CHEMOTHERAPY INDUCED RENAL AND HAEMATOLOGICAL TOXICITIES IN PATIENTS WITH INVASIVE CERVICAL CANCER UNDERGOING CONCURRENT CHEMO-RADIATION

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DECLARATION

This is to certify that this work is entirely my own and not of any other person unless explicitly acknowledged (including citation of published and unpublished sources). This work has not previously been submitted in any form to the Durban University of

Technology or any other institution for assessment or any other purpose.

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LIST OF ABBREVIATIONS

%	-	Percentage
µmol	-	Micromole
5-FU	-	Fluorouracil
AIDS	-	Acquired Immune Deficiency Syndrome
AIF	-	Apoptosis Inducing Factor
ANC	-	Absolute Neutrophil Count
ATP	-	Adenosine Triphosphate
CCRT	-	Concurrent Chemo-Radiation
CDC	-	Centre for Disease Control
CG	-	Cockcroft-Gault
CIN	-	Cervical Intraepithelial Neoplasia
CT	-	Chemotherapy
DAMP	-	Damage-Associated Molecular Pattern Molecules
DNA	-	Deoxyribonucleic Acid
E	-	Early
eGFR	-	estimated Glomerular Filtration Rate
FBC	-	Full Blood Count
FIGO	-	International Federation of Gynaecology and Obstetrics
g/dL	-	grams per decilitre
GFR	-	Glomerular Filtration Rate
GGT	-	Gamma-Glutamyl Transpeptidase
GOG	-	Gynecologic Oncology Group
Gy	-	Gray
Hb	-	Haemoglobin
HIV	-	Human Immunodeficiency Virus
HIVAN	-	HIV-Associated Nephropathy
HPV	-	Human Papillomavirus
HSIL	-	High Grade Squamous Intraepithelial Lesions
HU	-	Hydroxyurea
IALCH	-	Inkosi Albert Luthuli Central Hospital
L	-	Litre (unit of volume)
L	-	Late (HPV genome)

LSIL	-	Low grade Squamous Intraepithelial Lesions
m^2	-	square metre
MDRD	-	Modification of Diet in Renal Disease
mg	-	milligram
min	-	minute
ml	-	millilitre
mmol	-	millimole
n	-	number of patients
NCI	-	National Cancer Institute
NHLS	-	National Health Laboratory Service
OCT	-	Organic Cation Transporter
OCT2	-	Organic Cation Transporter 2
OS	-	Overall Survival
PAP	-	Papanicolaou
PFS	-	Progression-Free Survival
PLT	-	Platelets
ROS	-	Reactive Oxygen Species
RT	-	Radiation/Radiotherapy
RTOG	-	Radiation Therapy Oncology Group
SIL	-	Squamous Intraepithelial Lesions
sd	-	Standard Deviation
SWOG	-	Southwest Oncology Group
TLR	-	Toll-Receptors
TLR4	-	Toll-Receptor 4
TNFα	-	Tumour Necrosis Factor alpha
WBC	-	White Blood Cells
WHO	-	World Health Organisation

ABSTRACT

Cervical cancer is the most commonly diagnosed form of cancer in women of the developing world. Globally, the standardised treatment for women with invasive cervical cancer is concurrent chemo-radiation. Despite the survival benefit of concurrent chemo-radiation, there are concerns about associated toxicities and their harmful effects. Limited evidence shows the monitoring of the renal and haematological effects in invasive cervical cancer patients receiving concurrent chemo-radiation, compounded by women's biological vulnerability to human immunodeficiency virus (HIV), particularly in South Africa.

In this prospective quantitative descriptive study, participants that presented for treatment were selected upon meeting the inclusion criteria. The study used a sample of 82 women, 32 (39%) of whom were HIV positive. Females between the ages of 21 and 75 years formed part of the study. All participants were undergoing concurrent chemo-radiation treatment at the Inkosi Albert Luthuli Central Hospital at the time of data collection.

This study aimed to determine the renal and haematological toxicities associated with the chemotherapy component of concurrent chemo-radiation in patients with invasive cervical cancer, using renal and haematological biomarkers. The biomarkers, urea, creatinine and estimated glomerular filtration rate assessed renal toxicity. The full blood count biomarkers haemoglobin, white blood cells, platelets and absolute neutrophil count assessed haematological toxicity.

The main finding was haematological toxicity in both HIV positive and HIV negative participants. No renal toxicity was found in this study among both the HIV positive and negative participants. Seventy (85%) of participants had stage II invasive cervical cancer. Ninety three percent of the cohort was diagnosed with invasive squamous cell carcinoma. The study found that the chemotherapy treatment completion rates for HIV negative and HIV positive participants were similar. Both groups were just as likely to complete the chemotherapy part of concurrent chemo-radiation. Based on the findings

of this study, the same concurrent chemo-radiation protocol may be applied to both HIV negative and HIV positive women with invasive cervical cancer, however, further research using a larger population followed over a longer period is highly recommended.

CHAPTER ONE: INTRODUCTION

In 2018, an estimated 570 000 new cases of cervical cancer were diagnosed worldwide (Bray *et al* 2018:394-424). In the same year, 311 000 women died of cervical cancer worldwide (Bray *et al* 2018:394-424). The highest incidence and mortality rates are seen in low to middle-income countries (World Health Organisation 2014:8). This is mainly due to the lack of organised cervical cancer screening and inadequate access to treatment in these countries (Berek and Hacker 2015:242). In South Africa, the total number of new cervical cancer cases diagnosed in 2016 was 7327 (National Institute of Communicable Diseases 2016:1-38). This figure represents 17.33% of all cancers diagnosed histologically in South Africa in 2014 (National Institute of Communicable Diseases 2016:1-38). HIV positive women are at an increased risk for cervical cancer (Ghebre *et al* 2017:106). In the African setting, HIV infection is a common co-morbidity infection in patients with invasive cervical cancer (Gichangi *et al* 2005:405-411).

Women infected with HIV have a higher prevalence of persistent high-risk human papillomavirus (HPV) infection (Ghebre *et al* 2017:101-108). High-risk HPV infection is a precursor of cancer (Berek and Hacker 2015:244). Persistent high-risk HPV infection increases the likelihood of developing precancerous lesions on the cervix, which could progress to invasive cervical cancer (Newton and Mould 2016:7-13). The standardised treatment for invasive cervical cancer is concurrent chemo-radiation (CCRT) (Kirwan *et al* 2003:217). In South Africa, CCRT is the standard of care, where resource constraints permit (Simonds *et al* 2012:2971-2979). Radiation/radiotherapy (RT) and chemotherapy (CT) are initiated simultaneously when the concurrent therapy schedule is used (Rose 2002:272). CCRT is also referred to as concurrent chemoradiotherapy or concomitant chemoradiotherapy. The goal of CCRT is to maximise tumour death by CT and to minimise tumour repopulation (Albuqueque *et al* 2011:1043-1047). CCRT improves overall survival (OS) and progression-free survival (PFS) in locally advanced cervical cancer (Green *et al* 2005:1-54). Despite the survival benefit of CCRT, there were still major concerns about the associated toxicities seen in patients (Kirwan 2003:217).

Haematological toxicities have been reported in patients that undergo CCRT for cervical cancer (Simonds *et al* 2015:884-890). These patients have an increased risk of developing neutropenia, thrombocytopenia and anaemia (Albuqueque *et al* 2011:1043-1047). CCRT toxicities may lead to treatment interruptions, sub-optimal CT doses and inferior treatment outcomes (Harjani 2015:29). There is limited evidence on the monitoring of the renal and haematological toxicities in invasive cervical cancer patients undergoing CCRT in the local population and nationally. The published randomised CCRT trials were conducted under controlled research settings mainly in the United States of America (Abu-Rustum *et al* 2001:88-91). These trials did not compare the outcome of CCRT for cervical cancer in women with HIV and those without (Alongi *et al* 2017:384). In sub-Saharan Africa, AMC-081 was the first phase II clinical trial to investigate the outcome of CCRT in HIV positive women with invasive cervical cancer undergoing CCRT (Einstein *et al* 2019:20-25). The findings of AMC-081 support the administration of standard doses of CCRT as the standard of care for HIV positive women with invasive cervical cancer undergoing CCRT (Einstein *et al* 2019:20-25).

This study aimed to determine the renal and haematological toxicities associated with the CT component of CCRT in patients with invasive cervical cancer, using renal and haematological biomarkers. The acute toxicity due to CCRT is higher than the toxicity of radiation only (Vale 2008:1-42). This prospective descriptive study was conducted at the Inkosi Albert Luthuli Central Hospital (IALCH). The sample population consisted of patients undergoing CCRT treatment for invasive cervical cancer. The objectives were to evaluate the profile of patients qualifying for CCRT, to investigate possible renal and haematological toxicities associated with CT in CCRT and to compare the renal and haematological toxicities in HIV negative and positive patients.

CHAPTER TWO: LITERATURE REVIEW

High incidence and mortality rates for cervical cancer are seen in Africa (Bray *et al* 2018:394-424). However, only 1 recently published randomised trial was done in Africa (Einstein *et al* 2019:20-25). Retrospective studies comparing the response of HIV negative and HIV positive patients undergoing CCRT for invasive cervical cancer have been done in South Africa (Alongi *et al* 2017: 384). None of the retrospective CCRT studies were done in the local Kwa-Zulu Natal population. In the present study, the results of renal and haematological effects due to CCRT in the local population of HIV positive and negative women were investigated. This literature review covers the epidemiology of cervical cancer and its relevance to the South African population with reference to HIV status.

The management of cervical cancer and the challenges it poses in South Africa are discussed, with emphasis on the modes of management of the CT component of CCRT and the biomarkers used to monitor CT toxicity. A review of clinical trials on CCRT and related studies is also included.

2.1 Cervical cancer in South Africa

Cervical cancer is the key contributor to the high morbidity and mortality in South Africa (Botha and Richter 2015:33-34). It has been identified as 1 of 5 priority cancers in South Africa (South Africa. Department of Health 2017:1-52). The other 4 priority cancers are lung cancer, colorectal cancer, prostate cancer and breast cancer (South Africa. Department of Health 2017:1-52). The infrastructure and capacity to treat cancer patients varies throughout the country (South Africa. Department of Health 2017:1-52). Screening and treatment of pre-cancerous lesions as well as education and awareness occur at primary health care level (South Africa. Department of Health 2017:1-52). The cervical cancer screening program covers a small percentage of the population (Wu *et al* 2017:572-582). The coverage and quality of care in the primary health care units varies nationwide (South Africa. Department of Health 2017:1-52). Tertiary specialist units in South Africa are unable to provide optimal patient care due

to challenges such as understaffing and poorly equipped units (South Africa. Department of Health 2017:1-52). These are some of the contributory factors to the high prevalence of cervical cancer in South Africa (Botha and Richter 2015:33-34). Other factors contributing to the high prevalence rate include conflicting health care needs, low doctor/population ratio, high prevalence of HIV, affordability, cultural taboos and anxiety linked to the lack or delayed screening of papanicolaou (pap) smears (South Africa. Department of Health 2017:1-52). Low income countries have only 2.5 physicians per 10 000 people (Wu *et al* 2017:572-582). Comparatively, high income countries have 28.7 physicians per 10 000 people (Wu *et al* 2017:572-582). These factors result in cervical cancer being diagnosed late, despite it being a preventable disease (Botha and Richter 2015:33-34). Due to the late diagnosis, patients present with advanced stages of the disease (Moodley 2009:11-13)

2.1.1 Precancerous lesions

Cervical cancer begins with a precancerous phase, which, if detected and treated early, could result in a decrease in cervical cancer prevalence and mortality (Moodley 2009:11-13). The definition of pre-cancerous lesions or dysplasia as per the World Health Organisation (WHO) is a “lesion in which part of the epithelium was replaced by cells showing varying degrees of atypia”. HPV infects the cells in the basal layer of the cervical epithelium in the transformation zone containing HPV specific receptors (Berek and Hacker 2015:242-260). The basal layer comprises the proliferating cellular component of stratified epithelia in which the viral genome is established (Berek and Hacker 2015:242-260). HPV-positive cervical epithelial cells support the amplification of the viral genome (World Health Organisation 2007:47-51).

The genomes of all HPV types contain approximately 8 open-reading frames (World Health Organisation 2007:47). Each open-reading frame is divided into 3 functional parts: the early (E) region that encodes proteins E1-E7; the late (L) region that contains the proteins L1-L2 and the long control region for the replication and transcription of viral deoxyribonucleic acid (DNA) (World Health Organisation 2007:47-51). The proteins E1-E7 are necessary for viral replication (World Health Organisation 2007:47-

51). The proteins L1-L2 are structural proteins necessary for viral assembly (World Health Organisation 2007:47-51).

In HPV infection, cellular changes occur mainly in the lower third of the epithelium and are referred to as cervical intraepithelial neoplasia (CIN) or low grade squamous intraepithelial lesions (LSIL) (Basu *et al* 2018:1-8). Usually HPV infections clear due to natural immunity and are less likely to initiate malignancy (Berek and Hacker 2015:242-260).

If HPV persists, and there is integration of high risk HPV into the genome of the cervical epithelial cells, this may cause malignant transformation (Basu *et al* 2018:1-8). The tumour suppression genes, p53 and pRB, are inactivated by the viral proteins E6 and E7, resulting in interference of the normal cell cycle and malignant transformation of the cells (Basu *et al* 2018:1-8). Cells support the amplification of the viral genome, giving rise to high grade precancers and cancers that are categorised as CIN2 and CIN3 (Basu *et al* 2018:1-8). CIN2 and CIN3 are also known as high grade squamous intraepithelial lesions (HSIL) (Basu *et al* 2018:1-8).

In an attempt to quantify the extent of dysplasia on the thickness of the epithelium, the term CIN was proposed by Richardt in 1973 (Berek and Hacker 2015:243). Richardt described three grades of CIN, namely CIN1 (mild dysplasia), CIN2 (moderate dysplasia) and CIN3 (severe dysplasia/carcinoma *in situ*) (Berek and Hacker 2015:243).

The most recent terminology for CIN, based on the 2001 Bethesda System is squamous intraepithelial lesions (SIL) (Solomon *et al* 2002:2114-2119). The terminology LSIL and HSIL was introduced by the 1988 Bethesda System (Solomon *et al* 2002:2114-2119). The terminology LSIL and HSIL is used to report the spectrum of non-invasive squamous cervical abnormalities (Solomon *et al* 2002:211-2119).

2.1.2 Progression of precancerous lesions to cervical cancer

The steps in the development of invasive cervical cancer can be described as follows, firstly infection of the epithelium of the transformation zone with 1 or more of the oncogenic HPV types; this leads to viral persistence or regression; if persistence occurs, the lesion progresses to SIL which can also persist, regress or progress. SIL starts of as LSIL, which can regress, persist or progress; if this progresses then this leads to HSIL which can progress to invasive cervical cancer (Berek and Hacker 2015:254). LSIL is more frequently associated with a transient HPV infection that has the tendency to regress or disappear (World Health Organisation 2007:139). Whereas HSIL is more frequently associated with HPV persistence and there is a high risk of progression to cervical cancer (World Health Organisation 2007:139).

2.1.3 Aetiology of cervical cancer

The cause of cervical cancer is persistent infection with 1 or more of the oncogenic HPV subtypes (Newton and Mould 2016:7-13). HPV is the most common sexually transmitted infection (Basu *et al* 2018:1-8). There are more than 40 genital HPV types (World Health Organisation 2007:47-51).

In a study by Hanisch *et al* (2013:696-702), HPV DNA for 37 genotypes (6,11,16,18,26,31,33,35,39,40,42,45,51,52,53,54,55,56,57,58,59,61,62,64,66,67,68, 69,70,71,72,73,81,82,83,84,89) were detected in cervical swabs. The low risk oncogenic subtypes include HPV 6 and 11 and are detected in low grade cervical lesions (Berek and Hacker 2015:260). The high-risk or oncogenic subtypes of HPV include HPV 16,18,31,33,35,39,45,51,52,56,58,59 and 68 (Hanisch *et al* 2013:696-702). The prevalence of HPV infection is influenced by rural/urban and geographical regions in South Africa (Mbulawa *et al* 2018:1-15). The Western Cape region has a lower prevalence (44-71%) of HPV infections than Gauteng (85%) (Mbulawa *et al* 2018:1-15). However, Cape Town women are more likely to have multiple HPV infections than Soweto women (Mbulawa *et al* 2018:1-15).

High-risk oncogenic subtypes of HPV other than HPV 16 and 18 cause lesions that are smaller in size, less severe and more treatable (Basu *et al* 2018:1-8). HPV 16 is detected with the greatest frequency in HPV-related invasive cervical cancer (Berek and Hacker 2015:260). HPV 16 is associated with approximately 50% of cervical squamous cell carcinomas (Berek and Hacker 2015:260). Squamous cell carcinoma is the most common type of cervical cancer followed by adenocarcinoma (Newton and Mould 2016:7-13). The precursor for the development of adenocarcinoma is cervical glandular intraepithelial neoplasia in the endocervical glandular cells (Newton and Mould 2016:7-13). HPV 16 is associated with approximately 50% of cervical adenocarcinomas. HPV 18 is also associated with the development of cervical adenocarcinomas (Berek and Hacker 2015:260). HPV 18 is the second most common HPV type in invasive cervical cancer (Berek and Hacker 2015:260). Other co-factors that may influence the progression from infection to cervical cancer include HIV, smoking, multiparity, age at first full term pregnancy and the use of oral contraceptives (Berek and Hacker 2015:260-262).

In HIV positive women, HPV infections are more prevalent and persistent (Newton and Mould 2016:7-13). Persistent high risk HPV infection is the most important risk factor for the development of cervical cancer (Newton and Mould 2016:7-13). The likelihood of HPV clearance in HIV positive women is decreased with lower CD4 cell counts and co-infection with 2 or more high risk HPV types (Firnaber *et al* 2012:1-6). CD4 and CD8 cells make up the majority of T lymphocytes (Hoffbrand and Moss 2016:1-281). T-lymphocytes mediate cellular immunity whilst B-lymphocytes mediate adaptive immunity (Hoffbrand and Moss 2016:1-281). CD4 and CD8 cells make up the majority of T lymphocytes (Hoffbrand and Moss 2016:1-281).

The decline in CD4 T cells results in a loss of cell-mediated immunity (Firnaber *et al* 2012:1-6). The progressive destruction of CD4 T cells and the loss of cell-mediated immunity, predisposes the body to opportunistic infections and cancer (Ghebre *et al* 2017:101-108). Hanisch *et al* (2013:696-702) found that the prevalence of multiple HPV types was higher in HIV positive women compared to HIV negative women. Women with lower CD4 cell counts and lower CD4/CD8 ratio have higher rates of SIL

(Ghebre *et al* 2017:101-108). Early initiation and sustained antiretroviral treatment is likely to reduce the incidence and progression of SIL (Ghebre *et al* 2017:101-108). The risk of LSIL progressing to higher grades is greater in HIV positive women with lower CD4 counts (Basu *et al* 2018:1-8). HSIL can progress to invasive cervical cancer (Berek and Hacker 2015:254).

2.2 The management of cervical cancer

2.2.1 Staging of cervical cancer

Cervical cancer staging and management are done in accordance with the International Federation of Gynaecology and Obstetrics (FIGO) guidelines (Newton and Mould 2016:7-13). A clinical examination is performed to determine the FIGO stage (Newton and Mould 2016:7-13). The FIGO staging system for cervical cancer describes stages I to IV of the disease, based on tumour size and the extent of spread of the disease within the pelvis and to distant organs (World Health Organisation 2014:1-386). They are described in terms of the following stages (Percorelli 2009:103-104): Stage I: The carcinoma is confined to the cervix, Stage II: Cancer has spread outside the cervix into the upper vagina, but not to the pelvic wall, Stage III: Cancer has spread to the lower third of the vagina or to the pelvic wall and Stage IV: Cancer has spread to surrounding organs or organs.

Each of the stages can be further subdivided (Percorelli 2009:103-104): Stage IA: Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5.0 mm and largest extension ≤7.0 mm, Stage IB: Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA, Stage IIA: Without parametrial invasion, Stage IIB: With obvious parametrial invasion, Stage IIIA1: Tumour involves lower third of the vagina, with no extension to the pelvic wall, Stage IIIA2: Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney, Stage IVA: Spread of the growth to adjacent organs and Stage IVB: Spread to distant organs.

2.2.2 Approach to patient management

Patient management and treatment options are discussed by a multidisciplinary team consisting of oncologists, gynaecologists, histopathologists and nursing staff. The treatment for early stage cervical cancer is generally surgery (Moodley *et al* 2009:11-13). In the more advanced stages of cervical cancer, CCRT is usually the recommended treatment (Moodley *et al* 2009:11-13). CCRT became an established treatment for patients with invasive cervical cancer after an announcement by the National Cancer Institute (NCI) in February 1999 (Kirwan *et al* 2003:217-226). The clinical announcement by the NCI recommended the combination of CT and RT for the treatment of patients with invasive cervical cancer (Grady 1999).

In South Africa, CCRT is generally the standard of care for invasive cervical cancer but it is associated with toxicities (Simonds *et al* 2012:2971-2979). The haematological toxicities seen in patients that undergo CCRT for cervical cancer have been well documented (Simonds *et al* 2015:884-890). A paucity in literature is the lack of data on the renal toxicities of CCRT. The CCRT toxicities may lead to treatment interruptions, sub-optimal CT doses and inferior treatment outcomes (Harjani 2015:29). In the present study both the renal and haematological toxicities associated with CCRT in invasive cervical cancer patients undergoing CCRT were investigated.

2.2.3 HIV positive patients and CCRT

The management of HIV positive patients presents challenges. One of the potential risks of treating HIV positive women with CCRT, is the risk of increased morbidity due to opportunistic infection as a result of immunosuppression (Simonds *et al* 2012: 2971-2979). In South Africa, the same CCRT protocol is applied to both HIV negative and positive patients with invasive cervical cancer. The studies by Einstein *et al* (2019:20-25) and Mdletshe *et al* (2016:24-28) found that the CCRT protocol administered to HIV negative women was well tolerated by HIV positive women. Simonds *et al* (2015:884-890) investigated the HIV status and haematological toxicity among cervical cancer patients undergoing CCRT. The study found that haematological toxicity is higher among HIV positive compared to HIV negative women. In the present study,

haematological and renal toxicities were compared amongst HIV positive and negative participants.

2.2.4 Challenges in patient management

Limitations in health systems impede optimal cancer prevention and control (South Africa. Department of Health 2017:1-52). In sub-Saharan Africa, the number of people per pathologist ranges from 84 133 to 9 264 500 (Wu *et al* 2017:572-582). Comparatively, the number of people per pathologist ranges from 15 000 to 20 000 in the United Kingdom and United States (Wu *et al* 2017:572-582). In South Africa, the barriers to CT and RT are inadequate personnel coupled with the lack of functional equipment (South Africa. Department of Health 2017:1-52). Additional barriers are long waiting times for RT treatment and limited access to treatment as treatment centres may be far from the patient's place of residence (South Africa. Department of Health 2017:1-52). This is compounded by a shortage of trained staff, long waiting times prior to commencement of treatment and some patients presenting with renal dysfunction when they start treatment.

The impact of cervical cancer on South African communities is complex and associated with poverty, cultural factors, social justice, gender race, ethnicity and geography (South Africa. Department of Health 2017:1-52). Women from poor economic countries generally present with more advanced disease, have less access to treatment centres and have a higher case to fatality rate than women in high income countries (South Africa. Department of Health 2017:1-68). Delays of up to 7 months have been reported in South Africa from the onset of symptoms until treatment of the disease (Wu *et al* 2017:572-582). Some centres have reported delays of up to 37 weeks (South Africa. Department of Health 2017:1-52). Delays of more than 12 weeks for treatment is likely to result in poorer patient outcomes (South Africa. Department of Health 2017:1-52). The limitations of current cancer services in South Africa can be summed up as: poor service delivery, healthcare staff shortages, lack of information, poorly accessible medical products/vaccines/technology, lack of finances and lack of government commitment (South Africa. Department of Health 2017:1-52).

2.3 Modes of management of the CT component of CCRT

2.3.1 Use of cisplatin as a CT drug

In South Africa, the use of cancer medicines is approved by the National Essential Medicines Lists Committee (South Africa. Department of Health 2017:1-52). This is based on clinical evidence provided by the WHO Essential Medicines Lists for Oncology in low- and middle-income countries (South Africa. Department of Health 2017:1-52). The cytotoxic drug approved for CCRT by WHO is cisplatin (World Health Organisation model list of essential medicines 2017). CCRT using cisplatin as the CT agent is the standard of care for the treatment of invasive cervical cancer (Einstein *et al* 2019:20-25). According to Dasari and Tchounwou (2014:364-378) cisplatin is an antineoplastic drug used in the treatment of many solid-organ cancers.

The trade names of cisplatin are cisplatin or cis-diamminedichloroplatinum (II) (CDDP). The mode of action of cisplatin is to bind DNA and form crosslinks (Pabla and Dong 2008:994-1007). The crosslinking leads to DNA damage (Dasari and Tchounwou 2014:364-378). DNA damage causes the arrest of DNA synthesis and replication resulting in apoptosis or cell death (Pabla and Dong 2008:994-1007). Although the use of cisplatin results in the death of cancer cells, it is also associated with toxicities (Pabla and Dong 2008:994-1007).

2.3.2 Toxicities associated with cisplatin

The toxicities resulting from cisplatin use include ototoxicity, gastrointestinal toxicity, myelosuppression, allergic reactions and most notably, nephrotoxicity (Dasari and Tchounwou 2014:364-378). There is a higher risk of acute kidney injury in the HIV positive population (Wyatt and White 2015:1-4). In acute kidney injury, there is a rapid decrease in renal function and accumulation of waste products, like urea (Ozkok and Edelstein 2014:1-18). The mechanisms of cisplatin-induced acute kidney injury are: proximal tubular injury, oxidative stress, inflammation and vascular injury in the kidney (Ozkok and Edelstein 2014:1-8). In the HIV positive population, HIV-associated nephropathy (HIVAN) may present as acute kidney injury or chronic kidney disease

but is not encountered frequency due to antiretroviral treatment (Wyatt and White 2015:1-4). Other HIV-associated kidney disease includes HIV immune complex kidney disease and thrombotic microangiopathy (Wyatt and White 2015:1-4).

2.3.3 Cisplatin nephrotoxicity

Nephrotoxicity is the result of the deterioration in renal function caused by the toxic effects of cisplatin (Yao *et al* 2007:115-124). The nephrotoxicity of cisplatin is attributed to the high concentration of cisplatin in the kidneys (Yao *et al* 2007:115-124). Cisplatin-induced tubular cell injury results in inflammation and apoptosis. Cisplatin enters renal tubular cells by passive diffusion and mediation by organic cation transporters (OCT's). Organic cation transporter 2 (OCT2) is mainly responsible for cisplatin uptake in the kidney (Pabla and Dong 2008:1-11). Cisplatin becomes activated after uptake in the kidney cells (Dasari and Tchounwou 2014:364-378). After activation, cisplatin becomes a more potent toxin (Pabla and Dong 2008:1-11). Cisplatin is metabolised by gamma-glutamyl transpeptidase (GGT) and cysteine-S-conjugate b-lyase to a potent nephrotoxin (Yao *et al* 2007:115-124). The nephrotoxic cisplatin induces intracellular injury in the kidneys (Manohar and Leung 2017:1-11).

This results in the release of damage-associated molecular pattern molecules (DAMPs) (Manohar and Leung 2017:1-11). DAMPs act on toll-receptors (TLRs), mainly toll-receptor 4 (TLR4), causing the release of cytokines like tumour necrosis factor alpha (TNFα) and chemokines (Manohar and Leung 2017:1-11). Cisplatin binds to DNA and forms cross links, which arrests DNA synthesis and replication (Pabla and Dong 2008:1-11). DNA damage leads to the activation of the protein p53 (Dasari and Tchounwou 2014:364-378). The protein p53 is a mediator of cisplatin- induced apoptosis or cell death (Miller *et al* 2010:2490-2518). Cancer cells exhibit greater oxidative stress than normal cells (Dasari and Tchounwou 2014:364-378). This is due to the production of reactive oxygen species (ROS) in the presence of cisplatin (Yao *et al* 2007:115-124). ROS production is due to DNA damage, mitochondrial dysfunction or inflammatory triggers and can cause apoptosis (Manohar and Leung 2017:1-11). Cisplatin causes mitochondrial dysfunction in kidney cells, which has several related effects (Miller *et al* 2010:2490-2518). Adenosine triphosphate (ATP)

synthesis decreases and the stressed cell has to function in starvation mode (Pabla and Dong 2008:1-11). Caspase-9 mediators are activated and cause caspase dependant apoptosis (Pabla and Dong 2008:1-11). Apoptosis inducing factor (AIF) is also released is from the organelles and causes caspase independent apoptosis (Pabla and Dong 2008:1-11).

2.3.4 Cisplatin nephrotoxicity prevention strategies

Cisplatin nephrotoxicity can be prevented if adequate diuresis is maintained during treatment (Ozkok and Edelstein 2014:1-18). With adequate diuresis, the drug concentration in the renal tubules is reduced (Kumar and Clark 2017: 596-602). However, even with aggressive hydration, nephrotoxicity still occurs (Yao *et al* 2007:115-124). As per standard operating procedures in accordance with WHO approved guidelines, a patient's renal function is assessed prior to administration of cisplatin (Ozkok and Edelstein 2014:1-18). Furthermore, to prevent nephrotoxicity, full intravenous hydration is administered prior to and after cisplatin administration. There is a narrow therapeutic window between effective treatment of cancer and toxicity because cytotoxic drugs like cisplatin are not cancer-specific (Kumar and Clark 2017:596-602). The dose and schedule of CT are limited by toxicity (Kumar and Clark 2017:596-602). Therefore, it is important to monitor the renal function of the patient as well as the full blood count (FBC). In the present study, renal and haematological biomarkers were monitored for the duration of CT to assess toxicity.

2.4 Biomarkers used to monitor CT toxicity

2.4.1 Renal toxicity biomarkers

Since cisplatin is a cytotoxic drug, it is important to assess the renal function and FBC prior to commencement of CT and for the duration of CT (Kumar and Clark 2017:596-602). The blood tests urea, creatinine and glomerular filtration rate (GFR) are used to evaluate renal toxicity (Kim and Moon 2012:268-272). Other laboratory tests used to assess renal function include calcium, phosphate, parathyroid hormone, urine microscopy and urine osmolarity (Stewart and Pasha 2018:213-216). However, due

to financial constraints, these tests are not routinely done at the IALCH. In the present study, the biomarkers urea, creatinine and estimated glomerular filtration rate (eGFR) were used to assess renal toxicity.

The kidneys are the organs responsible for the management of fluid balance, waste product removal¸ acid-base balance, endocrine function and electrolyte homeostasis (Stewart and Pasha 2018:213-216). The waste products removed by the kidney include urea and creatinine. Urea is a product of protein metabolism and is filtered by the glomerulus (Stewart and Pasha 2018:213-216). The concentration of urea is affected by several factors including the hydration state of the patient, dietary protein intake and liver function (Stewart and Pasha 2018:213-216). Generally, an increase in urea concentration can be seen when there is a decreased GFR (Stewart and Pasha 2018:213-216). Creatinine is another waste product filtered by the kidney (Stewart and Pasha 2018:213-216). Creatinine is generated when creatine compounds from muscle are metabolised (Stewart and Pasha 2018:213-216). It is liberated into the blood stream at a steady state (National Kidney Foundation 2002:1-327). Creatinine concentration in blood is proportional to muscle mass and varies depending on age, race and gender (National Kidney Foundation 2002:1-327). Serum creatinine is also expected to increase after consumption of meat meals (Naicker 2012:235-237).

Creatinine is considered a more precise biomarker than urea in the evaluation of renal function (Stewart and Pasha 2018:213-216). The most common endogenous marker used to assess renal function is creatinine (Stewart and Pasha 2018:213-216). The GFR is generally accepted as the best overall measure of renal function (National Kidney Foundation 2002:1-327). GFR is the rate that plasma is cleared of substances by filtration of blood through the kidneys (Stewart and Pasha 2018:213-216). The normal level of GFR varies based on age, gender and body size (National Kidney Foundation 2002:1-327). By convention, the GFR is adjusted to a standard body surface area of 1.73 m^2 for adults (National Kidney Foundation 2002:1-327). The Cockcroft-Gault (CG) equation and the Modification of Diet in Renal Disease (MDRD) equation are the two most commonly used formulae to calculate creatinine clearance (Stewart and Pasha 2018:213-216). In 2002, the Kidney Disease Outcomes Quality

Initiative of the National Kidney Foundation recommended the use of the MDRD prediction equation for eGFR (National Kidney Foundation 2002:1-327). The MDRD equation used to calculate eGFR is (ml/min/1.73 m^2) = 186 x (serum creatinine (umol/l)/88.4$^{-1.154}$ x age $^{-0.203}$ x 1.12 (if black) x 0.742 (if female) (National Kidney Foundation 2002:1-327).

The National Health Laboratory Service (NHLS) eGFR values are calculated using the MDRD equation but the ethnicity factor is not applied (Naicker 2012:235-237). The formula was modified for use in NHLS laboratories following a study done at the Chris Hani Baragwanath hospital in Soweto, Johannesburg (Naicker 2012:235-237). The study found that when the ethnicity factor was applied, there was an overall eGFR median positive bias of 27% (Naicker 2012:235-237). The eGFR overall median positive bias decreased to 5% when the ethnicity factor was not applied (Naicker 2012:235-237). As a result of this study, NHLS laboratories' use the same MDRD formula for both black and white patients (Naicker 2012:235-237). "Black" includes patients of Indian and Coloured descent (Naicker 2012:235-237).

2.4.2 Haematological toxicity biomarkers

When bone marrow activity is decreased, there are fewer circulating red blood cells, white blood cells (WBC) and platelets (PLT) (Hoffbrand and Moss 2016:4). In the bone marrow, all the cells of the blood and immune system are derived from the pluripotent stem cells (Hoffbrand and Moss 2016:4). The two main branches of the haemopoietic lineage are the myeloid arm and the lymphoid arm (Hoffbrand and Moss 2016:10). Stem cells give rise to progenitor cells which differentiate to form red blood cells, granulocytes (neutrophils, eosinophils and basophils), monocytes, PLT and B and T lymphocytes (Hoffbrand and Moss 2016:10).

The red blood cells carry oxygen to the tissue and return carbon dioxide (Hoffbrand and Moss 2016:16). In order to achieve this gaseous exchange, the red cells carry the protein, haemoglobin (Hb) (Hoffbrand and Moss 2016:17). Reduction in Hb concentration below normal for the age and sex of the patient results in anaemia (Hoffbrand and Moss 2016:19). Anaemia is a common condition in patients with malignancy

(Lind *et al* 2002:1243-1249). The anaemia associated with malignancy may be due to both myelosuppression of stem cells by tumour cell products, such as tumour necrosis factor and CT (Lind *et al* :2002:1243-1249). Anaemia reduces the oxygen-carrying capacity of blood to meet bodily requirements (Waugh and Grant 2018:61-77). Anaemia is a strong risk factor for disease progression to acquired immune deficiency syndrome (AIDS) in HIV positive patients, independent of the CD4 count and viral load (Takuva *et al* 2013:1-6). Anaemia is managed by red cell transfusions (Waugh and Grant 2018:61-77).

Hb concentration is influenced by the interaction between genetic and environmental factors, as well as nutritional factors, age, sex and altitude (Barrera-Reyes and Tejero 2019:32-46). Genetic variations in genes encoding RBC enzymes and membranes affect Hb concentrations (Barrera-Reyes and Tejero 2019:32-46). As altitude increases, partial pressure of oxygen decreases, resulting in a lower oxygen saturation of red blood cells and an increase in erythropoiesis as an adaptive response (Silubonde *et al* 2020:1-13). In South Africa, Hb values are generally not adjusted for altitude as recommended by WHO (Silubonde *et al* 2020:1-13). Failure to adjust Hb values for altitude may lead to an underestimation of anaemia (Silubonde *et al* 2020:1-13). Radiation does not have much impact on Hb levels as red blood cells do not have a nucleus (George-Gay and Parker 2003:96-117). Low Hb may lead to tumour hypoxia, which could reduce the effectiveness of treatment (Waugh and Grant 2018:61-77). Hypoxia can influence tumour cells and result in increased resistance of the tumour to CT (Waugh and Grant 2018:61-77).

WBC play an important role in defence and immunity (Hoffbrand and Moss 2016:88). A decrease in WBC is referred to as leukopenia (George-Gay and Parker 2003:96-117). The WBC count usually falls following RT and CT as haematopoietic stem cell proliferation and maturation in the bone marrow is suppressed (George-Gay and Parker 2003:96-117). WBC can be divided into two broad groups namely phagocytes and lymphocytes (Hoffbrand and Moss 2016:88). Phagocytes include the granulocytes neutrophils, eosinophils and basophils (Hoffbrand and Moss 2016:88). The main function of neutrophils is to defend the body against bacterial infections (Hoffbrand and Moss 2016:101). When the absolute neutrophil count (ANC) falls below the normal limit it, is referred to as neutropaenia (Hoffbrand and Moss 2016:95). Neutropaenia is

often seen following CT due to the use of cytotoxic drugs (Hoffbrand and Moss 2016:95). Severe neutropaenia predisposes the patient to infection (Hoffbrand and Moss 2016:95). Patients with neutropaenia are managed by broad-spectrum antibiotics and fluid resuscitation (Waugh and Grant 2018:604).

Among HIV positive women, there is an increased risk of neutropenia during CCRT and they are less likely to complete CT with cisplatin (Vendrell *et al* 2018:1-6). Cancer treatment is a competing cause of neutropaenia in HIV positive patients and may increase the risk of CCRT-induced neutropaenia, which may influence the course of the patients treatment and the risk of infection (Vendrell *et al* 2018:1-6). Myelosuppression and neutropenia occurs in up to 30% to 83% of HIV positive patients (Vendrell *et al* 2018:1-6). Patients receiving fewer than 5 cycles of cisplatin have a decreased OS when compared with those who completed the treatment.(Vendrell *et al* 2018:1-6).

PLT are produced from megakaryocytes in the bone marrow (Hoffbrand and Moss 2016:277). The main function of PLT is the formation of mechanical plugs in response to vascular injury (Hoffbrand and Moss 2016:267). When the platelet count falls below the normal limit, it is referred to as thrombocytopaenia (Hoffbrand and Moss 2016:281). One of the causes of thrombocytopaenia is the use of cytotoxic drugs during CT (Hoffbrand and Moss 2016:281). Severe thrombocytopaenia can cause skin and mucous membrane bleeding (Hoffbrand and Moss 2016:289). Thrombocytopaenia is managed by platelet transfusions (Waugh and Grant 2018:61-77).

2.4.3 Grading of toxicities

Toxicity grading criteria provides a framework for evaluating the adverse effects of treatment (National Cancer Institute 1999:1-27). Grading refers to the scoring of any treatment-related adverse event experienced by a patient (National Cancer Institute 1999:1-27). The NCI (National Cancer Institute 1999:1-27) describes an adverse event as “any unfavourable symptom, sign, or disease (including an abnormal laboratory

finding) temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure".

The general definition of toxicity grades are (National Cancer Institute 1999:1-27): Grade 1: mild adverse event, Grade 2: moderate adverse event, Grade 3: severe and undesirable adverse event, Grade 4: life-threatening or disabling adverse event and Grade 5: death related to adverse event. The renal and haematological toxicities in the present study were graded using the Cooperative Group Common Toxicity Criteria (Appendix G) (Radiation Therapy Oncology Group 2019)

2.5 CCRT clinical trials and prior studies

The clinical trials from which the fundamentals of treatment for invasive cervical cancer were developed and prior studies by Simonds *et al* in 2012, 2015 and 2018, have been reviewed as these studies are a reference point for the present study.

2.5.1 CCRT randomised clinical trials

The NCI recommendation to combine CT with RT for the treatment of invasive cervical cancer was based on the findings of 5 randomised phase III clinical trials by 3 of NCI's Clinical Trials Cooperatives Groups (Rose 2002:270-278). These 3 groups were: Gynecologic Oncology Group (GOG), Radiation Therapy Oncology Group (RTOG) and Southwest Oncology Group (SWOG) (Rose 2002:270-278). The 5 randomised phase III clinical trials were: GOG 85, GOG 120, GOG 123. SWOG 8797 and RTOG 9001 (Rose *et al* 2002:270-278). The 5 randomised clinical trials have shown that despite the toxicities, CCRT improves PFS and OS rates in women with advanced cervical cancer (Table 1).

Table 1:NCI randomised trials in patients with advanced cervical cancer

TRIAL	ACCRUAL PERIOD	STAGE	ELIGIBILITY	ARM/GROUPS	COMMENTS
Whitney *et al* (1999:1339-1348) GOG 85	1986-1990	IIB to IVA	368	Arm 1 (n=191): RT plus hydroxyurea (HU) Arm 2 (n=177): RT plus concomitant cisplatin and fluorouracil (5-FU)	Haematologic and gastrointestinal adverse effects were the predominant findings in both arms. Better PFS and OS in arm 2.
Rose *et al* (1999:1144-1153) GOG 120	1992-1997	IIB to IVA	526	Group 1 (n=176): RT plus concomitant cisplatin Group 2 (n=173): RT plus concomitant cisplatin, 5-FU and HU Group 3 (n=177): RT plus HU	Haematologic toxicity was the principal adverse effect in all 3 groups. Higher PFS and OS rates in the two groups that received cisplatin.
Keys *et al* (1999:1154-1160) GOG 123	1992-1993	IB Bulky	369	Arm 1 (n=186): RT followed by adjuvant hysterectomy Arm 2 (n=183): RT plus concomitant cisplatin followed by adjuvant hysterectomy	Haematologic and gastrointestinal adverse effects were the predominant findings in both arms. Higher PFS and OS rates in arm 2.
Morris *et al* (1999:1137-1143) RTOG 9001	1990-1997	IB to IVA	403	Arm 1 (n=193): RT Arm 2 (n=195): RT plus concomitant cisplatin and 5-FU	Haematologic toxicity was higher in arm 2. Higher PFS and OS rates in the combined-therapy group.
Peters *et al* (2000:1606-1612) SWOG 8797	1991-1996	IA2 to IIA	268	Arm 1 (n=116): Radical hysterectomy plus RT Arm 2 (n=127): Radical hysterectomy plus RT plus concomitant cisplatin and 5-FU	Haematologic and gastrointestinal toxicity were more frequent in arm 2. PFS and OS rates were higher arm 2.

2.5.1.1 GOG 85

The goal of GOG 85 was to compare whether treatment with RT plus HU was superior to treatment with RT plus 5-FU and cisplatin and to quantitate the relative toxicities (Whitney *et al* 1999:1339-1348). Patients were evaluated for adverse effects,

according to the GOG adverse effects criteria (Table 2) (Whitney *et al* 1999:1339-1348). Haematologic and gastrointestinal adverse effects were the predominant findings in both groups (Whitney et al 1999:1339-1348). The study concluded that the superior chemo-radiation regimen in patients with locally advanced cervical cancer was RT, 5-FU and cisplatin (Whitney et al 1999:1339-1348). In the present study, a similar CCRT regimen was used to treat participants with invasive cervical cancer.

Table 2: Adverse effects of GOG 85 (Whitney *et al* 1999:1339-1348)

ADVERSE EFFECT	**Group 1** HU (n=188)					**Group 2** 5-FU/cisplatin (n=169)				
	Grade (%) * 0 – absence of adverse effect 1 - not stated in journal article 2 - not stated in journal article 3 - severe effect 4 - life-threatening effect					Grade (%) * 0 – absence of adverse effect 1 - not stated in journal article 2 - not stated in journal article 3- severe effect 4 – life-threatening effect				
	0	1	2	3	4	0	1	2	3	4
WBC	17.0	18.1	40.4	21.8	2.7	55	23.1	18.3	2.4	1.2
PLT	94.7	3.7	1.1	0.0	0.5	96.4	2.4	1.2	0	0
Other	75.0	5.9	13.3	4.8	1.1	73.4	14.2	9.5	2.4	0.6

* Due to rounding off, not all percentages total 100

2.5.1.2 GOG 120

RT was combined with 3 CT regimens to determine which combination was most effective for the treatment of patients with advanced cervical cancer (Rose *et al* 1999: 1144-1153). Adverse effects were evaluated according to the NCI Common Toxicity Criteria. The principal adverse effect in this study was haematologic toxicity (Table 3) (Rose *et al* 1999:1144-1153). RT and cisplatin CT were recommended as the standard treatment for patients with locally advanced cervical cancer (Rose et al 1999:1144-1153). In the present study, participants received RT and cisplatin CT as the standard treatment for invasive cervical cancer.

Table 3: Adverse effects of GOG 120 (Rose *et al* 1999:1144-1153)

ADVERSE EFFECT	Group 1 RT and Cisplatin (n=176)					Group 2 RT, cisplatin,5-FU, HU (n=173)					Group 3 RT and HU (n=177)				
	Grade (%) * 0 – absence of adverse effect 1 – minimal effect 2 – mild effect 3- moderate effect 4 – severe effect					Grade (%) * 0 – absence of adverse effect 1 – minimal effect 2 – mild effect 3- moderate effect 4 – severe effect					Grade (%) * 0 – absence of adverse effect 1 – minimal effect 2 – mild effect 3- moderate effect 4 – severe effect				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Leukopenia	34	17	26	21	2	8	9	37	41	5	18	8	53	20	1
Thrombocytopaenia	79	15	4	2	0	73	22	2	3	1	92	7	1	1	0
Other haematologic	45	13	27	10	5	28	10	28	23	10	36	12	35	16	2

* Due to rounding off, not all percentages total 100

2.5.1.3 GOG 123

The aim of GOG 123 was to determine if PFS and OS were improved in patients with bulky stage IB cervical cancer treated with weekly infusions of cisplatin and RT (Keys *et al* 1999:1154-1160). The NCI Common Toxicity Criteria was used to assess adverse effects (Keys *et al* 1999:1154-1160). The main adverse effects were haematologic and gastrointestinal toxicity (Table 4) (Keys *et al* 1999:1154-1160). The study provided evidence that weekly infusions of cisplatin with RT improved PFS and OS in women with bulky stage IB cervical cancer (Keys et al 1999:1154-1160).

Table 4: Adverse effects of GOG 123 (Keys *et al* 1999:1154-1160)

ADVERSE EFFECT	**RT alone** (n=186)					**RT and cisplatin** (n=183)				
	Grade (%) * 0 – absence of adverse effect 1 – minimal effect 2 – mild effect 3- moderate effect 4 – severe effect					Grade (%) * 0 – absence of adverse effect 1 – minimal effect 2 – mild effect 3- moderate effect 4 – severe effect				
	0	1	2	3	4	0	1	2	3	4
Haematologic	80	10	9	2	0	23	20	36	18	3

*Due to rounding off, not all percentages total 100

2.5.1.4 RTOG 9001

RTOG 9001 combined RT with 5-FU and cisplatin CT to determine the effectiveness of treatment in patients with advanced cervical cancer (Morris *et al* 1999:1137-1143). Toxicity was assessed using several criteria: Cooperative Group Common Toxicity Criteria, the Acute Radiation Morbidity Scoring Criteria, and the late Morbidity Scoring Scheme of the RTOG and the European organisation for research and treatment of cancer (Morris *et al* 1999:1137-1143). The study found that both local and distant recurrences of cervical cancer were reduced by CCRT treatment (Morris *et al*:1137-1143). This resulted in higher OS and disease-free survival rates in women with high-risk cervical cancer (Morris *et al* 1999:1137-1143).

Table 5: Side-effects of RTOG 9001 (Morris *et al* 1999:1137-1143)

Side effect	Worst side effects reported during treatment or within 60 days after completion of treatment					
	RT alone (n=193)			**RT and CT** (n=195)		
	Grade (%) 3-moderate effect 4-severe effect 5-fatal effect			Grade (%) 3-moderate effect 4-severe effect 5-fatal effect		
	3	4	5	3	4	5
Haematologic	2	0	0	57	16	0

2.5.1.5 SWOG 8797

The aim of SWOG 8797 was to determine if the survival of early stage patients with cervical cancer was improved when cisplatin and 5-FU CT was combined with RT. Toxicities were evaluated using SWOG criteria. Grade 3 and 4 haematological and gastrointestinal toxicity was more frequent in the combined therapy group (Table 6).

Table 6: Major toxicities of SWOG 8797 (Peters *et al* 1999:1606-1612)

Toxicity	**RT** (n=112)						**CT + RT** (n=122)					
	Grade (%) * 0 – no adverse effect or within normal limits 1 – mild adverse event 2- moderate adverse event 3 – severe and undesirable adverse event 4- life-threatening or disabling adverse event 5 – death related to adverse event						Grade (%) * 0 – no adverse effect or within normal limits 1 – mild adverse event 2- moderate adverse event 3 – severe and undesirable adverse event 4- life-threatening or disabling adverse event 5 – death related to adverse event					
	0	1	2	3	4	5	0	1	2	3	4	5
Anaemia	78	11	12	0	0	0	52	23	22	3	1	0
Granulocytopenia	90	6	1	2	1	0	36	15	20	20	9	0
Leukopenia	42	43	14	1	0	0	12	14	39	33	3	0
Renal failure	100	0	0	0	0	0	99	0	0	0	0	1

The 5 NCI clinical trials (GOG 85, GOG 120, GOG 123. SWOG 8797 and RTOG 9001) have shown the benefit of cisplatin-based CCRT for the treatment of invasive cervical cancer (Rose *et al* 2002:270-278). However, none of these trials were conducted in low-income countries (Rose *et al* 2002:270-278). In addition, the 5 NCI trials did not compare the outcome of CCRT in HIV positive women (Alongi *et al* 2017:384). Cervical cancer HIV positive patients should be treated according to the same guidelines as patients without HIV (National Comprehensive Cancer Network 2018). The participants in the present study, were HIV positive and HIV negative women from the local Kwa-Zulu Natal population undergoing treatment for invasive cervical cancer at the IALCH.

2.5.2 Systematic review and meta-analysis of CCRT trials

The 2 most recent systematic reviews and meta-analysis of randomised CCRT clinical trials were done by Green *et al* in 2005 and the American Society of Clinical Oncology in 2008. The aim of both reviews was to compare the effectiveness of CCRT with RT alone. The review by Green *et al* (2005:1-54) was based on 24 trials carried out in the 1980s and 1990s. Another systematic review and meta-analysis of individual patient data from 18 randomised CCRT clinical trials was conducted by the American Society

of Clinical Oncology (Vale 2008:1-45). Both reviews provided evidence that CCRT offers a substantial benefit for women with cervical cancer than RT alone (Green at al 2005:1-54 and Vale 2008:1-45). Acute haematological toxicity was greater when patients were treated with CCRT compared to RT alone but this was outweighed by the improved OS and PFS rates (Green at al 2005:1-54).

2.5.3 CCRT prior studies

Prior to 2019, there were no published randomised clinical trials that compared the outcome of CCRT in HIV positive patients with invasive cervical cancer (Einstein *et al* 2019:20-25). The only data available was from observational, retrospective studies done in low income countries (Alongi 2017:379-393).

2.5.3.1 CCRT prior studies in South Africa

CCRT studies were done in South Africa by Simonds *et al* in 2012, 2015 and 2018 (Table 7). These studies differentiated between HIV negative and HIV positive patients.

Table 7: CCRT prior studies in South Africa

Study	Treatment	HIV negative	HIV positive
Simonds *et al* 2012: 2971-2979	RT + weekly cisplatin CT	n=324	n=59
Simonds *et al* 2015:884-890	RT + weekly cisplatin CT	n=177	n=36
Simonds *et al* 2018: 215-220	RT + weekly cisplatin CT	n=421	n=71

The retrospective study by Simonds *et al* (2012:2971-2979) compared the completion and early response to CCRT between HIV positive and HIV negative patients with locally advanced cervical cancer in South Africa. The study found that HIV positive women presented at more advanced stages of cervical cancer and at a younger age than HIV negative women (Simonds *et al* 2012:2971-2979). Another retrospective

study by Simonds *et al* (2015:884-890) investigated the HIV status and haematological toxicity among cervical cancer patients undergoing CCRT. Toxicities were scored as per RTOG guidelines (Table 8) (Simonds *et al* 2015:884-890). The study found that haematological toxicity was higher among HIV positive compared to HIV negative women (Simonds *et al* 2015:884-890).

Table 8:Toxicities by HIV status (Simonds *et al* 2015:884-890)

Toxicities	Grade 2 toxicities		Grade 3-4 toxicities	
	HIV negative (n=177)	HIV positive (n=36)	HIV negative (n=177)	HIV positive (n=36)
Leukopenia	47 (27%)	10 (28%)	18 (10%)	11 (31%)
Thrombocytopaenia	3 (2%)	2 (6%)	0	1 (3%)
Anaemia	71 (40%)	23 (64%)	12 (7%)	3 (8%)
Neutropaenia	15 (9%)	7 (19%)	7 (4%)	3 (8%)
Creatinine	0	0	4 (2%)	0

In a 2018 prospective study, Simonds *et al* (2018:215-220) found that the overall survival in the cohort of 492 patients was >40% and that HIV positive patients had poorer overall survival than HIV negative patients. Most patients in the cohort received 40 mg/m^2 of weekly cisplatin (Simonds *et al* 2018:215-220). At least 4 cycles of CT were completed by 76% of HIV negative patients compared to 58% of HIV positive patients (Simonds *et al* 2018:215-220). The study concluded that there is justification for the provision of the best possible care to HIV positive patients with cervical cancer.

The historical clinical trials were not done in Africa and also did not differentiate between HIV positive and negative women. The 2012 and 2015 studies by Simonds *et al* were both retrospective studies. The present study is a prospective study that includes both HIV positive and HIV negative women with invasive cervical cancer undergoing CCRT treatment. A paucity in literature was the lack of data on the outcome of CCRT in the local population. The present study will address this by providing data on the renal and haematological toxicities of CCRT in the local population of women undergoing CCRT treatment for invasive cervical cancer.

CHAPTER THREE: RESEARCH METHODOLOGY

This chapter contains an outline of the methods used in accordance with the aims and objectives of the study to obtain and evaluate the data collected. It contains a description of the sampling and study population, ethical considerations, sampling techniques and data analysis.

3.1 Study Design

This was a prospective quantitative descriptive study conducted between November 2018 to July 2019.

3.2 Sample population and sampling

The sample population was drawn from the pool of patients eligible for CCRT at the Oncology Unit of the IALCH. This hospital is 1 of 3 hospitals in KZN that offers CCRT treatment for invasive cervical cancer (South Africa. Department of Health 2017:1-52). The other 2 hospitals are Addington hospital in Durban and Grey's hospital in Pietermaritzburg (South Africa. Department of Health 2017:1-52). The study population included women of all races and at different ages that were diagnosed with invasive cervical cancer. The sample size for this study was calculated using unpublished data from the Oncology Unit of the IALCH. The data was obtained by the researcher from the databases of the Oncology Unit.

Power analysis for a chi square-test was conducted in G*Power to determine a sufficient sample size using an alpha of 0.05, a power of 0.80, and a medium effect size (w = 0.3) (Faul *et al*., 2013). Based on the aforementioned assumptions, the desired sample size is 82.

3.3 Data collection

Eighty-two patients undergoing CCRT for invasive cervical cancer at the IALCH were eligible to participate in this study following informed consent. Participants were categorised into HIV positive and HIV negative patients from the sample pool of eligible patients. Participants were sourced with the assistance of the IALCH oncologists, nursing staff and databases. Demographic information that was collected from the Oncology Unit's database included the following: date of birth, age, ethnic group, place of residence and the following clinical parameters: histology, FIGO stage, HIV status, CD4 count, antiretroviral treatment, protocol for cervical cancer, other illnesses and treatment) were recorded (Appendix B). Prior to CT, patients had routine blood specimens drawn to check their renal and haematology biomarkers. The biomarkers investigated in the present study, were routinely assessed as part of the patient's treatment and no additional biomarkers were done for this study. Biomarker testing was conducted by the NHLS laboratories based at the IALCH complex.

3.4 CCRT procedures

The treatment protocol for all participants was concurrent weekly cisplatin CT plus RT for approximately 5 weeks. The external beam radiation dose was 50.4Gy in 1.8Gy fractions Monday to Friday. Treatment was neo-adjuvant and curative.

Cisplatin was used as the single agent CT drug of choice. The recommended dosage was either 30mg/m2 or 40 mg/m2 as prescribed by the oncologist. The preferred day for CT administration was Wednesday, but CT could have been administered on any day prior to RT.

The IALCH guidelines for CT were as follows (Bhadree, 2019).

i) if the eGFR was 60ml/min or more, weekly cisplatin of either 30mg/m2 or 40mg/m2 was prescribed by the oncologist
ii) CT was deferred if the eGFR was less than 60ml/min and resumed once the eGFR was greater than 60 ml/min
iii) patients were transfused if the Hb dropped to 7g/dL or below

iv) CT was deferred if the ANC dropped below 1 x 10^9/L and resumed once the ANC recovered
v) CT was deferred if the PLT dropped below 75 x 10^9/L
vi) CT was discontinued if the Hb, ANC or PLT did not recover

The results for the patients' renal and haematological biomarkers were monitored for the duration of the CCRT treatment, which was between 5 to 8 weeks. The patients' renal and haematological baseline and post CCRT biomarker results were also monitored. Post CCRT biomarkers results were monitored 1 week after completion of CCRT treatment. Biomarker results for urea, creatinine and eGFR were used to assess renal toxicity. The FBC biomarker results for WBC, Hb, PLT and ANC were used to assess haematological toxicities. Results were accessed using the IALCH databases. Patients proceeded with CCRT once the results of their renal and haematological biomarkers were evaluated by an oncologist.

Confounders such as the patients CD4 count were controlled. The CD4 count was done by the base clinic and checked by the oncologist prior to prescribing CT. The CD4 count was not monitored for the duration of CT. However, this did not pose a problem as the CD4 count was not expected to fluctuate much for the duration of CT. Also, patients with lower CD4 counts may have a decreased lymphocyte count, but not specifically a neutropaenia, which was monitored in this study. Antiretroviral therapy was started for all HIV positive participants that were not already receiving the treatment prior to commencement of CCRT.

3.5 Ethical considerations and recruitment

Ethical clearance for this study was obtained from the Durban University of Technology Ethics Committee (Appendix C). Permission to proceed with this study was obtained from the Kwa-Zulu Natal Department of Health (Appendix D), IALCH (Appendix E) and the Provincial Health Research Committee (Appendix F). Written informed consent was obtained from participants prior to inclusion in the study (Appendix A). Participation in this study was voluntary and participants were not coerced into participating. Participants were informed that they would be free to

withdraw from the study at any time. All participant information was strictly confidential. Patients were identified using a study record number.

3.6 Inclusion and exclusion criteria

Participants recruited for this study had to meet the inclusion and exclusion criteria.

3.6.1 Inclusion criteria

Women with histologically confirmed invasive cervical cancer.

Qualification for CCRT as decided by a multi-disciplinary Team (standard of care)

3.6.2 Exclusion criteria

Renal impairment

Haematological disorders

Previously failed CT

Previous neo-adjuvant CT

Previous radiation therapy

Patients with hydronephrosis

Patients who decline to be part of the study

Patients who choose to withdraw from the study

3.7 Data Analysis

Patient demographics were analysed using tables and graphs. The biomarker results were analysed using tables and graphs. The Cooperative Group Common Toxicity Criteria was used to assess renal and haematological toxicity (Appendix G) (Radiation Therapy Oncology Group 2019). The Wilcoxon test was used for comparisons between 2 groups. The Kruskal Wallis test was used for comparison between more than 2 groups. Multivariate tests were used where applicable. The significance of the toxicities was determined using *p*-values. A *p*-value of <0.05 was considered significant.

CHAPTER FOUR: RESULTS

In this chapter, the study results are presented. These include the demographic information of the participants qualifying for CCRT and the laboratory analysis of possible toxicities associated with CT in CCRT among a sample of both HIV positive and negative participants.

4.1 Patient profile

4.1.1 Sample population

Ninety women with invasive cervical cancer undergoing CCRT treatment were recruited to participate in this study. Based on the exclusion criteria, 8 women were excluded (Figure 1).

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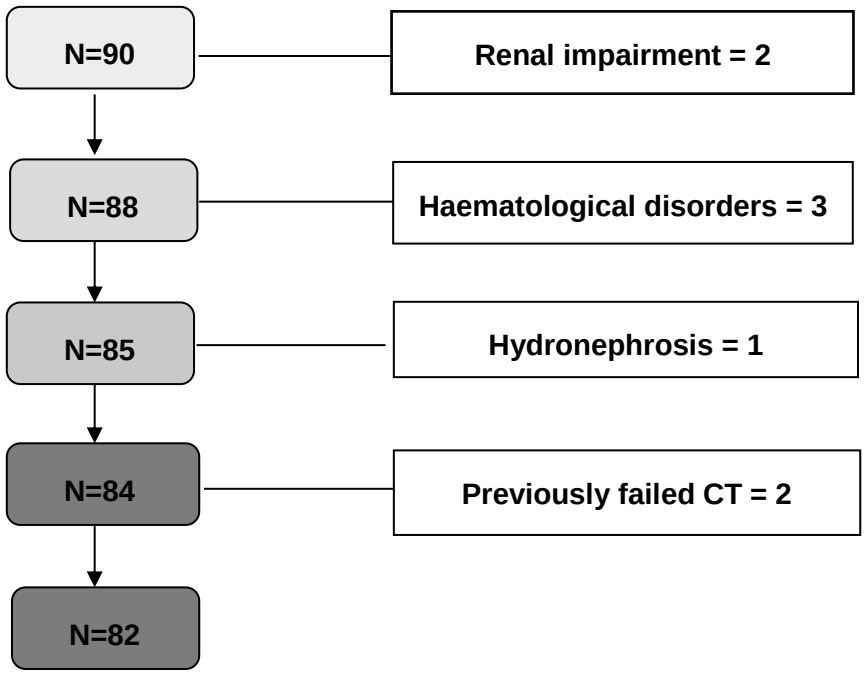

Figure 1: Sample population and exclusions

The reasons for the exclusions were renal impairment, haematological disorders, hydronephrosis and previously failed CT. The total number of participants included in this study was 82, which is consistent with the desired sample size.

4.1.2 Demographics by age

Participants were grouped according to age (Figure 2) and HIV status (Table 9).

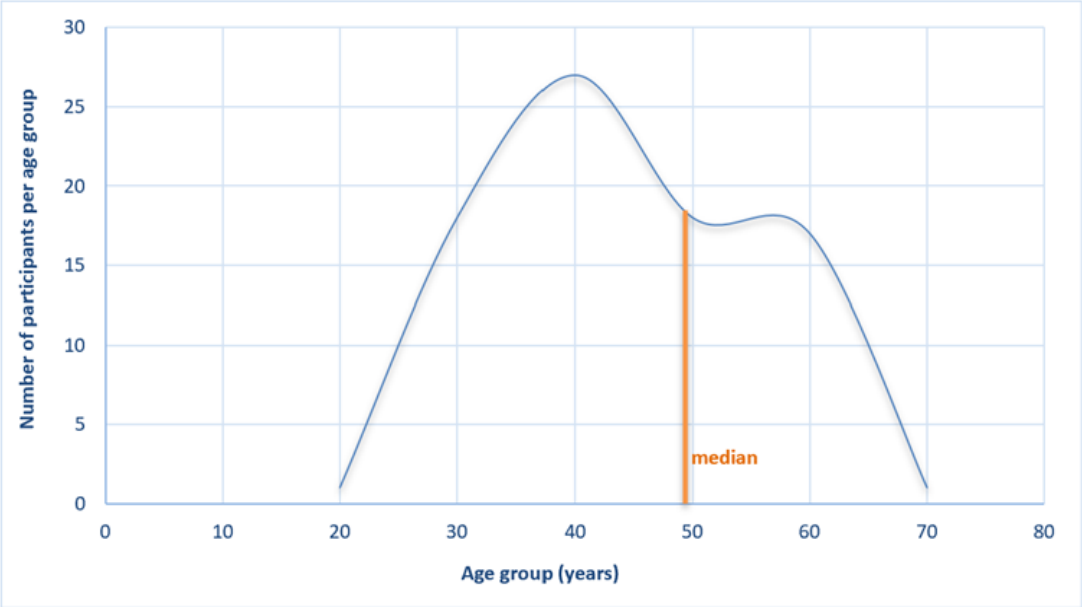

Figure 2: Distribution of sample population based on age

The median age of the sample population was 49 years old (range 21-75 years old). A significant finding was that 86.6% of the cohort were over the age of 35.

Table 9: Age distribution of participants by HIV status

Variable	HIV negative n=50	HIV positive n=32	p-value
Median age [25-71]	**52** [32-71]	**43** [25-68]	<0.01

The median age of HIV negative women was 52 years old compared to HIV positive women which was 43 years old. A significant finding was that the median age of HIV positive women was 9 years younger than HIV negative women.

4.1.3 Demographics by ethnic group

The distribution of participants according to their ethnicity is shown in Figure 3.

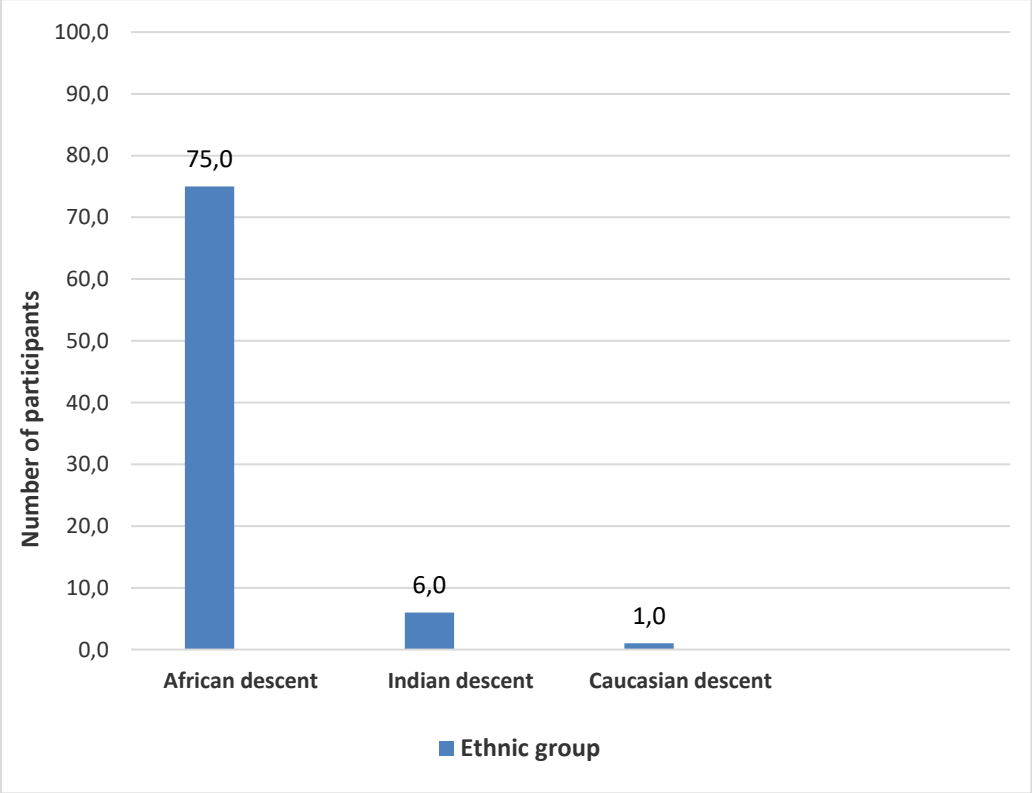

Figure 3: Ethnic group distribution of participants qualifying for CCRT

Of the 82 patients qualifying for CCRT, 75 (92%) were of African descent, 6 (7%) were of Indian descent and 1 (1%) was of Caucasian descent (p- value <0.01). The majority of patients undergoing CCRT treatment at the IALCH were of African descent.

4.1.4 Demographics by disease profile

4.1.4.1 Demographics by histology

In this study, participants presented with tumours that were either squamous cell carcinoma or adenocarcinoma (Figure 4). Participants were further grouped by their histolopathological diagnosis and HIV status (Table 10).

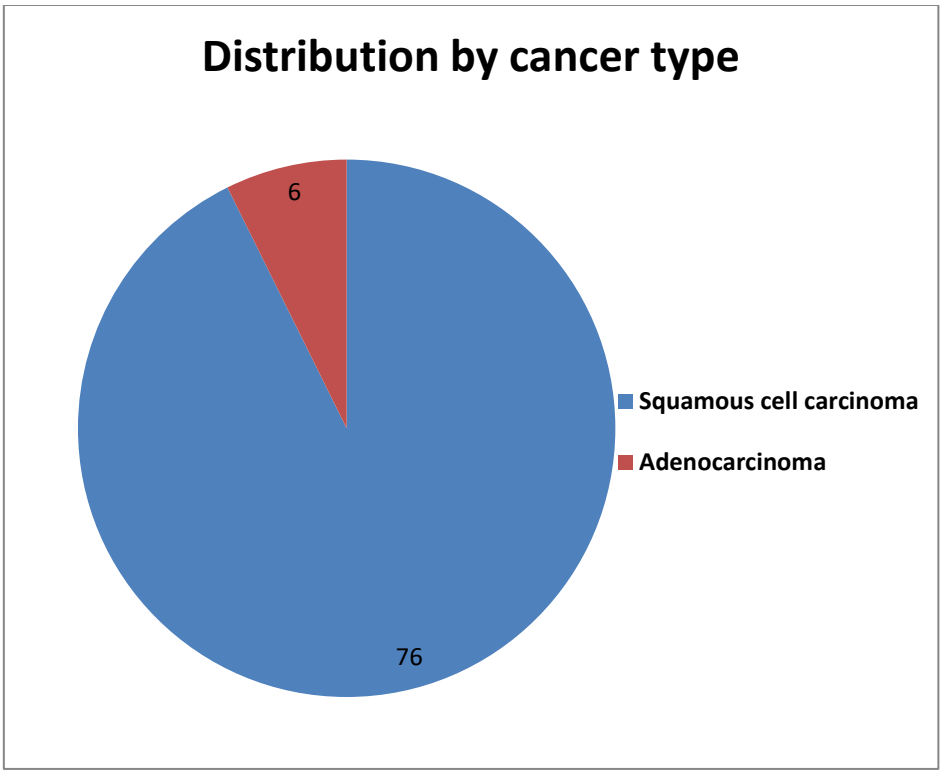

Figure 4: Distribution of histological type of cancer

Squamous cell carcinoma was the predominant histopathological diagnosis in 93% of participants. The remaining 7% of participants presented with adenocarcinoma ($p<0.01$).

Table 10: Distribution of histology of participants undergoing CCRT by HIV status

Variable	HIV negative n=50	HIV positive n=32	p-value
Squamous cell carcinoma	45 (90%)	31 (97%)	0.108
Adenocarcinoma	5 (10%)	1 (3%)	0.102

There was no significant difference in the histopathological diagnoses of squamous cell carcinoma and adenocarcinoma between HIV positive and HIV negative participants.

4.1.4.2 Demographics by disease stage

The disease stage variation of participants is represented in figure 5. The disease stage variation of participants by HIV status is tabulated in Table 11.

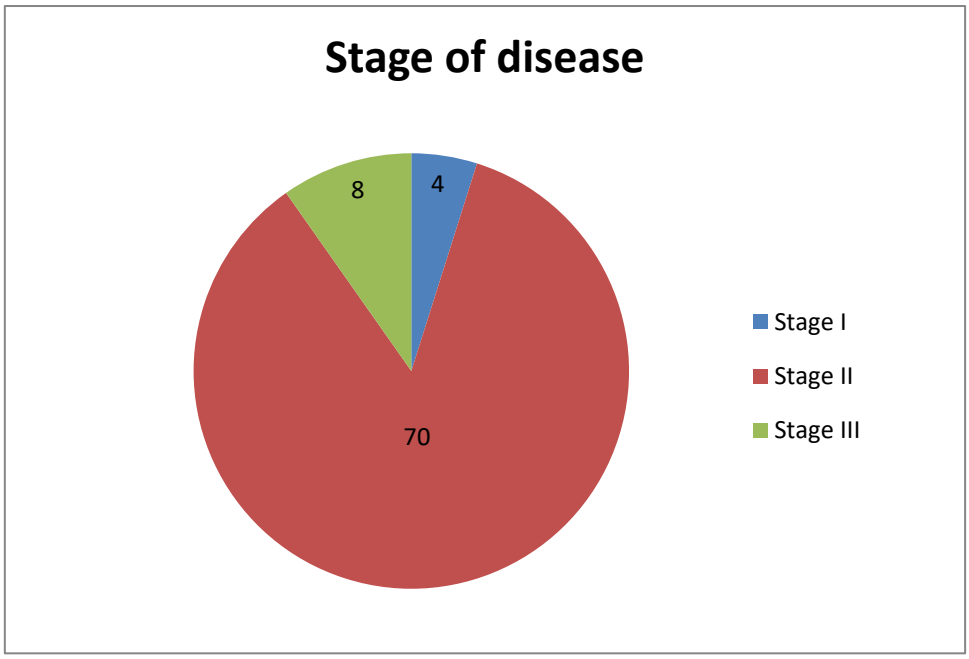

Figure 5: Distribution of stage of disease of participants undergoing CCRT

The 70 participants with stage II disease made up 85% of the sample population. Four participants (5%) with stage I disease were treated with CCRT due to them not being eligible for surgery. Eight participants (10%) with stage III disease had CCRT as they did not show evidence of pelvic wall involvement.

Table 11: Distribution of stage of disease of participants undergoing CCRT by HIV status

Variable	HIV negative n=50	HIV positive n=32	p-value
Stage I	3 (6%)	1 (3%)	0.317
Stage II	43 (86%)	27 (84%)	0.056
Stage III	4 (8%)	4 (13%)	1.000

There was no significant difference in the disease stage variation between HIV positive and HIV negative participants.

4.1.5 Treatment delivery and compliance

Participants were required to complete 5 cycles of CT. The variables related to treatment delivery and compliance based on the HIV status of participants are represented in Table 12.

Table 12: HIV status in relation to therapy

Variable	HIV negative n=50	HIV positive n=32	p-value	Total n=82
	N	n		n
Mean number of cycles completed	5 (96%)	5 (94%)		5 (95%)
Number of participants who did not complete therapy	2 (4%)	2 (6%)	0.641	4 (5%)
-absconded during treatment	1 (1%)	2 (6%)	0.557	3 (4%)
-treatment discontinued by physician	1 (1%)	0	1.000	1
Number of participants who had treatment delays	3 (6%)	3 (9%)	0.674	6 (7%)
-low Hb	0	1 (3%)	0.390	1 (1%)
-low ANC	1 (2%)	2 (6%)	0.557	3 (4%)
-low eGFR	2 (4%)	0	0.518	2 (2%)
Number of participants requiring hospitalisation	1 (2%)	2 (6%)	0.557	3 (4%)
-transfused	1 (2%)	1 (3%)	1.000	2 (2%)
-grade 1 toxicity	1 (1%)	0	1.000	1 (1%)
Death	1 (2%)	0	1.000	1 (1%)

The average number of CT cycles completed by participants in this study was 5, regardless of HIV status. Ninety five percent of participants completed 5 cycles of CT with very few treatment gaps. Overall, compliance of participants to CT was excellent. There was one non-treatment related death. The participant developed meningitis a week after completion of CCRT.

4.2 Toxicities

4.2.1 Renal toxicities associated with CT in CCRT

Table 13 represents a summary of the mean renal biomarkers results from baseline to post CCRT, including the biomarker range and standard deviation (sd). The eGFR remained unchanged during the treatment and post CCRT.

Table 13: Mean results for renal biomarkers

Biomarker and range	Baseline and sd	Cycle 1 and sd	Cycle 2 and sd	Cycle 3 and sd	Cycle 4 and sd	Cycle 5 and sd	Post CCRT and sd
Urea [2.1-7.1] mmol/L	4.4 [1.5]	4.3 [1.5]	4.5 [1.6]	4.5 [1.5]	4.3 [1.6]	5.3 [1.5]	5.6 [1.8]
Creatinine [49-90] umol/L	65 [13.1]	67 [14.8]	69 [15.6]	69 [16.9]	68 [14.4]	69 [17.8]	72 [23.3]
eGFR >60 ml/min	>60	>60	>60	>60	>60	>60	>60

Each participants' renal biomarkers results from baseline to post CCRT, were analysed and used to grade the renal toxicities. Toxicities were graded using the Cooperative Group Common Toxicity Criteria (Appendix G) (Radiation Therapy Oncology Group 2019). The reference ranges for each toxicity grade is included in

Appendix G. The toxicity grade reflects the most severe degree occurring during the duration of CCRT. Based on the Cooperative Group Common Toxicity Criteria, no renal toxicities were evident.

4.2.2 Haematological toxicities associated with CT in CCRT

Table 14 represents a summary of the mean haematological biomarkers results from baseline to post CCRT of all participants, including the biomarker range and sd.

Table 14: Mean results for haematological biomarkers

Biomarker and reference range	Baseline and sd	Cycle 1 and sd	Cycle 2 and sd	Cycle 3 and sd	Cycle 4 and sd	Cycle 5 and sd	Post CCRT and sd
Hb [12.0-15.0] g/dL	11.1 [1.5]	10.9 [1.4]	11.0 [1.5]	10.6 [1.4]	10.5 [1.4]	10.3 [1.3]	10.1 [1.4]
WBC [3.9-12.6 x10^9/L]	6.86 [3.0]	7.19 [3.98]	5.79 [2.46]	5.23 [2.83]	4.61 [2.5]	3.64 [1.34]	2.87 [0.59]
PLT [186-454 x 10^9/L]	302 [98]	296 [142]	275 [115]	249 [92]	216 [74]	186 [87]	141 [36]
ANC [3.9-12.6 x10^9/L]	4.04 [2.9]	4.15 [2.4]	3.44 [1.43]	3.31 [1.51]	2.74 [1.72]	2.33 [0.67]	1.5 [0.42]

Toxicities were graded using the Cooperative Group Common Toxicity Criteria (Appendix G) (Radiation Therapy Oncology Group 2019). The reference ranges for each toxicity grade is included in Appendix G. The toxicity grade reflects the most severe degree occurring during treatment. In order to determine the most severe toxicity grade, each participant's haematological biomarker results, from baseline to post CCRT, was analysed (Table 15).

Table 15: Toxicities in participants post CCRT according to grade

Toxicity type	Grade 1-2 toxicity	Grade 3-4 toxicity
	n	n
Hb	61 (74%)	6 (7%)
WBC	25 (31%)	4 (5%)
PLT	22 (27%)	0
ANC	15 (18%)	1 (1%)
	p-value	p-value
WBC versus Hb	<0.001	0.7657
WBC versus PLT	0.624	0.0587
WBC versus ANC	0.040	0.2155
PLT versus Hb	<0.001	0.0137
PLT versus ANC	0.161	0.4675
ANC versus Hb	<0.001	0.0678

There was evidence of grade 1-2 and grade 3-4 haematological toxicities. Grade 1-2 haematological toxicity was the principal adverse effect. Hb was more significantly affected than other cellular components in blood.

4.3 Toxicities by HIV status

The haematological toxicities were compared by HIV status (Table 16).

Table 16: Haematological toxicities in participants post CCRT by HIV status

	Grade 1-2 toxicity		Grade 3-4 toxicity	
Toxicity type	**HIV negative**	**HIV positive**	**HIV negative**	**HIV positive**
	n	n	n	n
Hb	34 (68%)	27 (84%)	2 (4%)	4 (13%)
WBC	13 (26%)	12 (38%)	2 (4%)	2 (6%)
PLT	11 (22%)	11 (34%)	0	0
ANC	8 (16%)	7 (22%)	0	1 (3%)
	p-value	p-value	p-value	p-value
WBC versus Hb	<0.001	<0.001	1.000	0.4921
WBC versus PLT	0.815	1.000	0.4949	0.6719
WBC versus ANC	0.326	0.274	0.4949	1.000
PLT versus Hb	<0.001	<0.001	0.4949	0.1132
PLT versus ANC	0.611	0.405	-	1.000
ANC versus Hb	<0.001	<0.001	0.4949	0.3547

There was evidence of grade 1-2 and grade 3-4 haematological toxicities in both HIV negative and HIV positive participants. Grade 1-2 haematological toxicity was the predominant finding regardless of HIV status. Hb was more significantly affected than other cellular components in blood in both HIV positive and HIV negative participants.

4.4 Trends per treatment cycle for haematological biomarkers

The trend for the haematological biomarkers, Hb, WBC, PLT and ANC from baseline to post CCRT in the total population are represented in figures 6-9.

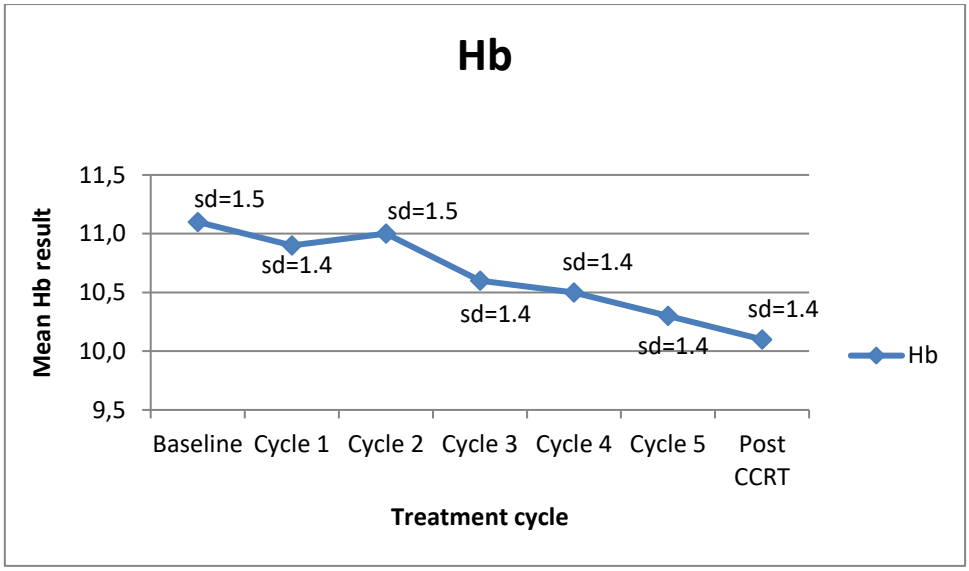

Figure 6: Trend for Hb based on the mean result per treatment cycle

The normal range for Hb is 12.0-15.0 g/dL. The Hb dropped from an average baseline level of 11.1 to 10.1 post CCRT amongst all participants. The p-value was <0.01. The decrease in Hb was more noticeable from treatment cycle 2.

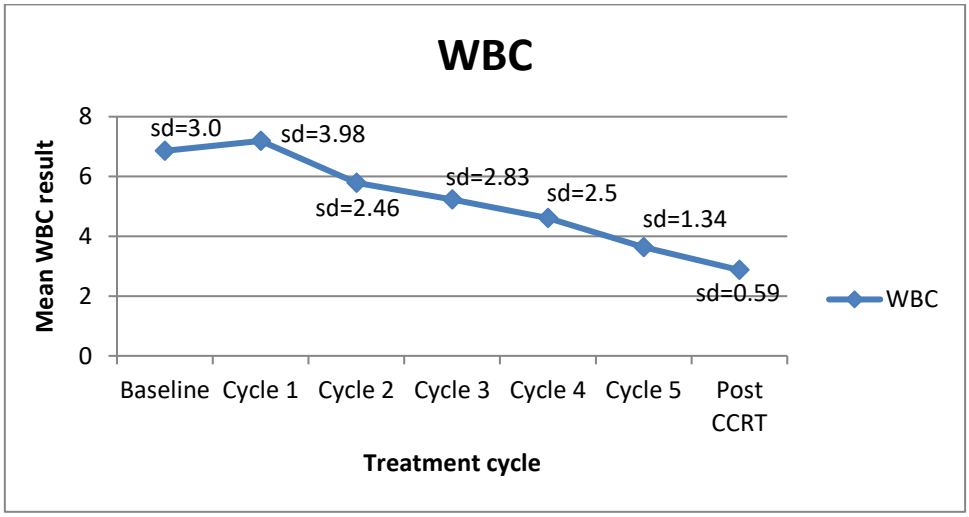

Figure 7: Trend for WBC based on the mean result per treatment cycle

The normal range for WBC is 3.9 – 12.6 x 10^9/L. The WBC dropped from a baseline level of 6.86 to 2.87 post CCRT. The p-value was <0.01. A decrease in WBC is more noticeable from treatment cycle 1.

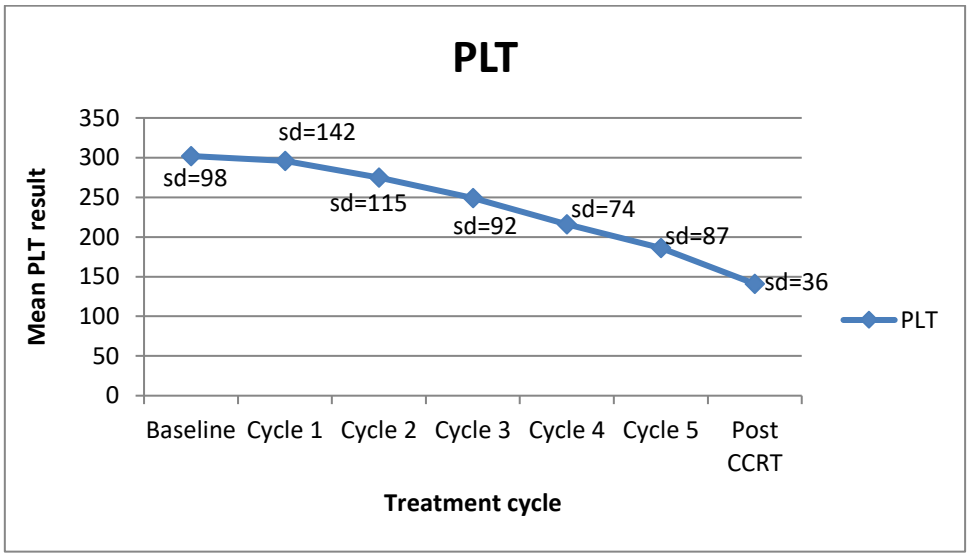

Figure 8: Trend for PLT based on the mean result per treatment cycle

The normal range for PLT is 186 -454 x 10^9/L. The PLT dropped from a baseline level of 302 to 141 post CCRT. The p-value was <0.01. A decrease in PLT is more noticeable from treatment cycle 1.

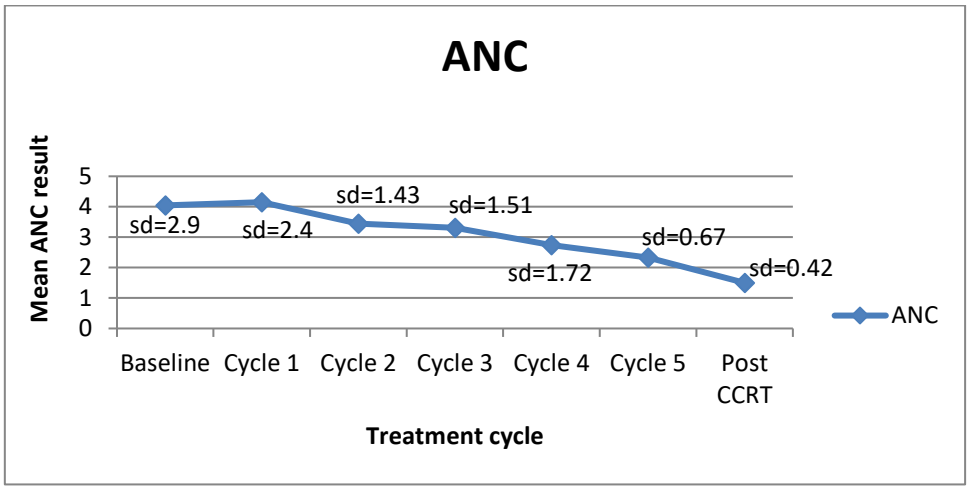

Figure 9: Trend for ANC based on the mean result per treatment cycle

The normal range for ANC is 3.9 -12.6 x 10^9/L. The ANC dropped from a baseline level of 4.04 to 1.5 post CCRT. The p-value was <0.01.A decrease in ANC is more noticeable from treatment cycle 1.

4.5 Trends per treatment cycle for renal biomarkers

The trend for the renal biomarkers, urea and creatinine from baseline to post CCRT are represented in figures 10 and 11.

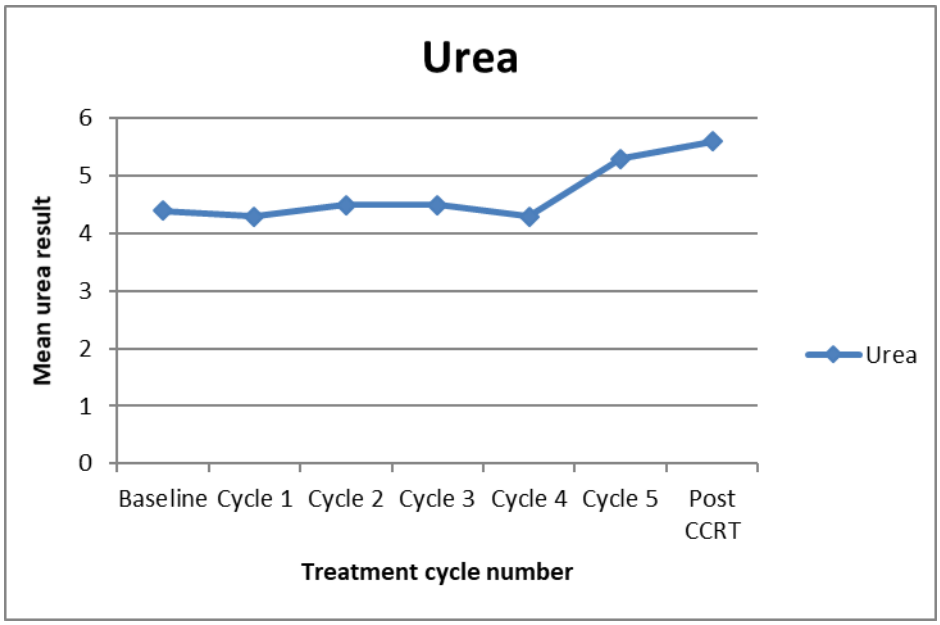

Figure 10: Trend for urea based on the mean result per treatment cycle

The normal range for urea is 2.1-7.1 mmol/L. The Urea increased from a baseline level of 4.4 to 5.6 post CCRT. The p-value was 0.437. An increase in Urea is evident from treatment cycle 4.

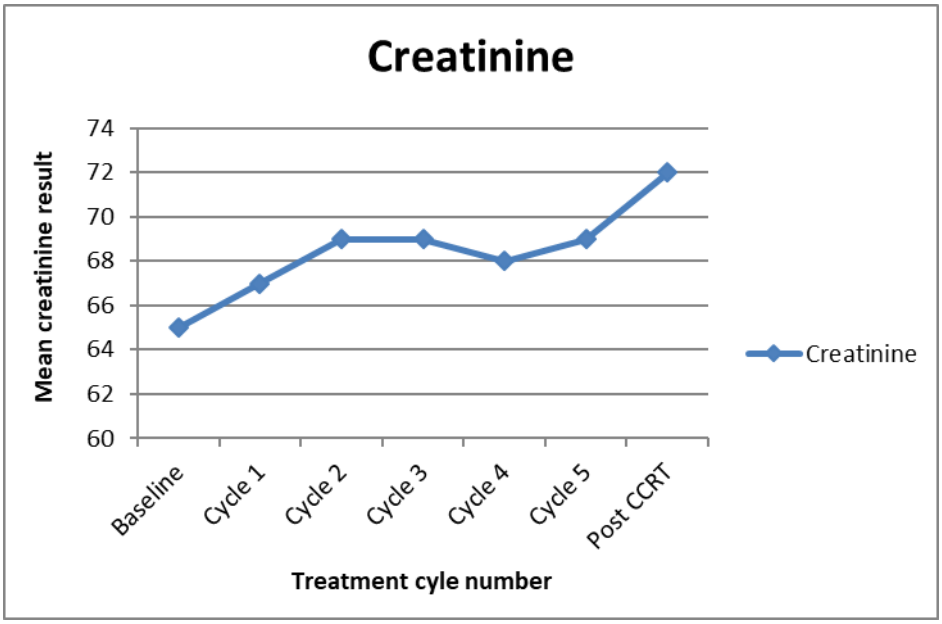

Figure 11: Trend for creatinine based on the mean result per treatment cycle

The normal range for creatinine is 49 – 90 µmol/L. The Creatinine increased from a baseline level of 65 to 72 post CCRT. The p-value was 0.002. An increase in Creatinine is evident from treatment cycle 4.

CHAPTER FIVE: DISCUSSION AND LIMITATIONS

5.1 DISCUSSION

5.1.1 Patient profile

In the present study, the median age of the participants was 49 years old in the total population and 43 years old in HIV positive participants. Cervical cancer occurs at a younger age in HIV positive participants. These findings were similar in the study by Simonds *et al* (2015:884-890) and in the clinical trial by Einstein et al (2019:20-25).

The risk of developing cervical cancer is up to 7 times higher in HIV positive women compared to HIV negative women due to the higher HPV persistent prevalence in HIV positive women (Basu *et al* 2018:1-8). Sexually active women HIV positive women should be screened more frequently for cervical cancer (Basu *et al* 2018:1-8). Cervical cancer is linked to advanced HIV infection and it is accepted as an AIDS defining malignancy by the Centre for Disease Control (CDC) (Ghebre *et al* 2017:101-108). Cervical cancer has a more aggressive natural history and poor treatment outcome in HIV positive women (Basu *et al* 2018:1-8). There is significant T cell dysfunction due to the interaction of the tumour and active HIV infection (Ghebre *et al* 2017:101-108). CT drugs can induce immunodeficiency and cause the depletion of CD4 T lymphocytes (Ghebre *et al* 2017:101-108). The progression of cervical cancer is higher with lower CD4 counts (Firnaber *et al* 2012:1-6). The use of antiretroviral treatment in HIV positive women does not reduce the risk of developing cervical cancer (Basu *et al* 2018:1-8). However, the rate of tumour progression is slower at lower CD4 counts in HIV positive women on antiretroviral treatment (Firnaber *et al* 2012:1-6).

The incidence of cervical cancer has remained unchanged in South Africa even though a national screening policy has been in place since 2002 (South Africa. Department of Health 2017:1-68). A drawback to the current cervical cancer screening program is that it offers screening services only (South Africa. Department of Health 2017:1-68). The revised cervical cancer prevention and control policy offers a more holistic approach and includes prevention, screening, diagnosis, treatment and palliative care (South Africa. Department of Health 2017:1-68). Also, new guidelines are included for

cervical cancer screening of HIV positive women (South Africa. Department of Health 2017:1-68), which will facilitate the early diagnosis and treatment of cervical cancer.

The ethnicity of South African female population is 80.8% of women are of Black descent, 2.4% are of Indian descent, 7.9% are of Caucasian descent and 8.8% are of Coloured descent (South Africa. Department of Statistics 2019:1-24). The sample population for the present study was representative of the South African population for women of Black descent. The most common histologic carcinomas are squamous cell carcinoma followed by adenocarcinoma (Newton and Mould 2016:7-13). The prevalence of HPV 16 is increased in squamous cell carcinoma (Bulk *et al* 2006:171-175). In adenocarcinoma, HPV 18 is more prevalent (Bulk *et al* 2006:171-175). In South Africa, more than 60% of cervical cancer cases are due to HPV 16 and 18 (South Africa. Department of Health 2017:1-52).

In the studies by Simonds *et al* (2012:2971-2979 and 2015:884-890), over 90% of HIV positive and HIV negative participants presented with squamous cell carcinoma. In the present study, the findings were similar and HIV status was not associated with histopathological diagnosis. Approximately 90% of both HIV positive and HIV negative participants had squamous cell carcinoma. The predominant disease stage at which the CCRT was initiated in the present study was stage II. Stage II and stage III disease were the predominant disease stages in both the Simonds *et al* studies (2012:2971-2979 and 2015:884-890). The advanced disease stage at which women with cervical cancer present is possibly due to cervical cancer cases being diagnosed late in South Africa (Botha and Richter 2015:33-34). The late diagnosis is due to limitations in the South African health care system (South Africa. Department of Health 2017:1-52). The limitations can be summed up as inadequate screening, inadequately trained personnel, lack of finances and lack of knowledge about the disease (Wu *et al* 2017:572-582).

5.1.2 Toxicities associated with CT

Tolerance for CT in the present study was high (>90%) regardless of HIV status compared to the previous two Simonds studies, which had a tolerance of between 60 and 70% (Simonds *et al* 2012:2971-2979 and 2015:884-890). High tolerance for CT in the present study was most likely due to the use of a lower cisplatin dose (30mg/m^2) upfront for the majority of participants. In the Simonds studies, the cisplatin dose commenced at 40 mg/m^2 and had to be reduced if renal function deteriorated (Simonds *et al* 2012:2971-2979 and 2015:884-890). No cisplatin dosage adjustments were required in the present study as the renal function of participants did not deteriorate significantly. In the present study, Grade 1-2 haematological toxicity was the predominant finding, regardless of HIV status.

In both HIV positive and negative participants, Hb was more significantly decreased than other cellular components, followed by WBC. The findings were similar in the study by Simonds et al (2015:884-890). Haematological toxicity was most likely due to myelosuppression, which is a side effect of CT and cytotoxic drugs (Hoffbrand and Moss 2016:95). The changes are usually reversible after withdrawal of the drug (Hoffbrand and Moss 2016:95). Anaemia is defined as Hb <10 g/dL (Takuva *et al* 2013:1-6). The cause of anaemia is mainly impaired erythropoiesis resulting from the release of inflammatory cytokines as well as decreased production of haematopoietic growth factors, together with malabsorption and impaired recycling of iron (Takuva *et al* 2013:1-6). Other causes of anaemia include nutritional deficiencies, haemolysis, malignant bone marrow infiltration and bone marrow infection (Takuva *et al* 2013:1-6). Even in HIV positive patients receiving antiretroviral treatment, anaemia is a strong risk factor for disease progression to AIDS and an increased risk of death (Tavuka *et al* 2013:1-6).

In the present study, none of the participants had renal toxicity regardless of HIV status. Renal toxicity was a finding in 4 (2.3%) HIV negative patients in the study by Simonds *et al* (2015:884-890). None of the HIV positive patients had renal toxicity in the same study. The absence of renal toxicity in the present study is possibly due to an improved dosing regimen. The majority of participants in the present study were

prescribed 30 mg/m2 cisplatin compared to 40 mg/m2 in the study by Simonds *et al* (2015:884-890).

5.2 LIMITATIONS

This was a cross-sectional study hence the study population was small and the findings need to be replicated in more extensive studies. Whilst the study population was generally similar to the South African population, it may not be entirely representative of the female population distribution. The biomarkers urea and creatinine are used to assess renal function in state hospitals in South Africa. However, these biomarkers lack sensitivity and specificity (Kim and Moon 2012: 268-272). Serum cystatin is a more sensitive biomarker that can be used to assess renal function (Naicker 2007:2). However, due to financial constraints, it is not routinely requested in state hospitals in South Africa (Naicker 2007:2).

There are late referrals from the base clinics resulting in patients presenting with advanced stages of cervical cancer. There are also treatment delays following a referral from the base clinics due to a shortage of oncologists and radiotherapists. This results in long waiting times before commencement of treatment and the possibility of progression of the disease before treatment. CD4 counts for HIV positive patients are done by the base clinics before referral to IALCH. However, the results of the CD4 counts were not always available when the patient is referred to as IALCH. In the present study, this did not pose a problem as we were looking at CT and neutropaenia without simultaneously monitoring the CD4 response.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

This prospective study aimed to determine the renal and haematological toxicities associated with the CT component of CCRT in patients with invasive cervical cancer, using renal and haematological biomarkers. Eighty-two women undergoing CCRT treatment for invasive cervical cancer at the IALCH were recruited to participate in this study. This study evaluated the profile of patients qualifying for CCRT and investigated the renal and haematological toxicities associated with the CT component of CCRT. A comparison was done between the renal and haematological toxicities in HIV positive and HIV negative participants. No renal toxicities were identified in this study. The predominant finding was haematological toxicity in both HIV positive and HIV negative participants. The blood component that was most significantly decreased was Hb, followed by WBC. The CT component of CCRT was well tolerated in both HIV positive and HIV negative participants. Compliance to planned CT was excellent regardless of HIV status and there were minimal treatment delays. There was 1 non-treatment related death. Based on this study, the same CCRT protocol can be applied to both HIV positive and negative patients. However, the study population was small and focussed on the CT component of CCRT. These findings need to be replicated in more extensive studies that include the effects of both the CT and RT component of CCRT.

6.2 Recommendations

The majority of the cohort in the current study presented with advanced stages of cervical cancer, possibly due to late diagnosis. The current cervical cancer screening policy is to offer all asymptomatic women above 30 years of age (regardless of HIV status), 3 free cervical cancer screening tests at 10-year intervals at a public health facility in South Africa. With the implementation of the new cervical cancer prevention policy, HIV positive women will be screened for cervical cancer at diagnosis and subsequently every 3 years, if the screening test is negative and annually if the screening test is positive. This is a promising development as it is evident in the current

study that HIV positive women present with cervical cancer at a younger age than their HIV negative counterparts. Earlier diagnosis and treatment of cervical cancer will offer women more treatment choices and prevent early mortality. The advantage of a well-managed screening programme would be a decrease in the incidence of cervical cancer as well as early diagnosis and treatment. The anticipation is that a more vigorous screening programme will be implemented when the revised cancer prevention and control policy is fully phased in by 2030.

The same CCRT protocol can be applied to both cohorts, this is a promising finding since the notion that HIV positive patients may not tolerate the same treatment regimen as well as the HIV negative patients exists, given that most of the historic clinical trials did not consider HIV status. More research on this aspect is required and the impact of CD4 counts should also be monitored. CD4 counts should be done routinely by the IALCH before the commencement of CCRT treatment for cervical cancer and the duration of treatment. This will enable serial monitoring of the CD4 count for the duration of CT and will serve as an additional monitoring tool. The assessment of patients' renal and haematological biomarkers for the administration of CT in the IALCH oncology unit is subjective as there is no specific protocol in place. For standardisation, validation and reproducibility, more research into this would be beneficial and should lead to the development of a standardized protocol for implementation. A drawback to using creatinine as a renal biomarker is that the creatinine concentration in blood is proportional to muscle mass and varies depending on age, race and gender. Additionally, serum creatinine concentration is expected to increase after consumption of meat meals. Cystatin C should be considered for the routine monitoring of renal function by the IALCH. Unlike creatinine, Cystatin C does not vary with muscle mass, gender, age, race and diet. Renal toxicity was not a finding in the present study. However, there was an increase in urea and creatinine concentration in blood from cycle 4 of CCRT treatment. This is suggestive of deterioration in renal function and needs to be investigated in further studies.

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APPENDIX A

LETTER OF INFORMATION

Title of research study:

Chemotherapy induced renal and haematological toxicities in patients with invasive cervical cancer undergoing concurrent chemo-radiation.

Principle investigator/researcher:

Miss Fathima Motala, student enrolled for the Master's Degree: Medical Laboratory Science at the Durban University of Technology.

Supervisors:

Dr Pavitra Pillay, PhD: Public Health

Dr Kamendran Govender, MBChB, MMED, MPhil

Brief introduction and purpose of the study:

You are invited to participate in a research study. The information in this letter will help you understand what the research is about and how it will contribute to the knowledge base. If there are any questions, which are not clearly explained in this letter, please do not hesitate to contact the investigator or the supervisors.

Patients undergoing treatment for invasive cervical cancer may develop kidney and blood toxicities. The purpose of the research study is to investigate these toxicities. We will measure renal and blood toxicities by checking your laboratory tests that are done as part of your routine monitoring whilst you are on treatment. It is hoped that this research study will provide information that is likely to contribute in the expansion of knowledge on this important topic as well as provide a better understanding of the outcome of this treatment in the local population. The information from the outcome of this study will be used to use to educate the community and healthcare workers about the toxicities of concurrent chemo-radiation (CCRT).

Outline of the procedures:

The research study will investigate the kidney and blood toxicities associated with CCRT in patients with invasive cervical cancer.

If you qualify for the research study, your patient profile data will be collected and the results of your kidney and blood tests will be monitored whilst you are undergoing chemotherapy.

You are required to have your kidney and blood biomarkers checked before each chemotherapy session and to proceed with your chemotherapy if your results permit. You will not have to undergo any additional procedures, spend any more time in hospital or experience any adverse effects if you participate in this research study.

Risks or Discomfort to the Participant:

You will not experience any risk or discomfort if you participate in this study.

Benefits:

It is hoped that this research study will increase our understanding of the renal and haematological toxicities associated with the chemotherapy component of chemo-radiation.

Reason/s why the participant may be withdrawn from the study:

Your participation in this research study is entirely voluntary. Your withdrawal at any time will not affect your medical treatment. There are no risks involved.

Remuneration:

There will be no remuneration to you.

Costs of the Study:

You will be liable for the normal costs for the routine medical procedures needed. There will be no extra costs.

Confidentiality:

All information obtained in this research study will be strictly confidential.
Data that may be reported in scientific journals or published will not include information that will identify you as a participant in this research study.

Research-related injury:

The research study will not cause any injury to you.

Persons to contact in the event of any problems or queries:

Please contact the researcher on 0832318233, my supervisor on 031 373 5423 or the Institutional Research administrator on 031 3732375. Complaints can be reported to the Director: Research and Postgraduate Support, Prof S Moyo on 031 3732577 or moyos@dut.ac.za

CONSENT

Statement of Agreement to Participate in the Research Study:

- I hereby confirm that I have been informed by the researcher, Fathima Motala, about the nature, conduct, benefits and risks of this study - Research Ethics Clearance Number _____.
- I have also received, read and understood the above written information (Participant Letter of Information) regarding the study.
- I am aware that the results of the study, including personal details regarding me sex, age, date of birth, initials and diagnosis will be anonymously processed into a study reports.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by the researcher.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.
- I understand that significant new findings developed during the course of this research which may relate to my participation will be made available to me.

_____ _____ _____ _____

Full Name of Participant **Date** **Time** **Signature/Right Thumb Print**

I, Fathima Motala, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

_____ _____ _____

Full Name of Researcher **Date** **Signature**

_____ _____ _____

Full Name of Witness (if applicable) Date **Signature**

_____ _____ _____

Full Name of Legal Guardian (if applicable) Date **Signature**

SYNTHESISE A

Inchwide Yolwazi kanye Nokuvuma

Isihloko socwaningo:
Ubuthi noma ubungozi obusezinsweni kanye nasegazini obudalwe ukusebenzisa imithi yokwelapha umdlavuza wesibeletho kanye nokwelashwa ngomshini wokushiswa(radiation). (Chemotherapy induced renal and haematological toxicities in patients with invasive cervical cancer undergoing concurrent chemo-radiation.)

Umncwaningi Ovelele:
Miss Fathima Motala, Umufundi obhalisele izifundo ze Master's Degree: Medical Laboratory Science kwisikhungo sezemfundo zase Durban University of Technology.

Umuphathi/Isekela Muphathi:

Dr Pavitra Pillay: PhD: Public Health
Dr Kamendran Govender: MBChB, MMED, MPhil

Ukuthula kafushane inhloso yocwaningo:
Uyamenywa ukuba ube yivolontiya kucwaningo. Ulwazi olukulencwadi luzokusiza ukuba uqonde ukuthi ucwaningo lungani nokuthi luzokwelekelela kanjani kulwazi. Uma kunemibuzo, engachazwanga kahle kulencwadi, sicela ungangabazi ukubuza umuncwaningi.
Iziguli ezithola lokukwelashwa ngesikhathi esifanayo zisebenzisa imithi kanye nemishini yokwelashwa (chemo-radiation) (CCRT) umdlavuza wesibeletho (invasive cervical cancer). Ngesikhathi besebenzisa lokukwelashwa izinso kanye negazi labo lingaba nobuthi noma libe sengozini. Inhloso yalolucwaningo ukuphenya ngokuthinteka kwezintso kanye negazi, kona kuzohlowa emagazini ozowahlolwa njengoba usebenzisa loku kwelashwa Kuyathembakala ukuthi lolucwaningo luzonikeza imiphumela noma ulwazi nokuqonda kangcono imiphumela yokwelashwa kwenani labantu bendawo. Lolulwazi lungasetshenziswa ukufundisa kangcono umuphakathi kanye nonompilo mayelana nobuthi bokusebenzisa lezizindlela zokwelashwa komdlavuza. (CCRT).

Inqubo yohlaka:

Ucwaningo luzophenya ngokuxhumana kobuthi obusezinsweni kanye nasegazini obenzeka uma welashelwa isifo somdlavuza wesibeletho.
Uma ufanelekile kucwaningo, imininingwane yakho njengesiguli izoqoqwa kanye nemiphumela yakho yezintso kanye negazi izobhekwa kabanzi ngesikhathi usathola ukwelashwa.

Kuyadingeka ukuba kutholwe kubhekwe izintso kanye negazi lakho kuqala ngaphambi kokuqala ukulashwa ngemithi uma imiphumela yakho isivumela. Ngeke kusadingeka ukuba uthole ezinye izindlela ezengeziwe noma kube nomuthethela omubi ngenxa yokubamba iqhaza kwakho kulolu-cwaningo.

Okuyinzuzo:
Kuthembakala ukuthil olucwaningo luzonikeza imiphumela noma bese lukhulisa ukuqonda kwethu ngokuxhumana kwezintso kanye negazi nesakhathi sokulashwa ngemithi yomdlavusa kanye nomshini (chemo-radiation).

Izizathu kungani ababambi qhaza bangayeka baphume kucwaningo:
Ukubamba kwakho iqhaza kulolucwaningo akuphoqelekile kungokokuzikhethela. Ukuyeka kwakho nganoma isiphi isikhathi angeke kube nomuthelela ekulashweni kwakho ngokwezempilo. Akukho ukuba yingozi okubandakanyekayo.

Amaholo:
Akukho iholo ngokubamba iqhaza.

Izindleko zocwaningo:
Uma ubambi'qhaza uzobhekana nezindleko ezijwayekile zesimiso zakhe zezempilo ezidingekayo; azikho izindleko ezengeziwe ezizodingeka.

Ukubayimfihlo:
Lonke ulwazi olutholiwe kulolu-cwaningo luzoqinisekiswa ukuthi luyimfihlo.
Imiphumela engabikwa kwiphephabhuku lososayensi noma lishicilelwe angeke libandakanye ulwazi oluzoveza wena njengesiguli kulolu cwaningo.

Idokodo lokuvuma

Isitatimende Sokuvuma ukubamba iqhaza kucwaningo:

- Ngiyuma ukungena kugcwaningo njengoba ngazisiwe ngohlobo ocwaningo ngokuchazelwa uFathima Motala. Research Ethics Clearance Number _____.
- Ngifundile, ngaqonda, nganeliseka mayelana nocwaningo. (Participant Letter of Information)
- Ngiyazi futhi ngiyaqonda ngemiphumela yocwaningo, kanye nemininingwane yami, ubulili, iminyaka, ilanga lokuzalwa, usuku engatholakala ngalo ukuthi nginomdlavuza akuyivela kuzohlala kuyimfihlo ekungenisweni kucwaningo.
- Ngokuqonda okulindeleke kucwaningo, ngiyavuma ukuthi idatha eliqoqiwe kucwaningo lufakwe ngumncwaningi kwi-computer.
- Kusukela luqala ucwaningo, ngaphandle kokucindezelwa, nokucwasa, ngingaphuma kuloucwaningo.
- Ngibe nethuba elanele lokubuza imibuzo ngalokho ngiyavuma ukungenelela ucwaningo ngaphandle kokuphoqwa ukungenele lolucwaningo.
- Ngiyaqonda ukubaluleka kwemiphumela yocwaningo ezotholakala ngalolucwaningo eqondene nami ngiyokwaziswa yona eqondene nami kulolucwaningo.

_____	_____	_____	_____
Igama lami	**Usuku**	**Isikhathi**	**Sayina/isithupha(right)**

Mina Fathima Motala, ngiyavuma ukuthi ongenele lolucwanongo ngimnikile incazelo yonke mayelana nobuhle nobungozi oluhambisana nocwaningo.

_____	_____	_____
Igama lomcwaningo	**Usuku**	**Sayina**
_____	_____	_____
Igama lofakazi (uma ekhona)	**Usuku**	**Sayina**
_____	_____	_____
Igama Logandale ngokusemthethweni	**Usuku**	**Sayina**

APPENDIX B

DEMOGRAPHICS AND CLINICAL DATA OF PATIENT

Study Record Number:

Date of Birth:

Age:

Ethnic group:

Residence-Urban/Rural:

Histology:

FIGO stage:

HIV status:

CD4 count:

On antiretroviral therapy:

TREATMENT PROTOCOL FOR CERVICAL CANCER:

_____

_____

_____

Any other illnesses: _____

_____

On any other treatment: _____

_____

APPENDIX C

Institutional Research Ethics Committee
Research and Postgraduate Support Directorate
2nd Floor, Berwyn Court
Gate 1, Steve Biko Campus
Durban University of Technology

P O Box 1334, Durban, South Africa, 4001

Tel: 031 373 2375
Email: lavishad@dut.ac.za
http://www.dut.ac.za/research/institutional_research_ethics

www.dut.ac.za

21 September 2018

Ms F Motala
68 Modem Bristow Crescent
Mayville
4091

Dear Ms F Motala

Chemotherapy induced renal and haematological toxicities in patients with invasive cervical cancer undergoing concurrent chemo-radiation

I am pleased to inform you that **PROVISIONAL APPROVAL** has been granted to your proposal.

- Obtaining and submitting the necessary gatekeeper permission/s to Institutional Research Ethics Committee (IREC).

PLEASE NOTE THAT THIS IS NOT A FINAL APPROVAL LETTER. KINDLY SUBMIT THE ABOVE MENTIONED DOCUMENTS WITHIN THREE MONTHS TO THE IREC OFFICE. DATA COLLECTION CAN ONLY COMMENCE WHEN IREC ISSUES FULL APPROVAL

The Proposal has been allocated the following Ethical Clearance number **IREC 116/18**. Please use this number in all communication with this office.

Approval has been granted for a period of two years, before the expiry of which you are required to apply for safety monitoring and annual recertification. Please use the Safety Monitoring and Annual Recertification Report form which can be found in the Standard Operating Procedures [SOP's] of the IREC. This form must be submitted to the IREC at least 3 months before the ethics approval for the study expires.

Yours Sincerely

Professor J K Adam
Chairperson: IREC

Institutional Research Ethics Committee
Research and Postgraduate Support Directorate
2nd Floor, Berwyn Court
Gate 1, Steve Biko Campus
Durban University of Technology

P O Box 1334, Durban, South Africa, 4001

Tel: 031 373 2375
Email: lavishad@dut.ac.za
http://www.dut.ac.za/research/institutional_research_ethics

www.dut.ac.za

31 October 2018

Ms F Motala
68 Modem Bristow Crescent
Mayville
4091

Dear Ms F Motala

Chemotherapy induced renal and haematological toxicities in patients with invasive cervical cancer undergoing concurrent chemo-radiation

The Institutional Research Ethics Committee acknowledges receipt of your gatekeeper permission letters.

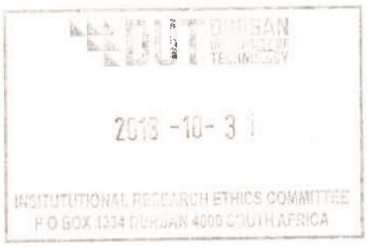
Please note that FULL APPROVAL is granted to your research proposal. You may proceed with data collection.

Any adverse events [serious or minor] which occur in connection with this study and/or which may alter its ethical consideration must be reported to the IREC according to the IREC Standard Operating Procedures (SOP's).

Please note that any deviations from the approved proposal require the approval of the IREC as outlined in the IREC SOP's.

Yours Sincerely,

Professor J K Adam
Chairperson: IREC



APPENDIX D

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X08, Mayville, 4058
Tel: 0312401059 Fax: 0312401050 Email: ursulanun@ialch.co.za
www.kznhealth.gov.za

Office of The Medical Manager
IALCH

25 September 2018

Ms F Motala
68 Modem Bristow Crescent
Mayville
4091

Dear Ms Motala

Re: Approved Research: Ref No: IREC 116/18: Chemotherapy induced renal and haematological toxicities in patients with invasive cervical cancer undergoing concurrent chemo-radiation.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langalibalele Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg, 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

Dr L P Mtshali pp
Medical Manager

APPENDIX E

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:
Office of The Medical Manager
IALCH

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X08, Mayville, 4058
Tel: 0312401059 Fax: 0312401050 Email: ursulanun@ialch.co.za
www.kznhealth.gov.za

Reference: IREC 116/18
Enquiries: Medical Management

25 October 2018

Ms F Motala
68 Modem Bristow Crescent
Mayville

Dear Ms Motala

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **Chemotherapy induced renal and haematological toxicities in patients with invasive cervical cancer undergoing concurrent chemo-radiation**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

.....

Dr L P Mtshali pp
Medical Manager

APPENDIX F

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:
Health Research & Knowledge Management

Physical Address: 330 Langalibalele Street, Pietermaritburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

NHRD Ref: KZ_201810_008

Dear Ms F. Motala
DUT

Approval of research

1. The research proposal titled **'Chemotherapy induced and haematological toxicities in patients with invasive cervical cancer undergoing concurrent chemo-radiation'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.
   b. Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.
   c. Provide an interim progress report and final report (electronic and hard copies) when your research is complete to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Dr E Lutge
Chairperson, Health Research Committee
Date: 25/10/18

Fighting Disease, Fighting Poverty, Giving Hope

APPENDIX G

Cooperative Group Common Toxicity Criteria (Radiation Therapy Oncology Group 2019)

Instructions

1. Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When two criteria are available for similar toxicities, the one resulting in the more severe grade should be used.
3. Toxicity grade = 5 if that toxicity caused the death of the patient.
4. Refer to detailed toxicity guidelines in the protocol, or to RTOG Headquarters for toxicity not covered on this table.
5. The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.
6. An accurate baseline prior to start of therapy is necessary.

	TOXICITY	- 0 -	- 1 -	- 2 -	- 3 -	- 4 -
Blood/Bone Marrow	WBC	>=4.0	3.0-3.9	2.0-2.9	1.0-1.9	<1.0
	Platelets	WNL	75.0 - normal	50.0 - 74.9	25.0 - 49.9	<25.0
	Haemoglobin	WNL	10.0 - normal	8.0 - 10.0	6.5 - 7.9	<6.5
	Granulocytes/Bands	>=2.0	1.5 - 1.9	1.0 - 1.2	0.5 - 0.9	<0.5
	Lymphocytes	>=2.0	1.5 - 1.9	1.0 - 1.2	0.5 - 0.9	<0.5
	Haemorrhage (Clinical)	None	Mild, no transfusion	Gross, 1-2 unit's transfusion per episode	Gross, 3-4 unit's transfusion per episode	Massive, 3-4 unit's transfusion per episode
	Infection	None	Mild	Moderate	Severe	Life-threatening
Gastro- intestinal	Nausea	None	Able to eat/ reasonable intake	Intake significantly decreased but can eat	No significant intake	-------
	Vomiting	None	1 episode in 24 hours	2-5 episodes in 24 hours	6-10 episodes in 24 hours	>10 episodes in 24 hours or requiring parenteral support
	Diarrhea	None	Increase of 2-3 stools per day over pre-Rx	Increase of 4-6 stools/day, or nocturnal stools, or moderate cramping	Increase of 7-9 stools/day or incontinence or severe cramping	Increase of >=10 stools/day or grossly bloody Diarrhea, or need for parenteral support
	Stomatitis	None	Painless ulcers, erythema or mild soreness	Painful erythema, edema or ulcers but can eat	Painful erythema, edema or ulcers and cannot eat	Requires parenteral or enteral support
Liver	Bilirubin	WNL	-------	<1.5 X N	1.5 - 3.0 X N	>3.0 X N
	Transaminase (SGOT, SGPT)	WNL	<=2.5 X N	2.6 - 5.0 X N	5.1 - 20.0 X N	>20.0 X N
	Alkaline Phosphatase or S'nucleotidase	WNL	<=2.5 X N	2.6 - 5.0 X N	5.1 - 20.0 X N	>20.0 X N

	Liver/clinical	No change from baseline	-------	-------	Precoma	Hepatic coma
Kidney/ bladder	Creatinine	WNL	<1.5 X N	1.5 - 3.0 X N	3.1 - 6.0 X N	>6.0 X N
	Proteinuria	No change	1 + or < 0.3 g% or <3 g/1	2 - 3+ or 0.3 - 1.0 g% or 3 - 10 g/1	4+ or >1.0 g% or >10 g/1	Nephrotic syndrome
	Haematuria	Negative	Micro only	Gross/no clots	Gross + clots	Requires transfusion
	Alopecia	No loss	Mild hair loss	Pronounced or total hair loss	-------	-------
	Pulmonary	None or no change	Asymptomatic with abnormality in PFTUs	Dyspnea on significant exertion	Dyspnea at normal level of activity	Dyspnea at rest
Heart	Cardiac dysrhythmias	None	Asymptomatic/ transient/ requiring no therapy	Recurrent or persistent/ no therapy required	Requires treatment	Requires monitoring or hypotension or ventricular tachycardia or fibrillation
	Cardiac function	None	Asymptomatic/ decline of resting ejection fraction by <20% of baseline value	Asymptomatic/ decline of resting ejection friction by >20% of baseline value	Mild CHF, responsive to therapy	Severe or refractory CHF
	Cardiac/ ischemia	None	Non-specific T-wave flattening	Asymptomatic/ST and T wave changes suggesting ischemia	Angina without evidence for infarction	Acute myocardial infarction
	Cardiac/pericardial	None	Asymptomatic effusion/ no intervention required	Pericarditis (rub, chest pain, ECG changes	Symptomatic effusion: drainage required	Tamponade/ drainage urgently required
Blood Pressure	Hypertension	None or no change	Asymptomatic/ transient increase by	Recurrent or persistent increase by >20 mm Hg	Requires therapy	Hypertensive crisis

			>20 mm Hg (d) or to >150/100 if previously WNL/ No treatment required	(D) or to >150/100 if previously WNL/ No treatment required		
	Hypotension	None or no change	Changes requiring no therapy/ including transient orthostatic hypotension	Requires fluid replacement or other therapy but not hospitalization	Requires therapy and hospitalization/ resolves within 48 hours of stopping the agent	Requires therapy and hospitalization for >48 hrs after stopping the agent
Neurologic	Neurological / sensory	None or no change	Mild paresthesias / loss of deep tendon reflexes	Mild or moderate objective sensory loss/ moderate paresthesias	Severe objective sensory loss or paresthesias that interfere with function	-------
	Neurological / motor	None or no change	Subjective weakness/ no objective findings	Mild objective weakness without significant impairment of function	Objective weakness with impairment of function	Paralysis
	Neurological / cortical	None	Mild somnolence or agitation	Moderate somnolence or agitation	Severe somnolence, agitation, confusion, disorientation or hallucinations	Coma, seizures, toxic paralysis
	Neurological / cerebellar	None	Slight incoordination/ dysdiadokinesis	Intention tremor, dysmetria, slurred speech, nystagmus	Locomotor ataxia	Cerebellar necrosis

	Neurological / mood	No change	Mild anxiety or depression	Moderate anxiety or depression	Severe anxiety or depression	Suicidal ideation
	Neurological / headache	None	Mild	Moderate or severe but transient	Unrelenting and severe	-------
	Neurological / constipation	None or no change	Mild	Moderate	Severe	Ileus >96 hours
	Neurological /hearing	None or no change	Asymptomatic/ hearing loss on audiometry only	Tinnitus	Hearing loss interfering with function but correctable with hearing aid	Deafness not correctable
	Neurological /vision	None or no change	-------	-------	Symptomatic subtotal loss of vision	Blindness
	Skin	None or no change	Scattered macular or papular eruption or erythema that is asymptomatic	Scattered macular or papular eruption or erythema with pruritis or other associated symptoms	Generalized symptomatic macular, papular, or vesicular eruption	Exfoliative dermatitis or ulcerating dermatitis
	Allergy	None	Transient rash/drug fever <38°C, 100.4°F	Urticaria, drug fever = 38°C, 100.4°F/ mild bronchospasm	Serum sickness, bronchospasm, requiring parenteral medication	Anaphylaxis
	Fever in absence of infection	None	37.1 - 38.0°C, 98.7 - 100.4°F	38.1 - 40.0°C, 100.5 - 104.0°F	>40.0°C/>104.0°F for less than 24 hours	>40.0°C/104.0°F for more than 24 hrs or fever accompanied by hypertension
	Local	None	Pain	Pain and swelling with inflammation or phlebitis	Ulceration	Plastic surgery indicated

	Weight gain/loss	<5.0%	5.0 - 9.9%	10.0 - 19.9%	>=20.0%	-------
Metabolic	Hyperglycaemia	<116	116-160	161-250	251 - 500	>500 or ketoacidosis
	Hypoglycaemia	>64	55-64	40-54	30-39	<30
	Amylase	WNL	<1.5 X N	1.5 - 2.0 X N	2.1 - 5.0 X N	>5.1 X N
	Hypercalcemia	<10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.5	>=13.5
	Hypocalcaemia	>8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	<=6.0
	Hypomagnesemia	>1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	<=0.5
Coagulation	Fibrinogen	WNL	0.99 - 0.75 X N	0.74 - 0.50 X N	0.49 - 0.25 X N	<=0.24 X N
	Prothrombin time	WNL	1.01 - 1.25 X N	1.26 - 1.50	1.51 - 2.00 X N	>=2.00 X N
	Partial thromboplastin time	WNL	1.01 - 1.66 X N	1.67 - 2.33 X N	2.34 - 3.00 X N	>3.00 X N