QUALITY OF LIFE AND SIDE EFFECT ASSESSMENT IN SOUTH AFRICAN PATIENTS UNDERGOING ANDROGEN DEPRIVATION THERAPY

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DECLARATION

I, John Demetrios Baladakis, declare that this research report is my own work. It is submitted for the admission to the degree of Master of Medicine in Urology by the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

…… (Signature of candidate)

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On this day:

ABSTRACT

Quality of life and side effect assessment in South African patients undergoing androgen deprivation therapy

Background: In South Africa, prostate cancer is the second most commonly diagnosed cancer and accounts for 13% of male cancer related deaths. Androgen deprivation therapy (ADT) is a mainstay in the management of metastatic prostate cancer. Despite broadening indications and widespread use of ADT, it is not an innocuous treatment. The aim of this study was to determine the impact of ADT on the quality of life (QOL) and common side effects experienced by a subset of South African patients with prostate cancer.

Methods A prospective, contextual, descriptive study was performed. The European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-30) was used in conjunction with the QLQ- PR 25, to assess QOL and disease-specific impact.

Results: ADT was most commonly prescribed for patients with metastatic prostate cancer 86 (56.9%). Continuous ADT was the favoured regime with a mean duration of 41.5 ± 31.2 months. Only 11 (7.2%) of the patients underwent bilateral orchiectomy. New onset hypercholesterolaemia occurred in 71 (46.7%) of the population and was associated with a continuous ADT regime 60 (87.0%). Patients had overall good QOL for the five functional scales although prostate specific symptoms had relatively high symptom scores. Only 99 (66.0%) of the study population reported ongoing sexual activity. A significant difference was found for overall QOL between patients on intermittent ADT and those on continuous ADT ($p= 0.0107$).

Conclusion: Several pertinent issues have been highlighted with regards to the side effect profile in this population and the need for ongoing screening and management, including a patient-centered approach.

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LIST OF ABBREVIATIONS

ADT	Androgen deprivation therapy
BMD	Bone mineral density
CPA	Cyproterone acetate
DEXA	Dual energy x-ray absorptiometry
EAU	European Association of Urology
EBRT	External beam radiotherapy
ED	Erectile dysfunction
EORTC	European Organisation for Research and Treatment of Cancer
FSH	Follicle stimulating hormone
FTI	Free testosterone index
GS	Gleason score
HbA1c	Glycosylated haemoglobin
HDL	High density lipoprotein
ISUP	International Society of Urological Pathology
LDL	Low density lipoprotein
LH	Luteinising hormone
LH-RH	Luteinising hormone releasing hormone
NIDDM	Non-insulin dependent diabetes mellitus
NO	New onset
PCa	Prostate cancer
PSA	Prostate specific antigen
QOL	Quality of life
SERMs	Selective estrogen receptor modulators
SEUG	South European Urological Group

SNRI	Serotonin-noradrenaline reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
SWOG	Southwest Oncology Group
UK	United Kingdom
USA	United States of America

CHAPTER 1: OVERVIEW OF THE STUDY

1.1 Introduction

This chapter on the quality of life (QOL) in men with prostate cancer (PCa) on androgen deprivation therapy (ADT) will address the background to the study, aims, objectives and the problem statement. Finally, an overview of the study and its significance will be provided.

1.2 Background

PCa is the most commonly diagnosed cancer in men in the USA, UK (1) and the second most common after basal cell carcinoma in South Africa comprising of 18.45% of all new histologically diagnosed cancers (2). It is also the second leading cause of cancer death in South Africa and accounts for approximately 13% of male cancer deaths (3). Due to improvements in diagnosis and treatment, an increasing number of men are living for an extended time with prostate cancer (1). This fact highlights the importance of understanding the complications and effects on QOL of patients undergoing treatment.

Androgen deprivation therapy (ADT) is a mainstay in the management of metastatic prostate cancer. ADT results in either a reduction in circulating testosterone levels or reduction of binding of androgens to the androgen binding receptors. The benefits of ADT were first described by Charles Brenton Huggins in 1941 and in 1966 he was awarded the Nobel Prize in Physiology or Medicine (4) for pioneering the use of ADT in prostate cancer. Today there are many options available to patients who require ADT, namely orchiectomy or a variety of pharmacological agents. Orchiectomy (the surgical removal of the testes bilaterally) remains the most economically effective form of ADT and some studies have suggested that patients undergoing this treatment may have an improved quality of life compared to counterparts on medical ADT (5).

Although orchiectomy has been shown to be a simple, safe, and highly effective treatment option to achieve castrate levels of testosterone in patients (<50ng/dL), many patients are hesitant to

undertake this surgery. Fortunately, some medical monotherapy options available to patients, have been shown to have an equivalent survival rate when compared to orchiectomy (6).
The growing availability of these agents has led, in recent years, to an extension in the use of ADT. ADT is still indicated for use in patients with both symptomatic and asymptomatic metastatic prostate cancer, however, it is now also indicated as a primary therapy in men with localised disease unfit for surgical or radiation therapy (7). Furthermore, it is used as an adjunct in patients with intermediate or high risk localised cancer undergoing radiation therapy, where it has been shown to have a survival benefit (8) Finally, ADT can also be used in patients after biochemical relapse post-surgery or radiation for presumed localised disease.

Despite the broadening indications and widespread use of ADT, it is important to remember that this is not an innocuous management option. There is a broad body of literature addressing the impact of ADT on the physical, sexual and psychological health of men on these agents. The adverse effects include decreased QOL, impairment of mood and cognitive function, hot flushes, impaired sexual function, osteoporosis, anaemia, adverse changes in body composition and increase in cardio-metabolic risk. Although many of these side effects can be attributed to the reduction of testosterone levels, it is also important to take into account the reduction of oestrogen levels that occur as a result of the reduced aromatization of testosterone (9). The oestrogen induced side effects include increased fracture risk, hot flashes, gynecomastia, serum lipid changes and memory loss.

QOL has been shown to be decreased in patients on ADT especially in the areas of physical health, general health and physical function (10). There are a number of validated clinical research questionnaires such as the SF-36 (10) and the EORTC QLQ-C30 combined with the prostate cancer specific EORTC QLQ-PR25 (11,12) used to assess QOL of cancer patients. The EORTIC questionnaires review several symptoms specifically related to prostate cancer including mobility, appetite, urination and bowel movements, depression, anxiety, pain, finances and sexual function. Many of these symptoms can be further aggravated by the use of ADT.

The impact of ADT on cognitive function is not clear, with some studies suggesting that it impairs memory, attention and executive functions (13) while other studies fail to show any

effect (14). The rate of depressive symptoms has also been found to be higher in the group on ADT compared to both cancer free and cancer control patients not on ADT (15).

Hot flushes occur in up to 50% of men receiving ADT and is the result of the abrupt withdrawal of sex hormones from the circulation resulting in the lowering of the temperature set point in the preoptic area of the anterior hypothalamus. This results in the inappropriate activation of peripheral thermoregulatory mechanisms (1). Hot flushes often don't resolve on their own and their occurrence is ascribed as a major contributor to the discontinuation of ADT.

There is a very significant decline in sexual function in men receiving ADT for prostate cancer (1,16). There is a reduction in both libido and erection, decrease testosterone levels result in decreased penile arterial inflow, venous leakage and impaired nitric oxide response. Despite the reduction in libido, some men remain troubled by their erectile dysfunction (ED) and many find this to be the single most troubling complication (17). Men who respond to ED treatment have been shown to have an increased QOL for both themselves and their partners (18). Patients may also experience a reduction in penile length and testicular size (19,20) which may negatively impact on self-perception, confidence as well as masculinity.

Gynaecomastia, the enlargement of breast tissue is a common side effect with the use of non-steroidal anti androgens. Mastodynia or breast pain, may further complicate gynaecomastia. Although the incidence of gynecomastia can be as high as 85%, in men on Bicalutamide monotherapy (21), it is more commonly quoted as 13-22% in men receiving combined blockade (22). The occurrence of gynaecomastia has been noted to affect body image thus further negatively impacting quality of life. This together with other feminizing features has resulted in avoidance tactics in social situations (23).

The use of ADT is associated with a decrease in bone mineral density (BMD) that is most marked in the first year of treatment but continues to a lesser degree thereafter (1). Moreover, these changes show no improvement after cessation of treatment. This combined with an already increased incidence of osteoporosis in men with advanced prostate cancer (24) results in an increased risk of fracture (25).

The metabolic consequences of androgen deprivation therapy have been well documented. The most commonly recognised metabolic changes are those of body composition, lipid profile and insulin resistance. Body composition changes include a decrease in skeletal muscle with an increase in body fat percentage. There appears to be a correlation between duration of therapy and the degree to which body composition is affected (26).

We are aware that there is a change in the lipid profile of patients undergoing ADT, however, there has been no consensus in the literature as to the exact pattern of change. The literature quotes changes to include an increased LDL, total cholesterol and triglycerides to observations where only a change in total and HDL cholesterol were seen.

Increased insulin resistance is an association independent of age and body composition, furthermore, it is a continuum, where short term therapy leads to reduced insulin sensitivity while long term ADT causes hyperglycaemia, increased risk of metabolic syndrome and type 2 diabetes mellitus (1). It has been shown that after only12 weeks of combined androgen blockade there is a significant decrease in insulin sensitivity resulting in an increase in fasting plasma insulin (27).

As a result of the above mentioned metabolic changes it is not surprising that the incidence of metabolic syndrome in men on ADT is increased compared to controls (28). According to the Adult Treatment Panel III guidelines the diagnosis of metabolic syndrome requires three of the five recognised criteria: (1) serum triglycerides ≥150 mg/dl, (2) high-density lipoprotein (HDL) < 40 mg/dl, (3) fasting serum glucose >110 mg/dl, (4) waist circumference ≥102cm, and (5) blood pressure ≥130/85mmHg (29). However, it has been noted that patients on ADT primarily meet these criteria through an increase in insulin resistance, body composition and lipid profile changes as previously discussed.

The metabolic risks may increase the risks for cardiovascular changes and events. There is a paucity of literature that well defines the specific population of men on ADT who are at greatest cardiovascular risk from treatment. It is probably prudent to assume an increased risk of cardiovascular disease and thus ongoing surveillance is a key aspect in these patients.
To try and mitigate the complications associated with ADT an intermittent form of dosing was developed. Intermittent ADT (IADT) allows for the discontinuation of ADT once the prostate

specific antigen (PSA) level falls below a predetermined threshold. Patients are closely monitored, and ADT restarted when the PSA level rises. It is important that patients undergoing IADT are highly motivated and compliant with follow-up. Unfortunately, Schulman et al were unable to demonstrate any benefit in IADT compered to continuous ADT with regards to QOL. They did demonstrate a potential benefit in cost (30).

Sonn et al found a poor correlation between treating physicians perception of symptom and QOL and patients self-assessment of health related quality of life (31). In order to overcome this significant limitation studies have been carried out in Germany (32) and Japan (33) in order to better understand the impact of ADT on specific populations and to improve patient centred outcome evaluations. It is thought that ethnicity may impact the risk and degree of complications (34). There is currently limited national literature in South Africa addressing this pressing issue in our diverse population, thus patients may not be receiving optimal care. This study aims to assess this situation and potentially rectify it.

1.3 Problem statement

Prostate cancer is the fourth most common cancer worldwide and the fifth leading cause of cancer death in men. The use of prostate specific antigen for screening has led to earlier detection and institution of appropriate therapy. Currently, there is a large subset of patients who are not eligible for curative treatment. As a result, some of these patients are started on ADT to reduce complications of metastatic PCa and improve QOL. However, the impact of ADT associated adverse effects; including physical, psychological and sexual have to be considered when instituting therapy in this subset of patients. Moreover, the impact may further compound pre-existing disease processes found in this aging population.

Despite ongoing research and the development of new agents with the potential to improve not only QOL but overall survival, these agents are unlikely to be available for use in the near future as they are either in various stages of testing or due to the high cost when used. Furthermore, there is a paucity of literature regarding the impact on QOL of ADT in patients with PCa living in South Africa. As a result, there is limited information to guide current practice and improve patient outcomes.

1.4 Aims and objectives

1.4.1 Aim

The aim of this study was to determine the impact of ADT on the QOL and common side effects experienced by a subset of South African patients with prostate cancer attending the urology oncology clinic using the EORTC QLQ-30, EORTC PR-25 and physician questionnaire.

1.4.2 Objectives

The primary objectives of this study were:

- to describe the population of patients currently receiving ADT, the most commonly prescribed methods of ADT and common side effects of ADT treatment in our patient population
- to describe the perceived impact of ADT on the physical, psychological and sexual health of patients receiving treatment

The secondary objectives of this study were:

- to compare the stage of prostate cancer at presentation, the preferred modality of ADT and ADT side effect profile for different race groups
- to compare the impact on the QOL between single agent medical management, complete medical androgen blockade and surgical orchiectomy
- to compare the QOL of patients on ADT with hormone-sensitive prostate cancer to those with castrate resistant prostate cancer

1.5 Demarcation of study

The study was conducted at the Urology Oncology clinic held on Thursday at the Charlotte Maxeke Johannesburg Academic Hospital in area 456.

1.6 Ethical considerations

Permission to conduct this study was obtained from the relevant authorities. Informed consent was obtained from patients who agreed to participate in the study prior to completing the questionnaire. The study was conducted adhering to good clinical research practice in accordance with the South African Good Practice Guidelines (34) and the Helsinki Declaration (35).

1.7 Research methods

See section 3.0 Research methodology regarding study design, site, population, sample and data analysis.

1.8 Summary

In this chapter, an overview of the study has been given. The literature review is presented in the following chapter.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction and Epidemiology

Worldwide, cancer is becoming one of the leading causes of mortality, with great variability in the patterns of cancer between regions (35). According to the GLOBOCAN study which looked at the incidence of new cases of cancer in 2012, there was an estimated 1 112 000 new cases of prostate cancer globally which accounted for 7.9% of all new cancer cases and 15% of new cancer cases diagnosed in men. As a result, it is currently the fourth most common cause of cancer in both sexes and second most common in males being second only to lung cancer worldwide. It is the fifth leading cause of cancer death in males accounting for an estimated 307 000 male deaths per year, which is 6.6% of the total male cancer related deaths (36).

It is interesting to note that of the estimated new cases the majority, 759 000 (70%) occurred in the developed regions whilst only 353 000 (30%) occurred in the so called developing regions (36). As such, there still remains a 25-fold difference in the incidence of new PCa cases worldwide with the incidence in the relatively developed countries such as Australia, New Zealand and North America remaining high compared to the developing regions of the Caribbean, southern Africa and the Asian populations (36, 37). However, the data reported in such a study relies on data capturing in specific registries and thus is subject to the quality of both incidence as well morbidity and mortality reporting in these registries. It has been noted that in most of the African and some of the populous Asian countries such registries are subject to either poor input or are non-existent requiring inferences to be made based on the data from the surrounding regional countries. Furthermore, the international differences in PCa incidence are most likely attributable to the variation in diagnostic practices (37).

Similarly, there remains a 10-fold variation in the mortality ranging from three per 100 000 to 30 per 100 000. The mortality is particularly high in populations of African descent including the sub-Saharan African and Caribbean populations and lowest in populations of Asian descent. However, the cumulative risk of male death from cancer is 20% higher in more developed regions, as such PCa is currently the third most common cause of cancer death in developed countries whilst it is only the sixth most common cause in developing countries (36). Since the median age of diagnosis for PCa is 60 years old, it is estimated that with the continued

population growth as well as the increasingly aging population and earlier detection due to screening modalities, there will be an increase in both the incidence and mortality of PCa by 2030 (37).

In South Africa, PCa is currently the second most commonly diagnosed cancer after basal cell carcinoma and comprises 18.45% of all new histologically diagnosed cancers (2). It is also the second leading cause of cancer death in South Africa and accounts for approximately 13% of male cancer deaths (3).

2.2 Aetiology

The relationship between prostatic epithelial atrophy in the face of castration was recognised by Hunter as far back as 1840 (38). The cornerstone for the treatment of metastatic PCa with androgen deprivation therapy came when Huggins recognised that there was biochemical analogy between benign prostatic epithelium and prostate carcinoma. As such, the potential of carcinoma to respond to both medical and surgical castration with atrophy, similar to benign epithelium, was recognised. Furthermore, the presence of acid phosphatase in the human prostate gland and the associated increase in the serum levels in the presence of primary and metastatic prostate disease had previously been published.

In 1941, Huggins et al. (39) published a study looking at the effect of castration or exogenous oestrogen administration on serum acid phosphatase as well as the effect of exogenous androgen injection. The findings of the study supported a decline in serum acid phosphatase toward or to normal limits in patients following castration or injection of large amounts of oestrogen. There was a further decline in serum alkaline phosphatase albeit delayed and more slowly compared with the acid phosphatase level. Conversely, it was found that in patients with prostatic carcinoma, the injection of exogenous androgens was associated with a sharp rise in serum acid phosphatase which in one patient returned to baseline following cessation (40).

Although the role of androgens in PCa had been highlighted, the effect of androgen deprivation and the associated side effects came to the fore. Furthermore, the emergence of androgen-refractory disease particularly evident in hypogonadal males, prompted investigation into the role of adrenal androgens in disease progression following castration (39). Attempts at bilateral

adrenalectomies, pituitary irradiation and hypophysectomy were superseded only by a high mortality rate and thus the entity of androgen independent disease, synonymous with the lethal form of disease, was recognised (41).

Despite the early work recognising the role of serum androgen concentrations in the development and progression of prostate cancer, the recently proposed Saturation Model suggests a limited role in androgen-dependent growth of prostate cancer. It focuses on androgen-receptor kinetics and the fact that at or near castration levels of testosterone and 5α-dihydrotestosterone, there is saturation of androgen-receptor binding. As a result, a further increase in androgen concentrations above this Saturation point will have no additional effect on prostatic tissue growth. Thus, even at physiological levels, there exists an excess of both testosterone and 5α-dihydrotestosterone, for optimal prostate growth. It is only when the serum concentration of testosterone is at or below castrate levels, defined as less than 50ng/dl, that a fall in prostate specific androgen level and prostate volume is seen. Any variation of testosterone levels within physiological and supraphysiological concentrations have not been shown to have any effect. Thus, the advocates of this model propose a limit in the ability of androgens to stimulate growth of PCa above castrate or near-castrate levels (42).

2.3 Diagnosis and Staging

In 1970, Richard Ablin discovered prostate specific androgen (PSA), a glycoprotein produced by the prostate gland. Also known as kallikrein-3, it serves to liquefy semen, promote sperm motility and dissolve cervical mucus (43). The role of PSA in the early detection of PCa was recognised in 1991, when Catalona et al. (44) in a cohort of 1653 patients who received both PSA screening and digital rectal examination showed the addition of PSA to improve sensitivity when concurrently assessed. Of the 112 men with a PSA of four or greater, biopsy confirmed the presence of malignancy in 37 (33%) (44). However, there are a number of additional states in which PSA maybe raised, including prostatitis, benign hypertrophy and prostate manipulation, thus limiting the specificity for diagnosing cancer (43,45). Furthermore, it has been recognised that the normal range of PSA may increase with age requiring that it is used in correlation with history and clinical findings to prevent unnecessary further biopsy, testing and treatment (43).

Despite these limitations, PSA remains a more reliable predictor of PCa compared to either digital rectal examination or transrectal ultrasound (46).

PCa screening remains one of the most controversial topics in urology currently. Screening has been shown to allow for early detection and improved oncological outcomes following treatment. However, a number of meta-analyses have failed to show any PCa-specific mortality benefit to PSA screening in non-selected patient populations. Indiscriminate PSA screening has been associated with unnecessary biopsy in the face of a high false-positive PSA rate, over diagnosis of low-risk disease and unjustified morbidity from both biopsy and treatment particularly of low-risk disease (43,45,47). In a sub-analysis of the data of the European Randomised Study of Screening for Prostate Cancer (ERSPC) it has been suggested that three PSA measurements made between 45 and 60 years of age will be effective in reducing harm associated with over diagnosis of PCa whilst still effectively stratifying those at risk for appropriate early detection and management (48).

Current recommendations for screening differ between different professional organisations. As there remains no high level evidence or consensus on optimal time for repeat PSA screening it may be prudent to follow a more individualised risk-adapted strategy for the well-informed population in whom life expectancy is at least ten to fifteen years at time of screening and thus would benefit from early detection of disease (49). In South Africa, this approach may not be ideal as it has previously been recognised that particularly in the black South African population both the age of presentation and severity of disease are more advanced. A number of reasons for such presentation include delayed diagnosis, particularly secondary to delayed presentation until symptomatic, as well as lack of easy access to health care facilities and a specific PCa screening programme in more rural locations. Finally, as has been alluded to, it appears that the black population with advanced disease tend to have a more aggressive form of PCa and thus may benefit from earlier detection (50,51).

Biopsy of the prostate is performed based on the PSA in conjunction with a suspicious digital rectal examination. It is prudent to take into account the patient's age, comorbidities, family history and potential therapeutic consequences in order to prevent unnecessary biopsy and all its inherent risks (52). Biopsy based on a minimal elevation of PSA alone is not currently advocated and PSA should be repeated some weeks later to ensure no other cause of slightly elevated PSA including ejaculation, urinary tract infections and prostate manipulation is responsible for the

isolated elevation (53). The gold standard for prostate biopsy requires the use of an ultrasound-guided technique through a transrectal approach (49).

Confirmed diagnosis of PCa is made on the histology of the prostate biopsy. Carcinoma positive biopsies will report the following elements: "

- type of carcinoma;
- primary and secondary/ worst Gleason grade (per biopsy site);
- percentage high-grade carcinoma (global);
- extent of carcinoma (in mm or percentage) (at least per biopsy site);
- if present: extra-prostatic extension, seminal vesicle invasion, lymphovascular invasion, intraductal carcinoma/cribriform pattern, peri-neural invasion;
- International Society of Urological Pathology (ISUP) 2014 grade." (49)

Clinical behaviour and response to treatment is most strongly predicted by the Gleason score. It consists of two values providing a score out of ten. The first value represents the most common histopathology seen in the biopsy core, whilst the second is the second most dominant histological type. If only one tissue type exists, the first value is doubled to provide a score out of ten. Where more than two patterns of tissue exist, the most common and highest grades are combined to provide the Gleason score. In the face of carcinoma, a score of four or less will never be reported. Based on the Gleason score patients are further categorised into grades 1 to 5 based on the International Society of Urological Pathology. The role of the grading is to provide standardisation of PCa grading with other carcinomas, ensure that even the most differentiated PCa have a Gleason score of at least 6 and to differentiate between the significance of Gleason score of 7 namely between one that comprises a score of 3+4 (grade 2) versus 4+3 (grade 3) (54).

Following histological grading patients are then risk stratified according to the D'Amico classification (see Table 2.1), based on their PSA level, Gleason and ISUP grade and clinical staging according to the Tumour Node Metastasis classification of Pca. This allows standardisation and streamlining of treatment based on the treatment recommendations determined through clinical data of homologous groups. It further categorises patients based on their risk of recurrence following prostatectomy or external beam radiotherapy (49,55).

Table 2.1 Risk groups for biochemical recurrence of localised and locally advanced disease (49)

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL **and** GS < 7 (ISUP grade 1) **and** cT1-2a	PSA 10-20 ng/mL **or** GS 7 (ISUP grade 2/3) **or** cT2b	PSA > 20 ng/mL **or** GS > 7 (ISUP grade 4/5) **or** cT2c	any PSA any GS cT3-4 **or** cN+ any ISUP grade
Localised			**Locally advanced**

2.4 Androgen Deprivation Therapy (ADT)

There are multiple treatment modalities available for the treatment of Pca depending on whether there is low-, intermediate- or high-risk of recurrence, as well as taking into account the patient's comorbidities life expectancy and wishes. ADT refers to any intervention that results in either blockade of the androgen receptor or reduced biosynthesis of androgen receptor agonists such that the target cell receptors are no longer activated. This may be achieved either surgically (see 2.4.1 Bilateral orchiectomy) via castration or medically (see 2.4.2 Medical Treatment) through the use of a number of different pharmacological agents either individually or in combination. The resultant hypogonadism is thought to improve survival at different stages of PCa, however, the adverse metabolic complications and the potential effect on overall survival has led to a focus on both reducing and treating the associated metabolic complications (56).

Current recommendations for the use of ADT are as follows:

- In clinically localised and locally advanced disease it is indicated post-operatively in those found to have pelvic lymph node involvement (pN+) following radical prostatectomy or in combination with external beam radiotherapy where there is clinically localised intermediate- or high-risk disease;
- Use in patients with biochemically recurrent PCa following definitive management;

- Patients with metastatic PCa for improvement in quality of life rather than improvement of cancer-specific mortality; and
- Patients with locally advanced PCa without metastases (M0), high risk disease who will not or cannot receive local treatment, ADT monotherapy may be offered (57).

2.4.1 Bilateral Orchiectomy

Bilateral orchiectomy is a simple outpatient procedure that can be done under local anaesthetic. It effectively ablates the androgen source and results in a decrease in circulating serum testosterone levels to below 50ng/dl, considered castrate level, and by 90% within 24 hours of the procedure. It has been shown to be effective in both the reduction of pain associated with metastatic disease, and to improve performance status in those with advanced disease (58,59). To date there is no data suggesting superiority of orchiectomy over medical ADT with regard to survival. However, surgical castration is often not considered an acceptable treatment choice by patients due the psychological impact related to the disfigurement and permanence of the procedure. The impact is considerable economic cost as use of medical ADT has been shown to far exceed the cost of orchiectomy when use extends beyond three to five months (58).

2.4.2 Medical Treatment

There are a number of different drugs which act on different facets of the androgen axis to achieve blockade. The mechanisms employed include inhibition of androgen synthesis, antiandrogens and inhibition of the luteinizing hormone releasing hormone (LH-RH) and finally inhibition of luteinizing hormone (LH) release respectively (58). These agents are used in monotherapy or different combinations depending on the indication for treatment as well as the stage of disease (See Table 2.2).

Table 2.2 Agents associated with the different mechanisms of androgen axis blockade

Class of agent (58)	**Mechanism of action**	**Pharmacology**	**Indications**
Inhibition of androgen synthesis *e.g.* Aminoglutethimide Ketoconazole Abiraterone	Inhibition of CYP17 in the adrenal gland and by tumour reducing androgen production from steroids (57). Ketoconazole achieves castrate levels of testosterone within 4 hours of 1st dose administration (58).	Ketaconazole an antifungal agent provides an immediately reversible decrease in testosterone. Requires continuous 8hrly dosing of 400mg. Increases in testosterone to low-normal levels may occur after 5 months of continuous treatment (58). Abiraterone is more potent resulting in irreversible inhibition of CPY17. Aldosterone and cortisol suppression with associated adrenocorticotrophic hormone rise responsible for side effects (49,58).	Second-line therapy in advanced PCa. Abiraterone is specifically indicated in men who have progressed after prior docetaxel chemotherapy (57). STAMPEDE showed statistically significant benefit on overall and failure free survival from adding abiraterone at the start of ADT (70).
Antiandrogens *e.g.* Steroidal: Cyproterone acetate (CPA) Non-steroidal: Flutamide Bicalutamide Nilutamide Enzalutamide	Bind directly to androgen receptor thereby competitively preventing binding of testosterone or DHT (57). Non-steroidal cause no change/ slight increase in testosterone levels. Steroidal agents cross the blood brain barrier resulting in progestational effects via central inhibition(49). CPA poorer overall survival compared to LH-RH agonists (71).	Steroidal synthetic analogues of hydroxyprogesterone. CPA $t_{1/2}$ 31-41 hrs but 2-3x/d dosing to total of 100mg (49,58). Non-steroidal antiandrogens preserve testosterone level which is thought to improve libido, BMD and physical function (72). All agents associated with potential hepatic toxicity requiring regular LFT monitoring. Flutamide not registered for monotherapy. Enzalutamide higher affinity for AR than bicalutamide. It blocks nuclear transfer thereby preventing possible agonist effect (49).	Indicated in combination with LH-RH agonist for combined androgen blockade in advanced PCa. 2nd-line therapy after progression on LH-RH agonist monotherapy (57). Symptomatic control of LH-RH agonist side effects especially hot flushes. Used in the prevention of flare phenomenon associated with LH-RH agonist initiation (49,58).

Table 2.2 Agents associated with the different mechanisms of androgen axis blockade cont.

LH-RH agonists *e.g.* Diethylstilbestrol Leuprolide acetate Goserelin Triptorelin	Causes downregulation of GnRH receptors in the anterior pituitary thereby reducing LH and testosterone production (57). Produce transient flare phenomenon 2-3d after administration lasting 1 week (49). Castration levels of testosterone 2-4 wks; comparable to orchiectomy (6,73).	Depot preparations delivered every 1-, 2-, 3-, 6-monthly or yearly depending on agent and preparation used. Agent dependent storage temperatures and requirement for reconstitution. Given s/c or IMI (49).	Clinically localised and locally advanced disease. Biochemically recurrent disease. Metastatic PCa. Combination therapy with EBRT. Currently 1st-line agents used for ADT (57).
LH-RH antagonists *e.g* Abarelix Degarelix	Directly inhibits GnRH receptors in the anterior pituitary (57). Castrate levels achieved by 3d. Suggested PSA progression-free survival and death benefit at 1yr with degarelix compared to leuprolin (74). Improved cardiovascular profile in men with pre-existing cardiovascular disease.	Only available in monthly depot preparations. Degarelix dosing- 240mg initially followed by 80mg monthly (49). Significant risk of anaphylaxis with abarelix throughout treatment duration not seen with degarelix (58).	Metastatic PCa. CS21A outcomes suggest degarelix as a comparable alternative to LH-RH agonists (74).

Despite evidence as to the benefit of ADT in terms of metastatic disease progression, quality of life and improved treatment outcomes when used in combination with EBRT; when compared to EBRT alone, there is some debate as to the overall impact on survival and quality of life. This debate is due primarily to the numerous side effects associated with ADT which will be discussed in detail in Section 2.6 (60). The result is a question as to the timing of initiation of ADT for reduced disease progression and improved survival versus the impact on survival of the potential side effects of the various agents.

The European Organization for Research and Treatment of Cancer (EORTC) randomized trial 30891 published final results from a 12 year follow up where they tried to elucidate the relationship between different initiation time of ADT, disease progression and survival end points. It was a randomised controlled trial consisting of 492 patients in the immediate treatment group and 493 in the deferred treatment group, where treatment was initiated at the time of disease progression. They found a statistically significant difference in time to first objective

disease progression ($p < 0.0001$) in favour of immediate ADT. However, they failed to show any significance in time to castrate-resistant disease or PCa specific mortality in al by those with aggressive disease. It was suggested that overall survival was improved in the immediate ADT treatment arm compared to the deferred treatment arm (61).

The results of the phase III trial, Timing of ADT in patients with prostate cancer with a rising PSA (TOAD), differ slightly to those of the EORTC trial. In this randomised, multicentre, non-blinded trial, 293 men with PSA relapse, following failed curative therapy and who were no longer suitable for further curative treatment, were randomised to either immediate therapy (n=142) or delayed therapy (n=151). Their findings were that 5-year overall survival was significantly improved in the immediate therapy arm (91.2%) compared to the delayed arm (86.4%) with a p-value of 0.047. Furthermore, they found that the rate of treatment related adverse events didn't differ between the two treatment groups. These findings provided important evidence of survival rates when informing patients of their treatment options (62).

The side effects related to castration levels of testosterone, resulted in investigation and use of the oral oestrogen diethylstilboestrol. Oestrogen is known to be a potent inhibitor of hypothalamic GnRH secretion, moreover, oestrodiol is 1000-fold more potent in the suppression of LH and follicle stimulating hormone (FSH) secretion from the pituitary when compared to testosterone and thus results in the suppression of testosterone production (63). It was initially thought to be beneficial as it has a positive side effect profile in terms of bone mineral density and bone health (64). However, despite trials that looked at the efficacy of diethylstilboestrol at various different doses, even at the lowest doses the severe side effects, particularly pertaining to thromboembolic phenomena has precluded their use as part of first line ADT regimes (65,66).

Another topic of debate and ongoing research in ADT and PCa is the efficacy of intermittent ADT compared to continuous ADT. Despite the recognised benefits on disease progression and potential survival, the negative impact of both short- and long-term side effects on patient QOL has led to the development of an intermittent regime. The premise behind intermittent therapy is that once castration levels of testosterone are achieved and tumour regression induced, ADT is discontinued until a rise in PSA. The proposed benefits of intermittent ADT cessation include:

- longer time to androgen-independent disease and thus castrate-resistance;

- recovery of near normal testosterone levels with a reduction in ADT related side effects and thus improved QOL;
- reduced medication use and side effect management costs associated with continuous therapy. (67)

In 2012 the EUA recognised intermittent ADT as a treatment modality and published guidelines for its use. The guidelines recommend initial treatment with ADT for six to nine months at which time provided the PSA level is <4ng/ml in metastatic disease and <0.5ng/ml in relapsing disease, ADT can be stopped. Treatment is reinitiated when PSA levels rise to 10-15ng/ml in metastatic disease or 4- 10ng/ ml in the absence of metastases. Despite these guidelines there still exists uncertainty as to the optimal duration of initial treatment as well as the PSA thresholds used to guide cessation and re-initiation of therapy (68).

The Southwest Oncology Group (SWOG) JPR.7 trial in 2011 was a phase III study comparing the treatment-related side effects and effect on QOL between those on intermittent versus continuous ADT with an 83-month follow-up. They found no overall survival benefit of one regime over the other. However, analysis of the deaths showed that for those on intermittent ADT, there were marginally more cancer-related deaths but that the non-cancer related death rate was slightly improved. In terms of time to progression there was a significant improvement with intermittent ADT ($p=0.024$). A beneficial side effect profile was demonstrated particularly with regards to sexual function and QOL. QOL domains which showed significant improvement included physical function, fatigue, urinary symptoms, hot flushes and erectile function ($p\leq0.01$). Despite these benefits, no differences for either cardiovascular or osteoporotic risk were reported (69).

The South European Uroncological Group (SEUG) 9401 had similar findings to SWOG JPR.7 with regards to comparable overall survival, once again with a slight increase in cancer related deaths in the intermittent group. Similarly, it found continuous ADT to be associated with increased death from other causes particularly emphasising an excess in cardiovascular related deaths. Unlike the SWOG group the data did not support a benefit in time to progression between the two arms. Furthermore, significant benefit was only demonstrated for reduction in hot flushes ($p<0.01$) although there was a trend to reduced side effects in the intermittent group. They did demonstrate an improvement in sexual activity and function in the intermittent group where 28% still reported sexual activity compared to only 10% in the continuous group (44).

SEUG 9901 demonstrated improved QOL in terms of headache, gynaecomastia, hot flushes and sexual function (45).

The SWOG 9346 trial published its data in 2013. The trial included 3040 men but only 1535 were included in the analysis with 765 men randomised to the continuous ADT arm and 770 to the intermittent ADT arm. The primary outcomes were overall survival and QOL between intermittent and continuous ADT. The outcome at a 9.8 median follow-up was a median survival of 5.1 versus 5.8 for intermittent and continuous ADT respectively with a hazard death ratio of 1.10 (CI 90% 0.99-1.23). This suggests a 20% greater risk of death for the intermittent group. However, due to the lack of adverse events significant inferiority of intermittent ADT could not be demonstrated and as such they felt the results were statistically inconclusive. In terms of QOL data, they demonstrated significant benefit for erectile function ($p< 0.001$) and mental health ($p= 0.003$) at three months in the intermittent ADT group. The demonstrated benefit was lost beyond three months. Thus, the data demonstrating improved QOL for patients receiving intermittent ADT remains equivocal (46).

2.5 ADT Side Effects

The side effects associated with ADT can be divided into two groups due to:

1. primary testosterone deficiency and;
2. oestrogen deficiency.

2.5.1 Primary Testosterone Deficiency

Primary testosterone deficiency results in body composition changes, insulin resistance, sexual dysfunction and anaemia.

2.5.1.1 Increased fat mass, decreased lean body mass (change in body composition)

The castrate levels of testosterone associated with ADT are responsible for the development of obesity and sarcopenia (75,76). These changes occur as early as three to six months after the

initiation of ADT (77). Studies to quantify the degrees of change in body composition have yielded the following results: after 12 months of ADT LH-RH agonists caused a 7-11% increase in body fat with a loss of 2-4% of lean tissue (78). Furthermore, the distribution of body fat accumulation was related more to gain in subcutaneous than intra-abdominal fat (78).

This is contrast to the findings of Hamilton et al. in 2011 (79) where they showed that increase in body fat occurred both subcutaneously and viscerally. Despite these abdominal changes, it has been noted that the changes in composition of the upper and lower limbs exceeds those in the trunk (80) with increases of 3.3%, 2.7% and 2.5% respectively. There is some evidence to suggest that a longer duration of treatment is associated with worsening of body composition change (25). However, in a study of 65 men over a 12 month period it was shown that longer exposure to ADT prior to partaking in the study was an independent predictor for less fact accumulation and loss of lean body mass (26). It appears that weight gain occurs more commonly in the younger patient population (< 65 years of age) and those who have a BMI < 30 kg/m^2 at the onset of treatment. It is suggested that these findings may be associated with the baseline serum gonadal steroid concentrations, body composition and age which may be responsible for the differences in fat change and distribution seen with ADT (76).

The mechanisms for change in fat distribution on ADT are not fully understood. It is thought that the increase in abdominal fat may be the result of visceral adipocyte androgen receptors which require testosterone for fatty acid mobilisation (81). The low testosterone levels have also been implicated in reduced lipolysis (77). Another theory is that androgens play a role in preventing stem cells from differentiating into adipocytes, thus in the absence of testosterone this process may proceed unhindered (82).

The current concern regarding sarcopenic obesity is that the reduced muscle mass is associated with decrease muscle strength, fatigue, weakness and thus functional mobility (83). The result is an increase in falls in patients who have a potentially higher risk for bone fractures (discussed in detail later) (84). To date, there are no proven strategies for either the prevention or treatment of body composition changes. However, there have been a number of studies looking at the impact of exercise on quality of life, exercise behaviour and fatigue in cancer survivors (85). There were some questions as to the applicability of these findings in men as the majority of evidence comes from those with breast cancer. Furthermore, there is little data on long-term effect including

adverse events despite what appears to be benefit in the short-term (85) or on the most beneficial type of exercise.

In 2010, Galvao et al (86) published a study comparing the effect of a 12 week combined resistance and aerobic training program to usual care in patients receiving ADT. They found that in the intervention group there was an increase in lean body mass, muscle strength and endurance. Furthermore, there appeared to be a beneficial impact on both general health and fatigue (86). Similarly, in a study conducted in Australia by Cormie et al (87), there was significant improvements in appendicular lean mass preservation, reduced trunk and whole body fat gain as well as muscle strength and fatigue (87). These findings have been supported in the latest study by Wall et al (88).

2.5.1.2 Insulin resistance/ diabetes

It has been well established that testosterone levels are closely related to insulin sensitivity and as such low levels, as in ADT, are associated with insulin resistance and non-insulin dependent diabetes mellitus (NIDDM). These findings have been confirmed by an interventional study of 23 middle aged hypogonadal obese males whose insulin sensitivity improved with the administration of eight months of testosterone (20). It has been noted that within 12 weeks of ADT initiation there is an increase in serum insulin levels by 26-65% (27,89) whilst Smith et al (27) demonstrated a 12.8% decrease in insulin sensitivity. Interestingly both studies noted that during the initial three to six months of treatment, although serum insulin levels increased, serum glucose levels remained normal.

The mechanism responsible for such changes are not fully understood, but inherent in the development of these two conditions are the changes in body composition whereby increases in abdominal fat mass are associated with insulin resistance which is further aggravated by the reduction in lean body mass and thus glucose uptake into muscle (90). There is some speculations that the associated increase in the pro-inflammatory cytokines interleukin-6, resistin (91) and tissue necrosis factor-α (92) may contribute to the development of insulin resistance.

The development of hyperglycaemia and NIDDM appears to require treatment for one year or more before manifesting. Three large observational studies including the SEER trial, analysis of the Canadian database and Veterans health care administration have shown an increased incident

risk in men with PCa receiving ADT of 16-44% (93–95). Most recently in in study by Tsai et al (96), primary ADT was associated with a 1.61-fold increased risk of developing diabetes with a number needed to harm of 29. The risk was more apparent in patients 70 years or younger. Thus, they concluded that ADT had a 60% increased risk of diabetes (96).

To date no evidence-based guidelines have been developed for men currently on ADT with regards to management of these risks. However, it is prudent to treat these patients as a high risk population who require screening at baseline as well as yearly follow-up. Screening is performed with the used of plasma fasting glucose and glycosylated haemoglobin (HbA1c) levels. An HbA1c level between 6.0-6.5% or plasma fasting glucose level of 5.5-7.0 should prompt counselling of patients on long-term ADT particularly regarding lifestyle modification including weight loss and exercise (97).

Patients known with diabetes who are subsequently started on ADT for treatment for PCa have been shown to have significant worsening of glucose control, as compared to baseline HbA1c, at one year ($p=0.008$) and two years ($p=0.03$) after treatment initiation compared to the controls (98). It was further found that patients with pre-existing diabetes started on ADT were more likely to require addition hypoglycaemic agents with a hazard ratio of 1.20 (95% CI=1.09-1.32) (98). As a result, it is recommended that this subpopulation of patients on ADT have more frequent follow-up with a low threshold to improve glucose control through modification of their hypoglycaemic treatment (97). Furthermore, there is some evidence that the use of metformin may provide some protection in this population group against the development of additional metabolic side effects. Currently, there is insufficient data to suggest its use in nondiabetics (99).

2.5.1.3 Sexual dysfunction (loss of libido/ erectile dysfunction/penis length)

Sexual dysfunction is a given in patients receiving ADT due to the reduction in serum testosterone levels. It is associated with both loss of libido as well as erectile dysfunction related to venous leakage and impaired function of nitiric oxide leading to reduced arterial inflow (100). In a retrospective study by Potosky et al (101), it was found that prior to either surgical or medical ADT both groups had a similar interest in sexual activity. Following treatment 51% of those who were originally interested in sex expressed no interest after treatment. Furthermore, of those who were previously sexually active, 73% reported cessation of sexual activity. Of those

who were impotent before, 69% reported new onset of impotence. There appeared to be no difference between the surgical and medical ADT groups. However, following initiation of treatment those who underwent orchiectomy, had slightly worse perceived sexual functioning although it did not reach statistical significance (101).

A reduction in penile and testicular size is distressing side effect of ADT which is rarely discussed. A pathological study of 24 testes previously treated with buserelin for a year, histologically demonstrated interstitial fibrosis and collagenisation (50%) with associated atrophy of the Leydig cells in 92% of the specimens with 50% showing seminiferous tubule atrophy, prominent degeneration of the Sertoli cells and total tubular hyalinization (20). Furthermore, in a prospective trial of 47 men who received a LH-RH agonist either goserelin or leuprolide acetate three monthly for 9 months with subsequent initiation of EBRT at seven months for seven weeks, the stretched penile length was assessed before starting treatment and three monthly thereafter. The results indicated a gradual shortening of penile length which reached statistical significance (mean length 14.2 to 8.6cm; $p<0.001$) at a mean of 18 months follow up (19).

It is important to recognise the major morbidity resulting from sexual dysfunction in men receiving ADT. It is not only an issue regarding the patient's own physiological and emotional health but should be considered a couple's issue that requires specific counselling prior to treatment to reduce the associated regret. Importantly, there exist a number of potential treatment options including the use of intermittent ADT, reducing the period on ADT and antiandrogen monotherapy instead of an LH-RH agonist (60). Furthermore, pharmacotherapy in the form of a phosphodiesterase-5 inhibitor, intracavernosal injections of vasoactive agents such as alprostadil , vacuum constriction devices or penile prosthesis can be considered in those with erectile dysfunction (102).

Intermittent ADT as already discussed allows recovery of testosterone in the "off-period" to near normal lower levels of testosterone. Intermittent ADT has been shown to be non-inferior for overall survival in a non-inferiority trial of 1386-patients receiving either continuous or intermittent ADT after primary or salvage therapy without evidence of metastases. However, desire for sexual activity was significantly improved in the intermittent ADT group ($p< 0.001$) (103). Despite these promising results, one cannot extrapolate this data to men with metastatic disease since there appears to be a significant benefit in terms of erectile function ($p< 0.001$), to

date there is still no evidence that cancer specific survival with intermittent ADT is comparable to continuous (104).

The antiandrogen monotherapy to date cannot be advocated for treatment of PCa as there is no evidence in which their use is oncologically as effective as the use of a LH-RH agonist (6). Despite the lack of evidence there is a suggestion that antiandrogen monotherapy may improve sexual function compared to the LH-RH agonists (72).

2.5.1.4 Anaemia

Anaemia is a common adverse effect associated with PCa. Whilst the exacerbation of anaemia by ADT is a common finding, this occurs in a population who are at substantial risk of additional co-morbidities. Anaemia is a prognostic indicator of poor outcome with an increase RR of death of 47% (21-78%) in PCa (105). Tomasz et al. (106) similarly found that a decline in haemoglobin after three months of treatment with ADT independently predicted shorter survival (HR=1.10 per 1g/dl decline; p=0.0035). Furthermore, decline in haemoglobin was also associated with a shorter progression free survival (HR-1.08 per 1g/dl decline; p=0.013) (106). However, there is currently no evidence that treatment of ADT-related anaemia has an impact on mortality in PCa (107). Due to the stimulatory role of androgens in erythropoiesis, it is not surprising that patients undergoing ADT experience anaemia. Moreover, the severity of anaemia is associated with the duration of treatment (107). There is a suggestion that a decline in haemoglobin of >1g/dl following the first month of ADT may in fact be predictive of PSA failure (105).

A clinically significant decline in haemoglobin levels following orchiectomy was shown in a study of 64 patients with a mean age of 68 years. Postoperative follow-up occurred at three intervals: 90-180 days, 181 to 360 days and >720 days. For all of the follow-up intervals a significant decline in haemoglobin was noted ($p<0.0001$. Finally, of the 64 patients, 37 (58%) demonstrated a decline in haemoglobin to levels below normal postoperatively (108).

In terms of the effect of ADT on haemoglobin level, Timilshina et al. (109) compared to the baseline haemoglobin levels in patients with PCa and no ADT (14.1g.dl), PCa on ADT (14.4g/dl) and healthy controls (14.9g/dl). The decline in ADT users was significant (($p<0.001$) with a decline of 0.89 g/dl compared to 0.056 and 0.203g/dl in PCa controls and healthy controls

respectively. Risk factors associated with significant decline in haemoglobin in PCa participants included black race (p<0/001), use of ADT (p<0.001) and lower activity of daily living score (p<0.001). Age did not seem to play a role in anaemia development (109).

2.5.2 Oestrogen Deficiency

Oestrogen deficiency is associated with osteoporosis, increased cardiovascular disease morbidity, hot flushes, gynaecomastia and cognitive impairment.

2.5.2.1 Decreased bone density with associated increase in fracture risk

There is a well-recognised association between ADT and reduced bone mineral density (BMD). A five- to tenfold increase in the rate of bone loss at various skeletal sites (including the spine, hip, upper limb and whole body) has been demonstrated in a number of studies (80,110,111). Furthermore, the decrease in BMD, appears to be greatest in the first 12 months following initiation of ADT although, continued deterioration has been demonstrated years after initial investigation with an average loss of approximately 1.5% per year after the second year of treatment being quoted by some (110–113). Following cessation of ADT, there is no recovery of BMD where bone loss has already been established (24). Of note Hussain et al (24), found that of 174 men with prostate cancer who were treatment naïve, 42% were osteoporotic and 37% osteopaenic, compared to only a 27% incidence of osteoporosis in the control group, thus, suggesting that PCa in itself is high risk for the development of osteoporosis.

It is known that in both men on ADT and postmenopausal women, that the rate of bone remodelling is substantially increased as a result of the reduction in serum oestrogens. The pathophysiology associated with such bone remodelling includes upregulation of osteoclastogenesis and osteoblastogenesis in the marrow secondary to increased cytokines, in particular interleukin-6. Interleukin-6 production is inhibited in the presence of oestrogens and androgens. Furthermore, the reduced oestrogen is associated with failure to suppress tissue necrosis factor, macrophage- colony stimulating factor and interleukin-1 which play a further role in bone loss. Amplification of one of the above mentioned cytokines may serve to activate the cascade and thus compound the problem. Initially there is an increase in osteroblast activity, however, it is the osteoclastic bone resorption function which occurs at a faster rate with the

result new bone being less dense thus resulting in a net loss of BMD. The effect is further worsened as a reduced serum oestrogen results in delayed osteoclast apoptosis, thus extending the life of the osteoclast and further resulting in deep bone cavities (114).

High risk patients with PCa on ADT who demonstrate a reduction in BMD are at increased risk for fractures (25,115). A 10-15% reduction in BMD results in double the risk of suffering a fracture (116). Shahinian et al (25), analysed the SEER database of 50613 men with prostate cancer with primary outcomes of any fracture or a fracture resulting in hospitalisation. They found that of the participants who survived at least five years following diagnosis, 19.4% who received ADT had an associated fracture in the preceding years as compared to only 12.6% of those who had not received ADT ($p<0.001$). Similar findings were made by Smith et al (117), where they demonstrated a relative risk of fracture for persons on LH-RH agonists compared to those not exposed of 1.21 (95% CI 1.09 to 1.34). Risks associated with a decreased risk of bone fracture include an increased BMI ($p=0.024$), black race ($p=0.009$) and whilst increased duration of ADT was found to significantly increased risk ($p=0.003$) (118) as was the number of three monthly doses of LH-RH received in both the 12- and 24- month periods subsequent to diagnosis ($p<0.001$) (25). Fractures have been shown to independently adversely affect not only quality of life but also overall survival (119).

A number of strategies have been investigated to reduce the impact of ADT on bone health. Grossmann et al. (84) suggest prior to starting ADT that all men are assessed for their baseline fracture risk including laboratory testing, dual energy x-ray absorptiometry (DEXA) to asses pre-existing BMD and thoracolumbar vertebral x-rays in patients with osteopaenia to exclude clinically silent vertebral fractures. They further advocate the assessment of clinical risk factors for fracture and risk of fall using the FRAX assessment tool. The limitation of the FRAX assessment tool is that it has not been validated for use in patients on ADT and doesn't take into account the impact ADT has on bone health thus potentially underestimating the risk. The DEXA scan should be repeated yearly, with further monitoring on an individual basis (84).

The use of calcium and vitamin D supplementation remains controversial. Current recommendations include supplementation of 1000 mg/d of calcium in patients less than 70 years of age with an increase to 1200 mg/d of calcium over 70 years. Vitamin D supplementation is suggested at 400-800 iu/d and 800-1200 iu/d in those under 50 years of age and those older than 50 respectively (120).

However, in a review by Datta et al. (121) from 2012, looking at the benefit of vitamin D and calcium supplementation for the prevention of bone loss in men on ADT, there was no trial in which supplementation was compared to no intervention. The review included 12 trials all of which used a placebo together with vitamin D and calcium as the control group which was compared to the intervention being tested together with vitamin D and calcium. The ranges of calcium and vitamin D doses used were 500-1000 mg/d and 200-500 iu/d respectively. There was a failure to show cessation of bone loss in the placebo group of all 12 trials. Moreover, there is concern regarding excessive vitamin D and calcium supplementation as high levels of both have been implicated in the development of PCa. Furthermore, excess calcium is responsible for increased cardiovascular risk in a population already at risk. Thus, supplementation should not exceed current recommended daily allowances (121).

The use of anti-resorptive treatment has been shown to reduce both bone loss and the risk of fracture. Serpa Neto et al. (122) conducted a systematic review and meta-analysis of 15 trials, including 2643 participants, looking at the efficacy of various bisphosphonates in the prevention of bone loss in men on ADT. Bisphosphonates were shown to have significant benefit in preventing osteoporosis ($p<0.00001$) and fractures ($p=0.005$). Improvements in bone density in the lumbar spine and femoral neck were 5.18±3.38% and 2.35±1.16% compared to the placebo group. In terms of number needed to treat to prevent osteoporosis and fracture, zoledronic acid had the greatest effect with a number needed to treat of 2.68 and 149 respectively. Furthermore, in a RCT comparing 4mg of zoledronic acid to placebo over one year, there was a significant increase in BMD in the lumbar spine ($p=0.012$) and femoral neck, trochanter and total hip ($p<0.001$) with a mean increase in BMD of 5.6% in the intervention group(123).

The benefit on BMD from the use of bisphosphonates was associated with only mild adverse effects affecting mainly the cardiovascular and gastrointestinal tract (nausea, diarrhoea, constipation and anorexia). However, it was only the risk of nausea with a RR 1.21 (95% CI, 0.99–1.49) that reached statistical significance (122). Zoledronic acid in particular was associated with an increased incidence of lower limb oedema compared to the placebo group as well as general adverse effects including musculoskeletal pain, fatigue, anaemia and fever (123).

Denosumab, a human monoclonal antibody, has an effect on osteoclast formation, function and survival as a result of its effect on the receptor site for the nuclear factor-κβ activator (124). In 2008 a double-blind, multicentre RCT including 734 patients with non-metastatic PCa on ADT,

randomised to either placebo or 60mg of denosumab six monthly was published in the New England Journal of Medicine. Denosumab was associated with significant increase in BMD at all measured sites after 24 months. The significance was present even with subgroup analysis of older patients and those with a low baseline BMD at commencement of treatment. In particular, there was a significant increase in BMD at one month and throughout the 36-month follow-up, with a mean 6.7% increase, at the lumbar spine ((p<0.001). In terms of new vertebral fractures there was reduced incidence at 12, 24 and 36 months with an overall 62% reduced risk compared to the placebo group. there was no difference between the groups in time to first clinical fracture at any site (124). Denosumab is currently licenced for the prevention of bone loss in men receiving ADT in more than 30 countries (60).

The use of Selective Oestrogen Receptor Modulators (SERMs), has been shown to have a beneficial effect on BMD in patients receiving ADT. Toremifene, a second generation SERM, when used in patients on ADT has been demonstrated to significantly increase BMD, reduce markers of bone turnover, reduce the rate of vertebral and other site fractures and improve lipid profile. Despite these benefits, there is some concern over the increased incidence of venous thromboembolic events when using toremifene compared to use of a placebo (125).

Although evidence exists as to the benefit of antiandrogen monotherapy on bone health compared to the use of a LH-RH agonist (6,72), this strategy cannot be advocated for due to the lack of evidence of equivalence in terms of survival .

2.5.2.2 Cardiovascular risk (incl. lipid profile, metabolic syndrome)

The cardiovascular and metabolic consequences of ADT have been well established through a number large observational and randomised controlled studies. There exists little similarity between the different trials with regards to population characteristics, length of observation, type and duration of ADT, thus making comparison difficult. To date, the non-cancer causes of death exceed those related to the PCa itself, with mortality from cardiovascular disorders alone being similar to those attributable to PCa (126). There is some suggestion that different agents may impact the degree to which cardiovascular disease is affected, particularly with regard to some benefit of the LH-RH antagonists over the LH-RH agonists in men with pre-existing cardiovascular disease (HR: 0.44; 95% confidence interval, 0.26-0.74; p=0.002) (127).

Reported effects on lipid profile following treatment with ADT are variable. The most common findings regarding change in lipid profile are an increase in total and low-density lipoprotein (LDL) cholesterol (76,128) in addition to an increase in triglycerides and high-density lipoprotein cholesterol (76). However, these findings have not been consistent, with others reporting only a significant increase in total and HDL cholesterol (89) or a lack of evidence for change in lipid profile following intervention with ADT (77). Most recently Salvador et al. (129) evaluated the effect of single agent ADT and maximal androgen blockade on lipid profile. They found a transient, but significant increase in total LDL cholesterol at six months. However, these changes were no longer apparent at 12 months of treatment. Furthermore, there was no difference in the two treatment groups (129). Finally, HDL cholesterol is considered protective against cardiovascular disease. However, to date there is no evidence to suggest that the associate increase in patients on ADT is protective (76).

The increases in abdominal circumference, serum glucose and changes in lipid profile, with the exception of HDL cholesterol, have resulted in an association between ADT and metabolic syndrome. Furthermore, it is known that reduced testosterone and sex-hormone-binding-globulin (SBHG) are independent predictors of metabolic syndrome. Current data suggests that the prevalence of metabolic syndrome in men receiving ADT for at least a year is between 14.7%-55% irrespective of concomitant risk factors and PCa stage (128,130). Slight differences have been elicited between the classically described metabolic syndrome and that attributable to ADT, namely the approximately 5% increase in HDL and failure to demonstrate a change in blood pressure (76,130,131). The latter was found despite previous evidence to suggest a decreased in systemic arterial compliance on ADT (89).

The above mentioned adverse effects have led to the evaluation for a link between ADT and accelerated cardiovascular disease. Keating et al. assessed the SEER database and found the risk of both coronary artery disease and sudden cardiac death to increase by 16% in those on ADT (93). Similar findings for adjusted risk were made from the Veterans Healthcare Administration and the population based Swedish studies using the National Prostate Cancer Register (95,132). However, the retrospective trial performed in 2009 by Nanda et al. (133) found that excess cardiovascular risk was confined to those with a pre-existing history of cardiovascular disease or myocardial infarction. Furthermore, the associated twofold increase in all-cause mortality was confined to patients with more than one cardiovascular risk factor (133).

Currently there is limited evidence regarding the association between ADT and stroke (134). A meta-analysis by Meng et al. (135) showed a 12% increased incidence of stroke in ADT users, however, this finding did not reach statistical significance. Of note, the use of LH-RH agonists, a combination of LH-RH agonist and antiandrogen and orchiectomy were significantly associated with stroke ($p<0.001$). The use of antiandrogens alone did not seem to significantly impact stroke risk (135).

As a result of the inherent risk for cardiovascular disorder related to ADT, the FDA has issued a warning when initiating ADT and a consensus paper from the American Heart, Cancer Society and Urological Associations whereby they advocate weighing the benefit of ADT to the possible adverse cardiac risk in those with pre-existing disease, patients initiated on ADT be referred to a primary physician for periodic follow-up and the use of secondary prevention measures according to the AHA and other organisations in those who develop cardiovascular disease (136).

2.5.2.3 Vasomotor symptoms (hot flushes)

Hot flushes are defined as "an uncomfortable sensation of heat or sweating that can even be associated with extreme distress, light-headedness, palpitation or marked sleep disturbances" (1). The incidence of hot flushes in men on ADT varies, but is quoted to be between 58-96% (72,137,138) with 48 % of men still complaining of symptoms 5 years after the initiation of treatment (137). In a study looking at 43 participants receiving neoadjuvant ADT whilst awaiting radical prostatectomy the incidence of hot flushes resolved with cessation of treatment with an additional 11% reporting an improvement in symptoms three months later (139). The incidence of hot flushes may impact significantly on the QOL of men on ADT.

The pathophysiology of hot flushes although not fully understood, is thought to be similar to that postulated to cause the same symptoms in post-menopausal females. Withdrawal of the sex hormones, particularly oestrogen, results in a decrease in serum endorphins and catecholamines thereby affecting the hypothalamic feedback loop and reducing the thermoregulatory set-point of the thermoregulatory nucleus in the medial preoptic area of the anterior hypothalamus. In addition, the reduced circulating catecholamines and endorphins cause an inappropriate release of noradrenaline and serotonin in response to minor changes in temperature. The intra-hypothalamic release of noradrenaline is thought to be responsible for the change in temperature set-point and

activation of heat loss mechanisms (140). Known triggers of hot flushes include stress, anxiety, alcohol and an increase in ambient temperature (1).

Current treatment strategies include the use of selective serotonin reuptake inhibitors (SSRIs), Serotonin-noradrenaline reuptake inhibitors (SNRIs), gabapentin, medroxyprogesterone acetate, the antiandrogen cyproterone acetate in addition to various alternative therapies including acupuncture. Venlafaxine, a SNRI has been shown to reduce the hot flush score (frequency x severity) by more than 50% in patient receiving ADT after four weeks of treatment. It demonstrated a significant decrease in severe and very severe hot flushes ($p=0.003$) (141). The use of paroxetine, a SSRI, was evaluated in 18 patients on ADT, with an initial dose of 12.5 mg/d which was increased 37.5 mg/d during the following four weeks. The paroxetine was well tolerated and reduced both the median frequency and hot flush score (142). A limitation of both of the above studies was the smaller number of participants.

A more recent randomised controlled trial compared the efficacy of venlafaxine, cyproterone acetate and medroxyprogesterone in the management of hot flushes. 311 participants were randomised to receive either 75mg of venlafaxine, 20mg of medroxyprogesterone or 100mg of cyproterone acetate daily. Although all three treatment arms were associated with a significant reduction in hot flushes from baseline ($p<0.0001$), venlafaxine was found to be inferior to both medroxyprogesterone and cyproterone acetate regardless of the observation interval. Furthermore, there appeared to be no significant difference in symptom outcome between the medroxyprogesterone and cyproterone acetate groups. However, there was a slight increase in the number of participants who experienced serious adverse effect in the cyproterone acetate group (7 vs. 5) although this increase was statistically significant (143).

The use of gabapentin, a structural analogue of GABA, which acts on $\alpha_2\delta$ voltage-gated calcium channels subunits of sensory nerves, is well described for epilepsy and neuropathic pain. In a double-blind randomised control trial by Loprinzi et al. (144), gabapentin was shown to reduce the incidence of hot flashes at three different doses (300, 600 or 900mg/d). however, it failed to reach significance when compared to the placebo arm of the study (144).

Two prospective trials have evaluated the use of acupuncture in the treatment of hot flushes. The first by Harding et al. (145) in 2008 evaluated 60 men on a LH-RH agonist who underwent auricular acupuncture for ten weeks. They found a decrease in hot flush severity from 5.0 to 2.1

($p<0.01$) (145). Similarly, Ashamalla et al. (146) assessed the effect of a ten-point bilateral acupuncture protocol in 17 men on ADT experiencing hot flashes. They assessed the efficacy at two weeks, six weeks, seven and eight months. There appeared to be an improvement in symptomatology at all time points with the greatest improvement in hot flush score at six weeks with a reported 89.2% symptom improvement (146).

2.5.2.4 Gynaecomastia

Gynaecomastia and mastodynia are commonly experienced, the incidence of which is dependent on the regime of ADT taken. In patients receiving non-steroidal antiandrogen monotherapy with bicalutamide 150mg daily the incidence of gynaecomastia was found to be as high as 85% (21). In contrast the quoted incidence for those on complete ADT is much lower between 13-22% (22). The development of gynaecomastia and mastodynia are associated with potentially negative psychological and emotional effects not to mention physical discomfort which may result in decreased physical activity (147).

The development of gynaecomastia is related to the decrease in serum testosterone levels, secondary to removal of the primary source or blockade of the LH-RH receptors, leading to an increase in the oestrogen-to-testosterone ratio. Both steroidal and non-steroidal antiandrogens block androgenic receptors in the breast allowing unopposed oestrogen stimulation. Steroidal antiandrogens further block the negative feedback of androgens at the hypothalamus and pituitary thus further promoting the effect of oestrogen. Although the different agents promote gynaecomastia via differing mechanisms, when used in combination with a LH-RH agonist the reduction in circulating testosterone available for conversion into oestrogen is proposed to be responsible for the reduced incidence compared to antiandrogen monotherapy (22).

Current treatment options include prophylactic radiotherapy, prophylactic tamoxifene or liposuction. A randomized Scandinavian trial (SPCG-7/SFUO-3) compared the use of neoadjuvant ADT and radiotherapy with neoadjuvant ADT alone, with a one-year follow-up in 253 participants. The use of single fraction (12 to 15 Gy) electrons was shown to reduce the incidence of gynaecomastia from 71% to 28% compared to those who did not receive treatment at one year. Subjectively, patients who received radiotherapy and those who did not reported a perceived increase in breast size of 44% and 78% respectively. There was a significant reduction

in reported breast pain at one year in the radiotherapy group ($p<0.001$) (148). Tyrell et al. (21) had similar findings with a single dose of radiotherapy (10 Gy) in the reduction of bicalutamide associated gynaecomastia. Although there was a reduction in the radiotherapy group in mastodynia it was not significant. However, the reduction in pain severity was significantly improved in the radiotherapy group ($p=0.0429$) (21).

The use of tamoxifen for the reduction of gynaecomastia was demonstrated by Boccardo et al. (149) in a RCT where tamoxifen was found to significantly reduce the incidence of gynaecomastia and mastodynia to 10% ($p<0.001$) and 6% ($p=0.004$) respectively. Use of tamoxifen was compared to that of radiotherapy in the prevention of gynaecomastia and mastodynia. Although there was no difference in the QOL between either group (150), and they were both superior to the placebo group, it appeared that tamoxifen was superior to radiotherapy particularly once gynaecomastia was established (150,151).

2.5.2 5 Cognition, mood and memory

In 2002 Moffat et al. (152) looked at the effect of the physiological age-associated decline in serum testosterone (both total and free) on neuropsychological performance in men aged 50-91 years. The study included 407 participants with a mean follow up period of ten years. They found that mean testosterone levels only significantly correlated with a poor attention/concentration index. Conversely, it was the free testosterone index (FTI) which had a high predictive value, with a high baseline FTI associated with improved outcomes in visual and verbal memory, visuomotor scanning and visuospatial rotation. Furthermore, men considered to be hypogonadal had lower cognitive functioning in terms of visual memory, immediate and delayed verbal memory, visuomotor scanning and visuospatial rotation (152).

Despite the above evidence, the exact impact of ADT on cognition and mood remains an area for ongoing research. Sub-analysis of the SEER database assessed the risk of physician diagnosis of cognitive impairment, depression and constitutional symptoms in men surviving at least five years after diagnosis. Initial analysis suggested that those receiving ADT were more likely to develop at least one of the above three diagnosis (31.3%) compared to those without PCa (23.7% ($p<0.001$)). However, following correction for age, stage of disease and comorbidities, the risk of associated symptoms were either abolished or no longer significant (153).

The largest prospective study to date was conducted by Alhibai et al. (154) who looked at three age and education matched groups: 77 with PCa starting continuous ADT, 82 both in the group not with PCa not receiving ADT and healthy controls. They conducted 14 neuropsychological tests at baseline, six and twelve months. They found no association between ADT and a decline in 8 of the domains. However, there was a significant decline in a single test in immediate memory ($p=0.029$), working memory ($p=0.031$) and visuospatial ability ($p=0.034$) at twelve months. Despite these finding they concluded that there was no consistent decline in cognitive function in elderly men with PCa receiving ADT as they could not confirm the above findings with other analytical approaches in the same domains (154).

In a study comparing the effect of intermittent ADT on healthy controls, cognitive function and mood tests were administered at baseline, after three and nine months of ADT and then three months after cessation of treatment. The ADT group exhibited evidence reduced function in terms of spatial reasoning and ability as well as working memory. There were further significant increases in self-reporting of mood components including anxiety, fatigue and depression. There was a suggestion that the effect was greatest at three months after initiation of treatment with a return towards baseline at completion of initiation ADT at nine months. Furthermore, there appeared to be a return to baseline functioning in most of the affected domains after ADT cessation (155).

2.6 QOL

The use of ADT has resulted in longer duration of survival with PCa. However, longer cancer specific survival does not equate to a necessarily improved quality of life. In addition to the knowledge of living with cancer, patients' QOL including physical, psychological and sexual functioning, are impacted by the disease itself as well as the adverse effects of ADT.

The EUA advocates the use of validated tools such as the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-30 and prostate specific EORTC QLQ-PR 25 for the assessment of patient reported outcome measures (45). The EORTC QLQ-30 consists of five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting) in addition to a number of single symptom items (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea), a global health status/ QOL scale and finally

assessment of patient perceived financial impact. The use of the EORTC QLQ-30 is intended for use with a wide population. The development of the condition-specific EORTC QLQ-PR 25 was established to assess health related QOL in PCa sufferers, assessing urinary, bowel and treatment-related symptoms, as well as sexual activity and sexual function specifically as they relate to PCa (11,45).

Herr et al. (156) conducted a cohort study in 2000 in which 144 men with locally advanced disease or biochemical failure after curative therapy were offered either immediate treatment with ADT (n=70) or delayed initiation (n=65). Prior to making a decision patients were fully counselled on both the risks and benefits of ADT. The ADT group were offered orchiectomy, single agent LH-HR agonist leuprolide or combined leuprolide and the antiandrogen flutamide. Patients general QOL of life was assessed at baseline, six months and a year after enrolment into the study using the EORTC, Intrusion subscale of the Impact of Event Scale and Selby's QL Uniscale. At six months and a year there was no difference in the scores between the groups or within the individual groups themselves. Although they demonstrated a trend towards greater psychological distress in those on ADT, this finding was not significant. When subgroup analysis was done the significant differences in terms of worse functioning was found in the hormone group for physical function, fatigue and sexual problems. Moreover, there appeared to be a greater trend towards psychological distress in those on ADT. The above-mentioned findings resulted in significantly decreased scores for overall quality of health ($p=0.001$). Interestingly, when comparing combined androgen blockade to either orchiectomy or monotherapy, there were worse scores for fatigue, general health, psychological distress and worry about cancer (156).

Similar findings were published from a study conducted in Japan. They found that patients who received ADT for PCa, had significant deteriorations in sexual function at 3 ($p<0.05$), 6 and 12 months ($p<0.005$) although sexual bother scores improved at both 6 and 12 months. In addition, the use of ADT markedly improved urinary function and urinary bother ($p<0.05$) (33).

There is evidence to suggest that patients and their partners are not always well informed about the negative impact ADT may have on physical health, psychological well-being as well as sexual function and health, which is associated with a negative impact on couples' relationships. Walker et al. (157) demonstrated that both patients and partners had poor awareness of the common side effects including anaemia, change in memory, loss of body hair, mastodynia and

depression. The partners were more commonly aware of the psychological effects of ADT ($p=0.01$) but it was the patients who were more aware of the potential for decrease in both penile length and testicular size ($p=0.02$) (157). This discrepancy in patient and partner knowledge following initiation of ADT has led to emphasis being placed on accurate counselling and provision of knowledge in order to facilitate the patient's informed consent and an active participation in treatment decision making (33,157).

CHAPTER 3: RESEARCH METHODOLOGY

3.1 Introduction

This chapter will describe the research methodology of the study. It will include research design, study population, the sampling process and study methods.

3.2 Ethical Considerations

Approval to conduct this study was obtained from the Graduate Studies Committee and the Human Research Ethics Committee (Medical) of the University of the Witwatersrand (Appendix A).

The study was conducted prospectively, and the identifying information of the patients remained anonymous. Patients on ADT attending the urology clinic were invited to take part in the study and were given an information letter (Appendix B). Informed consent (Appendix C) was obtained from patients who agreed to take part in the study and complete the questionnaire. Questionnaires and data sheets were sealed in an envelope and placed in a secure box. The corresponding consent was filed separately. Participation in the study was voluntary, thus respondents could withdraw from the study at any time should they so choose.

All the questionnaires and data collected were kept confidential as only the researcher and supervisors had access to the raw data. The data will be stored securely for six years after completion of the study.

The study was conducted adhering to good clinical research practice in accordance with the South African Good Practice Guidelines (34) and the Helsinki Declaration (35).

Should the study find significant impact of ADT on the various spheres of health (physical, sexual and psychological), the information will be used to better inform both clinicians with regards to monitoring for adverse physical effects as well as addressing and counselling patients more appropriately.

3.3 Study Design

The research design used in this study was a prospective, contextual, descriptive design.

A prospective study is defined as a study in which individuals are selected because of specific factors that are to be examined for an outcome. In this study questionnaires were completed by patients on ADT and the data sheet completed by the attending physician to determine the impact of ADT on QOL.

The context refers to a body or world and the concerns unique to the individuals arising from this world. The study was contextual as it only evaluated the QOL issues relating to patients on ADT who were attending the urology oncology clinic at CMJAH in Johannesburg.

A descriptive study is used to identify phenomena and the associated variables. This study was descriptive as it described the perceived impact of ADT on the QOL of patient with PCa.

3.4 Study Population

The study population included all males attending the urology oncology clinic at CMJAH with prostate cancer who were currently on ADT for a duration of at least 3 months. Consent to conduct the study at CMJAH was obtained from the CEO (Appendix D). The following patients categories will be considered: patients with metastatic prostate cancer for palliation, patients with intermediate or high risk prostate cancer awaiting external beam intensity modulation radiotherapy (ERBT), patients with intermediate or high risk prostate cancer with high likelihood of disease progression who are not candidates for surgery or radiotherapy or who refuse other treatment or as part of salvage therapy in patients who have undergone treatment with curative intent who have biochemical recurrence (rising PSA).

3.5 Study Sample

3.5.1 Sample size

The sample size was determined in consultation with a biostatistician. The average number of patients on ADT attending the urology oncology clinic is 20 per day (measured over 2 months). Patients on ADT in general are followed up three monthly. A confidence interval of 0.05 was considered adequate and a required sample size of 148 patients was calculated using Slovin's formula. A sample of between 100 and 200 patients (148) was targeted to ensure an appropriate representation of the study population in question. Due to the required sample size the study was conducted over a period of 6 weeks.

3.5.2 Sampling method

Sampling was done using a convenience sampling method. This is defined as a non-random sampling method resulting in participants being selected because of the ease of volunteering or selecting a unit because of ease of accessibility. Men on ADT attending the clinic during the study period formed a readily accessible unit for sampling and were eligible to partake in the study.

3.6 Inclusion and Exclusion Criteria

All men with PCa on ADT for at least three months, attending the urology oncology clinic at CMJAH were invited to participate in the study.

The following patients with PCa on ADT were considered for inclusion in the study:

- patients with metastatic prostate cancer for palliation,
- patients with intermediate or high-risk prostate cancer awaiting external beam intensity modulation radiotherapy (ERBT),
- patients with intermediate or high-risk prostate cancer with high likelihood of disease progression who are not candidates for surgery or radiotherapy,
- patients with intermediate or high-risk prostate cancer with high likelihood of disease progression who refuse other treatment, and

- use of ADT as salvage therapy in patients who have undergone treatment with curative intent who have biochemical recurrence (rising PSA).

The following exclusion criteria were applied to the study:

- patients with castrate resistant prostate cancer on alternative cytotoxic chemotherapeutic agents or hormonal agents not administered in the Urology Oncology clinic,
- patients currently receiving ERBT, and
- patients who decline to partake in the study.

3.7 Data Collection

3.7.1 Data collection instrument

The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-30, a questionnaire (Appendix E) consisting of 30 questions, was used to assess the quality of life in patients. It is an instrument that has been validated in over 100 languages and used worldwide in over 3000 studies assessing QOL in cancer patients. It is intended for use in a wide population. The EORTC QLQ-30 consists of five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting) in addition to a number of single symptom items (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea), a global health status/ QOL scale and finally assessment of patient perceived financial impact. The development of the disease-specific EORTC QLQ-PR 25 (Appendix F) supplementation is used to assess patient outcomes from the same group. It assesses urinary, bowel and treatment-related symptoms, as well as sexual activity and sexual function specifically as they relate to PCa. The questionnaires were available in English, Zulu, Sotho, Afrikaans and Xhosa.

Additional patient demographics (patient age, employment status, PSA at diagnosis, initial Gleason score including perineural or lymphovascular involvement and the percentage of the prostate biopsy sample representing cancerous cells, risk stratification according to D'Amico, BMI, waist circumference, treatment regimen, duration of treatment, additional investigations) and the most recent laboratory results (haemoglobin, mean corpuscular volume, HBA1c, lipid profile) were captured by the treating physician on a separate data sheet (Appendix G) during the routine clinic visit. No additional laboratory testing was done for the purpose of this study, the

above-mentioned tests are performed as part of standard of care treatment. Any missing results were marked as not applicable (N/A) on the datasheet.

3.7.2 Data collection method

During the study period questionnaires were handed out to eligible patients on ADT attending the aforementioned clinic. An information letter regarding participation and the purpose of the study was made available to all those invited to participate. Upon agreeing to participate patients completed the informed consent form in addition to completing the accompanying questionnaire. Questionnaires were allocated a study number which corresponded to the signed consent forms. The consent and questionnaires were stored separately.

Questionnaires and envelopes were allocated a study number to monitor the number of questionnaires returned. To ensure confidentiality, questionnaires were completed anonymously and once completed placed in an unmarked envelope. Patients then proceeded to their consultation where the attending physician completed the data sheet provided, including the corresponding study number on the envelope. This completed data sheet was placed in the envelope containing the questionnaire, sealed and placed in a sealed data collection box.

As the questionnaire requests potentially identifying data at the top of the first page, once collected this information was separated from the corresponding questionnaire and stored in a separate secure file. These documents are linked by a corresponding study number.

3.7.3 Data analysis

A Microsoft Excel® spreadsheet was used to capture all survey data. The data was analysed, aided by a statistician using Microsoft Excel® and GraphPad InStatTM. Descriptive statistics were used to analyse the data. For categorical data, frequencies and percentages were used. Symmetrically distributed variables were analysed using means and standard deviations. For data with skewed distribution, the median was calculated. Furthermore, for comparison between groups, a t-test was used where appropriate. A level of significance of 0.05 and 95% confidence intervals was used. Due to the relatively small ideal sample size, where data was missing from linear scales, the value was not included in the total sample size used for calculation. Scoring of

the QOL responses from the EORTC QLQ-30 and PR-25 were performed according to the scoring manual provided (158).

3.8 Validity and Reliability

Validity and reliability were used to ensure that the study's conclusions were in keeping with the study design and results analysis. The validity is the extent to which a measurement represents a true value. Threats to validity can occur throughout the research process and include factors external to the study. Reliability ensures the consistency of the result achieved.

The validity and reliability of this study were ensured by:

- the use of an appropriate study design and data gathering techniques
- the use of an internationally validated questionnaire to assess impact on QOL
- emphasis was placed on anonymity to ensure participants answered in accordance with their current practice.

3.9 Summary

The research methodology was discussed in this chapter. In the following chapter (Chapter 4) the results and discussion are presented.

CHAPTER 4: RESULTS AND DISCUSSION

4.1 Introduction

The sample realisation, results of the study and the discussion are presented in this chapter.

4.2 Sample Realisation

A total of 154 men with PCa on ADT, currently attending the Urology Oncology clinic at CMJAH between May and July 2017, met the inclusion criteria for participating in the study. Two of the patients declined to participate in the study as the questionnaire was not available in their preferred language. Thus, 152 questionnaires were included for statistical analysis. As patients attend the clinic on a three monthly cycle, the total population attending the clinic is 231. Thus, the sample size comprises approximately 66.7% of the total population of men with PCa on ADT attending the clinic.

Due to the small number of patients in the Caucasian, Indian and Coloured groups, comparisons to look for race specific differences in both side effects and QOL could not be performed.

4.3 Results

All percentages in the results are reported according to the number of complete answers obtained for each question. The percentages, means, standard deviations and medians will be presented to one decimal place. The error in the measurement is represented as ± standard deviation (SD)

4.3.1 Population Characteristics

4.3.1.1 Patient demographics and biometrics

The mean age at completion of the questionnaire was 69.9 ± 8.2 years. The African group made up the largest proportion of patients attending the clinic with a 76.2% representation (115 of total). The patients had an average BMI of 27.1 ±4.8 and a mean waist circumference of 101.0 ±12.8cm. See Table 4.1 for Patient characteristics.

The results for some of the common side effects of ADT were as follows; in terms of new onset (NO) disease after initiation of ADT, only NO hypercholesterolaemia was a significant finding in the total population with 71 (46.7%) being newly diagnosed. For lipid profile the mean total cholesterol was 4.5 ± 1.1, triglycerides mean was 1.7 ± 1.1, LDL mean was 2.9 ± 1.0 and the HDL mean was 1.2 ± 0.4. Of the patients diagnosed with hypercholesterolaemia following initiation of ADT, only 49 (69.0%) were started appropriately on a statin in the clinic.

It appeared that NO hypercholesterolaemia was associated most strongly with ADT for metastatic disease with 42 of the 69 (60.9%) patients having metastatic disease. The mean duration of treatment with ADT leading to hypercholesterolaemia was 32.8 ± 32.1 months (median 21 months). Finally, the development of hypercholesterolaemia appeared to be more common in patients taking continuous ADT with 60 of the 69 patients having been on a continuous regime. The mean duration of treatment in those on continuous ADT was 34.5 ± 33.9 months compared to those on intermittent treatment where the mean was 21 ± 9.0 months.

The number of patients diagnosed with new onset DM was low. However, 13 (8.6%) of the patients had no HbA1c or any other form of glucose testing documented after ADT initiation. The average HbA1c of the study population was 6.3 ± 1.5. For patients with pre-existing DM prior to initiation of ADT, the mean HbA1c was higher with a mean of 7.8 ± 1.8.

According to the Adult Treatment Panel III guidelines for the diagnosis of metabolic syndrome, 46 (30.3%) of the patients attending the Urology oncology clinic with PCa on ADT, met the criteria. The most predominant risk factors included waist circumference >102cm and hypertension.

Table 4.1 Patient characteristics and biometrics

Patient demographics	**Number (percentage) n (%)**
Age	
40-49	1 (0.7)
50-59	17 (11.2)
60-69	66 (43.4)
70-79	52 (34.2)
≥80	16 (10.5)
Race	
Caucasian	18 (11.9)
African	115 (76.2)
Indian	6 (4.0)
Coloured	12 (7.9)
New onset disease	
Diabetes mellitus	2 (1.3)
Hypercholesterolaemia	71 (46.7)
Cardiovascular disease	1 (0.7)
Biometrics	**Mean (SD)**
BMI	27.1 (4.8)
Waist circumference	101.0 (12.8)

Anaemia is a well-documented complication of ADT. The mean Hb of the study population was 13.5 ± 1.5 g/dL. Of the 151 patients with a readily available Hb, 49 patients had anaemia according to the WHO definition and classification with 35 (23.2%) having mild anaemia, 13 (8.6%) moderate anaemia and 1 (0.7%) severe anaemia.

4.3.2 Prostate Cancer Specific Population Data

The mean PSA on diagnosis and initiation of ADT are high with a large variation in values. However, there was no significant difference in PSA at the time of PCa diagnosis and PSA when ADT is initiated indicating timely institution of treatment (p=0.882).

The majority of the population was on a continuous regime of ADT, either medical or surgical, with a mean duration of 41.5 ± 31.2 months (median 31.0 months). Only 21 patients were receiving intermittent ADT with a mean duration on treatment of 23.1 ±18.2 months (median 19

months). Furthermore, only one patient had received continuous ADT for less than 9 months prior to commencing intermittent dosing. Of the patients receiving ADT whilst awaiting EBRT, the average duration of time on ADT was 12.3± 10.6 months (median 7.6 months). We excluded a 80 year old male reportedly awaiting EBRT from the statistic as he reported having been on continuous ADT for 66 months, however, was unlikely a candidate due to his age.

Of the 33 patients on maximal androgen blockade, 23 (69.7%) have castrate resistant disease. The average age of this specific patient population is 69.4 ±8.0 years with an average duration of continuous ADT of 54.9 ± 35.4 months.

A total of 69 patients were reported to be on cyproterone acetate at the time of the study. 10 (6.6%) of the patients receiving cyproterone acetate were on the agent to prevent the flair phenomenon, whilst 26 (17.2%) of the patients were using the agent for symptom control, specifically treatment of hot flushes. Of the 26 patients reported to be on the agent for symptom control only 11 of those patients reported their hot flushes to affect them "very much" and "all the time" according to the EORTC QLQ-30 survey. Furthermore, an additional 7 patients not reported to be on cyproterone acetate for symptom control specifically, rated their hot flushes as affecting them "very much" or "all the time". Moreover, 50 (33.6%) of the total patient population rated the presence of hot flushes to occur "very much" and "all the time".

Out of 120 patients on continuous ADT attending the clinic, 20 patients missed a dose of ADT, an average number of 2.2 doses being missed. The number of patients on continuous ADT who delayed a dose was 42, with an average number of 1.8 doses being delayed by more than two weeks. Only 12 (7.9%) of the study population reported having had an injection site complication during their treatment with ADT.

Table 4.2 Prostate cancer and ADT specific data

Prostate cancer specific data	**Mean (SD); Median**
PSA	
Diagnosis	258.2 (684.1); 39
Initiation of ADT	270.1 (678.2); 56.8
Current	55.5 (392.5); 1.95
Gleason score	7.7 (1.1); 7.0
	Number (percentage) n (%)
Extraprostatic spread	
Lymphovascular involvement	72 (49.7)
Perineural involvement	2 (1.4)
Clinical T stage at diagnosis	
T1	45 (32.6)
T2	30 (21.8)
T3	50 (36.2)
T4	13 (9.4)
D'Amico classification	
Low	3 (2.0)
Intermediate	14 (9.5)
High	130 (88.4)
Missing data	6 (3.9)
Castrate resistant disease	26 (17.1)
Indication for ADT	
Metastatic PCa	86 (56.9)
Awaiting ERBT	33 (21.9)
Other	16 (10.6)
ADT regime	
Continuous (medical)	120 (78.9)
Intermittent	21 (13.8)
Orchiectomy	11 (7.2)
ADT agent	
LHRH agonist	125 (82.2)
Cyproterone acetate	72 (47.4)
Bicalutamide	2 (1.3)
Ketaconazole	0 (0.0)
Steroids	0 (0.0)
Maximal androgen blockade	33 (21.7)

4.3.3 QOL Outcomes

The QOL outcomes were assessed using the EORTC QLQ-30 survey and PR-25 supplement. The mean and medians for the five different functional scales assessed are shown in Figure 4.1. Poor function was assessed to be a mean and, or median that fell between 0 to 50 percent, once the raw scores had been standardised. As can be seen from the table below, the mean QOL for the five functional scales was greater than 70 percent, with a median of more than 80 percent, thus indicating overall good function. The medians for the functional scales were consistently higher than the means suggesting that there are only a small number of patients in the total population with low QOL statistics.

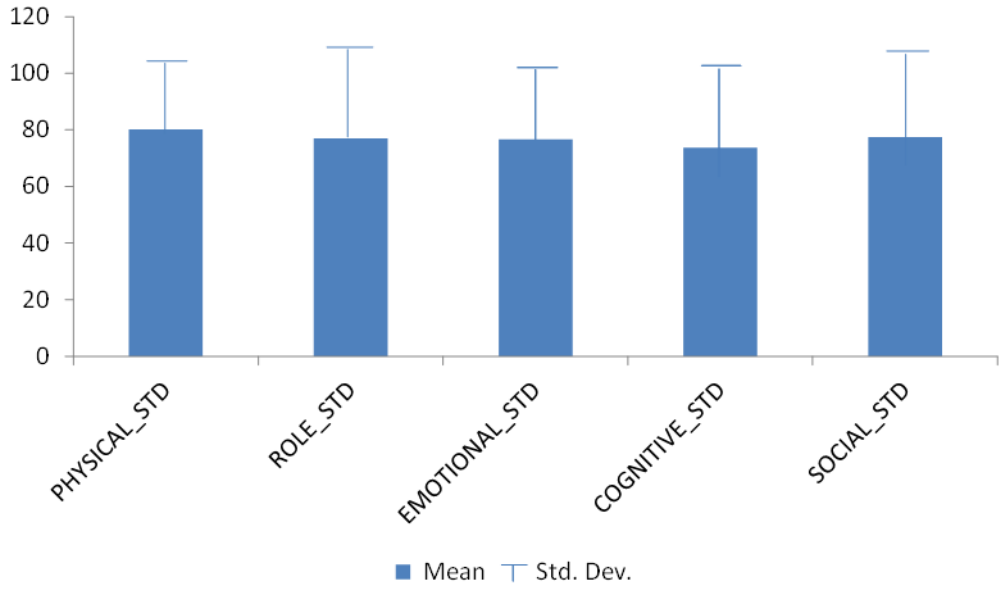

Figure 4.1 Functional scales assessed according to the EORTC QLQ-30

Note: Standardised functional scales fall between 0 and 100 with the higher outcome representing a higher the level of functioning.

The symptom scales assess presence and impact of symptoms on QOL. Thus, a score above 50 percent was considered to be significant ($p<0.05$) with regard to the presence of a symptom. For further analysis of generalised symptoms known to be associated with the presence of non-benign disease see Figure 4.2. Of the symptoms assessed pain had the highest score with a mean of 31.0 ± 29.6 (median 33.3).

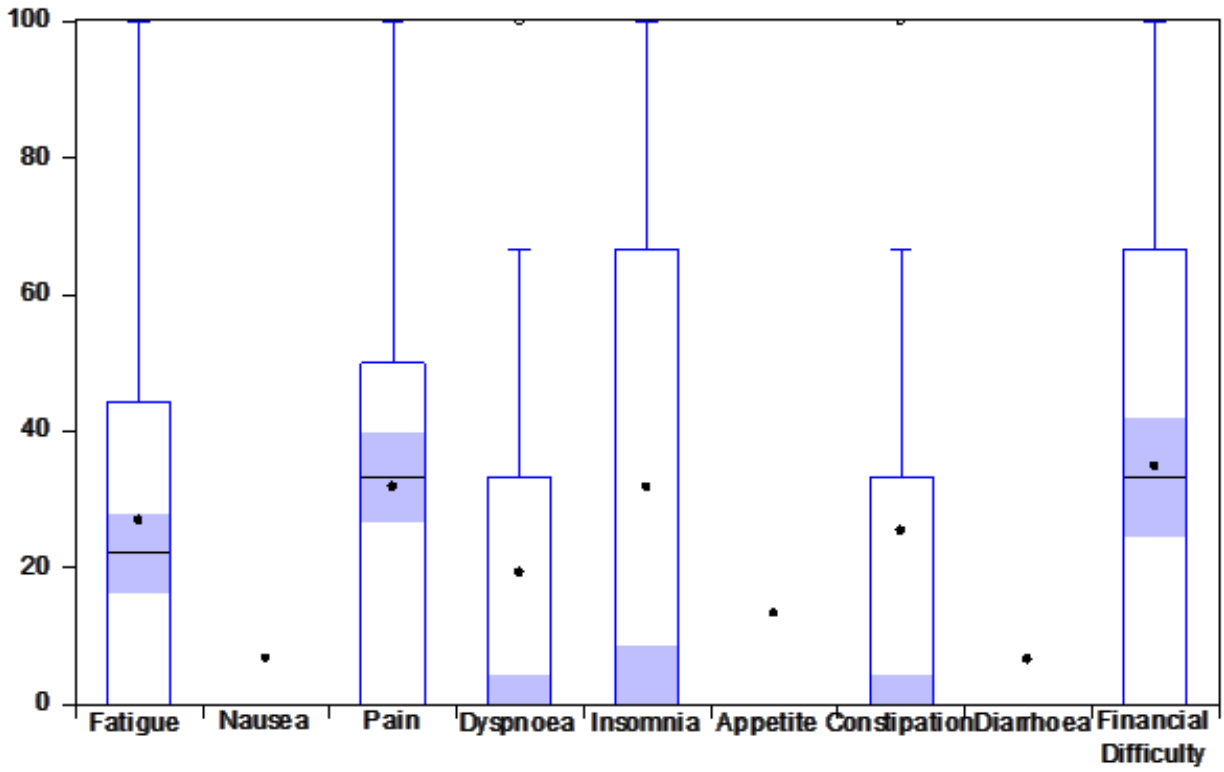

Figure 4.2 Symptom scale from EORTC QLQ- 30

Note: Standardised symptom scales fall between 0 and 100 with the higher outcome representing a higher level of functioning.

The PCa specific symptoms assessed included urinary, bowel and treatment related symptoms. In terms of urinary symptoms, there was a fairly consistent descending trend in severity of daytime urinary frequency reported. In contrast, there was a fairly evident increase in the number of patients reporting night frequency to be present "very much" and "all the time". Although the need to hurry to the toilet was present, it was not as prevalent as that suggested by either daytime or night frequency (Figure 4.3).

There appeared to be little difference between either the regimen of ADT or the duration on continuous ADT or intermittent ADT with regard to the presence of urinary symptoms (Figure 4.4).

Hormonal side effects as a result of ADT include hot flushes and mastodynia. Self-reporting of mastodynia was relatively low, whilst the presence of significant hot flushes was more commonly reported, it affected less than half of the total study population (See Figure 4.5).

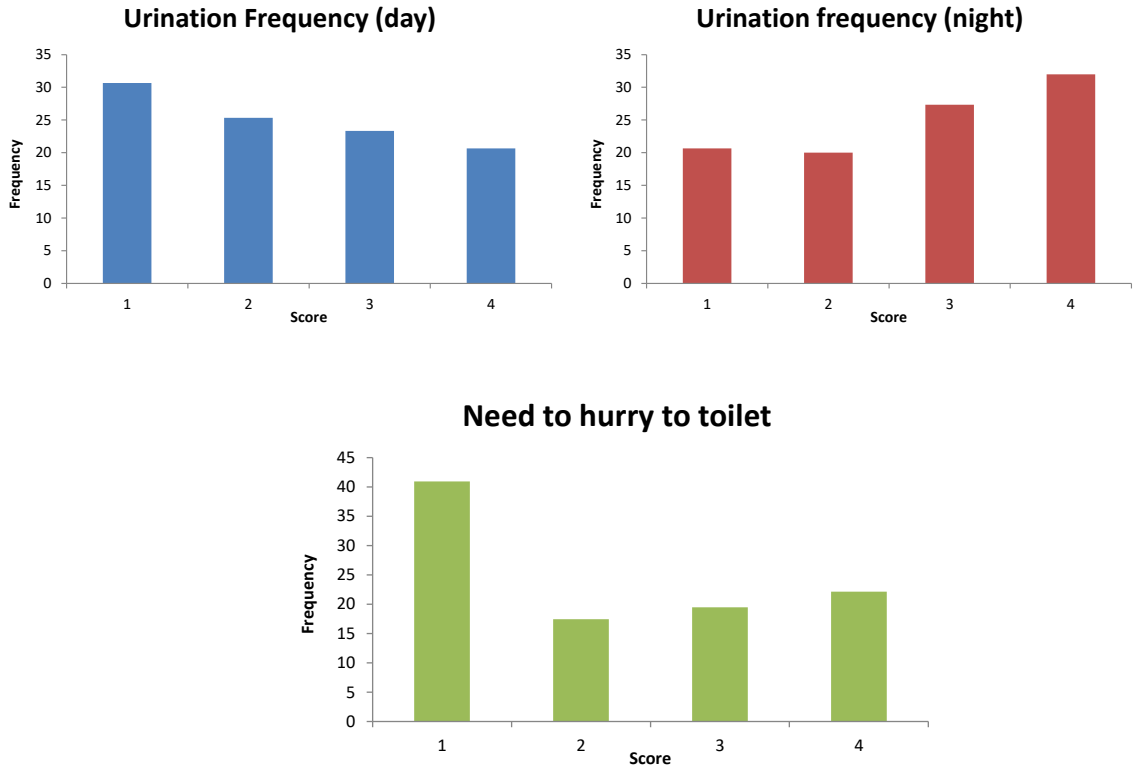

Figure 4.3 Urinary symptoms raw data by question

Note: These graphs show the frequency of answers to the following questions: During the past week, have you had to urinate frequently during the day? During the past week, have you had to urinate frequently at night? During the past week, when you felt the urge to pass urine, did you have to hurry to get to the toilet? With 1 representing "Not at all", 2 "A little", 3 "Quite a bit" and 4 "Very much".

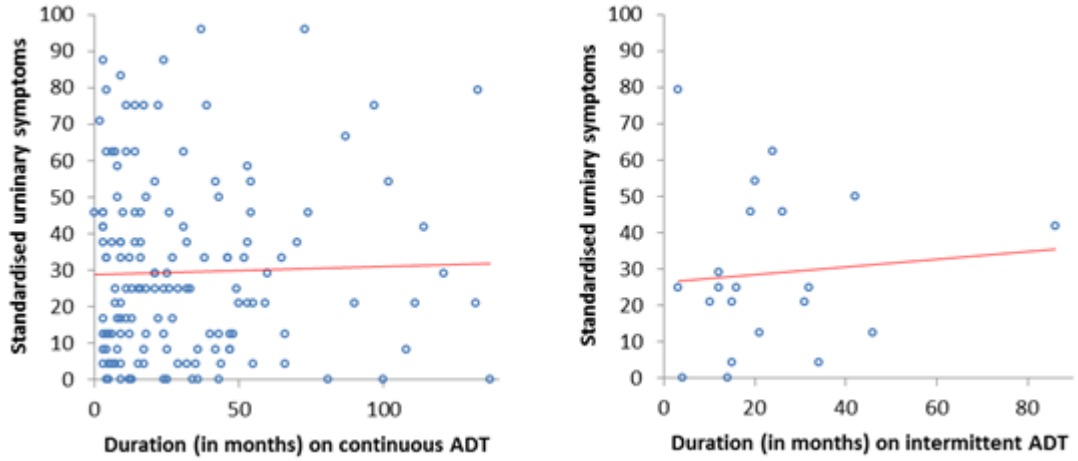

Figure 4.4 Comparison between the duration of continuous and intermittent ADT and the impact on urinary symptoms

Note: Standardised urinary symptoms is a summary measure which summarises the overall urinary symptoms of the patient. It is measured on a scale of 0 to 100 with the higher the number, the worse the urinary symptoms.

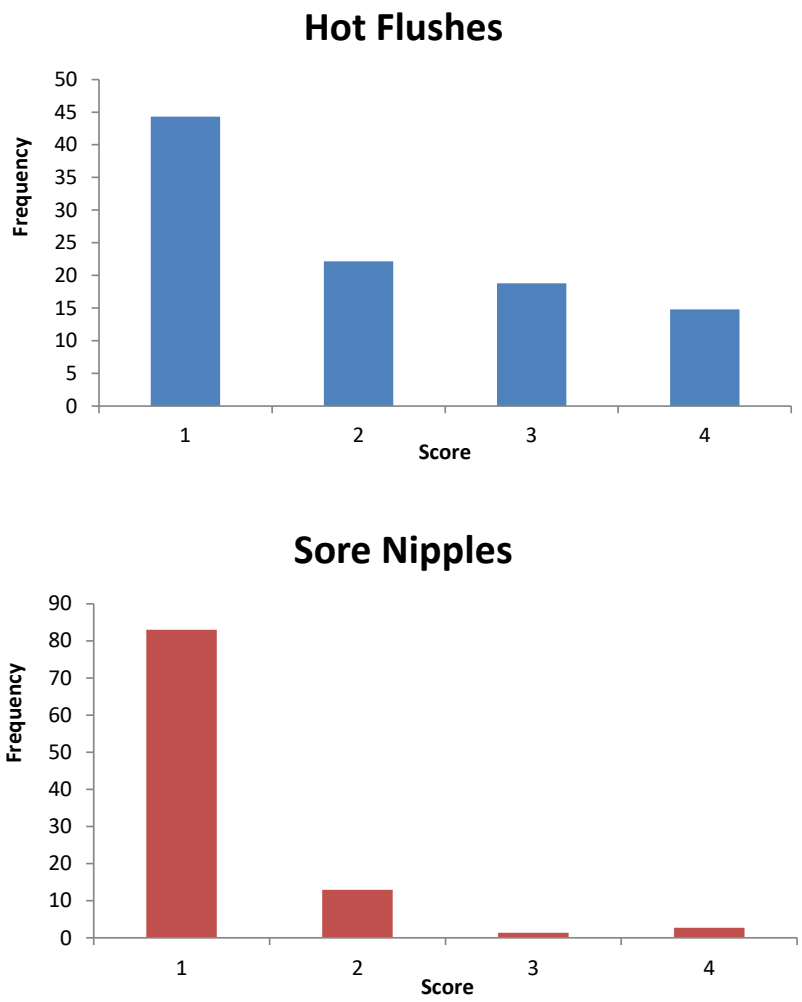

Figure 4.5 Frequency of reported hot flushes and mastodynia

Note: These graphs show the frequency of answers to the following questions: During the past week, did you have hot flushes? During the past week, have you had sore or enlarged nipples or breasts? With 1 representing "Not at all", 2 "A little", 3 "Quite a bit" and 4 "Very much".

Finally, sexual activity and function were assessed in patients currently receiving ADT. A total of 149 patients completed the question regarding an interest in sex. Of this number, 62 (41.6%) of patients reported that they had no interest in sex at all, whilst 33 (22.1%) reported having only a little interest in sexual activity. Furthermore, of those who completed this section, 54 (36.2%) patients reported their interest in sex as either quite a bit or very interested.

In terms of sexual activity, only 99 (66.0%) of the study population reported they were still sexually active. 47.6% of men on ADT for metastatic disease still reported some sexual activity, whilst only 38.1% of men awaiting EBRT were still sexually active. Of the patients awaiting EBRT 51.5% reported no sexual activity in the preceding three months and only 23.3% still reported an interest in sex.

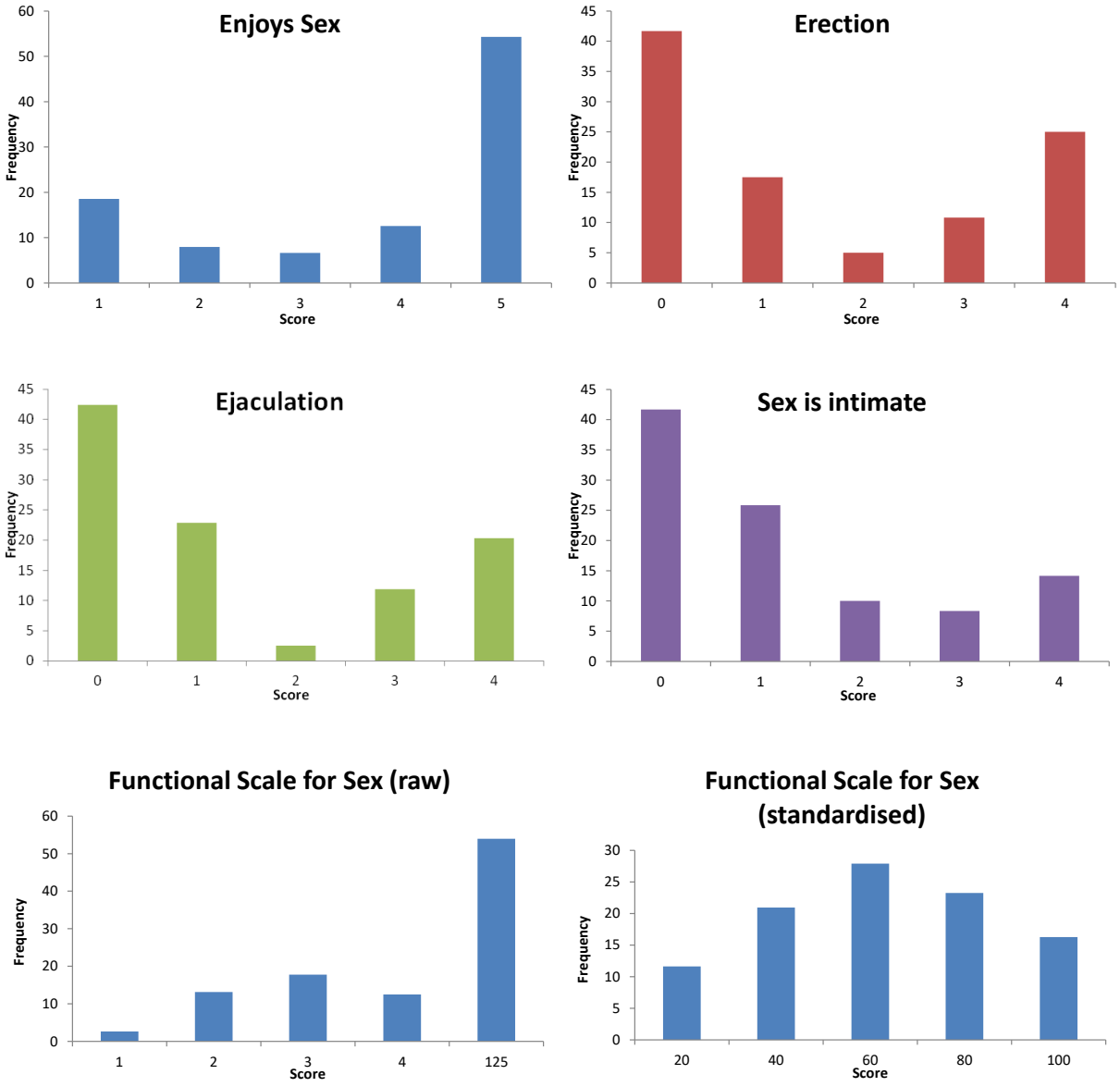

Figure 4.6 Raw data of sexual interest, activity and function

Note: These graphs show the frequency of answers to the following questions: During the last 4 weeks, to what extent was sex enjoyable for you? During the last 4 weeks, did you have difficulty getting or maintaining an erection? During the last 4 weeks, did you have ejaculation problems (eg. Dry ejaculation)? During the last 4 weeks, have you felt uncomfortable about being sexually intimate? With 1 representing "Not at all", 2 "A little", 3 "Quite a bit" and 4 "Very much". The final two graphs represent a summary of overall sexual functioning. The first shows the raw scores as calculated, with "125" representing incomplete answers for those questions included in the summary. The second shows the standardized functional scale excluding those with incomplete answers.

Global QOL was found to be low in 54 (33.8%) of the total study population. There was a significant difference in overall QOL between patients on intermittent ADT and those on

continuous ADT with a p= 0.0107 mean 76.9 ± 25.7 vs mean 60.4 ± 27.9. Of the patients with low global QOL, 61 percent were on ADT for metastatic PCa and 20.8 percent were awaiting EBRT. Only 20.4 percent of patients with low QOL had concomitant castrate resistant disease. Patients who had undergone orchiectomy, reported a better QOL with 11% scoring less than 50% for overall QOL. In terms of treatment compliance, overall QOL did not appear to be a significant determinant for defaulting treatment with only 7 (29.2%) of the 24 defaulters reporting a reduced QOL. Of the patients who delayed a single dose of treatment by two or more weeks, only 16 (31.4%) reported having an overall poor QOL (see Figure 4.7).

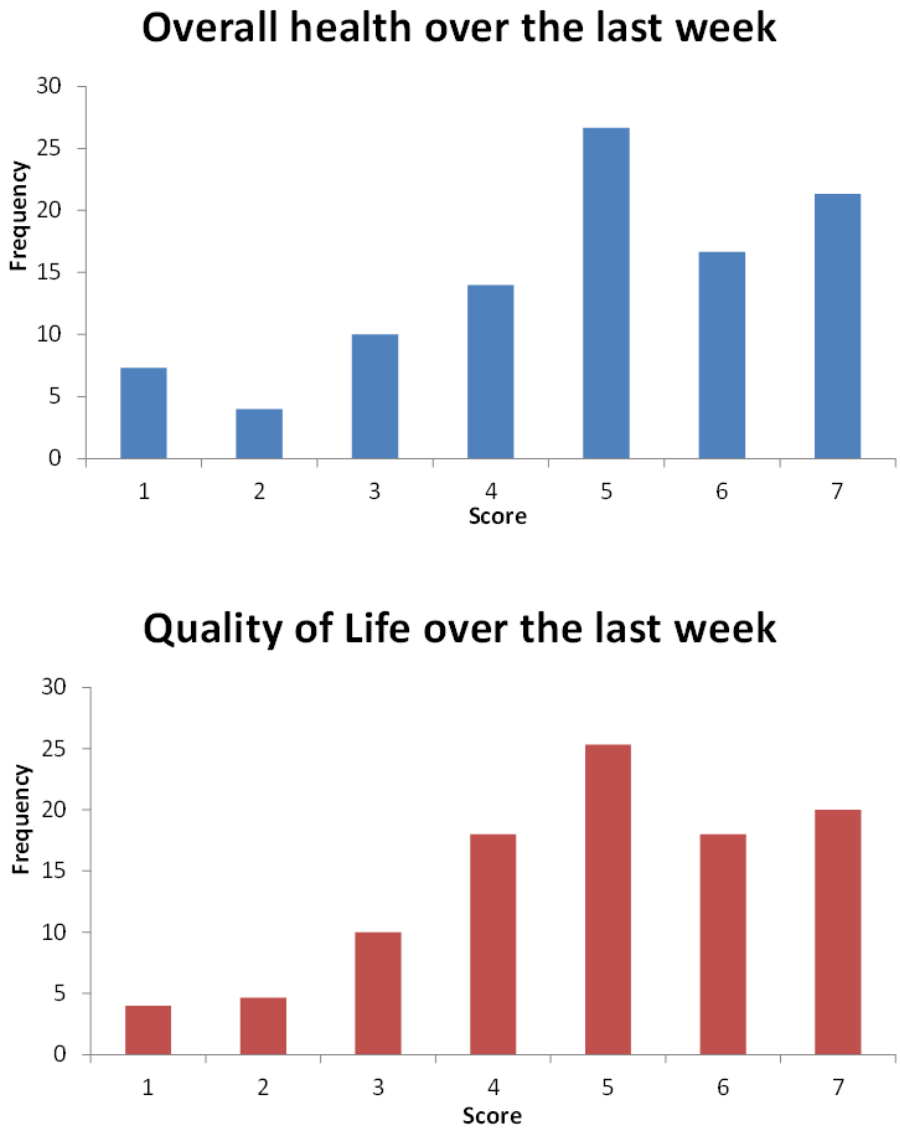

Figure 4.7 Overall health and QOL in the preceding week

Note: These graphs show the Scale from 1-7 with 1 Very poor and 7 Excellent.

4.4 Discussion

The indications for ADT are continuing to expand. As a result, there is a growing population of patients receiving and experiencing side effects from the use of ADT. It has previously been found that approximately half of the patients with PCa will receive ADT at some point in their treatment (157). Similar findings have been demonstrated for the South African population by Heyns et al (50). Due to the impact of ADT on QOL, one can no longer look at survival benefit alone, when initiating ADT (33). Furthermore, it has been shown that there is poor patient understanding with regard to the associated adverse effects of ADT (157).

The PSA at diagnosis in our study is in keeping with the findings from an analysis of men attending the Urologic Oncology clinic at Tygerburg Hospital in the Western Cape, South Africa (50). Although the mean PSA at diagnosis was slightly higher than in our population (258.2 vs 526.3) the median PSA's were similar (39.0 vs 33.5). This is in contrast to Le Roux et al (51), where the mean PSA was 652 with a median of 154 in patients presenting to Edendale Hospital, KwaZulu-Natal, South Africa with PCa. The discrepancy found may be as a result of poor access to health care with delayed presentation and screening for disease particularly in a rural setting. Furthermore, it is important to note, that the patient populations in KwaZulu-Natal and the Western Cape included men presenting with all stages of prostate cancer, whereas over half our study population (56.9%) were receiving ADT for metastatic, high risk disease.

It is well recognised that orchiectomy is the most cost-effective form of ADT available. However, this form of ADT is not readily acceptable to the majority of patients due to the psychological and social impact it is perceived to have. Furthermore, it has been suggested that patients are more likely to prefer medical management as the fear of mutilation, loss of masculinity are compounded by the irreversibility of surgery (101). As a result, one of the well documented benefits of intermittent ADT is the potential to not only reduce the cost of treating the associated sides effects, but by reducing the number of doses, there is inherent cost saving.

In terms of the metabolic complications associated with ADT prevalence of metabolic syndrome was 30.3%. As previously mentioned the two most common components were hypertension and a waist circumference of >102 cm. It is difficult to determine whether these two components existed prior to initiation of ADT. However, as these patients are considered high risk for developing metabolic syndrome, it stands to reason that initiation of treatment may exacerbate

them further. There remains some debate as to whether or not abdominal fat accumulation is subcutaneous and visceral or subcutaneous alone. Therefore, in a patient with pre-existing risk for cardiovascular morbidity it is important to reduce burden of disease with appropriate monitoring, dietary and exercise advice when commencing treatment with ADT. The benefits of exercise on cancer specific QOL are well known and will contribute to improving morbidity (85).

The finding of NO hypercholesterolaemia in 71 (46.6%) of our population was predominantly due to an increase in both total and LDL cholesterol which is in keeping with the findings of Braga-Basaria et al (128) and Smith et al (76). Of concern is the relatively low percentage (69%) of newly diagnosed patients who were started on appropriate medical therapy, although it was difficult to assess whether appropriate lifestyle counselling had taken place. There is still weak, inconsistent evidence as to the protective role of statins in the development of PCa, but their use in the treatment of hypercholesterolaemia is well established. In addition, the pleiotropic effects may be potentially beneficial in a population considered high risk for cardiovascular disease. It is however, important to note that a few experimental studies on the effect of statins with regard to PCa have suggested a potential for enhanced carcinogenesis (159). In the absence of large phase III trials, it would be prudent to prescribe these agents in patients with NO hypercholesterolaemia.

In contrast to the NO hypercholesterolaemia, the NO of DM and coronary artery disease was very low. Furthermore, contrary to existing studies, our population with pre-existing DM appeared to have good glycaemic control, with a mean HbA1C of 7.8 ± 1.8, despite the use of ADT (98). It would be interesting to do further studies into the antihyperglycaemic agents our diabetic patients are currently on, as metformin has been shown to not only protect against the development of additional metabolic complications, but may also be protective against the development of PCa and disease progression (99,160).

Despite the relative resource constrained environment in South Africa, only 11 (7.2%) of our patient population had undergone orchiectomy and only an additional 21 (13.8%) were on intermittent ADT. Our study indicated that 7 patients previously on intermittent ADT had been restarted on a continuous regime due to rising PSA. It is interesting to note that of the 11 patients who had undergone orchiectomy, only one patient reported significant feelings of reduced masculinity as a result of the treatment. Furthermore, there appeared to be a higher percentage of patients on continuous ADT who complained about reduced feelings of masculinity. This finding

should be interpreted with caution due to the small number of patients having undergone orchiectomy. Moreover, the use of intermittent ADT in patients with metastatic prostate cancer must be considered on a patient-by-patient basis as high volume disease may be a contraindication to its use (161).

The use of adjuvant and neoadjuvant ADT in patients who qualify for EBRT is well-documented. Its use in combination therapy with EBRT in intermediate and high risk PCa has been definitively proven (8). The current recommendations are to start ADT when EBRT is initiated or for two to three months prior to its use. In our population 33 (29.2%) are currently on ADT whilst awaiting EBRT. The average duration of ADT treatment in this group was 12.3 ± 10.6 months. Furthermore, 25 (75.8%) of the patients were classified with high risk disease and an additional 7 (21.2%) with intermediate risk disease.

Currently the literature regarding the use of prolonged neoadjuvant ADT prior to EBRT has failed to show any survival benefit (162). However, there remains concern with the use of prolonged ADT in this group as 51.5% reported no sexual activity in the preceding three months and they comprised 20.8% of the group who rated their overall QOL as low. This is particularly pertinent as ADT may be discontinued post EBRT provided there is response to treatment. Furthermore, there is evidence from studies on intermittent ADT, to suggest that long-term ADT use may impair testosterone recovery even with treatment cessation (163). This subgroup of patients are becoming more relevant to the urologist as with increased screening so the population who qualify for EBRT will expand. Thus, it is important to diversify with regards to the treatment options available to patients particularly as radical prostatectomy may not be acceptable to all patients.

Although it is known that prostate volume is not the only determinant of voiding symptoms, Choi et al (164). demonstrated an improvement in these symptoms in patients on ADT. They attributed these changes to a significant decrease in prostate volume. The reduced volume was associated with an improvement in the International Prostate Symptom Score and maximal uroflow. In contrast, our population reported a high concern with regard to urinary symptoms, both daytime frequency and specifically nighttime frequency. It is important to note that these symptoms were assessed from a subjective point of view and thus studies looking at prostate volume and uroflow before and after ADT initiation would be a more objective assessment of the problem.

In addition to concerns about urinary symptoms, there was profound concern regarding sexual interest, function and activity. These findings are in keeping with similar studies performed in various population groups (33,165). An increase in sexual dysfunction should be adequately explained to both the patient and their partner as this has been known to increase emotional distress and may affect important interpersonal relationships. In addition, if not fully understood, these issues may contribute to poor compliance (157).

Hormonal side effects were not a significant complaint of our patient cohort. However, of the 50 patients complaining of severe hot flushes only 18 were receiving cyproterone acetate for symptom control specifically. This is in keeping with the finding of Sonn et al. (31) who showed a discrepancy between doctor and patient perceptions regarding QOL. This is particularly relevant as of the 26 patients receiving cyproterone acetate for symptom control 57.7% had comparatively less symptoms.

Given the significant adverse effects of ADT, compliance could potentially be an issue. However, we found that only 35% of the study population on continuous ADT delayed a dose by two weeks or more. Although this was not part of the formal data sheet, on discussion with patients, the delay seemed to be the result of scheduling or transport issues.

Our study showed a significant improvement in overall QOL in patients on intermittent ADT compared to those on continuous ADT ($p=0.0107$). Although this finding should be interpreted with caution due to the small intermittent ADT sample size 21 (13.8%), it should be further explored, as previous studies have failed to show a definitive benefit of intermittent ADT. The benefit of improved testosterone levels and potential recovery of sexual interest, function and activity as well as an improvement in urinary symptoms, may be particularly beneficial responses in those who qualify for intermittent ADT (104,166,167). Despite symptom and QOL improvement, it is necessary to counsel patients as to the potential of a reduced cancer progression survival.

CHAPTER 5: SUMMARY, LIMITATIONS, RECOMMENDATIONS AND CONCLUSION

5.1 Introduction

In this chapter a summary of the study is presented. It will further address the limitations and recommendations from the study. The overall study conclusion will be presented.

5.2 Study Summary

5.2.1 Aim

The aim of this study was to determine the impact of ADT on the QOL and common side effects experienced by a subset of South African patients with prostate cancer attending the urology oncology clinic using the EORTC QLQ-30, EORTC PR-25 and physician questionnaire.

5.2.2 Objectives

The primary objectives of this study were:

- to describe the population of patients currently receiving ADT, the most commonly prescribed methods of ADT and common side effects of ADT treatment in our patient population
- to describe the perceived impact of ADT on the physical, psychological and sexual health of patients receiving treatment

The secondary objectives of this study were:

- to compare the stage of prostate cancer at presentation, the preferred modality of ADT and ADT side effect profile for different race groups
- to compare the impact on the QOL between single agent medical management, complete medical androgen blockade and surgical orchiectomy
- to compare the QOL of patients on ADT with hormone-sensitive prostate cancer to those with castrate resistant prostate cancer

5.2 Summary of the Methodology

A prospective, contextual, descriptive study was performed to determine the QOL of life in men with PCa receiving ADT. The QOL was assessed using the EORTC QLQ-30 and EORTC QLQ-PR 25, internationally validated questionnaires to assess patient outcomes in those suffering from malignancy with additional disease specific focus.

All men with PCa on ADT attending the Urology Oncology clinic at CMJAH were invited to participate in the study during the study period. Patients received an information letter, consent form and questionnaire in an unmarked envelope. Those who consented to participate in the study completed the questionnaire, then had a data sheet completed by the attending physician. Both the questionnaire and data sheet were placed in a sealed envelope and sealed box. Questionnaires/ data sheets and consent had corresponding numbers but were stored separately. Participation in the study was voluntary, thus, patients could withdraw from the study at any time should they choose to.

Descriptive and inferential statistics were used to analyse the data.

5.3 Summary of the Main Findings

The mean age at completion of the questionnaire was 69.9 ± 8.2 years. The African group made up the largest proportion of patients attending the clinic 115 (76.2%). New onset hypercholesterolaemia occurred in 71 (46.7%) of the population after ADT initiation and was most strongly associated with ADT for metastatic prostate cancer 42 (60.9%) and those on continuous ADT 60 (87.0%).

The average BMI was 27.1 ±4.8 and mean waist circumference was 101.0cm ±12.8cm, with 46 (30.3%) of patient population meeting the criteria for metabolic syndrome. Anaemia occurred in 32.4% of the population and only one patient fulfilled the criteria for severe anaemia (Hb = 7.9).

Mean PSA at diagnosis and initiation were relatively high, however, there was no significant difference in the mean PSA from the time of diagnosis to the initiation of ADT p= 0.882.

The majority of patients were on ADT for metastatic PCa 86 (56.9%) whilst 33 (21.9%) were awaiting EBRT. Continuous ADT was most commonly used with a mean duration of of 41.5 ±

31.2 months (median 31.0 months). Only 11 (7.2%) of patients had undergone a bilateral orchiectomy.

In terms of QOL, patients had overall good QOL for the five functional scales. Prostate specific symptoms including daytime urinary frequency and night frequency had high symptom scores. Men on continuous ADT formed the majority of men who still reported an interest in sex with 27 (87.1%) of the total having a high score. In terms of sexual activity, only 99 (66.0%) of the study population reported they were still sexually active.

Finally, global QOL was found to be low in only 54 (33.8%) of the total study population. There appeared to be a significant difference in overall QOL between patients on intermittent ADT and those on continuous ADT with a p= 0.0107 (mean 76.9 ± 25.7 vs mean 60.4 ± 27.9).

5.4 Limitations

The patient population was derived from the public sector only and as such access to some of the agents commonly used in ADT was limited and may have biased the side effect profiles seen. Currently one of the major drug groups, LHRH antagonists, used in ADT is not available in the public sector. Although not definitively proven, early trials suggest a better cardiovascular side effect profile particularly in patients with pre-existing cardiovascular disease in whom ADT is being initiated. Furthermore, the impact of socioeconomic status on the perceived effect of ADT on QOL may not have been appreciated.

The cohort of patients that the study examined were diagnosed and treated by a variety of urologist and as a result there may have be inconsistencies in the allocation of the clinical T-stage used for risk stratification. The cohort only consisted of patients attending the CMJAH Urology Oncology clinic as a result, patients having previously been on ADT with intolerable side effects may no longer attend the clinic and thus, were not eligible for inclusion in the study.

The use of a self-administered questionnaire has a number of limitations including failure to fully complete the questionnaire, an inability to obtain additional information or clarification from the provider as well as respondents and finally, the desire to provide an answer which is socially acceptable rather than answering according to actual experience.

5.5 Recommendations

Racial differences with regard to side effects and QOL issues could not be elucidated due to the patient population used. Thus, it is recommended that a larger, multi-institutional study be undertaken to further elucidate this.

This study suggested an improved QOL in the patients on intermittent ADT, this finding has not been confirmed in other larger trials, thus a larger South African trial is warranted.

Finally, a study examining bone health in this population is recommended as this study was limited in its ability to review this side effect.

5.6 Conclusion

This study highlighted the common side effects and QOL issues of a subset of South African patients on ADT for a variety of reasons. A number of pertinent issues have arisen particularly with regard to the development of hypercholesterolemia in this population and the need for screening and appropriate management. Furthermore, the low treatment rate of prominent side effects such as hot-flushes has emphasized the need for a patient centered approach to management. Due to the concern that patients awaiting EBRT are being exposed to prolonged periods of ADT, alternative treatment strategies such as low dose brachytherapy can be considered to alleviate the burden. The use of Intermittent ADT or surgical orchiectomy are viable options to reduce both the cost of treatment and potentially the side effects associated with ADT and warrant larger studies with a control arm.

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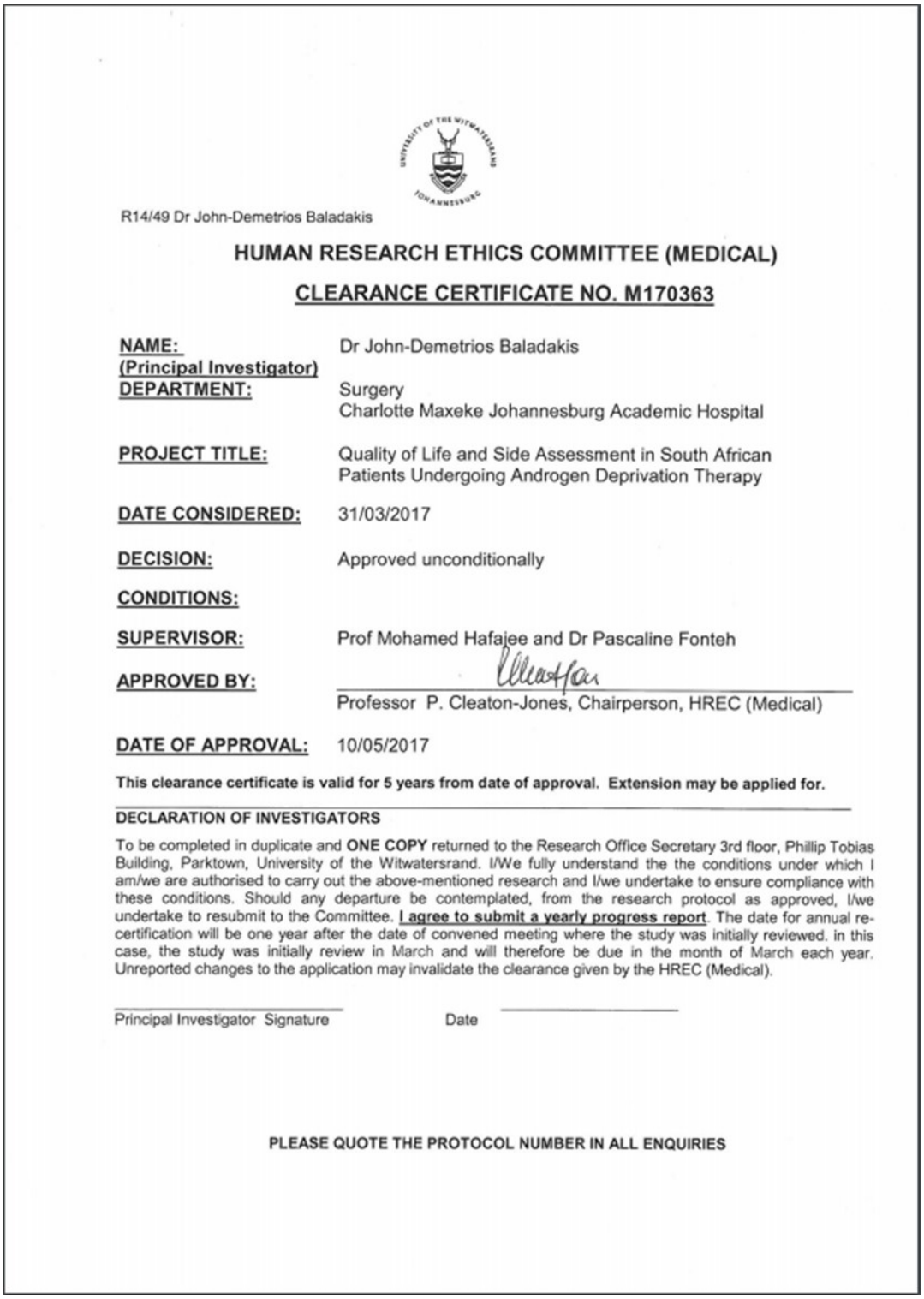
CHAPTER 7: APPENDICES

7.1 Appendix A: Ethics Approval



R14/49 Dr John-Demetrios Baladakis

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170363

NAME: (Principal Investigator)	Dr John-Demetrios Baladakis
DEPARTMENT:	Surgery Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Quality of Life and Side Assessment in South African Patients Undergoing Androgen Deprivation Therapy
DATE CONSIDERED:	31/03/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Mohamed Hafajee and Dr Pascaline Fonteh
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	10/05/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in March and will therefore be due in the month of March each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

7.2 Appendix B: Participant Information letter

Date: 2017

Re: Quality of life and side effect assessment in South African patients undergoing androgen deprivation therapy

Hello, I am Dr John Baladakis, a urology registrar at the University of the Witwatersrand. I would like to invite you to take part in a research study.

In this study, I will be looking at how the use of androgen deprivation therapy (ADT) for men with prostate cancer impacts on your quality of life. Approval to conduct this study has been obtained from Postgraduate Committee and the Human Research Ethics Committee (number) of the University of the Witwatersrand. The aim of this study is to understand the impact of ADT on our patient's quality of life to better address the side effects as well as the approach to ADT in our patients.

I would like to invite you to partake in this study by completing the questionnaire that follows. The questionnaire includes 55 questions that look at how both your cancer and specific treatment impact on various aspects of your quality of life. It is available in English, Zulu, Afrikaans, Sotho and Xhosa. Following completion of this questionnaire, the doctor that sees you today will complete another form with information and laboratory results about your disease treatment. Completion of the questionnaire will take approximately 20 minutes and can be done whilst waiting to be seen by your urologist. Participation in the study is voluntary and will have no impact on consultation or your care.

No identifying information will be requested on the questionnaire. All completed questionnaires will remain confidential and anonymity is ensured. Please place the completed questionnaire in the unmarked envelope provided. This envelope will be handed to your urologist and it together with the form completed by the doctor will be sealed and placed in a sealed data collection box. The results of the study will be made available to you if requested.

If you have any queries you can contact me on 082 954 7115 or send an email on JDBaladakis@gmail.com. Further queries may be directed to the WITS Human Research Ethics Committee (Medical).

- Chairperson: Prof Cleaton-Jones: peter.cleaton-jones1@wits.ac.za

- Administrators: Ms Zanele Ndlovu/ Mr Rhulani Mkansi/ Mr Lebo Moeng
Tel 011 717 2700/2656/1234/1252

Email: HREC-Medical.ResearchOffice@wits.ac.za

Thank you for your time.

Regards

Dr JD Baladakis

7.3 Appendix C: Informed Consent

Consent Form: Use of Clinical Information for Research

Dear Patient,

Hello, I am Dr John Baladakis one of the Urology Registrars at The University of the Witwatersrand, I am currently conducting research aimed at understanding the quality of life of patient with prostate cancer undergoing androgen deprivation therapy. This research makes use an anonymous questionnaire and a physician completed data sheet. Your previous blood results and histology will also be collected. No additional testing is necessary for this study. The use of such information is subject to the following:

1. Approval from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand.
2. Identity of a patient from whose file information is extracted is never revealed to anyone but the researcher unless specific consent is obtained to do so. The information gathered does not contain the name of the patient but only a coded number to maintain anonymity.

We are requesting your consent to use the above information for research. However, should you choose not to participate in this study it will not compromise your treatment in any way. If at any time you choose to no longer be involved in the study you are free to do so and it will not affect your care in any way.

Should you wish to contact us at any stage regarding consent, contact Dr JD Baladakis at (082) 9547115.

A. Consent Given

I_____ hereby give consent for my records to be used as per the above-mentioned conditions for the purpose of research:

PATIENT: _____ DATE: _____

B. Consent Not Given

I _____ do not give consent for my records to be used:

PATIENT: _____DATE: _____

7.4 Appendix D: CMJAH CEO Approval

GAUTENG PROVINCE
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Mr. J. Maepa
Office of the Clinical Director
Tell: (011) 488-3365
Email:johannes.maepa@gauteng.gov.za
28 February 2017

Dear Dr JD Baladakis

STUDY TITLE: Quality of life and side effect assessment in South African patients undergoing androgen deprivation therapy.

Permission to conduct the above mentioned study is provisionally approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your ethics clearance as soon as the study is approved by the Ethics committee for the CEO's to give you the final approval to conduct the study.

Supported/~~not supported~~

Dr M.I. Mofokeng
Clinical Director
DATE: 1/3/2017

Approved/not approved

Ms G. Bogoshi
Chief Executive Officer
Date: 06-03-2017

7.5 Appendix E: EORTC QLQ-30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|
Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|
Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

7.6 Appendix F: EORTC QLQ-PR25

ENGLISH

EORTC QLQ - PR25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week	Not at all	A little	Quite a bit	Very much
31. Have you had to urinate frequently **during the day**?	1	2	3	4
32. Have you had to urinate frequently **at night**?	1	2	3	4
33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35. Have you had difficulty going out of the house because you needed to be close to a toilet?	1	2	3	4
36. Have you had any unintentional release (leakage) of urine?	1	2	3	4
37. Did you have pain when you urinated?	1	2	3	4
38. Answer this question only if you wear an incontinence aid. Has wearing an incontinence aid been a problem for you?	1	2	3	4
39. Have your daily activities been limited by your urinary problems?	1	2	3	4
40. Have your daily activities been limited by your bowel problems?	1	2	3	4
41. Have you had any unintentional release (leakage) of stools?	1	2	3	4
42. Have you had blood in your stools?	1	2	3	4
43. Did you have a bloated feeling in your abdomen?	1	2	3	4
44. Did you have hot flushes?	1	2	3	4
45. Have you had sore or enlarged nipples or breasts?	1	2	3	4
46. Have you had swelling in your legs or ankles?	1	2	3	4

Please go to the next page

During the last 4 weeks…	Not at all	A little	Quite a bit	Very much
47. Has weight **loss** been a problem for you?	1	2	3	4
48. Has weight **gain** been a problem for you?	1	2	3	4
49. Have you felt less masculine as a result of your illness or treatment?	1	2	3	4
50. To what extent were you interested in sex?	1	2	3	4
51. To what extent were you sexually active (with or without intercourse)?	1	2	3	4

PLEASE ANSWER THE NEXT FOUR QUESTIONS ONLY IF YOU HAVE BEEN SEXUALLY ACTIVE OVER THE LAST 4 WEEKS

52. To what extent was sex enjoyable for you?	1	2	3	4
53. Did you have difficulty getting or maintaining an erection?	1	2	3	4
54. Did you have ejaculation problems (eg dry ejaculation)?	1	2	3	4
55. Have you felt uncomfortable about being sexually intimate?	1	2	3	4

7.7 Appendix G: Data Sheet

Quality of life and side effect assessment in South African patients undergoing androgen deprivation therapy

To be completed by Urologist:

Patient demographics:

Age:										
Race	Caucasian		African		Indian		Coloured		Other	

Patient data and laboratory results

BMI:	Weight	Kg	Height	cm						
	Waist circumference									
Known with:	Hypertension		Yes		No					
	Diabetes		Yes		No					
	Cardiovascular disease		Yes		No					
	Hypercholesterolemia		Yes		No					
New Onset:	Diabetes		Yes		No					
	Cardiovascular disease		Yes		No					
	Hypercholesterolemia		Yes		No					
Lipid Profile	Total		Trig.		HDL		LDL			
Patient currently on statin?			Yes		No					
If yes, was it started after ADT initiation?			Yes		No					
HB										
MCV			MCHC							
HBA1c										

Prostate cancer specific details:

Gleason Score		+			
PSA on diagnosis					
Perineural involvement		Yes		No	
Lymphovascular involvement		Yes		No	
Percentage cores involved					
Clinical T stage on diagnosis					
D'Amico Classification					
Current PSA					
PSA on initiation					
Castrate resistant disease*		Yes		No	

* Ensure that testosterone levels are confirmed as < 50 ng/mL, before diagnosing with biochemical progression (Three consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir & a PSA > 2ng/mL)

Presence of metastasis	Yes		No	
Awaiting EBRT	Yes		No	

ADT after failure of definitive therapy*	Yes		No	

*Including EBRT, radical prostatectomy or brachytherapy.

ADT Treatment:

Surgical orchiectomy			Yes		No	
Regimen of ADT	Intermittent		Continuous			
If intermittent:	Current		Yes		No	
	Previously		Yes		No	
	Duration on I-ADT (months)					
If continuous‡:	Duration on ADT (months)					

‡If the patient was previously on intermittent ADT and stopped, please fill in the months from the first administration of any ADT

Current ADT agents:

Cyproterone acetate				
Bicalutamide				
LHRH agonist		Injection site complications		
Ketoconazole		Steroids		
Is the patient on maximum androgen blockade?	Yes		No	
Is the use of Anti Androgen to reduce risk of flair phenomenon?	Yes		No	
Is Cyproterone Acetate being used for symptom control?	Yes		No	

Compliance:

How many 3 monthly doses of LHRH agonist has the patient missed?	
How many times was the monthly doses of LHRH agonists delayed by 2 weeks or more?	