UNIVERSITY of RWANDA

COLLEGE OF MEDICINE & HEALTH SCIENCES
SCHOOL OF MEDICINE & PHARMACY

Pattern and management of prostate cancer in Rwanda: a multicenter prospective study

A dissertation submitted in partial fulfillment for the requirements towards the award of the degree of Masters of Medicine in Urology at the University of Rwanda

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DECLARATION

Researcher:

I, **Dr. Alexandre NYIRIMODOKA**, declare that this research "**Pattern and management of prostate cancer in Rwanda: a multicenter prospective study''** is my work and has never been submitted to any University for any professional or academic award.

Signature: Date:…/…./…

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I hereby declare that this research: "**Pattern and management of prostate cancer in Rwanda: a multicenter prospective study ‘**was submitted by Dr. Alexandre NYIRIMODOKA with my approval.

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Dr. Alexandre NYIRIMODOKA

DEDICATIONS

To God the almighty for whom I owe my existence, for his love and blessings.

To my beloved parents who did everything so that I become what I am today.

To my brothers and sisters.

To my teachers and mentors in Urology and Medicine in general.

To my patients, fellow doctors and all my friends who participated in my training.

I dedicate this work.

LIST OF ABBREVIATIONS

AUR: Acute Urinary Retention

CHUK: Kigali University Teaching Hospital

CRPC: Castrate Resistant Prostate Cancer

CT scan: Computed Tomography scan

DHT: Dihydrotestosterone

DRE: Digital Rectal Exam

ISUP: International Society of Urological Pathology

KFH: King Faisal Hospital, Rwanda

LMICs: Lower and Middle-Income Countries

LUTS: Lower Urinary Tract Symptoms

MRI: Magnetic Resonance Imaging

mpMRI: Multiparametric MRI

NCCN: National Comprehensive Cancer Network

OPD: Outpatient Department

Pca: Prostate Cancer

PSA: Prostate Specific Antigen

RMH: Rwanda Military Hospital

TRUSS: Transrectal Ultrasound Scans

US: Ultrasound

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ABSTRACT

Background: Prostate cancer remains a global health burden. It is aggressive among black of African ancestry. Inadequate awareness as well as insufficient diagnostic and management capacity, lead to its delayed presentation with associated morbidity and mortality in Sub-Saharan Africa and Rwanda in particular. This study describes the burden, characteristics and management options of prostate cancer in Rwanda.

Method: This observational prospective descriptive study included all Rwandan patients diagnosed histologically with prostate cancer over 6 months, from September 2018 to February 2019 in the 3 national urology units. We described their demographic and clinical characteristics and estimated age standardized incidence rate of prostate cancer referring to the WHO average standard population between 2000-2025.

Results: The study enrolled 108 Rwandans whose biopsies were positive out of 153 taken. Their mean age was 71.3 years (SD=8.5). The most affected age group was 61-70 years having 42.59% (46/108) patients. The age range was 44-89 years. Almost everybody consulted because of symptoms related to urinary flow. Thus 99.07% (107/108) had lower urinary tract symptoms (LUTS); 46.3% (50/108) had acute urinary retention (AUR) and 21.3% (23/108) had neurological impairment of lower limb related to spinal metastasis. Only 12.96 % (14/108) had a positive family history and 39.81% (43/108) didn't know about their family history. Delay of the consultation was common with mean symptoms duration of 12 months and 90.74 % (98/108) had symptoms more than 3 months prior to the consultation. The Prostate specific antigen (PSA) was high with 85.05 % (91/107) having PSA >20 ng/ml. A total PSA >20 ng/ml correlated with having metastatic disease (adjusted odd ratio (aOR) = 13.22, p-value = 0.026). The mean PSA was 100ng/ml; range 1.69-10000 ng/ml. Most patients presented with advanced disease as 37.96% (41/108) were metastatic; 26.85% (29/108) locally advanced; 18.52% (20/108) were localized and 16.67% (18/108) were not fully staged. The majority had high grade tumor where 74.07% (80/107) had Gleason score of 8 or more and a mean Gleason sum of 8. Among 67 patients treated, androgen deprivation therapy (ADT) was offered to 76.12% (51/67) as primary treatment and 14.92% (10/67) were on ADT while waiting for combining with curative radiotherapy; 8.96% (6/67) underwent radical Prostatectomy during the study period. Bilateral orchidectomy was offered to 54.1% (33/61) and medical ADT in 45.9% (28/61). Medical ADT included goserelin which follows

bicalutamide in 53.57% (15/28); cyproterone acetate in 35.71% (10/28) and ketoconazole in 10.71% (3/28). The age standardized incidence rate of prostate cancer in Rwanda is estimated at 13.56 per 100000men above 45 years.

Conclusion: Late presentation of patients with prostate cancer generally in LMICs; Rwanda included leads to the detection of mainly advanced and high grade tumors making the clinician short of treatment options. It is imperative to increase access to specialized health care facilities while raising awareness of prostate cancer among the general population to tackle the mortality and morbidity associated with unnecessary delays.

Keywords: prostate cancer, Rwanda, RMH, CHUK, KFH, age standardized incidence rate, PSA, LMICs.

I. INTRODUCTION

1.1. Background

Prostate cancer is the 4th most common cancer in the world and 2nd most diagnosed (15%) of all cancers in men (Ferlay *et al.*, 2012). Developed countries have a higher incidence of prostate cancer than do LMICs due to the availability of PSA screening (Ferlay *et al.*, 2012), resulting in 70% of all prostate cancers being diagnosed in developed countries(Ferlay *et al.*, 2012).

Prostate cancer has the lowest incidence in Asia where the age standardized incidence rate is estimated at 4.5 per 100000 population in South-Central Asia (Ferlay *et al.*, 2012). Its highest incidence was found by Adeloye et Al in Australia and Northern America with age standardized incidence rate (ASR) of 111.6 and 97.2 per 100,000, respectively. The estimated age standardized incidence (ASR) of prostate cancer in Africa is 22 (95%CI:19.9-23.9) per 100000 population (Adeloye *et al.*, 2016). It is the fifth leading cause of cancer related death and accounts for 6.6% of cancer related death in men (Ferlay *et al.*, 2012). The age standardized death rate for prostate cancer is 14.2 per 100000 globally (Pishgar *et al.*, 2017). The incidence is lower in Africa because of a lack of awareness, screening and diagnostic modalities leading to underdiagnosis, and therefore, underestimation of the true incidence in Africa.

Some studies associated lower age of prostate cancer (Pca) diagnosis with poorer outcomes (Lin, Porter and Montgomery, 2009) (Salinas *et al.*, 2014). However, with advances in early detection and curative treatment, there is no significant difference in outcome after curative treatment in organ confined disease irrespective of the age of diagnosis (Alibhai *et al.*, 2004). Instead, studies have found a significant association between older age and high grade prostate cancer (Muralidhar *et al.*, 2015).

The only well-established risk factors for prostate cancer are older age, black race/ethnicity, and a family history of prostate cancer (Giovannucci *et al.*, 2007) (Center *et al.*, 2012). The aggressivity of prostate cancer in black men has been found in several studies comparing black men to white revealing that black men tend to have higher Gleason score, higher total PSA, and younger age at diagnosis (Shao *et al.*, 2009) (Moul *et al.*, 1995).

The aggressivity of prostate cancer among black men of African descent also was fond to vary geographically, where black men residing in sub-Saharan African had a more aggressive disease than other men of African descent. Timothy et al described in their study that geographical locations have an impact on nature of prostate cancer because they found higher Gleason score in tumors of sub-Saharan Africans men compared to those of men of African descent residing in United Kingdom (UK) and United State (US) (Timothy R. Rebbeck, 2013). They found that most tumors were higher stage (T3/T4) in Sub-Saharan Africans compared to other African descent residing in other regions of study. It is not clear whether these differences are due to health care access only or other differences in environmental exposure (Timothy R. Rebbeck, 2013).

The issue of racial difference in prostate cancer was also studied in treatment modalities of prostate cancer in some series in United State and revealed that black American with origin in Africa were more likely to receive androgen deprivation therapy as primary treatment (Mcginley, Tay and Moul, 2016). Furthermore, black Americans who received definitive treatment were more likely to receive radiotherapy (Mahal *et al.*, 2014) compared to white men. Where treatment with curative intent was possible, black had 18% curative treatment less relative to white men. All those constitute an explanation of higher morbidity in African American compared to white (Mahal *et al.*, 2014).

Worldwide, PSA based prostate cancer screening is controversial due to the lack of evidence proving a survival benefit with significant morbidity associated with treatment. Findings of a study comparing risk and benefit of prostate cancer screening recommended that the decision of screening should be based on the patient's decision who will be willing to accept the side effect of treatment (Wever *et al.*, 2012). In contrast to most high income countries trying to reduce unnecessary PSA based prostate cancer screening to avoid overtreatment, there is still a paucity of PSA screening even when it is clinically indicated in several regions of LMICs. This leads to late presentation with advanced disease and underestimation of incidences of prostate cancer in LMICs.

The current standard histological reporting of prostate cancer guides the clinician to individualize treatment according to its aggressivity as evidenced by its histological grade. Therefore each prostate cancer biopsy is given its specific Gleason score and Gleason grade

group according to international society of urological pathology (ISUP) 2014 consensus (Jonathan I. Epstein *et al.*, 2016), (Egevad *et al.*, 2002) (Chen and Zhou, 2016).

In Africa, the incidence of prostate cancer is not very well known due to paucity of screening modalities, poor awareness across the population, lack of access to health care and absence of a formal cancer registry in several African countries that contribute to the scarcity of data (Tiwari *et al.*, 2015).

Late presentation of prostate cancer is common in Africa with the majority presenting with symptoms whereas, in the developed countries where PSA screening is available, the majority of patients present with no symptoms and have localized disease (Brawley, 2012b). In one study done in South Africa, only 3.3% of patients with prostate cancer presented to the urologist because of elevated PSA and other 80.4% of patients with prostate cancer presented because of symptoms related to the urinary flow (Tindall *et al.*, 2014).

A community based prostate cancer screening done in Nigeria found a high prevalence of screening-detected prostate cancer of 1.046% (1046/100000population) with a serum total PSA>10 ng/ml in 95% of the screened population that was enrolled from the community after advertising the in media calling people above 40 years to come for screening. A Gleason score of more than 7 was reported in 74.4% in the same study (Ikuerowo *et al.*, 2013)

In Uganda, the Uganda cancer institute found that many of their subjects presented with the aggressive disease with a Gleason score of 9-10 in 66.7% of patients and a median baseline PSA of 91.3. Late presentation was common where 90% of patients had stage 4 disease so that only 14.9% underwent radical prostatectomy with curative intent (Cooney, Okuku and Orem, 2016).

In one survey of Rwanda ministry of health done in all health facilities in 2014, a total of 320 cases of prostate cancer were identified over a 1year period (Health Ministry Information System, 2015). The incidence of prostate cancer in Butare, Rwanda was estimated at 1.02/100000 population between 1991-1994 whereas it was estimated at 35/100000 in Uganda, Kampala between 1991-2006 (Adeloye *et al.*, 2016).

Population based cancer registries in Africa in general, and in Rwanda in particular, are not yet in common practice making data on cancer not readily available. King Faisal Hospital, Rwanda is the only hospital to have started a cancer registry in Rwanda.

Though black with African ancestry are most affected and have poorer outcomes in high-income country studies, there is a scarcity of published studies on prostate cancer burden, its characteristics, and management among black Africans.

The few studies done in Rwanda were lacking data on the clinical characterization of prostate cancer and some of them were including patients diagnosed with prostate cancer without histology confirmation. The current study will shed a light on the burden, characteristics, and management of prostate cancer in Rwandans.

1.2. Problem statement and justification of the study

Although black Africans and black men with African ancestry have a higher rate of prostate cancer with a higher grade at the time of diagnosis compared with the rest of the world, there is a scarcity of published literature on profile of prostate cancer and its management options in black African men in general and in Rwanda in particular. The current study will contribute new knowledge on the clinical characteristics and management options of prostate cancer in Rwanda. This study has enrolled histologically confirmed cancer removing any bias that may be introduced by relying only on clinical diagnosis as seen in previous global estimates including cancers diagnosed clinically. The results of this study will hopefully educate policymakers to recognize the importance of timely detection and management of prostate cancer to reduce morbidity and mortality of this disease in Rwanda.

1.3. Research question

What are the clinical presentations, pathological patterns and management options of prostate cancer among Rwandans?

1.4. Objectives of the study.

I.4.1. General objective.

To determine the clinical presentations, pathological patterns and management options of patients with prostate cancer among Rwandans.

1.4.2. Specific objectives:

- To describe the demographic characteristics of patients with prostate cancer.
- To determine the clinical characteristics of patients with prostate cancer.

- To describe the management options offered to patients with prostate cancer.
- To determine the incidence of prostate cancer in Rwanda.

II. LITERATURE REVIEW

Epidemiology

Prostate cancer is the fourth most common cancer in general and the second most common cancer in men (Ferlay *et al.*, 2012). It is the 5th cause of cancer related death in men in 2012 (Ferlay *et al.*, 2012). It had the highest age standardized incidence rate of 159.6/100000 in 2008 in the US (Timothy R. Rebbeck, 2013). The verdict is still out there, meaning that reduction in mortality due to PSA testing is still controversial. However, in countries where PSA testing is performed routinely, late stage prostate cancer presentation rates have decreased (Timothy R. Rebbeck, 2013) (Mcginley, Tay, and Moul, 2016).

In LMICs where early detection strategies and care seeking behavior among the population are not well developed, late detection is still a burden and contributes to limited options of treatment with significant mortality and morbidity (Ph and Roza, 2009).

Risk factors

Family history predisposes 5 to 10% of the risk of prostate cancer (Akin and Hricak, 2007). Age, race and fatty diet, are risk factors in some published papers (Giovannucci et al., 2007). Black men are more affected with a relative incidence of 1.6 compared to white and tend to have more aggressive disease. The mortality is 2.4 times higher in black men than in white men (Timothy R. Rebbeck, 2013) (Giovannucci et al., 2007).

Testosterone is transformed into dihydrotestosterone (DHT) by type two 5α reductase in the prostate, to regulate and sustain the progression of prostate cancer. Some genes, inflammatory mediators and oxidative stress also were found significant in casual relationship studies (Sfanos and de Marzo, 2012).

Data provide evidence that prostate cancer can be inherited through a mendelian pattern with autosomal dominant rare but high penetrance allele (Cartert et al., 1992). Germline mutation in HOXB13 G84E allele and BRCA1/2 is demonstrable in families who have early onset disease and many family members affected by prostate cancer (Zuhlke et al., 2012) that is why the new trend is to include genetic and biochemical tests in some specific patients (‘NCCN guidelines version4.2018’, 2018) (Mottet N, Bellmunt and Briers, 2017).

Physical findings

Early prostate cancer has no clinical manifestation. Development of lower urinary tract symptoms, back pain, bone pain, and weakness of lower limbs are associated with advanced disease. The only effective method of disease detection in the early stage is informed PSA and digital rectal exam (DRE) screening in the population at risk. In developed countries where informed PSA screening is in use, the detection of early disease is common. Treatment for early stage disease is curative in intention and associated with better outcomes (Brawley, 2012b). In contrast to LMICs, where almost every patient comes late with advanced disease, treatment with curative intent is much less common leading to significantly higher rates of mortality and morbidity (Tindall et al., 2014) (Cooney, Okuku and Orem, 2016). If a patient at risk develops symptoms related to urinary flow, he should get baseline screening to avoid the late presentation of prostate cancer (William Hamilton, 2006).

The community health care providers can detect early palpable prostate cancer using DRE especially when PSA testing is not readily available. It is well proven that a combination of DRE and PSA increases sensitivity and positive predictive value in detecting Pca (W.L. *et al.*, 2001). However, literature shows that DRE alone has an acceptable positive predictive value of 21 % compared to 32% of PSA (Catalona *et al.*, 1994) (Schro *et al.*, 1998). Therefore, DRE alone can serve a cost effective screening tool for prostate cancer in areas where the capacity of systematic PSA testing is lacking.

Early detection

PSA has replaced DRE in the screening of early organ confined prostate cancer in many developed countries. Its combination with DRE increases sensitivity and specificity. A widely used cut off of PSA >= 4 ng/ml has a high specificity of 93.6% and low sensitivity of 20.5% (Ankerst and Thompson, 2006). The combination of DRE and PSA has a greater positive predictive value compared to each one on its own (Catalona et al., 1994). The widespread use of PSA testing in developed countries led to the overdiagnosis and overtreatment of some indolent low risk organ confined diseases with subsequent treatment associated morbidity (Sandhu and Andriole, 2012). An example of the USA, the rate of overdiagnosis is estimated at 53% (range50-60%) (Etzioni *et al.*, 2002) (Draisma *et al.*, 2003). Recent studies failed to demonstrate the benefits of PSA based prostate cancer screening in terms of improving survival and quality of life in the general population

(Manser, 2013). This prompted readjustment of early detection guidelines where PSA screening remains the informed decision of a patient who has a good life expectancy and will accept side effects related to treatment (Wever et al., 2012) (Manser, 2013).

Recent guidelines recommend further molecular biology and genetic testing in some specific patients to further characterize the tumor and/or increase the sensitivity and specificity in prostate cancer detection ('NCCN guidelines version4.2018', 2018). Newer methods using molecular biology tests (like PCA3, 4K, and others) to determine the aggressiveness of the disease beyond PSA and DRE are being utilized to reveal whom to treat and whom to observe (NCCN_guidelines, 2019).

In LMICs, where PSA and DRE screening policy and capacity are lacking, as in the study of Tindall et al, 83% of most patients presented with signs of advanced cancer like LUTS, lower back pain or erectile dysfunction (Tindall et al., 2014). This contributes to an underestimation of the burden of prostate cancer in LMICs because only late cases with symptoms of advanced disease seek treatment (Cooney, Okuku and Orem, 2016) (Tindall et al., 2014).

Histology and risk stratification

Transrectal systematic 12 core biopsies have become a standard and increased cancer detection compared to the old Sextan scheme. Patients are generally screened for any coagulation disorder and are given prophylactic fluoroquinolone to prevent subsequent infection (Mottet N, Bellmunt and Briers, 2017). To increase the diagnostic yield of prostate biopsy while reducing unnecessary biopsies, some guidelines have recommended starting with multiparametric MRI especially in clinically insignificant tumors (NCCN_guidelines, 2019). In most LMICs and Rwanda particular, scarcity of equipped pathology laboratory facilities and personnel; unavailability of transrectal ultrasound scan (TRUSS) biopsy facilities in some places, and poor public awareness of prostate cancer in population delay the diagnosis and management of prostate cancer.

ISUP consensus 2014 has characterized prostate cancer histologically while predicting its clinical behavior using Gleason score, Gleason grade group, perineural invasion, vascular invasion and cancer volume (Chen and Zhou, 2016). The pathological characteristics are combined with PSA level, clinical stage and life expectancy for risk stratification while tailoring care to each patient accordingly to avoiding overtreatment which might be associated with increased morbidity (Lee, 2018).

Black men of African ancestry demonstrate a higher Gleason score compared to other races and this explains the aggressivity associated with prostate cancer in that group (Shao et al., 2009) (Moul et al., 1995). Different guidelines recommend the classification of patients according to their risk or recurrence after local treatment where 3-6risk groups (Nicolas Mottet et al., 2017) have been defined (Lee, 2018).

In this paper, we followed risk stratification as defined by European Urological Association (EAU) – European Society for Radiotherapy and Oncology(ESTRO) – European Society of Urogenital Radiology (ESUR) –International Society of Geriatric Oncology (SIOG) guidelines on prostate cancer, 2019 as shown in table 1 (N. Mottet et al., 2019)

Table 1: Risk stratification for prostate cancer.

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

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate specific antigen.

The current histological reporting of prostate cancer system include Gleason score and prognostic Gleason grade group as established by ISUP consensus in 2014 (see table 2) (Jonathan I Epstein *et al.*, 2016).

Table 2: International Society of Urological Pathology (ISUP) 2014 grade groups.(Jonathan I Epstein *et al.*, 2016)

Gleason score	Grade group
<=6 (3+3 or 3+2 or 2+3 or 2+2)	1
7 (3 + 4)	2
7 (4 + 3)	3
8 (4+4 or 3+5 or 5+3)	4
9–10	5

Staging

Imaging ranging from transrectal ultrasound guided prostate biopsies for diagnosis and staging imaging has been helping in diagnosis and guiding the management (Akin and Hricak, 2007). TNM classification is now widely accepted where T (tumor) is evaluated on DRE or mpMRI (Nicolas Mottet *et al.*, 2017); N (node) can either be evaluated by pelvic MRI or pelvic CT scan and M (metastasis) with MRI, CT scan or bone scan based on

individual nomograms and risk group (Lee, 2018) (Pullar and Shah, 2016) (Nicolas Mottet *et al.*, 2017).

Studies have demonstrated that PSA, Gleason score and clinical T stage have strong predictiveness to the pathological stage of the disease and nomograms are made available for use in clinical practice to guide patient treatment (Partin *et al.*, 1997).

The TNM classification is used in this study to guide the individualized management of patients (see table 3 below) (N Mottet *et al.*, 2017)

Table 3: Clinical Tumor Node Metastasis (TNM) classification of Pca.

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T1	A clinically inapparent tumor that is not palpable
T2	A tumor that is palpable and confined within the prostate
T3	Tumor extends through the prostatic capsule
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis
	M1a Non-regional lymph node(s)
	M1b Bone(s
	M1c Other site(s)

Management

The management options for the localized disease include active surveillance for low grade disease, curative radiotherapy and radical prostatectomy for more aggressive disease and watchful waiting for the elderly. Less commonly used therapies for the localized disease include proton beam, cryotherapy, and High Intensity Focused Ultrasound (HIFU) (Lee, 2018).

There are still controversies in the management of high risk localized and high risk of locally advanced cancers. Several guidelines opt for androgen deprivation therapy combined with external beam radiation therapy; others recommend surgery with adjuvant treatment ('NCCN guidelines version4.2018', 2018) (N. Mottet *et al.*, 2019).

Management of metastatic disease includes medical or surgery androgen deprivation therapy, chemotherapy, immunotherapy and radiotherapy with the possibility of offering a combination of more than one option according to patient presentation and guidelines in use.

Palliative management may provide the best supportive care including bisphosphonate, calcium and vitamin D supplementation, painkillers, spinal decompression, radiotherapy of a painful lesion, chanelling TURP and urethral or suprapubic catheterization (Lee, 2018) (N. Mottet *et al.*, 2019).

In case of castrate resistant prostate cancer, second line drugs like abiraterone (CYP17 inhibitor), enzalutamide (androgen receptor blocker), Sipuleucel-T (immunotherapy), docetaxel (chemotherapy) or other new drugs being developed are recommended in different guidelines ('NCCN guidelines version4.2018', 2018) (N. Mottet *et al.*, 2019).

III. METHODS

3.1. Study design

This was a cross-sectional prospective descriptive study of patients diagnosed with prostate cancer from September 2018 to February 2019.

3.2. Study settings

The study was conducted in 3 Rwandan referral hospitals where urology units were running during the study period: Kigali University Teaching Hospital (CHUK), Rwanda Military Hospital (RMH) and King Faisal Hospital, Rwanda (KFH).

- **CHUK**, KIGALI University Teaching Hospital is a 560 bed-capacity public hospital located in Kigali city. The surgery department accounts for 25% of the hospital beds. Its 3 urologists receive urology patient through OPD clinic and emergency departments. Patients with urologic conditions present either at OPD clinic, emergency department or internal medicine if they came in hospital for other associated conditions. After their review, the urologist eventually does a biopsy if they meet the criteria for it. CHUK serves people from the South, North, and Western Provinces. But each patient holds the right to choose which hospital he will consult.

- **RMH** (Rwanda Military Hospital) is a 500-bed capacity, public hospital, located in Kigali city. It has a urology unit run by 2 permanent urologists and 3 other visiting one. They receive and do biopsies of patients suspected to have prostate cancer and manage them accordingly, setting are almost similar to those of CHUK. It generally receives patients from Eastern Province and Kigali city.

- **KFH** (King Faisal Hospital), a 160-bed capacity hospital with a surgical ward having 39 beds located in Kigali city as well it is a semi-private hospital receiving all patients referred from other tertiary hospitals or those who can afford the cost of health care there. Patients with urologic conditions are received by one of the 3 urologists through the OPD clinic, emergency department or consult from other departments. If they meet the criteria for prostate biopsies, they are sent to radiology where prostate biopsy is done either by a radiologist or by a urologist. The cost of treatment is a bit higher

compared to the remaining 2 public hospitals cited above leading to a restricted number of patients who are consulted at KFH, Rwanda.

Most Rwandan patients seek care at health canter and are referred to the district hospital if necessary. A medical officer at a district hospital will refer to a tertiary level all patients suspected to have prostate cancer either based on symptoms and examination or willingness of patients to do a check-up. A small number of district hospitals can do the PSA test. Others transfer suspicious patients to tertiary level hospitals which are currently located in the capital city of Rwanda, Kigali.

Patients are generally classified according to the "*Ubudehe"* system ('Rwanda government board'), a long-standing Rwandan practice and culture of collective action and mutual support to solve problems within a community according to the individual needs ('Rwanda government board', no date). Therefore, categories range from 1 to 4; one being the poorest and 4 the richest group. The majority of patients have community-based health insurance (CBHI) that facilitates them to pay health services. The local government assists poor patients located in Ubudehe Category 1 to pay all health services.

Tumor staging; PSA testing; prostate biopsy; histological reporting and management of prostate cancer.

During the study period, criteria for prostate biopsies in all those 3 centers were abnormal prostate on digital rectal exam, high PSA, abnormal free to total PSA ratio and systematic prostate biopsy for bone metastasis of unknown primary. Specimens from transurethral resection of the prostate (TURP) and simple prostatectomy done in the study period were included as well.

A patient is generally seen in the clinic or the hospital when consulted by colleagues from other departments. Physical exam and basic relevant investigations including PSA are carried out accordingly. In the 3 study centers, PSA was performed using a similar machine "Cobas e411". Electrochemiluminescence immunoassay (ECLIA) was used in 3 respective centers to test free and total PSA in the study period.

Prostate biopsies were performed using core needle G18. Systematic extended 12 core biopsies were taken. However, in some cases where patients were clinically unstable with advanced palpable cancer, fewer cores could be taken to confirm the diagnosis histologically.

Every patient received a fluoroquinolone for 3 days starting one day prior to biopsy. Soap enema was not systematically done.

Pathologists referred to ISUP consensus 2014 for histology reporting. Therefore each histological report included at least: the type of tumor, Gleason score and grade group, primary Gleason pattern and its percentage, secondary pattern and is percentage, presence or absence of perineural invasion and lymphovascular invasion and number of cores received and the number of positive core overall. A patient could wait for 2 to 3 weeks to get results of histology and proceed for staging imaging when applicable.

The clinical exam was used to stage clinical T, pelvis and lumbosacral spine magnetic resonance imaging (MRI) or contrasted computed tomography scan (CT scan) serves to stage Nodes and distant metastasis in indicated patients. In very sick patients with clinically obvious distant metastases and abnormal renal function tests, plain bone x-ray could be used to look for bone metastases. To date, there is neither bone scan nor Positron Emission Tomography (PET) scan in the country. Patient management was generally based on National Comprehensive Cancer Network (NCCN) harmonized guidelines on prostate cancer for sub-Saharan Africa version 2.2017. However, during the study period, radical retropubic prostatectomy was the only curative treatment modality available in the country but the radiotherapy unit was being established and patients were put on a waiting list as it was going to be functional in short time to come.

3.3. Population.

This paper focused on Rwandan patients diagnosed with prostate cancer with positive biopsy in the above mentioned hospitals in the study period. Only Rwandan patients diagnosed with prostate cancer histologically have been enrolled in the study.

3.4. Inclusion criteria.

Rwandans patients diagnosed with prostate cancer with positive biopsy in the study period in 3 hospitals (CHUK, RMH, KFH) have been included in the study.

3.5. Exclusion criteria

- Patients with positive biopsies not taken in those 3 hospitals.
- A patient who refused to consent for the study.
- A patient diagnosed with prostate cancer who are not Rwandans.

3.6. Sample size calculation

The sample size for our study has been calculated basing on the estimated prevalence of 2.8% (Newton *et al.*, 1996), the sample size is estimated at 42 patients. The formula used for the calculation is depicted herewith.

$$\mathbf{n= (Z^2 *P (1-P))/e^2}$$

Where:

- **Z** = value from standard normal distribution corresponding to the desired confidence level (Z=1.96 for 95% CI).
- **P** is expected true proportion
- **e** is desired precision

3.7. Study period.

The study was conducted over 6months, from September 2018 to February 2019.

3.8. Data collection.

Demographic and some clinical data were taken on the day of results of the biopsy, and others have been taken when the patient was coming back for follow up. The data collector filled a predesigned questionnaire accordingly.

Conceptual framework.

We studied different variables that were interrelated as shown here down.

Independent variables:

- Complaints at presentation
- DRE findings

- PSA
- Perineural invasion
- vascular invasion

Dependent variables:

- Gleason score
- staging
- Management

Intervening variables:

- Comorbidity
- Age
- Duration of symptoms before the consultation
- Family history

3.9. Data analysis and statistics:

Data have been entered in Microsoft Excel 2007 and analyzed with Stata 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

We described clinical, demographic characteristics and management using frequencies and percentages for categorical data; and median and interquartile ranges for continuous data.

Bivariable analysis and multivariable logistic regression were done to explore:

- Factors associated with high grade prostate cancer
- Factors associated with metastasis of prostate cancer

- The relationship between continuous and categorical variables was assessed using the Kruskal-Wallis Rank Sum test.
- The relationship between categorical variables was assessed using Fisher's exact test.

- Confounders were controlled using logistic regression to determine the independent factors associated with outcomes.
- P-value of <0.05 was considered significant
- WHO standard average population between 2000 and 2025 has been used to calculate age standardized incidence ratio (Ahmad, Boschi-pinto and Lopez, 2001)
- We referred to the Rwandan population to calculate the incidence (National Institute of Statistics of Rwanda (NISR) and Ministry of Finance and Economic Planning (MINECOFIN) [Rwanda], 2012)
- The standard population at risk of prostate cancer was calculated by considering Rwandan men above 45 years standardized to WHO standard population between 2000-2025 (Ahmad, Boschi-pinto and Lopez, 2001).

3.10. Ethics and confidentiality

Patient identity was kept confidential and was separated from other data after data validation. Every patient was given a number when enrolled in the study different from his/her hospital number. Informed consent has been obtained from the patient before enrollment in the study.

The research proposal was reviewed and approved by the Institutional Review Board of the University of Rwanda. The ethical committees of CHUK, KFH, and RMH have approved this study prior to its implementation as well.

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

3.11. Study limitations.

Given that some patients presented with very advanced cancer with severe symptoms; sometimes we were forced to take a limited number of cores than desired. However, this didn't impact much on the results because those kinds of patients were having an advanced disease not requiring many cores to get the diagnosis. Another limitation was the poor socio-economic status of some of the study subjects who have been unable to come for the follow-up to complete the investigations on time and start treatment. We minimized its effect by calling those patients by phone and facilitating them to do all investigations in one day to

reduce their cost of transport. Another limitation was remarked on a few patients presented with obstructive uropathy and could not do staging imaging with contrast. Those were reevaluated for improvement of renal function after relieving obstruction and most of them showed improvement in renal function and did contrasted imaging.

IV. RESULTS

4.1. General description of results

Over 6 months, from September 2018 to February 2019, the study enrolled 108 Rwandan men who had positive biopsies for prostate cancer out of 153 patients who had undergone prostate biopsies. Overall, 64.7% (99/153) of biopsies were taken at CHUK, 24.18% (37/153) at RMH and 11.11% (17/153) at KFH. Among those 153 patients whose biopsies were taken, 146 of them were transrectal core biopsies; 6 were TURP chips and 1 was a simple prostatectomy specimen.

Of 153 subjects who had undergone prostate biopsies, 72.55% (111/153) patients were diagnosed with prostate adenocarcinoma and 27.45% (42/153) were benign prostate hyperplasia (BPH). In those having prostate cancer, 97.3% (108/111) of them were Rwandans and 2.7% (3/111) patients were foreigners. The mean number of prostate core taken was 11.2 (SD=2core) and the median number of the positive core for prostate cancer of 10 (IQR=7, 12).

The 108 participants were evenly distributed in Rwandan provinces with 28.7% (31/108), 20.37% (22/108), 18.52% (20/108), 17.6% (19/108) and 14.8% (16/108) patients residing in Southern, Eastern, Northern, Kigali City, and Western Province, respectively. The majority was insured with Community Based Health Insurance (CBHI) (89.81%, 97/108). Most of them were in Ubudehe category 3 (83.05%, 91/108). The mean age of the patient with prostate cancer was 71.29 years (range: 44-89). A proportion of 42.59% (46/108) was in the age group 61-70 years followed by 34.26% (46/108) in the group older than 75 years; 12.0% (13/108) for 71-75 years and latter 11.11% (12/108) patients were younger than 60 years.

The majority consulted for LUTS in 99.07% (107/108) followed by lower back pain/bone pain in 52.34% (56/107); acute urinary retention in 46.3% (50/108); erectile dysfunction in 37.04% (40/108); neurological impairment in lower limbs was noted in 21.3% (23/108) and hematuria in 4.67% (5/107). The median symptom duration prior to the consultation was 12 months (IQR=8, 24) and 90.74% (98/108) consulted with more than 3 months of symptoms. A family history of prostate cancer was present in 12.96% (14/108), unknown in 39.81% (43/108) and none in 47.22% (51/108).

The majority of patients had no comorbidity (81.48%, 88/108), whereas 12.04% (13/108) were hypertensive; 1.85 (2/108) had diabetes and 1.85(2/108) were HIV positive. Generally they had good performance status, with 75.7% (81/107); 12.15% (13/107); 9.35% (10/107) and 2.8% (3/107) having ECOG performance status score of 0; 1; 2 and 3 respectively.

The digital rectal exam revealed regular smooth prostate in 11.11% (12/108) patients and an abnormal prostate in 88.89% (96/108). The mean prostate size was 64 gr (SD=30.5) among 79 patients whose prostate size was determined. The median total PSA was 100 (range=1.69-10000 ng/ml). The majority of patients had total PSA greater than 20 ng/ml (91/107; 85.04%), however PSA range of 50-100 had 40.19% (43/107), PSA >100 ng/ml counts 33.64% (36/107); PSA less than 20 ng/ml counting 14.95% (16/107) and PSA between 20-50 ng/ml category had 11.21% (12/107) of patients.

A good proportion of patients had high risk locally advanced tumors where 35.19% (n=38) had T3; 34.26% (37/108) had T4; 18.52% (20/108) had T2 and 12.04 % (13/108) had T1. Among 108 subjects, 37.96% (41/108) had distant metastasis; 26.85% (29/108) had locally advanced; 18.52% (20/108) had localized disease and 16.67% (18/108) were not fully staged. The patient presented with high grade tumor where 44.86% (48/107) had grade group 5 followed by 29.91% (32/107) who had grade group 4; then16.82% (18/107) with grade group 3; and 7.48%(8/107) grade group 2 and later 0.93% (1/107) grade group1. Gleason score was 8 or more in 74.77% (80/107). Perineural invasion was present only in 59.26% (64/108) of cases. Patients with clinical T4 disease were more likely to have high grade prostate cancer (Gleason score >7) (adjusted odd ratio, aOR=16.13, p value=0.009), after adjusting through logistic regression model to PSA categories and perineural invasion.

Different modalities were used to stage patients. Therefore, abdomen and spine CT scan was used on 64.81% (70/108); pelvis and spine MRI in 10.19% (11/108) latter pelvis and lumbosacral spine x-ray was used in 6.48% (7/108) of patients but imaging was not done in 18.52% (20/108). A total PSA of more than 20ng/ml was associated with a higher risk of having distant metastasis (aOR =13.22, p value=0.026), after adjusting for Gleason sum, clinical T stage, and perineural invasion. In the study group, 103patients were seen in follow up consultations and among them 49.5% (51/103) underwent androgen deprivation (ADT) therapy as the only treatment versus 5.82% (6/103) that underwent radical retropubic prostatectomy; another 9.71% (10/103) patients received goserelin and bicalutamide while

waiting for radiotherapy which was in installation in the study period. Of 61 patients who received ADT (included 10 people who are on ADT while waiting for radiotherapy), 54.1% (33/61) underwent bilateral orchidectomy whereas 45.9% (28/61) received medical androgen deprivation therapy. In the 28 patients taking medical ADT, 53.57% (15/28) of them took bicalutamide as initiation followed by goserelin; 35.71% (10/28) took cyproterone acetate (androcur) and 10.71% (3/28) took ketoconazole. In 53 patients who presented with signs of lower urinary tract obstruction, 39.62 % (21/53) took medical therapy and 60.38% (32/53) are catheterized. Given the short period of data collection, patients were still on the waiting list for channel TURP during the study period and their data, as well as outcome data, are not appearing here.

The hospital based age standardized incidence rate of prostate cancer in Rwanda is estimated to be 13.56 per 100000 populations. This incidence is calculated considering that 108 new cases of prostate cancer were obtained in 6 months. The denominator is estimated to be men above 45 years who are at risk of prostate cancer. The current 5835103.1 Rwandan men number is then standardized to the WHO standard population between 2000-2025 (Ahmad, Boschi-pinto and Lopez, 2001).

4.2. Result tables

Table 4: Demographic characteristics of patients diagnosed with prostate cancer.

N=108

Province of origin (N=108)	**number**	**percent**
Kigali city	19	17.6
South	31	28.7
East	22	20.37
West	16	14.81
North	20	18.52
Age (N=108), (mean, range)	**71.29**	**44-89**
Age group (N=108)	**number**	**percent**
less than 60 years	12	11.11
61-70 years	46	42.59
71-75 years	13	12.04
more than 75 years	37	34.26
Ubudehe category (N=108)	**number**	**percent**
category 1	10	9.34
Category 2	4	3.74
category 3	91	85.05
Category 4	2	1.87
Insurance (N=108)	**number**	**percent**
Community Health Based Insurance (CBHI)	97	89.81
Rwanda Social Security Board Insurance (RSSB)	11	10.19

Table 5: Signs and symptoms at presentation

Presenting complaints	**number**	**percent**
Lower urinary tract symptoms (LUTS) (N=108)	107	99.07
Acute urinary retention (AUR) (N=108)	50	46.3
Lower back pain/bone pain (N=107)	56	52.34
neurological impairment in lower limbs (N=108)	23	21.3
erectile dysfunction (N=108)	40	37.04
Hematuria (N=107)	5	4.67
Symptoms duration in months(median, IQR)	12	(8,24)
Symptom duration in months (N=108)	**number**	**Percent**
Less than 3 month	10	9.26
3-6 months	10	9.26
6-12 months	43	39.81
12-24 months	30	27.78
more than 24 months	15	13.89
Family history of prostate cancer in 1st degree relative (N=108)	**number**	**percent**
No	51	47.22
Unknown	43	39.81
Yes	14	12.96
Comorbidity (N=108)	**number**	**percent**
Hypertension	13	12.04
Diabetes	2	1.85
HIV/AIDS	2	1.85
Other (cancer, cardiopathy,..)	3	2.78
None	88	81.48
ECOG† performance status score (N=107)	**number**	**percent**
0	81	75.7
1	13	12.15
2	10	9.35
3	3	2.8

† ECOG: Eastern Cooperative Oncology Group.

Table 6: Prostate cancer staging among participants

Imaging for staging (N=108)	**number**	**percent**
Pelvis and lumbosacral spine x ray	7	6.48
Abdomen and spine CT scan	70	64.81
abdomen and spine MRI	11	10.19
imaging was not done	20	18.52
Size of the prostate in ml (N=79) (mean, SD)	64	30.5
Clinical T stage (N=108)	**number**	**percent**
cT1	13	12.04
cT2	20	18.52
cT3	38	35.19
cT4	37	34.26
N stage (N=107)	**number**	**percent**
N1	47	43.93
NO	28	26.17
NX	32	29.91
M stage	**number**	**percent**
M0	39	36.45
M1B	37	34.58
M1C	3	2.8
MX	28	26.17
Stage of prostate cancer (N=90)	**number**	**percent**
Localized	20	18.52
Locally advanced(T3,T4,N+)	29	26.85
Metastatic	41	37.96
Not fully staged	18	16.67

Table 7: Total prostate specific antigen (PSA) level at presentation among participants

			Age group in years (%)				
Total PSA (N=107)	**N**	**%**	**<60**	**60-70**	**70-75**	**75+**	**P value**
less than 10 ng/ml	4	3.74	0	2(50%)	1(25%)	1(25%)	
10-20 ng/ml	12	11.21	2(16.67)	5(41.87%)	3(25%)	2(16.67%)	0.71
20-50 ng/ml	12	11.21	0(0)	6(50%)	2(16.67%)	4(33.33%)	
50-100 ng/ml	43	40.19	7(16.28%)	17(39.53%)	4(9.3%)	15(34.88%)	
More than 100 ng/ml	36	33.64	3(8.33%)	15(41.67%)	3(8.33%)	15(41.67%)	

Median PSA= 100ng/ml, range= (1.69-10000)

Table 8: Histology of prostate cancer among participants

Gleason Score	**grade group**	**number**	**percent**	
<=6(3+3)	grade group 1	1	0.93	**Gleason <= 7**
7(3+4)	grade group 2	8	7.48	27 = 25.23%
7(4+3)	grade group 3	18	16.82	
8(4+4 or 3+5 or 5+3)	grade group 4	32	29.91	**Gleason > 7**
9 or 10	grade group 5	48	44.86	80 = 74.77%
Perineural invasion (N = 108)		**number**	**percent**	
	yes	64	59.26	
	no	44	40.74	
Gleason sum (mean, SD*)		8	1	
Number of core took (N = 99) (mean, SD)		11.2	2	
Positive cores (N = 93) (median, IQR)**		10	(7,12)	
Indication of biopsy (N= 108)		**number**	**percent**	
	abnormal DRE*** and high PSA	94	87.04	
	high PSA only	10	9.26	
	abnormal tPSA/fPSA ratio	1	0.92	
	abnormal DRE only	2	1.85	
	systematic prostate biopsy for bone metastasis of unknown primary	1	0.93	

*SD: Standard deviation

** IQR: Interquartile range

*** DRE: Digital rectal exam

Table 9: Management options of prostate cancer

Treatment options done and suggested (N = 103), n (%)	**treated**	**waiting for treatment**
ADT alone	51(77.27%)	15(22.73%)
RRP	6(42.86%)	8(57.14%)
ADT+EBRT	10(45.45%)*	12(54.56%)
EBRT	0(0%)	1(100%)
total	67(65.05%)	36(34.95)
Among 67 treated	**number**	**percent**
ADT* alone	51	76.12
RRP**	6	8.96
started ADT waiting for EBRT***	10	14.92
Type of ADT (N = 61)	**number**	**percent**
bilateral orchidectomy	33	54.1
medical ADT	28	45.9
Type of medical ADT (N = 28)	**number**	**percent**
bicalutamide then goserelin	15	53.57
cyrpoteron acetate (androcure)	10	35.71
ketoconazole	3	10.71
Management of lower urinary tract obstruction (N= 53)	**number**	**percent**
urethral catheter	19	35.85
suprapubic catheter	13	24.53
one or combined medical therapy	21	39.62

*ADT: androgen deprivation therapy

**RRP: Radical retropubic prostatectomy

***10 people are on goserelin while waiting for combination with external beam radiation therapy (EBRT)

Inferential statistics.

Table 10: Bivariable analysis of factors associated with high grade prostate cancer

		high grade prostate cancer		
Clinical T	**N**	**n**	**%**	**P value**
cT1	13	6	46.15	
cT2	20	13	65	0.001
cT3	38	27	71.05	
cT4	36	34	94.44	
PNI	**N**	**n**	**%**	**P-value**
no	43	25	58.14	0.002
yes	64	55	85.94	
PSA categories	**N**	**n**	**%**	**P-value**
less than 10 ng/ml	4	2	50	
10-20 ng/ml	12	7	58.33	0.089
20-50 ng/ml	12	7	58.33	
50-100 ng/ml	42	32	76.19	
more than 100 ng/ml	36	31	86.11	
Age categories	**N**	**n**	**%**	**P-value**
less than 60years	12	10	83.33	
61-70 years	45	31	68.89	0.73
71-75 years	13	10	76.92	
more than 75 years	37	29	78.38	

Table 11: Multivariable analysis of factors associated with high grade prostate cancer

	Gleason sum>7					
	unadjusted model			adjusted model		
Clinical T	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
cT1	**1**			1		
cT2	2.6	(0.59-11.30)	0.2	2.68	(0.45-15.69)	0.27
cT3	3.43	(0.89-13.18)	0.07	2.55	(0.44-14.73)	0.29
cT4	23.8	(3.81-148.44)	0.001	16.13	(1.98-131.02)	**0.009†**
PNI						
no	1			1		
yes	4.32	(1.70-10.9)	0.002	4.25	(1.52-11.90)	**0.006**
PSA categories						
< 10 ng/ml	1			1		
10-20 ng/ml	1.4	(0.14-13.56)	0.77	0.82	(0.04-15.39)	0.89
20-50 ng/ml	1.4	(0.14-13.56)	0.77	0.92	(0.04-19.89)	0.95
50-100 ng/ml	3.2	(0.39-25.73)	0.27	1.23	(0.06-22.12)	0.88
> 100 ng/ml	6.2	(0.70-54.61)	0.1	2.38	(0.11-49.09)	0.57

†Clinical T4 is significantly associated with high grade cancer (P value=0.009)

Table 12: Bivariable analysis of factors associated with prostate cancer metastasis.

		Metastasis of prostate cancer		
PSA category	**N**	**n**	**%**	**P value**
<= 20 ng/ml	13	**1**	7.69	
> 20 ng/ml	75	**39**	520	**0.005**
Gleason sum				
Gleason<=7	**25**	**3**	12	**<0.0001**
Gleason >7	**64**	**36**	56.25	
Clinical T				
cT1	**10**	**1**	10	**0.001**
cT2	**20**	**8**	40	
cT3	**30**	**9**	30	
cT4	**29**	**21**	72.41	
PNI				
no	**35**	**11**	31.43	**0.08**
yes	**54**	**28**	51.85	

Table 13: Multivariable analysis of factors associated with metastasis of prostate cancer

	Metastasis of prostate cancer					
	unadjusted model			adjusted model		
PSA category	**OR**	**95% CI**	**p value**	**OR**	**95% CI**	**p value**
<= 20 ng/ml	**1**			**1**		
> 20 ng/ml†	13	1.6-105	**0.016**	13.22	1.35-128	**0.026**
Gleason sum						
Gleason<=7	**1**			1		
Gleason > 7	9.42	2.56-34.71	**0.001**	4.76	1.1-20.6	**0.036**
Clinical T						
cT1	1			1		
cT2	6	0.63-57.0	0.12	3.37	0.24-46.06	0.36
cT3	3.85	0.42-35.11	0.23	1.29	0.1-16.43	0.84
cT4	23.62	2.56-217.67	**0.005**	7.7	0.57-101	0.12
PNI						
no	1			1		
yes	2.26		**0.07**	1.76	0.58-5.36	0.315

p value < 0.05 is significant

†PSA > 20 ng/ml significantly predicts metastasis of prostate cancer (p value = 0.026)

Table 14: Summary of characteristics of patients with prostate cancer

ASR incidence/100000		**13.56/100000**	
PSA (N=107)		**number**	**percent**
	>20 ng/ml	91	85.04
	<20 ng/ml	16	14.96
PSA ng/ml (median, range)		100	1.69-10000
Gleason sum (N=107)	<=7	27	25.23
	>7	80	74.77
Gleason sum (mean, SD)		8	1
Number of core taken (N=99) (mean, SD)		11.2	2
Number of positive core (N=90) (median, IQR)		10	(7,12)
Staging, (N=108)	Localized	20	18.52
	locally advanced(T3,T4,N+)	29	26.85
	metastatic	41	37.96
	Not fully staged	18	16.67
Age (N=108), in years (mean, range)		71.29	44-89
Symptoms, (N=108)	LUTS	107	99.07
	AUR	50	46.3
	neurological impairment in lower limbs	23	21.3
Symptoms duration in months (median, IQR)		12	8,24
Family History	unknown	43	39.81
	yes	14	12.96
Treatment (N=67)	ADT alone	51	76.12
	RRP	6	8.96
	started ADT waiting for EBRT	10	14.92
Type of ADT(N=61)	bilateral orchidectomy	33	54.1
	medical ADT	28	45.9
Medical ADT (N=28)	bicalutamide then goserelin	15	53.57
	cyproterone acetate(androcure	10	35.71
	ketoconazole	3	10.71
Management of LUTO* (N=53)	urethral catheter	19	35.85
	suprapubic catheter	13	24.53
	one or combined medical therapy	21	39.62

*LUTO: lower urinary tract obstruction

V. DISCUSSION

Over 6 months, the current study enrolled 108 Rwandans diagnosed with prostate cancer. They were evenly distributed across the country. Their mean age is 71.29 years with a range of 44-89 years, this is consistent with the findings in one study on blacks of South Africa where their mean age was 71 years and a range of 45-101 years (Tindall *et al.*, 2014). The most affected age group was 60-70 years, counting 42.49% of patients however a group of more than 75 years had a good proportion of symptomatic prostate cancer as well (34.26%).

This study reveals even distribution of high grade histology in all age groups. This differs from findings of some other studies that showed an association of elder ages with high grade tumors (Pepe and Pennisi, 2014). The median symptoms duration was 12 months IQR (8, 24) and 90.74% (98/108) had symptoms more than 3 months prior to the consultation. This is consistent with the findings of the study of Forbes et al where he found that patients with lower urinary tract symptom associated with prostate cancer were most likely to present late compared to other studied cancers. Lack of awareness of the significance of symptoms was a common reason for the delay (Forbes *et al.*, 2014) (Tiwari *et al.*, 2015). Other studies revealed that benign prostate hyperplasia (BPH) related LUTS in prostate cancer patient may be due to the fact that BPH can coexist with prostate cancer thus its symptoms not influencing the behavior of prostate cancer (Weight *et al.*, 2013) (Young *et al.*, 2015). However, symptoms were found to have a significant positive predictive value for prostate cancer in some other series (William Hamilton, 2006), therefore confirming the need for an early consultation when those symptoms appear to avoid unnecessary delays.

In this study, only 13.96% (14/108) participants had a positive family history of prostate cancer in the first degree relative. Although the findings are comparable with other studies where family history was present in 12% (Weight *et al.*, 2013), it is possible that in the current paper, the family history is underreported because many patients don't know what killed their relatives as prostate cancer diagnosis was not widespread in Rwanda a few years ago. Patients with a family history were likely to present between 60-70 years old, where 13/14 (92.85%) presented in that age range (p value=0.001) however their PSA, Gleason score and clinical T stage were similar to other study participants. This is in agreement with other studies where earlier onset was a fact with a mean age of diagnosis was 62.8 years (Cremers *et al.*, 2016).

The current study detected 108 new cases of prostate cancer in Rwanda making a country estimate of age standardized incidence rate of 13.56 per 100000 men year. This underestimates the true incidence of prostate cancer in the country as these only accounts for patients who presented to the hospital. There might be some patients in the community having asymptomatic cancers, or too sick to travel to Kigali or lacking financial means to travel to the hospital who didn't show up. However, this is comparable to the incidence of prostate cancer in Africa estimated by Adeloye et al to be 13.3/100000 population between 2010 and 2015 (Adeloye *et al.*, 2016). This age standardized incidence is less compared to the one found in New Zealand/Australia and Northern America of 111.6 and 97.2/100000 respectively but higher than the worldwide lowest incidence as low as 10.5 and 4.5 in Eastern and South Central Asia (Ferlay *et al.*, 2012).

Where awareness and PSA screening are strong, the incidence of prostate cancer has been shown to rise, with the example of Europe where the highest age standardized incidence of prostate cancer was estimated by Ferlay et al to be 189/100000 in Ireland and lowest in Albania (37/100000) (Ferlay *et al.*, 2018). The estimated incidence is lower compared to 40.6 per 100000 found in Kenya using the Nairobi cancer registry (Korir *et al.*, 2015). This difference is believed to be based on different awareness of prostate cancer across the population. It is believed that the variability in the incidence of prostate cancer worldwide is due to the difference in the accessibility of health care in African countries, health seeking behavior of African people (Methods R. et Al, 2007), lack of prostate cancer awareness in general population of Rwanda and Africa in general, and nonexistent PSA based prostate cancer detection in most African countries and other LMICs.

An abnormal digital rectal exam was found in 88.89% (96/108) of patients with prostate cancer. This means that even without PSA testing, the clinician could have detected 88.89% of mostly advanced cancer cases. From this finding, DRE can be confidently used as first line prostate cancer detection methods in setting where systematic PSA is lacking because its positive predictive value was found to be in acceptable range especially in those patients with high PSA (Catalona et al., 1994) (Schro et al., 1998).

The current study demonstrated that 99.07% consulted with lower urinary tract symptoms. This means that people tend to consults if they have a bothering symptom, leading to delayed presentation probably due to poor knowledge about prostate cancer in the community or

difficulty in accessing specialized health facilities (Methods R. et al, 2007). These contribute to the detection of a big proportion of advanced prostate cancer wherein the current paper, 37.96% (41/108) patients had distant metastasis and 26.85% (29/108) patients had locally advanced disease. These findings are comparable with other studies done in Sub-Saharan Africa like in Uganda where 90% presented with stage IV prostate cancer (Cooney, Okuku and Orem, 2016). A comparable result was found in a study done in South Africa where most patients with prostate cancer consult because of symptoms related to urinary flow (Tindall *et al.*, 2014). The finding is in contrast with studies done in high income countries like the USA where localized prostate cancer are commonly detected with only 4% presenting with distant metastasis (Brawley, 2012a)

The median PSA at presentation in this study was 100ng/ml (ranging from 1.69-10000). This is comparable to other studies like Uganda where the median baseline PSA was 91.3 (range19.3-311.5) ng/ml (Cooney, Okuku and Orem, 2016). Findings are opposed to a study in Italy where the median PSA was 9.6 ng/ml (Pepe and Pennisi, 2014).

Our findings are in favor of Gleason score of 8 or more in 74.77% of patients, with a median Gleason of 8 confirming the presence of more aggressive disease in Rwandan in particular and in black in general. Similar results were found in Nigeria where 74.4 % of prostate cancer detected in a study was having a Gleason score of 8 or more (Ikuerowo *et al.*, 2013). In contrast to the finding among Caucasian in Italy where the Gleason was relatively lower with a median Gleason Score of 7 (Pepe and Pennisi, 2014) and in the USA where the Gleason scores of 8 or more were found in 15.2% (Herget *et al.*, 2016) (Brawley, 2012a).

Our study found that total PSA >20ng/ml is associated with distant metastasis (aOR=13.22; p value=0.026). The same findings were revealed in other several studies where a PSA >20 ng/ml consistently correlated with bone metastasis (Singh *et al.*, 2012) (Mittal *et al.*, 2013).

Among 67 patients who have already received treatment in this study, 76.12% (51/67) had received ADT as the only treatment modality compared to 8.95% (6/67) who underwent radical prostatectomy with curative intent. The findings are different from what is found in the US where radical prostatectomy rate was 25.5% and radiotherapy 45.5% (Mahal *et al.*, 2014).

Urologists in Rwanda refer to NCCN guidelines version 4.2018 on prostate cancer for patient care. Patients who were fitting for radiotherapy were still on the waiting list as the unit was being established in Rwanda during the study period (Kisambira", 2017). The majority of patients still accept bilateral orchidectomy (33/61, 54.1%) which is a cost effective technique (De Paula *et al.*, 2003) (Rud *et al.*, 2011) as not many of them can afford medical androgen deprivation therapy. This is in contrast to the finding of other studies performed in LMICs like Uganda where bilateral orchidectomy was as low as 29.2% (Cooney, Okuku and Orem, 2016) for unclear reasons.

The common denominator is the late presentation in many LMICs leading to the detection of more advanced disease where curative intent in no longer an option and patients often suffer long debilitating courses. Similar findings are shared in different studies done in African countries where the majority of patient presents with advanced diseases when curative intent is no longer a possibility and almost every patient receives androgen deprivation therapy with rare radical therapy (Cooney, Okuku and Orem, 2016). The late presentation in LMICs can also be attributed to the lack of adapted prostate cancer screening policies in most of their communities as opposed to the developed countries where screening policies, access to health care, and population awareness are improved in most areas (Ebell, Thai, and Royalty, 2018). The late detection can also be attributed to the fact that Rwanda still has a small number of urologists and limited diagnosis facilities making patients waiting for long time before consultation("Mnistry of health, 2018)

The detection of primarily advanced and high grade disease in the majority of LMICs should prompt the development of a specific prostate cancer screening guidelines for LMICs (Ikuerowo *et al.*, 2013) to tackle the associated morbidity and mortality in sub-Saharan Africa.

VI. CONCLUSION AND RECOMMENDATIONS

6.1. Conclusion

Prostate cancer is a real global health burden, especially in Sub-Saharan Africa. Inadequate public awareness, scarcity of specialized health facilities, and lack of policy on early detection and management of prostate cancer lead to its late presentation, where palliative treatment is the remaining option. LMICs are in front of a dilemma between starting PSA based prostate cancer screening that may lead to the detection of many patients going beyond their treatment capacity but also, on the other hand, a laissez-faire attitude put them in a painful condition of managing more patients with advanced disease. Therefore, there should be a middle way aiming at seeing patients earlier when the cancer is still controllable (localized and locally advanced stage) through systematic DRE in men above 50 years and PSA to those having abnormal DRE.

6.2. Recommendations.

- We recommend widespread use of digital rectal exam; PSA based informed testing for diagnosis purpose in clinically indicated patients by general practitioners district hospitals of Rwanda especially on men above 50 years to allow detection of prostate cancer when they are still curable in order tackle mortality and morbidity associated with late presentation.

- We recommend the development of national guidelines on the management and early diagnosis of prostate cancer to help practitioners in early diagnose to reduce the current mortality and morbidity due to the advanced stage in Rwanda.

- Increase public awareness in the local population about prostate cancer so that Rwandan people get the habit to do an informed checkup of prostate cancer.

- People with a positive family history of prostate cancer should be informed to get earlier PSA and DRE screening

- Bigger studies for a longer period on the profile of prostate cancer in Rwanda to further characterize some aspects like genetic inheritance and risk factors and outcome of care that have not been elicited in the current paper are recommended.

VII. REFERENCES

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VIII. APPENDIX

Informed Consent

Title of the study: pattern and management of prostate cancer in Rwanda: a multicenter prospective study

I, …… agree to participate in the study

Pattern and management of Prostate cancer in black Rwandans: a multicenter prospective study.

I am aware that participation in the study is voluntary and I will not be paid for the participation. Also, 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

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Supervisor: Prof Emile RWAMASIRABO Tel- 0788 35 66 47

Chairperson Institutional Review Board CMHS: Prof Kato J. NJUNWA Tel 0788490522

Deputy Chairperson CMHS/IRB: 0783 340 040

Data collection form

Demographic characteristics

Date: ….. /….. /…….

Title of the study: Pattern and management of prostate cancer in Rwandans: a multicenter prospective study

Demographic characteristics:

1. Patient ID number …….

2. Initials….

3. New Identifier:…..

4. Tel:.....

5. Hospital consulted for the first time of symptoms:….

6. Hospital where biopsy is taken:….

7. DOB …. /…../….. Nationality……

8. *Referring hospital>>>

9. District of origin…

10. Marital status: a) Single.., b) Married… , c) Widowed…

11. Insurance: a) No:…. b) Yes:….

*Type of insurance:…

12. Ubudehe category: a) Categ1 b) Categ 2 c) Categ 3 d) Categ 4

Clinical characteristics

13. Complaints: a) LUTS b) AUR c) Lower back pain d) Erectile dysfunction

e) Lower limb weakness/neurological impairment f) Hematuria/hematospermia g) Check up h) Incidental when consulted for other conditions i) Other:…(precise)

14. Date of the first consultation:….

15. Duration of symptoms:…

16. PSA: Free:…. Total:…

17. DRE: a) Normal:…. b) Abnormal (Nodular, firm, hard)

*Clinical T:…. Size of prostate:…

18. Indication of biopsy: a) high PSA b) Abnormal DRE C) Both, d) Mets suspected to come from the prostate.

19. Biopsy: a) Transrectal core biopsies b) TURP specimen

c) Specimen from simple prostatectomy

*Number of cores taken if transrectal core biopsies….

20) Complication of prostate biopsy: a) no…b) yes… c) Precise..

21. Histology results: a) Histological Type… b) Gleason score:… c)Gleason grade group:… d)Number of core taken… e) Number of cores with cancer… f) PNI:… yes no g) LVI: no/yes h) Presence of inflammation: yes/ no

22. Imaging for staging: a) Abdominal pelvic CT scan… b) Pelvis MRI… c) Simple x-ray… d) Not done… e) Other…

g) N stage:… h) M stage:…

23. Factors associated with prostate cancer

a) Family history in first degree relative: yes/no b) Unkown:….

24. Comorbidities: a) None b) HIV/AIDS C) Hepatitis C d) Hypertention

e) Diabetes mellitus f) Hepatitis B j) Other cancer…(precise) h) Others…(precise)

25. ECOG score: a) 0 b) 1 c) 2 d) 3 e) 4 f) 5

26. EAU risk groups: a) Low risk b)intermediate risk c) high risk e) regional risk d) metastatics

Treatment options:

27. Primary Treatment options: a) Watchful waiting….. b) Active surveillance…. c) Radical prostatectomy…. d) External beam radiotherapy and ADT:… e) Brachytherapy:….. f) ADT alone

28. Type of ADT: a) Medical b) bilateral orchidectomy

29. Type of medical ADT: Precise

30. Chemotherapy:…. (Precise the molecules)

31. treatment of LUTO: a) Tunnel TURP… b) Urethral catheter… c) Suprapubic catheter,…

32. Other best supportive cares:

d) Bisphosphonate e) Calcium f) Vitamin D g) Painkillers h) other (precise)….

CMHS/IRB ethical approval notice

UNIVERSITY OF RWANDA — COLLEGE OF MEDICINE AND HEALTH SCIENCES

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 10th /07/2018

Dr Alexandre NYIRIMODOKA
School of Medicine and Pharmacy, CMHS, UR

Approval Notice: No 245/CMHS IRB/2018

Your Project Title ***"Pattern And Management Of Prostate Cancer In Rwandans: A Multicenter Prospective Study"*** has been evaluated by CMHS Institutional Review Board.

		Involved in the decision		
			No (Reason)	
Name of Members	**Institute**	Yes	**Absent**	**Withdrawn from the proceeding**
Prof Kato J. Njunwa	UR-CMHS		X	
Prof Jean Bosco Gahutu	UR-CMHS	X		
Dr Brenda Asiimwe-Kateera	UR-CMHS	X		
Prof Ntaganira Joseph	UR-CMHS	X		
Dr Tumusiime K. David	UR-CMHS	X		
Dr Kayonga N. Egide	UR-CMHS	X		
Mr Kanyoni Maurice	UR-CMHS	X		
Prof Munyanshongore Cyprien	UR-CMHS	X		
Mrs Ruzindana Landrine	Kicukiro district		X	
Dr Gishoma Darius	UR-CMHS	X		
Dr Donatilla Mukamana	UR-CMHS	X		
Prof Kyamanywa Patrick	UR-CMHS		X	
Prof Condo Umutesi Jeannine	UR-CMHS		X	
Dr Nyirazinyoye Laetitia	UR-CMHS	X		
Dr Nkeramihigo Emmanuel	UR-CMHS		X	
Sr Maliboli Marie Josee	CHUK	X		
Dr Mudenge Charles	Centre Psycho-Social	X		

After reviewing your protocol during the IRB meeting of where quorum was met and revisions made on the advice of the CMHS IRB submitted on 21st May 2018, **Approval has been granted to your study.**

EMAIL: researchcenter@ur.ac.rw P.O. Box: 3286, Kigali, Rwanda WEBSITE: http://cmhs.ur.ac.rw/ www.ur.ac.rw

Please note that approval of the protocol and consent form is valid for **12 months.**

You are responsible for fulfilling the following requirements:

1. Changes, amendments, and addenda to the protocol or consent form must be submitted to the committee for review and approval, prior to activation of the changes.
2. Only approved consent forms are to be used in the enrolment of participants.
3. All consent forms signed by subjects should be retained on file. The IRB may conduct audits of all study records, and consent documentation may be part of such audits.
4. A continuing review application must be submitted to the IRB in a timely fashion and before expiry of this approval
5. Failure to submit a continuing review application will result in termination of the study
6. Notify the IRB committee once the study is finished

Sincerely,

Date of Approval: The 10th July 2018

Expiration date: The 10th July 2019

for Professor Kato J. NJUNWA
Chairperson Institutional Review Board,
College of Medicine and Health Sciences, UR

Prof. UB Gakwaya
Vice Chair

Cc:
- Principal College of Medicine and Health Sciences, UR
- University Director of Research and Postgraduate Studies, UR