UNIVERSITY of RWANDA

COLLEGE OF MEDICINE & HEALTH SCIENCES

SCHOOL OF MEDICINE & PHARMACY

DEPARTMENT OF SURGERY

# PRACTICAL APPROACH TO ADVANCED PROSTATE CANCER MANAGEMENT IN COMMUNITY IN RWANDA.

*Dissertation submitted in partial fulfillment of the requirements for the award of the degree of Master of Medicine in Urology of the University of Rwanda*

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Kigali, May 31st, 2019

## DECLARATION

I, Dr. NZEYIMANA N. Innocent, hereby declare to the best of my knowledge that this dissertation: **"Practical approach to advanced prostate cancer management in community in Rwanda"** and its entire content have never been submitted to any institution of higher learning for any academic award.

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**ACKNOWLEDGEMENTS**

*I would like to thank everyone who, through any support, helped me during my residency program: my lecturers, my fellow colleagues, and all great persons; I unconditionally met.*

*My inestimable gratitude goes to Prof. Emile Rwamasirabo, for the supervision, guidance and tremendous support to accomplish this work.*

*I can't forget the irrepressible support of Dr. Rusatira J. Christophe, especially on the analysis part. His expertise made this work possible.*

*My special recognitions to the department of surgery of the University of Rwanda for their commitment to improve surgical training in Rwanda.*

*Thank you to my family and friends for their love and support.*

*May God bless you!*

**DEDICATION**

*To my beloved wife:*
*Clemence Muziranenge,*

*To my beloved Parents:*
*Busoro & Uwimana,*

*To my Children:*
*Mboneza I Lana & Mboneza G Layan*

*To my siblings,*

*To my teachers,*

*To my Friends*

I dedicate this humble work

*NZEYIMANA N. INNOCENT*

## LIST OF ABBREVIATIONS

**ADT:** Androgen deprivation therapy

**BPH:** Benign prostatic hypertrophy

**BSO**: Bilateral subcapsular orchidectomy

**CBHI**: Community based health insurance

**CHUK**: Centre Hospitalier Universitaire de Kigali

**COHSASA:** Council for Health Service acrreditation of Southern Africa

**DRE:** Digital rectal examination

**KFH**: King Faisal Hospital

**LMIC:** Low and Middle Income Countries

**LUTS:** Lower urinary tract symptoms

**NCCN:** National Comprehensive Cancer Network

**PSA**: Prostatic specific antigen

**RMH**: Rwanda Military Hospital

**RP**: Radical prostatectomy

**RRP**: Retropubic radical prostatectomy

**SAPCS**: Southern African Prostate Cancer Study

**SD:** Standard deviation

**TRUS:** Trans-rectal Ultrasound

**TURP**: Transurethral resection of the prostate

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## ABSTRACT

**Background**: Prostate cancer is the second most common cancer in men and 6th leading cause of mortality. If not recognized early, patients with advanced disease can get debilitating complications such as spinal cord compression and fractures which can otherwise be prevented by early androgen deprivation therapy. Our research intends to contribute more knowledge about the practical approach to the management of advanced prostate cancer in the community for the prevention of debilitating complications.

**Objectives:** To determine clinical parameters and PSA threshold for effective clinical diagnosis of advanced prostate cancer in the community.
**Methods**: A prospective cross-sectional observational study was conducted at three referral hospitals in Kigali on patients who presented with clinical suspicion of advanced prostate cancer from October 2018 to February 2019. All patients underwent prostate biopsy as well as metastatic work up, for those who were eligible. Statistical analysis was done using STATA 14.2.

**Results:** During the study period, we enrolled 114 patients. The median age was 70 years (IQR 65-79 years) and mean (±SD) age was 71 ± 9 years; 75 (65.8 %) patients were enrolled from CHUK, 35 (30.7%) from RMH and 4 (3.5%) from KFH. In total 14 (12.3%) patients and 100 (87.7%) patients were found to have benign disease and cancer respectively. Among those who had cancer, 85 (85%) had advanced prostate cancer (locally advanced and metastatic); All the 10.5% of patients with family history of prostate cancer were positive (both first and second level) however, 34.2% of respondents didn't remember about family history of prostate cancer; 75.5% were unemployed or not working because of the illness; 110/114 (96.5%) were symptomatic at presentation while 3/4 were discovered through systematic screening. Common presenting symptoms were: lower urinary tract symptoms (80.7%), back pain (54.4%) and urine retention (36.8%). All patients with paraplegia had advanced cancer and all who reported weight loss had cancer. The mean duration of symptoms before consultation was 14.2 months. On DRE examination, 102/114 patients were found to have abnormal prostate with at least one palpable nodule and 75.3% had multinodular prostate which involved both lobes in 71 (70.3%) patients. Abnormal digital rectal examination (DRE) was a strong risk factor for both cancer and advanced disease. Prostate cancer was found in 92.2% of those with abnormal DRE compared to 41.7% in those with normal DRE (p=0.001). Also, cancer was significantly found in 96.1% of those with multinodular prostate (p=0.02) and had high odds (OR: 14.6; CI 3.41-62.25) of having advanced prostate cancer (p<0.001). The mean (±SD) PSA was 643.3 ± 1829.8 ng/ml and the median (range) was 100 ng/ml (9.05-10,000ng/ml) for the whole study population. PSA levels of patients with histologically confirmed benign disease had a mean of 35.8ng/ml (9.05 - 98.5ng/ml) and none had PSA> 100ng/ml. Patients with localized prostate cancer had mean PSA of 66.3ng/ml while those with advanced prostate cancer had mean PSA of 841.4 ng/ml respectively. All patients with PSA of 100 ng/ml or above had cancer and advanced prostate cancer. 49/85 that had complete metastatic workup had bone metastasis; 77.5% had back pain (p=0.001) and 47/49 had abnormal DRE.

**Conclusion:** The results show that there is a significant correlation between back pain and bone metastasis in patients with prostate cancer. All patients with abnormal DRE and PSA above 100 ng/ml had advanced prostate cancer. There is correlation between back pain, abnormal DRE and PSA above 100 ng/ml with advanced cancer and bone metastasis.

# CHAPTER I: INTRODUCTION

## 1.1 Background

Prostate cancer is the malignant transformation of the prostate gland. It is the second most common solid malignancies in men (1). One of the important determinants of treatment options and prognosis is the timing of presentation. If prostate cancer is discovered in an early stage the patient may maintain a normal life expectancy (2).

Prostate cancer is the most common cancer in men in the USA with approximately 189,890 new cases diagnosed and more than 26,000 deaths in 2016(2). In Europe, prostate cancer is among the top four most common cancers according to a recent study done in 40 countries by Ferlay et al. This study found 450,000 new cases of prostate cancer in 2018 (3). Siegel et al studied the incidence variation by race and found that African-Americans have a 59% higher incidence, the race adjusted incidence was therefore 152 per 100.000 men per year (2). In Africa, there is generally no PSA screening policy or National cancer registries. Adeloye estimated the incidence for Africa at 13.3/100,000 on meta-analysis study with data published from 16 African countries (4). Ferlay found the incidence worldwide to be 10.5/100,000, 111.6/ 100,000 in Australia, 97.2/100,000 in North America, and 4.5/100,000 in Eastern and South central Asia (5). Prostate cancer is responsible for 10% of cancer related death in the US making it the second leading cause (6).

Different risk factors contribute to the prognosis including time of presentation, social economic status and race. In terms of race, black men have a higher risk of advanced disease at presentation leading to few curative options (7).Forbes et al studied causes for presentation delay and found several significant psychological contributors such as embarrassment, concern about what the doctor might find, difficulty scheduling doctor appointments and worry about wasting the doctor's time (8).

In Rwanda, there are no published studies available on prostate cancer. Current observations, however, suggest that the incidence of prostate cancer is increasing. While this may in part be due to increasing prostatic specific antigen (PSA) test availability and longer life expectancy, patients presenting with the disease are often in later states with advanced disease. This limits treatment options and reduces management with curative intent. In addition to poor awareness,

delayed recognition and late pathological confirmation contribute to late presentation and preventable complications. The level of awareness is low across Africa with one study from Benin suggesting the mean knowledge about risk factors, symptoms and treatment to be as low as 3.4/10 (9). Meanwhile, early detection and improved knowledge has been found to contribute to the reduction of mortality rate from prostate cancer (10).

Prostate cancer is usually indolent which increases the risk of late presentation. It is suspected when PSA levels are raised and/or digital rectal examination (DRE) is abnormal or symptoms suggestive of metastasis. However, symptoms often do not appear until an advanced stage. Delayed presentation results in late diagnosis which increases patient risk of complications such as urine retention, spinal cord compression and pathological fractures. While definitive diagnosis is only possible with biopsy, a study done in Ghana found that PSA levels above 50 ng/ml and abnormal DRE correlate with positive biopsy results (11).
The current research intends to contribute more knowledge about the practical approach to advanced prostate cancer in the community.

## 1.2 Definitions

*Localized prostate cancer*: disease confined to the prostate gland

*Advanced prostate cancer*: Stage of the disease in which the tumor has already spread beyond the organ. It is further subdivided in two distinct categories

-*Locally advanced prostate cancer*: cancer which has infiltrated the surrounding tissues, involvement of seminal vesicles or extension to adjacent organs with inclusion of those patients with regional lymph nodes without distant metastasis (T3-4N+-M0).

-*Metastatic prostate cancer*: cancer which has disseminated to the bones, LNs beyond pelvis or distant organs

- *Community:* In the study, community refers to Health Centers, District Hospitals, and Provincial Hospitals where specialists care is not easily available and where most of patients present with late complications due advanced prostate cancer such as pathological fractures, spinal cord compression, acute urine retention.

## 1.3 Problem statement

Most patients with prostate cancer in Rwanda present initially to community healthcare facility. These patients must then be transferred to referral hospitals for investigations and specialized management as histopathological confirmation is required for definitive diagnosis. Currently, however, urologists, pathologists and oncologist can only be found in the capital city, Kigali (Figure 1.1). Late initial presentation and the accumulation of delays in reaching referral hospitals leads to debilitating complications such as pathological fractures and spinal cord compression. Early initiation of androgen deprivation therapy is an effective way of preventing complications and an accessible treatment strategy that can be implemented at community health facilities.

**Figure 1.1. Map of Rwanda depicting the location of the 3 research sites**


## *1.4* Justification of the study

To our knowledge there are no published studies on practical management of advanced prostate cancer in the community in Rwanda. There is observational evidence that the numbers of advanced prostate cancer and associated complications are increasing at the community level. The current referral system for transferring these patients to referral hospitals increases delays and often prevents early management. Therefore, there is a need to develop guidelines for

practitioners in the community to define clear diagnostic tools that will guide them toward early management of advanced prostate cancer to prevent complications.

## *1.5* Hypothesis

Advanced prostate cancer can be accurately diagnosed and managed at the community level in Rwanda by appropriate clinical assessment and PSA levels.

## 1.6 Research question

What clinical parameters can guide clinicians at the community level to establish an accurate clinical diagnosis and initiate of early androgen deprivation therapy in advanced prostate cancer patients to reduce debilitating complications?

## 1.7 Study Objectives

### *1.7.1 General objective*

To determine the practical approach to advanced prostate cancer in the community in Rwanda.

### *1.7.2. Specific objectives*

- To determine the demographic features of patients with advanced prostate cancer
- To determine the most common presentations of patients with advanced prostate cancer
- To define the clinical stage of prostate cancer at presentation of patients
- To correlate the clinical presentation with histology results
- To determine clinical parameters and PSA threshold for effective diagnosis of advanced prostate cancer in the community
- To determine the most common complications

# CHAPTER II: LITTERATURE REVIEW

## 2.1 Worldwide epidemiology of advanced prostate cancer

The epidemiology of prostate cancer varies across the world. In general, it is the second most common cancer in men (12) accounting for 9.7% of all cancers diagnoses in men (13). The incidence is highest in western countries and lowest Asian countries (14). The variations in incidence may be due to deficiency in cancer registration, inadequacy of health care systems, genetic predispositions and environmental differences (15)(16). PSA screening is an effective tool in the treatment of prostate cancer but is somewhat controversial because of overtreatment of low-grade tumors. PSA screening has led to increased diagnosis and identification of prostate cancer, but, it should be done on an individualized basis with the decision made between patients and physician (17). The risk of prostate cancer also increases with age (16)(18).

In Africa, the incidence varies in different regions. It is lowest in West Africa (4.7-19.8/ 100.000 man-years), intermediate in Southern Africa (14.3-21.8) and highest in East Africa (10.7-38.1) (19). The prevalence in Nigeria ranges from 300 - 1046/100,000 while it is 1087/100,000 in Kenya (20)(21). These numbers do, however, vary based on study as findings using Nairobi cancer registry have found an incidence of 40.6/100,000 in Kenya (22). Methods et al in their study done on 330 cancer patients attending a cancer institute in Tanzania, found that the difference of incidence is due to different level of awareness, education, accessibility to health care and health seeking behaviors in Africans (23). There is limited literature on prostate cancer in Rwanda. The most recent numbers suggest by the GLOBOCAN 2012 reports the estimated age-standardized incidence to be 25.6 /100,000 while the estimated age-standardized death rate is 21.7/100,000 (24).

## 2.2 Clinical presentation of patients with prostate cancer

Patients with advanced prostate cancer may be asymptomatic or symptomatic. They may present with signs and symptoms of bladder outlet obstruction, back pain, or neurological complications due to spinal metastasis. These symptoms are common amongst the elderly , a population at increased risk of delays in seeking medical care (25). Clinically, prostate cancer is suspected when there is an abnormal prostate on DRE such as a hard, irregular, or nodular prostate and/or an increased PSA.

Prostate cancer is especially problematic in low income countries due to delayed presentation of patients. These delays may partly be explained by a lack of screening protocols and poor access to health facilities. Prostate cancer at a young age is more common in patients of the black race and is one of the risk factors for presentation at an advanced stage (7). The Southern African Prostate Cancer Study (SAPCS) done by Tindall et al on over 1000 participants with or without cancer, comparing prostate cancer in African- Americans and Black South-Africans found that 17.2% of African-Americans have a PSA- level of more than 20 ng/ml versus 83.2% of black South-Africans. Similarly, 17% African- Americans versus 36% Black South-Africans presented with a Gleason Score (GS) more than 7 (26).

In a study conducted by Okuku et al at the Uganda Cancer Institute involving 182 patients with histologically confirmed prostate cancer, 51.1% of patients had a PSA- level> 100 ng/ml and 66.7% of all the patients had a GS of 9 or 10 (27). In Nigeria a study done by Ikuerowo et al on men above 40 conducted during a community-based awareness program showed that the majority of the patients with prostate cancer presented with advanced disease (75%) where 26% had organ confined, 40% locally advanced and 35% metastatic disease (20). In Rwanda, an unpublished retrospective study carried out in a referral hospital revealed that 52.6% of the patients with prostate cancer were in the poorest prognostic GS grade groups of 4 and 5.

## 2.3 Clinical Criteria for advanced prostate cancer

The NCCN for Sub-Saharan Africa defines advanced prostate cancer as those having at least cT3 disease, GS >8, PSA > 20 ng/ml or evidence of metastasis on imaging studies (28).

The PSA value is an important predictor of disease progression and disease extent. In Korea, Jeet al observed that 21.8% of the patients with a PSA- level between 4-20 ng/ml had prostate cancer while 100% of those with a PSA- level > 100 ng/ml were diagnosed with prostate cancer beyond the prostate(29).In Kenya, Ojuka et al found that PSA of more than 100 ng/ml can predict bone metastasis (30).

DRE can be used to predict the extent of disease, but it has a low sensitivity and a lack of reproducibility. DRE performed by an experienced physician can be effective at predicting advanced prostate cancer but must performed in combination with other parameters especially in suspected organ-confined disease (31). A systematic review on the accuracy of DRE for diagnosing prostate cancer have found that DRE performed in general practice is accurate with a specificity of 90.7% and a positive predictive value of 42.3% (32). Seo et al examined 4967

Korean men above 40 who underwent prostate biopsies because of raised PSA or suspicious DRE and found that cancer was detected in 17% of those with normal DRE findings while it was detected in 33.4% in those with PSA between 4-9.9 ng/ml and suspicious DRE (33). Catalona also did a study on 6630 voluntary men over 50 and found that PSA detect more cancer than DRE (82% vs 55%) and that the detection rate increases when both methods were combined. The positive predictive value (PPV) was 32% for PSA and 21% for DRE(34)(35). Abnormal DRE was also found to significantly increase the detection rate (47.4% vs 23%) by Shim et al on 1369 men aged 45-79 years who visited the department of urology (36).

## 2.4 Efficacy of imaging in staging

Transrectal ultrasound (TRUS) can be used for diagnosis of advanced prostate cancer but has low sensitivity. Prostate cancer is found in 56.3% of patients with hypoechoic nodules on TRUS while mixed echogenicity and capsular distortion have detected cancer in 33.8% and 31.3% respectively (37).

Imaging modalities are used for the staging of prostate cancer. CT scan or MRI are used to assess lymph nodes and organ metastasis while bone scan using either MRI or CT-scan, Technetium-99 or Ga-PSMA-PET/CT are used to assess bone metastasis (38). Routine use of bone scan is not recommended but is necessary in those having a PSA- level> 20 ng/ml, GS 8 to 10 or T3 and T4 disease. Cross-sectional imaging for assessment of lymphadenopathies are essential in T3 and above disease. MRI has been the preferred imaging modality for many years, but its sensitivity is nowadays comparable to a CT- scan's. Currently bone scintigraphy is not available and the access to both CT and MRI are insufficient in Rwanda. However, CT-scan is more accessible and affordable compared to MRI.

## 2.5 Complications of advanced prostate cancer

Though prostate cancer is not generally an aggressive cancer, it can lead to debilitating complications and lower quality of life especially when diagnosed at late stages (39). There are many complications of untreated advanced prostate cancer including fractures, spinal cord compression, hypercalcemia, vertebra collapse, urinary tract obstruction, anaemia and severe pain (40)(41). Aside from lowering quality of life, these complications add a financial burden to the family (42). Saad et al studied the impact of skeletal related events (SREs) in patients with castrate resistant metastatic disease and found that SREs significantly decrease the health related quality of life in patients with spinal cord compression having the largest impact (43).

## 2.6 PSA and bone metastasis

High PSA level may predict presence of bone metastasis but doesn't necessarily correlate with survival (44)(45). Kamaleshwaram et al did a retrospective analysis of 322 consecutive prostate cancer patients subjected to bone scan and found that 70% of patients with positive bone scan had serum PSA >100 ng/ml while only 2% had PSA < 20ng/ml (46). Investigation for bone metastasis is indicated in patients with chronic back pain and if serum PSA is above 20 ng/ml (47). Pai et al from India found that all patients with positive bone scintigraphy had serum PSA > 20ng/ml on their study done on 72 patients with confirmed prostate cancer (48).

## 2.7 Management options in advanced prostate cancer in LIC

Advanced prostate cancer cannot be completely cured. All management options at later stages are intended to minimize disease progression or palliate symptoms. Options include androgen deprivation therapy (medical or surgical), salvage radiotherapy, hormone therapy and chemotherapy. Androgen deprivation therapy (ADT) is effective for those having non-castrate resistant prostate cancer, relieves symptoms, and improves the quality of life (49) despite its significant complications that are normally easier to manage (50). The increase in 5 years overall survival varies between 78-88% from different studies for patients treated with ADT for high risk or locally advanced disease (51). ADT has also been shown to decrease the rate of cord compression, decrease in rate of ureteral obstruction, decrease in extra skeletal metastasis and decrease in rate of pathologic fracture in patients with advanced disease (52). Studies have found no significant difference on survival between ADT alone and ADT combined with radiation therapy (53).

Alan So found that 50% of advanced prostate cancer patients experienced at least one skeletal related event (SRE) over a 2 years period if untreated (54). There are different options (with varying effects) of preventing complications in patients with advanced prostate cancer. David et al did a review on the effects of skeletal related events and found that bisphosphonates were effective in preventing complications and maintain quality of life (39). Many other drugs like second generation antihormonal drugs, such as abiraterone, as well as radiopharmaceuticals, such as Radium-223 dichloride, reduce SREs, bone pain and prolong survival while stereotactic radiation and radiosurgery can be used in case of oligometastatic prostate (38)(40). Supportive measures and lifestyle change (smoking cessation, moderate caffeine and alcohol, regular exercises), chemotherapy and human monoclonal antibody such as Denosumab also prevent and treat complications (50)(41)(54).

Medical castration with LHRH agonists/antagonists is as effective as surgical castration (bilateral orchidectomy) but medical therapy is more expensive which makes bilateral orchidectomy the practical modality of ADT in LMICs. However, the psychological barriers of bilateral subcapsular orchidectomy (BSO) are extensive for many patients especially in our setting where testicular prosthesis are not available.

## 2.7 Scarcity of specialized care in Lower- and Middle-Income Countries

In most of LMICs there is a lack of specialized human resources. For instance, general surgeon density in LMICs ranged from 0.13 to 1.57 per 100,000 population (55). Urologists and histopathologists are among the scarcest professionals. There is less than one pathologist per 500,000 people in Sub-Saharan Africa compared to one pathologist per 15,000 to 20,000 people in the United States (56).

In Rwanda, only 8 urologists and 6 histopathologists are available in the whole country. Furthermore, all work in 3 referral hospitals located in the capital city. It is difficult and expensive to access these services for many patients living in rural areas.

# CHAPTER III: METHODOLOGY

## 3.1 Study design

A cross-sectional observational study was conducted at three referral hospitals in Kigali between June 2018 and February 2019 to determine the most accurate parameters for clinical diagnosis of advanced cancer of the prostate in the community in Rwanda. Data were collected over a period of 6 months from September 2018 to February 2019.

## 3.2 Study setting

The study was conducted in the 3 urology units at King Faisal Hospital (KFH), Centre Hospitalier Universitaire de Kigali (CHUK) and Rwanda Military Hospital (RMH), Rwanda. KFH is a tertiary hospital accredited by COHSASA and has a capacity of 160 beds, CHUK contains 560 beds and RMH has 500 beds. All 3 centers run at least 4 urology clinics every week and 3 operating days. CHUK and RMH receive mostly patients referred from district hospitals. All patients presenting with urological complaints from all over the country are referred to those three urology units.

## 3.3. Study description

Selected patients presenting to one of the three participating hospitals with urology complaints were eligible for enrollment in the study. Patients presented to urologist through scheduled consultation, A & E, or upon referral from primary treating physician due to PSA > 20 ng/ml and/or signs of advanced prostate cancer such as back pain, lower limb paresthesia or paralysis, and weight loss. All PSA at the 3-study sites were done using Cobas® e411 analyzer machine manufactured by Hitachi. Electrochemiluminescence immunoassay and Roche diagnostic kit was used at all centers. Upon clinical suspicion of advanced prostate cancer, Patients were requested to sign a written consent after full explanation of the procedure and objective of the study. The enrolled patients underwent double sextant transrectal prostate core needle biopsy (TRUS guided at KFH and finger guided at CHUK and RMH) using G18or G22 x 25 cm BARD® MAX-CORE® disposable core biopsy instruments. The histopathological analysis was performed by general histopathologists and reports generated using the standard ISUP consensus 2014 which reports the number of received cores, number of positive cores, type of tumor, tumor volume on each core, presence or absence of perineural and lympho-vascular invasion, Gleason score and the prognostic grade group.

**Table 3 1. 2014 ISUP Gleason score and Gleason grade groups**(57)

| Gleason Grade group | Score | Definition |
|---|---|---|
| 1 | 3+3=6 | Only individual discrete well-formed glands |
| 2 | 3+4=7 | Predominantly well-formed glands with a lesser component of poorly/fused/cribriform glands |
| 3 | 4+3=7 | Predominantly poorly formed/fused/cribriform glands with a lesser component of well-formed glands |
| 4 | 5+3, 3+5, 4+4 (Gleason score 8) | Only poorly formed/fused/cribriform glands(>95%) or Predominantly well-formed glands and lesser component lacking glands or Predominantly lacking glands and a lesser component of well-formed glands |
| 5 | Gleason scores 9 and 10 | Lack of gland formation (or with necrosis) (>95%) with or without formed/fused /cribriform glands |

After positive biopsy for prostate cancer an MRI of the pelvis and lumbar spine or an abdomino-pelvic and thoraco-lumbar CT scan was requested for clinical staging. Preference was due to availability of imaging modality at the study hospital, lack of contra-indications, and affordability by patients.

A predesigned questionnaire was availed in all urology consultation rooms at all the study hospitals. After every consultation day the researcher collected all forms initiated by consulting doctors and updated them continuously throughout the work up process of the enrolled patients.

### 3.4 Study Population

Patients with clinical suspicion of advanced prostate cancer who present to King Faisal Hospital, Rwanda Military Hospital and Kigali University Teaching Hospital, Rwanda.

### 3.5 Inclusion and exclusion criteria

#### 3.5.1 Inclusion criteria

All patients with clinical suspicion (symptoms and signs of bone metastasis, suspicious DRE and elevated PSA> 20 ng/ml) of advanced prostate cancer presenting in clinic, reviewed at AE, or in ward were included in this study after receiving written consent.

#### 3.5.2 Exclusion criteria

- Patients who have been diagnosed with prostate cancer before our study period.
- Patients who decide to withdraw from the study or die before the completion of work up and staging.

### 3.6 Sample size calculation

The study population was estimated using a single proportion for sample calculation formula. We opted to use an estimated prevalence of 2.8% as per previous study done in Rwanda(58).

$$n = (Z^2 \times P(1 - P))/e^2$$

The sample size was estimated at 42 cases.

**42**= $1.96^2$ x 0.028 (1-0.028)/$0.05^2$

Where Z = value from standard normal distribution corresponding to the desired confidence level (Z= 1.96 for 95% CI);

P = expected true proportion;

e = desired precision (half desired CI width)

### 3.7 Data collection process

A questionnaire was filled out by the researcher or treating physician in presence of the patient. This was followed up continuously based upon the availability of results.

The questionnaire included the following data:

- Demographic data and identifier
- Family history
- Symptoms (LUTS, urine retention, back pain, lower limb paresthesia, lower limb paralysis, erectile dysfunction, fatigue, weight loss, …)
- Duration of symptoms
- Characteristics of prostate on DRE (T staging)
- PSA- value
- Gleason score on core needle biopsy
- Metastasis on imaging (lymph nodes, bones, lung, liver, other)
- Social economic status ("*Ubudehe"* category): "*ubudehe*" reflect the degree of social and economic vulnerabilities/ Household vulnerability ranking (Social protection and VUP report, NISR 2013/2014)
- Insurance type
- Referred or not
- Perception of orchidectomy (embarrassing, no problem, can't accept it)

### 3.8 Data processing and Analysis

Descriptive statistics were used for description of demographic and other baseline characteristics of enrolled patients. Proportions by population characteristics were estimated. Median and mean estimates for age were also estimated to determine the distribution and age range of the study population. Proportion estimates were also generated to determine the frequency of symptoms at patients' presentation. The distribution of PSA values and staging were determined using frequency estimates. Chi-square tests were used to test for relationships between groups of patients with different characteristics. Bivariate, multivariable, and logistic regresses were also carried out using STATA *14.1* to assess additional relationships. The outcome variable for the first multivariable model was the diagnosis of either BPH or prostatitis or cancer, and the second multivariable model outcome variable was the staging of cancer as localized or advanced. The multivariable analysis included dependent variables that were statistically significant in the bivariate model and their p-values were not close to 0.05. Because these variables were dichotomous, a logistics model was appropriate for the analysis. However, because of the sample size, different commands were used to ensure reliable estimates with relatively small sample sizes and large variabilities.

### 3.9 Ethical considerations and Confidentiality

Patient identity was kept confidential, and every patient was given a number when enrolled in the study different from his/her IP hospital number.

The consent was signed by the patient or next of kin where applicable before enrollment in the study.

The research proposal was submitted to the Department of Surgery /Urology MMed Program and the Research Ethic Committee of the Faculty of Medicine at the University of Rwanda for review and approval.

The research proposal was presented to the Ethic Committee at all study centers for approval as well.

Data collection records were kept as soft copy in a secured password protected computer and hard copies will be stored in a secured locker for 5years.

### 3.10 Study Limitations

The investigations were done at different hospitals, by different interpreters and operators who manipulate machines and calibrate them. There may have been discrepancy in how this was done leading to a source of measurement bias.

The questionnaire contained several subjective questions and there was no way to verify answers. Furthermore, patients were asked questions regarding retrospective events such as disease duration. This may have been a source of recall bias.

# CHAPTER IV: RESULTS

## 4.1 Descriptive data characteristics

This study initially enrolled 123 patients based on PSA > 20 ng/ml or signs of advanced disease such as multinodular prostate, back pain, lower limb paraesthesia or paralysis; 9 patients were lost to follow up during their assessment thus 114 patients were included in analysis. Based on the above inclusion criteria, 14 patients were found to have benign conditions while 100 had cancer.

Patients' demographic characteristics were analysed and found that 75 (65.8%) patients were from CHUK, 35 (30.7%) patients from RMH and 4 (3.5%) patients from KFH. The median (IQR) age was 70 years (65 - 79 years) and the mean (SD) age was 71 years (± 9 years); with their age distributed as follows: less than 60 years (12.3%); 61-70 years (41.2%); 71-80 years (26.3%); more than 80 years (20.2%). 92.1 % were married while 1.8%, 5.2% and 0.9% were single, widower and divorced respectively (Table4.1.1).

Geographic distribution was as follows: 29% were from the Southern Province; 19.3% were from the East; 17.5% from Kigali city; 17.5% from the North and 16.7% from the western province. There was no significant association between province and diagnosis; 95.5% of patients from the East, 90.9 % from the South, 84.2 % from the West, 80 % from both Kigali city, and the North were found to have cancer (Table4.1.1).

Most patients (55.3%) denied family history of prostate cancer while 34.2% didn't know and 10.5% reported family history of prostate cancer. Among the 12 patients who reported history of prostate cancer in the family, 66.7% reported first level relative while 33.3% reported second level relationship. All patients with a family history had cancer (Table 4.1.1).

Majority of patients (75.5%) were unemployed or not working because of illness; 110/114 (96.5%) patients consulted because they were symptomatic while only 4 patients came for prostate cancer screening purpose. For those who came for screening, three were found to have prostate cancer and one had advanced disease.

Most of patients consulted primary health facilities first and 86.6% of patients enrolled in this study were transferred from district hospitals. Patients' social economic status were characterized using "*ubudehe*" categories where the higher the category the wealthier the person is. 61.4% of patients were in category three while 30.7% and 7% were in social status category two and category one respectively.

## Table 4.1.1 Demographic characteristics of study population

| Characteristics | All participants %(N) | Benign cases %(N) | Cancer cases %(N) | Localized cancer %(N) | Advanced cancer %(N) |
|---|---|---|---|---|---|
| **Age (Years)** | | P=0.834 | | P=0.553 | |
| less or equal to 60 | 12.3(14) | 14.3(2) | 85.7(12) | 8.3(1) | 91.7(11) |
| 61-80 | 67.5(77) | 13(10) | 87(67) | 17.7(12) | 82.3(56) |
| Above 80 | 20.2(23) | 8.7(2) | 91.3(21) | 10(2) | 90(18) |
| **Hospital of affiliation** | | P=0.302 | | P=0.005 | |
| KFH | 3.5(4) | 25(1) | 75(3) | 66.7(2) | 33.3(1) |
| CHUK | 65.8(75) | 14.7(11) | 85.3(64) | 18.8(12) | 81.2(52) |
| RMH | 30.7(35) | 5.7(2) | 94.3(33) | 3.03(1) | 96.97(32) |
| **Marital status** | | P=0.013 | | P= 0.569 | |
| Single | 1.8(2) | 50(1) | 50(1) | 0(0) | 100(1) |
| Married | 92.1(105) | 11.4(12) | 88.6(93) | 16(15) | 84(79) |
| Widower | 5.2(6) | 16.7(0) | 100(6) | 0.0(0) | 100(5) |
| Divorced | 0.9(1) | 100(1) | 0.0(0) | 0.0(0) | 0.0(0) |
| **Province of residence** | | P=0.304 | | P= 0.312 | |
| Kigali city | 17.5(20) | 20(4) | 80(16) | 25(4) | 72(12) |
| Eastern | 19.3(22) | 4.5(1) | 95.5(21) | 19.1(4) | 80.9(17) |
| Western | 16.7(19) | 15.8(3) | 84.2(16) | 18.7(3) | 81.3(13) |
| Northern | 17.5(20) | 10(4) | 80(16) | 0(0) | 100(17) |
| Southern | 29(33) | 6(2) | 94(31) | 13.3(4) | 86.7(26) |
| **Occupation** | | P=0.247 | | P=0.737 | |
| Unemployed/not working because of illness | 75.5(86) | 10.6(10) | 89.4(84) | 14.46(12) | 85.54(71) |
| Employed & self-employed | 24.6(28) | 20(4) | 80(16) | 18.75(3) | 81.25(13) |
| **Family history of prostate cancer** | | P=0.135 | | P= 0.158 | |
| Yes | 10.5(12) | 0(0) | 100(12) | 33.3(4) | 66.7(8) |
| No | 55.3(63) | 17.5(11) | 82.5(52) | 11.5(6) | 88.5(46) |
| Don't know | 34.2(39) | 7.7(3) | 92.3(36) | 13.9(5) | 86.1(31) |
| **level of relationship with the family member** | | | | P=0.083 | |
| First (Parents, sibling) | 66.7 (8) | 0(0) | 100(8) | 50(4) | 50(4) |
| Second (uncles, cousins) | 33.3 (4) | 0(0) | 100(4) | 0(0) | 100(4) |
| **Reason of consultation** | | P=0.430 | | **P=0.011** | |
| Screening | 3.5(4) | 25(1) | 75(3) | 66.7(2) | 33.3(1) |
| Sick | 96.5(110) | 11.8(13) | 88.2(97) | 13.4(13) | 86.6(84) |
| **SE (Ubudehe) category** | | P=0.480 | | **P=0.037** | |
| Ubudehe one | 7(8) | 0(0) | 100(8) | 0(0) | 100(8) |
| Ubudehe two | 30.7(35) | 8.6(3) | 91.4(32) | 9.4(3) | 90.6(29) |
| Ubudehe three | 61.4(70) | 15.7(11) | 84.3(59) | 18.6(11) | 81.4(48) |
| Ubudehe four | 0.9(1) | 0(0) | 100(1) | 100(1) | 0(0) |
| **Reference from other facility** | | P=0.717 | | **P=0.006** | |
| Yes | 88.6(101) | 11.9(12) | 88.1(89) | 11.4(10) | 88.6(78) |
| No | 11.4(13) | 15.34(2) | 84.6(11) | 41.7(5) | 58.3(7) |
| **Median age (IQR) in yrs** | | 70 (65-79) | Range (44-91) | | |
| **Mean age (Range) in yrs** | | 71± 9 | | | |

Fourteen patients had benign prostatic disease despite elevated PSA. Twelve of them had BPH and 2 had Prostatitis. Ten out of fourteen patients were between 60-80 years. None of these patients had positive family history for prostate cancer but 3 of them didn't know. Most patients (11/14) with benign disease presented with lower urinary tract symptoms while half presented with urine retention. Only 3 out of 14 patients had back pain and none had paraplegia or weight loss. In general, patients with benign disease had lower PSA levels compared to those with cancer ($p<0.0001$). The majority were below 50 ng/ml, and none had PSA above 100 ng/ml (Table 4.1.2).

**Table 4.1. 2 Characteristics of patients with benign disease**

| **Parameters** | **N** | **%** |
|---|---|---|
| Age in years | | |
| <60 | 2 | 14.3 |
| 60-80 | 10 | 71.4 |
| >80 | 2 | 14.3 |
| Family history | | |
| Positive | 0 | 0 |
| Negative | 11 | 78.6 |
| Don't know | 3 | 21.4 |
| Duration of symptoms | | |
| < 3 months | 5 | 35.7 |
| 3-6 months | 2 | 14.3 |
| 6-12 months | 4 | 28.6 |
| 12-24 months | 0 | 0 |
| > 24 months | 3 | 21.4 |
| Symptoms | | |
| LUTS | 11 | 78.6 |
| Urine retention | 7 | 50 |
| back pain | 3 | 21.4 |
| presence of nodule | 8 | 57 |
| one nodule | 5 | 62.5 |
| nodule < 5 mm | 6 | 75 |
| one lobe involved | 6 | 75 |
| PSA | | |
| <50 | 11 | 78.6 |
| 50-100 ng/ml | 3 | 21.4 |
| >100 ng/ml | 0 | 0 |

Most patients were symptomatic at presentation. Only 4/114 patients (3.5%) came for screening purpose. Lower urinary tract symptoms (LUTS) were the most common complaint (N=92) followed by back pain (N=64) and urine retention (N=42). All patients who presented with paraplegia had advanced disease and all patients with weight loss had cancer (p= 0.026) (Table 4.1.3).

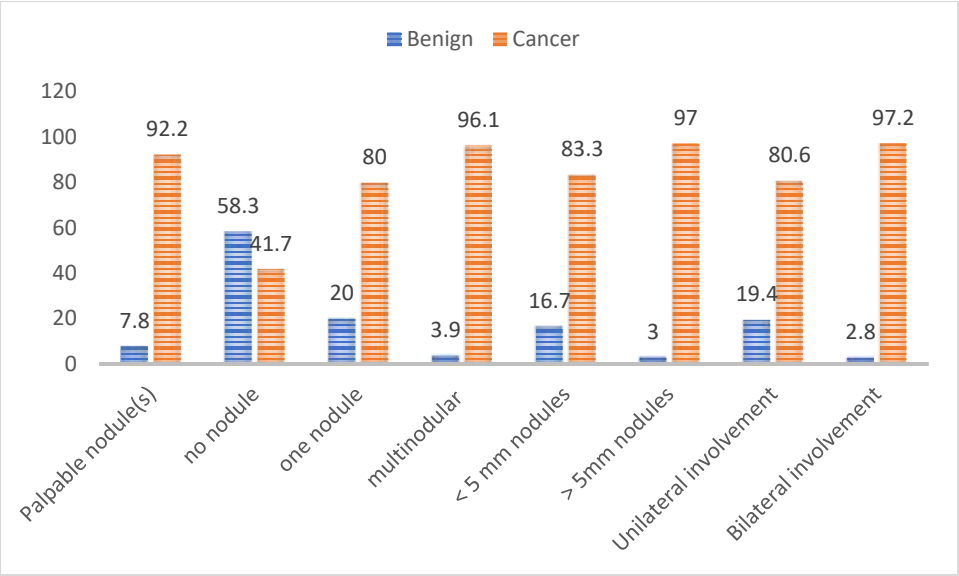
**Table 4.1.3 Distribution of presenting symptoms**

| Symptoms at presentation | Frequency N(%) | Cancer N (%) | p-value | Advanced cancer N(%) | p-value |
|---|---|---|---|---|---|
| LUTS alone | 92(80.7) | 80(87) | 0.941 | 68(85.0) | 0.915 |
| Urine retention | 42 | 34(80.9) | 0.165 | 30(88.2) | 0.566 |
| Back pain | 62(54.4) | 59(95.2) | **0.007** | 53(89.8) | 0.282 |
| Lower limb paresthesia | 33 | 31(93.9) | 0.224 | 28(90.3) | 0.381 |
| Paralysis | 7 | 7(100) | 0.308 | 7(100) | 0.59 |
| Weight loss | 23 | 23(100) | **0.038** | 19(82.6) | 0.743 |
| Erectile dysfunction | 17 | 16(94.1) | 0.463 | 15(93.8) | 0.454 |
| Hematuria | 13 | 11(84.6) | 0.68 | 11 (100) | 0.204 |

The mean (±SD) duration of symptoms was 14 months (±16 months), median 8.5 months (IQR 3-16 months) (range 0-84 months). The distribution was as follows: Within 3 months 29 (25.4%), 3-6 months 20 (17.6%), 6-12 months 31 (27.2%), 12-24 months 17 (14.9%) and greater than 24 months 17 (14.9%). There was no association between duration of symptoms and the diagnosis but all patients whose duration of symptoms was 12-24 months had cancer. 80 (70.2 %) patients denied having any comorbidities while 32 (28%) were hypertensive and 6 (5.3%) had both hypertension and diabetes mellitus.

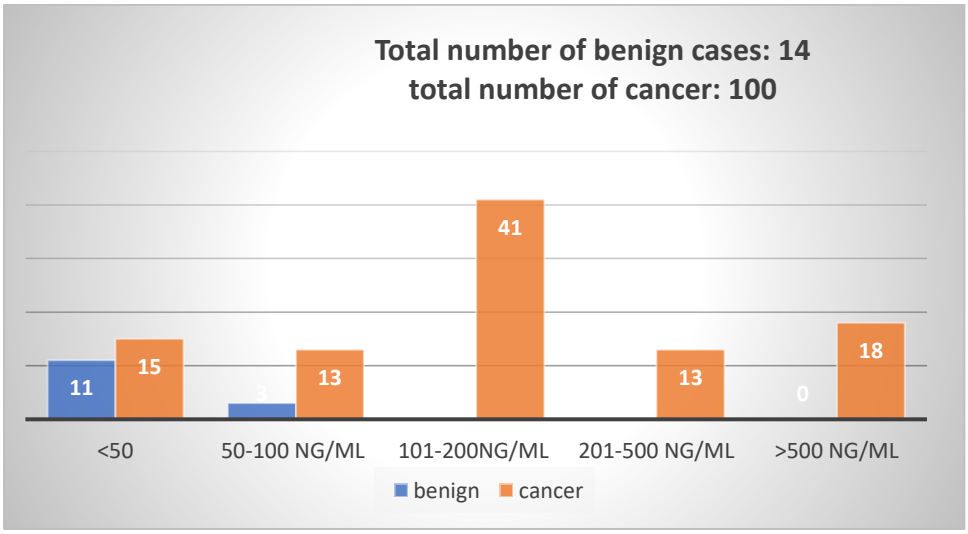
Findings on DRE were as follows: 102 (89.5%) had at least one palpable nodule, 76 (75.3%) had multinodular prostate, and 71 (70.3%) had nodules in both lobes. Prostate cancer was found in 92.2% of those with palpable nodules, 41.7% of those without palpable nodule(s), 80% of those with one nodule, 96.1% of those with multinodular prostate, and 97.2% of those with bilateral lobes involvement (Figure 4.1.1).

**Figure 4.1.1 Distribution of diagnosis according to clinical (DRE) findings**




The mean (±SD) PSA was 643.3 ng/ml (± 1828.8 ng/ml) while the median PSA was 100 ng/ml (IQR 69 – 260 ng/ml) (range 9.05 - 10000 ng/ml). Most patients (41/114, 36%) had PSA between 100 - 200 ng/ml, all had cancer, and 87.8% of them had advanced disease. There were 26/114 (22.8%) patients with PSA less than 50 ng/ml where 15 of them had cancer. There were 16/114 (14%) patients with PSA between 50-100 ng/ml and 13 of them had cancer. There were 13/114 (11.4%) patients with PSA between 201- 500 ng/ml and all had cancer. Lastly, 18/114 (15.8%) patients had PSA more than 500 ng/ml and all had cancer (Figure 4.1.2).

**Figure 4.1 2 Distribution of diagnosis according to PSA values**



Prostate biopsy results, imaging results for those confirmed to have cancer, as well as clinical stages are displayed in Table 4.3. A hundred (87.7%) patients were found to have prostate cancer while 14 (12.3%) patients had benign disease (12 BPH and 2 prostatitis). Gleason score grading was distributed in cancer patients as follows: 1 (1%) grade I, 4 (4%) grade II, 17 (17%) grade III, 27 (27%) grade IV and 51 (51%) grade V. Most patients had high grade prostate cancer and 78 % of cancer patients were in the high-risk prognostic group.

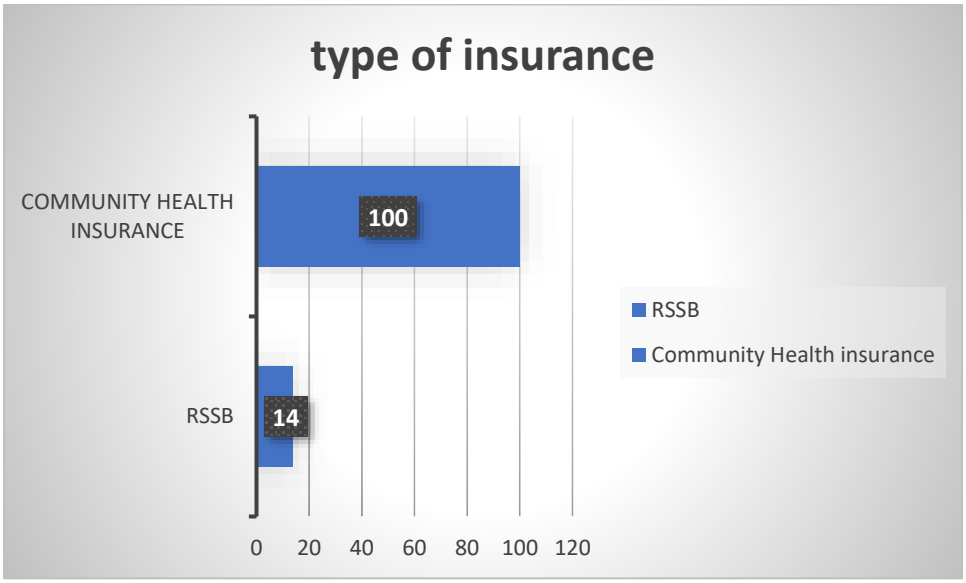
Of the 100 patients who had prostate cancer, 85 (85%) have been able to complete metastatic workup (CT or MRI); 64 (92.7%) had pelvic lymph nodes, 49 (71%) had bone metastasis and 9 (13.2%) had distant metastasis. 16 (16%) patients were free of pelvic lymph nodes and any metastasis. Majority of patients 70 (70%) were classified as stage IV (Table 4.1.4).

**Table 4.1.4 Investigation results and staging**

| **Parameters** | **N** | **%** |
|---|---|---|
| **Biopsy results (N=114)** | | |
| Prostate cancer | 100 | 87.7 |
| Grade I (3+3=6) | 1 | 1.0 |
| Grade II (3+4=7) | 4 | 4.0 |
| Grade III (4+3=7) | 17 | 17.0 |
| Grade IV (3+5/4+4/5+3=8) | 27 | 27.0 |
| Grade V (4+5/5+4=9; 5+5=10) | 51 | 51.0 |
| Benign | 14 | 12.3 |
| **Imaging results (N=85)** | | |
| Not assessed | 15 | 15.0 |
| No metastasis | 16 | 16.0 |
| Metastasis | 69 | 69.0 |
| Pelvic lymph nodes | 64 | 92.7 |
| Bone metastasis | 49 | 71.0 |
| Distant metastasis (Liver, Lungs, ..) | 9 | 13.0 |
| **Clinical staging (N=100)** | | |
| Stage I | 3 | 3.0 |
| Stage II | 12 | 12.0 |
| Stage III | 15 | 15.0 |
| Stage IV | 70 | 70.0 |

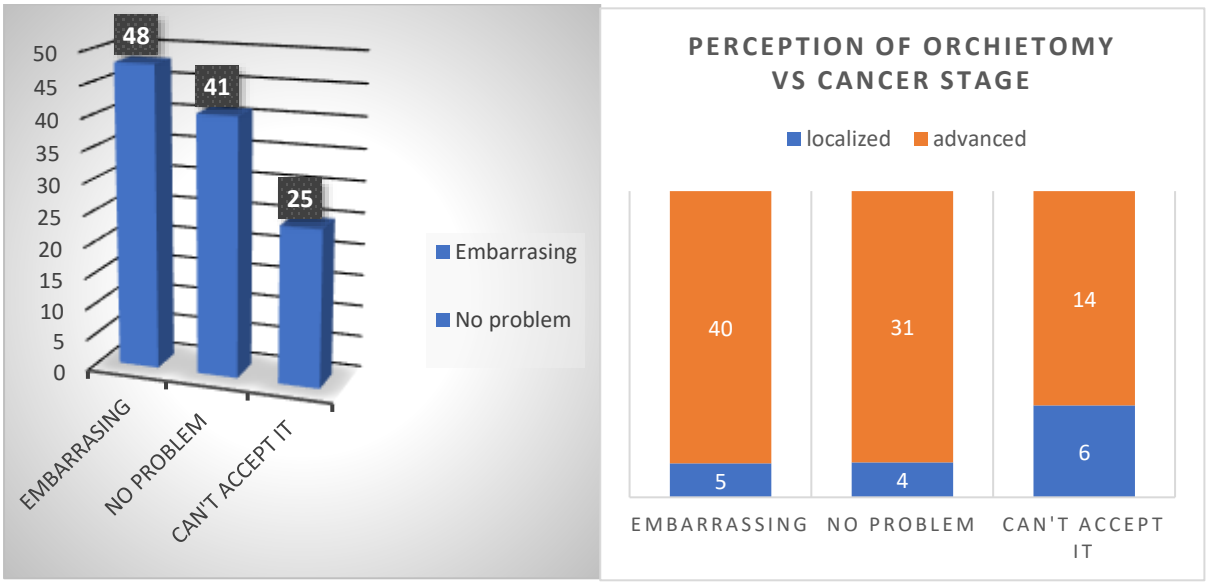
All patients had medical insurance and most of them (100, 87.7%) had community-based health insurance (CBHI) while 14 (12.3%) had Rwanda social security board (RSSB) insurance (Fig 4.1.3).

**Figure 4.1.3 Medical Insurance coverage**




All patients were asked about their perception of orchidectomy and 89 (78%) replied that they would accept it while 25 (22%) replied that they would not accept it in anyway. However, 54% of those who would accept it admit that they though it would be an embarrassing procedure. 71% of those who would accept orchidectomy had advanced prostate cancer (Figure 4.1.4).

**Figure 4.1.4 Perception of orchidectomy**



## 4.2. Bivariate and multivariable analysis

In the present study, there was no significant difference between age groups regarding benign or malignant prostate cancer ($p > 0.05$). Similarly, there was no significant difference amongst hospitals ($p= 0.202$). All patients with family history of prostate cancer were found to have cancer while 81% of those who denied family history of prostate cancer and 92.3% of those who did not know their family history were found to have cancer. Socio-economic status and duration of symptoms were not significantly associated with diagnosis (table 4.2.1).

A PSA level above 50 ng/ml was significantly associated with an increased risk of prostate cancer ($p<0.05$); 94% of patients with PSA between 50-100 ng/ml, 100% of those between with PSA of 100 ng/ml and above were found to have cancer. When adjusted for confounders, PSA > 100 ng/ml was associated with a 100% chance of having prostate cancer.

All DRE findings had significant correlation with the diagnosis of prostate cancer. 95% of those diagnosed with cancer had at least one palpable nodule vs 53.3% in benign ($p < 0.001$). 78.7 % of those diagnosed had multinodular prostate vs 37.5% in benign ($p=0.020$). Lastly, 73.4% of those diagnosed had involvement of both lobes' vs 25% in those with benign disease ($p=0.01$). When adjusted for confounders, however, none of the DRE findings had significant correlation with having cancer.

The duration of symptoms was not significantly associated with cancer diagnosis. However, all patients who reported duration of symptoms to be between 12-24 months were diagnosed with prostate cancer.

Elevated PSA has significantly correlated with pelvic node and bone metastasis. PSA between 50-100ng/ml had 5 times the odds of having bone metastasis (95% CI, 1.03- 24.28; $p=0.046$), while PSA levels between 100-200 ng/ml had 39 times the odds (95% CI; 6.6-231.5; $p<0.001$).

**Table 4.2.1 correlation of clinical parameters to the diagnosis of cancer (unadjusted and adjusted estimates)**

| Characteristic | Unadjusted odds ratio (P-value) | (95% CI) | Adjusted odds ratio (P-value) | (95% CI) |
|---|---|---|---|---|
| **Age category** | | | | |
| <60 | Ref | | Ref | |
| 61-80 | 1.12(0.89) | (0.22 - 5.74) | - | - |
| >80 | 1.75(0.59) | (0.22 - 14.07) | - | - |
| **Palpable nodule** | **0.09(<0.001)** | (0.022 – 0.32) | - | - |
| **Multinodular prostate** | **6.17(0.02)** | (1.36 - 28.03) | - | - |
| **Nodules > 5 mm** | **6.4(0.03)** | (1.22 - 33.59) | 3.78(0.17) | (0.57 - 24.96) |
| **Nodules in both lobes** | **8.28(0.01)** | (1.57 - 43.74) | 4.73(0.10) | (0.74 - 30.29) |
| **PSA group** | | | | |
| <50 | Ref | | Ref | |
| 50-99.9 ng/ml | 3.18(0.125) | (0.72 - 13.92) | 1.51(0.64) | (0.26 - 8.81) |
| 100-200ng/ml | 1* | - | **1*** | - |
| 201-500 ng/ml | 1* | - | **1*** | - |
| >500 ng/ml | 1* | - | **1*** | - |
| **Duration of the symptoms** | | | | |
| < 3 months | Ref | | Ref | |
| 3-6 months | 1.88(0.48) | (0.33 - 10.79) | - | - |
| 6-12 months | 1.08(0.91) | (0.28 - 4.21) | - | - |
| 12-24 months | 1* | | | |
| >24 months | 0.97(0.97) | (0.2 - 4.7) | - | - |

**Predicts the outcome perfectly*

As the PSA increases, the likelihood of having advanced disease significantly increased. Nine (60%) patients with PSA < 50 ng/ml were above clinical stage 3 compared to 39 (81.3%) patients with PSA between 50-100 ng/ml. All patients above 100 ng/ml had advanced stages (p=0.007).

Patients with PSA between 50-100 ng/ml had 2.89 times the odds of having advanced cancer but this was not statistically significant (p=0.1). PSA above 100 ng/ml perfectly predicted having advanced disease even if they were adjusted for confounders.

DRE findings, especially palpable nodules, multinodular prostate and involvement of both lobes, have increased odds of having advanced disease. Palpable nodule(s) had 30.5 times the odds of having advanced disease compared to having no palpable nodules ($p < 0.01$), while having multinodular and bilateral involvement of prostate increased the odds by 14.5 ($p<0.01$) and 42.5 ($p<0.01$) respectively.

When adjusted, only the location of nodules (unilateral vs bilateral) was statistically significant. Bilateral nodules had 45 times the odds of advanced prostate cancer compared to unilateral nodules ($p < 0.01$). Age and duration of symptoms were not associated with advanced disease even when unadjusted (Table 4.2.2).

**Table 4.2.2 Unadjusted and adjusted estimates for participants to have low stage or advanced cancer**

| Characteristic | Unadjusted odds ratio (P-value) | (95% CI) | Adjusted odds ratio (P-value) | (95% CI) |
|---|---|---|---|---|
| **Age category** | | | | |
| <60 | Ref | | Ref | |
| 61-80 | 0.42(0.43) | (0.05 - 3.61) | 1.28 (0.85) | (0.09 – 18.11) |
| >80 | 0.82(0.88) | (0.07 - 10.12) | 4.81 (0.37) | (0.15 – 154.7) |
| **Palpable nodule** | **30.5(<0.001)** | (3.13 - 298.53) | - | - |
| **Multinodular** | 14.56**(<0.001)** | (3.41 - 62.25) | - | - |
| **Nodule > 5 mm** | 1.27(0.72) | (0.34 - 4.74) | - | - |
| **Bilateral nodules** | 42.5**(0.001)** | (5.07 - 356.4) | 41.77**(0.02)** | (3.94 - 442.8) |
| **PSA group** | | | | |
| <50 | Ref | | Ref | |
| 50-99.9 ng/ml | 1.67(0.52) | (0.35 - 7.87) | 3.33(0.30) | (0.34 - 32.49) |
| 100-200ng/ml | 4.8 **(0.027**) | (1.19 – 19.34) | 8.55 **(0.049)** | (1.01 – 72.7) |
| 201-500 ng/ml | 1* | - | 1* | - |
| >500 ng/ml | 1* | - | 1* | - |
| **Duration of the symptoms** | | | | |
| < 3 months | Ref | | | |
| 3-6 months | 0.71(0.7) | (0.13 - 4.04) | - | - |
| 6-12 months | 0.82(0.81) | (0.16 - 4.11) | - | - |
| 12-24 months | 2.29(0.49) | (0.22 - 24.08) | - | - |
| >24 months | 0.36(0.23) | (0.07 - 1.91) | - | - |

*Predicts the outcome perfectly

## CHAPTER V: DISCUSSION

Prostate cancer is the second most common cancer in men (12). Its detection at early stage has increased following the introduction of PSA screening and has led to dramatic reduction of mortality (59). In Rwanda, however, we have observed many patients presenting with advanced disease and complications. Most patients do not present until symptoms arise as only 3.5% of patients in this study came for prostate cancer screening. Ogundele found that the awareness of prostate cancer is low in Africa (60) leading to late presentation with advanced disease. This was similarly found by Akinremi et al in a screening done in Nigeria (61).

The median age of our patients was 70 years and mean was 71 years which is similar to studies in Kenya and South Africa which found a mean age of 71.07 years and 71 years respectively (30)(26). Furthermore the mean age was found to be 71 years in patients without bone metastasis and 76 years in those with bone metastasis in a study done on 80 newly diagnosed prostate cancer patients in India (62). A study done in Port Harcourt, Nigeria found a mean age of 71.6 years and 91.5% of patients presented with features of advanced disease (63). Though it is generally known that prostate cancer is a disease of the elderly, one patient in this study was a young man (44 years old) who presented with paraplegia and severe back pain. He was found to have metastatic disease. Patients as young as 28 have been reported by Gupta who treated a 28 year old patient presenting with LUTS and was found to have advanced prostate cancer (64). Prostate cancer which presents at a younger age is aggressive. In the current study, the likelihood of having cancer is low for patients below 60 years then increases between 60-80 years before decreasing for patients above 80 years. Adeloye et al observed an increasing trend in prostate cancer incidence with advancing age (4). Pepe and Pennesi also found that Gleason score of 8 or more significantly correlated with patients above 80 years ($p=0.0001$) (65).

Patients with prostate cancer family history accounted 10.5% though there may be underreporting because a big number didn't know their family history. Among those with positive family history 66.7% had first level relationship with the affected relative. As expected, all patients who reported having family history of prostate cancer whether first level or second, were diagnosed with prostate cancer. This is different from a study done in Nigeria where 6.3 % had positive family history, only a third of them had their first level relative (brother) affected and 35.4 % presented with stage IV disease (66). The mean age of patients with positive family history was 66 years which is less than the general mean age but higher

than what was found by Cremers et al that those with positive family history had earlier onset with mean age of 62 years (67).

Most of our patients (88.6%) were referred from district hospitals. This means they had to pass through the referral system from health centre to district hospital and then to a referral hospital before seeing a urologist. That process takes time and may be one of the reasons patients presented with advanced disease and adverse complications. The mean duration of symptoms in the current study was 14.2 months which is consistent with what was found by Forbes et al. This study examined causes for delay in presentation for 2371 patients and found patients with prostate cancer were more likely to delay care compared to other patients. These delays were mainly attributed to lack of awareness (68). In India, Tiwari et al found that patients with little or no education are likely to present with advanced cancer as well as those who were diagnosed in the community compared to those who presented directly (69).

Correlation of duration to worse disease stage is not clear in this study. All patients who reported the duration of symptoms between 12 and 24 months, however, had cancer and 94% of them were advanced. In this study, many patients where symptomatic at presentation. Similar to findings in black South-Africans, this mainly included urinary symptoms (26) but did not significantly predict having cancer. This finding is in contrast to a study done by William et al on 217 prostate cancer patients in UK which found that symptoms have a significant positive predictive value for diagnosing prostate cancer (70). Other studies suggest that early prostate cancer is asymptomatic while locally advanced disease may lead to lower urinary tract symptoms that are similar to those of benign prostatic hyperplasia (71). In this current study, we can't rely on the presence, duration, or severity of symptoms to predict prostate cancer. This is similar to the findings of Weight et al who was unable to find any association between symptoms themselves and prostate cancer (72). However, this study did show a clear correlation between back pain and bone metastasis ($p=0.001$).

Findings on DRE were found to predict having advanced disease. Palpable nodules, multinodular prostate, nodules > 5mm and involvement of both lobes of prostate all had significant positive unadjusted odds ratios regarding advanced disease ($p < 0.05$). However, none were statistical significance when adjusted. Previous studies on the accuracy of DRE in diagnosing prostate cancer found that an abnormal DRE carries 42.3% risk of malignancy (32). Ojewola et al also studied the usefulness of PSA and DRE and found that neither PSA nor DRE

is sensitive, specific, predictive, or accurate enough on its own to be an ideal diagnostic test for prostate cancer. Detection rate, however, did increase when both were combined (73).

The mean PSA value was 643.2 ng/ml which is similar to levels found in blacks from South Africa. This study found that blacks presented with higher stage, grade and serum PSA (766.2 ng/ml) compared to whites (196.1 ng/ml) (7). Khalid et al studied 150 consecutive Sudanese patients with median age of 73 years who were newly diagnosed with prostate cancer and found that the mean serum PSA was 63.55 ng/ml. This was higher in those with bone metastasis at 84.32 ng/ml $\pm$ 53.93 ng/ml compared to 47.18 $\pm$ 37.58 ng/ml in those without metastasis (74). As PSA increases above 20 ng/ml the likelihood of having advanced disease increases (46)(75). Khalid et al, further found that among patients with serum PSA above 20 ng/ml, 62.6% had high grade score, 31.3% had intermediate score, and 6.1% had low grade score (74). The same trend was observed by Hudson et al where increasing PSA was associated with higher clinical stage of prostate cancer (76).

In the current study, no significant association was found between patients with PSA levels below 50 ng/ml and those between 50-100 ng/ml with regards to advanced cancer. However, PSA above 100 ng/ml perfectly predicted advanced prostate cancer. The similar threshold of 100 ng/ml was found in a study done in Kenya by Ojuka et al (30) which was highly associated with bone metastasis but different to many other studies where the cut off is 20 mg/ml (77)(78). Jang et al also found that all patients with PSA above 100 ng/ml had advanced disease (29). Another study revealed that PSA is independently associated with bone metastasis (OR: 1.005, 95%CI 1.001-1.010, p= 0.016) (62). Furthermore, a study done in South Africa by Heyns concluded that PSA above or equal to 60 ng/ml has a positive predictive value of 98% for the presence of adenocarcinoma and may be used as surrogate to histological diagnosis when facilities for biopsy are limited (79).

While increased PSA remains a significant predictor of cancer(34), it should be noted that in the current study 12 out of 14 patients with benign prostate had PSA above 20 ng/ml, 9 of them had PSA between 20-50 ng/ml and 3 had PSA between 50-100 ng/ml. Seven out of 14 patients with benign disease had no palpable nodules on DRE. These are different from what was found by Malati et al where all patients with benign disease had PSA levels below 28 ng/ml and only 8.2% had PSA above 10 ng/ml (80). Amayo et al, found the maximum PSA in patients with benign disease was 36 ng/ml (81) while it was 44 ng/ml in a study done by Stamey et al (82). Iya et al found an elevated mean at 35.5 ng/ml in patients with benign disease (83).

The finding of late presentation in this study is comparable to what was found by Okuku in Uganda where 90% presented in stage IV disease (27). High grade cancer (Gleason score of 8 or above) was found in 78% of patients in the current study which is comparable to what was found in Nigeria by Ikuerewo et al (74.4%) (84). This, however, was different from Caucasians who have been found to have a median Gleason score of 7 (65). The median PSA in the current study was 100ng/ml which is a higher than 91.3 ng/ml found by Cooney et al in Uganda (85) and 9.6 ng/ml found by Pepe in Italy (65). Different laboratory technics may explain the large differences.

The role of biopsy in advanced prostate cancer is undisputable. It is equally important, however, to ensure that debilitating complications are prevented when early affective diagnosis of advanced disease is possible with valid clinical parameters. Heyns in South Africa in a study of 3,960 patients with cancer of the prostate suggested PSA of 60 ng/ml and above had a positive predictive value of 98% for the presence of adenocarcinoma of the prostate and recommended using it as a surrogate for biopsy (86). In the benign disease group of the current study, the maximum PSA value is 98.5 ng/ml while all patients with PSA of 100 ng/ml and above had cancer. The combination of abnormal DRE and PSA of 100 ng/ml is an effective guide to establish an accurate diagnosis of cancer when histopathology is unavailable. When the above parameters are combined with back pain, there should be high suspicion of bone metastasis indicating the need for early androgen deprivation therapy by bilateral orchidectomy if the patient is well informed and consents.

## CHAPTER VI: CONCLUSION AND RECOMMENDATIONS

### *6.1 Conclusion*

The results of this study show that there is a significant correlation between back pain and bone metastasis in patients with prostate cancer. All patients with abnormal DRE and PSA above 100 ng/ml had advanced prostate cancer. There is correlation between back pain, abnormal DRE and PSA above 100 ng/ml with advanced cancer and bone metastasis. These patients would therefore benefit from early ADT. Orchidectomy is the treatment of choice as it is the most cost-effective prevention of acute skeletal complications and leads to a better quality of life. After the initiation of therapy, all patients should be referred for further management

### *6.2 Recommendations*

- There should be awareness program to general population and practitioners about prostate cancer
- PSA testing should be available to patients using community-based health insurance
- PSA should be sought early for patients with family history of prostate cancer
- ADT, specifically with bilateral orchidectomy, should be offered to selected patients with PSA above 100 ng/ml, abnormal DRE, and bone metastasis.
- Train practitioners in District hospitals to diagnose prostate cancer and encourage early referral
- Train practitioners to clinically diagnose advanced prostate cancer especially those with high risk of skeletal complications (spinal cord compression, fractures)
- Train practitioners in the community to carry out bilateral orchidectomy after patient education and consent in patients with advanced cancer to prevent acute skeletal complications.
- To have at least one hospital centre with bone scan facility for accurate diagnosis of bone metastasis
- More studies are needed to understand better the profile of advanced prostate cancer
- Need for a more expanded study

## CHAPTER VII: REFERENCES


1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: Defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol. 2006;24(14):2137–50.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin. 2016;66(1):7–30.
3. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer [Internet]. 2018 Nov [cited 2019 May 24];103:356–87. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30100160
4. Adeloye D, David RA, Aderemi AV, Iseolorunkanmi A, Oyedokun A, Iweala EEJ, et al. An Estimate of the Incidence of Prostate Cancer in Africa: A Systematic Review and Meta-Analysis. Shore N, editor. PLoS One [Internet]. 2016 Apr 13 [cited 2019 May 14];11(4):e0153496. Available from: http://dx.plos.org/10.1371/journal.pone.0153496
5. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer [Internet]. 2015 Mar 1 [cited 2019 May 24];136(5):E359–86. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25220842
6. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin [Internet]. 2014;64(1):9–29. Available from: http://onlinelibrary.wiley.com/doi/10.3322/caac.21208/full%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/24399786
7. Heyns C, Fisher M, Lecuona A, van der Merwe A. Prostate cancer among different racial groups in the western cape: Presenting features and management. South African Med J. 2011;101(4):267–70.
8. Forbes LJL, Warburton F, Richards MA, Ramirez AJ. Risk factors for delay in symptomatic presentation : a survey of cancer patients. Br J Cancer [Internet]. 2014;111(3):581–8. Available from: http://dx.doi.org/10.1038/bjc.2014.304
9. University of Benin. College of Medical Sciences. J, Obarisiagbon E, Nwajei C, Osaigbovo E, Okolo J, Akinyele A. Journal of medicine & biomedical research. [Internet]. Vol. 12, Journal of Medicine and Biomedical Research. College of Medical Sciences, University of Benin; [cited 2019 May 16]. 42–47 p. Available from: https://www.ajol.info/index.php/jmbr/article/view/104621

10. Edalat F. NIH Public Access. 2012;40(6):1301–15.
11. Yeboah FA, Acheampong E, Gyasi-Sarpong CK, Aboah K, Laing EF, Obirikorang C, et al. Nomogram for predicting the probability of the positive outcome of prostate biopsies among Ghanaian men. African J Urol [Internet]. 2018;24(1):45–53. Available from: https://doi.org/10.1016/j.afju.2017.09.004
12. Banerjee S. Worldwide Prostate Cancer Epidemiology: Differences Between Regions, Races, and Awareness Programs. Int J Clin Exp Med Sci [Internet]. 2016;2(1):1. Available from: http://www.sciencepublishinggroup.com/journal/paperinfo?journalid=335&doi=10.11648/j.ijcems.20160201.11
13. Parkin D., Bray F., Devesa S. Cancer burden in the year 2000. The global picture. Eur J Cancer [Internet]. 2001 Sep 1 [cited 2018 May 9];37:4–66. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0959804901002672
14. Quinn M, Babb P. Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part I: International comparisons. BJU Int. 2002;90(2):162–73.
15. Kanavos P. The rising burden of cancer in the developing world. Ann Oncol. 2006;17(SUPPL. 8):15–23.
16. Narod S. Genetic epidemiology of prostate cancer. 1999;1423(1):F1-13.
17. Agbo C, Shuaibu S. Jos Journal of Medicine [Internet]. Vol. 10, Jos Journal of Medicine. Univ; 2009 [cited 2019 May 16]. 32–34 p. Available from: https://www.ajol.info/index.php/jjm/article/view/139604
18. Bashir MN. MINI-REVIEW Epidemiology of Prostate Cancer. 2015;16(2012):5137–41.
19. Chu LW, Ritchey J, Devesa SS, Quraishi SM, Zhang H, Hsing AW. Prostate cancer incidence rates in Africa. Prostate Cancer [Internet]. 2011 Aug 1 [cited 2018 May 9];2011:947870. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22111004
20. Ikuerowo SO, Omisanjo OA, Bioku MJ, Ajala MO, Nonyelim Mordi VP, Esho JO. Prevalence and characteristics of prostate cancer among participants of a communitybased screening in Nigeria using serum prostate specific antigen and digital rectal examination. Pan Afr Med J. 2013;15:1–7.
21. PROSTATE CANCER AWARENESS, KNOWLEDGE, PERCEPTION ON SELF-VULNERABILITY AND UPTAKE OF SCREENING AMONG MEN IN NAIROBI COUNTY, KENYA WANYAGAH PAUL (MBA). 2013 [cited 2018 May 9];

Available from: http://ir-library.ku.ac.ke/bitstream/handle/123456789/9005/Wanyagah%2C Paul.pdf?sequence=1

22. Korir A, Okerosi N, Ronoh V, Mutuma G, Parkin M. Incidence of cancer in Nairobi, Kenya (2004-2008). Int J Cancer. 2015;137(9):2053–9.
23. East African Public Health Association. MR, Kombe D, Yuma S, Mtiro H& MG. East African journal of public health. [Internet]. Vol. 4, East African Journal of Public Health. East African Public Health Association; [cited 2019 May 25]. 19–22 p. Available from: http://www.bioline.org.br/abstract?lp07004
24. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359–86.
25. Cunningham-Burley S, Allbutt H, Garraway WM, Lee AJ, Russell EBAW. Perceptions of urinary symptoms and health-care-seeking behaviour amongst men aged 40-79 years. Br J Gen Pract. 1996;46(407):349–52.
26. Tindall EA, Monare LR, Petersen DC, Zyl S van, Hardie R-A, Segone AM, et al. Clinical Presentation of Prostate Cancer in Black South Africans. Prostate [Internet]. 2014 Jun [cited 2019 May 19];74(8):880. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24723425
27. Okuku F, Orem J, Holoya G, De Boer C, Thompson CL, Cooney MM. Prostate Cancer Burden at the Uganda Cancer Institute. J Glob Oncol [Internet]. 2016;2(4):181–5. Available from: http://ascopubs.org/doi/10.1200/JGO.2015.001040
28. Lee RT. Prostate Cancer. Integr Med [Internet]. 2018;790-799.e2. Available from: http://linkinghub.elsevier.com/retrieve/pii/B9780323358682000803
29. Jang J, Kim Y. Is prostate biopsy essential to diagnose prostate cancer in the older patient with extremely high prostate-specific antigen? Korean J Urol [Internet]. 2012;82–6. Available from: http://synapse.koreamed.org/DOIx.php?id=10.4111/kju.2012.53.2.82
30. Ojuka D, Majicha S, Ngugi P. Can PSA Predict Bone Metastasis amongst Newly Diagnosed Prostate Cancer Patients ? 2018;15(1):4–7.
31. Littrup PJ, Kane RA, Mettlin CJ, Murphy GP, Lee F, Toi A, et al. Cost-effective prostate cancer detection. Reduction of low-yield biopsies. Cancer. 1994;74(12):3146–58.
32. Jones D, Friend C, Dreher A, Allgar V, Macleod U. The diagnostic test accuracy of

rectal examination for prostate cancer diagnosis in symptomatic patients: a systematic review. [cited 2019 May 12]; Available from: https://doi.org/10.1186/s12875-018-0765-y

33. Seo HK, Chung MK, Ryu SB, Lee KH, Korean Urological Oncologic Society Prostate Cancer Study Group. Detection Rate of Prostate Cancer According to Prostate-Specific Antigen and Digital Rectal Examination in Korean Men: A Nationwide Multicenter Study. Urology [Internet]. 2007 Dec [cited 2019 May 20];70(6):1109–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18158028
34. Catalona WJ, Richie JP, Ahmann FR, Hudson MLA, Scardino PT, Flanigan RC, et al. Comparison of Digital Rectal Examination and Serum Prostate Specific Antigen in the Early Detection of Prostate Cancer : Results of a Multicenter Clinical Trial of 6 , 630 Men. J Urol [Internet]. 1994;151(5):1283–90. Available from: http://dx.doi.org/10.1016/S0022-5347(17)35233-3
35. Chadwick DJ, Kemple T, Astley JP, MacIver AG, Gillatt DA, Abrams P, et al. Pilot study of screening for prostate cancer in general practice. Lancet (London, England) [Internet]. 1991 Sep 7 [cited 2019 May 20];338(8767):613–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1715503
36. Shim HB, Lee SE, Park HK, Ku JH. Digital rectal examination as a prostate cancer-screening method in a country with a low incidence of prostate cancer. Prostate Cancer Prostatic Dis [Internet]. 2007 Sep 13 [cited 2019 May 20];10(3):250–5. Available from: http://www.nature.com/articles/4500944
37. Ahmed M, Maitama H, Bello A, Kalayi G, Mbibu H. Transrectal ultrasound findings in patients with advanced prostate cancer. Ann Niger Med [Internet]. 2010;4(2):59. Available from: http://www.anmjournal.com/text.asp?2010/4/2/59/78274
38. Hegemann M, Maas M, Rausch S, Walz S, Bedke J, Stenzl A, et al. Current concepts and trends in the treatment of bone metastases in patients with advanced prostate cancer. Asian J Androl [Internet]. 2017 Dec 29 [cited 2019 May 21];21(1):12. Available from: http://www.ajandrology.com/text.asp?2019/21/1/12/221199
39. Crawford ED. Skeletal Complications in Men with Prostate Cancer: Effects on Quality-of-Life Outcomes throughout the Continuum of Care. Eur Urol Suppl [Internet]. 2004 Nov 1 [cited 2019 May 21];3(5):10–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1569905604000648
40. McMurtry CT, McMurtry JM. Metastatic prostate cancer: complications and treatment. J Am Geriatr Soc [Internet]. 2003 Aug [cited 2019 May 21];51(8):1136–42. Available

from: http://www.ncbi.nlm.nih.gov/pubmed/12890079

41. Smith JA, Soloway MS, Young MJ. Complications of advanced prostate cancer. Urology [Internet]. 1999 Dec [cited 2019 May 21];54(6A Suppl):8–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10606278
42. Common Bone Complications in Advanced Prostate Cancer Patients Lead to Increased Medical Costs - NewYork-Presbyterian [Internet]. [cited 2019 May 21]. Available from: https://www.nyp.org/news/Common-Bone-Complications-in-Advanced-Prostate-Cancer-Patients
43. Saad F, Ivanescu C, Phung D, Loriot Y, Abhyankar S, Beer TM, et al. Skeletal-related events significantly impact health-related quality of life in metastatic castration-resistant prostate cancer: data from PREVAIL and AFFIRM trials. Prostate Cancer Prostatic Dis [Internet]. 2017 Mar 3 [cited 2019 May 21];20(1):110–6. Available from: http://www.nature.com/articles/pcan201662
44. 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 [Internet]. 2015 Mar [cited 2019 May 21];3(1):10–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26157761
45. Amoako Y, Hammond EB, Assasie-Gyimah A, Laryea D, Ankrah A, Amoah G. Prostate-specific antigen and risk of bone metastases in west Africans with prostate cancer. World J Nucl Med [Internet]. 2019 [cited 2019 May 21];18(2):143. Available from: http://www.wjnm.org/text.asp?2019/18/2/143/255504
46. Kamaleshwaran KK, Mittal BR, Harisankar CNB, Bhattacharya A, Singh SK, Mandal AK. Predictive value of serum prostate specific antigen in detecting bone metastasis in prostate cancer patients using bone scintigraphy. Indian J Nucl Med [Internet]. 2012 Apr [cited 2019 May 21];27(2):81–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23723577
47. Petrylak DP. Risk Factors for the Development of Bone Metastases in Prostate Cancer. [cited 2019 May 21]; Available from: www.eu-acme.org/
48. Pai K, Salgaonkar G, Kudva R, Hegde P. BRITISH BIOMEDICAL BULLETIN Original Diagnostic Correlation between Serum PSA, Gleason Score and Bone Scan Results in Prostatic Cancer Patients with Bone Metastasis [Internet]. 2015 [cited 2019 May 21]. Available from: www.bbbulletin.org
49. Nabid A, Carrier N, Martin A-G, Bahary J-P, Lemaire C, Vass S, et al. Duration of Androgen Deprivation Therapy in High-risk Prostate Cancer: A Randomized Phase III

Trial. 2018 [cited 2019 May 20]; Available from: https://doi.org/10.1016/j.eururo.2018.06.018

50. Luz MA, Aprikian AG. Preventing bone complications in advanced prostate cancer. Curr Oncol [Internet]. 2010 Sep [cited 2019 May 21];17 Suppl 2(Suppl 2):S65-71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20882136
51. Pope AJ, Abel PD. PART-WORK The ninth in a series of articles on prostate cancer Androgen deprivation therapy for prostate cancer and its complications [Internet]. [cited 2019 May 20]. Available from: www.tugsh.com
52. Das M. Androgen deprivation therapy for prostate cancer. Lancet Oncol [Internet]. 2017;18(10):e567. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1470204517306708
53. Boevé LMS, Hulshof MCCM, Vis AN, Zwinderman AH, Twisk JWR, Witjes WPJ, et al. Effect on Survival of Androgen Deprivation Therapy Alone Compared to Androgen Deprivation Therapy Combined with Concurrent Radiation Therapy to the Prostate in Patients with Primary Bone Metastatic Prostate Cancer in a Prospective Randomised Clinical Trial: Data from the HORRAD Trial. Eur Urol [Internet]. 2019 Mar 1 [cited 2019 May 20];75(3):410–8. Available from: https://www.sciencedirect.com/science/article/pii/S0302283818306584
54. So A, Chin J, Fleshner N, Saad F. Management of skeletal-related events in patients with advanced prostate cancer and bone metastases: Incorporating new agents into clinical practice. Can Urol Assoc J [Internet]. 2012 Dec [cited 2019 May 21];6(6):465–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23282666
55. Hoyler M, Finlayson SRG, McClain CD, Meara JG, Hagander L. Shortage of doctors, shortage of data: A review of the global surgery, obstetrics, and anesthesia workforce literature. World J Surg. 2014;38(2):269–80.
56. Sayed S, Lukande R, Fleming KA. Providing Pathology Support in Low-Income Countries. J Glob Oncol [Internet]. 2015;1(1):3–6. Available from: http://jgo.ascopubs.org/content/early/2015/08/04/JGO.2015.000943.full
57. Shah MB, Raju K, G HK. Revisiting Prostate Biopsy with 2014 ISUP Modified Gleason Score and Gleason Grade — A Cross Section Study. 2014;5(12):2918–25.
58. Ngilimana P, Grulich A, Beral V, Sindikubwabo B. CANCER IN RWANDA. 1996;81:75–81.
59. Schröder FH, Hugosson J, Roobol MJ, Tammela TLJ, Ciatto S, Nelen V, et al. Prostate-Cancer Mortality at 11 Years of Follow-up. N Engl J Med [Internet]. 2012

Mar 15 [cited 2019 May 14];366(11):981–90. Available from: http://www.nejm.org/doi/abs/10.1056/NEJMoa1113135

60. Ogundele SO, Ikuerowo SO. A Survey of the Awareness of Prostate Cancer and its Screening among Men Attending the Outpatient Clinics of a Tertiary Health Center in Lagos, Nigeria. Niger J Surg Off Publ Niger Surg Res Soc [Internet]. 2015 [cited 2019 May 15];21(2):115–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26425064
61. Akinremi T, Adeniyi A, Olutunde A, Oduniyi A, Ogo C. Need for and relevance of prostate cancer screening in Nigeria. Ecancermedicalscience [Internet]. 2014 [cited 2019 May 15];8:457. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25228913
62. Chen Y, Lin Y, Nie P, Jiang W, Liu Y, Yuan R, et al. Associations of Prostate-Specific Antigen, Prostate Carcinoma Tissue Gleason Score, and Androgen Receptor Expression with Bone Metastasis in Patients with Prostate Carcinoma. Med Sci Monit [Internet]. 2017 Apr 12 [cited 2018 May 9];23:1768–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28400549
63. Eke N, Sapira M. Prostate cancer in Port Harcourt, Nigeria: features and outcome. Niger J Surg Res [Internet]. 2002 Jan 1 [cited 2019 May 16];4(1):34–44. Available from: http://www.ajol.info/index.php/njsr/article/view/12167
64. Gupta S, Gupta A, Saini AK, Majumder K, Sinha K, Chahal A. Prostate Cancer: How Young is too Young? Curr Urol [Internet]. 2017 Jan [cited 2019 May 15];9(4):212–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28413383
65. Pepe P, Pennisi M. Gleason score stratification according to age at diagnosis in 1028 men. Contemp Oncol (Poznan, Poland) [Internet]. 2015 [cited 2019 May 24];19(6):471–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26843845
66. Adewumi AO, Anthonia SC, Alabi AS, Amina FO, Kingsley KK. Pattern of prostate cancer among a Nigerian population: A study in a single tertiary care centre. Niger J Med [Internet]. [cited 2019 May 17];25(1):70–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29963824
67. Cremers RG, Aben KK, van Oort IM, Sedelaar JPM, Vasen HF, Vermeulen SH, et al. The clinical phenotype of hereditary versus sporadic prostate cancer: HPC definition revisited. Prostate [Internet]. 2016 Jul [cited 2019 May 24];76(10):897–904. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26989049
68. Forbes LJL, Warburton F, Richards MA, Ramirez AJ. Risk factors for delay in symptomatic presentation: a survey of cancer patients. Br J Cancer [Internet]. 2014 Jul

10 [cited 2018 May 9];111(3):581–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24918824

69. Tiwari V, Yogi V, Ghori HU, Singh OP, Peepre K, Yadav S, et al. Identifying the Factors Causing Delayed Presentation of Cancer Patients to a Government Medical College of Central India. J Clin Diagn Res [Internet]. 2015 Sep [cited 2019 May 24];9(9):XC09-XC12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26500996
70. Hamilton W, Sharp DJ, Peters TJ, Round AP. Clinical features of prostate cancer before diagnosis: a population-based, case-control study. Br J Gen Pract [Internet]. 2006 Oct 1 [cited 2019 May 24];56(531):756–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17007705
71. Hamilton W, Sharp D. Symptomatic diagnosis of prostate cancer in primary care: a structured review. Br J Gen Pract [Internet]. 2004 Aug [cited 2019 May 13];54(505):617–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15296564
72. Weight CJ, Kim SP, Jacobson DJ, McGree ME, Boorjian SA, Thompson RH, et al. The effect of benign lower urinary tract symptoms on subsequent prostate cancer testing and diagnosis. Eur Urol [Internet]. 2013 Jun [cited 2019 May 24];63(6):1021–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23313032
73. Ojewola RW, Tijani KH, Jeje EA, Ogunjimi MA, Anunobi CC, Adesanya AO. An evaluation of usefulness of prostate specific antigen and digital rectal examination in the diagnosis of prostate cancer in an unscreened population:experience in a Nigerian teaching hospital. West Afr J Med [Internet]. [cited 2019 May 17];32(1):8–13. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23613288
74. Khalid KE, Brair AI, Elhaj AM, Ali KE. Prostate-specific antigen level and risk of bone metastasis in Sudanese patients with prostate cancer. Saudi J Kidney Dis Transpl [Internet]. 2011 Sep [cited 2019 May 21];22(5):1041–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21912047
75. Kamaleshwaran KK, Mittal BR, Harisankar CNB, Bhattacharya A, Singh SK, Mandal AK. Predictive value of serum prostate specific antigen in detecting bone metastasis in prostate cancer patients using bone scintigraphy. Indian J Nucl Med [Internet]. 2012 Apr [cited 2019 May 25];27(2):81–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23723577
76. Hudson MLA, Bahnson RR, Catalona WJ. WITH PROSTATE CANCER. J Urol [Internet]. 1989;142(4):1011–7. Available from: http://dx.doi.org/10.1016/S0022-

5347(17)38972-3

77. Zaman MU, Fatima N, Sajjad Z. Metastasis on bone scan with low prostate specific antigen (≤20 ng/ml) and Gleason's score (. Asian Pac J Cancer Prev [Internet]. 2011 [cited 2019 May 15];12(6):1529–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22126493

78. ISHIZUKA O, TANABE T, NAKAYAMA T, KAWAKAMI M, KINEBUCHI Y, NISHIZAWA O. Prostate-specific antigen, Gleason sum and clinical T stage for predicting the need for radionuclide bone scan for prostate cancer patients in Japan. Int J Urol [Internet]. 2005 Aug [cited 2019 May 15];12(8):728–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16174046

79. Heyns CF, Naudé AM, Ahmed G, Stopforth HB, Stellmacher GA, Visser AJ. Serum prostate-specific antigen as surrogate for the histological diagnosis of prostate cancer. South African Med J. 2001;91(8):685–8.

80. Malati T, Kumari GR, Murthy PVLN, Reddy CR, Prakash BS. PROSTATE SPECIFIC ANTIGEN IN PATIENTS OF BENIGN PROSTATE HYPERTROPHY AND CARCINOMA PROSTATE [Internet]. Vol. 21, Indian Journal of Clinical Biochemistry. 2006 [cited 2019 May 15]. Available from: http://medind.nic.in/iaf/t06/i1/iaft06i1p34.pdf

81. Amayo A, Obara W. Serum prostate specific antigen levels in men with benign prostatic hyperplasia and cancer of prostate. East Afr Med J [Internet]. 2004 Jan [cited 2019 May 27];81(1):22–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15080511

82. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-Specific Antigen as a Serum Marker for Adenocarcinoma of the Prostate. N Engl J Med [Internet]. 1987 Oct 8 [cited 2019 May 27];317(15):909–16. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2442609

83. Iya D, Chanchani S, Belmonte J, Morris D, Glew R, Van der Jagt D. Prostate specific antigen in Africans: a study in Nigerian men. Vol. 5, Nigerian Journal of Surgical Research. 2011.

84. Ikuerowo SO, Omisanjo OA, Bioku MJ, Ajala MO, Nonyelim VP, Esho JO. Prevalence and characteristics of prostate cancer among participants of a community-based screening in Nigeria using serum prostate specific antigen and digital rectal examination. Pan Afr Med J [Internet]. 2013 [cited 2018 May 9];15. Available from: http://www.panafrican-med-journal.com/content/article/15/129/full/

85. Cooney MM, Okuku F, Orem J. Prostate Cancer Burden at the Uganda Cancer Institute. 2016;1–5.
86. Heyns CF, Naude AM, Ahmed G, Stopforth HB, Stellmacher GA, Visser AJ. Serum prostate-specific antigen as surrogate for the Histological diagnosis of Prostate cancer. South African Med J [Internet]. [cited 2019 May 16];91(8):685–9. Available from: https://www.ajol.info/index.php/samj/article/view/140044

## APPENDIX A: STATING OF PROSTATE CANCER

### TNM Clinical staging systems for prostate cancer

| 1997 | 1992 | DESCRIPTION |
|---|---|---|
| TX | TX | Primary tumor cannot be assessed |
| T0 | T0 | No evidence of primary tumor |
| T1 | T1 | Nonpalpable tumor—not evident by imaging |
| T1a | T1a | Tumor found in tissue removed at TUR; ≤5% is cancerous and histologic grade <7 |
| T1b | T1b | Tumor found in tissue removed at TUR; >5% is cancerous or histologic grade >7 |
| T1c | T1c | Tumor identified by prostate needle biopsy due to elevation in PSA |
| T2 | T2 | Palpable tumor confined to the prostate |
| T2a | | Tumor involves one lobe or less |
| | T2a | Tumor involves less than half of one lobe by normal tissue on all sides |
| T2b | | Tumor involves more than one lobe |
| | T2b | Tumor involves more than half of a lobe but not both lobes |
| None | T2c | Tumor involves more than one lobe |
| T3 | T3 | Palpable tumor beyond prostate |
| T3a | T3a | Unilateral extracapsular extension |
| T3b | T3b | Bilateral extracapsular extension |
| T3c | T3c | Tumor invades seminal vesicle(s) |
| T4 | T4 | Tumor is fixed or invades adjacent structures (not seminal vesicles) |
| T4a | T4a | Tumor invades bladder neck, external sphincter, and/or rectum |
| T4b | T4b | Tumor invades levator muscle and/or fixed to pelvic wall |
| N(+) | N(+) | Involvement of regional lymph nodes |
| NX | NX | Regional lymph nodes cannot be assessed |
| N0 | N0 | No lymph node metastases |
| N1 | N1 | Metastases in single regional lymph node, ≤2 cm in dimension |
| N2 | N2 | Metastases in single (>2 but ≤5 cm) or multiple with none >5 cm |
| N3 | N3 | Metastases in regional lymph node >5 cm in dimension |
| M(+) | M(+) | Distant metastatic spread |
| MX | MX | Distant metastases cannot be assessed |
| M0 | M0 | No evidence of distant metastases |
| M1 | M1 | Distant metastases |
| M1a | M1a | Involvement of nonregional lymph nodes |
| M1b | M1b | Involvement of bones |
| M1c | M1c | Involvement of other distant sites |

| | AJCC Prostate Cancer Stage Groupings | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Stage I | | Stage IIa | | | | Stage IIb | | | III | Stage IV | | | |
| Jewett-Whitmore stage | A1 | | A2, B0-2 | | | | | | | C1-3 | D1 | | D2 | |
| TNM stage | T1a-c N0M0 | T2a N0M0 | T1a-c N0M0 | T1a-c N0M0 | T2a N0M0 | T2a N0M0 | T2b N0M0 | T2c N0M0 | T1-2 N0M0 | T1-2 N0M0 | T3a-b N0M0 | T4 N0M0 | Any T N1M0 | Any T Any N M1 |
| Gleason score | ≤6 | ≤6 | 7 | ≤6 | ≤6 | 7 | ≤7 | Any | Any | ≥8 | Any | Any | Any | Any |
| PSA level (ng/ml) | <10 | <10 | <20 | 10-19.9 | 10-19.9 | <20 | <20 | Any | ≥20 | Any | Any | Any | Any | Any |

## APPENDIX B: RESEARCH COORDINATION

1. Investigator, Research Coordinator: Dr Innocent N. NZEYIMANA

   Resident in Urology at College of Medicine and Health Sciences/ University of Rwanda

2. Principal Investigator, Supervisor: Prof Emile RWAMASIRABO

   Urology MMed Program Coordinator at College of Medicine and Health Sciences/ University of Rwanda

## APPENDIX C: DATA COLLECTION TOOL

**PRACTICAL APPROACH TO ADVANCED PROSTATE CANCER MANAGEMENT IN COMMUNITY IN RWANDA**

1. Initials:…….
2. Patient ID number …….
3. New identifier: APC ……
4. Hospital: 1 KFH 2 CHUK 3 RMH
5. Age: ……
6. Marital status: 1 Single 2 Married 3 Widower 4 Divorced
7. Province of origin: 1 Kigali city 2 Eastern 3 Western 4 Northern 5 Southern
8. Current activity: 1 unemployed 2 employed / self-employed 3 retired
9. Family history of prostate cancer: 1 yes 2 No 3 Don't know
10. If yes, level of relationship: 1 First (Parents, sibling) 2 Second (grand parent, uncles, cousins) 3 Other
11. Reason of consultation: 1 Screening 2 Sick
12. Symptoms at presentation: 1 LUTS 2 urine retention 3 back pain 4 Lower limb paresthesia 5 paralysis 6 erectile dysfunction 7 weight loss 8 Hematuria
13. Duration of symptoms : …….. months
14. Comorbidities: 1 Hypertension 2 Diabetes 3 Cancer (specify) ……4 None
15. Presence of palpable nodules on DRE: 1 Yes 2 No
16. If Yes, number of nodules: 1 one 2 multinodular
17. Size of nodule: 1 <5mm 2 >5 mm
18. Location of nodules: 1 One lobe involved 2 both lobes involved
19. PSA- value: ……(ng/ml)
20. If PSA 4-10 ng/ml, % FPSA: 1 <20% 2 > 20%
21. Prostate core needle Biopsy results: 1 BPH 2 Prostatitis 3 Prostate cancer
22. If cancer, Gleason score: 1 3+3=6 2 3+4=7 3 4+3=7 4 4+4/5+3=8 5 4+5/5+4=9 6 5+5=10
23. Metastasis on imaging: 1 Pelvic LNs 2 bones 3 other distant site (specify):.... 4 None
24. Clinical stage: ……..
25. Social economic status (Ubudehe category): 1 one 2 two 3 three 4 four
26. Insurance type; 1 RSSB 2 MMI 3 MUSA 4 Private 5 No insurance
27. Referred: 1 Yes 2 No
28. Perception of orchidectomy: 1 embarrassing 2 no problem 3 can't accept it

## APPENDIX D: INFORMATION SHEET AND INFORMED CONSENT - ENGLISH

### INFORMATION SHEET

We are doing a research study on ***"Practical approach to advanced prostate cancer management in community in Rwanda"***
If you decide that you want to be part of this study, you will be asked by a clinician to answer questions related to the study.

The study aims at determining the relationship of clinical presentations and other investigations with the biopsy results in patients with advanced cancer. The findings will be used to determine the proper and affordable way of treating this cancer in our settings.

We won't do anything dangerous to your life and being part of the study will not affect your treatment. You are free to join the study and free to leave without any consequence. Your name won't appear anywhere and the information you will provide will be kept confidential.

For any question, contact:

Investigator: Dr NZEYIMANA N. INNOCENT Tel: **0788 70 17 27**
Email: innocent.n.nzeyimana@gmail.com

### CONSENT FORM

I, …… agree to participate in the study
**"*PRACTICAL APPROACH TO ADVANCED PROSTATE CANCER MANAGEMENT INCOMMUNITY IN RWANDA*"**

I am aware that participation in the study is voluntary and I will not be paid for the participation. In addition, all information provided will be treated with confidentiality and that my anonymity will be maintained.
I am aware that the result of this study may be published but I will not be identified as an individual. I reserve the right to withdraw from the study at any time if I so wish.

| | | |
|---|---|---|
| ……. | …….. …… | ……. |
| Name of participant | Signature of participant | Date |
| ……. | ……. ……. | ……. |
| Name of researcher | Signature of researcher | Date |

Principle researcher: Dr Innocent N. NZEYIMANA Tel: 0788 70 17 27
Supervisor: Prof Emile RWAMASIRABO Tel- 0788 35 66 47
Institutional Review Board CMHS Prof Gahutu J. Bosco Tel: 0783 340 040

## APPENDIX E: AMAKURU K'UBUSHAKASHATSI NO KWEMERA KUJYA MU BUSHAKASHATSI

### AMAKURU K'UBUSHAKASHATSI

Turakora ubushakashatsi kuri "***"Practical approach to advanced prostate cancer management in community in Rwanda*"**

Niwemera kwitabira ububushakashatsi, umuganga azagira ibibazo akubaza bijyanye n'uburwayi bwawe aribwo Kanseri ya Porositate.

Ububushakashatsi bugamije kureba ibimenyetso n'ibindibiranga iyi kanseri abarwayi bo mu Rwanda bagaragaza, igihe bigaragarira bigahuzwa n'ibisubizo by'utunyama dufatwa kuri porositate. Ibi bikazafasha kureba uburyo bwo kuyivura bujyanye n'ubushobozi bw'abaturage b' u Rwanda.

Nta kintu gishobora kwangiza ubuzima bwawe tuzakora, uzavurwa uko wakagombye kuvurwa kandi kujya mu bushakashatsi n'ubushake. Amakuru yawe azabikwa mw'ibanga kandi ntabwo amazina yawe azagaragazwa.

Ufite ikibazo wabaza:

Umushakashatsi mukuru: Dr NZEYIMANA N. INNOCENT Telefoni: 0788 70 17 27

### AMASEZERANO YO KWEMERA KUJYA MU BUSHAKASHATSI

Jyewe, ……nemeye kujya mu ubushakashatsi bwitwa:

***"Practical approach to advanced prostate cancer management in community in Rwanda*"**

Nasobanuriwe ko kujya muri ububushakashatsi ari ubushake bwanjye, ko ntagihembo ntegereje guhabwa, kandi ko nzagirirwa ibanga kugiti cyanjye ndetse n'amakuru yose nzatanga.

Nasobanuriwe ko ibizava muri ububushakashatsi bizatangazwa ariko ko ntazerekanwa nk'umuntu kugiti cye.

Mfite uburenganzira bwo kuva muri ububushakashats iigihe cyose nabishakira.

……. …….. …… …… …….

Amazinay'umurwayi Umukono w'umurway iItaliki

…….. ……. …….. ……..

Amazina y'umushakashatsi Umukono w'umushakashats iItaliki

Ukeneye ibindi bisobanuro wahamagara:

Uyoboye ubushakashatsi: Dr Innocent N. NZEYIMANA Telephone: 0788 70 17 27

- E-mail: **nzinnongango@gmail.com**,

Abajyanama: -Prof Emile RWAMASIRABO Tel- 0788 35 66 47

- Institutional Review Board CMHS Prof Gahutu J. Bosco Tel: 0783 340 040