Comparison of the Costs of Treating Prostate Cancer with Standard Chemotherapy Regimens versus Targeted Nuclear Medicines

by

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Submitted in partial fulfilment of the requirements for the degree of
Master of Pharmacy (Pharmacoeconomics) in the
Discipline of Pharmaceutical Sciences, College of Health Sciences,
University of KwaZulu-Natal

May 2020

Candidate's Declaration

I, Nomaswazi C. Gabela **(214571801),** hereby declare that:

i. The research reported in this dissertation, except where otherwise indicated, is my own original work.

ii. The work described in this dissertation has not been submitted to the University of KwaZulu-Natal (UKZN) or other tertiary institutions for purposes of obtaining an academic qualification, whether by myself or any other party.

iii. This dissertation does not contain any other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons or organisation.

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Date: 8th May 2020

Supervisor's Declaration

As the candidate's supervisor of research, I, **Revd. Dr Lehlohonolo J. Mathibe**, agree to the submission of this dissertation.

Supervisor: Revd. Lehlohonolo J. Mathibe, PhD

Signature: 

Date: 8th May 2020

International Conference Presentation

Nomaswazi Gabela & Lehlohonolo J. Mathibe. "*Cost-Benefit Analysis and Prescribing Patterns of ^{177}Lu-n.c.a-PSMA at Selected Tertiary Hospitals in South Africa*". A podium presentation at the **10th International Conference on ISOTOPES (10ICI)**, Kuala Lumpur, Malaysia in February 2020.

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Acknowledgements

I would like to thank the following people, without whom this research would not have been completed:

- My research supervisor, Revd. Lehlohonolo Mathibe (PhD), for his continuous guidance, leadership and encouragement throughout this process. I am forever grateful.
- My mentor and advisor, Ms Mapula Letsoalo, who took an interest and guided me with the nuclear medicine concept.
- The Scientists at NTP Radioisotopes, Dr. Otto Knoesen and Andile Ntlokwana for all the assistance with the radioisotopes information and knowledge imparted.
- Professor Mike Sathekge and Ms Cindy Davis at the Steve Biko Hospital, Nuclear Medicine Department, for opening your doors and making this study a reality.
- Dr Shona Bhadree and Dr Nozipho Nyakale of the Oncology and Nuclear Medicine Departments at the Inkosi Albert Luthuli Central Hospital, for opening your doors and making this study a reality.
- Lastly, but not least, my humble gratitude goes to Tanya Francis, at Annually Managed Expenditure (AME) Healthcare Africa, Information Technology department, Inkosi Albert Luthuli Central Hospital, for selflessly and unconditionally assisting with the patient data, and going an extra mile to discuss and assist with all the costing issues. I am indeed, eternally grateful.

To all of you, without you, this work would not have been possible! I thank you, from the bottom of my heart.

Dedication

This work is dedicated to the Almighty God for enabling me to go through this process; for His strength, guidance and wisdom. I also dedicate it to my husband, Mandla Gabela, and my children -- Smiso, Nokukhanya and Sbongumusa, for their continued support and patience, throughout this journey.

List of Abbreviations

3-D	3-Dimension
3-DMB	3-D Mapping Biopsy
ABC Model	Activity Based Costing Model
AIDS	Acquired Immunodeficiency Virus
APAF-1	Apoptotic Protease Activity Factor 1
AR	Androgen Receptor
BC	Breast Cancer
BPH	Benign Prostatic Hyperplasia
BRCA	Breast Cancer Gene
CANSA	Cancer Association of South Africa
Caspases	Cysteine aspartate protease enzymes
CBA	Cost Benefit Analysis
CCC	Clear–Cell Carcinoma
CC	Colorectal Cancer
CCa	Cervical Cancer
CCL2	Chemokine Ligand 2
CEA	Cost Effectiveness Analysis
CLR	C-type lectin receptors
CSCs	Cancer Stem Cells
CMA	Cost Minimisation Analysis
CT	Computed Tomography
CUA	Cost Utility Analysis
CXCL8	Chemokine ligand 8

DNA	Deoxyribonucleic Acid
DM	Diabetes Mellitus
DoH	Department of Health
DRE	Digital Rectal Examination
EBRT	External Beam Radiation Therapy
EBV	Epstein Barr Virus
EC	Endometrioid Carcinoma
EGF	Epidermal growth factor
ER	Estrogen receptor
GEP–NET	Gastro-Entero-Pancreatic–Neuroendocrine Tumours
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HER2	Human epidermal growth factor receptor 2
HGSC	High Grade Serous Carcinoma
HICs	High Income Countries
HIV	Human Immunodeficiency Virus
H. pylori	*Helicobacter pylori*
I	Iodine
IALCH	Inkosi Albert Luthuli Central Hospital
ICD	International Classification of Diseases (ICD)
IL-1	Interleukin - 1
IL-6	Interleukin - 2
IL-17	Interleukin -17
IL-23	Interleukin -23

IPD	In-patient Department
KZN	KwaZulu-Natal
LC	Lung Cancer
LCa	Liver Cancer
LGSC	Low grade serous Carcinoma
LMIC	Low and Medium Income Countries
LRP	Laparoscopic Radical Prostatectomy
Lu	Lutetium
Lu-177-n.c.a	Lutetium -177-non-carrier added
LuPRLT	Lutetium PSMA Radiological Therapy
MC	Mucinous Carcinoma
MCC	Medicines Control Council
mCRPC	Metastatic castration-resistant Prostate cancer
MEDRECON	Medical record number
MHSPC	Metastatic hormone sensitive prostate cancer
NCA	Non Carrier Added
NDoH	National Department of Health
NF-κB	Nuclear factor kappa B
NO	Nitric Oxide
NOD-Like	Nucleotide binding oligomerisation domain like receptors
NSCLC	Non–Small Cell Lung Cancer
NTP	Nuclear Technology Products
OPD	Out-Patient Department
PAMP	Pathogen – associated molecular patterns
PCa	Prostate Cancer

PSA	Prostate specific antigen
PSMA	Prostate specific membrane antigen
PR	Progesterone receptor
PRR	Pattern recognition receptors
QALYs	Quality-adjusted-life-years
QoL	Quality of life
ROS	Reactive oxygen species
RP	Radical Prostatectomy
RSA	Republic of South Africa
SA	South Africa
SC	Stomach Cancer
SCLC	Small Cell Lung Cancer
SOC	State-owned company
SSA	Sub-Saharan Africa
STAT3	Signal transducer and activator of transcription
TLRs	Toll Like Receptors
TNBC	Triple-negative breast cancers
TNF-α	Tumour necrosis factor - alpha
TNM	Stage, Nodal, Distant metastasis
TREMs	Triggering receptors expressed on myeloid cells
TRUS	Trans–rectal Ultrasound
ULS	Ultrasound
UK	United Kingdom
UPFS	Uniform Patient Fee Schedule
US	United States

USA	United States of America
UV	Ultra Violet
VIA	Visual inspection with acetic acid.
WHO	World Health Organisation
XMRV	Xenotropic MuLV–related virus

Scientific Symbols and Units

β	Beta
€	Euros
ϒ	Gamma
mL	millilitre
mmHg	millimeter of mercury
%	percentage
£	Pounds
Sec	second
mL/sec	millilitre/second
Ng	Nano grams
Ng/mL	Nano grams/mL
R	Rand
$	Dollar (US)
mg	Milligram
Kev	Kilo electron volts
Gbq/mg	Gigabecquerel/milligram

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ABSTRACT

Background: Healthcare costs for the treatment of mCRPC continue to rise year on year. However, with the advent of targeted Nuclear medicine and continued treatment with standard chemotherapy regimen for the treatment of mCRPC the costs are still not known.

Aim: We sought to compare the costs of treating mCRPC with standard chemotherapy regimen versus targeted Nuclear Medicine.

Methods: We conducted a retrospective and prospective inferential study on patients, diagnosed with mCRPC, aged >18 years at Steve Biko Academic Hospital (SBAH), Pretoria and Inkosi Albert Luthuli Central Hospital (IALCH) in Durban, South Africa. The patients were referred to the treatment centres between the periods 1 January 2017 and 24 November 2019. We employed the International Classification of Diseases, 10th Revision Code system to identify mCRPC patients and match them with their Medical Record Number using MediTech^{TM} computer Software program at IALCH, and a thorough patient file audit at SBAH was used to identify patients who were treated for mCRPC in this hospital during the study period. Treatment, Imaging, Screening, Out-patient and hospitalisation costs were extracted from the MediTech^{TM} system using the Activity Based Costing Model and costs were compared to the costs derived from the patient files for the Nuclear Medicine patients.

Results: A total of 60 patients (n=49, Chemotherapy Cohort, and n=11, Nuclear Medicine Cohort) with mCRPC, Mean ages at diagnosis 66 and 61 years respectively. The most common chemotherapy used were Bicalutamide, Goserelin and Docetaxel, compared to one comparator Lu-PSMA-Radioligand. The total healthcare costs for Chemotherapy were estimated at 500 000USD ($), whilst the costs for Lu-PSMA-Radioligand averaged 184 000USD ($). Imaging costs for chemotherapy were 37% higher than Lu-PSMA costs, in- hospital and out-patient costs accounted for 88% of the total healthcare costs.

Conclusions: For the treatment of metastatic resistant Prostate Cancer, patients treated with Chemotherapy regimen incur more cost for chemotherapy (43%) and imaging (37%) than patients treated with targeted nuclear medicine. Chemotherapy treated patients experience more in-patient and out-patient days compared to patients treated with targeted nuclear medicine. There are significantly more chemotherapy cycles and drug combinations that contribute to the higher chemotherapy costs.

CHAPTER 1: Introduction and Literature Review

1.1 Cancer

The World Health Organization (WHO) defines cancer as a large and diverse group of deadly disease, which is characterised by the abnormal multiplication and growth of the body's own cells (WHO, 2018). Cancer is expected to rank as the leading cause of death and the single most important barrier to increasing life expectancy in every country of the world in the 21st century (Bray *et al.,* 2018). This disease constitutes a major public health burden globally. An increasing trend has been observed over the past 20 years in the new cases and deaths from different cancer worldwide, especially in low-and middle-income countries (LMICs), owing to varying lifestyles, behavioural patterns and geographic and environmental factors (Adeloye *et al.,* 2016).

Carcinogenesis is recognised as a multistep process in which a series of genetic alterations occurs within a cell, and through processes of promotion and progression, leads to malignancy (Rubin & Williams, 2001). It is also reported that cancer cells do not respond to the normal processes that regulate cell growth, proliferation, and survival, and they cannot carry out the physiological functions of their normal differentiated (mature) counterparts (Koda-Kimble *et al*., 2009).

Cancer can be classified as benign or malignant. Benign cancers are usually localised to the organs or sites where they occur, and they are generally easier to manage and are less fatal. However, malignant cancers have the ability to migrate beyond their usual boundaries and can cause death (WHO "2018"). Malignant cancer cells have been observed to exhibit self-sufficiency in growth signals. They are also due to insensitivity to apoptotic stimuli such as the apoptotic protease activity factor-1 (APAF-1), as was reported by Sun & Peng (2009). The apoptotic protease activity

factor-1 usually binds to cysteine aspartate protease enzymes 9 (caspase-9), which activates cell death. Thereafter, caspase-3 is believed to play a critical role in execution of cell death (Sun & Peng, 2009). As a result of weakened inhibitory signalling pathways in aberrant cells, proliferation becomes uncontrollable. Furthermore, a sustained pathological angiogenesis causes cancer growth by enabling capillary blood supply, with oxygen and nutrients, to the tumour area (Vassilev & DePamphilis, 2017). This brings about unsustainable tumour growth and metastasis to distant sites utilising unusual metabolic pathways to generate energy needed by the cells in order to survive and to thrive (Warburg, 1931).

1.1.1 Cancer Aetiology

The WHO and numerous other researchers reported that there are at least five groups of factors that are considered as the main causes of cancer; environmental factors (i.e., "modifiable risk factors"), genetic predispositions (WHO, Fact Sheet No: 297, 2015), some medical therapies (e.g. cytotoxic chemotherapy, immunosuppressive therapy or radiation therapy, (Koda–Kimble *et al*., 2009), chronic inflammation and "cancer stem cells" (CSC). The latter was espoused recently by Tomasetti & Vogelstein (2015). Recently, Vassilev and colleagues (2017) reported that some tissues give rise to human cancers millions of times more often than other tissue types either through random mutations (intrinsic factors) or due to exposure to viruses, chemical carcinogens and radiation (extrinsic factors), during a person's lifetime (Vassilev *et al.*, 2017).

1.1.1.1 Environmental Factors

Youlden and colleagues (2008) have cited environmental factors such as smoke, asbestos, air pollution, coal heating, combustible material, tobacco use, alcohol use, infection (bacterial and

viral) ionisation irradiation and outdoor particulate matter to be associated with a variety of cancers which include lung and liver cancers (Youlden *et al*., 2008).

Key (1994), described cigarette smoking as a major cause of lung cancer. Dietary factors such as high intake of meat or animal fat have been associated with colorectal and prostate cancers. Other than diet, sedentary lifestyles have also been linked to many cancers including the prostate and liver cancers. Torre and colleagues (2016), listed occupational exposure such as asbestos and air pollution amongst the causes of lung cancer. Importantly, smoking has been widely accepted as one of the main causes of lung cancer and colorectal cancer.

Predisposition to bacteria and viruses such as *Helicobacter pylori* and human papillomavirus (HPV) cause stomach and ovarian cancer, respectively. Viruses such as Hepatitis B and C predispose individuals to liver cancer (Torre *et al*., 2016).

1.1.1.2 Genetic Predisposition

Over recent decades, a number of genes that cause predisposition to cancer have been identified (Turnbull & Hodgson, 2005). These authors further have also reported that in the majority of families, the increased incidence of cancers is due to multifactorial aetiology with a number of lower penetrance cancer predisposition genes interacting with environmental factors.

Genetic mutations due to dietary habits and certain medications (e.g. hormone replacement therapy) have been found to be associated with a variety of cancer (Youlden *et al.*, 2008). In a study conducted by Torre *et al.* (2015), genetic makeup, being overweight/obesity, growth, ethnicity, and ageing population and changing reproductive patterns associated with urbanisation

and economic development were reported to be associated with certain cancers such as breast and ovarian and prostate cancers.

Ethnicity, such as being black or African American, has been associated with predisposition to prostate cancer (Key, 1994). Turnbull & Hodgson, (2005) have also reported that alterations in germ line cancer predisposition genes, namely; tumour suppressor genes (TSG) and oncogenes (OG), have been found to be associated with inherited cancer predisposition.

It was reported by Koda-Kimble and colleagues (2009) that damage to cellular DNA can result in mutations that lead to the development of oncogenes and loss or inactivation of tumour suppressor genes. These authors further stated that oncogenes arise from normal genes called proto – oncogenes through genetic alterations such as chromosomal translocations, deletions, insertions and point mutations. It is their over activity or presence in certain forms that may lead to the development of cancer (Koda-Kimble *et al*., 2009).

Rubin and Williams (2001) also reported that intrinsic cellular oncogenes, growth suppressor genes and the dysregulation of steps that control cell cycle, cell proliferation, and differentiation through gene expression play interactive roles that transform normal cells into a premalignant state and ultimately into malignancy.

The tumour suppressor genes have been defined by Koda–Kimble *et al*.,(2009) as normal genes that encode for proteins that suppress inappropriate cell division or growth. It is reported by these authors that gene losses or mutations of these genes can cause these proteins to become inactivated, eliminating the normal inhibition of cell division. It is therefore believed that multiple genetic

mutations, including activation of oncogenes and loss or inactivation of tumour suppressor genes within a cell, are necessary for malignant transformation (Koda-Kimble *et al*., 2009).

Injury to cells and microbial infection initiate a cascade of inflammatory processes. However, inadequate anti-inflammatory response or repeated infections may predispose human cells to chronic inflammation (Medzhitov, 2010). The events that lead to chronic inflammation are discussed below.

1.1.1.3 Chronic Inflammation

It is estimated that the underlying infections and inflammatory responses cause 15-20% of all deaths from cancer worldwide (Mantovani *et al*., 2008). Therefore, numerous studies have been conducted dating back to the 19th century to elucidate the link between cancer and chronic inflammation. Observations of infections with a number of microorganisms such as *Helicobacter. pylori*, Epstein Bar virus (EBV) and Schistosoma species, to name a few, have been associated with various cancer types and there is a strong suggestion that chronic inflammation is involved in tumour initiation, promotion and progression (Lin & Karin, 2007). Immune deregulation and autoimmunity have also been found to precede tumour development (Grivennikov *et al*., 2010).

Medzhitov (2010) describes the inflammatory process as a pathway that consists of inducers, sensors, mediators and target tissues. An infection or injury to the cell initiates the inflammatory response, and this induction is detected by the sensors such as Toll-like receptors (TLRs) expressed on tissue, resident macrophages, dendritic cells and mast cells (Medzhitov, 2010). The receptors recognise pathogen-associated molecular patterns (PAMP), such as cell wall components and nucleic acids (Lin & Karin, 2007). Microbial detection is achieved through germ line-encoded pattern-recognition receptors (PRRs). These receptors survey both the intracellular and

extracellular space for microbial determinants that serve as indicators of infection and induce the innate immune responses to protect from infectious threats (Medzhitov 2010). Lin and colleague further stated that PPRs include TLRs, nucleotide-binding oligomerization domain like (NOD-like) receptors, C-type lectin receptors (CLRs) and triggering receptors expressed on myeloid cells (TREMs) (Lin & Karin, 2007). The interaction between PAMPs and PPRs results in the activation of inflammatory cells and initiation of host responses whose major purpose is to eliminate and kill invading organisms. However, inadequate pathogen eradication, prolonged inflammatory signalling, and defects in anti-inflammatory mechanisms can all lead to chronic inflammation and benefit tumour development (Lin & Karin, 2010).

In the main, the production of mediators such as cytokines, chemokines (CCL2 & CXCL8), bioactive amines, eicosanoids and products of proteolytic cascades such as bradykinin, as well as prostaglandins have been associated with cancer. Notably, Interleukin-1 (IL-1), Interleukin-6 (IL-6), and Interleukin-17 (IL-17) are potent inflammatory cytokines that have been linked with tumourigenesis (Medzhitov, 2010). In particular, IL-6 promotes inflammation, tissue damage, compensatory cell proliferation and ultimately formation of tumour (Grivennikov *et al*., 2010). It has also been observed that the downstream mediators us as STAT3 and NF-κB, activate genes that control cell survival, proliferation, angiogenesis and invasion. More importantly, Calcinotto and colleagues (2018) have recently demonstrated that Interleukin-23 (IL-23) is the inflammatory cytokine that play a major role in the development of resistant prostate cancer (Calcinotto *et al*., 2018).

1.1.1.4 Cancer Stem Cell

In a study by Tomasetti and Vogelstein (2015), it was reported that many genomic changes occur simply by chance during normal deoxyribonucleic acid (DNA) replication, rather than as a result

of carcinogenic factors. This is because most cells in tissues are partially or fully differentiated cells and are typically short-lived, and unlikely to initiate a tumour. Therefore, cancer results from genetic mutations that are either inherited or acquired through DNA replication errors and environmental insults (Vassilev *et al*., 2017). However, it can also be as a result of stem cells that retain their ability to proliferate repeatedly (Vassilev *et al*., 2017).

The stem cells are the only cells that can self-renew and are responsible for the development and maintenance of the tissue's architecture. Therefore, they have the capacity to initiate the tumour (Tomasetti & Vogelstein, 2015). It was also stated by Tomasetti & Vogelstein (2015) that three mutations occur every time a normal human cell divides, as a result an inference was made to conclude that the root causes of the correlation between stem cell division and cancer incidences were the driver gene mutations that randomly result from these cell divisions.

1.1.2 Epidemiology and Global Burden of Cancer

Globocan (2018), data indicate that cancer incidences and mortality are rapidly growing worldwide, and the reasons are complex, with aging, growth population as well as changes in the prevalence and distribution of the main risk factors for cancer, several of which are associated with socio-economic development, being at the centre of this epidemic (Bray *et al.,* 2018). In 2012 alone, there were 14.1 million new cases and 8.2 million deaths from cancer globally, and this burden is expected to rise with over 75 million prevalent cases, 27 million incident cases, and 17 million cancer deaths expected globally by 2030 (Adeloye *et al.,* 2016). Recently, Fitzmaurice (2018) reported that 7.2 million cancer cases were reported in 2016 worldwide and 8.9 million deaths. Most new cases of cancer are now found in Africa and LMICs, increasing from 15% in 1970, to 56% in 2008, and projected to reach about 70% by 2030 (Adeloye *et al.,* 2016).

Cancer constitutes an enormous burden on society across the world. Recent studies have reported that the prevalence of cancer is increasing mainly because of the growth and rapid aging of the global populations (Torre *et al.,* 2015; Martins, 2016). Smoking, obesity, physical inactivity, and changing reproductive patterns, urbanisation and economic development have also been associated with high incidences of cancer in the western developed world (Torre *et al.,* 2015).

1.1.2.1 Cancer Incidences Globally

Globally, cancer is the second leading cause of death and accounted for 8.8 million deaths in 2015 (WHO, 2017). Lung, prostate, colorectal, stomach and liver cancers are the most common types of cancer in men, while breast, colorectal, lung, cervix and stomach cancers are the most common among women (WHO, 2017). Over the years, the burden has shifted towards the less developed countries, which currently account for about 57% of cases and 65% of cancer deaths worldwide (Torre *et al*., 2015). It is reported that lung cancer is the leading cause of cancer death among males in both more and less developed countries, and has surpassed breast cancer as the leading cause of cancer death among females in more developed countries (Torre *et al*., 2015).

1.2.1.2 Cancer Incidences in sub-Saharan Africa

Lorenzino and colleagues (2018), recently reported that there were 626 399 new cancer cases in sub-Saharan Africa in 2012 (Lorenzino *et al*., 2018). This represents 4.4% of the 14.1 million new cancer cases globally. This is almost the same number (i.e., 667 000) of cancer cases that was estimated to have occurred in 2008 for the whole of Africa. Meaning, the sub-Saharan region accounts for the bulk of cases and deaths due to cancer in Africa.

1.2.1.3 Cancer Incidences in South Africa

South Africa, in particular, has been ranked 50th on the World Cancer Research Fund's list of countries with the highest cancer prevalence rates (CANSA, 2018). Furthermore, the South African Medical Research Council reported that in 2012 cancer was the fifth leading cause of death in South Africa, causing 8.7% of all reported deaths (CANSA, 2018). However, prevalence patterns of cancer in South Africa are similar to global trends although local data is insufficient due to under-reporting (Singh *et al*., 2015). For example, prostate cancer is also the leading organ-specific cancer diagnosed amongst South African men followed by lung, oesophagus, colon/rectum and bladder cancer. Amongst South African women too, breast cancer is the most prevalent cancer, followed by cervical, uterus, colorectal and oesophageal cancers (CANSA, 2018).

In South Africa, 6807 cases of prostate cancer, 1839 of colorectal and 1743 of lung cancer were reported in 2012 in South African men, accounting for 18.45%, 4.98% and 4.72% respectively. 8203 cases of breast cancer, 5785 cervical cancer cases and 1558 colorectal cases were reported in South African women, accounting for 21.79%, 15.37% and 4.14% of cancer cases respectively (CANSA, 2018).

1.2 Prostate Cancer (PCa)

Underwood & Cross (2009) defined prostate cancer as an adenocarcinoma that occurs in men usually above 50 years of age. It is reported by the authors that the tumour is rare below the age of 50 years of age, with the peak incidence between the ages of 65 – 75 years (Underwood & Cross, 2009). The prostate is a gland in the male reproductive system, located below the man's bladder and is responsible for the secretion of the seminal fluid (Shalini *et al*., 2011). This fluid acts as a

nutrient rich transport medium for sperm, produced by the testes. The hormone testosterone influences the prostate. The prostate is about the size of a walnut, estimated to weigh 20g to 25g as reported by De Vita *et al*., 2015). The authors further state that the seminal fluid is rich in Prostate Specific Antigen (PSA). It is reported by the same, that the prostate is located deep in the pelvis between the bladder and the external urinary sphincter, anterior to the rectum below the pubis. It is because of this location, which is a critical anatomic juncture, that it is believed that cancers of the prostate and the treatment thereof, place urinary, sexual and bowel function at risk (De Vita, *et al*., 2015)

Rubin & Williams (2001) reported that the normal anatomy of the prostate is considered to be made up of anatomic zones, namely, the peripheral zone (makes up 70% of the glandular tissues of the prostate gland), the central zone (surrounds the ejaculatory ducts), and the transition zone (surrounds the urethra). In addition to these zones, there is a non-glandular anterior fibromuscular stroma (Rubin & Williams, 2001; De Vita, *et al*., 2015).

The peripheral zone has been reported to be the region most prone to the development of carcinomas, whilst very few cancers originate from the central zone and only 15% of cancers originate in the transition zone (De Vita, *et al*., 2015).

In patients with cancer, the prostate gland enlarges and squeezes the urethra, and may slow or stop normal urine flow. Prostate cancer is a hormone-dependent and epithelial-derived tumour, which result from uncontrolled growth of genetically unstable transformed cells (Shalini *et al.*, 2011). High androgen receptor (AR) level in primary tumour predicts increased prostate cancer-specific mortality. However, the mechanisms that regulate AR function in prostate cancer are poorly known

(Shalini *et al.*, 2011). It has been reported that infection with sexually transmitted infections chlamydia, gonorrhoea, or syphilis increases the risk of PCa (Mustafa, *et al*., 2016).

1.2.1 Epidemiology of Prostate Cancer

In a recent study conducted by Dong and colleagues, it was reported that approximately 160 000 new diagnosis of PCa and over 29 000 deaths were estimated to occur in the United States in 2018. The authors also reported that in 2012, 400 000 European men were newly diagnosed with PCa out of a global 1.1 million new cases. (Dong, *et al*., 2018). Wen *et al. (2019)* also reported that of men diagnosed with PCa, 6 in 10 are men aged 65 years or over. It was also stated by Wen and colleagues that the median age at the time of PC diagnosis is 66 years, with the rates of death highest among men aged 75 -84 years.

The incidences of PCa vary across the globe (Le Roux *et al.,* 2015). Prostate cancer is the second most common cancer and the fifth leading cause of cancer-associated mortality among men worldwide (Ilic *et al.,* 2018). Over 1.3 million new cases and 359 000 deaths were projected for PCa in 2018 worldwide (Bray, *et al.,* 2018). In South Africa, PCa is the most frequently diagnosed cancer in men, and is second only to lung cancer in terms of mortality (Dewar *et al.,* 2018).

Prostate cancer is the leading cause of cancer deaths among 46 countries particularly Sub-Saharan Africa and the Caribbean, and the mortality rates are elevated in the Sub-Saharan Africa regions such as Benin, South Africa, Zambia and Zimbabwe as well as the Caribbean (Barbados, Jamaica and Haiti (Bray, *et al.,* 2018). Trinidad and Tobago studies have also reported prostate cancer as the most common cancer in men (Persuad *et al.,* 2018). In the United Kingdom and the United States of America, black men of different backgrounds are at a higher risk of developing PCa

(Machironi *et al.,* 2018). Adeloye (2016) and Bray and colleagues (2018) have reported that the mortality rates from PCa are generally higher in predominantly black African populations compared to other races.

In north America, black men present with more aggressive and advanced disease than men of other ethnic groups with a worse prognosis (Le Roux, *et al.,* 2015). Men with west African ancestry living elsewhere, such as south America, the United Kingdom and the Caribbean, have similarly high rates of prostate cancer. However, studies focused on South Africa have uniformly found PCa to be more common in white than black South Africans (Dewar *et al.,* 2018). However, Le Roux and colleagues (2015) reported that the majority of PCa patients in public South African hospitals were predominantly black and presented with advanced or metastatic disease.

This disparity is also noted in other studies and has been attributed to under-diagnosing of PCa in the African black population (Dewar *et al.,* 2018). Lower PCa incidence and mortality rates were observed in northern Africa at 10.6 and 7.0 per 100 000 compared to the average rates in Sub-Saharan Africa (SSA) with 34.3 and 22.1 per 100 000, respectively, and these were attributed to relatively higher poverty levels, dietary differences, genetic differences and the presence of infectious diseases in sub-Saharan Africa (Adeloye *et al.,* 2016).

Cancer Association of South Africa (CANSA) cites the lack of adequate information supplied to the Cancer registry by the pathological laboratories for all patients tested to be a hurdle in the availability of up to date PCa data in South Africa (CANSA, 2018).

There is substantial geographic variation in the incidences of PCa. Almost 75% of the registered cases occur in developed regions like Australia, New Zealand, United States and Europe, which is

likely due to the widespread use of prostate specific antigen (PSA) screening test as well as biopsy in these regions (Saraf, 2013). Screening for PCa remains controversial because of limitations in randomised trials including contamination and under-representation of black men (Ilic *et al.,* 2018). The United States Preventative Services Task force recommended an individualised screening approach among men aged 55-69 based on patient-clinician discussion (Persuad, *et al.,* 2018). Screening for prostate cancer with PSA aims to detect prostate cancer at an early stage, to enhance the success rates curative treatment and to reduce the overall and disease-specific mortality (Ilic *et al.*, 2018). Screening by a combination of digital rectal examination (DRE) and PSA testing is recommended by many experts since a proportion of clinically significant cancers may be potentially missed by utilising PSA alone (Ilic *et al*., 2018).

1.2.2 Aetiology of Prostate Cancer

Many authors have reported that the aetiology of prostate cancer is unknown. However, it has been widely reported also that many cancers of the prostate are hormone (Androgen) dependent (Underwood & Cross, 2009). Dong and colleagues (2018) stated that the androgen receptor (AR) is a key regulator of normal prostate function as well as cancer development. Rubin & Williams (2001) have also reported that men castrated early in life rarely develop PCa, implicating the male hormone testosterone as a requirement for PCa.

In a study conducted by Jang *et al.* (2016), it was stated that in Castrate Resistant Prostate Cancer (CRPC), it has been proven and widely accepted that an androgen receptor signalling activity is persistent and that residual androgens continue to drive AR signalling activity (Jang, *et al*., 2016). The authors further stated that molecular studies have shown that tumour progression in CRPC is related to AR-associated signalling mechanisms which include AR overexpression and

amplification, AR mutations, and increased AR ligand expression in the surrounding stroma. In another study by Gravis (2018), constitutive activation of the AR, alternative splicing events, and proliferation of prostate tumour cells independent of androgens have been found to contribute to castration resistance (Gravis, 2019).

1.2.3 Risk Factors of Prostate Cancer

The risk of PCa increases with age, family history of the disease, genetics, dietary fat and/or meat intake and a history of sexually transmitted disease (Shalini *et al.,* 2011; Gul *et al.,* 2016). It is reported that lower Vitamin D blood levels may increase the risk of PCa development (Shalini *et al.,* 2011). In comparison with both breast and colon cancer, which are usually the two cancers with well-recognised familial tendencies, prostate cancer has been reported to have a higher degree of heritability (Shalini *et al.,* 2011).

1.2.3.1 Age

De Vita *et al*. (2015) have reported that clinically detected PCa is rare before the age of 40, but incidence increases with age and continues to rise through the ninth decade of life. This has been noted by Gul *et al*. (2016) who stated that more notably, the risk of PCa has been found to be greatest for men over 65, and very rarely occurs under the age of 40 years. However, it has been reported that most men diagnosed with PCa do not die from it (Rubin & Williams, 2001). Mustafa *et al*. (2016) also reported that autopsy studies of Chinese, German, Israeli, Jamaican, Swedish and Ugandan men who died of other causes have found PCa in 30% of men in their 50s, and 80% of men in their 70s.

1.2.3.2 Genetic Susceptibility & Family History

De Vita *et al*. (2015) reported that men with a first degree relative with PCa have a two to three fold increased risk of developing PCa, and those with two or more first degree relatives affected have a five to eleven fold increased risk compared to the general population.

It has been stated by Rubin & Williams (2001) that the incidence of PCA among blacks in the US is nearly two fold that of whites and forty times that of native Japanese males. However, it has been further stated by Rubin and Williams (2001) that these major differences may be a result of diet or other lifestyle changes because the risk increases among Asian men who adopt a western lifestyle.

1.2.4 Clinical Manifestations of Prostatic Cancer

Underwood & Cross (2009) reported that diseases of the prostate are common causes of urinary problems in men, characterised by the enlargement of the organ resulting in compression of the intraprostatic portion of the urethra and this leads to impaired urine flow, an increased risk of urinary infections and in some cases acute retention off urine requiring urgent relief catheterisation. In studies conducted by Slater (2019) it was reported that PCa symptoms do not usually manifest in the early stages of the disease, but later when the disease has progressed. These include abdominal pain, anaemia, bloody semen, haematuria, fatigue, incontinence, leg inflammation, spinal compression and weight loss (Slater, 2019). Advanced PCa causes additional symptoms due to metastases as reported by Mustafa and colleagues (2016). These include bone pain, often in the vertebrae, pelvic or ribs as well as the proximal spread to the femur (Mustafa et al., 2016).

Pathological fractures and peripheral lymphadenopathy due to metastatic carcinoma are occasionally other initial clinical presentations, as well as rectal examination revealing a hard, craggy prostate (Underwood & Cross, 2009). Clinically, there are five clinical subtypes of prostate cancer based on location of metastatic sites. Namely; (1) locally progressing tumours with no metastasis, (2) rising prostate specific antigen (PSA) with no detectable metastasis, (3) nodal spread with no visceral disease, (4) detectable bone metastasis, and (5) visceral disease with liver and lung metastasis (Scher *et al*., 2008). However, this clinical classification does not define biology of the disease, and it fails to reflect the latest imaging technology used for the diagnosis and screening technology for prostate cancer (Cheng *et al*., 2012).

1.2.5 PCa Screening and Diagnosis

Standardised screening tests can help identify diseases in asymptomatic individuals (screening) or help diagnose a disease in symptomatic individuals (early detection), Koda-Kimble, *et al*., (2009). The authors further list four basic requirements that should be met by screening tests namely, (1) There must be good evidence that the test is effective in reducing morbidity or mortality, for example, effective treatment must be available for the screened disease, (2) the benefits of the test must outweigh its risks, (3) the costs of the test should be in balance with its presumed benefits, and (4) the test should be practical and feasible within the existing health care setting (Koda - Kimble *et al.,* 2009).

The goal of cancer screening for early detection of PCa is to prevent death and suffering from the disease through early therapeutic intervention (De Vita *et al*., 2015). The Prostate Cancer Foundation of South Africa, advocates for a final decision about treatment to be made by the fully

informed patient, assisted by his wife and / or other family members who should be given access to complete and unbiased information from all the experts who may be involved in his treatment (Segone, *et al*., 2013). Underwood & Cross (2009) reported that there are four common ways to diagnose localised or non-metastatic PCa, namely (1) Digital Rectal Examination (DRE), (2) Serum Prostate Specific Antigen (PSA), (3) Trans-rectal Ultrasonography (TRUS), and (4) Needle Biopsy.

It was recently reported by Segone and colleagues (2013) that asymptomatic PCa can be diagnosed early by routine cancer screening. This screening process involves (PSA) blood test, a DRE in men above the age of 50, or 45 if there is a family history of PCa, biopsy staging and grading of PCa.

1.2.5.1 Prostate Specific Antigen (PSA)

PSA is a protein that is secreted by prostate cells. This test gives better short term outcomes after diagnosis (Shalini *et al.*, 2011). PSA is defined as a 28kDa protein of a Kallikrein family, a group of serine proteases whose genes are found in the chromosome 19q13 (De Vita, *et al*., 2015). It is produced by normal and malignant epithelium and secreted into the seminal fluid. It is said that PSA is not only involved in screening for early detection of PCa, but also in detection of recurrences and disease progression (Walker & Edwards, 2003). The increased levels of PSA in the blood stream are indicative of compromised prostate cells, and therefore, PSA is released into the blood stream. It is reported that the normal PSA range is between 0 and 4 ng/mL. Levels above 4 ng/mL are indicative of malignancy (The Urology Hospital, 2017). However, it has been stated also that raised PSA levels have been found to be associated with benign prostatic hyperplasia (BPH), prostatitis and injury to the prostate due to biopsy or catheterisation. Physical activity, infection and medication have been found to be associated with either suppression of (latter) or increased levels (former) of PSA (Huebner *et al.,* 2015). More importantly, since PCa grows very

slow, routine screening is not recommended for the elderly men, i.e., those who are older than 70 years, and with a life expectancy of less than ten years (USPSTF, 2018).

The advent of PCa screening, has however not been met without some controversies. Many authors have reported that over diagnosis increased markedly after the introduction of PSA screening. Two categories of over diagnosis have been defined by De Vita and colleagues (2015), namely (1) Detection of histologically defined cancers not destined to metastasise or harm the patient, and (2) the detection of cancers not destined to metastasise or cause harm in the life span of the specific patient. However, PSA is still widely advocated for PCa screening because it is objective, easily measured, reproducible, non-invasive and inexpensive (De Vita, *et al*., 2015).

1.2.3.2 Digital Rectal Examination (DRE)

This method involves clinical assessment of the prostate gland by the insertion of a gloved finger into the rectum ((The Urology Hospital, 2017). The aim of this test is to determine the size and consistency of the gland, and also to determine the presence of cancerous nodules. Where nodules are suspected, a prostate biopsy is performed (The Urology Hospital, 2017).

It is a recommendation by De Vita and colleagues (2015) that the physical examination should focus on a thorough DRE of the prostate, although palpable nodes can sometimes be detected in the inguinal or supraclavicular areas. Areas of induration within the prostate, extension through the capsule, or involvement of the seminal vesicles should be detected carefully. The authors further state that DRE results are associated with pathologic stage and prognosis, and are the principal basis for assigning T stage of the cancer (De Vita *et al*., 2015).

The DRE method has been reported by Rubin & Williams (2001) to lack sensitivity and specificity. The authors also stated that roughly 50% of suspicious nodules turn out to be cancer, however, many cancers are not palpable, and it has been found that many cancers detected by DRE are locally advanced and probably not curable. (Rubin & Williams, 2001). The authors further mentioned that it is recommended to do a PSA screening before obtaining a DRE, as the examination may increase the PSA slightly. However, a DRE performed before obtaining a PSA reading has very little impact on PSA values in men without PCa. The authors have also stated that where abnormalities are present during DRE or PSA test, further investigations should be sought, and these include trans-rectal ultrasound and prostate biopsy (Rubin & Williams, 2001).

1.2.3.3 Biopsy

Prostate biopsy is performed if the findings with either PSA or DRE, or both are found to be abnormal (Leslie & Siref, 2018). A TRUS is used to aid the placement of the biopsy needles that are used trans-rectally (Leslie & Siref, 2018). The Ultrasound is used to guide the biopsy procedure via a trans-rectal or trans-perineal route. The diagnosis of PCa is confirmed by needle biopsy and histological analysis of the biopsy specimens (The Urology Hospital, 2017).

Huebner & Barqawi (2015) have reported that an introduction of 3-D mapping biopsy (3DMB) has also displayed a substantial advancement in the evaluation of PCa. The 3DMB has the potential to omit a significant number of patients from active surveillance programs and in doing so avoid cases of under treatment. It is believed that this improvement in imaging will provide physicians with greater confidence and assurance when assessing the most pragmatic course of treatment for the patients (Huebner & Barqawi, 2015).

The development of 3DMB and focal ablative therapies are helping to elucidate the distinction between mortal and non-mortal PCas. The advancement of imaging technology is a crucial factor in eliminating the uncertainty that surrounds the treatment selection process and in increasing the utilization of active surveillance and less aggressive treatment modalities for the maximization of patient quality of life (Huebner & Barqawi 2015). Biopsy has been found to carry a risk of bleeding and infection in 3% - 4% of those undergoing the procedure, and is increased with the number of cores obtained. It is also reported that biopsy results are used not only to assign a Gleason score, but also to assess the volume and extent of the cancer by (1) determining the number of percentage of cores involved by cancer, (2) the amount of cancer in each core, and (3) the total length of cancer in all cores. These add important additional staging and prognostic information (De Vita, *et al*., 2015).

Parker et al., (2015) reported that indications for a repeat biopsy after a negative biopsy include a rising PSA, suspicious DRE, acinar proliferation, multifocal high grade prostatic intraepithelial neoplasia. It is reported that for patients with very aggressive tumours, where PSA levels are >20ng/ml and biopsy Gleason score >7, advanced local lesions (T3-4) or symptoms suggestive of metastatic disease should have imaging studies including a bone scan (Positron Emission Tomography (PET), a Computed Tomography (CT) scan of the chest, abdomen and pelvis (De Vita, *et al*., 2015).

1.2.4 Staging and Grading of PCa

The stage refers to the extent and spread of the disease while the grade refers to the aggressiveness of the tumour. The Gleason score, which range from 2 to 10, with 2 representing the well-differentiated tumours and 10 the least-differentiated tumours, is used to grade the cancer by

determining the glandular pattern when compared with a normal prostate (Gul *et al.*, 2011). The scores can also be categorised into groups that show similar biological behaviour such as low grade (well – differentiated), intermediate grade (moderate) and high grade (poorly-differentiated) (Gul *et al.*, 2011).

The authors further state that staging and grading assist in the determination of the extent of the disease and also the prognosis, such information is required for the decision making process for treatment and management of PCa. The tumor, node, and metastasis (TNM) staging system is used, and it involves the determination of the extent of primary lesions (T-stage), Nodal status (N) and distant metastases (M) (Gul *et al.*, 2011).

Parker et al., (2015) have recommended that localised disease should be classified as low risk (T1-T2a and GS ≤6 and PSA ≤10), Intermediate risk (T2b and /or GS 7 and / or PSA 10-20), and High risk (≥T2c or GS 8-10 or PSA above 20). The purpose of the grading system is to note dominant primary pattern and add the next most frequent secondary pattern to give a combined score (Underwood *et al*., 2009). The authors report that where only one pattern of differentiation is seen, as often as it applies in small biopsy, the number is then doubled. Aggressive tumours are graded (5+5 = 10) and are poorly differentiated, and are characterised by acinar differentiation that is no longer apparent in strands of tumour cells or cribriform structures with central necrosis may be found. . Moderately differentiated (3+4 or 4+3 = 7) have fused glands or cribriform structures, and well differentiated (3, will be doubled) comprise of separated, somewhat irregular, gland or acinar profiles that infiltrate into normal glands at the edge of the mass (Rubin & Williams, 2001 & De Vita *et al.*, 2015). Parker and colleagues (2015) recommend that Clinical T stage should be evaluated by DRE. However, MRI has been found to provide more accurate T staging (Parker, *et al*., 2015). Patients diagnosed incidentally as having PCa following TURP are considered to have

a stage T1a or T1b signifying focal and diffuse disease according to Rubin & Williams (2001). If a patient has non-palpable disease not detected by imaging, T1c is used. This stage is also referred to as Stage I PCa.

Palpable tumour contained within the gland and limited to one lobe is stage T2a and T2b (Stage II) if both lobes are involved. The authors' further state that once the tumour has extended through the capsule, the stage is T3a (Stage III). If involvement is focal or T3b if either seminal vesicle is involved. Involvement of the lymph nodes is classified N1-3 (Stage IV) depending on size (Rubin *et al*., 2001, Parker *et al*., 2015).

Prostate cancer spread has been described by Underwood and colleagues (2009) to occur in three modalities namely (1) direct, (2) via lymphaticts, and (3) via blood. Direct spread involves stromal invasion, prostatic capsule, urethra, bladder base and seminal vesicle. Spread via lymphatics includes spread to the sacral, iliac and para-aortic nodes. When cancer spreads via the blood, it metastasises to the bone (pelvis, lumbosacral spine and femur) lungs and liver (Underwood *et al*., 2009).

This spread of PCa is monitored using a number of imaging techniques, of note is the Galium-68-PSMA PET/CT Scan for cancer imaging. Accurate staging of patients with PCa is important for therapeutic decision-making (Hofman *et al.,* 2018). The authors further state that the use of diagnostic imaging is showing rapid growth worldwide, and Ga-68_PSMA ligand PET/CT promises accurate staging of primary prostate cancer and re-staging after biochemical recurrence (Hofman *et al.,* 2018).

1.2.5 Management of Prostate Cancer

Prostate cancer diagnostic and treatment guidelines of South Africa, outlines the different treatment modalities of PCa, according to the staging and grading of the PCa. The different stages and their treatment modalities are discussed below:

1.2.5.1 Clinically Localised Prostate Cancer

It is reported that some tumours of the prostate grow slowly and remain asymptomatic, so the man will eventually die with the tumour, but not from it (Rahman *et al*., 2017). Also, depending on the characteristics of the cancer, age and comorbidities, some men would benefit greatly by aggressive treatment, whereas others would suffer harm (Parker *et al*., 2015). Numerous studies have reported that at diagnosis approximately 70% of men will have the cancer confined to the prostate gland (Underwood *et al*., 2009).

With the advent of PSA screening and imaging of the PCa, progression of the cancer can be identified at its early stages in order to increase survival and quality of life (Lipke & Sundaram 2005). A variety of treatment modalities for PCa have been identified and evaluated by numerous studies as observed in this study during literature review.

Treatment modalities for clinically localised PCa as listed in the South African Prostate cancer diagnostic and treatment guidelines include (1) deferred treatment which includes (active surveillance and watchful waiting), (2) Surgical Interventions (which include Radical Prostatectomy), (3) Radiotherapy, (3) Cryotherapy, and (4) Androgen Deprivation Therapy (Segone *et al*., 2013).

1.2.5.1.1 Active Surveillance (AS)

De Vita and colleagues (2015) define "active surveillance" as a planned treatment of monitoring a patient with a potentially curable PCa (PSA < 10ng/ml, GS ≤ 6, T1 – 2a, PSA density <0.15 – 0.2 and ≤ 50% of PCa in any biopsy core). This is based on the likelihood that the cancer will progress, delaying active treatment until signs of progression to a more aggressive, potentially lethal cancer are detected (De Vita, *et al*., 2015). It is recommended that patients should commit to a regular follow up with DRE and PSA. A repeat biopsy is indicated after 12 – 24 months or if there is any sign of disease progression by examination or markers (Segone *et al*., 2013).

1.2.5.1.2 Wait-and-See Approach

It is reported that in elderly non-symptomatic patients, discovered during a screening test, watchful waiting combined with active surveillance is recommended. This process involves close monitoring of the patient's condition without any application of therapy. Where changes occur in symptoms and / or lab tests results, treatment may be considered and implemented. However, such treatment, although of a limited therapeutic value, is important for timely discovering and relieving the painful symptoms, thus substantially improving the patient's quality of life (Morgia *et al.*, 2013).

1.2.5.1.3 Surgical Interventions

Morgia *et al.* (2013) listed two types of radical prostatectomy, namely open radical prostatectomy and laparoscopic radical prostatectomy. The open radical prostatectomy is the option for the treatment of early detected prostate cancer, provided the patient is in good health and the tumour is localised. It includes the removal of seminal vesicles and the surrounding tissue (Morgia *et al.*, 2013). Two main techniques of radical prostatectomy have been identified, namely retro pubic and perineal prostatectomy.

In retro pubic-prostatectomy, the prostate is removed via an incision made in the abdominal wall, with concomitant elimination of nearby lymph nodes. The process can be either anterograde or retrograde. In perineal prostatectomy, the prostate is cut out through an incision made in the perineum area. A separate abdominal incision shall be performed for the removal of the lymph nodes (Morgia *et al.,* 2013).

The laparoscopic radical prostatectomy was introduced in the 1990s (Lipke & Sundaram, 2005). It is characterised by less aggressive surgical procedures. The removal of the prostate is via small incisions performed by laparoscopic surgical tools. It is reported that this technique appears to produce results at least as good as the open radical prostatectomy. Lipke & Sundaram, (2005) further stated that laparoscopic radical prostatectomy (LRP) has been found to be beneficial to the patient by causing less blood loss and less pain, as well as shortening the patient's hospital stay and recovery time. Side effects rates after LRP have been found to be similar to those following open prostatectomy. Bladder control recovery may take longer, however, the nerve sparing procedure for erectile function restoration is similar to the open surgery (Margio *et al.,* 2013).

1.2.5.1.4 Radiation Therapy

Sack *et al* (2016) stated that cryotherapy/cryosurgery and radiotherapy are common primary, salvage and/or adjuvant treatment options offered for the management of localised prostate cancer. Two types of radiation therapy for the treatment of PCa have been identified namely, external beam radiation therapy (EBRT) and internal radiation therapy or brachytherapy. In EBRT a dose of ionising radiation is generated by an external x-ray source and are delivered to the target area, the prostate (Vanneste *et al*., 2016).

Brachytherapy uses radioisotopes such as Iodine-125, Strontium- 89 and Palladium – 103. The radioisotope of choice is implanted enclosed in a protective radioactive substance sealed in a special needle, seed or catheter wire, allowing the ionizing radiation to escape and destroy the tumour and the surrounding tissue and preventing it from moving further and dissolving in body fluids (Margio *et al.,* 2013). This process prevents damage to healthy tissues, as only the tumour and the specific surrounding area affected. The ideal candidates for brachytherapy are patients with PSA <10 ng/ml, Gleason <6, CT1 – 2, IPSS <10, Qmax>15 ml/sec and prostatic volume <50cc (Margio *et al.,* 2013).

Brachytherapy has been found to be a valid therapeutic option, yielding excellent results that are comparable with those of radical surgery and are considered to be better than those of EBRT. The disease – free survival rates have been observed to reach 70% - 75% following 12 years post – therapy (Margio *et al.,* 2013). EBRT and brachytherapy have been found to be potentially curative therapies for PCa (Vanneste *et al*., 2016).

1.2.5.1.5 Cryosurgery

Cryosurgery is also known as cryoablation or cryotherapy. It is a method whose main mechanism of injury is by coagulation necrosis (Rodriguez *et al*., 2013). The effect of ice on cell membranes is an immediate disruption by mechanical direct effect. The ultimate goal of cryotherapy is cell death by necrosis and apoptosis (Rodriguez *et al*., 2013).

Spinal or epidural anaesthesia is applied during this procedure, and TRUS is used to guide the process. Ultrasound images are vital to ensure that tumour destruction occurs without too much damage to nearby tissues. Warm salt water is circulated concomitantly through a catheter in the urethra, to prevent it from freezing. However, it was reported that this procedure is only

advantageous for early detected cancers, and less effective for more advanced prostate tumours (Sack *et al.,* 2016).

1.2.5.1.6 Androgen Deprivation Therapy (ADT)

Androgen Deprivation therapy, is defined by Gravis as the standard treatment for metastatic disease, and it includes surgical and/ or medical castration and has been used for decades (Gravis, 2018), Medical castration is achieved through the use of gonadotropin – releasing hormone receptor agonists or antagonists (El-Amm & Aragon-Ching, 2019). AR antagonists competitively bind to the AR and block the binding of endogenous androgens and thus interrupt the androgen-dependent cellular cascade that leads to progression of prostate cancer (Xu & Qiu, 2019).

It is reported that testosterone and the more potent dihydrotestosterone are the two main androgens that are responsible for the growth of the prostate by binding to the androgen receptor (El-Amm & Aragon-Ching, 2019). The ADT, according to Jang and colleagues (2016) includes Luteinising hormone releasing hormone analogues such as Goserelin that act by reducing the amount of testosterone produced by the testes. It is reported that in order to avoid the initial flare effect when these are administered, anti – androgen therapy with flutamide or bicalutamide should precede or co-administered with LHRH agonist for at least 7 days (Jang, *et al*., 2016).

Goserelin is an agonist analogue of gonadotropin-releasing hormone that induces hypogonadism by reducing the secretion of gonadotropin and therefore testosterone (Bolla *et al.*, (1997). Goserelin is given as a subcutaneous dose of 3.6mg monthly or 10.8mg every 3 months; however, in other studies it has been administered subcutaneously every 4 weeks starting on the day of irradiation (Bolla *et al*., 1997).

The following advantages have been associated with the use of Goserelin: (1). Studies have shown that it improves overall survival of patients with locally advanced prostate cancer. (2). Goserelin has been found to show advantages over radiotherapy in terms of local control, incidence of distant metastasis and progression –free survival. (3). The use of the depot preparation of a Luteinising hormone releasing hormone (LHRH) analogue to supress gonadotropin and sex hormone secretion offers the convenience of once a monthly injections when LHRH analogues are required for long term treatment of elderly patients with prostatic cancer and children with precocious puberty (Sciarra *et al*., 2016).

De Vita et al., (2015) reported that even though ADT has been widely used for decades, there are numerous side effects that are associated with the use of ADT and these have been grouped under the "androgen deprivation syndrome", and include hot flushes, a decrease in libido, erectile dysfunction, impotence, fatigue, anaemia, weight gain and alteration in fat metabolism, loss of muscle mass and weakness, bone loss, a decrease in mental acuity, mood swings, personality changes, memory loss, depression, insomnia and cardiovascular events (De Vita *et al*., 2015).

Combination therapy has been found to enhance efficacy through more complete inhibition of major pro-survival pathways or suppression of multiple pro-survival factors, and has been proven very effective for the treatment of advanced cancers (Dong, *et al*., 2018). Combination therapies of ADT and chemotherapeutic agents have been investigated for the treatment of various stages of PCa in a number of clinical trials that included the CHAARTED, SWOG – 9916 and STAMPEDE to name a few. Progression from low risk and intermediate risk to high risk PCa requires treatment modalities that are properly planned based on the presentation of the disease and other patient factors and assessment of potential outcomes.

1.2.5.1.7 Chemotherapy for Advanced Prostate Cancer

Chemotherapy involves the use of cytotoxic drugs to kill the cancer cells while simultaneously limiting undesirable and unacceptable toxicity to the neighbouring cells (Buchler & Harland 2007). Generally, different combinations or drugs (or drug regimens) are administered intermittently over two to three weeks to allow for the recovery of the bone marrow and restoration of the immune function in between treatment courses (Mkele, 2010).

Factors to be considered when choosing the most appropriate drugs to use for a chemotherapy regimen include the type of cancer being treated, the stage of the cancer, the tumour size, the site(s) of the metastases, the patient's age and general state of health, the presence of other serious co-morbidities, as well as the cost of the drug treatment (Mkele, 2010).

Mitoxantrone and estramustine (Emcyt®), were the first approved chemotherapy agents that were utilised for PCa patients to help control pain to relieve symptoms associated with their metastatic disease (Shalini *et al.,* 2013). Mitoxantrone belongs to the anthracyclines group of anti-tumour antibiotics that interfere with the enzymes involved in DNA replication. These agents function in all phases of the cell cycle. High doses of these drugs have been associated with cardiac damage, as a result life time dose limits are often placed on these drugs (Mkele, 2010). Prednisolone is often used along with mitoxantrone to improve survival, quality of life and pain response (Collins *et al*., 2006).

Other than mitoxantrane, docetaxel which belongs to the large plant-derived taxane group of chemotherapy drugs is also used a first-line drug to in patients with PCa (Segone *et al.*, 2013). It causes cell death by inhibiting depolymerisation of the contractile protein tubulin during mitosis

(Tannock *et al*., (2004); Chiuri *et al*., 2009). Taxanes are used to treat many other types of cancers including breast, lung, myelomas, lymphomas and leukaemia (Mkele, 2010).

However, androgen suppressor regimens have been widely used as either first line prior to chemotherapy use or as an adjunct to radiotherapy in order to suppress the secretion of testosterone in patients with advanced stage (Oefelein, 2008). In South Africa, Goserelin (Zoladex®) continues to be used as one of the primary regimen for androgen suppression in the public sector.

Fizazi and colleagues (2015) reported that in 2004, following results from the TAX 327 study, Docetaxel was approved as first – line chemotherapy for the treatment of patients with mCRPC and was the first drug to demonstrate improved survival in this setting.

With the advent of systemic agents that have been approved for the treatment of mCRPC, the goals of treatment have been optimised to include pain management where bone metastasis have been observed. In the STAMPEDE and CHAARTED trials, Zoledronic acid (a bisphosphonate), Radium 23 (Radioisotopes) and Denosumab (a rank ligand inhibitor) have been used as monotherapy or in combination with chemotherapy for palliation in advanced PCa, especially in men with high-volume, osseous metastatic disease (Teo *et al*., 2019; Parker, *et al*., 2015).

Numerous authors have reported that patterns of disease development differ from patient to patient. De Vita, *et al*.,(2015) stated that the pattern that develops in a patient is influenced in part by the extent of disease at the time ADT was first initiated, therefore, the therapeutic objective for mCRPC patients is to prevent development of bone metastasis, and the likelihood varies highly between patients.

Overall survival, quality of life, delayed disease progression have been defined in numerous studies as the goals of treatment. The choice of treatment is dependent on an informed patient decision and also on the availability of treatment, costs and complications (Segone, *et al*., 2013). In the 20th century the FDA approved six systemic agents following evidence of improved overall survival in patients with different PCa states. The literature review has demonstrated that many research studies are being undertaken worldwide to further elucidate PCa treatment options. With the advent of chemotherapy, chemotherapy in combination with ADT, palliation with bisphosphonates, and immunotherapeutic agents, the use of radioisotopes has also been investigated.

1.2.5.1.8 Radiopharmaceuticals/Targeted Nuclear Medicine

Chemotherapy is often less effective in carcinomas, such as the non-Hodgkins lymphomas, because some cancer cells are inaccessible to drugs. Therefore radioactive isotopes emitting β and/or ϒ rays, such as iodine-131 (I-131) and lutetium-177 (Lu-177) have been used effectively to kill cancer cells that cannot be reached by commonly used cytotoxic drugs (DeNardo *et al*., 2004).

Radiopharmaceuticals are medicinal formulations containing radioisotopes which are safe for administration in humans for diagnosis or therapy (WHO, 2008). Targeted radionuclide therapy, therefore, involves the use of radiopharmaceuticals to selectively deliver cytotoxic levels of radiation to a disease site, as this would potentially deliver the absorbed radiation dose more selectively to cancerous tissues (Jadvar, 2017)

Radioactive iodine-131 (I-131) plays a significant role as an adjunct radionuclide therapy for the treatment of thyroid cancer in particular (Luster *et al*., 2017). Iodine-131 behaves like a “magic

bullet" that accumulate in the thyroid follicular cells through the sodium iodide symporter (NIS), also known as cotransporter, protein and kills cells it penetrates by β decay mode (Ambikalmajan and Furn, 2015).

The I-131 emits β and ϒ particles thereby killing thyroid cells and decreasing thyroid hormone production (Al-Qahtani *et al*., 2014). I-131 has been found to have potential antineoplastic activity and its therapy is associated with substantial albeit rare side effects, while gastro-intestinal problems, salivary and lacrimal gland complications, gonadal dysfunction have been reported (Schlumberger *et al*., 2012).

Chemically, lutetium belongs to one of the two special groups of the Periodic Table called the lanthanides, which starts with lantham (La, Z= 57), and ends with lutetium (Lu, Z= 71). Lutetium is a medium-energy β-emitter with a maximum energy of 0.5 MeV and a maximum tissue penetration of 2mm (European Medicines Agency 2016). The average β energy is equivalent to 0.13MeV. Lutetium also emits low energy gamma (**ϒ**) rays at 208KeV (11%) and 113 KeV (6.4%), allowing scintigraphy and subsequent dosimetry with the same therapeutic compound if needed (European Medicines Agency, 2016).

In South Africa (SA) Lu-177 is used only under strict Section 21 of the Medicines and Related Substances Act (Act 101 of 1965) for the treatment of many different cancers both in public and private settings. However, Brazil and Germany have been listed as the countries in which Lu-177 is registered under the respective drug regulatory agencies (Rahbar *et al*., 2017). Recently, the FDA in the US approved Lu-177 dotatate injection, for intravenous use (Choy, 2018).

It is reported by the EMA, that the shorter β range of Lu-177 compared to other radio therapeutic agents such as Yttrium provides better irradiation of small tumours, sparing surrounding tissue and low energy, low abundance gamma (ϒ) emissions which are useful for imaging (Kabasakal *et al*., 2017). ^{177}Lu- decays to Hafnium (Hf-177), with a half-life (t1/2) of 6.647 days. This relatively long t1/2 provides logistic advantages that facilitate its supply to other locations far from manufacturing sites (European Medicines Agency., 2016). When labelled with therapeutic radionuclides e.g. ^{177}Lu - n.c.a-PSMA, peptide molecules (PSMA in this case), have a potential to destroy receptor-expressing tumours, an approach referred to as peptide receptor radionuclide therapy (PRRT) (Ambikalmajan and Furn, 2015).

^{177}Lu – PSMA radioligand therapy (LuPRLT) is mainly used for patients with mCRPC who are resistant to established drugs (von Eyben, *et al*., 2019). It is for this reason therefore, that this study aims to compare the costs of treatment of patients with mCRPC treated with standard chemotherapy compared to ^{177}Lu – n.c.a PSMA at Steve Biko Academic Hospital.

1.3 Economic Burden of Cancer

The costs of treating cancer escalates to billions of dollars per annum, globally. Medical expenditures for PCa in America, were estimated to be $11.85 billion in 2010 and projected to reach $16.34 billion in 2020 (Chilira *et al.*, 2011). The economic impact of cancer is now a reality and is expected to continue to rise causing concern across all countries, wealthy or poor (Vanderpuye & Yarney, 2014). In Africa, most patients and their families have to bear the cost of treatment from already meagre resources. Budg*et al*locations imbalances, which favour communicable diseases, contribute to the low percentage of cancer treatment resources (Vanderpuye & Yarney, 2014).

In South Africa, the Medicine and Related Substances Act, Act 101 of 1965, was used to introduce the Single Exit Price (SEP), for medicines in SA, in August 2004. The SEP is the price at which a manufacturer must sell to all pharmacies, irrespective of volume sold. The regulations require that the extent of the price adjustment should be based on inflation indicators and the need to ensure the availability, affordability and quality of medicines and scheduled substances in the Republic (Mngadi, 2014).

However, due to the patent laws, Kahn (2017) stated that these allow the manufacturing companies to price cancer drugs at unaffordable prices to the general public and also those also covered by Medical Aids in South Africa. Various cases have been cited, where new cancer treatments are not affordable due to high costs, and the SEP regulations do not apply. Therefore, economic evaluations of various cancer treatments using, either single or combinations of strategies such as cost-utility, cost-effectiveness, cost-minimisation and/or cost-benefit analyses, are needed.

Globally, the ever increasing costs continue to hamper access and availability of effective cancer drugs to multitudes of desperate patients who urgently need therapy for survival (The Lancet, 2018). It is reported that in South Africa, there is limited competition between suppliers of medicinal products, especially cancer drugs due to patent laws (Gray, 2009). Therefore, recently, calls have been made to change intellectual property regime and patent laws for medicines, because the current system inhibits competition and keeps drug prices at unaffordable levels (Kahn, 2017). The management of PCa remains complex depending on the stage at which it is detected, age of the patient, presence of co-morbidities and treatment norms and strategies employed in a particular health system (Saraf, 2013).

With the advent of new PCa therapies, it is important to understand the economic impact of their adoption in health plans (Bui *et al.*, 2016). However, for the treatment of metastatic, castrate-resistant prostate cancer, the FDA has not approved any PSMA targeting radionuclide therapy (Nitipir *et al.*, 2017).

Screening and imaging of PCa forms part of the costs that are incurred for the treatment of PCa. Bone scintigraphy and PET/CT scan costs need to be taken into consideration towards PCa costs. Irrespective of the treatment employed, the clinical and economic implications have been observed to be large (Saraf, 2013).

1.4 Pharmacoeconomics Tools

Baldi and Kumar define Pharmacoeconomics as "*that branch of Healthcare Economics that identifies, measures, and compares the costs and consequences of drug therapy to healthcare systems and society*" (Baldi & Kumar, 2013). Economic evaluation methods or tools such as cost-utility analysis (CUA), cost-effectiveness analysis (CEA), cost- minimisation analysis (CMA) and cost-benefit analysis (CBA) are increasingly being used by decision makers to inform resource allocation and development of healthcare policies (Jacobsen et al., 2020, & Baldi *et al*., 2013).

1.4.1 Cost-utility Analysis

CUA is reported to be the best economic evaluation method to make decisions about health resource allocation. The CUA compares the costs of different procedures with their outcomes measured in "utility based" units, that sis units that relate to a person's level of wellbeing (Robinson, 1993).

In CUA, health gain is measured by an artificial unit quality-adjusted life-years (QALYs), which combines the quality of life (QoL) and the survival benefit of patients (Bodrogi & Kalo, 2010). To calculate the QALYs, the expected life-years are weighted by their quality. The quality weight of perfect health 1 (one), utility weight of death 0 (zero). Comparison between alternative procedures or programs can then be based on the marginal cost per QALY gained (Bodrogi & Kalo, 2010; Robinson, 1993).

1.4.2 Cost-effectiveness Analysis

Cost-effectiveness analysis is concerned with technical efficiency issues such as the identification of ways to achieve goals or spending a given budget (Miller 2009). Health benefits are measured by natural units and traditional clinical trials end points (Bodrogi & Kalo, 2010). Clinical diagnostic or device outcomes such as mmHg blood pressure reduction or mmol/L LDL cholesterol reduction can be used in CEA, only if improvement in these intermediate outcomes results in similar improvement in hard end points. Measurements costs are done in monetary terms (Bodrogi & Kalo, 2010).

It is reported that CEA are relatively straightforward to carry out and are sufficient for addressing many health questions in health care. However, the general drawback is that health programmes with different aims cannot be compared with one another using CEA (Miller, 2009). Miller (2009) also concludes that CEA not only assumes that the outcome of the health programme is worthwhile but also that it is the most appropriate measure.

1.4.3 Cost-Minimisation Analysis

Walter & Zehetmayer (2016) state that "*CMA is a pharmacoeconomic tool that is used and applied when comparing multiple drugs of equal efficacy and equal tolerability*". Once the health consequences are established to be the same, a CMA would compare all cost between treatments to determine the option with the least cost (Baldi & Kumar, 2013). The objective of CMA is to select the least costly intervention among multiple equivalent. However, CMA cannot be used to evaluate programmes or therapies that lead to different outcomes. It is appropriate to use CMA when comparing two or more therapeutically equivalent agents or alternate dosing regimens of the same agent (Bodrogi & Kalo, 2010). Measurement or assessment of costs in CMA is measured in monetary terms (Walter & Zehetmayer, 2016).

1.4.4 Cost-benefit Analysis (CBA)

Baldi & Kumar, (2013) describe CBA as the most comprehensive and the most difficult of all economic evaluation techniques. CBA is reported to involve the assignment of monetary value to the benefits, thereby facilitating easy comparison of costs and benefits, as a result totally different interventions can be compared, making it a useful tool (like CUA) for resource allocation by policy-makers (Bodrogi & Kalo, 2010). CBA is a basic tool that allows for the identification, measurement, and comparison of the benefits and costs of a programme or treatment alternative (Baldi & Kumar, 2013).

The benefits of CBA are that it is employed when comparing treatment alternatives in which the costs and benefits do not occur simultaneously. Also, CBA can be used when comparing programmes with different objectives because all benefits are converted into dollars and to

evaluate a single programme or compare multiple programmes (Walter & Zehetmayer 2016). The benefits realised from a programme or treatment alternative are compared with the costs of providing it. Both the costs and the benefits are measured and converted into equivalent dollars in the year in which they will occur. Future costs and benefits are discounted or reduced to their current value (Bodrogi & Kalo, 2010). This method addresses the question of willingness to pay for the intervention being rendered. However, it may ignore intangible benefits (pain, anxiety, and stress) that are difficult to express in monetary terms (Baldi & Kumar, 2013).

1.5 The Aim of this Study

The aim of the study was to analyse the costs associated with treating mCRPC with standard chemotherapy regimens when compared with the costs incurred for mCRPC in SA. These data were vital to inform policy, funds allocation for PCa treatment both in public and private health care.

1.6 Study Objectives

a) To investigate the direct medical costs incurred by PCa patients treated for mCRPC with standard chemotherapy at selected public hospitals in South Africa.
b) To investigate the direct medical costs incurred by PCa patients treated for mCRPC with targeted nuclear medicine (^{177}Lu –n.c.a-PSMA) standard chemotherapy at selected public hospitals in South Africa.
c) To compare the costs and or benefits of treating mCRPC patients with general chemotherapy versus targeted nuclear medicine (^{177}Lu –n.c.a-PSMA) using either the private or public economic model as per hospital's model.

1.7 Research Questions

a) What are the direct medical costs of treating mCRPC with standard chemotherapy regimen such as docetaxel /prednisone/goreseline in South Africa?

b) What are the direct medical costs of treating mCRPC with targeted nuclear medicine such as ^{177}Lu-n.c.a- PSMA in South Africa?

c) What are monetary benefits of treating PCa with docetaxel//prednisone/ goreseline regimen versus Lu-177-n.c.a- PSMA?

d) What is the overall survival for patients treated with standard chemotherapy compared to the patients treated with targeted nuclear medicine?

e) Were there any significant biochemical responses observed during treatment?

CHAPTER 2: Methodology

2.1 Approval of Research Protocol

The study protocol, and subsequent annual re-certifications, was approved by the UKZN Biomedical Research Ethics Committee (Ref.: BE458/18); the University of Pretoria Faculty of Health Sciences Research Ethics Committee (Ref.: 747/2018)061/09); KwaZulu-Natal Department of Health (as well all applicable authorities/head of departments at the Inkosi Albert Luthuli Central Hospital & the Addington Hospital, Durban); the Gauteng Department of Health (as well all applicable authorities/head of departments at the Steve Biko Academic Hospital). Approval was obtained from the NTP Radioisotope, which also signed a memorandum of understanding with the UKZN, please refer to Addendum A.

2.2 Study Design and Setting

This was a retrospective and prospective inferential study, conducted mainly on patients aged >18 years at Steve Biko Academic Hospital (SBAH), Pretoria, the Inkosi Albert Luthuli Central Hospital (IALCH) in Durban, South Africa and Addington Hospital, Durban. The patients who were referred to the treatment centres between the periods 1 January 2017 and 24 November 2019 were included in this study.

In particular, data were collected from the Nuclear Medicine Department (at the SBAH) and from the Medical Oncology, Urology, Radiation Oncology as well as Nuclear Medicine Divisions at the IALCH. Patients were identified using MediTech™, a paperless, electronic hospital information system at the IALCH. MediTech™, a computerised data system, in which data is stored on tables

in the data repository, a Standardized Query Language (SQL) for requesting information from a database. Clinical and billing (charges) from the data repository using SQL extraction queries with parameters (e.g. required ICD codes, patient race, age, medicine charges, imaging and laboratory costs). Identified patients were then grouped by ICD-10 Codes listed on the data base for PCa, were sourced. This system uses the same race categories as those used by the South African census to categorise race in South Africa - namely Asian, Black, Coloured, White and other. At SBAH, the patient records (files) were manually accessed, and a thorough manual audit was performed to identify patients who were treated for mCRPC at this hospital between the period of 1st January 2017 to 24 November 2019. Data extracted from the patient files was recorded in the data collection sheet.

2.3 Study Population & Inclusion Criteria

The study population was prostate cancer patients with mCRPC that were treated at the chosen research sites from the 1st of January 2017 to the 31st December 2019 within the Nuclear Medicine Unit at Steve Biko Academic Hospital and Oncology, Urology, Radiation Oncology and Nuclear Medicine units at IALCH Hospitals respectively. All prostate cancers as defined in the International Classification of Diseases (ICD) were categories into four prostate cancer groups namely Carcinoma in situ (D07.5), Benign neoplasm of the prostate (D29.1), Prostate neoplasm of unknown behaviour (D40.0) and Malignant neoplasm of the prostate (C61). All patients with the ICD-10 Code C61 were included in the study and patients with the ICD -10 Code patients (D07.5, D29 and D40.0) were excluded.

Critical data points such as race, patient age at diagnosis, patient age at last visit, PSA value (in mg/ml), chemotherapy, laboratory, imaging, in-hospital and out-patient costs were analysed and included as direct medical costs. Pain management, side effects management and adjuvant therapy

costs were also analysed. Indirect medical costs such as transportation and personal care were not included in the study.

Patients were excluded if the records showed that treatment ceased prior to the treatment period, were not of male gender, were under the age of 18, were male diagnosed with mCRPC but treated with other Nuclear Medicine Radioisotopes other than Lu-PSMA, and were coded with ICD 10 Code C61, but no chemotherapy treatment was available on the records. Patient records of those who demised during the study period were included. Records with the following information were included in the costs comparison analysis of standard chemotherapy regimen versus targeted nuclear medicines for PCa at these hospitals.

2.3.1 Demographic Information

Patient age, race, gender and medical record number were used for the identification of the patient and were necessary for extraction of data from the MediTech™ system as well as manual analysis of the patient files.

2.3.2 Dates of First and Last Visits

The dates of first and the last visits were used for determining the status of the patient during the study. That is whether the patient was still alive, deceased or lost to follow up. The date of the first visit was also used to link the patient's current age with the age at diagnosis. This was crucial in order to determine the overall survival of the patient since diagnosed with PCa.

2.3.3 Clinical Assessment Records

The Gleason score, where applicable, and PSA levels or frequency of testing were recorded. This information was necessary for the staging of the PCa as well as the monitoring of biochemical recurrence.

2.3.4 Out-patient and In-patient Days for 2017-2019

This information was used to determine the number of visits in the out-patient (day visit to consult with the oncologist, radiologist, urological specialist or first time consultation and patient is not admitted to a ward), emergency as well as in-patients (hospital admission) in order to calculate the costs incurred for hospitalisation and consultation in the Nuclear Medicine, emergency unit, urology and medical and radiation oncology wards during the study period.

2.3.5 Imaging and Screening Details

Information related to the imaging and screening tests performed for the included patients was necessary to calculate the costs related to each of the therapeutic options.

2.3.6 Treatment Regimens

Chemotherapy and nuclear medicine regimens details were required in order to calculate costs associated with each treatment. This information was also used to determine the inclusion or the exclusion of the patients during the study period.

2.3.7 Hospital Classification Coding System

Hospital classification coding system was recorded for each patient in order to assign costs. This was done in order to elucidate the mode of payment (state, medical aid or out of pocket). According to June (2002) the national department of health (NDoH) has classified patients into two main groups for the purposes of service determination, namely full paying patients and subsidised patients. Full paying patients include externally funded patients, patients being treated by their private practitioner and other categories of non-South African citizens and are liable for full uniform patient fee schedule (UPFS) fees. Subsidised patients are patients who do not fall in the category of full paying patients, and are further categorised based on their ability to pay for health services into four categories: H0, H1, H2 and H3. The fees payable by subsidised patients are expressed as a percentage of the fees payable by full paying patients as determined by the (UPFS). H0 patients qualify for full subsidisation, H1, H2, and H3 patients qualify for partial subsidisation (June, 2002).

2.3.8 Patient Status

The patient status during the study was classified into three categories alive, deceased and lost to follow up (where patients could not be accounted for between 2017-2019). This information was necessary in order to determine both mortality and overall survival during the study period.

2.4 Sampling Procedure

At the IALCH, the MediTech™ system was used as the primary tool to extract data for patients diagnosed with PCa. The patient information on MediTech™ was stratified by ward and ICD 10

codes. The ICD-10 code C61 (metastatic neoplasm of the prostate) is used to determine the sample of adult male patients aged 18 years and above to be observed under study. The patients are also sampled based on the chemotherapy regimen that they received from this treatment centre for the period between 1 January 2017 to 24 November 2019. Both live and deceased patient records for the period under study are included as the sample for this study. The exclusion criteria includes patients whose records indicate other ICD-10 codes of PCa, that is not malignant, as well as no treatment with chemotherapy. At the SBAH the patient files were used as the primary data source. Sample included male patients aged 18 years and above, diagnosed with mCRPC and treated with nuclear medicine ^{177}Lu-n.c.a- PSMA between 1 January 2017 – 24 November 2019.

2.5 Costing Model and the Costs Analysed

For each patient in our sample we calculated expenditure as the total of all costs in the files or MediTech™ records over the 2017-2019 period, based on the treatment cycles received for chemotherapy regimen, nuclear regimen, imaging, laboratory screening, as well as hospitalisation costs where applicable. We collected imaging (Gallium-68) PET/ CT Scan, renal imaging, tumour localisation imaging costs and laboratory screening costs (FBC, LFTs U&E) from the Nuclear Medicine unit and the National Health Laboratory services respectively. Lu-PSMA costs were collected from the planning charts in the patients files. Any other costs that were related to the treatment regimens, such as technical costs, renal imaging costs, as well as the prophylaxis and aminosteryl costs were collected from the patients files.

At the IALCH, the MediTech™ system to extract most of the data through the ABC (activity-based costing) model, was used. This includes both the ABC Facility rates, where the 2018/2019 costing rates were used as they were the latest completed financial year and the latest average costs. The

ABC Facility costs are the average costs of the patients visit (out-patient department (OPD) or Emergency Unit) or in-patient stay. The ABC Facility costs were based on the visit charges. The visit charges contain all visit details where the patients listed on the Meditech™ system have been ICD 10 coded between 1 January 2017 and 24 November 2019. The visits charges in the ABC Facility Cost model include both the out-patient and in-patient costs as well as the treatment costs incurred during the study period for the chemotherapy regimen.

All the chemotherapy costs on MediTech™ using the visits information from the ABC costs, were extracted and downloaded for analyses. Where chemotherapy costs were not available, we searched on MediTech™ for chemotherapy regimen issued to the patients during the OPD or in-patient or emergency unit. The frequency of doses supplied was also recorded in order to aid in the calculation of the total costs incurred. On MediTech™, the chemotherapy costs were standardised for each treatment regimen regardless of combination used, therefore we adopted the same costing for the data where costs were not available, but the regimen was known. We also noted the treatment cycles for each regimen in order to calculate the final costs. From the data obtained we grouped patient chemotherapy regimen into eleven different regimens as per monotherapy or combination used per patient during the study period.

In-patient days costs for the period of 2017-2019 were extracted from MediTech™ for the total number of in-patient occupancy days as ICD 10 coded for Prostate Cancer (ICD-10 code C61). These costs were linked to the patient's medical record number. Laboratory and imaging costs were extracted from MediTech™ system and were stratified per ward where the patient visited or was admitted during the study period. The costs of bone palliation treatment for patients with mCRPC were analysed and costs of the treatment were calculated.

Although PCa cancer treatment is associated with a variety of side effects, only the cost of treatment for prevention of nausea and vomiting was considered, as this was the only available data. The costs of prednisone as the regimen used in combination with docetaxel in chemotherapy as part of the prophylaxis or comprehensive patient care, was analysed.

Expenditure on radiotherapy as a monotherapy was excluded. However, for patients who were concurrently treated with radiotherapy, such costs were included as part of the OPD costs.

2.6 Data Analyses

Data were analysed using the Statistical Program IBM SPSS, Version 26 for statistical manipulations and analyses. The data analysis did not include health outcomes such as life-years gained and quality adjusted life-years (QALYs). Descriptive statistics for frequencies, means, minimum and maximum values, and where applicable standard deviation were used.

CHAPTER 3: Findings

3.1 Chemotherapy Cohort

The records of 339 patients, who met inclusion criteria, were included in this study. The results are tabulated in Table 1. The results indicate that the majority of the patients (96.8%) were diagnosed with malignant neoplasm of the prostate also known as metastatic castrate resistant prostate cancer. Patients with ICD 10 codes D07.5, D29.1 and D40.0 were excluded from the study.

Table 3.1: Overall population: All ICD 10 Codes:

ICD 10 Code	Description	Count of MEDRECNO	Percentage (%)
C61	Malignant neoplasm of the prostate	328	96.8
D07.5	Carcinoma in Situ	1	0.3
D29.1	Benign neoplasm, prostate	1	0.3
D40.0	Neoplasm of uncertain or unknown behaviour, prostate	9	2.6
Total		339	100

Of the 328 patients diagnosed with the malignant neoplasm of the prostate, 263 (80%) were not treated with Chemotherapy and therefore they were excluded in the study. These results are shown in table 3.2.

Table 3.2: Number of patients with ICD 10 code: C61 per race treated and not treated with Chemotherapy.

Race	Asian	Black	Coloured	Other	White	Grand Total
Treated	16	39	1	1	8	65
Not treated	49	160	15	4	35	263
Grand Total	65	199	16	5	43	328
Percentage (%)	24.62	60	1.54	1.54	12.31	100

Of the C61 ICD 10 Coded patients, 65 (24.62%) were Asian, 199 (60.00%) were black, 16 (1.54%) were coloured, 5 (1.54%) were classified as other and 43 (12.31%) were of white race. These results indicate that the majority of the patients in this cohort are black and this is consistent with the study conducted by Dewar and colleagues (2018) who stated that black men and men with West African ancestry are at a higher risk of being diagnosed with PCa. The results are also in line with the WHO statistics for PCa and numerous other studies in which black ethnicity is associated with a higher risk of PCa diagnosis.

We further categorised patients in the cohort per treatment regimen. The results indicated that 188 (57.3%), patients were treated with chemotherapy while 42.7% (n=140) were treated with Radiotherapy only. The patients who were treated with Radiotherapy only were excluded from the study. Of the 57.3% chemotherapy treated patients, 16 (23%) were Asian, 39 were black, 1 were coloured and other respectively, while the white race comprised of only 8 patients.

Further analysis of the chemotherapy regimen used per patient showed that of the black population in the study only 28 were treated with the chemotherapy as confirmed by MediTech™ records and the 11 were excluded because there was no history of the chemotherapy regimen on the records and 1 was a child below the age of 3. Of the 16 Asian patients, five were excluded because the medical records did not include chemotherapy regimen. The exclusion and inclusion of the patients in this cohort is illustrated in Figure 3.1.

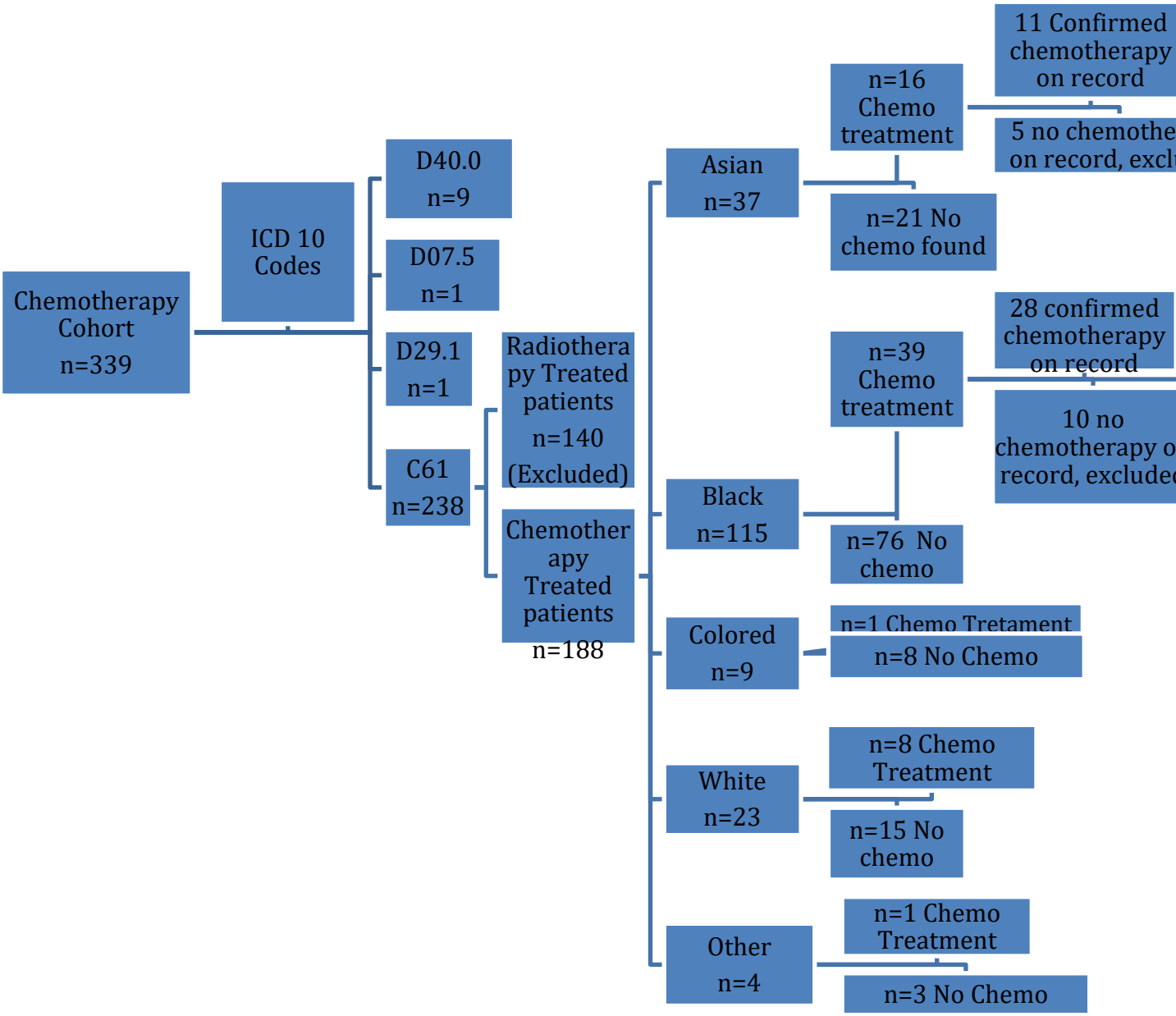

Figure 3.1: Exclusion and inclusion of patients for the chemotherapy cohort

3.2 Nuclear Medicine Cohort

A total of 26 patient records were reviewed at SBAH (N=26). 11 patients (42.7%) met the inclusion criteria and 15 patients (57.7%) were excluded from the study. The reasons for exclusion included the following, 47% were of female gender, 20% were treated prior to the study period, 13%, were treated with a targeted nuclear medicine regimen other than Lu-PSMA and 13% were not treated with any targeted nuclear medicine. Forty five (45%) percent of the included population in the cohort were black, and 55% were white. The results indicate that in this population the majority of the patients were white, however, this can be attributed to the small size of the cohort and the percentage of patients excluded for not meeting the inclusion criteria. Figure 3.2 illustrates the percentages of patients that met and those that did not meet the inclusion criteria. The reasons are also stated. Other demographic parameters such as age were analysed and compared for the study cohorts.

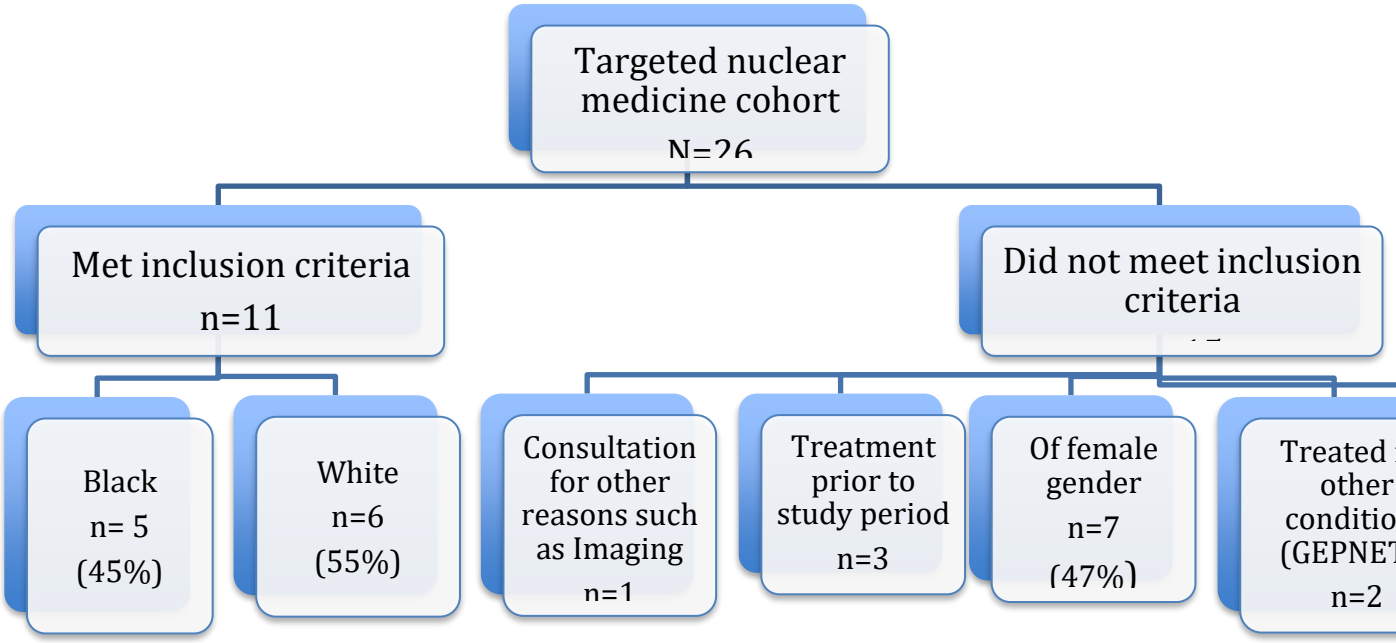

Figure 3.2: Population distribution of the Nuclear Medicine Cohort

3.3 Average Patient-Age at Diagnosis.

We used descriptive statistics to analyse the age at diagnosis of the two study groups. The results indicated that the mean age at diagnosis were 61.2 and 66.3 for the nuclear medicine and chemotherapy cohorts respectively. Age at diagnosis is between 41.4 and 80.9 for the nuclear medicine cohort and 43.6 and 89.0 for the chemotherapy cohort with standard deviations of 6.6 and 7.6 respectively. Our data indicates that the age at diagnosis is within the acceptable age range.

Table 3.3: Age at diagnosis for Nuclear Medicine and Chemotherapy cohorts

	N	Minimum	Maximum	Mean	Standard Deviation (sd)
Nuclear medicine Cohort age at diagnosis	11	50.0	76.0	61.2	6.6
Chemotherapy cohort age at diagnosis	49	51.0	81.0	66.3	7.6

3.4 Patient Status during the Study

We reviewed the patient's health status during the study in order determine the overall survival during both chemotherapy and Lu-PSMA treatment. Our results indicate that for the nuclear medicine cohort, 63.6% of the patients were alive during the study, 27.3% and 9.1% were either deceased or lost to follow up respectively.

Table 3.4: Nuclear Medicine cohort patient status

Patient status	Frequency	Percentage (%)
Alive	7	63.6
Deceased	3	27.3
Lost to follow up	1	9.1
Total	11	100

We performed a similar frequency analysis for the chemotherapy cohort. 71.4% of the patients were alive during the study, 2% and 26.5% were either deceased or lost to follow up respectively.

These results indicate that there was a higher percentage of mortality in the nuclear medicine cohort. This may be attributed to a smaller population size as well as adequate reporting of the mortality to the treatment site. The results also indicate that in both cohorts there was 9.1% and 26.5% of patients lost to follow up.

Table 3.5 Chemotherapy cohort patient status

Patient status	Frequency	Percentage (%)
Alive	35	71.4
Deceased	1	2
Lost to follow up	13	26.5
Total	49	100

3.5 Gleason score and PSA levels in the Nuclear Medicine Cohort

On presentation at the treatment site, the patient undergoes a number of screening and imaging tests. These include PSA screening as well as imaging in order to determine the cancer stage and the level of metastasis in the body. The Gleason score is used to aid with the prognosis and the PSA is valuable in monitoring and evaluation of biochemical response and recurrence (Gul *et al*., 2011). We performed statistical analysis of the PSA and Gleason scores for the Nuclear medicine cohort only. There were no data available for the chemotherapy cohort.

Table 3.6: Nuclear medicine cohort Gleason score

Gleason score Range	Frequency	Percentage (%)
>/=6	1	9.1
7-8	5	45.5
9+	1	9.1
Unknown	4	36.4
Total	11	100

Of the 11 patients with a Gleason score value, our results demonstrate that 9.1% had a Gleason score of 9 and 6 respectively. A Gleason score indicates the aggressiveness of the tumour (Gul *et*

al., 2011) and a score of 9 indicates a least- differentiated tumour, with an unfavourable prognosis, whilst the Gleason score of 6 according to Parker *et al*., (2015*)* indicates a low risk localised tumour However, both these patients were still alive during the study. Reference is made to their PSA levels and indication of biochemical recurrence with successive PSA screening for the next cycles of treatment. 45.5% of the patients had a Gleason score of 7-8, indicating least differentiated tumours, and 36.4% of the patient had an unknown Gleason score. This data is in line with the findings by Parker *et al*.,(2015) that a Gleason score of >7 is suggestive of metastatic disease. The chemotherapy cohort Gleason score values were also not indicated. We further evaluated the PSA levels of the nuclear medicine cohort. The PSA levels for this cohort were evaluated at the start of the treatment and data indicates a mean PSA level of 4.57ng/L.

3.6 Costs

3.6.1 Chemotherapy Cohort

A total of 11 patients (22.4%) of the cohort were hospitalised, with a mean hospitalisation days of 13 days, minimum days of hospitalisation being 2 day, and to a maximum of 60 days. Two patients' in-hospitalisation costs (18%) of this sub-population were excluded because the patients were hospitalised due to non-cancer related conditions (Cardio-Thoracic surgery and Aortic stenosis respectively), however, their OPD related costs were included in the OPD costs. Costs are expressed in US Dollars, as per exchange rate as at 06 January 2020, the results are illustrated in figure 4.3 below.

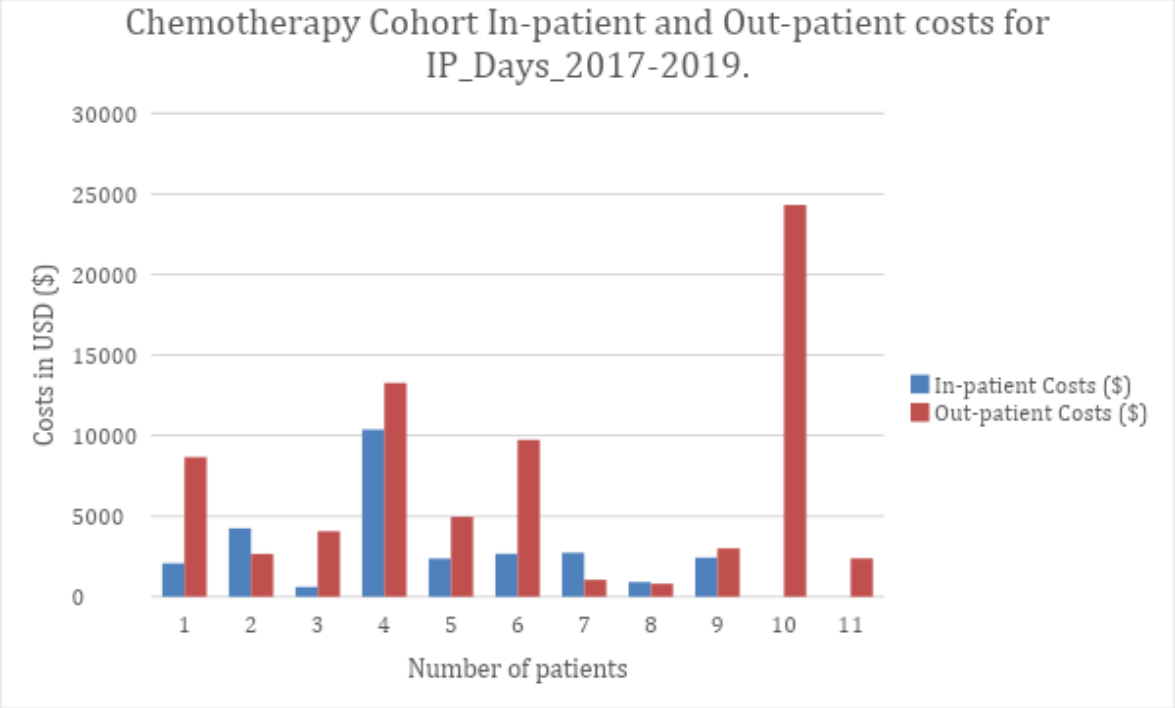

Figure 3.3: In-patient costs vs out-patient costs for the hospitalised sub-population of the chemotherapy cohort.

The results suggest that out-patient costs are higher than in-patient costs, this is consistent with the number of days as reflected per visit. An average cost of 25 000$ was incurred for a maximum 90 days out-patient visits, compared to an in hospital cost of 10 000$ incurred for a maximum of 60 days. Out-patient days do not include chemotherapy costs.

More than 80% of the patients incurred laboratory costs at an average of 500$, whilst less than 10% incurred costs at an average cost of between 500-1000$. Less than 5% of the patients incurred costs between 1500-2000$ as reflected in figure 4.4.

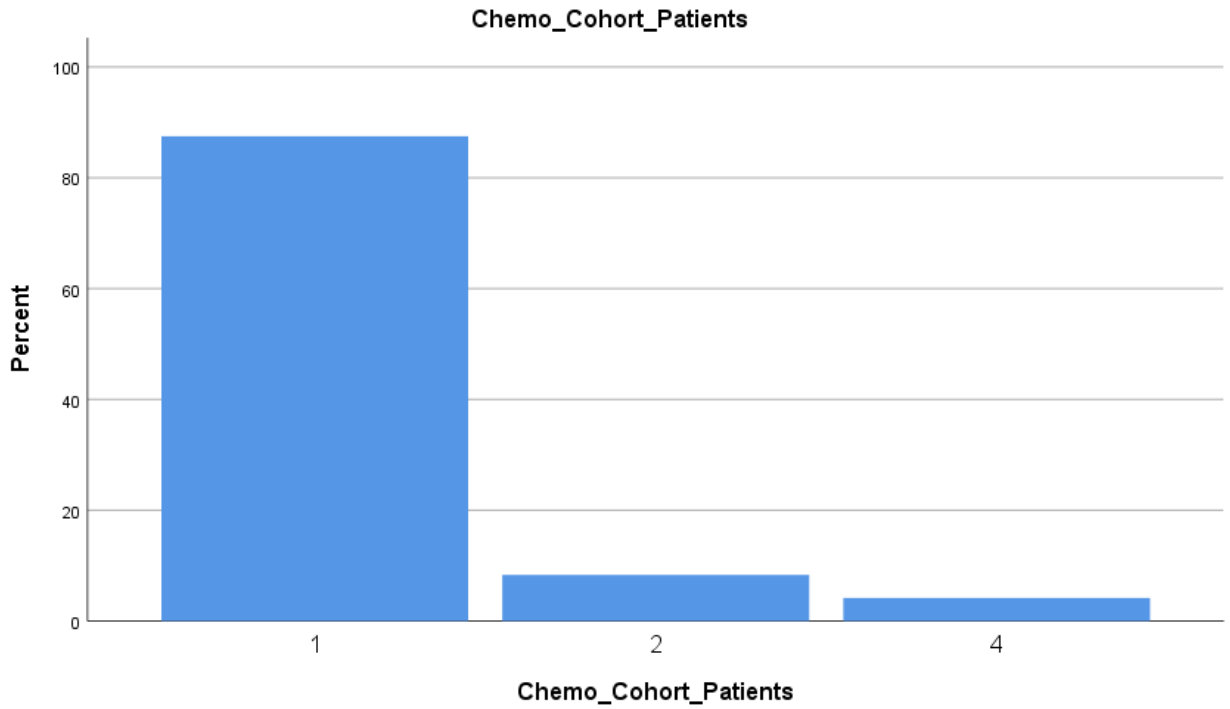

Figure 3.4: Distribution of patients per laboratory costs incurred.

Our results therefor suggests that in this cohort, laboratory costs incurred averaged between a minimum of 500$ and a maximum of 2000$. The screening for PSA was also evaluated as part of the laboratory costs at IALCH.

Table 3.7: Number of PSA level screening tests for the chemotherapy cohort.

Number of PSA screening tests	Frequency	Percentage (%)
1-10	42	91.3
10-20	2	4.3
20-30	1	2.2
30-40	1	2.2
Total	46	100.0

Our results indicate that 91.3% of the cohort had between 1 and 10 PSA screening tests performed during the study. The average cost for PSA screening in this cohort was estimated at 28USD ($) for a single test. 4.3% of the cohort had between 10 and 20 PSA tests performed. 2.2% had between 20 and 30 and 30 and 40 PSA tests respectively. Compared to the nuclear medicine cohort, the

chemotherapy cohort had more frequent PSA tests performed. In this cohort, 8% of the patients were not screened for PSA level and 22% had one PSA screening. A decline in PSA levels was observed in 35% of the patients, whilst an increase (indicative of biochemical recurrence) was observed in 33% and only 2% showed a stable (unchanging) PSA level during the study period.

We therefore sought to determine the costs that are incurred for chemotherapy related side effects, bone palliation as well as the use of Prednisone during chemotherapy. We performed a detailed manual search on MediTech™, for the costs of all regimen used for pain management, bone palliation as well as for nausea and vomiting as a common side effect. The results are illustrated in Figure 3.5 below.

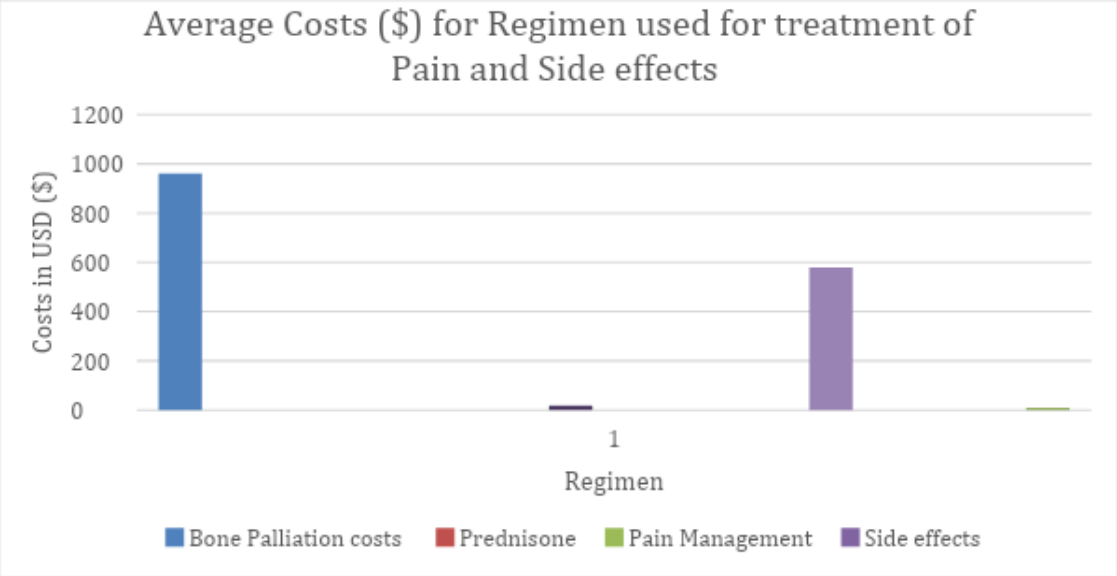

Figure 3.5: Average costs for medication used with Chemotherapy.

There were three commonly used chemotherapy regimens for the treatment of PCa. These were, docetaxel + bicalutamide + goserelin. Docetaxel was used as monotherapy in 11% of the cohort, whilst 34% were treated with a combination of goserelin and bicalutamide. Twenty one (21%)

percent of the cohort were treated with goserelin as monotherapy, and 11% with a combination of goserelin + bicalutamide + docetaxel. It was also noted that a combination of bicalutamide + docetaxel was used in the treatment of 6% of the cohort, whilst cyproterone was administered in 6% of the cohort. Other combinations accounted for 2% each in the cohort. As result, and as shown in Figure 3.7, the costs drivers were found to be docetaxel, goserelin and bicalutamide.

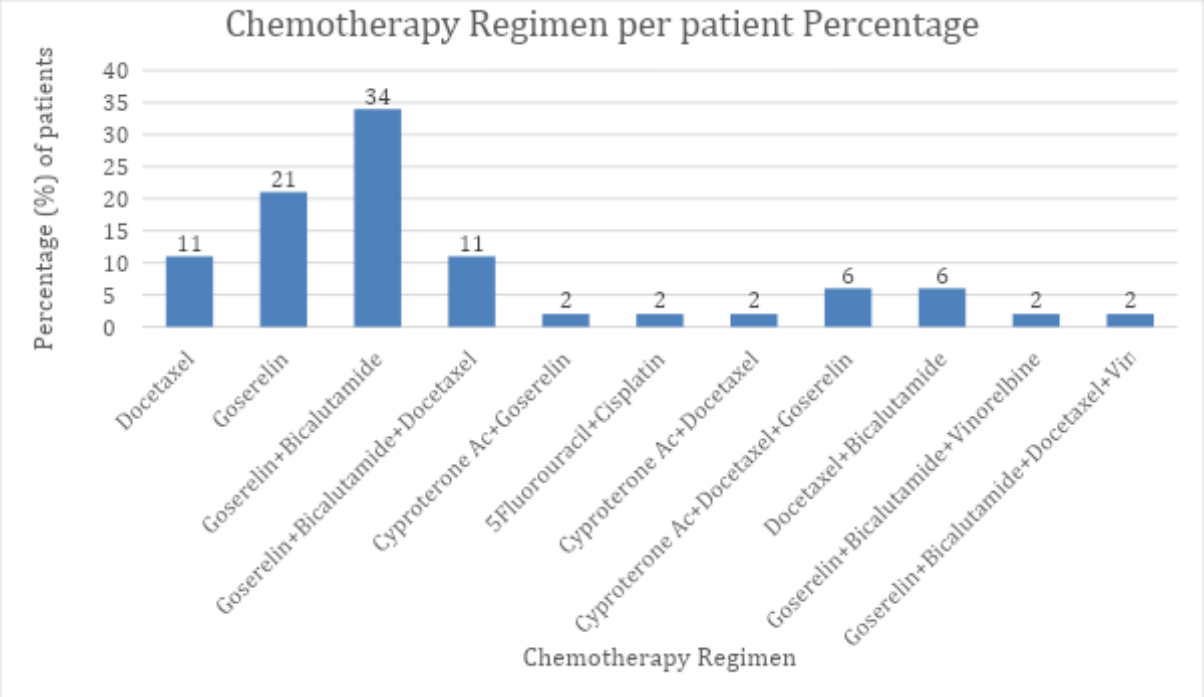

Figure 3.6: Chemotherapy Regimen

We sourced all chemotherapy related costs from the ABC Facility costs. The results indicate that chemotherapy costs have been standardised to an average cost of 454$ (R6462.00) per chemotherapy cycle. We computed costs for the cohort, and discovered that 16% of the patients were not assigned chemotherapy costs even though the regimen were known. No costs were assigned to these patients as no generalisation on cost allocation could be applied.

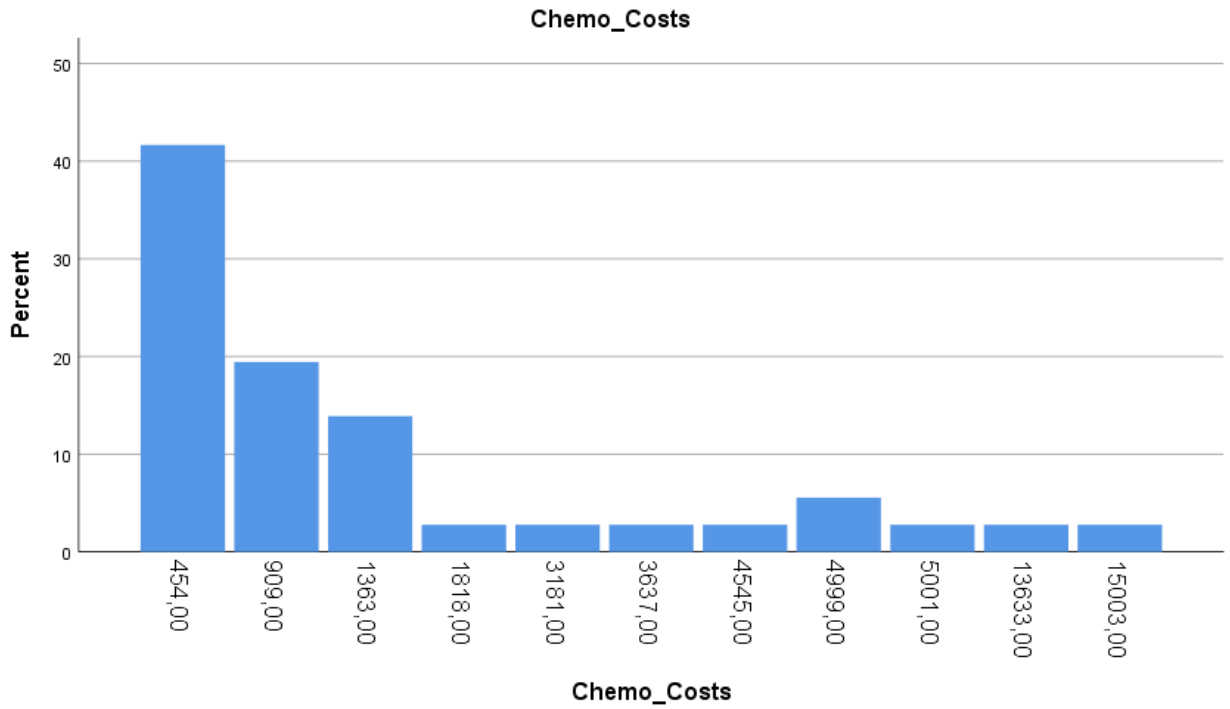

Figure 3.7: Percentage distribution of chemotherapy costs per treatment cycle.

The number of Chemotherapy treatment cycles received by patients in this cohort ranged from one cycle (454US$) to 33 chemotherapy cycles (15003US$). More than 40% of the patients in this cohort received one cycle of chemotherapy at an average cost of 454US$. Almost 20% of this cohort received 2 chemotherapy cycles at an average cost of 909US$. About 15% of the patients received three cycles of chemotherapy averaging 1363US$. Less than 5% of the patients had more than 4 cycles of chemotherapy. Two patients had 30 and 33 cycles of chemotherapy at average costs of 13 600 and 15 000 US$ respectively.

The administration of chemotherapy was found to be associated with a number of directly related costs that ranged from laboratory monitoring costs, specialists costs, radiotherapy costs, imaging costs, screening costs as well as the management of complications associated with the disease. We computed OPD related costs using data from the ABC costing model and expressed them in US Dollars as per exchange rate on 06 January 2020.

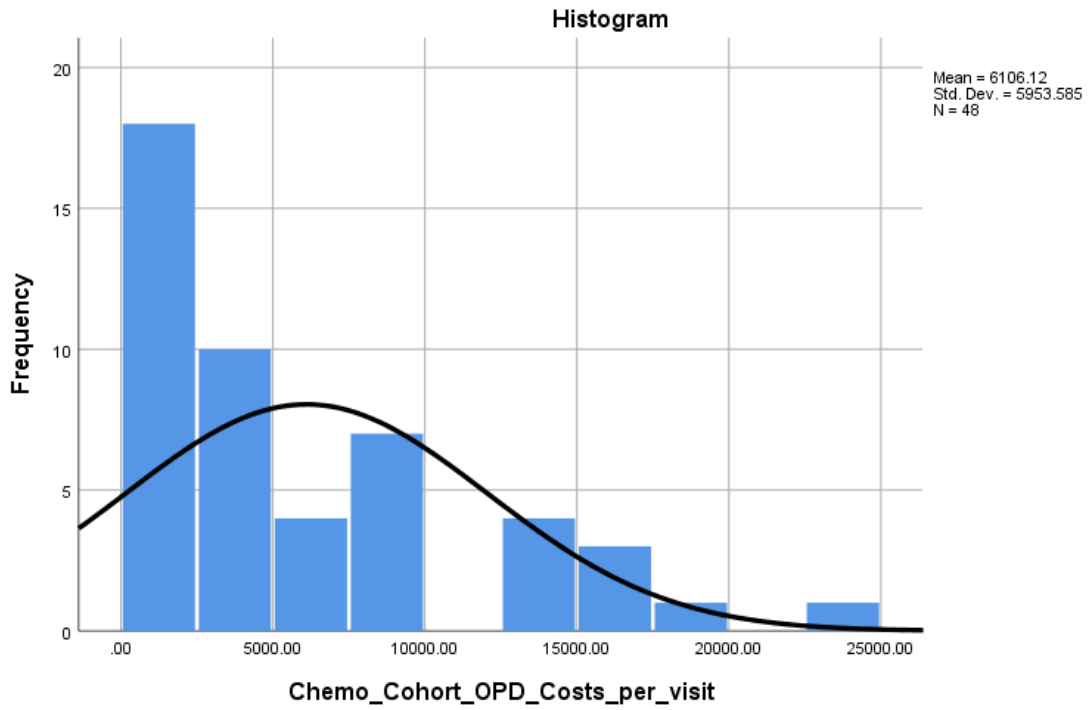

Figure 3.8: OPD related costs associated with chemotherapy administration.

The OPD costs were not individually analysed per patient, but were bundled up as relevant costs that were included in each patient's visit. These included Urological specialist visits (124$), radiotherapy costs from 332$ for example. The costs associated with drawing and analysis of chemotherapy bloods were averaged at 504$. The results in Figure 3.8 indicate that the distribution of these costs differ from patient to patient, as the level of treatment differs. However, it should be noted that these costs in this cohort, were critical in the estimation of the costs associated with chemotherapy treatment in this institution. Further analysis of these costs is discussed in the next chapter. Once the OPD costs and In-patients costs were analysed, we then presented imaging costs for each patient.

Imaging techniques at this institution for the Chemotherapy cohort included Gamma Imaging, PET and CT scanning, general X-rays as well as TH Tumour analysis for a patient treated with Lu-

PSMA in the nuclear medicine unit. We extracted this data from the ABC costing model on MediTech™, and the results are shown in Figure 3.9.

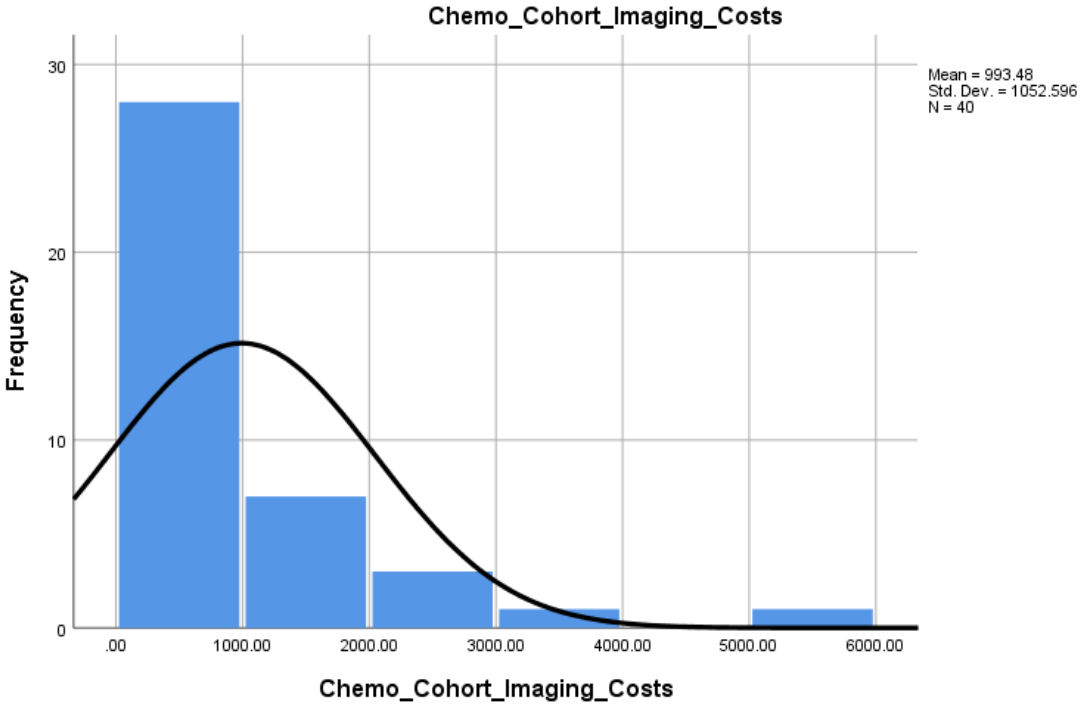

Figure 3.9: Distribution of Imaging costs

Our data indicates that the mean imaging costs were 993$, with a maximum costs of 5550$. These were attributed to a combination of imaging modalities used in this institution. The results suggest that imaging costs for the majority of the patients were averaged between 1000$ and 2000$. However, some costs escalated to an average of 5550$, which contributed largely to the total chemotherapy costs in this cohort. The results also indicated that 18% of the patients in the cohort did not have any imaging tests performed.

We then sought to determine the overall costs of chemotherapy treatment in this cohort. The costs were extracted from MediTech™ using the ABC Costing model. We converted the total costs and presented them in US Dollars.

We calculated total costs based on the ABC Facility costing model. The total costs included visits (in-patient and out-patient visits), Imaging costs as well as the surgical costs for those patients that had been hospitalised due to surgery. It should be noted that surgery costs were not included in this study, but in order to be able to compute total costs we included them as they appeared in the ABC costing model.

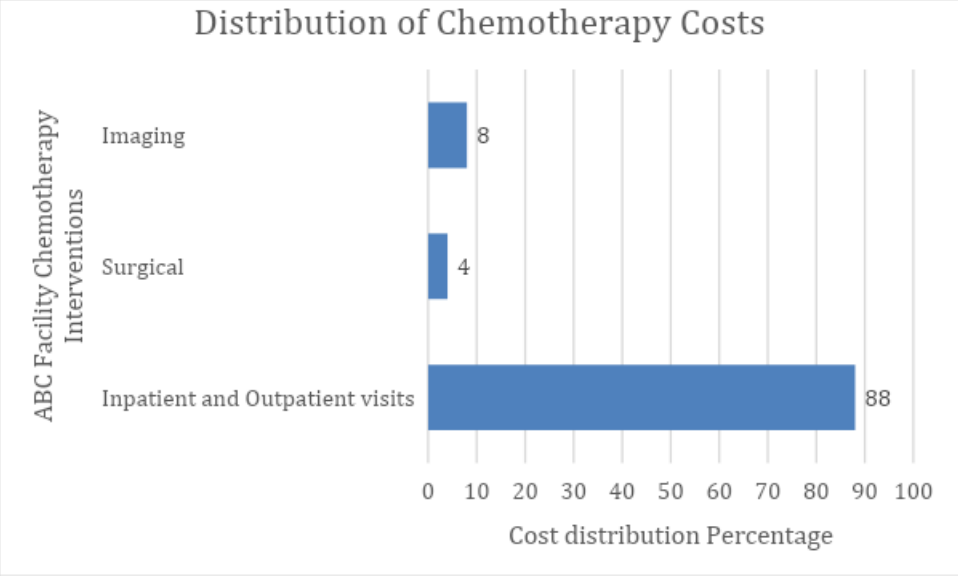

Figure 3.10: Distribution of Chemotherapy costs for the Chemotherapy Cohort.

The results indicate that the cost drivers in chemotherapy treatment are the number of visits in-patient and out-patient visits and imaging costs, which accounted for 88% and 8% of the total costs respectively. Costs incurred by patients visiting the hospital included chemotherapy regimen costs, direct medical costs such as hospitalisation costs, laboratory costs, specialists costs, costs incurred for admission in oncology wards, as well as costs that were incurred for complications of the disease.

Surgical costs accounted for 4% of the costs for this cohort. Our results indicate that on average healthcare costs incurred for cancer chemotherapy account for almost 500 000$, over a period of

3 years. We also noted that medical costs included bone palliation where there has been skeletal metastasis, the treatment of side effects as well as supporting regimen such as Prednisone. These costs were then compared to the costs incurred when patients are treated with targeted Nuclear medicine in a tertiary hospital in Johannesburg, South Africa.

3.6.2 Nuclear Medicine Cohort

In this cohort, records of 11 patients who were treated at the SBAH for metastatic castrate resistant PCa, were retrieved and analysed. Each patient was reviewed for PSA screening, Gleason score at the beginning of treatment as well as the regimen used. As shown in Figure 3.11, the findings of this study indicate that of the 11 patients, 9% of the cohort received 5cycles and a maximum of 6 cycles of Lutetium treatment respectively. 54.5% of the cohort received 4 treatment cycles of Lutetium and 27% received three cycles.

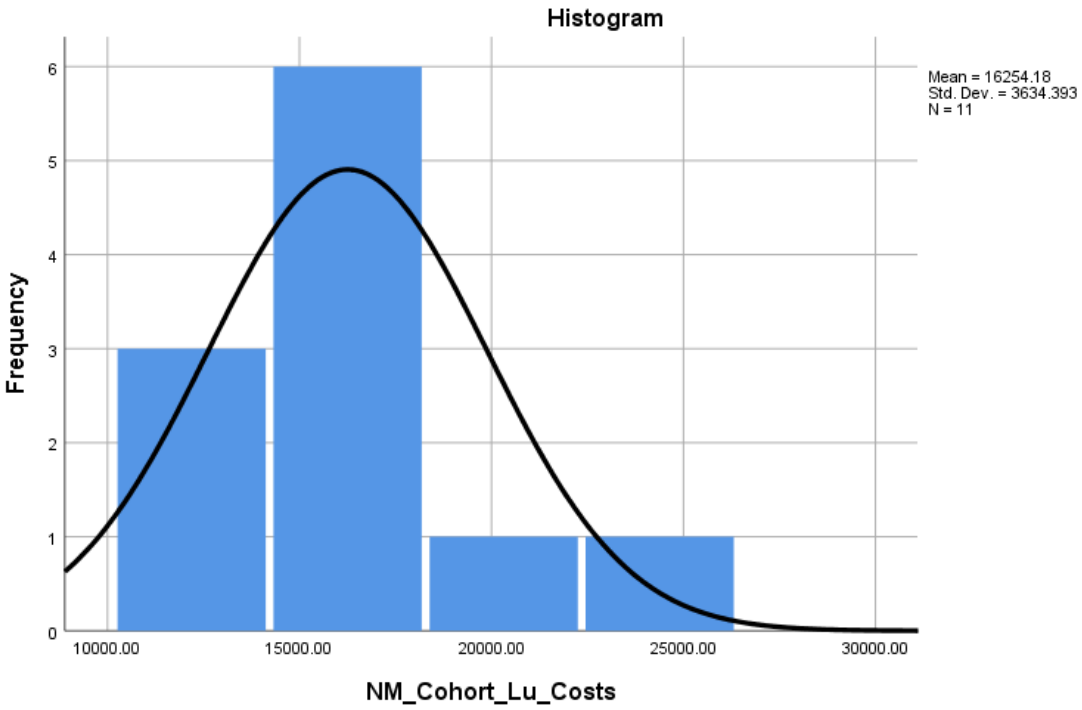

Figure 3.11: Costs of Lutetium per patient.

The majority of patients (55%) incurred an average cost of 16 250$, and 18% of the patients with more cycles of Lu-PSMA administered incurred costs above 25 000$. The mean costs of Lu-PSMA are 16 200$, and a standard deviation of 3634.393. Therefore the costs of Lu-PSMA are between 5350$ and 27 100$.

We calculated costs for aminosteryl 8% which was administered with each dose of Lu-PSMA and a maximum cost of 450$ was incurred by 27% of the cohort. For each cycle of Lutetium administered, the patient or payer incurres a standardised technical cost that covers utility and administrative cost. This cost is equivalent to a ward fee that the chemotherapy cohort also incurred. We calculated an average cost of 335$ for the recommended 4 Lu-PSMA cycles. These costs will be incorporated to the Lu-PSMA costs for the calculation of total costs for the nuclear medicine cohort.

Three imaging modalities were used for this cohort, namely Gallium imaging, Renal Imaging as well as tumour localisation. Gallium scan is performed per cycle of Lu-PSMA administration. We present descriptive statistics in Table 3.8 below for the minimum and maximum costs incurred.

Table 3.8: Imaging Costs for the nuclear medicine cohort:

	N	Minimum	Maximum	Mean	Standard Deviation (sd)
Galium – 68 costs	11	1363.0	2726.0	1817.1	406.3
Tumour localisation costs	11	182.0	364.0	306.1	73.6
Renal imaging costs	11	91.0	308.0	158.5	82.8

Our data indicates that maximum costs of 2700$, 360$ and 308$ were incurred for Ga-68-PSMA, tumour localisation and renal imaging respectively for this cohort.

Two weeks prior to the administration of Lu-PSMA, the patient undergoes laboratory testing. We performed an analysis of laboratory costs for this cohort and the results suggest that an average cost of 450$ was incurred by 55% of this cohort, whilst only 9% incurred costs to the maximum of 680$, with a standard deviation of 98.371. Our data therefore suggests that laboratory costs for this cohort range between 157$ and 750$. Of the 11 patients reviewed, only 1 patient reported xerostomia as a side effect for the nuclear medicine cohort. No treatment costs were allocated for this side effect.

We therefore computed total costs for Lutetium treatment for this cohort. We present this data in Figure 3.12

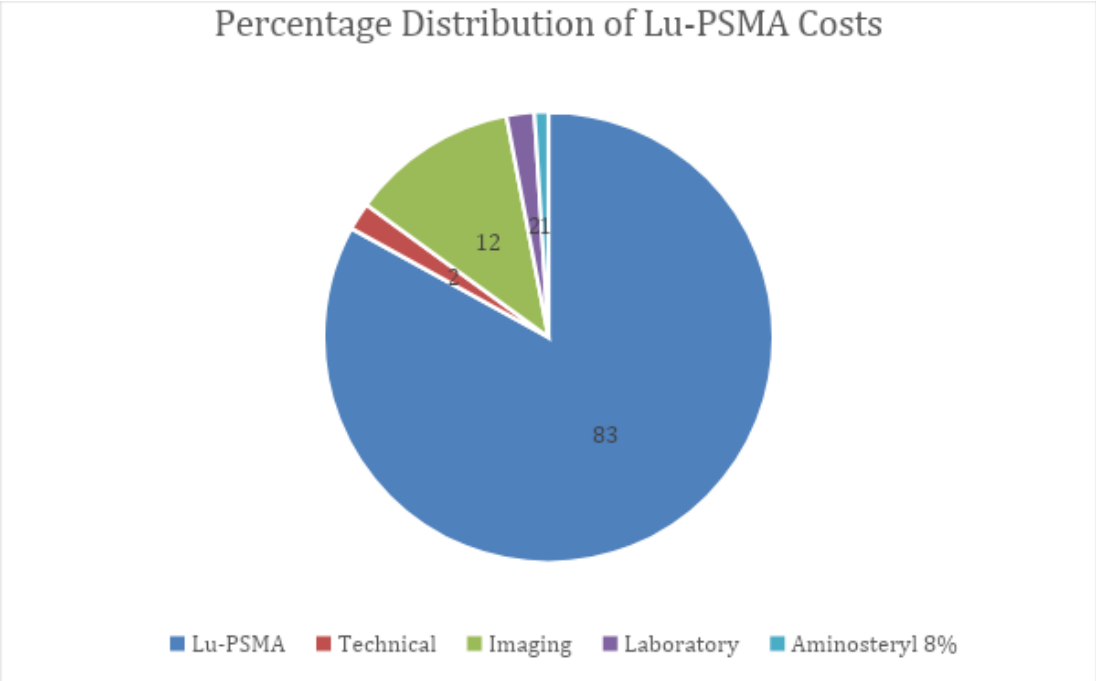

Figure 3.12: Percentage distribution of Lutetium Costs.

The total costs for the treatment of mCRPC for this cohort amounted to 215 380$ for the period of study. The cost drivers were found to be Lu-PSMA costs and imaging costs accounting for 83%

and 12% of the costs respectively. Laboratory / screening and Technical costs accounted for 2% each respectively. The administration of aminosteryl 8% for renal protection accounted for 1% of the cost. The results therefore suggest that Lu-PSMA is the cost driver for the costs incurred for this cohort amounting to 179 000$.

In order to compare the costs for the treatment of prostate cancer as aimed by this study, we compared costs incurred for chemotherapy regimens against the Lutetium costs. The cost comparison is illustrated in Figure 3.13.

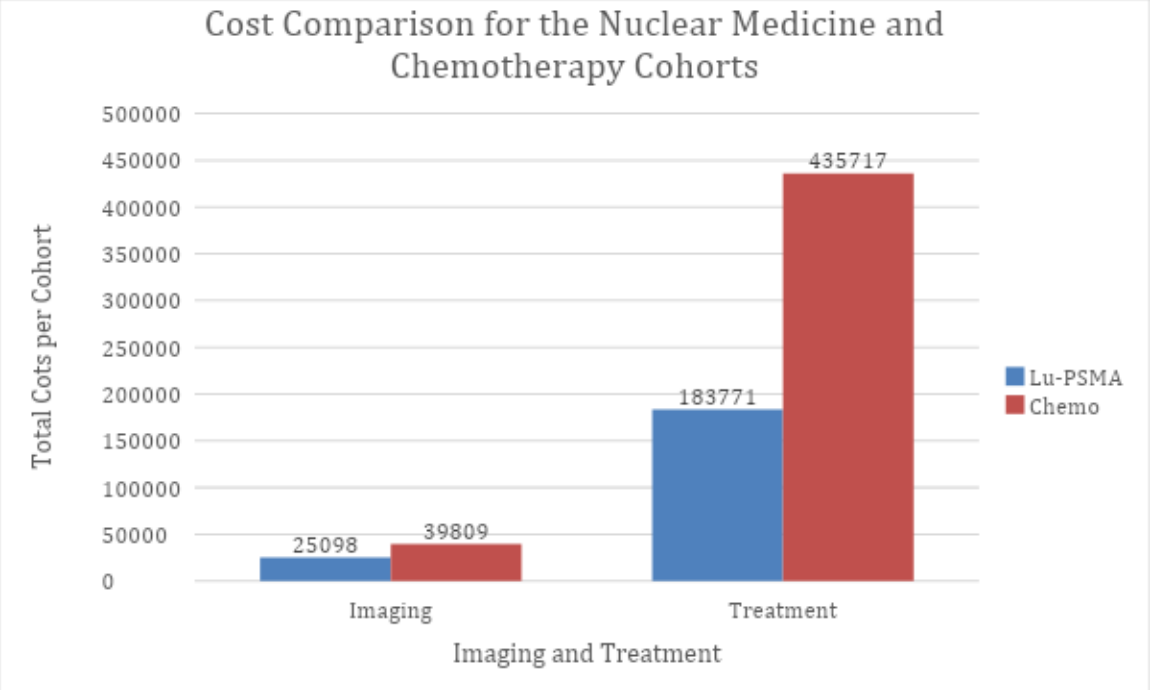

Figure 3.13: Cost comparison for the Nuclear Medicine and Chemotherapy Cohorts.

Our results suggest that the cost of chemotherapy treatment are 58% higher than the cost of nuclear medicine. This can be attributed to the differences in population sizes as well as a number of factors that need to be explored. The treatment costs in both cohorts include the laboratory / screening

costs. In the chemotherapy cohort these include both in-patient and out-patient visits, which may account for the difference in costs that is observed.

The imaging costs were observed to be higher for the chemotherapy cohort when compared to the nuclear medicine cohort. This difference is estimated to be around 37% of the total costs. This observation may also be attributed to the difference in population size as well as the frequency of imaging that each patient in the cohort was exposed to.

3.7 Costs per patient per visit

In order for us to be able to calculate the costs incurred by the patients per visit, we used the total costs incurred by the patient at the end of the study and divided them by the total number of visits of the patient in each institution, and obtained an average cost per visit for each patient. We then performed a one sample t-test for each in order determine if the differences in costs were statistically significant, and we obtained the following results illustrated in table…

Table 3. 9 : One sample Tests for Nuclear Medicine and Chemotherapy Cohorts

Cohort	N	Mean	Standard Deviation	Std Error Mean	t	df	Sig (2-tailed)	Mean Difference	95% Confidence interval of difference	
									Lower	Upper
Chemo	49	762	1511.26	215.89	0.002	48	0.998	0.48980	-433.5955	434.5751
Nuclear Medicine	11	4900	47.27	14.25	-0.06	10	0.995	-0.9091	-31.8462	31.6644

The total number of visits for the chemotherapy cohort varied from a single visit to 130 hospital visits per patient whilst the nuclear medicine cohort visits varied from 3 to 6 cycles per patient. Data from 11 and 49 patients respectively was statistically analysed.

3.8 A Rare Case of Prostatic Rhabdomyosarcoma

This patient's data were analysed separately because of his age, which did not meet the inclusion criteria. This male patient, of black race and born on the 22nd January 2015, was diagnosed with primary Stage 4 rhabdomyosarcoma. The records showed that he was HIV exposed. First visit at the hospital was on 2017/06/05, and between that period and 2018/06/08, patient visited mainly in the Paediatric Oncology, Haematology Unit, Paediatric ICU, Paediatric surgery and Paediatric High Care. In this hospital, the patient was registered with the ICD 10 code, C61: Malignant neoplasm of the prostate.

During this period, the patient had one out-patient visit and 20 in-patient admissions, with a total number of in-patient days = 187. No radiotherapy was given, but was treated with chemotherapy from 2017/02/22 to 2018/03/26. These visits incurred a total cost of R968 121.22 (68317.22$).

Between 2017/06/05 and 2018/06/08, this patient underwent several procedures in the paediatric surgery department, which included prostatectomy, cystectomy, ureterostomy and two more other procedures with a total cost of R112 236 (7920$). Chemotherapy regimens included vincristine, cyclophosphamide, ifosfamide, dactinomycin and doxorubicin. Mesna and filgrastim were administered to counteract the side effects of cyclophosphamide and chemotherapy regimen side effects respectively. Morphine elixir was used for pain management. The data also shows that various antibiotics and other treatment modalities were used during the admission in both paediatric surgery wards and paediatric ICU and high care. The costs of these were added to the costs of the visit. The total costs for this patient were R 1 097 657.00 (77458.05$). Imaging procedures included CT scans of the chest, general X-rays of the abdomen, the right hip and the

ultrasound (electrocardiogram) of the thorax to the value of R17300 (1220$). On the 8th of June 2018, the patient demised.

CHAPTER 4: Discussion, Limitations, Recommendations and Conclusion

4.1 Age at Diagnosis and patient status during the study.

Our results indicated that the mean ages at diagnosis for both cohorts were 61.18 and 66.33 respectively. Age at diagnosis ranged from 41.4 and 80.9 for the Nuclear Medicine Cohort and This data is also supported by the finding by Dewar et al who stated that Black men are diagnosed at a younger age and have more severe disease characteristics (Dewar *et al,* 2018).

For each cohort 9.1% for nuclear medicine and 26.5% of the patients were lost to follow up respectively. This suggests that these patients cannot be accounted for as their health status cannot be confirmed for this period. This is also made difficult by the fact that South Africa does not have a Prostate cancer registry, even though national registries for breast and cervical cancer exist (Hayes, *et al.*, 2017).

4.2 The Cost of Treating PCa

This study successfully investigated the costs associated with treating metastatic castrate-resistant prostate cancer with standard chemotherapy regimens when compared with the costs incurred for metastatic castrate-resistant prostate cancer treatment using targeted nuclear medicine at three tertiary hospitals in South Africa. More importantly, this is the first study in SA to compare costs of Lu-PSMA to that of chemotherapy regimen costs.

This study indicated that in the chemotherapy cohort, the majority of the patients were Black (57%). This is in line with the findings of the study by Dewar *et al.*, (2018) and the WHO statistics,

2018 that stated and indicated respectively that Black men are at a higher risk of being diagnosed with PCa. Numerous studies both in developed and developing countries have also indicated that being male and of African ethnicity predisposes to PCa.

However, it should be noted that in the nuclear medicine cohort, the majority of the patients (55%) were white. This may be attributed to the population size. However, it also raises a question that was raised by Dewar and colleagues (2018) before, as they espoused that studies focused on SA have uniformly found PCa to be more common in white than Black South Africans, and they attributed this to lower socio-economic status that an average SA black male might be less likely to be screened for PCa, than his other racial counterparts.

Pollard *et al.*(2016), stated that of men diagnosed with PCa, between 10% -20% will develop mCRPC within 5 years of diagnosis after receiving hormone ablation therapy for metastatic disease and diagnosis or recurrence. In this study we noted that of the 49 and 11 patients reviewed respectively, 6% in the chemotherapy cohort were diagnosed approximately 7 years ago, whilst in the nuclear medicine category, the longest diagnosis (9%) dates back to 22 years ago. This is noteworthy for this study for two reasons, namely (1), Lu-PSMA is used as third line therapy, when patients do not respond to any third line chemotherapy, and in most cases, this is end-stage treatment, which in this case also may account for the high mortality rate observed in this cohort, and (2), for the chemotherapy cohort at IALCH, the chemotherapy regimen used, suggests that most patients were being treated for palliation of hormone- dependent advanced PCa as well as locally advanced prostate cancer in combination with radiotherapy, which accounted for the high costs that were incurred in this cohort.

The chemotherapy cohort results indicate that the majority of the patients were treated with combination therapy as opposed to monotherapy. 11 chemotherapy regimen were observed (figure 3.6). For cost allocation in this cohort, we identified 22% of the patients in which chemotherapy costs were not assigned, even though patients were treated with chemotherapy as evidenced in the records, cost calculations could not be performed as the chemotherapy costs were standardised and cycles varied from patient to patient.

Gillesen *et al*., (2018) stated that in mCRPC, there are currently no combination treatment strategies for survival-prolonging agents that have shown an overall survival benefit as compared with monotherapy. Our study can relate to this statement as observed with the number of combination therapies that have been used in this cohort. In this cohort, the cost drivers were found to be goserelin, docetaxel and bicalutamide. These drugs were used in monotherapy and/ or in combination.

11% and 21% of patients were treated with docetaxel and goserelin monotherapy respectively, whilst 34% of patients were treated with bicalutamide and goserelin combination, 11% were treated with docetaxel, bicalutamide and goserelin combination and 6% docetaxel and bicalutamide combination. Docetaxel, according to De Vita *et al.,* (2015) is approved as the first and 3rd line chemotherapy in both symptomatic and asymptomatic PCa patients. It is the only pharmaceutical that has shown to have survival benefits (Pollard *et al.,* 2016). In a study carried out by Beebe-Dimer and colleagues (2018) it is stated that lack of consensus exists regarding the clinical benefit of bicalutamide use, either alone or in combination with a LHRH like goserelin.

Our study also noted the chronic use of goserelin in this cohort, as it shows that in 21% of the patients goserelin was used as monotherapy. Beebe-Dimer *et al.,*(2018) further state that medical

or chemical ADT involves chronic administration of the LHRH agonists or antagonist. The findings of this study are consistent with these authors 'statement as the data indicates that in the cohort a maximum of 30 cycles of chemotherapy was administered to the value of 13 633$ for one patient during the study period. Chemotherapy costs (121 800$) for this cohort accounted for 29.4% of the out-patient costs**.**

Bicalutamide is a non-steroidal first generation anti-androgen, FDA approved for use in combination therapy with a LHRH analogue, approved for the treatment of stage D2 metastatic carcinoma of the prostate (Beebe-Dimer, *et al.*, 2018). It blocks the effects of adrenal androgens at the androgen receptor to potentially prevent testosterone flare, hence its widespread use in this cohort. None of the recently FDA approved chemotherapy regimens such as arbiraterone, enzalutamide and cabazitaxel were used in this cohort.

The utility costs included costs for radiotherapy, urology specialist, radiology, haematology, oncology/ chemo bloods, treatment of oncological complications, general urology and oncology visits. These costs were deemed direct costs as they contributed to the holistic healthcare approach for the patient. This accounted (292 682$) for 70.4% of the out-patient costs.

Both docetaxel and Lu-PSMA are indicated for the treatment of mCRPC (De Vita *et al*., 2015; Von Eyben *et al*., 2017). In the nuclear medicine cohort, lutetium costs accounted for 83% of the total costs (178 796$). If chemotherapy costs are separated from the utility costs they account for 121 800$, and when compared to lutetium costs (178 796$), the lutetium costs are 1.5 times the costs of chemotherapy. Lutetium according to Von Eyben *et al.,(*2017) is associated with a PSA decline of more than 50%. In the nuclear medicine cohort, a decline in PSA of between 23% and 51% was observed in 36.4% of the cohort. Biochemical recurrence was also observed in 36.4% of

the patients, no further analysis was performed in 27.3% of the cohort. PSA screening costs were incorporated into the lab costs (4975$) and accounted for 1.3% of the total lutetium costs.

The total costs of imaging were 25 098$ and 39 809$ for the nuclear medicine and chemotherapy cohorts respectively. The costs incurred for imaging the chemotherapy cohort were 61% higher than the costs for the nuclear medicine cohort. Ga-68-PSMA PET/CT scan was used for the nuclear medicine cohort, together with the renal scan and the tumour localising imaging. The low costs associated with this cohort may be due to the size of the population and may not reflect the actual costs that may be incurred if the size of the population increased.

The higher costs associated with the chemotherapy imaging may also be attributed to a larger population size for this cohort. In this cohort a variety of imaging procedures were utilised at IALCH, due to the diverse nature of the patients. Several imaging scans were used which included the Gamma camera, CT planning scanning, PET scans, General X-Rays as well as TH tumour localising scans for nuclear medicine. Of noteworthy in this context, was the individual costs of the Ga-68-PET/CT Scan (452$), compared to a Gamma scan (664$) per cycle. This difference in costs may have contributed to the high costs incurred for the chemotherapy cohort. We needed to identify if the differences in these costs were statistically significant.

The treatment costs were found to be 183 771$ and 435 717$ for the nuclear medicine and the chemotherapy cohorts respectively. The costs of treating the chemotherapy cohort were found to be 2.4 times higher than the nuclear medicine cohort. A number of plausible contributing factors were identified. In the nuclear medicine cohort, the total treatment costs were driven by the cost of the Lutetium itself (83% of the total costs), no hospitalisation costs were reported to be incurred by this cohort compared to the chemotherapy cohort where in-patient costs, out-patient costs, and

direct chemotherapy were incurred. Laboratory/screening costs also had a direct contribution to the escalation of treatment costs for the chemotherapy cohort.

Our findings also indicated that the costs for a single visit for Chemotherapy range significantly wide, from a minimum of $12 to a maximum of $9096, whereas the costs for a single visit for nuclear medicine have a much narrower range (a uniform distribution) from a minimum of $4826 to a maximum of $4926 for the two cohorts when compared. The data showed that nuclear medicine costs approach uniformity and better predictability compared to chemotherapy costs.

Our data also indicated that the standard deviation in costs for chemotherapy is quite big ($1511) compared to a very small standard deviation ($47) in nuclear medicine treatment. These differences are statistically significant for a patient who will need to plan their therapy upfront in order to be able to complete their cycles without running into financial challenges in the middle of the treatment regimen.

We sought to investigate if there were monetary and overall survival benefits in treating prostate cancer with chemotherapy regimen compared to nuclear medicine regimen. From the results obtained, in a cohort of 49 patients in chemotherapy cohort, one death was reported, which is suggestive of a low mortality rate in this cohort. However, 20.4% in this cohort were lost to follow up. The causes could not be determined as no reasons were stipulated in the records, neither is there an existence of a prostate cancer registry in SA where such deaths if there were, could be confirmed. 77.6% of the patients were still alive. From an observational point, the survival rate in this cohort is stable. From the perspective of costs, it was evidenced by the high costs in incurred by this cohort in imaging costs, out-patient and in-patient costs, and laboratory costs that health benefits outweigh monetary benefits in this cohort.

In the nuclear medicine cohort, 27.3% were deceased, 9.1% lost to follow up and 63.6% alive. The mortality rate in this cohort is higher than in the chemotherapy cohort. This may be attributed to the fact that patients who were treated in this treatment centre, some were no longer responsive to

third line chemotherapy, biochemical recurrence was also observed that was suggestive of end stage disease. No decisive overall survival could be determined based on the small size of the population and that to the author's knowledge, this is the first cost comparison study where lutetium is compared to standard chemotherapy, therefore no model could be created or referenced to calculate the overall survival, except to compare the percentages of patients still alive at the end of the study. The results indicate that 63.6% of the cohort were still alive at the end of this study, and therefore, from the observational point, overall survival is stable for this cohort.

We also sought to investigate if there was any biochemical recurrence observed with monitoring of the PSA levels during the treatment of the patients with each regimen type.

PSA levels were monitored for the Nuclear Medicine cohort and it was observed that in 27.3% of the patients, only one PSA level was obtained and no further analysis for these patients was conducted. In 36.4% it was noted that there was biochemical recurrence with fluctuations in PSA levels during the treatment cycles. PSA level declines in the range of 23-51% were observed in 36.4% of the cohort. This result is consistent with the findings of Von Eyben and colleagues (2017) where PSA levels with the treatment of Lu-PSMA were observed to decline up to a level </=50%. This might be a plausible explanation as to the overall survival that has been observed in the nuclear medicine cohort.

Biochemical recurrence was observed in 33% of the chemotherapy cohort, whilst 35% of the cohort showed a decline in the PSA levels. Only 2% of the cohort had an unchanged PSA level during the study. 8% of the cohort did not have PSA monitoring or screening, and 22% had a single screening test for PSA levels. Our results indicated that for the majority of the patients, the treatment modalities used, caused a decline in the PSA levels, which was indicative of disease

improvement, whilst in 33% disease progression was observed. For all patients treated, costs were incurred, we also focused on the payment modalities and who incurred the costs.

South Africa has a two-tiered healthcare system where the majority of the population relies on the government for healthcare services. In this study, our results indicated that for the chemotherapy cohort, 90% of the patients were classified as H0 (non-paying patients), 6% were classified as H1, 2% were classified as H2 and H3 respectively. However, in the nuclear medicine cohort, the majority of patients (64%) were classified as PH which meant that they were either paying out of pocket (14% of the 64%), or medical aid funded (50% of the 64%). 27% and 9% of the nuclear medicine cohort were classified as H0 and H2 respectively.

Our findings therefore suggests that the majority of the patients are state funded for the chemotherapy cohort, whilst in the nuclear medicine cohort the patients or the healthcare funder incurs the majority of the costs. These findings are consistent with the findings of Addae-Korankye (2013) who reported that the ability of the national governments to provide funding for healthcare and to sustain the funding is a huge responsibility. In this case, South Africa is no exception, as our findings suggest that the burden of Prostate cancer in public hospitals lies with the national department of health to fund the hospitalisation, imaging, laboratory and treatment costs for the majority of patients with Metastatic castration resistant prostate cancer. Medical aids play a crucial role in addressing the financial burden of this disease, however, it is only a minority of the population studied as this study indicates, that are covered by the medical aid and therefore are able to access nuclear medicine treatment.

Future research is needed to evaluate such disparities, costs incurred for the treatment of prostate cancer by medical insurers, patients and the national government to assist decision makers and policy makers.

4.3 Limitations of this Study

The following limitations were observed for this study:

- Gleason score values were not available from MediTech™, for accurate staging of the patients in the chemotherapy cohort.
- Missing data points were observed for the 11% of the chemotherapy cohort for chemotherapy costs. This impacted on the presentation of the total costs of chemotherapy for this cohort.
- The unavailability of dexamethasone and ondansetron costs for the nuclear medicine cohort, impacted on the presentation of the overall costs for this cohort. We also note that the administration of Lu-PSMA is accomplished by ensuring that there is hepatic protection during the administration, supportive care in the form of a cortisone administration as well as antiemetic regimen. The data obtained did not provide costs for the antiemetic and cortisone, and these were not be included in this study. However, it should be noted that Dexamethasone injection and Ondansetron were intravenously administered with each dose of Lutetium.
- Our study could not effectively address the duration of treatment as treatment costs were presented as part of the total visits, and the study design did not accommodate the determination of treatment duration.
- The researcher could not have direct access to the MediTech™ system to access clinical records as the system is managed by the IT department at IALCH and authorisation could

not be obtained. PSA records also could be accessed, but it could not be determined when treatment modalities were adjusted for patients with biochemical recurrence.

- A small sample size was obtained at SBAH and the results could not be generalised to the SA population.

4.4 Recommendations

The following are the recommendations of this study for the improvement of clinical practice at the SBAH, Nuclear Medicine Department;

- medical personnel conduct a random audit of patient files in order to ensure accurate data management.
- records of information on all the charges of tests including drugs that are used for the administration of lutetium such as dexamethasone and ondansetron, be kept in order for the costs to be readily available to researchers and to enhance clinical practice and judgement.

At IALCH;

- continuous improvement of the MediTech™ system, and training of personnel to ensure that data integrity is preserved, and errors are timeously corrected in order to ensure that no data is missing, recommended.

Further studies on prostate cancer costs and clinical evaluation such as combination therapies used and the rationale behind such therapies need to be conducted for a better understanding of the treatment modalities used in this hospital.

It is also recommended that a PCa registry be created for SA to ensure that there is traceability of patients diagnosed with PCa.

4.5 Conclusion

In conclusion, the findings of this study suggest that for the treatment of metastatic resistant prostate cancer, this study indicates that patients treated with chemotherapy is more costly as compare to targeted nuclear medicine. However, a larger survey or audit research is needed to confirm the findings of this study.

4.6 Disclosure

Nomaswazi Gabela, is an employee of NTP-Radioisotopes. This tuition fees for this study were funded by NTP – Radioisotopes, the manufacturers of Lu-177-n.c.a. However, NTP Radio-isotopes did not contribute in the data analysis and the compilation of the research findings. The author is responsible for this work.

References

1. Addae-Korankye A. 2013.Challenges of financing healthcare in Ghana: The case of National Health Insurance Scheme (NHIS). International Journal of Asian Social Sciences. 2013, 3(2):511-522.
2. Adeloye D, David RA, Aderemi AV, Iseolorunkanmi A, Oyedokun A, Iweala EEJ, et al. (2016) An Estimate of the Incidence of Prostate Cancer in Africa: A Systematic Review and MetaAnalysis. PLoS ONE 11(4): e0153496. doi:10.1371/ journal.pone.0153496.

3. Ambikalmajan MRP.; Furn FK Jr. 2015. Evolving important role of Lutetium – 177 for therapeutic Nuclear Medicine. Current Radiopharmaceuticals. (8): 78 – 85.

4. Baldi A., Kumar S. 2013. Pharmacoeconomics: Principles, Methods and Economic Evaluation of drug therapies. PharmaTechMedica. 2 5); 362-369.

5. Beebe-Dimmer et al (2018). Patterns of Bicalutamide use in Prostate Cancer Treatment: A US Realworld analysis using the SEER-Medicare Database. Advanced Therapeutics (2018) 35:1438-1451.

6. Becerra V.; Avila M., Jimenez J.; Cortes- Sanabria L.; Pardo Y.; Garin O.; Pont A.; Alonso J.; Cots F.; Ferrer M. 2016. Multicentric Spanish group of clinically localised prostate cancer. BioMed Central Health Service Research. 16 (1): 541.

7. Bolla M., Gonzalez D., Warde P., Dubois JB., Mirimanoff R., Storme G., Bernier J., Kuten A., Strnberg C., Gil T., Collette L., Pierart M. 1997. Improved survivavl in patients with

locally advanced prostate cancer treated with radiotherapy and Goserelin. The new England Journal of Medicine. 337 (5): 295 – 300.

8. Bortel TEA.; Clark O.' Pompeo ACL.; Bretas FFH.; Sadi MV.; F U & dos Reis, RB. 2016. Efficacy and Safety of Combined Androgen Therapy (ADT) and Docetaxel Compared with ADT Alone for Metastatic Hormone – Naïve Prostate Cancer: A Systemic Review and Meta – Analysis. PLoS ONE 11(6): e0157660.

9. Bray F.; Ferlay J.; Soergomataram I.; Siegel RL.; Torre LA & Jemal A. 2018. Global Cancer Statistics 2018: Globocan Estimates of Incidence and Mortality Worldwide for 36 cancers in 185 Countries. CA: Cancer Journal Clin. 2018; 68: 394-424. American Cancer Society.

10. Buchler, T. & Harland, S.J. (2007). Chemotherapy for hormone resistsnt prostate cancer: Where are we today? Indian Journal of Urology. 2007 Jan-Mar; 23 (1): 55-60. Doi: 10.4103/0970-1591.30269.

11. Calcinotto A., Spataro C., Zagato E., Di Mitri D., Gil V., Crespo M., De Bernardis G., Losa M., Mirenda M., Pasquini E., Rinaldi A., Sumanasuriya S., Lambros M.B., Neeb A., Lucianò R., Bravi C.A., Nava-Rodrigues D., Dolling D., Prayer-Galetti T., Ferreira A., Briganti A., Esposito A., Barry S., Yuan W., Sharp A., de Bono J., Alimonti A. 2018. IL-23 secreted by myeloid cells drives castration-resistant prostate cancer. Nature doi: 10.1038/s41586-018-0266-0. [Epub ahead of print]

12. CANSA – The Cancer Association of South Africa "updated May 25 2018". Cancer Association of South Africa. Downloaded from http://www.cansa.org.za/cancer-incidence-in-south-africa on May 2018.
13. Cheng HH., Lin DW.,Yu EY. 2012. Advanced clinical states in prostate cancer. Urologic Clinics of North America 39 (4): 561 – 571
14. Chilira C.; Eranshaw SR.; Black L.; Mcdade C.; Roskell N.; Shannon P.; Montorsi F.; Andriole GL. 2011. Economic Analysis: Randomized, placebo- controlled clinical trial of Dutasteride in men at high risk for prostate cancer. Journal of Cancer Science & Therapy. 10: S3:004
15. Chiuri VE., Silvestris N., Lorusso V., Tinelli A. 2009. Efficacy and safety of the combination of docetaxel (Taxotere) with targeted therapies in the treatment of solid malignancies. Current Drug Targets 10 (10): 982 – 1000.
16. Choy M. 2018. Pharmaceutical Approval Update. Pharmacy and Therapeutics 43 (4): 207.
17. Collins R., Trowman R., Norman G., Light K., Birtle A., Fenwick E., Palmer S., Riemsma R. 2006. A systematic review of the effectiveness of docetaxel and mitoxantrone for the treatment of metastatic hormone-refractory prostate cancer. British Journal of Cancer. 95 (4): 457 – 462.
18. Collins et al (2007). A systematic review and economic model of the clinical effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer. Health Technology Assessment 2007:11 (2).

19. Correll ABS.; Barqawi AI. 2011. Prostate Cancer Chemoprevention: A current Review. Journal Cancer Science & Therapy.10:S3-002.

20. Cronje I., Paterson AC., Becker PJ. 2009. Colorectal cancer in South Africa: A heritable cause suspected in many black patients. South African Medical Journal. 99 (2): 103-106.

21. DeNardo GL., Kennel SJ., Siegel JA., Denardo SJ. 2004. Radiometals as payloads for radioimmunotherapy for lymphoma. Clinical Lymphoma 5 Suppl 1; S5 – S10.

22. Denny L. 2010. Cervical Cancer in South Africa: An overview of current status and prevention strategies. Cervical Cancer is distressingly common in developing countries. African Journals on Line. 28 (2): 70-73

23. De Paredes Esteban JCG & del Rey EJA. 2017. Docetaxel in hormone – sensitive advanced prostate cancer; GENESIS-SEFH evaluation report. Farmacia Hospitalaria. Vol 41 (4): 550 – 558.

24. DeVita VT.; Lawrence TS.; & Rosenberg SA. 2015. Cancer: Principles & Practice of Oncology, 10th Ed. Wolters Kluwer, Philadelphia. Pp 932 – 979.

25. Dong L.; Zieren RC.; Xue W.; de Reijke TM.; & Pienta KJ. 2019. Metastatic prostate cancer remains incurable, why? Asian Journal of Urology (2019) 6, 26-41.

26. Dewar M.; Kaestner l.; Zikhali Q.; Jehle K.; Sinha s.; & Lazarus J. 2018. Investigating racial diffrences in clinical and pathological features of prostate cancer in South African men. South African Journal of Surgery. Vol.56 No.2. 54-58

27. Draisma G.; Postma R.; Schroder FH.; van der Kwast TH.; de Koning HJ. 2006. Gleason score, age and screening: Modeling dedifferentiation in prostate cancer. International Journal of Cancer: 119: 2366 – 2371.

28. El-Amm J.; & Aaragon-Ching JB. 2019. The current Landscape of Treatment in Non-Metastatic Castration –Resistant Prostate Cancer. Clinical Medicine Insights: Oncology, Vol 13: 1-5.

29. Etheridge T.; Damodaran S.; Schultz A.; Richards KA.; Gawdzik J.; Yang B.; Cryns V.; & Jarrard DF. 2018. Combination Therapy with Androgen deprivation for hormone sensitive PCa. A new Frontier: Asian Journal of Urology (2019) 6, 57-64.

30. European Medicines Agency, Science Medicines Health. 2016. Assessment Report. International non- proprietary name: lutetium (177 Lu) chloride. EMA/CHMP/404078/2016. "Updated April 2016". Downloaded from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003999/WC500210144.pdf. on May 2018.

31. Filed JK., Duffy SW., Baldwin DR. Brain KE., Devaraj A., Eisen T., Green BA., Holemans JA., Kavanagh T., Kerr KM., Ledson M., Lifford KJ., McRonald FE., Nair A., Page RD., Parmar MK., Rintoul RC., Screaton N., Wald NJ., Weller D., Whynes DK.,

Williamson PR., Yadegarfar G., Hansell DM., 2016. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of Lung Cancer. South Hampton (UK): Health Technology Assessment. 20 (40).

32. Fitzmaurice C. 2018. Global, Regional, and National Cancer Incidence, Mortality, Years of life lost, Years lived with Disability, and Disability Adjusted Life-Years for 29 Cancer Groups, 1990 – 2016: A systematic Analysis for the Global Burden of Disease Study. Jama Oncology. 2018; 4(11): 1553-1568. Accessed 2019/11/11.

33. Fizazi K.; Jenkins C.; & Tannock IF. 2015. Should docetaxel be standard of care for patients with metastatic hormone-sensitive prostate cancer? Pro and contra. Annals of Oncology (2015) 26: 1660-1667.

34. Gaertner FC.; Halabi K.; Ahmadzadehfar H.; Kurping S.; Eppard E.; Kotsikopoulos C.; Liakos N.; Bundschuh R.A.; Strunk H.; Essler M. 2017. Uptake of PSMA- ligands in normal tissues is dependent on tumor load in patients with prostate cancer. Impact Journals. 8 (33): 55094 – 55103.

35. Gillesen et al (2018). Managementt of patients with advanced Prostate Cancer Consensus Conference APCC 2017. European Urology 73 (2018) 178-211.

36. GLOBOCAN: International agency for research on cancer WHO. 2012. Estimated cancer incidence, mortality and prevalence worldwide in 2012. 'Updated May 2018

. Downloaded from http://iarc.fr/old/FactSheets/cancers/prostate-new-asp. on May 2018.

37. Gravis G. 2018. Systemic treatment for metastatic prostate cancer. Asian Journal of Urology (2019) 6, 162 -168.

38. Gray AL. 2009. Medicine pricing interventions- the South African experience. Southern Medicine Review. 2 (2): 15-19.

39. Grivennikov SI., Greten FR., Karin M. 2010. Immunity, Inflammation, and Cancer. Cell. 140: 883-899.

40. Gul S.; E-Aimon U.; Ayub M. 2016. Prevalence and preventive measures of prostate cancer: A randomised study in public and private health care sector. Pharmaceutica Analytica Acta. 7 (2): 2153 – 2435.

41. Hayes VM., and Bornman R. 2017. Prostate Cancer in Southern Africa: Does Africa hold untapped potential to add value to the current understanding of a common disease?. Journal of Global Oncology. March, 2017.

42. Hofman *et al.,* 2018. A prospective randomised multicentre study of the impact of Gallium-68-PSMA PET/CT Imaging for stagig high-risk cancer prior to curative intent surgery or radiotherapy) proPSMA): Clinical Trial Protocol. BJU International 2018;122:783-793.

43. Huebner E.; Barqawi A.I. 2015. The risks and benefits of current treatment options for prostate cancer and future possibilities in advanced imaging and targeted therapy – A Review. Archives of Surgical Oncology. 1 (1).

44. Ilic D.; Djulbegovic M.; Jung JH.; Hwang EC.; Zhou Q.; Cleves A.; Agoritsas T.; & Dahm Philipp. 2018. Prostate cancer screening with prostate – specific antigen (PSA) test: a systematic review and meta-analysis. BMJ 2018;362:K3519.

45. Jadvar H. 2017. Targeted Radionuclide Therapy: An evolution toward precision cancer treatment. American Journal of Roentgenology. 209 (2): 277-288.

46. James ND.; Sydes MR.; Clarke NW *et al*., 2016. Addition of docetaxel, zoledronic acid, or both to first –line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;387: 1163-77.

47. Jacobsen E., Boyers D., and Avenell A. 2020. Challenges of Systematic Reviews of Economic Evaluations. A Review of Recent Reviews and an Obesity Case Study. Pharmacoeconomics. https://doi.org/10.1007/540273-019-00878-2.

48. Jang HS., Koo KC., Cho KS., & Chung BH. Survival Outcomes of Concurrent Treatment with Docetaxel and Androgen Deprivation Therapy in Metastatic Castration-Resistant Prostate Cancer. Yonsei Med J 2016 Sep;57(5):1070-1078 http://dx.doi.org/10.3349/ymj.2016.57.5.1070.

49. June G. 2002. NDoH: Explanation of the current policy regarding the classification of patients for the determination of fees.

50. Kabasakal L.; Toklu T.; Yeyin N.; Demirci E.; Abuqbeitah M.; Ocak M.; Aygun A.; Karayel E.; Pehlivanoglu H.; Selcuk, N.A. 2017. Lu-177-PSMA-617 Prostate – specific

membrane antigen inhibitor therapy in patients with castration – resistant prostate cancer: stability, bio – distribution and dosimetry. Molecular Imaging Radionucliear Therapy. (26) :62-68.

51. Kahn T. (2017). Patent laws lead to high prices for cancer drugs, activists say. "Updated 30 January 2018". Downloaded from https://www.businesslive.co.za/2018-01-30 on May 2018.

52. Kears et al (2018). PSA Screening, Prostate Biopsy, and Treatment of Prostate Cancer in the years surrounding the USPSTF Recommendation Against Prostate Cancer screening. Cancer, July 2018:2733-2739.

53. Koda-Kimble MA, Young LL, Kradjan WA, Guglielmo BJ: Applied therapeutics. The clinical use of drugs. 2009, Philadelphia: Lippincott Williams & Wilkins, 9.

54. Leek JT, Peng RD. Statistics. What is the question? Science 2015; 347(6228): 1314–1315.

55. Leslie SW., Siref LE. 2018. Cancer, Prostate. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing LLC, New York, United States of America. Downloaded from https://www.ncbi.nlm.nih.gov/books/NBK470550/ on 10 May 2018.

56. Le Roux HA.; Urry RJ.; Sartorius B.; & Aldous C. 2015. Prostate Cancer at a regional hospital in South Africa: we are only seeing the tip of an iceberg. South African Journal of Surgery. Vol.53 No.3&4 December 2015.

57. Lin W., & Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer. *J Clin Invest.* 2007;117(5):1175-1183. https://doi.org/10.1172/JCI31537.

58. Lipke M., Sundaram CP. 2005. Laparoscopic radical prostatectomy. Journal of minimul access surgery. 1 (4): 196-201.

59. Liu H., Wu H., Tseng Y., Zhang D., Zhu L., Dong L., Shen X., Liu T. 2018. Serum microRNA signatures and metabolimics have high diagnostic value in gastric cancer. BioMed Central. (18):415.

60. Liu C-Y., Chen K-F., Chen P-J. 2015. Treatment of Liver Cancer. Cold Spring Habor Perspectives in Medicine.5: 1-16.

61. Lorenzoni C., Oliveras L., Vilajeliu A., Carrilho C., Ismail MR., Castillo P., Augusto O., Sidat M., Menendez C., Garcia-Basteiro AL., Ordi J. Weak surveillance and policy attention to cancer in global health: the example of Mozambique. BMJ Global Health. 2018. (3):e000654.

62. Luster M., Pfestroff A., Hänscheid H., Verburg FA. 2017. Radioiodine Therapy. Seminars in Nuclear Medicine 47 (2): 126 – 134.

63. Maduirori et al (2018). Study of the relationship between Black men, culture and Prostate Cancer beliefs. Cogent Medicine. 2018, 5:1442636.

64. Mantovani A., Allavena P., Sica A., Balkwill, F. 2008. Cancer-related inflammation. NATURE. 454: 436 – 444.

65. Martins IJ. 2016. Anti-aging genes improve appetite regulation and reverse cell senescence and apoptosis in global populations. *Advances in Aging Research, 5*(1): 9-26.

66. Medzhitov R. 2010. Inflammation: New adventures of an old flame. Cell. 140:771-776.

67. Mc Cluggage, W.G. 2018. Towards developing a meaningful grading system for cervical squamous cell carcinoma. The journal of Pathology: Clinical Research. 4: 81 -85.

68. Mc Pherson K.; Steel CM.; Dixon JM. 2000. ABC of Breast Diseases: Breast Cancer – epidemiology, risk factors, and genetics. BMJ Global Health 321. 624 – 628.

69. Mervin MC.; Lowe A.; Gardiner RA.; Smith DP.; Aitken J.; Chambers SK.; Gordon L.G. 2017. What does it cost Medicare to diagnose and treat men with localised prostate cancer in the first year? Asia Pacific Clinical Oncology. 13 (3): 152 – 159.

70. Mkele G. 2010. Rational selection of cancer chemotherapy. South African Pharmacy Journal. 77 (5): 32 – 34.

71. Mngadi S. 2014. Overview of the Single Exit Price Adjustment Process. South African Pharmacy Journal. 81 (4): 49 -51.

72. Morgia G., Alnakib C., Russo GI. 2013. Application of new biotechnologies for prostate cancer treatment (Comparative analysis of Brachythearapy, Cryosurgery, Laparoscopy, Robotic arm and Cyberknife Methods). Clinical Pharmacology & Biopharmaceutics. 2:2.

73. Mustafa M.; Salih AF.; Illzam EM.; Sharifa AM.; Suleiman M.; & Hussain SS. 2016. Prostate Cancer: Pathophysiology, Diagnosis, and Prognosis. IOSR Journal of Dental and Medical Sciences. Vol 15, Issue 6 Ver II (June 2016), pp 04-11.

74. Nitipir C.; Niculae D.; Orlov C.;Barbu MA,; Popescu B.; Popa AM.; Pntea AMS, Stanciu AE.; Galateanu B.; Ginghina O.; Papadakis GZ.; Iotov BN.; Spandidos DA.; Tsatsakis AM & Negrei C. 2017. Update on radionuclide therapy in oncology (Review). Oncology Letters 14:7011-7015, 2017.

75. NCI – The (USA) National Cancer Institute. What is cancer? "Updated February 9, 2015". Downloaded from http://www.cancer.gov/about-cancer/what-is-cancer on May 2018.

76. Norum J. Nieder C. 2017. Treatments for metastatic prostate cancer (mPc): A Review of costing evidence. PharmacoEconomics 35. (12): 1223- 1236.

77. Oefelein MG 2008. Androgen suppression therapy and prostate cancer: Balancing the harms and the benefits. Cancer. 113 (12); 3275 -3278.

78. Parker C;, Gillessen S;, Heidenreich A;, & Horwich A. 2015. Prostate Cancer Algorithms: e-Update. Annals of Oncology 2015; 26 (Suppl63): v69-477.

79. Parker C.; Gillessen S.; Heidenrich A.; & Horwich A. 2015. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. Annals of Oncology 26 (Supplement 5): v69-v77.

80. Prat J. 2013. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. International Journal of Gynaecology and Obstetrics. 124: 1-5.

81. Rahman F.; Rahardjo HE.; Ariwicaksono SC.; Hafizar MGA.; Sembiring RE.; Patandung R.; Hidianingsih S.; & Hotasi SL. 2017. The Role of Docetaxel in Non-Castrate Resistant Metastatic Prostate Cancer: An Evidence – based Case Report. Indones Journal of Internal Medicine. Vol 49 (1): 75-78.

82. Rahbar *K.;* Ahmadzadehfar H.; Kratochwill C, *et al*. German Multicentre Study Investigating Lu-PSMA-617 Radioligand Therapy in Advanced Prostate Cancer Patients, *Journal of Nuclear Medicine*. 2017;58(1):85-90. Doi:10.2967/jnumed.116.183194.

83. Rajamanickam B.; Kuo AL.; Richard Y.; Kheng-Wei Y. 2012. Cancer and radiation therapy: Current advances and future directions. International Journal of Medical Sciences. 9 (3): 193 -199.

84. Rauscher et al (2016). Ga-68-PSMA ligand PET/CT in patients with Prostate Cancer: How we review and report: Cancer Imaging (2016). 16:14

85. Restelli U., Ceresoli GL.; Croce D.; Evangelista L.; Maffioli LS.; Gianocelli L.; Bombardien E. 2017. Economic burden of the management of metastatic castrate resistant prostate cancer in Italy: a cost of illness study. Cancer Management and Research. 9: 789 – 800.

86. Ricciuti B., Mencaroni C., Paglialunga L., Pacicillo F., Crino L., Chiari R., Metro G. 2016: Long noncoding RNAs: new insights into non-small cell lung cancer biology, diagnosis and therapy. Medical Oncology. 33 (2):18.

87. Ritch C.; & Cookson M. 2018. Recent trends in management of advanced prostate cancer. F1000Research 2018, 7. 1513.

88. RJHS Drug Alert. (2018). Drug Alert – FDA Approval – lutetium Lu 177 dotatate injection, for intravenous use (LUTATHERA ®). "updated Feb 2018". Downloaded in from https://www.rjhealthsystems.com/2018/02/07/new-drug-announcement-lutetium-lu-177 in March 2018.

89. Robinson R. 1993. Economic Evaluation and Healthcare: Cost – effectiveness Analysis. BioMed Journal. 307:793-795.

90. Rodriguez SA., Funez FA., Bravo CB., Rodriguez-Patron Rodriguez R., Mayayo ES., Palacios VH., Revilla FJB. 2013. Cryotherapy for primary treatment of prostate cancer: Intermediate term results of a prospective study from a single institution. Prostate Cancer. 2014:571576.

91. Rubin P;, & Williams JP. 2001. Clinical Oncology: A Multidisciplinary Approach for Physicians and Students, 8th Ed. Pg 458-460.

92. Sack BS.; Langenstroer P.; Guralnick ML.; Jacobsohn KM.; O'Connor RC. 2016. Cystectomy and urinary diversion for the management of a devastated lower urinary tract

following prostatic cryotherapy and / or radiotherapy. Wisconsin Medical Journal 115 (2): 70-73.

93. Saraf AA (2013). Geographic Variation in the costs of Prostate Cancer Care. http://elischolar.library.yale.edu/ysphtdl/1257.

94. Sartorius K., Sartorius B., Govender PS., Sharma V., Sheriff A. 2016. The future cost of cancer in South Africa: An interdisciplinary cost management strategy. South African Medical Journal.106 (10): 949-950.

95. Persuad S.; Persuad M.; Goetz L.; & Narinesingh D. 2018. The current state of prostate cancer treatment in Trinidad and Tobago. Ecancer 2018,12:828.

96. Schar BE. 2015. Screening for lung Cancer: A review. South African Pharmaceutical Journal. 2 (4): 101- 107.

97. Schroeck FR.; Jacobs BL.; Bhayani SB.; Nguyen PL.; Penson D.; Hu J. 2017. Cost of new technologies in prostate cancer treatment: Systematic review of costs and cost effectiveness of robotic- assisted laparoscopic, prostatectomy, intensity – modulated radiotherapy and proton beam therapy. European. Urology. 72 (5): 712 – 435.

98. Sinanovic E., Moodley J., Barone MA., Mall S., Cleary S. Harries J. 2009. The potential cost-effectiveness of adding a human papillomavirus vaccine to the cervical cancer screening programme in South Africa. Vaccine 27: 6196 – 6202.

99. Singh E., Underwood JM., Nattey C., Babb C., Sengayi M., Kellett P. 2015. South African National Cancer Registry: Effect of withheld data from private health systems on cancer incidence estimates. South African Medical Journal 105 (2): 107 – 109.

100. Scher HI., Halabi S., Tannock I., Morris M., Sternberg CN., Carducci MA., Eisenberger MA., Higano C., Bubley GJ., Dreicer R., Petrylak D., Kantoff P., Basch E., Kelly WK., Figg WD., Small EJ., Beer TM., Wilding G., Martin A., Hussain M. 2008. Prostate cancer clinical trials working group: Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. Journal of Clinical Oncology 26 (7); 1148 – 1159

101. Sciarra A., Fasulo A., Ciardi A., Petrangeli E., Gentilucci A., Maggi M., Innocenzi M., Pierella F., Gentile V., Salciccia S., Cattarino S. 2016. A meta – analysis and systematic review of randomised controlled trials with degarelix versus gonadotropin – releasing hormone agonists for advanced prostate cancer. Medicine (Baltimore). 95 (27): e3845.

102. Segone AM;, Haffejee M;, Wentzel, S;, Heyns CF;, Mutambirwa SBA;, Coetzee L;, Barnes R;, Porteous P;, Mackenzie M;, Bongers M;, de Kock MLS;, Bigalke M;, Moshokoa EM;, Chetty P;, & Naude A. 2013. Prostate Cancer Diagnostic and Treatment Guidelines. The Prostate Cancer Foundation of South Africa.

103. Shalini Jindal et al. 2011. Human Papillomavirus in Benign Prostatic Hyperplasia and Prostatic Adenocarcinoma patients. Pathology & Oncology Research. Vol 17: pgs. 613-617.

104. Sun Y., Peng Z-L., 2009. Programmed cell death and cancer. Postgraduate Medical Journal 85 (1001): 134 – 140.

105. The Lancet. 2018. Cancer drugs in China: affordability and creativity. Lancet 391 (1033); 1866. "updated 12 -18 May 2018". Downloaded from https://www.sciencedirect.com/science/article/pii/S0140673618310341. On May 2018.

106. Teo MY.; Rathkopf DE,; & Kantoff P. 2019. Treatment of Advanced Prostate Cancer. Annual Rev Medicine. 2019 Jnuary 27; 70: 479-499.

107. Tomasetti C., Vogelstein B., 2015. Cancer aetiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. Science 347 (6217); 78 – 81.

108. Torre LA.; Siegel RL; Ward EM.; Jemal, A. 2016. Global cancer incidence and mortality rates and trends- An Update. Cancer Epidemiology, Biomarkers and Prevention: 25 (1):16 – 27.

109. Torre LA., Bray F., Siegel RL.; Ferlay J., Lortet-Tieulent J., Jemal, A. 2015. Global Cancer Statistics, 2012. A Cancer Journal for Clinicians 65:87-108.

110. Turnbull C, Hodgson S. Genetic predisposition to cancer. *Clin Med (Lond)*. 2005;5(5):491-498. doi:10.7861/clinmedicine.5-5-491.

111. USPSTF - US Preventive Services Task Force. 2018. Screening for Prostate Cancer. The Journal of American Medical Association 319 (18); 1901 – 1913.

112. Underwood JCE;, & Cross SS. General and Systematic Pathology. (2009). 5th Ed. Churchill, Livingstone.

113. Vanderpuye V. DNK., Yarney J. 2014. Cost effectiveness of cancer therapies in Africa. Journal of Medical Diagnostic Methods.3 (1): 1000e108.

114. Vanneste BGL., Van Limbergen EJ., van Lin EN., van Roermund JGH., Lambin P. 2016. Prostate cancer radiation therapy: What do Clinicians have to know? Biomed Research International. 6829875.

115. Van Soet RJ.; & de Wit R. 2015. Irrefutable evidence for the use of docetaxel in newly diagnosed metastatic prostate cancer: results from the STAMPEDE and CHAARTED trials. BMC Medicine (2015) 13: 304.

116. Vassilev A., DePamphilis cML. 2017. Links between DNA Replication, stem cells and Cancer. Genes 8: 45.

117. Von Eyben FE.; Singh A.; *et al*. 2019. ^{177}Lu-PSMA radioligand therapy of predominant lymph node metastatic prostate cancer. Oncotarget, 2019, Vol.10, (25), pp: 2451 – 2461.

118. Von Eyben FE., Roviello G., Kiljunen T., Uprimny C., Virgolili I., Kairemo K., and Joensuu T. 2017. Third – line treatment and ^{177}Lu-PSMA radioligand therapy of metastatic castration-resistant prostate cancer: a systematic review. European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:496-508.

119. Walter E., Zehetmayer S. 2016. Guidelines for Health Economic Evaluations. 'Updated in 2016". Downloaded from https://www.ispor.org/PEguidelines/source/Guidelines_Austria.pdf. on 14 June 2018.

120. Wang K.; Ruan H.; Xu L.; Liu D.; Yang H.; Zhang x.; & Chen K. 2018. Recent advances on the progressive mechanism and therapy in castration –resistant prostate cancer. OncoTargets and Therapy 2018:11 3167 – 3178.

121. Wen L.; Yao J.; & Valderrama A. 2019. Evaluation of Treatment Patterns and Costs in Patients with Prostate Cancer and Bone Metastases. Journal of Managed care & Specialty Pharmacy. Vol 25 (3-b).

122. WHO – World Health Organisation. 2008. Radiopharmaceuticals: Final text for addition to the International Pharmacopoeia. "Updated in 2008". Downloaded from http://www.who.int/medicines/publications/pharmacopoeia/Radmethodanalysis.pdf. in May 2018.

123. WHO – World Health Organisation Press Release No.: 231, 2015. Most types of cancer not due to "bad luck" IARC responds to scientific article claiming that environmental and lifestyle factors account for less than one third of cancers. "Updated in 2015". Downloaded from http://www.who.int/. in May 2018.

124. Xu J.; & Qiu. 2019. Current opinion and mechanistic interpretation of combination therapy for castration – resistant prostate cancer. Asian Journal of Andrology (2019) 21, 270-278.

125. Yang TT., Cao N., Zang HH., Wei JB., Song XX., Yi DM., Chao SH., Zhang LD., Kong LF., Han SY., Yang YX., Ding SZ. 2018. Helicobacter pylori infection-induced H3Ser10 phosphorylation in stepwise gastric carcinogenesis and its clinical implications. Helicobacter. 15: ei2486.

126. Youlden DR.; Cramb SM.; Baade PD. 2008. The International Epidemiology of Lung Cancer. Geographical Distribution and Secular Trends. Journal of Thoracic Oncology. 3 (8): 819 – 831.

Appendix A: Research Ethical Approvals

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

25 October 2018

Mrs N Gabela (214571801)
School of Health Sciences
College of Health Sciences
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Protocol: Comparison of the costs of treating prostate cancer with standard chemotherapy regimens versus targeted nuclear medicines.
Degree: MMed
BREC Ref No: BE458/18

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 25 July 2018.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 12 October 2018 to BREC letter dated 10 September 2018 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval** and may begin as from 25 October 2018. Please ensure that site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from **25 October 2018.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 13 November 2018.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

Supervisor: mathibel@ukzn.ac.za
Postgrad admin: nenep1@ukzn.ac.za

Biomedical Research Ethics Committee
Professor V Rambiritch (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 2486 **Facsimile:** +27 (0) 31 260 4609 **Email:** brec@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

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100 YEARS OF ACADEMIC EXCELLENCE
Founding Campuses: Edgewood Howard College Medical School Pietermaritzburg Westville

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

- FWA 00002567, Approved dd 22 May 2002 and Expires 03/20/2022.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 03/14/2020.

24 October 2019

Approval Certificate
New Application

Ethics Reference No.: 747/2018
Title: Comparison of the Costs of Treating Prostate Cancer with Standard Chemotherapy Regimens versus Targeted Nuclear Medicines

Dear N Gabela

The **New Application** as supported by documents received between 2019-01-09 and 2019-10-23 for your research, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 2019-10-23.

Please note the following about your ethics approval:

- Ethics Approval is valid for 1 year and needs to be renewed annually by 2020-10-24.
- Please remember to use your protocol number (747/2018) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, monitor the conduct of your research, or suspend or withdraw ethics approval.

Ethics approval is subject to the following:

- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

Additional Conditions:

- Approval is conditional upon the Research Ethics Committee receiving approval from Department of Nuclear Medicine.

We wish you the best with your research.

Yours sincerely

Dr R Sommers
MBChB MMed (Int) MPharmMed PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health).

Research Ethics Committee
Room 4-60, Level 4, Tswelopele Building
University of Pretoria, Private Bag X323
Arcadia 0007, South Africa
Tel +27 (0)12 356 3084
Email deepeka.behari@up.ac.za
www.up.ac.za

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

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

DIRECTORATE:
Office of The Medical Manager
IALCH

Reference: BE 458/18
Enquiries: Medical Management

11 October 2019

Mrs N Gabela (214571801)
School of Clinical Medicine
College of Health Sciences

Dear Ms Gabela

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: **Comparison of the costs of treating prostate cancer with standard chemotherapy regimens versus targeted nuclear medicines.**

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 Dr N Tatenali
p/p **Medical Manager** Acting

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

ADDINGTON HOSPITAL

P.O. BOX 977
DURBAN
4000
Tel: 031-327-2970 Email: reshma.boodhai@kznhealth.gov.za
www.kznhealth.gov.za

OFFICE OF THE CHIEF EXECUTIVE OFFICER

Reference: *9/2/3/R*

Date: 30th October 2019

Principal Investigator:
- **Mrs N Gabela**

PERMISSION TO CONDUCT RESEARCH AT ADDINGTON HOSPITAL: "COMPARISON OF THE COST OF TREATING PROSTATE CANCER WITH STANDARD CHEMOTHERAPY REGIMENS VERSUS TARGETED NUCLEAR MEDICINES"

I have pleasure in informing you that permission has been granted to you by Addington Hospital Management to conduct the above research.

Please note the following:

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. Please ensure this office is informed before you commence your research.
4. Addington Hospital will not provide any resources for this research.
5. You will be expected to provide feedback on your findings to Addington Hospital.

DR M NDLANGISA
HOSPITAL MANAGER
ADDINGTON HOSPITAL

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

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

DIRECTORATE:
Health Research & Knowledge Management

NHRD Ref: KZ_201908_031

Dear Mrs N. Gabela
UKZN

Approval of research

1. The research proposal titled **'Comparison of the costs of treating prostate cancer with standard chemotherapy regimens versus targeted nuclear medicines'** 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: 26/09/19

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

STEVE BIKO ACADEMIC HOSPITAL

Enquiries: Dr JS Mangwane
Tel No: +2712 345 2018
Fax No: +2712 354 2151
e-mail: joseph.mangwane@gauteng.gov.za

For attention: ___Dr Lehlohonolo Mathibe
NHRD Ref Number: GP_201908_033
SBAH Ref Number: _____SBAH 201908_08

Re: REQUEST FOR PERMISION TO CONDUCT RESEARCH AT STEVE BIKO ACADEMIC HOSPITAL

TITLE:

Comparison of the Costs of Treating Prostate cancer with Standard Chemotherapy Regimens versus Targeted Nuclear Medicines

Permission is hereby granted for the above-mentioned research to be conducted at Steve Biko Academic Hospital.
This is done in accordance to the "Promotion of access to information act No 2 of 2000".
Please note that in addition to receiving approval from Hospital Research Committee, the researcher is expected to seek permission from all relevant department.
Furthermore, collection of data and consent for participation remain the responsibility of the researcher.
The hospital will not incur extra cost as a result of the research being conducted within the hospital.
You are also required to submit your final report or summary of your findings and recommendations to the office of the CEO.

Approved

Comment: _____
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.

Dr. J S. Mangwane
Manager: Medical Service

GAUTENG PROVINSIALE REGERING
DEPT VAN GESONDHEID
STEVE BIKO AKADEMIESE HOSPITAAL
STEVE BIKO ACADEMIC HOSPITAL
Date: 2019 -08- 27
PRIVAATSAK/PRIVATE BAG X169
PRETORIA 0001
GAUTENG PROVINCIAL GOVT
DEPT OF HEALTH

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

STEVE BIKO ACADEMIC HOSPITAL

Enquiries: Dr JS Mangwane
Tel No: +2712 345 2018
Fax No: +2712 354 2151
e-mail: joseph.mangwane@gauteng.gov.za

For attention: ___Dr Lehlohonolo Mathibe

NHRD Ref Number: GP_201908_033

SBAH Ref Number: _____SBAH 201908_08

Re: REQUEST FOR PERMISION TO CONDUCT RESEARCH AT STEVE BIKO ACADEMIC HOSPITAL

TITLE:

Comparison of the Costs of Treating Prostate cancer with Standard Chemotherapy Regimens versus Targeted Nuclear Medicines

Permission is hereby granted for the above-mentioned research to be conducted at Steve Biko Academic Hospital.
This is done in accordance to the "Promotion of access to information act No 2 of 2000".
Please note that in addition to receiving approval from Hospital Research Committee, the researcher is expected to seek permission from all relevant department.
Furthermore, collection of data and consent for participation remain the responsibility of the researcher.
The hospital will not incur extra cost as a result of the research being conducted within the hospital.
You are also required to submit your final report or summary of your findings and recommendations to the office of the CEO.

Approved

Comment: _____
. _____
. _____

GAUTENG PROVINSIALE REGERING
DEPT VAN GESONDHEID
STEVE BIKO AKADEMIESE HOSPITAAL
STEVE BIKO ACADEMIC HOSPITAL
Date: 2019 -08- 27
PRIVAATSAK/PRIVATE BAG X169
PRETORIA 0001
GAUTENG PROVINCIAL GOVT
DEPT OF HEALTH

Dr. J S. Mangwane
Manager: Medical Service

Appendix B: Non-Disclosure Agreement: NTP Radioisotopes

CONFIDENTIALITY AGREEMENT

entered into by and between:

NTP RADIOISOTOPES SOC Ltd

and

NOMASWAZI GABELA

and

UNIVERSITY OF KWAZULU-NATAL

PARTIES

The parties to this Agreement are:

NTP RADIOISOTOPES SOC Ltd, a subsidiary of the Nuclear Corporation of South Africa, having a principal place of business located at Building 1700, Pelindaba, Elias Motsoaledi Street Extension (Pretoria), Brits District, North West Province, duly represented by **Gavin Ball** in his capacity as **Acting Group Executive: Safety, Regulatory & Compliance** and being duly authorised thereto (hereinafter referred to as **"NTP"** or "**Disclosing Party**");

and

NOMASWAZI GABELA, an adult female with Identity Number 721027 0316 08 4 employed as a Quality Assurance Pharmacist by NTP and enrolled for Masters in Pharmacy (Pharmacoeconomics) at the University of Kwazulu-Natal.

and

UNIVERSITY OF KWAZULU-NATAL, a Higher Education Institution registered in terms of the Higher Education Act, duly represented by **Mr. Eric Njabulo Zuma** in his capacity as **Director of Governance & Administration** and he being duly authorised thereto (hereinafter referred to as "**Receiving Party**")

(hereinafter individually referred to as a "**Party**" and jointly as the "**Parties**")

Relating To: A Research Study to be conducted by the Receiving Parties at NTP Radioisotopes SOC LTD in relation to the Masters in Pharmacy (Pharmacoeconomics) enrolled by Nomaswazi Gabela ("**the Purpose**")

RECORDAL & UNDERTAKINGS:

A. The Parties hereto possess Confidential Information relating to the Purpose, all of which are regarded by them as commercial assets of considerable value.

B. NTP is willing to disclose Confidential Information to the other Parties in pursuance of the Purpose, subject to the terms and conditions as set out in this Agreement.

C. The Parties wish to set out their rights and obligations with respect to the use, handling, and further disclosure of Confidential Information which is disclosed by either Party to the other.

D. The Receiving Party hereby undertakes to ensure at all times that the secrecy provisions contained in the Nuclear Energy Act, 46 of 1999, as well as the security measures laid down by NTP from time to time are strictly observed.

E. All documentation containing classified information shall remain the property of NTP, and on termination or conclusion of the Training Programme (the Purpose), the Receiving Party shall ensure that all such documentation and copies thereof are left at NTP.

PRIVACY

A. The Receiving Party acknowledges that, in the course of the Research, he/she and/or its personnel may have access to and sight of personal information relating to persons whose personal information has been gathered by the other party.

B. The Receiving Party further acknowledges that he/she is aware that this information is regarded as strictly private to NTP and the particular person to whom it relates, that the information is, or may be subject, to the protection of privacy or data control legislation within South Africa or any other competent jurisdiction and that the improper disclosure of such information may render NTP liable to criminal or civil proceedings.

C. The Receiving Parties undertakes to ensure that only its personnel, representatives or agents who, in the course of the Purpose, need to have access to personal information recorded by NTP, are given such access and that they are aware of the obligation not to disclose such information to any third party.

D. The Receiving Party acknowledges the provisions of Section 63 of the Promotion of Access to Information Act 2000 (Act 2 of 2000). This Section provides that the parties must refuse a request for personal information relating to a third party who is a natural person, the disclosure of which is unreasonable.

E. The Receiving Party agree that in the event of a breach of the obligations established in this clause due to her/his wilful default or negligence or that of their personnel, agents or representatives, it shall indemnify against all direct damages suffered by NTP as a result of such breach.

PUBLICATION

A. The publication of the Research Material is subject to the final acceptance by NTP in writing.

B. If the Research Material is not accepted for publication by NTP, the portions of the Research Material which NTP finds to be unacceptable for publishing, shall be severed from the Research Material.

C. The Author(s) and the Receiving Parties shall hold harmless and indemnify NTP from any third party claims resulting from the publication of the Research Material.

D. The Receiving Parties and Authors undertakes to adhere to NTP's compliance with privacy legislations and regulations, patient confidentiality, including POPI compliant.

INFORMATION SECURITY

A. The Receiving Party acknowledges that it and all of its personnel that are granted access to NTP's premises, information or information systems shall be subject to the Information Security Policies, practices and procedures governing Information Security within NTP.

B. The Receiving Party shall ensure that all persons who are given access to NTP's premises, information or Information systems are aware of their obligations in terms of NTP's Information Security Controls.

C. Where necessary, in the sole discretion of an authorised representative of NTP, any other Party shall sign agreements governing their adherence to the Information Security controls required by NTP.

D. If the other Party is granted remote access to NTP's information system, whether for reasons of development or support, an agreement governing the provision of remote access shall be entered into prior to the provision of remote access.

E. The Receiving Parties acknowledge and agree that the Classified Information furnished hereunder is and shall remain the property of NTP.

NOW THEREFORE THE PARTIES AGREE AS FOLLOWS:

1. **DEFINITIONS**

1.1 "**Affiliate**" means any entity that directly or indirectly controls, is controlled by, or is under common control with a Party to this Agreement. "Control" for purposes of this definition means direct or indirect ownership or control of more than 50% of the voting interests of said entity;

1.2 "**Confidential Information**" means any tangible or intangible information received from the Disclosing Party directly or indirectly, which is not generally known to the public, including, but not limited, to technical information, specifications, data, process information or parameters, product information, research information, designs, materials, trade secrets, marketing information, pricing information, sales information, and any other information relating to the technology, processes, products, operations or business of the Disclosing Party;

1.3 "**Disclosing Party** " means NTP as the Party disclosing Confidential Information under this Agreement ;

1.4 **"Effective Date"** means the date of commencement of this Agreement, which shall be the date of last signature of this Agreement by the Parties or the date of the commencement of the Training Programme or Purpose, notwithstanding the date of last signature of this Agreement by the Parties;

1.5 "**Intellectual Property**" means any creation of the mind, including inventions (whether patentable or not); ideas, discoveries, inventions, technology, technical information, data, know how, trade secrets, drug master files, materials, designs; trademarks (whether registered or not), copyrightable works, methods or processes, information used in commerce such as customer information and list, price lists or pricing methodologies, supplier information and lists, data, and confidential information;

1.6 "**Intellectual Property Right**" means any right in respect of Intellectual Property;

1.7 "**Receiving Party**" means the Supervisor and/or Ms Gabela as the Party receiving Confidential Information under this Agreement.

2. **CONFIDENTIALITY**

NTP is willing to disclose its Confidential Information in respect of the Purpose, and the Receiving Party is willing to receive the same, and the Parties agree to do so, subject to the provisions of this Agreement, including the following provisions:

2.1 The Receiving Party shall keep strictly confidential and shall not disclose, directly or indirectly, or cause or permit to be disclosed, to any third party the Confidential Information, in whole or in part, without the prior written approval of the Disclosing Party.

2.2 The Receiving Party shall exercise no less care to safeguard the Confidential Information than the Receiving Party exercises in safeguarding its own Confidential Information, which care shall in any event not be less than reasonable care.

2.3 The Receiving Party shall not use the Confidential Information, for any purpose other than the Purpose, without prior written approval of the Disclosing Party.

2.4 The Receiving Party shall disclose the Confidential Information only to those of its officers, directors, employees, to whom disclosure is reasonably necessary in connection with the Purpose and who shall agree to be bound by the terms of this Agreement or are otherwise bound to the Receiving by the same restrictions as those imposed by this Agreement, provided that the Receiving Party will be responsible for any breach of this Agreement by its employees, officers, directors.

2.5 NTP may disclose Confidential Information received under this Agreement to its Affiliates provided that such Affiliate observes all the rights, restrictions and obligations for the protection of Confidential Information as set out in this Agreement.

2.6 The restrictions on the Receiving Party's disclosure and use of Confidential Information shall not apply to the extent that such information:

2.6.1 can be clearly demonstrated that is was already rightfully known to the Receiving Party prior to receipt from the Disclosing Party;
2.6.2 is or becomes public knowledge without breach of the Receiving Party's obligations under this Agreement;
2.6.3 is rightfully acquired by the Receiving Party from a third party with authority to disclose, without restriction on disclosure or use;
2.6.4 is independently developed by the Receiving Party without resort to the Disclosing Party's disclosure; or
2.6.5 is disclosed or used following the Receiving Party's receipt of express written consent from a duly authorised officer of the Disclosing Party.

Information which consists of a combination of more than one aspects shall not be deemed to be of public knowledge by virtue of the fact that said aspects have been disclosed separately.

2.7 If disclosure of Confidential Information is required or requested by a court order or statute, the Receiving Party shall promptly notify NTP in writing in such detail and give

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NTP a reasonable time, if possible, to seek a protective order or otherwise appear to intervene for the purposes of protecting the Confidential Information. Any disclosure under such a requirement shall be limited only to the information required.

2.8 Confidential Information shall not be mechanically copied or otherwise reproduced by the Receiving Party without the express written permission of NTP, except for such copies as the Receiving Party may require pursuant to this Agreement on a need-to-know basis for the purpose of the Purpose.

2.9 Upon written demand from NTP, or termination of this Agreement, whichever is earlier, the Receiving Party shall (1) cease all use of NTP's Confidential Information, and (2) within 30 days of the demand, return to NTP or destroy all documents or material embodying Confidential Information received under this Agreement, whether tangible or intangible (3) delete all Confidential Information residing on non-portable electronic media, e.g., e-mails and other electronic documents residing on networks. The requirements of this subsection 2.9 shall extend to excerpts, summaries or reports of Confidential Information, as well as all notes of verbal communications of Confidential Information. One copy may be retained for archival purposes only and for purposes of managing its obligations under this Agreement, and Receiving Party shall not make commercial use of the information.

2.10 The Receiving Party shall promptly advise NTP (in writing) if it learns of any misappropriation or unauthorized use or disclosure of Confidential Information by any person, including any Receiving Party personnel or former Receiving Party personnel. The Receiving Party shall take all steps reasonably requested by the Disclosing Party to limit, stop or otherwise remedy such misappropriation or unauthorized use or disclosure.

3. OWNERSHIP, PROVISION AND USE OF CONFIDENTIAL INFORMATION

3.1 The ownership of the Confidential Information disclosed under this Agreement by NTP vests and shall remain vested in NTP.

3.2 No provision of this Agreement shall create, imply or be construed to grant to the Receiving Party any title, licence or other rights in or to the Confidential Information and/or to any Intellectual Property or Intellectual Property Rights related thereto.

3.3 NTP provides the confidential information "as is" and disclosure thereof under this Agreement shall not constitute any representation, warranty, assurance, guarantee or inducement as to the accuracy. Completeness, or technical or scientific quality of the Confidential Information of NTP, and NTP shall have no liability to the Receiving Party as a result of the use of the Confidential Information by the Receiving Party. Only those specific representations and warranties, which may be made in a definitive agreement with respect to the Purpose when, as and if such an agreement is executed, shall have any legal effect.

3.4 The Receiving Party agrees not to file any patent applications, or applications for similar Intellectual Property rights, claiming any information, developments, discoveries, technologies, inventions and the like ("Developments") arising from the use of the Confidential Information for the Purpose under this Agreement, or that which could not have been made, developed or discovered without access to Confidential Information in terms of this Agreement.

4. **NO BINDING COMMITMENT**

4.1 This Agreement does not in any way constitute a binding commitment between the Parties, with respect to the Purpose, other than those set out specifically herein, and does not in any way constitute binding commitment on the part of either Party to enter into or complete negotiations or any transactions with the other Party.

4.2 In the event that the Parties enter into a subsequent written agreement, the terms of such agreement concerning confidentiality of information shall supersede any conflicting terms of this Agreement.

5. **DURATION**

5.1 This Agreement shall commence on the Effective Date and remain in effect until the earlier of:

5.1.1 the completion of the Purpose, or
5.1.2 the date on which the Parties enter into an agreement containing substantially similar confidentiality provisions, which agreement is intended to entirely supersede this Agreement, or
5.1.3 the date on which either Party terminates this Agreement upon thirty (30) days written notice to the other Party.

5.2 Any confidentiality obligations and liabilities for any breach thereof, shall survive any termination or expiration of this Agreement and shall continue until the Confidential Information comes into the public domain.

6. **BREACH**

6.1 The Parties acknowledge that breach of this Agreement by the Receiving Party would cause irreparable injury to NTP and that monetary damages may not be a sufficient remedy for such breach and NTP shall be entitled to equitable relief, including, but not limited to, an injunctory relief or specific performance, in the event of a breach of this Agreement.

6.2 Notwithstanding any other rights or remedies that NTP may have in terms of this agreement or at law, if the Receiving Party or any of the Receiving Party's personnel, contractors or agents is in any manner in breach of this agreement, NTP may require the Receiving Party to immediately:-

(a) Remedy the breach;
(b) Refrain from access to NTP's information or information systems;
(c) Remove themselves from any physical location under the control of NTP;
(d) Return any information or property belonging to or under the control of NTP.

7. **GOVERNING LAW AND DISPUTE RESOLUTION**

This Agreement shall be governed by and construed in terms of the laws of the Republic of South Africa.

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8. **NOTICES**

The Parties choose the following addresses as their *domicilium citandi executandi*;

8.1 **NTP**

Physical Address:	Elias Motsoaledi Street Extension (former Church Street West) R104 Pelindaba, Brits Magisterial District Madibeng Municipality Northwest Province South Africa
Fax No:	N/A
Email:	Nomaswazi@ntp.co.za

8.2 **Ms Nomaswazi Gabela**

Physical Address:	18 Boerneef Avenue Wilropark Roodepoort 1724
Email:	Nomaswazi@ntp.co.za / swazigabs@gmail.com.

8.3 **UKZN's details**:

Physical Address:	The Office of the Registrar c/o Legal Services VC's House, University Road, Westville, Durban, 3629
Email:	legalservices@ukzn.ac.za

8.4 Any notice delivered by hand shall be deemed to have been served at the time of delivery or sending. Any notice sent by facsimile or electronic mail (e-mail) shall be deemed to have been served on the expiry of 24 (twenty four) hours after it has been sent.

9. **ENTIRE AGREEMENT**

This Agreement constitutes the sole record of the agreement between the Parties in regard to its subject matter and replaces any prior agreement, which may exist between the Parties, and such prior agreement is of no further effect whatsoever.

N.G 55

10. **NO AMENDMENT OR VARIATION**

This Agreement cannot be varied, added to or cancelled otherwise than by means of a further written agreement between the Parties.

11. **WAIVER**

Any failure by NTP to insist upon strict adherence to any one or more of the terms of this Agreement on one or more occasions shall not be construed as a waiver of any such term by NTP nor deprive NTP of the right to require strict compliance thereafter with the same or any other term of this Agreement, and shall not affect the validity of this agreement or any part hereof or the right of NTP to enforce the provisions of this agreement.

12. **WARRANTY OF AUTHORITY**

The signatories to this Agreement personally warrant and represent that they have been duly authorised to sign this Agreement and thereby bind their respective Parties.

13. **COUNTERPARTS**

This Confidentiality Agreement may be signed in duplicate originals, each of which shall constitute an original document.

SIGNED AT Pelindaba **on this the** 10th **day of** October **2018**

WITNESSES:-

1. _____

2. _____

_____

For and on behalf of: NTP

SIGNED AT NTP on this the 3rd day of October 2018

WITNESSES:-

1. _____

2. _____

_____

For and on behalf of: Nomaswazi Gabela

SIGNED AT _____ on this the _____ day of _____ 2018

WITNESSES:-

1. _____

2. _____

_____

For and on behalf of: **UKZN**