FACTORS ASSOCIATED WITH TREATMENT OUTCOMES OF PROSTATE CANCER PATIENTS ON ANDROGEN DEPRIVATION THERAPY AT KENYATTA NATIONAL HOSPITAL

SERAH NJOKI GATHU (BPHARM)

U56/10998/2018

A Research dissertation submitted in partial fulfillment of the Requirement for the Award of the Degree of Master of Pharmacy in Clinical Pharmacy in the School of Pharmacy of The University of Nairobi.

November 2020

DECLARATION

Name of the student	Serah Njoki Gathu
Registration number	U56/10998/2018
College	College of Health Sciences
School	School of Pharmacy
Department	Pharmaceutics and Pharmacy Practice
Course work	Master of Pharmacy in Clinical Pharmacy
Title work	**Factors associated with treatment outcomes of Prostate Cancer Patients on Androgen Deprivation Therapy at Kenyatta National Hospital**

U56/10998/2018

I Serah Njoki Gathu

1. I understand what plagiarism is and I am aware of the University's policy in this regard.
2. I declare that this research proposal is my original work and has not been submitted elsewhere for examinations, an award, degree, publication. Where other people's work or my own work has been used, this has been acknowledged and referenced in accordance with the University of Nairobi requirements.
3. I have not sought or used the services of any professional agencies to produce this work
4. I have not allowed and shall not allow anyone to copy my work with the intention of passing it off as his/her own work.
5. I understand that any false claim in respect of this work shall result in disciplinary action in accordance with the university plagiarism policy

Signature  25-11-2020

SUPERVISOR'S APPROVAL

This is to certify that this research dissertation has been submitted for review with our approval as University Supervisors:

1. Dr George Mugendi

   MPharm (Clin Pharm)

   Department of Pharmaceutics and Pharmacy Practice

   School of Pharmacy, University of Nairobi

   Signature…  Date 25-11-2020……

2. Dr Lucy Tirop

   Pharmaceutical Sciences (PhD

   Department Pharmaceutics and Pharmacy Practice,

   School of Pharmacy, University of Nairobi

   Signature…..  Date……25/11/2020

DEDICATION

I wish to dedicate this work to my family and friends.

ACKNOWLEDGEMENTS

To God be all the glory for His grace.

Vote of thanks to my supervisors for their guidance and counsel throughout the research and writing of this dissertation.

To the Kenyatta National Hospital Pharmacy Department for their continuous support.

To the school of Pharmacy, Department of Pharmaceutics and Pharmacy Practice lecturers and staff for their relentless service in training and supervision of my work.

TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS AND ACRONYMNS

ADT	Androgen Deprivation Therapy
AJCC	American Joint Committee on Cancer
BCR	Biochemical recurrence
CAB	Combined Androgen Blockade
CRPC	Castrate Resistant Prostate Cancer
EBRT	External Beam Radiation Therapy
HB	Hemoglobin
KNH	Kenyatta National Hospital
LHRH	Luteinizing Hormone Release Hormone
NCCN	National Comprehensive Cancer Network
OS-	Overall survival
PCA	Prostate Cancer
PFS	Progression Free Survival
RT	Radiotherapy
RP-	Radical prostatectomy
TNM	Tumor, Node, Metastasis
UON	University of Nairobi

OPERATIONAL DEFINITIONS

Advanced Cancer or metastatic Cancer-This is defined as cancer that has spread to the lymph nodes and other parts of the body.

Androgen Deprivation Therapy (ADT) or Hormonal therapy is treatment used in prostate cancer patients that suppresses the production of testosterone.

Castrate Resistant Prostate Cancer (CRPC)-This is defined as prostate-specific antigen (PSA) progression despite primary androgen deprivation therapy (ADT) in the absence of obvious disease obtained through conventional imaging.

Localized cancer-This is the cancer that is confined within the prostate gland. It has not spread outside of the prostate gland or to any other parts of the body.

Locally advanced cancer- This is when the cancer has broken through the capsule of the prostate gland. It may have spread into the tissue around the prostate or spread to the seminal vesicles.

Overall survival- This is the period that patient survives

Prostate specific antigen failure (biochemical recurrence) -This is a rise in the blood level of PSA in prostate cancer patients after treatment with surgery or radiation. Two consecutive PSA values higher than 0.2 ng/mL.

Progression free survival-refers to survival without progression of the disease.

Treatment outcome- For the purpose of this study, treatment outcomes were progression free survival, castrate resistant prostate cancer and overall survival of patients.

ABSTRACT

Background

Androgen deprivation therapy is recommended in the management locally advanced and metastatic prostate cancer. The two available therapeutic options are orchiectomy and medical castration. The use of either orchiectomy or medical castration has proven to improve patient's quality of life and overall survival of the patients. Hormonal deprivation therapy at Kenyatta National Hospital has been used to reduce testosterone levels in conjunction with other therapies. Treatment outcomes include castrate resistant prostate cancer, progression-free survival and overall survival of patients. Several factors e.g. Prostate specific antigen levels, type of androgen deprivation therapy and duration of treatment can influence outcomes.

Objectives

To determine the prevalence of androgen deprivation therapy use among prostate cancer patients, to characterize the clinical profiles of prostate cancer patients on androgen deprivation therapy and to determine the treatment outcomes and the factors associated with androgen deprivation therapy.

Methodology

This was a retrospective cross-sectional study. We sampled 90 prostate cancer patients who met the eligibility criteria. Simple random sampling method of medical records was used for adult patient ≥18 years seen at Kenyatta National Hospital, with prostate cancer between January 2016 and December 2019. A predesigned data collection form was used to abstract data from patient records. Descriptive and inferential data analysis was done in 90 patients. STATA software version 16 was used for analysis.

Results

Ninety patients were enrolled with a mean age of s 70 years (SD +8.3). All the ninety patients were on androgen deprivation therapy. Forty-four patients (48%) had T3b – T4 tumor staging while 34 (38%) had T3a tumor staging whereas 69 patients (76%) had G3-Gleason 7 -10. Forty-eight patients (53%) were treated with a combination of medical androgen deprivation therapy and radiotherapy. Of the 90 patients, 14 (16%) developed hormonal refractory prostate cancer while 76 (84%) were in progression free survival state with a mean survival of 30 months. Duration of treatment, hemoglobin level and post prostate specific antigen after therapy were

significantly associated with castrate resistant prostate cancer and progression free survival at multivariate analysis. Linear regression analysis results demonstrated an association between overall survival and duration of treatment.

Conclusion

All patients were started on androgen deprivation therapy. Fourteen patients developed castrate resistant prostate cancer while seventy-six were at progression free survival state. The factors that were significantly associated to androgen deprivation treatment outcomes were duration of treatment, hemoglobin level and post prostate specific antigen while duration of treatment was associated with overall survival of patients.

CHAPTER ONE: INTRODUCTION

1.1 Background

Prostate cancer (PCA) is the 3rd most common cancer worldwide. It is the most frequently diagnosed cancer among men globally (1). In 2018, there were 1,276,106 new cases and 358,989 deaths (1). Mortality has been observed to be lower in white men as compared to African-American men (2).This has been associated with social, environmental and genetic factors. Through the Global Cancer Observatory, 2,293,818 new cases are estimated until 2040, with an expected variation in increase in mortality of 1.05 % (3).

In Africa, several studies have been done on prostate cancer. Wabinga *et al.* indicated a rise in the incidence rate (5.2%) in Kampala (Uganda) (4), while Chokunonga *et al*. indicated a rise incidence rate (6.4%) in Harare (Zimbabwe) (5). In both studies, the rise in cancer was associated with change of lifestyle and unhealthy behaviors due to urbanization. In Kenyatta National Hospital (KNH), Wasike *et al*. reported that the elderly 66-70 years presented with clinically advanced disease had an incidence rate of 76.5 patients/100,000 (6).

In 1941, Huggins and Hodges introduced surgical castration or the use of estrogenic injections as the therapy for PCA (7). However from 2004, androgen deprivation therapy (ADT) became a treatment modality for prostate cancer management (8). This therapy has two options, medical castration or orchiectomy (8). Prostate cancer management is based on the American Joint Committee on Cancer (AJCC) staging of the tumor (9) or risk stratification of the cancer, where the classification is based on tumor stage, Gleason pattern and PSA levels.

In Kenya, both medical castration and surgical castration (orchiectomy) are used for therapy depending on the patient specifics. Medical castration uses anti-androgens or Luteinizing Hormone Releasing Hormone (LHRH) as an antagonist or agonist with the option of combining both LHRH drug (Leuprolide, Goserelin, Triptorelin or Histrelin) and the antiandrogens. Depending on the drug used and staging of the tumor, it can be given as intermittent or continuous for up to one year. The LHRH antagonist used in ADT is Degarelix for advanced prostate cancer. The antiandrogen tablets include Flutamide, Bicalutamide and Nilutamide. They are used to control tumor flare that occurs due to the use LHRH agonist.

Overall survival (OS) and progression-free survival (PFS) of patients has been used in the recent past as primary end points of chemotherapy in several studies. Progression free survival has been used as an outcome to evaluate drug efficacy in clinical trials and as a marker for overall survival of patients. Patients who are free of clinical progression of the disease have an improved quality of life and the likelihood of prolonged survival (10). Halabi *et al.* investigated the association between the PFS and OS in castrate resistant prostate cancer patients. Those who had a PFS at 3 months had an OS of 9.2 months while those who had no PFS at 3 months had an OS of 17.8 months (11).

The use of hormonal therapy and radiotherapy is associated with reduced mortality and overall survival of patients (12)(13). Biochemical recurrence is associated with the duration of the hormonal therapy and survival of the patient. A PSA level of more than 0.2 ng/mL after 8 months after ADT post operation or post radiation was associated with mortality (14).

1.2 Statement of the problem

KNH currently treats a large population with PCA. For patients classified as intermediate- risk group or high and very high-risk patients, ADT is recommended. There is a knowledge gap on the treatment outcome of ADT on PCA patients therefore this study has investigated factors associated with this therapy. There are few studies in Africa indicating the treatment outcomes of the different treatment modalities of PCA. In Ghana, the reported adverse outcomes of radiotherapy and prostatectomy were erectile dysfunction and incontinence (15). The study results can be used as guide in identifying patients at risk of CRPC.

1.3 Research Question

What are the factors associated with treatment outcomes among prostate cancer patients managed with androgen deprivation therapy at Kenyatta National Hospital?

1.4 Objectives

1.4.1 General Objective

To evaluate the factors associated with treatment outcomes of androgen deprivation therapy among prostate cancer patients at Kenyatta National Hospital.

1.4.2 Specific objectives

1. To determine the prevalence of ADT use among prostate cancer patients at Kenyatta National Hospital.
2. To characterize the clinical profiles of prostate cancer patients receiving ADT at KNH.
3. To determine the treatment outcomes of ADT therapy and the factors associated with it among prostate cancer patients at KNH.

1.5 Justification of the study

Research on prostate cancer has been done widely in developed countries. The information obtained from this research has led to the development of different guidelines on PCA management. Kenyatta National Hospital has adopted the National Comprehensive Cancer Network (NCCN) guidelines in managing PCA. The risk stratification of patients has led to proper diagnosis and treatment in these patients.

Currently, there are few studies on prostate cancer in Africa. A study done in Nigeria indicated that PSA nadir > 4ng/mL was associated with the clinical progression of the disease (16). Mutua *et al*. described the cultural influences on PCA screening in Kenya (17) while Wasike *et al.* studied the characteristics of patients being treated for prostate cancer at KNH (18) indicating more need for research in Kenya. There is no research that has been done so far on the treatment outcomes of ADT in Kenya.

Clinical and pathological characteristics of patients influence the treatment outcomes of ADT. This study identified the factors associated with the treatment outcome of ADT use with the aim of identifying optimal treatment strategies that are affordable to patients for PCA management at KNH. The study will also assist health care professionals in improving or updating local guidelines on PCA management.

1.6 Significance of the study

This study identified the patients the factors associated with ADT treatment outcomes. The results will be of use in making clinical decisions based on patients at risk of progressing to hormonal refractory disease

1.7 Delimitations

The study was carried out at the Cancer Treatment Centre. The medical records of PCA patient were used for the data and using the eligibility criteria, information was collected using the data tool.

1.8 Study limitations

The main limitation is that the data reported here is limited to KNH therefore there will be the inability to generalize the results and need for further research. Being a retrospective study, any omissions or inaccuracies in patient records cannot be clarified. Furthermore, a preliminary survey indicated that the records lack medication and past medical history thus adverse effects of drugs and comorbidities cannot be evaluated in this study. Most records were incomplete and patients defaulted treatment and therefore the patients who had minimum treatment of 19 months were few. Lack of updated records or missing records became a challenge because KNH uses manual records.

1.9 Conceptual/Theoretical Framework

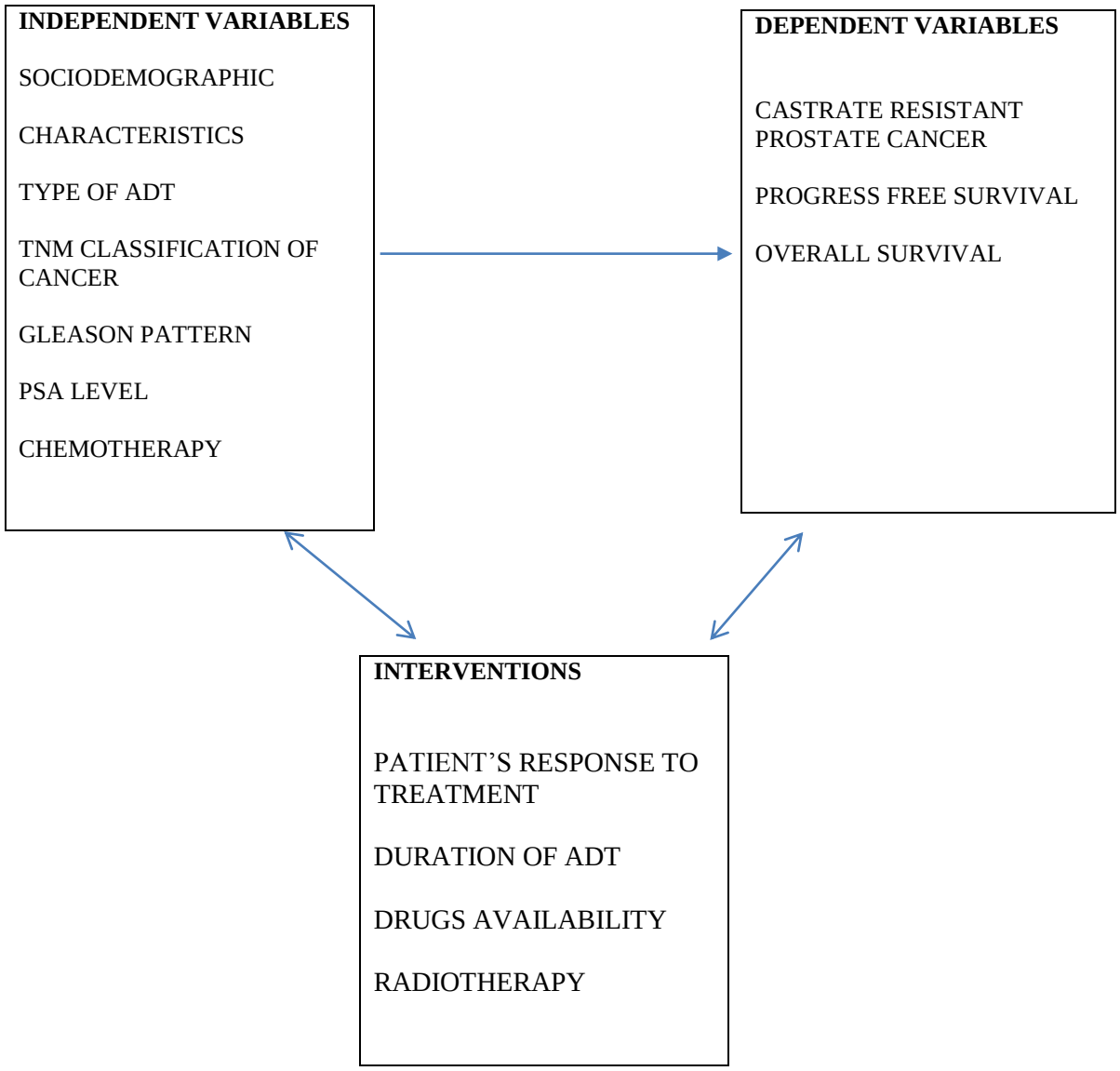

Figure 1-Conceptual/Theoretical framework

Author *Gathu,* 2020

The factors associated with treatment outcomes are the socio-demographic and clinical characteristics of the patient. ADT has been associated with castrate resistant prostate cancer. The use of chemotherapeutic agents has indicated improvement in the overall survival of patients. Tumor Node Metastasis (TNM) classification and Gleason pattern also affect PSA levels in patients who have had radical prostatectomy. PSA is also used as a predictor for overall survival of patients.

CHAPTER TWO: LITERATURE REVIEW

2.1 Risk factors associated with Prostate Cancer

Obesity and a high body mass index are associated with prostate cancer (19). Obesity is also associated with PCA after radical prostatectomy (20). Moriera *et al.* in a retrospective study indicated that cigarette smoking is associated with developing metastasis, Castrate Resistant Prostate Cancer (CRPC) and mortality after radical prostatectomy (21).

The risk of prostate cancer increases with age (1) with race being a risk factor between African-American and the white men (1). African-American men recorded the highest incidence rate while the lowest incidence is seen in men of American-Asian origin (22). These results have been associated with differences in both socioeconomic status and biologic factors of the PCA patients (23). This could be due to a lower quality of health care and low chances of PSA screening among PCA (24). Black men at age of 40 are at a higher risk, while white men with no family history of prostate cancer, the risk increases significantly after 50 years (25). Family history of shared genes, common lifestyle habits and carcinogens were identified in 20% of patients who developed cancer (26).

Studies have indicated that the average age of PCA diagnosis is between 65 years and 75 years. According to Diallo *et al.* the average age of patients diagnosed with PCA was 75.3 years in Senegal (27) while Amegbor *et al.* (28) and Sequeira *et al.* (29) found an average age of 70 years (Ghana) and 71.2 years (Portugal) respectively.

In Sub Saharan Africa, a study indicated that a low incident rate of PCA was due to inability to access healthcare services, unhealthy lifestyle and environmental factors (30) with most of the health care budget spent on tropical diseases while cancer receives little or no funding at all (31).

2.2 Tumor node metastasis classification of prostate cancer

There are four stages of prostate cancer. The clinical staging of prostate cancer was revised from the American Joint Committee on Cancer (AJCC) Tumor, Node, and Metastasis (TNM) system.

There are different methods of assessing the tumor stage. These methods include:

- Prostate biopsy
- Digital rectal examination
- Imaging modalities

2.3 Risk group stratification of prostate cancer

According to the National Comprehensive Cancer Network Guidelines (NCCN), PCA is managed based on risk stratification which classifies PCA according to clinical and pathological features with stage grouping (8).

The NCCN added two groups into the risk stratification of PCA, the very low-risk and very high-risk group of patients. The risk groups defined by the NCCN (Table 1) guidelines are as follows; Low risk group, intermediate risk group and high-risk group. The main objective of ADT is to lower the testosterone level to <50 ng/dL, an equivalent to castration (8).

For the very low-risk group, recommended therapy is active surveillance with selected interventions including radical prostatectomy (RP) and radiotherapy (RT). For the intermediate risk group, RT or brachytherapy with or without ADT is recommended. For the high and very high-risk groups, RP or RT is considered plus early or delayed ADT. Management might also include lymph node dissection for positive lymph node or positive resection margins. Metastatic PCA may require combination of ADT with chemotherapeutic agents (8). Total remission is considered if PSA nadir remains below 2.0 ng/dL after RT with or without ADT or 0.2 ng/dL after RP (32).

TABLE 2.1: RISK STRATIFICATION OF PROSTATE CANCER

RISK GROUP	PATHOLOGICAL FEATURES
Very Low	Stage **T(I)C**
	Grade group I
	PSA <10 ng/mL
	Prostate Specific Antigen density <0.15ng/ml
Low	Stage **T(I)-T(II)A**
	Grade group I
	Prostate Specific Antigen <10ng/mL
Intermediate	Stage **T(II)B-T(II)C**
	Grade group II or III
	Prostate Specific Antigen 10-20 ng/mL
High	Stage T**(III)A**
	Grade group IV or V
	Prostate Specific Antigen >20 ng/mL
Very High	Stage **T(III)B- T(IV)**
	Primary Gleason pattern V

2.4 Androgen deprivation therapy

Androgen deprivation therapy is classified into medical castration or orchiectomy. ADT can be given as neoadjuvant, concomitant or adjuvant in the management of locally advanced and advanced PCA. Drugs used in ADT include: LHRH (agonists and antagonists), antiandrogen drugs such as bicalutamide or combined oral blockade of LHRH agonist and antiandrogen drug (8).

2.5 Prostate cancer management

2.5.1 Localized prostate cancer

Radical prostatectomy (RP) and radiotherapy (RT) are recommended for localized PCA with monitoring of PSA levels. For low risk PCA, active surveillance is recommended, but for intermediate and high-risk PCA, RP is recommended (33). Active surveillance is required and if cancer progresses, there will be need to initiate ADT (34). A study comparing bicalutamide and dutasteride over bicalutamide indicated no clinical benefit in treating locally advanced and advanced PCA (35).

2.5.2 Locally advanced disease

The treatment of choice for locally advanced disease is ADT. Other treatment options include RP or RT with hormonal manipulations. In locally advanced cancer, combined use of ADT and RT improves overall survival compared to ADT alone (12). Souhami *et al.* demonstrated that patients on ADT for more than 5 years compared to those on ADT for less than five years treated with RT had a significant improvement in the overall survival and a lower risk of distant metastasis (36).

For patients in the intermediate risk group, short term use of ADT with RT is recommended with supported evidence showing increased survival of the patients (36,37). For high risk patients and very high-risk patients, a combination of EBRT and long-term ADT (2-3 years) is recommended (33,34). Monotherapy with an ADT is not currently recommended (8).

2.5.3 Metastatic prostate cancer

When patients progress to metastatic PCA, the ADT should not be discontinued. ADT has been shown to delay death by two months (40) while chemotherapy delays by one month (41). Zolendronic acid is recommended for patients with metastasis of the bone (8).

2.5.4 Castrate resistance prostate cancer

Castrate resistance prostate cancer develops in patients after receiving ADT (16). A study indicated that after a follow up of 39.9 months, patients on ADT had high levels of PSA and serum alkaline phosphatase with more bone lesions and an increased risk of CRPC (42). The time to develop CRPC has been estimated to be 19 months (43).

2.6 Chemotherapeutic agents

The use of docetaxel and cabazitaxel in the treatment of metastatic CRPC has shown remarkable decrease in PSA levels (44). The use of sipuleucel T has indicated that it improves the overall survival of patients.(45)

Harshman *et al.* also indicated that the use of ADT with or without docetaxel in metastatic cancer with a PSA $\leq$ 0.2 ng/dL at 7 months is prognostic marker for a longer overall survival of patients (46). Wu *et al.* demonstrated that the three-modality mode of ADT, EBRT and paclitaxel can be used in high risk prostate cancer patients. The maximum dose of paclitaxel that can be used weekly was 50 mg/m^2. This was done in patients who had localized prostate cancer or radical prostatectomy (47).

2.7 Treatment outcomes of androgen deprivation therapy

2.7.1 Biochemical recurrence

Prostate specific antigen is a prognostic marker of clinical progression of PCA (48).The disease progresses to CRPC despite ADT (49).The use of ADT with chemotherapeutic agent reduces PSA progression. Gravis *et al*. compared the addition of 3-weekly docetaxel to ADT and ADT alone. This indicated a significant reduction in PSA levels within six months (50).

Kim *et al.* indicated that pre and post levels of gleason score and PSA levels are all independent risk factors affecting the postoperative first serum PSA level in prostate cancer patients therefore risk stratification post-surgery may be a guide in patients receiving adjuvant therapies (51).

In localized prostate cancer, patients receiving ADT whose PSA level was above 0.2 ng/ mL were at higher risk of death from prostate cancer (52). Stewart *et al.* indicated that PSA failure is associated with prostate cancer mortality. A PSA level of more than 0.2 ng/mL after 8 months

after ADT post operation or post radiation was associated with mortality (14). Some studies have concluded that the use of neoadjuvant ADT with EBRT has clinical benefits. Roach *et al.* compared the use of goserelin with flutamide plus EBRT with EBRT alone. The result indicated that the prior group had lower risk of biochemical recurrence and distant metastasis (53).

2.7.2 Progression-free survival and overall survival of prostate cancer patients

Progression-free survival (PFS) is measured as an outcome that correlates symptomatic progression of the tumor. The progression includes measurable disease progression e.g gleason pattern or staging of PCA, rise in PSA levels and bone metastasis and (54).

Overall survival (OS) has also been used in many clinical trials and cohort studies as an outcome. However, the measurement of this outcome requires the use of large sample size that requires a lengthy follow up of period of time. PFS has been investigated to be a predictor of OS in CRPC. Patients who experienced the disease progression at three months had a median survival of 9.2 months while those who had no disease progression at three months had a median survival of 17.8 months (11). Berglund *et al.* study included ten year follow up of 55 patients on goserelin and flutamide. Out of these patients, 38% had clinical progression of the disease. The PFS was 7.5 years with a survival of 68% of the patients (55).

The use of ADT may influence the overall survival of patients. Harshman *et al.* demonstrated that patients had an overall survival of 75 months with a PSA level < 0.4ng/mL after the use of goserelin and bicalutamide for seven months followed by continuous administration of ADT (56). Borcardo *et al.* compared the use of bicalutamide with ADT (flutamide and goserelin). Patients were followed up for a period of 54 months and the conclusion was there were no significant differences in the duration of PFS and OS (57). PSA of 4 ng/mL or less after 7 months of ADT is a strong predictor of survival (58).

CHAPTER THREE: METHODOLOGY

3.1 Introduction

This chapter contains the methods that were used to carry out the study. The chapter also includes study location, target population, sample size calculation methods of sampling data management and ethical considerations of the study.

3.2 Research design

The study design was a retrospective cross-sectional study. The period was from January 2016 to December 2019.

3.3 Location of the study

The study was carried out at Kenyatta National Hospital, which is located in Upper Hill region in Nairobi County. The study was conducted at the cancer treatment center. The Hospital which is the largest public referral Hospital serves a diverse population from Kenya and receives patients as referrals from other hospitals and institutions. The bed capacity is 1800 with different specialized wards. The Hospital also serves as a teaching hospital of the University of Nairobi, College of Health Sciences. The Hospital has highly qualified medical personnel that are trained in all areas. The different specialties based on the services given include Oncology, Neurology, Nephrology, Infectious diseases, Endocrinology, Orthopedic surgery, General surgery, Gynecology and pediatrics.

3.4 Target population

The target population is records of all patients aged 18 years and above who are being treated for prostate cancer using ADT at KNH from January 2016 to December 2019.

3.5 Study population

The study population was records of patients aged 18 years and above who are receiving ADT for PCA treatment.

3.5.1 Inclusion criteria

- Patients who were already on ADT between January 2016 to December 2019.
- Patients aged 18 years and above.

3.5.2 Exclusion criteria

- Patients with incomplete clinical records**.**

3.6 Sample size estimation

This was a retrospective cross sectional study based on the international survey of ADT use in several countries (58). The number of patients on ADT was 38%. The Cochran formula for determining the sample size in cross-sectional studies is used (59):

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

Where:

- n= sample size
- z= statistic for 95% level of confidence, critical value 1.96
- p=Estimated proportion of patients receiving ADT- 38 %
- e= level of precision set at 0.05

n=

$$\frac{1.96^2 \times 0.38\ (1 - 0.38)}{0.05^2}$$

= 362 patients

For finite population

N-= Total number of patients that were on ADT during the four-year period

$$\frac{no}{1+no/N}$$

$$\frac{=362}{1+362/120} \quad =90 \text{ patients}$$

.

3.7 Sampling method

Simple random sampling method was used to identify prostate cancer patients receiving ADT within the period January 2016 to December 2019.

3.8 Research instrument

A well-structured data collection tool was designed to capture the socio-demographic characteristics, clinical characteristics of the patients and the treatment outcome of ADT from the selected files.

3.9 Data collection techniques

Using the data collection tool, socio-demographic and clinical characteristics, drug therapy and treatment outcome of ADT was abstracted from the patient files. The period studied was from January 2016 to December 2019.

3.10 Pretesting of the research instrument

The tool was piloted at the oncology pharmacy for review by the clinical pharmacist using patient files. This enabled proper capturing of all the required information. The tool was revised based on the feedback.

3.11 Variables

The variables under study include; socio-demographic characteristics (gender, age, level of education, marital status, income) and clinical characteristics (tumor staging, Gleason score, PSA level, biochemical recurrence,) and drug therapy information of the patients. The treatment outcome variables include castrate resistant prostate cancer, progression free survival and overall survival of the patients.

3.12 Validity

To ensure the validity of the results of the study, the research instruments were structured in a way that ensures the objectives of the study are met minimizing internal validity.

3.13 Reliability

Data collection tool was pretested to determine the internal reliability of the results through a pilot study. Improvements or amendments to ensure the reliability of the results was done. The tool was handed over to clinical pharmacist for more expertise information Reproducibility of results was ensured by collecting all relevant information from the patient records.

3.14 Data management

A serialized data collection tool was used to avoid duplication of data. After complete information entry into a database, data cleaning was done before analysis. Raw data was coded, cleaned, validated. All the data was backed up at the end of each clinic day in a flash disk and hard drive. After completion of data collection, the data was exported into STATA software 16.0 (StataCorp, USA) for data analysis.

3.15 Data analysis

Data was analyzed using STATA software (StataCorp, USA). Continuous variables such as age were summarized as measures of central tendency. Descriptive analysis was expressed through frequencies, percentages. Logistic regression was used to determine the factors associated with ADT treatment outcomes. Factors associated with overall survival were determined using linear regression.

3.16 Ethical considerations

Permission to carry out the study sought from KNH/UON Ethics and research committee and the approval protocol number was P165/03/2020 Ref KNH-ERC/A/152 dated 20th May 2020. Patient's outpatient numbers were not recorded but serialized with specific codes. This maintained the anonymity and privacy of the patients.

CHAPTER FOUR: RESULTS

4.1 Demographic characteristics

We enrolled 90 patients with prostate cancer with a mean age of 70 years (SD ± 8.3). Seventy-five patients (83%) were married, 36 (40%) had secondary school as their highest level of education. Half of the patients (50%) were self-employed, 50 (56%) were not cigarette smokers while also 49 (54%) did not consume alcohol. More than half of the respondents, 48 (52%) had normal BMI levels (Table 4.1).

Table 4.1: Demographic characteristics of the patients.

Variable		Frequency (n)	Percentage (%)
Age	Mean	70±8.3	
	Median	70(65 – 78 years)	
Marital status	Single	1	1
	Married	75	83
	Separated	8	9
	Widowed	6	7
Level of education	Informal	6	7
	Primary	26	28
	Secondary	36	40
	Tertiary	22	25
Employment status	Unemployed	27	30
	Employed	10	11
	Self employed	45	50
	Retired	8	8.9
Cigarette Smoking	Yes	40	44
	No	50	56
Alcohol consumption	Yes	41	46
	No	49	54
BMI	Mean (±SD)	24±4	
	Median (IQR)	24(21 – 27)	
	<18.5	8	9
	18.5 – 24.9	48	52
	25.0 – 29.9	27	30
	30 and Above	7	8

4.2 Baseline laboratory investigations

Sixty nine patients (77%) had low levels of neutrophils of less than 60%, 56 (62%) had normal hemoglobin levels of between 12g/dl and 17gdl and 76 (84%) of the patients had normal platelet count of between 150 cells/µL and 450 cells/µL. Prior to first treatment administration, most of the patients had very high levels of prostate specific antigen (PSA), 66 (73%) of greater than >20ng/dl as shown in Table 4.2.

Table 4.2: Baseline laboratory investigations of the patients

Variable		Frequency (n)	Percentage (%)
Neutrophil (%)	Mean ±SD	52±12.20	
	Median (IQR)	53(47.1 – 59.8)	
	<60	69	77
	60 – 70	17	19
	>70	4	4
Hemoglobin (g/dl)	Mean ±SD	13.92±4.3	
	Median (IQR)	13.65(12 – 15.2)	
	<12	30	33
	12 – 17	56	62
	>17	4	5
Platelet count (cells/µL)	Mean ±SD	294.41±106.59)	
	Median (IQR)	260.8(225.75 – 337)	
	<150	11	13
	150 – 450	76	84
	>450	3	9
Prostate Specific antigen (PSA)	<10ng/dl	6	7
	10 - 20ng/dl	18	20
	>20ng/dl	66	73

4.3 TNM Classification

In evaluating the pathological profile, the study focused on tumor staging, grading, lymph node and metastasis of the prostate cancer cells. The findings showed that, 44 (48%) had T3b – T4 tumor staging while 34 (38%) had T3a tumor staging. Majority of the respondents, 69 (76%) had G3-Gleason 7 -10 grading as shown in Table 4.3.

Table 4.3: TNM classification of the patients

	Pathological profile	Frequency (n)	Percentage (%)
Tumor staging	T1a - T2a	8	9
	T2b - T2c	4	5
	T3a	34	38
	T3b - T4	44	48
Grading	G1 -GLEASON 2-4	8	9
	G2-GLEASON 5-6	13	15
	G3-GLEASON 7 -10	69	76
Lymph node	NX	19	23
	NO	16	19
	N1	55	58
Metastasis	MX	28	33
	MO	15	15
	M1	47	52

4.4 Prostate cancer management

Thirty-three patients used medical ADT only as their first treatment while 7(8%) used prostatectomy and ADT as the first treatment. The results also further showed that 48 patients (53%) also used radiotherapy as shown in Table 4.4

Table 4.4: Prostate cancer management among patients

	Variable	Frequency (n=90)	Percentage (%)
First treatment (ADT)	ADT Medical	33	37
	ADT Surgical	2	2
	Radiotherapy with ADT	48	53
	Prostatectomy with ADT	7	8
Medication used	Goserilin alone	35	39.8
	Goserilin and Bicalutamide	53	60.2

4.4.1 Additional treatment in first treatment

Among the patients who had been given goserilin only, 11 (30.6%) used zoledronic and additional treatment while 4 (12.1%) used docetaxel as additional treatment while among those

who had combined goserilin and bicalutamide, 9 (17%) added zoledronic and 5 (9.4%) added docetaxel (Table 4.5).

Table 4.5: Additional drugs used in first treatment

		Additional treatment	
		Zoledronic Acid n (%)	Docetaxel n (%)
Medical ADT	Goserilin Only	11(30.6)	4 (12.1)
	Goserilin and Bicalutamide	9 (17)	5 (9.4)

4.4.2 Second Treatment

The analysis also showed that only 14 (15%) of the patients had second treatment. In assessing risk stratification for those who underwent second treatment, all had very high-risk PCA. Among those who had biochemical recurrence, the average time was 7 months after the first treatment with majority ranging from 5 to 11 months as presented in Table 4.6.

Table 4.6: Administration of ADT and second treatment among patients

		Frequency (n)	Percentage (%)
Administration of ADT	Adjuvant	58	64
	Neoadjuvant	1	1
	Concomitant	31	34
Second Treatment	Yes	14	19
	No	76	81
Time to Biochemical recurrence (months)	Mean ±SD	7.92 ±4.2	
	Median (IQR)	7(5 – 11)	
Risk Stratification for second treatment	Very High risk	14	100
ADT Second Treatment	Goserilin only	3	21.4
	Goserilin and Bicalutamide	11	78.6

4.4.3 Additional treatment used in second treatment

In assessing additional treatment in second treatment, 5 (37.7%) of the patients combined goserilin, bicalutamide and abiraterone while 8 (57%) combined goserilin, bicalutamide and docetaxel as shown in Table 4.7

Table 4.7 Additional drugs used in second treatment

		Additional treatment	
		Abiraterone n (%)	Docetaxel n (%)
Medical ADT	Goserilin Only	2(14.2)	3 (21.4)
	Goserilin and Bicalutamide	5 (37.7)	8 (57.1)

4.4.4 Duration of ADT and Post ADT Prostate Specific Antigen (PSA)

The average duration of ADT was 24 months with majority ranging between 17 and 27 months. Most of the patients had low PSA average 50 with less than 10ng/dL (55.6%) as shown in Table 4.8

Table 4.8: Duration of ADT and post ADT PSA among patients.

		Frequency (n)	Percentage (%)
Duration of ADT	Median (IQR)	24(17 – 27)	
Post ADT prostate specific antigen	<10ng/dL	50	55.6
	10 - 20ng/dL	13	14.4
	>20ng/dL	27	30

4.5 Outcomes of ADT

The outcomes of patients on ADT were also assessed. The findings revealed that the mean overall survival was 29.7 months with a standard deviation of 9.16. The median was 28 months with range between 24 and 38 months. Majority of the respondents, 76 (84%) were progression free while 14 (16%) were castrate resistant (Table 4.9).

Table 4.9: Outcomes of ADT

		Frequency (n)	Percentage (%)
Overall survival (Months)	Mean ± SD	29.7 ± 9.16	
	Median (IQR)	28 (24 – 38)	
Outcome	Castrate resistant	14	16
	Progression Free	76	84

4.6 Association between sociodemographic characteristics and ADT treatment outcomes among patients

A Fisher's exact test was conducted to determine the existing association between patient characteristics and ADT treatment outcome. The findings showed that there was a significant association between age, p =0.002, level of education, p =0.038, cigarette smoking, p =0.008, BMI, p =0.018 with ADT treatment outcome as shown in Table 4.10.

Table 4.10: Univariate test for association between sociodemographic characteristics and ADT treatment outcomes

Variables		Outcome		
		CRPC	**PFS**	**P-value**
Age of the respondents	<70 Years	2(14.3%)	45 (59.2%)	**0.003**
	>70 Years	12(85.7%)	31(40.8%)	
Marital status	Single	1(7.1%)	0	
	Married	10(71.4%)	65(85.5%)	0.065
	Separated	1(7.1%)	7(9.2%)	
	Widowed	2(14.3%)	4(5.3%)	
Employment	Unemployed	3(21.4%)	24(31.6%)	
	Employed	2(14.3%)	8(10.5%)	0.777
	Self employed	7(50%)	38(50%)	
	Retired	2(14.3%)	6(7.9%)	
Level of education	Informal	2(14.3%)	4(5.3%)	
	Primary	2(14.3%)	24(31%)	**0.038**
	Secondary	3(21.4%)	33(44%)	
	Tertiary	7(50%)	15(20%)	
Cigarette smoking	Yes	11(78.6%)	29(48.2%)	**0.008**
	No	3(21.4%)	47(61.8%)	
Alcohol consumption	Yes	8(57.1%)	33(43.4%)	0.343*
	No	6(42.9%)	43(56.6%)	
BMI	Underweight	3(21.4%)	5(6.8%)	
	Normal	3(21.4%)	44(59 %)	**0.018**
	Overweight	8(57.1%)	21(28.4%)	
	Obese	0	7(9.5%)	

4.7 Association between clinical characteristics and ADT treatment outcome among patient

A test for association was conducted to determine association between clinical characteristics and treatment outcomes. The results found that platelet count, p <0.001, Hb level, p<0.001, duration of ADT, p =0.029, Medical ADT =0.047 and PSA Post ADT, p<0.001, were significantly associated with ADT treatment outcomes as shown in Table 4.11.

Table 4.11: Univariate test for association between clinical characteristics and treatment outcomes

Variables		Outcome		
		CRPC	**PFS**	**P- value**
Neutrophil count	Low	12(85.7%)	57(75%)	
	Normal	1(7.1%)	16(21.1%)	0.356
	High	1(7.1%)	3(3.9%)	
Baseline PSA	<10ng/dL	0	6(8%)	
	10 - 20ng/dL	2(14.3%)	16(20%)	0.677
	>20ng/dL	12(85.7%)	54(72%)	
Platelet count	Low	8(57.1%)	3(4.1%)	
	Normal	5(35.7%)	71(93%)	<**0.001**
	High	1(7.1%)	2(3%)	
HB level	Lower	13(92.9%)	17(22.4%)	
	Normal	1(7.1%)	55(72.4%)	<**0.001**
	High	0	4(5.3%)	
Tumor staging	T1a - T2a	2(14.3%)	6(8%)	
	T2b - T2c	0	4(5.3%)	0.34
	T3a	3(21.4%)	31(41.3%)	
	T3b - T4	9(64.3%)	34(45.3%)	
Grading	G1 -GLEASON 2-4	1(7.1%)	7(9.5%)	
	G2-GLEASON 5-6	2(14.3%)	11(14.9%)	0.998
	G3-GLEASON 7 -10	11(78.6%)	56(75.7%)	
First treatment	Medical ADT Only	7(50%)	26(34.2%)	
	Orchiectomy	0	2(2.6%)	
	Radiotherapy with ADT	6(42.8%)	42(55.3%)	0.306
	Prostatectomy with ADT	1(7.1%)	6(7.9%)	
Medical ADT	Goserilin Only	9(64.3%)	26(35%)	
	Goserilin and Bicalutamide	5(35.7%)	48(65%)	**0.047***
Duration of ADT	<12 months	1(7.1%)	30(39.5%)	**0.029**
	>12 months	13(92.9%)	46(60.5%)	
Prostate Specific Antigen (Post ADT)	<10ng/dL	2(14.3%)	48(65%)	
	10 - 20ng/dL	3(21.4%)	10(13%)	**<0.001**
	>20ng/dL	9(64.3%)	18(22%)	
** Chi square test*				

4.8 Logistic regression analysis of factors associated with Castrate Resistant Prostate Cancer and Progression Free Survival

Age, cigarette smoking, Hb level, platelet count, medical ADT, duration of ADT and post ADT PSA had a significant association to ADT treatment outcomes. Younger patients (<70years) were 0.8 times less likely to become castrate resistant 95% CI [OR=0.81, 0.72 – 0.90]. Patients who smoke were 5.9 times more likely to become castrate resistant 95% CI [OR=5.9, 0.01 – 23.11]. Patients who took goserilin only as first ADT treatment were 6.5 times more likely to be castrate resistant, 95%CI [OR=6.518,1.671 – 25.42]. The results also found that patients who had less duration of ADT were 0.9 times less likely to become castrate resistant, 95% CI [OR=0.86,0.79 – 0.94]. Patients with lower Hb level were 1.5 times more likely to become castrate resistant, 95%CI [OR=1.5, 1.13 – 2.9] Patients who had lower platelet count were 16 times likely to become castrate resistant, 95% CI [3.87-67.14]. Patients who had lower post ADT mean prostate specific antigen were 0.29 times less likely to become castrate resistant 95% CI[OR=0.29,0.14-0.6]

A multivariate regression analysis was conducted to assess significant predictors of outcome on adjusted odds ratio. The results showed that, duration of ADT, hemoglobin level and average of PSA post ADT were significant predictors of ADT treatment outcome. Patients with lower duration of ADT were 0.8 times less likely to become castrate resistant, 95% CI [aOR=0.8, 0.65 – 0.98]. Patients with lower Hb level were 1.1 times more likely to become castrate resistant, 95%CI [aOR=1.1, 0.9– 3.2]. Patients who had lower post ADT mean prostate specific antigen were 0.21 times less likely to become castrate resistant 95% CI [aOR=0.21, 0.04– 0.98] as shown in Table 4.12.

Table 4.12: Bivariate and multivariate logistic regression of factors associated with Castrate Resistant Prostate Cancer and Progression Free Survival

Variables	Bivariate analysis				Multivariate analysis			
	cOR	95% Confidence Interval		P-value	aOR	[95% Conf.	Interval]	P-value
		Lower	Upper			Lower	Upper	
Age	0.8	0.72	0.90	**0.000**	0.2	0.01	2.05	0.16
Education	0.7	0.34	1.35	0.269				
Marital status	0.8	0.31	1.95	0.595				
Employment	0.8	0.44	1.43	0.436				
Alcohol use	1.7	0.55	5.50	0.347				
Cigarette smoking	5.9	1.53	23.11	**0.01**	8.1	0.54	121.61	0.131
BMI	1.1	0.51	2.31	0.828				
HB level	1.5	1.13	2.9	**0.000**	1.1	0.9	3.2	**0.026**
Baseline PSA	0.4	0.11	1.7	0.231				
Platelet count	16.1	3.87	67.14	**0.000**	0.42	0.017	10.35	0.597
Neutrophil level	1.3	0.41	4.33	0.633				
Tumor staging	0.9	0.44	1.68	0.658				
Grading	0.9	0.34	2.26	0.778				
First treatment	1.4	0.81	2.40	0.233				
Medical ADT	6.5	1.67	25.42	**0.007**	2.8	0.22	36.15	0.432
Duration of ADT	0.9	0.79	0.94	**0.001**	0.8	0.66	0.98	**0.028**
Prostate Specific Antigen (Post ADT)	0.3	0.14	0.6	**0.001**	0.2	0.04	0.98	**0.047**

Note: _cons estimates baseline odds.

4.9 Linear regression analysis of factors associated with overall survival

The linear regression results show that duration of ADT was a statistically significant predictor of survival among the patients. The findings show that an increase in one month of ADT is associated with 4.8 months increase in overall survival (p = 0.005) as shown in Table 4.13.

Table 4.13: Bivariate and multivariate linear regression of factors associated with overall survival

	Bivariate analysis			Multivariate analysis		
	Unadjusted β coefficient	**(95%CI)**	**P-value**	**Adjusted β coefficient**	**(95% CI)**	**P-value**
Age	0.98	(-2.9, 4.8)	0.617			
Education	1.6	(-0.5,3.8)	0.138			
Marital status	0.4	(-3,3.8)	0.83			
Employment	-1	(-2.9, 0.9)	0.281			
Cigarette smoking	1.5	(-2.4,5.4)	0.44			
Alcohol use	1.8	(-2.4,5.4)	0.37			
BMI	0.14	(-0.34,0.61)	0.57			
HB level	-0.08	(-0.5,0.34)	0.7			
Platelet count	0.002	(-0.02,0.02)	0.834			
Baseline PSA	2.8	(-0.45,5.9)	0.091	1.7	(-1.4,4.9)	0.293
Neutrophil level	-0.9	(-4.5,2.6)	0.603			
Tumor staging	0.5	(-1.6,2.6)	0.643			
Grading	0.8	(-3.1,4.8)	0.612			
First Treatment	0.9	(-0.8,2.8)	0.289			
Medical ADT treatment	0.8	(-3.1,4.8)	0.682			
Duration of ADT	6	(2.2, 9.9)	**0.002**	4.8	(0.8, 8.9)	**0.019**
Post ADT PSA	2.7	(0.6,4.9)	**0.013**	1.5	(-0.8, 3.8)	0.198

CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

In this study investigating factors associated with ADT treatment outcomes, we enrolled 90 prostate cancer patients all of whom were on ADT. ADT was used together with radiotherapy or after prostatectomy. Hemoglobin level, duration of ADT and PSA post ADT levels were significantly associated with the treatment outcomes. Duration of ADT was also significantly associated with the overall survival.

Globally, the use of ADT has increased over the last decade (61). In Europe, it is reported that up to 43% of PCA patients are initiated on ADT while the data from the USA and Canada indicates a 34% and 29% prevalence of ADT use respectively (62). All the patients investigated were on ADT confirming that this is the mainstay of therapy for patients with locally advanced prostate cancer and metastatic prostate cancer (8,63). A similar Sub Saharan study investigated the predictors of PFS among PCA and confirmed that all patients were started on ADT (16).

TNM classification, biochemical recurrence, medical ADT, duration of ADT, PSA levels were some of clinical characteristics of the patients that were investigated in this study. These variables have been found to be associated with ADT response and survival of the PCA patients in other studies (16,64–66).

In assessment of the TNM classification, almost half of the cancer patients presented with T3b – T4. This concurs with Wasike *et al.* who in a descriptive study reported that most patients are diagnosed at stage III and stage IV of PCA (67). This is similar to other studies that have also indicated that most patients present for treatment at stage III or stage IV of PCA (63,71).Seventy six percent of the patients had grade 3 (Gleason score of 7-10). These findings are comparable to Ji *et al.* who found out that most patients were in grade 3 (69). Similarly, Hori *et al.* in assessing patient characteristics, found that 46% of the patients had grade score of 8-10 (65). This

confirms that patients with PCA are more likely to be diagnosed at the advanced stage of PCA (70).

PSA has been used a biological marker for hormonal refractory disease (69,71,72). BCR has been defined in different studies using variables to assess efficacy of treatment (73) and as a predictor of CRPC (74). The average time to biochemical recurrence for patients in this study was 7 months. Sureka *et al*. concluded that biochemical recurrence was 10 months for patients to develop CRPC (74). Ji *et al*. also found analogous results where the average time to biochemical recurrence was 8 months (69). According to Elishmereni *et al.* time to biochemical recurrence of 67 days was used as clinical outcome for ADT (75). In a study conducted in Japan, it was found that biochemical recurrence was not associated with progression to CRPC (76). This was observed in our study but it did not show any significant association.

Patients in this study were treated with combination of radiotherapy and medical ADT with 53 patients (60%) on goserelin and bicalutamide. This combination has been observed to reduce mortality and disease progression in patients (37,77,78). In the Mottet *et al*. study, patients who had combined androgen blockade (LHRH and flutamide) with RT had longer PFS time compared to ADT alone (79). Similarly the use of leuprolin and RT has been shown to reduce clinical progression to metastatic progression compared to leuprolin alone (79). Additional treatment of docetaxel, zoledronic acid and abiraterone was observed in our study. Docetaxel was used along with zoledronic acid as chemotherapeutic agent. Docetaxel has been recommended as the one of the main drugs to be used in metastatic prostate cancer (80) while abiraterone is recommended for hormonal refractory prostate cancer (81).

A Sub Saharan study of black men revealed different results. Out of the PCA newly diagnosed patients, majority (65%) opted for orchiectomy compared to 2% of the patients in our study (16).

In a similar study conducted in India, 80% of the patients opted for surgical castration quoting higher cost of medical ADT (82).

The mean duration of ADT in our study was a median of 24 months. The recommended duration for treating high-risk PCA patients is 18-36 months years (8,83). This period has been studied and it has shown improved survival of patients (84) but a clinical trial was done to show the efficacy of ADT reducing the treatment period from 36 months to 18 months (85).

Majority of the patients (73%) presented with high baseline PSA >20 ng/mL at the beginning of the treatment and low PSA after treatment (60%). This confirms that the use of ADT lowers PSA in PCA. In a study done in Japan, baseline PSA level was 27.0 ng/ml and after ADT treatment it reached below 0.2ng/ml (25). Hah *et al*. also suggested that combined androgen blockade reduces the PSA levels after treatment (87).

Baseline hemoglobin levels, post ADT duration and duration of ADT were found to be significantly associated with CRPC. Low hemoglobin (<12g/L) was significantly associated with CRPC. This correlated with the Bournakis *et al*. study that anemia was significantly associated with CRPC and poor overall survival (88). Lin *et al.* found no association between Hb level and CRPC (71).

Patients investigated in our study who presented with low PSA values (<10ng/mL) were less likely to progress to CRPC. These results concur with those from a Japanese study where it was revealed that patients with PSA ≥20 ng/mL were associated with progression to CRPC (76). According to Hori *et al*. patients developed CRPC after a median follow up of 70 months. Predicting factors included high post ADT PSA values and shorter time to PSA nadir (65). Morote *et al.* analyzed 185 patients with prostate cancer and they found nadir PSA above 0.2 ng/ml was associated with 20 times likelihood progression to CRPC (89).

Patients who had ADT for less than 12 months were less likely to develop CRPC. There are no studies currently that clearly indicate the duration of ADT and the progression to CRPC. In the recent past, research has proven that ADT duration for PCA should be a minimum of 18 months (83,90). Rapid decline of PSA levels is observed on the first few months of ADT. The mechanisms to that effect have not been explained but there is a possibility of down regulation of PSA expression of androgen sensitive cells and over expression of androgen resistant cells (91). After 2-5 years, patients progress to hormonal refractory cancer (49,92) indicated by increasing serum levels of prostate specific antigen (PSA).This may be used as a probable explanation as to why a period of less than 12 months is less likely to be associated with CRPC.

Patients who progressed to CRPC (16%) were fewer than those who were at progression free survival state (84%). Time to CRPC was an average of seven months. This is comparable to studies that had patients who had hormonal refractory disease after receiving ADT treatment. According to Kwak *et al.* after a median follow up of 39 months, 117 patients (77.5%) had CRPC following hormonal therapy. In a retrospective study done in Japan, a total of 105 of the 387 patients enrolled progressed to CRPC after using combined androgen blockade in a median of 140 months (76).

Use of ADT has shown to improve overall survival in patients who have advanced prostate cancer. (84,85). A one month increase in the duration of ADT was found to be associated with 4.8 months increase in overall survival. This correlates with Souhami *et al*. where patients who had used ADT for 5 years had longer overall survival compared those who had ADT for less than five years (78). Bolla *et al*. also concluded that the overall survival improved with use of ADT in three years compared to six months in locally advanced prostate cancer patients (83). A different observation was made by Lu-Yao *et al.* where ADT was not associated with overall

survival of patients. Patients who had ADT were compared to those who had no ADT and there was no difference in overall survival in both groups (93). PSA nadir, radiotherapy and combined androgen blockade are variables in other studies that have prolonged survival in patients though in this study there was no significant association. Low PSA nadir <0.02ng/mL after ADT prolongs overall survival (91) while combined androgen blockade with RT improves overall survival in patients (79).

Strength of this was the ability to investigate the association different variables and treatment outcomes. Being a retrospective study, the major limitation encountered was the high number of incomplete medical records and patients defaulted treatment.

5.2 Conclusion

Medical androgen deprivation therapy is the treatment modality used for most prostate cancer patients at the KNH. Majority present at an advanced stage for treatment (stage III and stage IV). Combination of radiotherapy and ADT was also considered as part of the treatment for high-risk patients. A proportion of patients (16%) on ADT eventually progressed to hormonal refractory cancer. Hemoglobin levels, duration of ADT, PSA levels were associated with CRPC while duration of ADT was associated with overall survival. A one month increase in the duration of ADT was found to be associated with 4.8 months increase in overall survival.

5.3 Recommendations for policy and practice

1. Create awareness and early screening of PCA by providing screening services at county levels, so as to manage PCA at earlier stages.
2. Combined androgen blockade should be considered for all patients starting ADT at an advanced stage of the cancer.

5.4 Recommendations for research

Further research is needed to assess outcomes of bilateral orchiectomy vs medical ADT so as to provide better treatment in PCA patients. The research can include the complications that arise due to ADT with the aim of improving patient's quality of life.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.

2. Panigrahi GK, Praharaj PP, Kittaka H, Mridha AR, Black OM, Singh R, et al. Exosome proteomic analyses identify inflammatory phenotype and novel biomarkers in African American prostate cancer patients. Cancer Med. 2019 Jan 8;8(3):1110–23.

3. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144(8):1941–53.

4. Wabinga HR, Nambooze S, Amulen PM, Okello C, Mbus L, Parkin DM. Trends in the incidence of cancer in Kampala, Uganda 1991–2010. Int J Cancer. 2014;135(2):432–9.

5. Chokunonga E, Borok MZ, Chirenje ZM, Nyakabau AM, Parkin DM. Trends in the incidence of cancer in the black population of Harare, Zimbabwe 1991-2010. Int J Cancer. 2013 Aug 1;133(3):721–9.

6. Wasike RW, Magoha G a. O. Descriptive case series of patients presenting with cancer of the prostate and their management at Kenyatta National Hospital, Nairobi. East Afr Med J. 2007 Sep;84(9 Suppl):S31-35.

7. Huggins C. Studies on Prostatic Cancer. Cancer Res. :6.

8. Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T, et al. Prostate Cancer, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2019 May;17(5):479–505.

9. Prostate Cancer Stages and Other Ways to Assess Risk [Internet]. [cited 2020 Jan 24]. Available from: https://www.cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/staging.html

10. Robinson AG, Booth CM, Eisenhauer EA. Progression-free survival as an end-point in solid tumours--perspectives from clinical trials and clinical practice. Eur J Cancer Oxf Engl 1990. 2014 Sep;50(13):2303–8.

11. Halabi S, Vogelzang NJ, Ou S-S, Owzar K, Archer L, Small EJ. Progression-Free Survival as a Predictor of Overall Survival in Men With Castrate-Resistant Prostate Cancer. J Clin Oncol. 2009 Jun 10;27(17):2766.

12. Bekelman JE, Mitra N, Handorf EA, Uzzo RG, Hahn SA, Polsky D, et al. Effectiveness of Androgen-Deprivation Therapy and Radiotherapy for Older Men With Locally Advanced Prostate Cancer. J Clin Oncol. 2015 Jan 5;33(7):716–22.

13. Souhami L, Bae K, Pilepich M, Sandler H. Impact of the Duration of Adjuvant Hormonal Therapy in Patients With Locally Advanced Prostate Cancer Treated With Radiotherapy: A Secondary Analysis of RTOG 85-31. J Clin Oncol [Internet]. 2009 Mar 23 [cited 2020 Jan 24]; Available from: http://login.research4life.org/tacsgr1ascopubs_org/doi/pdf/10.1200/JCO.2008.17.4052

14. Stewart AJ, Scher HI, Chen M-H, McLeod DG, Carroll PR, Moul JW, et al. Prostate-Specific Antigen Nadir and Cancer-Specific Mortality Following Hormonal Therapy for Prostate-Specific Antigen Failure. J Clin Oncol. 2005 Sep 20;23(27):6556–60.

15. Kyei MY, Mensah EJ, Gepi-Attee S, Kwami D, Ampadu K, Asante E, et al. Outcomes after Radical Prostatectomy in Ghanaians: A Surgeon's Early Experience. ISRN Urol [Internet]. 2013 Apr 24 [cited 2020 Feb 14];2013. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3655646/

16. Bello JO. Predictors of survival outcomes in native sub Saharan black men newly diagnosed with metastatic prostate cancer. BMC Urol. 2017 May 30;17(1):39.

17. Mutua K, Pertet AM, Otieno C. Cultural factors associated with the intent to be screened for prostate cancer among adult men in a rural Kenyan community. BMC Public Health. 2017 Nov 1;17(1):1–8.

18. Wasike RW, Magoha G a. O. Descriptive case series of patients presenting with cancer of the prostate and their management at Kenyatta National Hospital, Nairobi. East Afr Med J. 2007 Sep;84(9 Suppl):S31-35.

19. Demark-Wahnefried W, Moyad MM. Dietary intervention in the management of prostate cancer: Curr Opin Urol. 2007 May;17(3):168–74.

20. Vidal AC, Howard LE, Sun SX, Cooperberg MR, Kane CJ, Aronson WJ, et al. Obesity and prostate cancer-specific mortality after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database. Prostate Cancer Prostatic Dis. 2017 Mar;20(1):72–8.

21. Moreira DM, Aronson WJ, Terris MK, Kane CJ, Amling CL, Cooperberg MR, et al. Cigarette smoking is associated with an increased risk of biochemical disease recurrence, metastasis, castration-resistant prostate cancer, and mortality after radical prostatectomy: results from the SEARCH database. Cancer. 2014 Jan 15;120(2):197–204.

22. Cancer Statistics Review, 1975-2013 - Previous Version - SEER Cancer Statistics Review [Internet]. SEER. [cited 2020 Jan 24]. Available from: https://seer.cancer.gov/archive/csr/1975_2013/index.html

23. Wu I, Modlin CS. Disparities in prostate cancer in African American men: what primary care physicians can do. Cleve Clin J Med. 2012 May;79(5):313–20.

24. Hosain GMM, Sanderson M, Du XL, Chan W, Strom SS. RACIAL/ETHNIC DIFFERENCES IN PREDICTORS OF PSA SCREENING IN A TRI-ETHNIC POPULATION. Cent Eur J Public Health. 2011 Mar;19(1):30–4.

25. Cancer of the Prostate - Cancer Stat Facts [Internet]. SEER. [cited 2020 Jan 24]. Available from: https://seer.cancer.gov/statfacts/html/prost.html

26. Ferrís-i-Tortajada J, García-i-Castell J, Berbel-Tornero O, Ortega-García JA. Factores de riesgo constitucionales en el cáncer de próstata. Actas Urol Esp. 2011 May 1;35(5):282–8.

27. Diallo Y. Metastatic Prostate Cancer: Clinical Aspects and Therapeutic Management in the Region of Thies Senegal. 8(224):6.

28. Amégbor K, Yao Seddoh T, Tengué K, Songne-Gnamkoulamba B, Napo-Koura G, James K. [Epidemiology and histopronostic of prostatic cancer in Togo: about 202 cases diagnosed at the laboratory of pathology of the Tokoin teaching hospital of Lome]. Progres En Urol J Assoc Francaise Urol Soc Francaise Urol. 2009 Feb;19(2):112–5.

29. Sequeira T, Ferreira PL, Teixeira J, Peres I, Oliveira J, Silveira A. Patient-Reported Outcomes in Prostate Cancer: Prospective Changes Analysis for Prognosis Prediction. J Cancer Ther. 2015;06(15):1238–48.

30. Global patterns of prostate cancer incidence, aggressiveness, and mortality in men of african descent. - PubMed - NCBI [Internet]. [cited 2020 Feb 10]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23476788

31. Jalloh. Prostate Cancer in Sub Saharan Africa. J Nephrol Urol Res [Internet]. 2013 [cited 2020 Feb 10]; Available from: http://www.synergypublishers.com/downloads/jnurv1n1a4/

32. Klotz L, O'Callaghan C, Ding K, Toren P, Dearnaley D, Higano CS, et al. Nadir Testosterone Within First Year of Androgen-Deprivation Therapy (ADT) Predicts for Time to Castration-Resistant Progression: A Secondary Analysis of the PR-7 Trial of Intermittent Versus Continuous ADT. J Clin Oncol. 2015 Apr 1;33(10):1151–6.

33. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, Santis MD, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2017 Apr 1;71(4):618–29.

34. Active Surveillance Has Become Standard Care for Men With Low-Risk Localized Prostate Cancer - The ASCO Post [Internet]. [cited 2020 Jan 24]. Available from: https://www.ascopost.com/issues/april-25-2016/active-surveillance-has-become-standard-care-for-men-with-low-risk-localized-prostate-cancer/?utm_source=TrendMD&utm_medium=cpc&utm_campaign=Prostate_Cancer_TrendMD_0

35. Dijkstra S, Witjes WPJ, Roos EPM, Vijverberg PLM, Geboers ADH, Bruins JL, et al. The AVOCAT study: Bicalutamide monotherapy versus combined bicalutamide plus dutasteride therapy for patients with locally advanced or metastatic carcinoma of the prostate-a long-term follow-up comparison and quality of life analysis. SpringerPlus. 2016;5:653.

36. Dal Pra A, Cury FL, Souhami L. Combining radiation therapy and androgen deprivation for localized prostate cancer—a critical review. Curr Oncol. 2010 Oct;17(5):28–38.

37. Jones CU, Hunt D, McGowan DG, Amin MB, Chetner MP, Bruner DW, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med. 2011 Jul 14;365(2):107–18.

38. Jones CU, Hunt D, McGowan DG, Amin MB, Chetner MP, Bruner DW, et al. Radiotherapy and Short-Term Androgen Deprivation for Localized Prostate Cancer [Internet]. http://dx.doi.org/10.1056/NEJMoa1012348. 2011 [cited 2020 Jan 24]. Available from: https://www.nejm.org/doi/10.1056/NEJMoa1012348?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dwww.ncbi.nlm.nih.gov

39. Denham JW, Steigler A, Lamb DS, Joseph D, Turner S, Matthews J, et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. Lancet Oncol. 2011 May 1;12(5):451–9.

40. Crawford ED, Eisenberger MA, McLeod DG, Spaulding JT, Benson R, Dorr FA, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. N Engl J Med. 1989 Aug 17;321(7):419–24.

41. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004 Oct 7;351(15):1502–12.

42. Koo KC, Park SU, Kim KH, Rha KH, Hong SJ, Yang SC, et al. Predictors of survival in prostate cancer patients with bone metastasis and extremely high prostate-specific antigen levels. Prostate Int. 2015 Mar;3(1):10–5.

43. Sharifi N, Dahut WL, Steinberg SM, Figg WD, Tarassoff C, Arlen P, et al. A retrospective study of the time to clinical endpoints for advanced prostate cancer. BJU Int. 2005;96(7):985–9.

44. Dayyani F, Gallick GE, Logothetis CJ, Corn PG. Novel Therapies for Metastatic Castrate-Resistant Prostate Cancer. JNCI J Natl Cancer Inst. 2011 Nov 16;103(22):1665–75.

45. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010 Jul 29;363(5):411–22.

46. Harshman LC, Chen Y-H, Liu G, Carducci MA, Jarrard D, Dreicer R, et al. Seven-Month Prostate-Specific Antigen Is Prognostic in Metastatic Hormone-Sensitive Prostate Cancer Treated With Androgen Deprivation With or Without Docetaxel. J Clin Oncol Off J Am Soc Clin Oncol. 2018 01;36(4):376–82.

47. Wu Y, Kwok Y, Mirmiran A, Goloubeva O, Mannuel H, Dawson N, et al. Weekly paclitaxel (P) with concurrent external beam radiation (EBRT) and androgen deprivation therapy (ADT) in high-risk prostate cancer (PC) patients with or without prior prostatectomy (RP). J Clin Oncol. 2009 May 20;27(15_suppl):5122–5122.

48. Nørgaard M, Jensen AØ, Jacobsen JB, Cetin K, Fryzek JP, Sørensen HT. Skeletal Related Events, Bone Metastasis and Survival of Prostate Cancer: A Population Based Cohort Study in Denmark (1999 to 2007). J Urol. 2010 Jul 1;184(1):162–7.

49. Harris WP, Mostaghel EA, Nelson PS, Montgomery B. Androgen deprivation therapy: progress in understanding mechanisms of resistance and optimizing androgen depletion. Nat Clin Pract Urol. 2009 Feb;6(2):76–85.

50. Gravis G, Fizazi K, Joly F, Oudard S, Priou F, Latorzeff I, et al. PSA response and early PSA progression evaluated in patients randomized in a phase III trial comparing androgen-

deprivation therapy (ADT) plus docetaxel versus ADT alone in hormone-naive metastatic prostate cancer (GETUG-AFU 15/0403). J Clin Oncol. 2011 Mar 1;29(7_suppl):10–10.

51. Kim JK, Jeong CW, Ku JH, Kim HH, Kwak C. Prostate specific antigen (PSA) persistence 6 weeks after radical prostatectomy and pelvic lymph node dissection as predictive factor of radiographic progression in node-positive prostate cancer patients. J Cancer. 2019 May 21;10(10):2237–42.

52. Shulman Michael J., Benaim Elie A. The natural history of androgen independent prostate cancer. J Urol. 2004 Jul 1;172(1):141–5.

53. Roach M, Bae K, Speight J, Wolkov HB, Rubin P, Lee RJ, et al. Short-Term Neoadjuvant Androgen Deprivation Therapy and External-Beam Radiotherapy for Locally Advanced Prostate Cancer: Long-Term Results of RTOG 8610. J Clin Oncol. 2008 Feb 1;26(4):585–91.

54. Bubley GJ, Carducci M, Dahut W, Dawson N, Daliani D, Eisenberger M, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol Off J Am Soc Clin Oncol. 1999 Nov;17(11):3461–7.

55. Berglund RK, Tangen CM, Powell IJ, Lowe BA, Haas GP, Carroll PR, et al.Ten-year follow-up of neoadjuvant therapy with goserelin acetate and flutamide prior to radical prostatectomy for clinical t3 and t4 prostate cancer: update on southwest oncology group study 9109. urology [internet]. 2012 mar [cited 2020 mar 31];79(3). available from: https://www.ncbi.nlm.nih.gov/pmc/articles/pmc3839235/

56. Harshman LC, Chen Y-H, Liu G, Carducci MA, Jarrard D, Dreicer R, et al. Seven-Month Prostate-Specific Antigen Is Prognostic in Metastatic Hormone-Sensitive Prostate Cancer Treated With Androgen Deprivation With or Without Docetaxel. J Clin Oncol. 2017 Dec 20;36(4):376–82.

57. Boccardo F, Barichello M, Battaglia M, Carmignani G, Comeri G, Ferraris V, et al. Bicalutamide Monotherapy versus Flutamide plus Goserelin in Prostate Cancer: Updated Results of a Multicentric Trial. Eur Urol. 2002 Nov 1;42(5):481–90.

58. Hussain M, Tangen CM, Higano C, Schelhammer PF, Faulkner J, Crawford ED, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). J Clin Oncol Off J Am Soc Clin Oncol. 2006 Aug 20;24(24):3984–90.

59. Liede A, Hallett DC, Hope K, Graham A, Arellano J, Shahinian VB. International survey of androgen deprivation therapy (ADT) for non-metastatic prostate cancer in 19 countries. ESMO Open [Internet]. 2016 Mar 18 [cited 2020 Feb 10];1(2). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5070274/

60. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? Indian J Psychol Med. 2013;35(2):121.

61. Rebbeck TR, Devesa SS, Chang B-L, Bunker CH, Cheng I, Cooney K, et al. Global patterns of prostate cancer incidence, aggressiveness, and mortality in men of african descent. Prostate Cancer. 2013;2013:560857.

62. Liede A, Hallett DC, Hope K, Graham A, Arellano J, Shahinian VB. International survey of androgen deprivation therapy (ADT) for non-metastatic prostate cancer in 19 countries. ESMO Open. 2016;1(2):e000040.

63. Huggins C. Studies on Prostatic Cancer. Cancer Res. :6.

64. Sharifi N, Dahut WL, Steinberg SM, Figg WD, Tarassoff C, Arlen P, et al. A retrospective study of the time to clinical endpoints for advanced prostate cancer. BJU Int. 2005 Nov;96(7):985–9.

65. Hori S, Jabbar T, Kachroo N, Vasconcelos JC, Robson CN, Gnanapragasam VJ. Outcomes and predictive factors for biochemical relapse following primary androgen deprivation

therapy in men with bone scan negative prostate cancer. J Cancer Res Clin Oncol. 2011 Feb 1;137(2):235–41.

66. Xiao H, Tan F, Goovaerts P, Adunlin G, Ali AA, Huang Y, et al. Factors Associated with Time-to-Treatment of Prostate Cancer in Florida. J Health Care Poor Underserved. 2013 Nov;24(4 0):132–46.

67. Wasike RW, Magoha G a. O. Descriptive case series of patients presenting with cancer of the prostate and their management at Kenyatta National Hospital, Nairobi. East Afr Med J. 2007 Sep;84(9 Suppl):S31-35.

68. Zhang G-M, Zhu Y, Chen H-T, Han C-T, Liu F, Xu J-F, et al. Association Between the Body Mass Index and Prostate Cancer at Biopsy is Modified by Genetic Risk: A Cross-Sectional Analysis in China. Medicine (Baltimore). 2015 Oct;94(42):e1603.

69. Ji G, Song G, Huang C, He S, Zhou L. Rapidly decreasing level of prostate-specific antigen during initial androgen deprivation therapy is a risk factor for early progression to castration-resistant prostate cancer: A retrospective study. Medicine (Baltimore). 2017 Sep;96(36):e7823.

70. Droz J-P, Balducci L, Bolla M, Emberton M, Fitzpatrick JM, Joniau S, et al. Management of prostate cancer in older men: recommendations of a working group of the International Society of Geriatric Oncology. BJU Int. 2010;106(4):462–9.

71. Lin T-T, Chen Y-H, Wu Y-P, Chen S-Z, Li X-D, Lin Y-Z, et al. Risk factors for progression to castration-resistant prostate cancer in metastatic prostate cancer patients. J Cancer. 2019 Sep 7;10(22):5608–13.

72. Use of Human Prostate-specific Antigen in Monitoring Prostate Cancer | Cancer Research [Internet]. [cited 2020 Nov 17]. Available from: https://cancerres.aacrjournals.org/content/41/10/3874.long

73. van den Bergh RCN, Albertse PC, Bangma CH, Freedlan SJ, Graefen M, Vickers A, et al. Timing of Curative Treatment for Prostate Cancer: A Systematic Review. Eur Urol. 2013 Aug;64(2):204–15.

74. Sureka SK, Maheshwari R, Agnihotri S, Mitash N, Ahmad S, Mandhani A. Predictors for progression of metastatic prostate cancer to castration-resistant prostate cancer in Indians. Indian J Med Res. 2016 May;143(Suppl 1):S68–73.

75. Elishmereni M, Kheifetz Y, Shukrun I, Bevan GH, Nandy D, McKenzie KM, et al. Predicting time to castration resistance in hormone sensitive prostate cancer by a personalization algorithm based on a mechanistic model integrating patient data: Predictive Algorithm for ADT Failure in HSPC. The Prostate. 2016 Jan;76(1):48–57.

76. Tamada S, Iguchi T, Kato M, Asakawa J, Kita K, Yasuda S, et al. Time to progression to castration-resistant prostate cancer after commencing combined androgen blockade for advanced hormone-sensitive prostate cancer. Oncotarget. 2018 Dec 11;9(97):36966–74.

77. Warde P, Mason M, Ding K, Kirkbride P, Brundage M, Cowan R, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet. 2011 Dec 17;378(9809):2104–11.

78. Souhami L, Bae K, Pilepich M, Sandler H. Impact of the duration of adjuvant hormonal therapy in patients with locally advanced prostate cancer treated with radiotherapy: a secondary analysis of RTOG 85-31. J Clin Oncol Off J Am Soc Clin Oncol. 2009 May 1;27(13):2137–43.

79. Mottet N, Peneau M, Mazeron J-J, Molinie V, Richaud P. Addition of Radiotherapy to Long-Term Androgen Deprivation in Locally Advanced Prostate Cancer: An Open Randomised Phase 3 Trial. Eur Urol. 2012 Aug 1;62(2):213–9.

80. De Dosso S, Berthold DR. Docetaxel in the management of prostate cancer: current standard of care and future directions. Expert Opin Pharmacother. 2008 Aug;9(11):1969–79.

81. Juárez Soto A, Caballero Cobos R, Campanario Pérez R, Saiz Marenco R, Herrera Torres M, Gamaza Martínez R, et al. [Abiraterone in castration resistant prostate cancer.]. Arch Esp Urol. 2018 Sep;71(8):651–63.

82. Singh P, Agrawal T, Yadav S, Nayak B, Seth A, Dogra PN. A comparative study of the effects of medical versus surgical androgen deprivation therapy on health-related quality of life in patients with metastatic carcinoma prostate. Indian J Cancer. 2018 Apr 1;55(2):148.

83. Bolla M, de Reijke TM, Van Tienhoven G, Van den Bergh ACM, Oddens J, Poortmans PMP, et al. Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med. 2009 Jun 11;360(24):2516–27.

84. Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff R-O, Storme G, et al. Improved Survival in Patients with Locally Advanced Prostate Cancer Treated with Radiotherapy and Goserelin [Internet]. http://dx.doi.org/10.1056/NEJM199707313370502. Massachusetts Medical Society; 2009 [cited 2020 Nov 19]. Available from: https://www.nejm.org/doi/10.1056/NEJM199707313370502

85. Bolla M. Re: High-risk Prostate Cancer Treated with Pelvic Radiotherapy and 36 Versus 18 Months of Androgen Blockade: Results of a Phase III Randomized Study [Abstract 3]. Eur Urol. 2013 Sep 1;64(3):513.

86. Kitagawa Y, Ueno S, Izumi K, Mizokami A, Hinotsu S, Akaza H, et al. Nadir prostate-specific antigen (PSA) level and time to PSA nadir following primary androgen deprivation therapy as independent prognostic factors in a Japanese large-scale prospective cohort study (J-CaP). J Cancer Res Clin Oncol. 2014 Apr 1;140(4):673–9.

87. Hah YS, Lee JS, Rha KH, Hong SJ, Chung BH, Koo KC. Effect of Prior Local Treatment and Prostate-Specific Antigen Kinetics during Androgen-Deprivation Therapy on the Survival of Castration-Resistant Prostate Cancer. Sci Rep. 2019 Aug 15;9(1):11899.

88. Dai D, Han S, Li L, Guo Y, Wei Y, Jin H, et al. Anemia is associated with poor outcomes of metastatic castration-resistant prostate cancer, a systematic review and meta-analysis. :10.

89. Morote J, Esquena S, Abascal JM, Trilla E, Cecchini L, Raventós CX, et al. Usefulness of prostate-specific antigen nadir as predictor of androgen-independent progression of metastatic prostate cancer. Int J Biol Markers. 2005 Dec;20(4):209–16.

90. Nabid A, Garant M-P, Martin A-G, Bahary J-P, Lemaire C, Vass S, et al. Duration of androgen deprivation therapy in high risk prostate cancer: Final results of a randomized phase III trial. J Clin Oncol. 2017 May 20;35(15_suppl):5008–5008.

91. Sasaki T, Onishi T, Hoshina A. Nadir PSA level and time to PSA nadir following primary androgen deprivation therapy are the early survival predictors for prostate cancer patients with bone metastasis. Prostate Cancer Prostatic Dis. 2011 Sep;14(3):248–52.

92. Crawford ED, Petrylak D, Sartor O. Navigating the evolving therapeutic landscape in advanced prostate cancer. Urol Oncol. 2017;35S:S1–13.

93. Lu-Yao GL, Albertsen PC, Moore DF, Shih W, Lin Y, DiPaola RS, et al. Fifteen-year survival outcomes following primary androgen-deprivation therapy for localized prostate cancer. JAMA Intern Med. 2014 Sep;174(9):1460–7.

APPENDICES

Appendix 1. Data collection tool

Patient details (file number) Study number…….

SOCIODEMOGRAPHIC CHARACTERISTICS

1. **AGE (in completed years)**
2. **MARITAL STATUS**

- ☐ SINGLE [0]
- ☐ MARRIED [1]
- ☐ SEPARATED/DIVORCED [2]
- ☐ WIDOWED [3]

3 EMPLOYMENT

- ☐ UNEMPLOYED [0]
- ☐ SELF EMPLOYED [1]
- ☐ EMPLOYED [2]
- ☐ RETIRED [3]

4 LEVEL OF EDUCATION

- ☐ INFORMAL [0]
- ☐ PRIMARY [1]
- ☐ SECONDARY[2]
- ☐ TERTIARY[3]

5 CIGARETTE SMOKING

- ☐ NO[0]
- ☐ YES[1]

6 ALCOHOL CONSUMPTION

- ☐ NO [0]
- ☐ YES [1]

7 WEIGHT(KG)

8 BMI(kg/m^2)

BASELINE LABORATORY INVESTIGATIONS

9 NEUTROPHIL COUNT ……..

10 HAEMOGLOBIN (g/dL) ……..

11 PLATELET COUNT (cells/µL) ……

12 PROSTATE SPECIFIC ANTIGEN

□ <10ng/dL[1] □ 10-20 ng/dL[2] □ >20ng/dL[3]

PATHOLOGICAL PROFILE

13 TUMOUR STAGING

□ T1a-T2a[1] □ T3a[3]

□ T2b-T2c[2] □ T3b-T4[4]

14 GRADING

□ GX[0] □ G2-GLEASON 5-6[2]

□ G1-GLEASON 2-4[1] □ G3-GLEASON 7-10[3]

15 LYMPH NODE

□ NX[0] □ NO[1] □ N1[2]

16 METASTASIS

□ MX[0] □ MO[1] □ M1[2]

PROSTATE CANCER MANAGEMENT

17 FIRST TREATMENT

□ ORCHIDECTOMY

- MEDICAL ADT
    - GOSERELIN [1.1]
    - BICALUTAMIDE [1.2]
    - OTHER ADDITIONAL DRUGS[1.3]
- PROSTATECTOMY WITH ADT
- RADIOTHERAPY WITH ADT

18 ADMINISTRATION OF ADT

- NEOADJUVANT
- ADJUVANT
- CONCOMITANT WITH RT

19 TIME TO BIOCHEMICAL RECCURENCE (MONTHS)…….

20 SECOND TREATMENT

- **YES**
- **NO**

21 RISK STRATIFICATION FOR SECOND TREATMENT

- LOW RISK[1]
- HIGH RISK [3]
- INTERMEDIATE RISK [2]
- VERY HIGH RISK [4]

22 ANDROGEN DEPRIVATION THERAPY

- ORCHIDECTOMY [1]
- MEDICAL 2.]

- GOSERELIN [2.1]
- BICALUTAMIDE [2.2]

23 DURATION OF ADT (MONTHS)……..

24 PROSTATE SPECIFIC ANTIGEN (POST ADT)

.....

□ <10ng/dL[1] □ 10-20 ng/dL[2] □ >20ng/dL[3]

25 OUTCOME

□ CASTRATE RESISTANT PROSTATE CANCER [1]

□ OVERALL SURVIVAL [2]

□ PROGRESSION FREE SURVIVAL [3]