of adverse responses for HIV+ and HIV- patients, respectively. A trend similar to the one deduced for the general condition of patients at follow-up, is also evident for the data related to adverse responses at follow-up.

During the first 3-month period subsequent to conclusion of treatment, the majority (48%) of HIV+ patients reported severe adverse responses, while the majority (62%) of HIV- patients reported moderate adverse responses. During the two subsequent follow-up intervals, at six and nine months after conclusion of treatment, the majority of HIV+ patients reported moderate adverse responses, while the majority of HIV- patients reported none. During the last three follow-up intervals, at 12, 15 and 18 months, respectively, after conclusion of treatment, HIV+ and HIV- patients reported no adverse responses.

4.4.2.4 Tumour responses at follow-up

The tumour responses of patients recorded during follow-up consultations were categorised into six groups, namely *total regression, partial regression, no response, progression, recurrence* and *distant metastasis*. A summary of the categories and a description of tumour responses are provided in appendix 2. Figure 4.3 presents a graphic distribution of the tumour responses of the two groups of patients during their follow-up visits. Calculation of percentages was based on the total number of patients in each group who reported for the scheduled follow-up consultations.

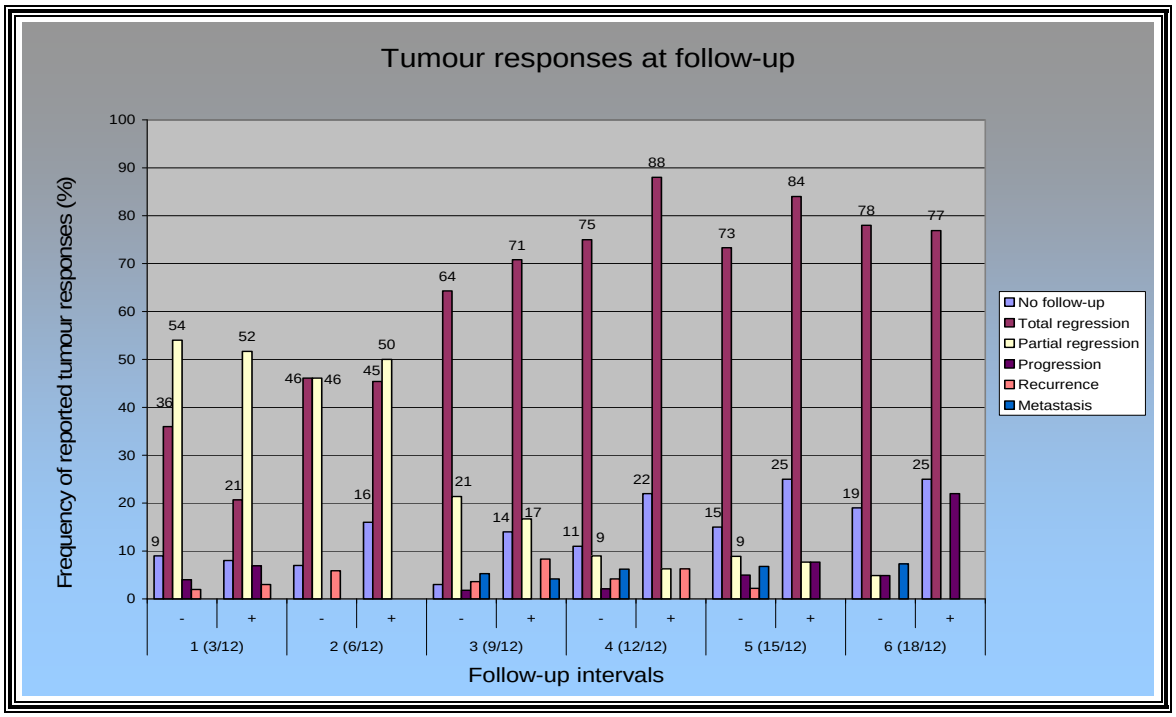

Figure 4.4 Tumour responses at follow-up

Follow-up 1: 3 Months after conclusion of treatment

Just more than half (52%) of HIV+ patients who turned up for follow-up consultations three months after conclusion of treatment had partial tumour regression, while 21% had total tumour regression. More than half the HIV- patients showed partial tumour regression, while 36% showed total tumour regression, three months after conclusion of treatment. There was no statistically significant difference ($p = 0.4144$) between HIV+ and HIV- patients in terms of tumour response three months after conclusion of treatment.

Follow-up 2: 6 Months after conclusion of treatment

During follow-up interval 2, six months after conclusion of treatment, 50% of HIV+ patients had partial tumour regression, whilst 45% had total tumour regression. There was an even distribution (45%) of partial and total tumour regression among HIV- patients, six months after conclusion of treatment. There was no statistically significant difference ($p = 0.5033$) between HIV+ and HIV- patients in terms of tumour response six months after conclusion of treatment.

Follow-up 3: 9 Months after conclusion of treatment

The majority (71%) of HIV+ patients had total tumour regression nine months after conclusion of treatment. Just less than two-thirds (64%) of the HIV- patients had total tumour regression nine months after conclusion of treatment. There was no statistically significant difference ($p = 0.5191$) between HIV+ and HIV- patients in terms of tumour response nine months after conclusion of treatment.

Follow-up 4: 12 Months after conclusion of treatment

The majority (88%) of HIV+ patients had total tumour regression. Three-quarters (75%) of HIV- patients had total tumour regression. There was no statistically significant difference ($p = 0.6971$) between HIV+ and HIV- patients in terms of tumour response in this period.

Follow-up 5: 15 Months after conclusion of treatment

During follow-up interval 5, 15 months after conclusion of treatment, the majority (84%) of HIV+ patients had total tumour regression. Just less than three-quarters (73%) of HIV- patients had total tumour regression 15 months after conclusion of treatment. There was no statistically significant difference ($p = 0.6453$) between HIV+ and HIV- patients in terms of tumour response 15 months after conclusion of treatment.

Follow-up 6: 18 Months after conclusion of treatment

During the last scheduled follow-up interval, 18 months after conclusion of treatment, just more than three-quarters (77%) of HIV+ patients had total tumour regression. More than three-quarters (78%) of HIV- patients had total tumour regression 18 months after conclusion of treatment. There was no statistically significant difference ($p = 0.1843$) between HIV+ and HIV- patients in terms of tumour response for this period.

Summary: Tumour responses of patients at follow-up

Throughout the 18-month follow-up period, there were no statistically significant differences between HIV+ and HIV- patients in terms of tumour response. A trend

similar to the one deduced for the general condition of patients at follow-up, is also evident for the data related to tumour response at follow-up.

The data from the first two follow-up intervals at three and six months, respectively, after conclusion of treatment show that most patients had partial tumour responses, whilst the data derived from the subsequent follow-up intervals, i.e. from 9 to 18 months after conclusion of treatment, suggest that most patients showed total tumour regression.

4.4.2.5 Survival

Out of 96 patients included in the data sub-analysis, there were 19 reported deaths, representing an 18-month overall survival rate of 80.2%. Twelve of the 19 reported deaths were HIV+ patients, whilst the remaining seven were HIV-. This implies a 67.6% 18-month overall survival rate for HIV+ patients, and an 88.1% rate for HIV- patients in the study.

4.5 CONCLUSION

This study analysed the general condition, tumour responses and adverse responses of HIV+ and HIV- patients treated for Ca Cx with the same treatment protocol. These variables were analysed to assess the patients' quality of life and to determine how HIV+ patients tolerated the radical treatment protocol. Although the aim of the current study was not to compare HIV+ and HIV- patients, parallel analyses of each group facilitated the drawing of inferences from the results.

Interpretation of data analysis can be tied to the three stages of the schedule the study investigated, namely the treatment phase, the first nine months after conclusion of treatment, and the second period of nine months after completion of treatment. The results and their relevance to the objectives of this study are discussed in chapter 5.

5. CHAPTER 5: DISCUSSION AND CONCLUSION

5.1 INTRODUCTION

This study retrospectively analysed the treatment responses of HIV+ and HIV- patients who received the same treatment for FIGO stage II and III Ca Cx with radical intent at DROUAH. The key objective of the current study was to determine how the HIV+ patients tolerated their treatment, especially in the light of their potentially compromised physiological condition. General condition of patients, adverse responses to treatment and tumour responses were used to determine overall outcomes and therapeutic benefits of the treatment. The HIV- patients were also analysed in order to benchmark the overall outcomes and therapeutic benefits of the treatment in terms of quality of life and tumour responses, in the absence of physiological challenges. This study (confirmed and motivated by a review of applicable sources) was based on the premise that the radical chemo-radiotherapy protocol used at DROUAH was the treatment of choice for Ca Cx.

The analysis of HIV- patients, therefore, only served as a reference; it was not used for the purposes of comparison. This chapter discusses the responses of FIGO stage II and III Ca Cx patients to the radical treatment protocol at DROUAH. The results regarding HIV+ patients' tolerance of the radical treatment, overall outcomes and therapeutic benefits of the treatment are also discussed. The challenges and shortcomings of the study are shared, and recommendations made. The study results are discussed next.

5.2 RESULTS OBTAINED FROM THE STUDY

An analysis was made of patients' general condition, adverse responses to treatment and tumour responses. The general condition of patients was analysed during treatment and for a short to medium period subsequent to the conclusion

of the treatment protocol. The analysis of adverse and tumour responses was based on short- to medium-term responses subsequent to the conclusion of the treatment protocol. The results concerning the general condition of patients are discussed first.

5.2.1 General condition of patients

The analysis of the general condition of patients was done with reference to two phases, namely the immediate term, and the short to medium term. The immediate-term analysis was based on patient data recorded during the treatment schedule. The short- to medium-term analysis was based on patient data recorded during follow-ups, i.e. after patients had completed their treatment. The immediate-term analysis was intended to gather evidence on how patients tolerated their treatment while they were receiving treatment (Novetsky *et al.* 2007:637). On the other hand, it was important to establish how the patients' quality of life was affected by the treatment, and to determine the therapeutic benefits of the treatment. This explains the short- to medium-term phase analysis of patients' general condition (Toita *et al.* 2005:677).

The immediate-term analysis of patients' general condition shows two different trends for the early and late stages of the treatment schedule, respectively. The early stages of treatment included weeks 1 to 4 of treatment, while the late stages included weeks 5 to 7 of treatment. During the early period of the treatment schedule, the HIV+ patients were in good general condition. The HIV+ patients' general condition deteriorated steadily during the first four weeks of treatment. During weeks 5 to 7 of treatment, there was a notable deterioration in the HIV+ patients' general condition. During this period, there were no reports of HIV+ patients in good general condition. There were no statistically significant differences between HIV+ and HIV- patients in terms of general condition during the early stages of treatment. However, during the late stages of treatment there were statistically significant differences between the two groups.

There were frequent reports of fatigue, dehydration, cystitis, loss of energy,

weight loss, anaemia and hypertension. These conditions were suspected to be a consequence of the treatment, and, therefore, were regarded as adverse responses to the treatment. The frequency and severity of these conditions seemed to increase during the later stages (weeks 5 to 7) of the treatment schedule.

Analysis of short- to medium-term data indicates that throughout the 18-month follow-up period no HIV+ patients were in good general condition. The diagnoses regarding their general condition were quite consistent, ranging from bad to fair. There were statistically significant differences between HIV+ and HIV- patients during the first nine months subsequent to treatment. During the second 9-month follow-up period, there were no statistically significant differences between HIV+ and HIV- patients in terms of general condition.

Similarly, the follow-up data also showed that the general condition of HIV+ patients was better during the second half of the 18-month follow-up period in comparison to the first half. Fatigue, dehydration, loss of energy, weight loss, anaemia and hypertension were also commonly reported during the follow-up analysis. Follow-up data obtained from patients' files also seemed to suggest an increase in the frequency of infectious conditions such as cystitis, flu and pneumonia.

The trends observed relating to the general condition of HIV+ patients at follow-up concur with the assertions of Losso *et al.* (2000:1616) that it is fairly common for the short-term side-effects to continue to get worse for a couple of weeks after the treatment, before they get better.

Abraham and Allegra (2001:221) believe there could be a correlation between the presence or absence of HIV and the responses of patients to the same standard of therapy, with the response to therapy expected to be worse in HIV+ patients than in HIV- patients. The current study was inspired by the hunches of some oncologists at DROUAH that HIV+ patients showed a poorer tolerance of

the radical treatment than their HIV- counterparts. The findings of the current study seem to concur with the findings of Abraham and Allegra (2001:221), justifying the hunches of oncologists in the Department.

Gallagher (2007:11) lists chronic fatigue and anaemia as some of the physiological changes caused by HIV/AIDS, with anaemia having a negative impact on the quality of life. Chronic fatigue is one of the most frequent and distressing symptoms that people infected with HIV report, and has been correlated with decreased quality of life and functional status (Voss *et al.* 2006:38). The prevalence of fatigue, dehydration, loss of energy, weight loss, anaemia and hypertension could be seen as the result of the combined effect of the chemo-radiotherapy the patients received and their HIV/AIDS infection. The results of the current study seem to correlate with the results of the two aforementioned studies of Voss *et al.* (2006:38) and Gallagher (2007:11), concerning the physiological changes caused by HIV/AIDS and the impact on the patients' quality of life.

The decline in the general condition of HIV+ patients during treatment, and within the first 9 months after treatment could be interpreted as a consequence of the effects of treatment. This apparent link between the general condition of patients and the short- to medium-term effects of the treatment could be interpreted as an indicator of patients' tolerance of the treatment they received. This would imply that HIV+ patients did not tolerate their treatment as well as HIV- patients, particularly in the immediate and short term. The low tolerance levels among HIV+ patients could be attributed to the physiological changes caused by HIV/AIDS, such as anaemia and chronic fatigue, which compromise the body's physical strength and defences (Gallagher 2007:11).

5.2.2 Adverse responses to treatment

The adverse responses to treatment were analysed over a maximum period of 18 months subsequent to the conclusion of treatment. This was done to determine the therapeutic benefits of the treatment and how the patients' quality

of life was influenced by the treatment. There were indications that within the first three months subsequent to treatment, a high incidence (48%) of severe adverse responses reported by HIV+ patients occurred.

During subsequent follow-ups, a decline was observed in the incidence and severity of the adverse responses that were reported. Some of the adverse responses that were commonly reported were diarrhoea, dysuria, lymphadenopathy, hydronephrosis, cystitis, vaginal stenosis, vaginal infections and fibrosis. These side-effects are consistent with those reported in the study conducted by Thomas (1999:1199).

The incidence and severity of adverse responses reported by HIV+ patients showed a steady decline during the first nine months after treatment, becoming stable during the second 9-month follow-up period. The decline in the incidence and severity of adverse responses seems to suggest that HIV+ patients were recovering from their adverse responses to treatment. During the second nine months after treatment, there was a high incidence of “no” adverse responses from HIV+ patients, suggesting full recovery from adverse responses to treatment.

Throughout the 18-month follow-up period, there were no statistically significant differences between HIV+ and HIV- patients. Despite this fact, there were indications that HIV- patients had an advantage over HIV+ patients in terms of the severity of adverse responses to treatment.

The advantage was seen during the first nine months after treatment. The differences in adverse responses between the first and second nine months following treatment, were consistent with the general condition of patients during follow-ups. These consistencies indicate a relationship between adverse responses and the general condition of patients, with the general condition improving in step with decreasing incidence of adverse responses.

It seems there was a relationship between the general condition of patients and their adverse responses, which naturally had an effect on their quality of life. The results of the current study support the findings of Abraham and Allegra (2001:221) that there could be a correlation between the presence or absence of HIV infection and the responses of patients to the same standard of therapy, with the response to therapy expected to be worse in HIV+ patients than in HIV- patients. There is support for the assertion by Voss *et al*. (2006:38) that the distressing symptoms reported by HIV+ patients, such as fatigue, have been correlated with decreased quality of life and functional status.

5.2.3 Tumour responses to treatment

Tumour responses were analysed with reference to short to medium periods following treatment, to determine the therapeutic benefits of treatment based on local tumour control. The HIV- patients were used to benchmark the therapeutic benefits of treatment in terms of quality of life and tumour response. Beahrs *et al* (1992:156) state that there are variations in tumour sizes between stage II and III Ca Cx, with a higher potential of cure in stage II than in stage III tumours. However, it was not the focus of the current study to differentiate between tumour responses amongst stage II and III tumours.

Within the first six months after treatment, most HIV+ patients showed partial tumour regression. During the subsequent follow-ups (from nine to 18 months subsequent to treatment), most HIV+ patients showed total tumour regression. There were no statistically significant differences between HIV+ and HIV- patients throughout the 18-month follow-up period.

The literature consulted for the current study indicates that the treatment outcomes for invasive Ca Cx in terms of local tumour control are poorer in HIV+ women than in HIV- women, with recurrence rates of up to 88% (Maiman *et al.* 1997:79). The results obtained could be interpreted to contradict the findings of Maiman *et al.* (1997:79), implying that the radical treatment protocol for Ca Cx at DROUAH offers no added therapeutic benefits to HIV+ patients in terms of

tumour responses. However, the results have to be interpreted in the context of the limitations and challenges identified during this study. This is discussed in section 5.4. The next section provides an overall perspective.

5.3 THE OVERALL OUTCOME OF TREATMENT

The overall outcome or efficacy of cancer treatment is measured by the extent to which local tumour control and overall and progression-free survival is improved, side-effects are reduced, and quality of life is enhanced (Novetsky *et al.* 2007:637). Tolerability of treatment modalities should not be compromised at the expense of improvements in the outcome of treatment, and neither should improved tolerability be attained at the expense of efficacy (Mitsuyasu 2001:23).

Medical scientists are always trying to use new research and technological developments to improve efficacy and enhance the overall outcomes of cancer treatment (De Vita *et al.* 2004:7). The hunches and concerns of local oncologists were inspired by and based on principles similar to those outlined by the aforementioned authors. The current study, therefore, wanted to address these concerns by analysing HIV+ patients' tolerance of the radical treatment for FIGO stage II and III Ca Cx at DROUAH. This analysis was based on the general condition of patients, adverse responses to treatment, and tumour responses.

The analyses of the variables related to the treatment of patients provided information on the efficacy or overall outcome of the treatment protocol relevant to this study. These analyses have been discussed in the preceding sections of this chapter. Certain inferences were drawn from the results of the study and the literature overview, and were expressed with some caution.

This study had to contend with challenges that could affect the conclusiveness of the results. Most of the challenges were the result of logistical and bureaucratic limitations. These limitations concerned the study population, the filing system in the Department, demographics, socio-economics, and the maximum follow-up

period that was used for this study. Challenges were also identified with regard to the conditions for ethical approval and the role of anti-retroviral (ARV) treatment. The topic of limitations and challenges are discussed in the next section.

5.4 LIMITATIONS AND CHALLENGES IDENTIFIED IN THIS STUDY

The interpretation of this study's results cannot be done properly without giving due consideration to certain limitations. Although 1603 patients were registered for treatment for Ca Cx at DROUAH from January 2002 to August 2006, the absolute number of patients included in the study was small. A total of 647 patients were treated with radical intent for FIGO stage II and III Ca Cx during the aforementioned period, with only 111 eligible for inclusion in accordance with the selection criteria for this study. The 111 patients represent 17.2% of patients who were treated for the same condition. The small study population makes the study less robust, and the findings need to be tested in studies that are more extensive.

The small study population can be attributed to, among other things, the filing system in the Department, demographics, socio-economic factors, and patient education and perceptions. DROUAH had a specific strategy for filing patient records. However, the success of this system depended on the co-operation of both staff members and patients. Clearly, there is a need for a quality control system in the filing section to ensure that filing is done in accordance with the stipulated protocol.

Demographics also presented some challenges to the data collection process. An example of such a challenge concerned the patients referred to the Department from the Northern Cape. Inter-provincial bureaucratic policies placed serious limitations on follow-up consultations and record-keeping with regard to these patients. Follow-up information on Northern Cape patients proved to be scanty. Another example of a demographic challenge concerned the patients who came from the rural parts of the Free State. Whenever these patients went home during treatment, it took a few days before they returned to continue with

their treatment. This caused undesirable interruptions in treatment, which, in some instances, also led to exclusion from the study.

Socio-economic conditions played a huge role in the well-being of patients. From the information in the patients' files it was noticeable that a considerable number of patients were from rural and impoverished parts of the region. Some of these patients depended on monthly state grants and financial support. From time to time, these patients had to interrupt their treatment to fetch their payouts and take care of domestic matters before they could return for treatment. This resulted in interruptions in the treatment schedule, which inevitably led to extended overall treatment times. In some cases, such interruptions led to exclusion from the study.

Patient education and perceptions seemed to have an impact on the patients' general approach to their treatment and follow-ups. Patients who had a reasonable understanding of their disease, as well as their need for treatment and follow-ups, responded positively to the treatment, specifically in terms of completing their treatment schedule and honouring follow-up appointments. The responses and the completeness of the data recorded in patients' files seemed to reflect the patients' level of awareness of the situation they found themselves in. Lack of understanding had an impact on patients' attitude towards their treatment, and subsequently on the availability of data in their files. It must be borne in mind that, for reasons already discussed, patients' personal and demographic data could not be disclosed. The apparent link between the availability of patient data and patients' social circumstances, therefore, was based on practical experience rather than scientific evidence.

The maximum follow-up period of 18 months used in this study, also proved to be challenging. Patients' records indicated that they defaulted on their follow-up appointments. Section 4.4.2.1 provides more details on this matter. Patients increasingly defaulted on their follow-up appointments as the period after conclusion of treatment became longer. This was especially true for the period 12

to 18 months after treatment. This meant that data became increasingly sparser over the 18-month follow-up period. Naturally, this scarcity of data has an effect on the reliability of the study results.

The improvement in the general condition of HIV+ patients during the second 9-month period following treatment would have been more accurately tested by means of a more extensive study with consistently available data throughout the envisaged follow-up time schedule. The same rationale is valid for the tumour responses. Longer, consistent follow-up schedules would have provided a more objective perspective on the tumour responses to treatment. This, in turn, would have led to a more accurate analysis of the therapeutic benefits of the treatment in terms of tumour control.

There are variations in tumour sizes between stage II and III Ca Cx, with a higher potential of cure in stage II than in stage III tumours (Beahrs *et al*. 1992:156). However, the current study did not differentiate between the variations in the responses amongst the two stages. In retrospect, this lack of differentiation was seen as a shortcoming of this study, because of the possible impact of staging on the tumour response rates. Tumour responses were used as a parameter to assess the overall therapeutic benefits of the radical chemo-radiotherapy treatment protocol in this study.

The data source form initially designed for this study was revised after the pilot study. At the beginning, the idea was to collect data via individual questionnaires. The revised data source form consisted of a single electronic data source sheet, mainly based on a coding system, as described in chapter 3. This data source form was used for all patients whose data was eligible for inclusion in the study. The coding system used on the data source form relied on clinical data being expressed as codes on the source form, with the index for reference purposes.

The clinical data found in patients' treatment files lacked detail. Data analysis depended on what the oncologists recorded in the files, which in turn depended

on how they interpreted what their patients communicated to them. Even though local oncologists seemed to have a common understanding of the terms they used to write their reports, these terms were not uniformly used in line with international systems such as the ECOG, EORTC and NCI Common Toxicity Criteria. Accordingly, the researcher entered into dialogue with the oncologists about the terminology to establish a standard interpretation of the data analysis.

General condition, adverse responses, tumour status and other clinical data obtained from patients' records were expressed as codes without textual qualification. The analysis of common toxicities, adverse responses and patient complaints recorded in the patients' treatment records could not be expressed qualitatively. The qualitative analysis was based on the descriptions assigned to the codes on the data source form.

Compliance with the conditions the Ethics Committee set for approval of this project implied that patients' demographics and personal data could not be used for this study. This meant that the impact of patients' personal circumstances on tolerance of treatment, adverse responses and quality of life could not be analysed. Matters concerning privacy and confidentiality are sensitive and the decision by the Ethics Committee is justifiable.

In November 2003, the Cabinet of the Republic of South Africa approved a national plan on HIV/AIDS prevention, care and treatment (Science in Africa 2004:7). The plan entailed placing 53 000 people on ARV treatment by the end of March 2004. As was the case with the treatment protocol relevant to this study, there were problems with the implementation of the national plan. In May 2004, the President shifted the target date to the end of March 2005, resulting in a one-year delay in the rollout of the plan (NUMSA, 2004). For this reason, the role of ARV's was not considered in this study.

5.5 RECOMMENDATIONS

The need to explore the links between clinical and social matters was expressed in preceding sections. However, matters relating to privacy and confidentiality are sensitive and need to be protected, as required by and enshrined in the Constitution of the Republic of South Africa. The decision by the Ethics Committee to protect information relating to patient identity, therefore, is justifiable.

Despite the limitations of the data source form, it was useful for the purposes of this project, since the aim of the study was to determine tolerance of treatment, and not the nature of adverse responses. However, it might be useful for any future studies to record and reflect on the extent and nature of adverse responses in order to provide qualitative comparisons with findings in the literature. In addition, it would be an invaluable innovation to have a standardised reference such as the ECOG or EORTC systems for use in the recording of patients' clinical data during follow-ups (Long, Monk, Huang, Grendys, McMeekin, Sorosky, Miller, Eaton and Fiorica 2006:539). Future research projects will then be based on a standard reporting system in comparison to the custom-made index that was designed for this study.

Regarding the study population in this study, follow-up data and the filing system were identified as key factors that require attention. The filing system should be strictly controlled to ensure adherence to filing protocols. The responsibility of filing should not be left solely to the discretion of administrative personnel; other health professionals should also be sensitised to the importance of, and the adherence to filing protocols.

During data collection there was an evident link between the availability of patients' follow-up data and their socio-economic conditions. It would appear that socio-economic problems are prevalent in all societies, and are here to stay. However, this problem can be tackled through vigorous and sustained patient

education and information programmes. Apart from the possible benefits in terms of early diagnosis, such programmes will go a long way towards eliminating problems related to treatment interruptions, defaults on follow-up schedules and communication with hospital staff to improve on statistics and patient records.

Future research in the field under discussion is encouraged. Future studies should consider investigating the role of social factors, such as nutrition and social support, particularly in HIV+ patients. The role of highly active anti-retroviral treatment (HAART), as well as the issue of overall survival rates, should also be considered as focus areas.

5.6 CONCLUSION

HIV+ patients treated at DROUAH for FIGO stage II and III Ca Cx with radical intent do not tolerate their treatment as well as their HIV- counterparts. The study results suggest that the overall quality of life of HIV+ patients was more adversely affected than that of HIV- patients, in terms of both general condition and the adverse responses that were reported. However, it appears that HIV+ patients recovered from the effects of treatment within nine months and showed responses similar to those of HIV- patients (where the same standard of therapy was used).

The tumour responses of HIV+ patients were analysed, with HIV- patients used to benchmark the therapeutic benefits in terms of quality of life and tumour response. There were no statistically significant differences between the tumour responses of HIV+ and HIV- patients, respectively. However, the therapeutic benefits of treatment must be considered in conjunction with the impact of the treatment on patients' overall quality of life. As stated earlier, the results did confirm that HIV+ patients showed less tolerance of treatment and poorer quality of life due to the adverse effects of treatment than HIV- patients.

Despite the limitations of the study, it appears that the 18-month overall survival

rate for HIV- patients was better than that for HIV+ patients, with survival rates of 67.6% and 88.1% for HIV+ and HIV- patients, respectively. However, the objectiveness and validity of these and other findings need to be tested by addressing the limitations outlined in section 5.4, and by considering the recommendations in section 5.5.

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7. ABBREVIATIONS

ABS	The American Brachytherapy Society
AIDS	Acquired Immune Deficiency Syndrome
AJCC	American Joint Committee on Cancer
ARV	Anti-retroviral treatment
Ca Cx	Cancer of the uterine cervix
CDC	United States Centres for Disease Control
CIN	Cervical Intraepithelial Neoplasia
CIS	Carcinoma-in-situ (CIS)
DROUAH	Department of Radiation Oncology - Universitas Annexe hospital, Bloemfontein
EBRT	External beam radiotherapy
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
FIGO	International Federation of Gynaecology and Obstetrics
HAART	Highly active anti-retroviral treatment
HDR	High dose-rate
HDR-ICBT	High dose-rate ICBT
HIV	Human Immunodeficiency Virus
HIV-	HIV-negative
HIV+	HIV-positive
HPV	Human Papilloma Virus (HPV)
ICBT	Intra-cavitary brachytherapy
ICRU	International Commission on Radiation Units and Measurements
LDR	Low dose-rate
LDR-ICBT	Low dose-rate ICBT
NCI	National Cancer Institute
NUMSA	National Union of Metal Workers of South Africa
OR	Odds ratio or relative risk
OTT	Overall treatment time (OTT)

SIL	Squamous Intra-epithelial Lesion
STD	Sexually transmitted disease
TB	Tuberculosis
U+E	Urea and electrolytes
UNAIDS	United Nations Joint Programme on HIV-AIDS
USA	United States of America
WHO	World Health Organisation

8. APPENDICES

Appendix 1: FIGO staging system

De Vita *et al*. 2004:887

The FIGO Staging System for Ca Cx (De Vita *et al*. 2004:887)

Stage	Description
I	Carcinoma that is strictly confined to the cervix; extension to the uterine corpus should be disregarded. The diagnosis of both Stages IA1 and IA2 should be based on microscopic examination of removed tissue, preferably a cone, which must include the entire lesion.
IA	Invasive cancer identified only microscopically. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm.
IA1	Stage IA1: Measured invasion of the stroma no greater than 3 mm in depth and no wider than 7 mm diameter.
IA2	Stage IA2: Measured invasion of stroma greater than 3 mm but no greater than 5 mm in depth and no wider than 7 mm in diameter.
IB	Stage IB: Clinical lesions confined to the cervix or preclinical lesions greater than Stage IA. All gross lesions even with superficial invasion are Stage IB cancers.
IB1	Stage IB1: Clinical lesions no greater than 4 cm in size.
IB2	Stage IB2: Clinical lesions greater than 4 cm in size.
II	Carcinoma that extends beyond the cervix, but does not extend into the pelvic wall. The carcinoma involves the vagina, but not as far as the lower third.
IIA	No obvious parametrial involvement. Involvement of up to the upper two-thirds of the vagina.
IAB	Obvious parametrial involvement, but not into the pelvic sidewall.
III	Carcinoma that has extended into the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumour and the

	pelvic sidewall. The tumour involves the lower third of the vagina. All cases with hydronephrosis or a non-functioning kidney are Stage III cancers.
IIIA	No extension into the pelvic sidewall but involvement of the lower third of the vagina.
IIIB	Extension into the pelvic sidewall or hydronephrosis or non-functioning kidney.
IV	Carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.
IVA	Spread of the tumour into adjacent pelvic organs.
IVB	Spread to distant organs.

Appendix 2: Index: Clinical variables and terminology

Index: General condition of patients – during treatment and at follow-up

Classification	Code	Description
Good	**1**	Pt visibly in good condition; No complaints[1]; No medical intervention[2] required
Fair	**2**	Pt stable; One or two complaints; Minor medical intervention required
Bad	**3**	Pt visibly unstable; More than two complaints; More intense medical intervention or minor hospitalisation[3] required
Poor	**4**	Deterioration to level requiring more serious hospitalisation; Partial interruption[4] of treatment protocol
Pre-terminal	**5**	Intense / long-term hospitalisation; Termination[5] of treatment; or death-related[6]
No follow-up	**0**	Pt did not report for the scheduled follow-up visit; No records for a particular follow-up were available in the file; Life status unknown[7]

The complaints, medical interventions and hospitalisation that were considered when categorising the general condition of patients had to be related to the chemo-radiotherapy treatment protocol.

[1]Complaints

Complaints were regarded as negative aspects, experiences or observations relating to treatment that were recorded in the patients' treatment files. The complaints that that were of interest to this study were those that were suspected to be a consequence of the chemo-radiotherapy that the patients received. A list of complaints was compiled from terminology that was encountered in the patients' files. Complaints that were recorded in patients' treatment files included diarrhoea, dysuria, lymphadenopathy, hydronephrosis, cystitis, vaginal stenosis, vaginal infections and fibrosis. Observations that the oncologists noted included: *patient is doing well; tolerating treatment well; severe diarrhoea; weight loss;*

nausea; blood count too low; swelling; pelvis feels tender; enlarged inguinal glands; vaginal infection; offensive discharge; no tumour; good tumour shrinkage; weak; enlarged pelvic mass/es; requires hospitalisation; for admission; and deteriorating.

[2]Medical intervention

Medical intervention referred to remedial action taken by the oncologists to address the complaints of the patients. Interventions varied from minor interventions like prescription of medication for mild pain, nausea, diarrhoea. More serious intervention required more intense intervention such as intravenous infusions for dehydration, blood transfusions for haematological deficiencies or referral to other medical specialists for more specialised management.

[3]Hospitalisation

Hospitalisation referred to situations where patients were admitted to hospital as part of the interventions for their complaints or conditions. Patients were hospitalised for various reasons under different conditions. Three different categories of hospitalisation are summarised, namely minor-, more serious-, and intense/long term hospitalisation.

Minor hospitalisation

Patients were hospitalised for limited periods where the condition could be addressed within a short period of time (1 to 3 days). An example can be given where patients were hospitalised for blood transfusion because the blood count had dropped to a level that required transfusion.

More serious hospitalisation

Hospitalisation involved more intense interventions over a longer period of time. Examples of such interventions were where patients were hospitalised for the treatment of severe infection or skin reaction over a few days (3 to 5 days).

Intense / long term hospitalisation

Hospitalisation involved more intense medical and nursing care over a longer term because patients' general condition had deteriorated to a level where they were only capable of limited self-care, confined to bed or chair.

[4]Interruption

Instances where patients had to temporarily stop treatment as part of the interventions to address the patients' complaints or conditions.

[5]Termination

Instances where patients had to stop treatment.

[6]Death-related

Patients had deteriorated to a state where continuation of treatment without intense medical care would most probably result in death. In the cases of follow-ups, patients were categorised as death-related if they were reported or suspected to be deceased. A prolonged absence from follow-up consultations subsequent to a pre-terminal general condition at the last follow-up was a basis for suspicion of death, even though death was not confirmed.

[7]Life status unknown

During follow-up some patients did not honour their follow-up schedules. There were instances where the patients were in a poor or pre-terminal condition during the last follow-up schedule. Some of these patients did not report for their subsequent follow-up schedule(s). In such cases the status of these patients was recorded as "life status unknown" because it there was no information at the time that the follow-up was scheduled.

Adverse responses of patients during follow-up consultations

Classification	Code	Description
No follow-up	**0**	Pt did not report for follow-up visit, no records in file, life status unknown
No adverse responses	**1**	No adverse responses to treatment reported
Moderate	**2**	Minor[8] responses reported, Require minor medical intervention
Severe	**3**	More complex[9] responses, Require more intense medical intervention, possible minor hospitalisation
Life-threatening	**4**	Life-threatening responses, Possible organic function/failure, More intense medical intervention, and long-term hospitalisation
Death related	**5**	Consequences resulting in death or pre-terminal condition

Adverse responses were defined as the negative responses to the chemo-radiotherapy treatment. These responses included temporary symptoms that could interfere with the activities of the patients' daily lives (Davey et al. 1999:851).

[8]Minor responses*

Responses to treatment result in patients being restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

[9]Complex responses*

Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

**ECOG Performance status index (Oken et al. 1982:652).*

Tumour responses of patients during follow-up consultations

Classification	Code	Description
No follow-up	**0**	Pt did not report for follow-up visit, no records in file, life status unknown
Total regression	**1**	No evidence of tumour or tumour masses present
Partial regression	**2**	Reduction in tumour size or mass
No response	**3**	No evidence of change in the tumour
Progression	**4**	Evidence of progression in tumour size or mass
Recurrence	**5**	Tumour has recurred in same area
Distant metastasis	**6**	Spread to local or distant areas in the body

Appendix 3: Patient data source form – Pilot study

Data Source Form – Pilot Project

1. Clinical Data				
Diagnosis:				
Squamous Cell Ca	Adenocarcinoma		Adeno-squamous	
Stage	IIA	IIB	IIIA	IIIB
HIV	Positive		Negative	
CD4 Count	Unknown	< 200	200 – 400	> 400
RPR Test	Positive	Negative	Unknown	

2. Treatment Data					
External Beam Irradiation (EBRT) – Tick off:					
Central Dose (Gy)	**Total Fractions**	**Dose per Fraction (Gy)**	**Total Dose**	**Total Time**	
2	**25**	**2**	**50**		
? Protocol Completed (If not, ? why)					

HDR Brachytherapy (Microselectron)					
Rectal Dose (Gy)	**Min. Dose at Point A (Gy)**	**Total Fractions**	**Total Time**		
? Protocol Completed (If not, ? why)					

Concurrent Chemotherapy - Cisplatin		
Dosage	**Cycles**	**Total time**
? Protocol Completed (If not, ? why)		

3. CLINICAL NOTES (OBSERVATIONS)					
3.1 ACUTE / IMMEDIATE EFFECTS / RESPONSES (EFFECTS DURING TREATMENT)					
GENERAL CONDITION (Short summary)					
Blood counts	**Haemoglb**	**Leuco.**	**Plts.**	**U+E**	**Creat.**
Week 1					
Week 2					
Week 3					
Week 4					
Week 5					
Week 6					

TUMOUR RESPONSES					
Tumour response	**Progr.**	**None**	**Part. Regr.**	**Tot. regr.**	**Mets.**
If mets – indicate area					

ADVERSE RESPONSES					
Response	**Complexity / Severity**	**Duration**	**Intervention**	**Comments**	
Nausea / Vomiting					
Fatigue					
Diarrhoea					
Rectum					
Bladder					
Haematol.					
GI					
Other:					

3.2 EARLY EFFECTS / RESPONSES – < 6 MONTHS FOLLOW-UP					
GENERAL CONDITION (Short summary)					
Blood Counts	**Haemoglb**	**Leuco.**	**Plts.**	**U+E**	**Creat.**
Follow-up 1					
Follow-up 2					
Follow-up 3					

TUMOUR RESPONSES					
Tumour response	**Progr.**	**None**	**Part. Regr.**	**Tot. regr.**	**Mets.**
If mets – indicate area					

ADVERSE RESPONSES					
Response	**Complexity / Severity**	**Duration**	**Intervention**	**Comments**	
Nausea / Vomiting					
Fatigue					
Diarrhoea					
Rectum					
Bladder					
Haematol.					
GI					
Other:					

3.3 INTERMEDIATE EFFECTS / RESPONSES – 7 - 12 MONTHS FOLLOW-UP					
GENERAL CONDITION (Short summary)					
Blood Counts	**Haemoglb**	**Leuco.**	**Plts.**	**U+E**	**Creat.**
Follow-up 1					
Follow-up 2					
Follow-up 3					

TUMOUR RESPONSES					
Tumour response	**Progr.**	**None**	**Part. Regr.**	**Tot. regr.**	**Mets.**
If mets – indicate area					

ADVERSE RESPONSES					
Response	**Complexity / Severity**	**Duration**	**Intervention**	**Comments**	
Nausea / Vomiting					
Fatigue					
Diarrhoea					
Rectum					
Bladder					
Haematol.					
GI					
Other:					

3.4 LATE EFFECTS / RESPONSES – > 12 MONTHS FOLLOW-UP					
GENERAL CONDITION (Short summary)					
Blood Counts	**Haemoglb**	**Leuco.**	**Plts.**	**U+E**	**Creat.**
Follow-up 1					
Follow-up 2					
Follow-up 3					

TUMOUR RESPONSES					
Tumour response	**Progr.**	**None**	**Part. Regr.**	**Tot. regr.**	**Mets.**
If mets – indicate area					

ADVERSE RESPONSES					
Response	**Complexity / Severity**	**Duration**	**Intervention**	**Comments**	
Nausea / Vomiting					
Fatigue					
Diarrhoea					
Rectum					
Bladder					
Haematol.					
GI					
Other:					

Appendix 4: Patient data source form – Revised

Patient Data Source Form - Revised

										General Condition - Weekly							Follow-up 1			Follow-up 2			Follow-up 3			Follow-up 4			Follow-up 5			Follow-up 6		
Patient	Diag	Stage	HIV	CD4	RPR	Gen. Condition	EBRT	HDRBT	Chemo	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	General	Tumour	Adverse	General	Tumour	Adverse	General	Tumour	Adverse	General	Tumour	Adverse	General	Tumour	Adverse	General	Tumour	Adverse
No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	30	31	32	34	35	36
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Patient Data Source Form - Index

		0	1	2	3	4	5	6
Diagnosis			Squamous	Adeno	Adeno-squam			
Stage			IIA	IIB	IIIA	IIIB		
HIV Status			Negative	Positive				
CD 4			<100	100 - 200	200 - 400	>400		
General Condition - Referral			Good	Fair	Bad	Poor	Pre-/Terminal	
RPR		Unknown	NEG	POS				
EBRT			Completed	Interrupted	Stopped			
HDRBT			Completed	Interrupted	Stopped			
Chemo			Completed	Interrupted	Stopped			
General Condition - Weekly			Good	Fair	Bad	Poor	Pre-/Terminal	
General Condition - Follow-up		No follow-up	Good	Fair	Bad	Poor	Pre-/Terminal	
Tumour status		No follow-up	Total regression	Partial regression	No response	Progression	Recurrence	Distant mets
Adverse effects		No follow-up	None	Mild	Moderate	Severe	Life-threatening	Death related
General Condition - Referral			**Good**	**Fair**				
Good	1	*Pt visibly in good (healthy) condition. Seems capable of tolerating treatment well.*						
Fair	2	*Pt in stable condition, Treatment justified.*						
General Condition - Weekly			**Good**	**Fair**	**Bad**	**Poor**	**Pre-/Terminal**	
Good	1	*Pt visibly in good condition, No complaints, or medical intervention*						
Fair	2	*Pt stable, with minor complaints, handling treatment well, Minor medical intervention*						
Bad	3	*Pt visibly unstable, with more than two complaints, More intense medical intervention or minor hospitalisation*						
Poor	4	*Deterioration to level of more serious hospitalisation, and partial termination of treatment protocol*						
Pre-terminal	5	*Long-term hospitalisation, termination of treatment, or death-related*						
General Condition - Follow-up		**No follow-up**	**Good**	**Fair**	**Bad**	**Poor**	**Pre-/Terminal**	
No follow-up	0	*Pt did not report for follow-up visit, no records in file, life status unknown*						
Good	1	*Pt visibly in good condition, No complaints, or medical intervention*						
Fair	2	*Pt stable, with minor complaints, handling treatment well, Minor medical intervention*						
Bad	3	*Pt visibly unstable, with more than two complaints, More intense medical intervention or minor hospitalisation*						
Poor	4	*Deterioration to level of more serious hospitalisation, and partial termination of treatment protocol*						
Pre-terminal	5	*Long-term hospitalisation, termination of treatment, or death-related*						

Tumour Status		0 No follow-up	1 Total regression	2 Partial regressio	3 No response	4 Recurrence	5 Distant mets	6
No follow-up	**0**	*Pt did not report for follow-up visit, no records in file, life status unknown*						
Total regress.	**1**	*No evidence of tumour or tumour masses present*						
Partial regress.	**2**	*Reduction in tumour size or mass*						
No response	**3**	*No evidence of change in the tumour*						
Progression	**4**	*Evidence of progression in tumour size or mass*						
Recurrence	**5**	*Tumour has recurred in same area*						
Distant mets	**6**	*Spread to local or distant areas in the body*						
Adverse Reactions/Responses		**No follow-up**	**Mild**	**Moderate**	**Severe**	**Life-threateni**	**Death-related**	
No follow-up	**0**	*Pt did not report for follow-up visit, no records in file, life status unknown*						
None	**1**	*No adverse responses to therapy reported*						
Moderate	**2**	*Minor responses reported, Require minor medical intervention*						
Severe	**3**	*More complex responses, Require more intense medical intervention, possible minor hospitalisation, eg. Infusion*						
Life-threatening	**4**	*Life-threatening responses, More intense medical intervention, and long-term hospitalisation*						
Death related	**5**	*Consequences resulting in death or pre-terminal condition*						

Appendix 5: Consent - Hospital Manager: Clinical Services

health
Department of Health
FREE STATE PROVINCE

Ref nr: H13/7

28 June 2007

Mr. S Masalla
Department Oncotherapy
Universitas Annex Hospital

Dear Mr. Masalla

RE: CONSENT TO ACCESS PATIENTS' RECORDS

We acknowledge receipt of your letter dated 17 June 2007 regarding the abovementioned.

Herewith, confirmation that your request has been granted. Consent is granted on condition that no patient information is published without the consent of the CEO.

Yours sincerely

DR NIC VAN ZYL
HEAD: CLINICAL SERVICES

DR NRJ VAN ZYL
2007-07-28
HEAD: CLINICAL SERVICES
UNIVERSITAS ACADEMIC HOSPITAL

Department of Health - Departement Gesondheid - Lefapha La Bophelo Bo Botle

Head: Clinical Services, Dr. NRJ van Zyl, Universitas Tertiary Hospital – P/Bag X20660, Bloemfontein 9300
Tel: 051-405 2866 – Fax: 051-444 0792, e-mail: vanzylnr@fshealth.gov.za – Room 1129, 1st Floor,
Universitas Tertiary Hospital, Bloemfontein

Appendix 6: Ethics approval

UNIVERSITEIT VAN DIE VRYSTAAT
UNIVERSITY OF THE FREE STATE
YUNIVESITHI YA FREISTATA

Direkteur: Fakulteitsadministrasie / Director: Faculty Administration
Fakulteit Gesondheidswetenskappe / Faculty of Health Sciences

Research Division
Internal Post Box G40
☎(051) 4052812
Fax nr (051) 4444359

E-mail address: grdkhs.md@mail.uovs.ac.za

Ms H Strauss

2007-08-15

MR SG MASALLA
P O BOX 19420
BLOEMSPRUIT
9364

Dear Mr Masalla

ETOVS NR 133/07
PRINCIPAL INVESTIGATOR: MR SG MASALLA
PROJECT TITLE: TREATMENT RESPONSES IN HIV-POSITIVE AND HIV-NEGATIVE PATIENTS TREATED FOR CERVIX CANCER WITH RADICAL INTENT AT UNIVERSITAS ANNEX HOSPITAL.

- You are hereby informed that the above-mentioned protocol was approved by the Ethics Committee on 14 August 2007 on condition that an approval letter has to be obtained from the biostatistician a copy of which has to be submitted to the Ethics Committee.
- The following documents are used by the Ethics Committee as guidance documents: Declaration of Helsinki, ICH, GCP and MRC guidelines on bio medical research. Clinical trial guidelines 2000 Department of Health RSA: Ethics in Health Research: Principles structure and processes Department of Health RSA 2004, the Constitution of the Ethics Committee of the Faculty of Health Sciences and the guidelines of the S.A. Medicines Control Council as well as laws and regulations with regard to the Control of Medicines
- Any amendment, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval.
- The Committee must be informed of any serious adverse event and/or termination of the study.
- A progress report should be submitted within one year of approval of longterm studies and a final report at completion of both short term and long term studies.
- Please refer to the ETOVS reference number in correspondence to the Ethics Committee secretariat.

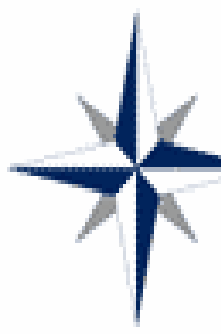
Yours faithfully

.....

for **PROF BB HOEK**
CHAIR: ETHICS COMMITTEE

Cc Dr H Friedrich-Nel, CUT, Bloemfontein
Dr MP Kahl, Dept of Oncology, Universitas Annex Hospital, Bloemfontein

Appendix 7: Certificate of language editing



Lingua
Victoris

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STATEMENT WITH REGARD TO LINGUISTIC EDITING OF M TECH DISSERTATION:

I hereby declare that I, Dr. ELJ (Ernie) Venter, was responsible for linguistic editing and proof-reading of the Master's dissertation by Mr. Sydney Masalla, entitled *Treatment responses in HIV-positive and HIV-negative patients treated for cervix cancer with radical intent at Universitas Annexe hospital.*

Dr. ELJ (Ernie) Venter *(D. Litt)*