Original Article

Clinical and Histopathological Profile of Patients with Prostate Cancer in Kampala, Uganda

James Joseph Yahaya

[1]*Department of Pathology, Makerere College of Health Sciences (MakCHS), Makerere University P. O. BOX 7076, Kampala-Uganda.*

[2]*Department of Anatomy and Histology, College of Health Sciences, The University of Dodoma, P. O. BOX 395, Dodoma, Tanzania. E-mail: mashimba2009@yahoo.com*

ABSTRACT

Background: Prostate cancer (PCa) is the most prevalent malignancy among adult men with marked variation in mortality rate across regions globally. Uganda has the highest incidence of prostate cancer in East Africa. This study explored the spectrum of clinical and histopathological profile of patients diagnosed with PCa in Uganda between 2012 and 2014 at the Department of pathology, Makerere College of Health Sciences (MakCHS).

Methods: This was a descriptive cross-sectional study aimed at providing an update of the spectrum of clinical and histopathological profile of patients with PC in Uganda. The study involved 211 cases diagnosed at the department of pathology between 2012 and 2014. After obtaining ethical clearance to carry out the study from the school of biomedical science; laboratory requisition forms collected, were used to extract the biodata information and also selection of the cases. Having selected the cases by using non-probability approach, tissue blocks were retrieved from the archive of the laboratory, sectioned and stained with haemtoxylin and eosin stains and cover-slipped before being examined by the investigator. Data generated were entered in the data collection form and analysis for frequency and descriptive statistics was done using SPSS version 16.0.

Results: The study involved 211 patients with prostate cancer. The median age at diagnosis was 70 years and most of them, 82.9% had total PSA≥ greater than 4.0ng/ml. Incomplete voiding of urine was the most common clinical feature which accounted for 43.6% and more than half, 61.2% of the patients had advanced disease. Almost half of the patients (44.6%) had Gleason score ≥8 and 47.9% of all the cases were in high risk group.

Conclusions: Majority of patients with PCa in Uganda have raised pre-treatment total PSA and most of them are diagnosed with advanced disease. They also have high parameters of biologically aggressive prostate cancer such as Gleason score, lymphovascular invasion, perineural invasion and positive surgical margins.

INTRODUCTION

Over the last 20 years, an increasing trend of various cancers has been observed in the new cases and deaths worldwide. The burden of cancers including PCa, is a red flag in low-and middle-income countries (LMICs). Although there is no clear scientific reason to explain the predilection of cancers in such areas, the arguments in the literature still propose that, it could be due to varying lifestyle and behavioural patterns, geographic, genetic and environmental factors.[1,2]

Pca still remains the most prevalent cancer in Uganda among men with the highest incidence rate in the East African region and also Africa at large. In 2010, Parkin *et al* reported that the age-standardized

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incidence rate of PCa in Uganda was 39.6 new cases per 100, 000.[3] Despite that this incidence rate is very high, however, it was once documented by Parkin *et al* that the incidence rate of PCa in Uganda was even approaching 65.0 new cases per 100, 000.[4] If these incidence rates are taken into consideration to map the burden of PCa in Uganda, then it would be that, the incidence rate of PCa in Uganda, is outweighing that of Africa which is 21.95 new cases per 100, 000 as reported by Aledoye *et al* in the Systematic Review and Meta-Analysis study done at the Covenant University, Ogun State, Nigeria.[5]

Deaths from PCa are next after those resulting from lung and oesophagus cancer among men in Uganda. In 2016, Okuku *et al* reported that about 25% of the patients diagnosed with PCa in Uganda, die within one year after diagnosis.[6] Generally speaking, the mortality rate of PCa patients in Uganda is very high even when compared to that of the neighbouring countries such as Tanzania, Kenya and Rwanda. According to the World Health Organization (WHO) report, published in 2017, it was reported that the annual age-adjusted death rates for Uganda, Tanzania, Rwanda and Kenya were 51.28, 35.77, 34.75 and 32.72 per 100, 000 respectively and the number of the patients dying of PCa annually was 2, 634, 3, 309, 537 and 2, 309 respectively. In the same report, Uganda was ranking 8th in the world for Pca related deaths among men.[7] Japan is one of the Asian countries in which PCa is very common. However, it experiences very low age-adjusted death rate of patients with PCa. In the review article of Chisato *et al*, it was reported that the age-adjusted death rate in patients with PCa was between 3.2 and 4.3 per 100, 000 and in 2005, there were 9,264 deaths from PCa, accounting for 4.7% of the total number of cancer deaths in Japan.[8]

It is known that the room for clinical features to alert men to seek medical services including screening and diagnosis of PCa is little. However, if such features are not just disregarded, they can in one way or another aid in making men get alarmed and hence start seeking screening services for possible detection of PCa at early stage. This in turn would help to reduce mortality and improve survival as well. Therefore, this study explored the spectrum of clinical and histopathological profile of patients diagnosed with PCa in Uganda between 2012 and 2014 at the Department of Pathology, Makerere College of Health Sciences (MakCHS).

MATERIAL AND METHODS

This was a cross-sectional descriptive study involving 211 cases of PCa diagnosed histologically at the Department of pathology, (MakCHS) between 2012 and 2014. Because of lacking database for all cancer cases at the department, a laboratory assistant was assigned the work of collecting the laboratory requisition forms after they were first identified by the investigator using the register book of the cases. The laboratory assistant also retrieved retrieved the archived formalin fixed paraffin embedded (FFPE) tissue blocks. Each selected case was assigned a unique identification number for ethical basis. Twenty-one cases (9.1%) were excluded from the study due to poor biopsy material and missing tissue blocks.

The patients' clinical information recorded in the laboratory request forms were extracted and in case of any missing clinical information, the patients' files from the medical record department were used to supplement the necessary missing information which was required for the study. The FFPE tissue block were left to cool at 4^0C on the embedding station for 2 hours before being sectioned with the microtome by the laboratory technician. The tissue blocks were then sectioned at thickness of 4μm followed by placing them on the hot plateat 60^0C for 1 hour and then staining them using standard Harris haematoxylin and eosin stains. The prepared slides were examined using a light microscope by the investigator. When evaluating the slides under microscope the following variables were recorded: tumour grade, presence of lymphovascular invasion (LVI) and perineural invasion (PNI) as well as seminal vesicle invasion (SVI) and positive surgical margin (PSM) for cases with radical prostatectomy (RP) specimens. Gleason score (GS) system was

used for tumour grading and grades were grouped as low grade: GS ≤ 6, intermediate grade: GS 7 and high grade: GS ≥ 8. Risk stratification of the cases for clinical outcomes was done using the D'Amico classification system established in 1998, in which patients were grouped as *low risk group*: PSA ≤ 10 ng/ml, clinical stage T1 – 2A, GS ≤ 6, *intermediate risk group*: PSA 10 – 20 ng/ml, clinical stage T2B, GS 7 and *high risk group*: PSA > 20 ng/ml, clinical stage > T2B. The generated data were collected using the data sheet collection form which was prepared. The collected data were then analyzed using SPSS version 16.0 (IBM SPSS, syntax Co Ltd, US).

RESULTS

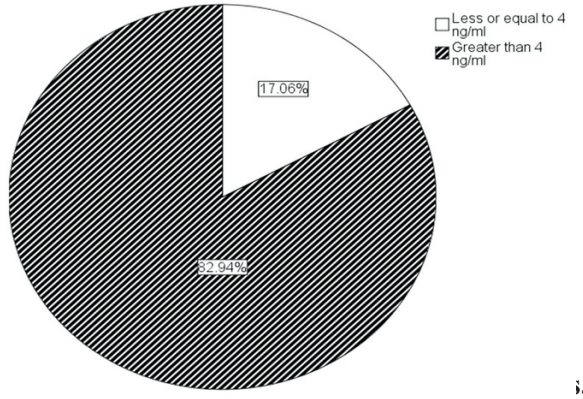
This study involved 211 patients diagnosed with prostate cancer (PCa) based on different tissue biopsies in the pathology laboratory at the Department of Pathology, MakCHS between January 2012 and December 2014. The mean age of the patient was 69.4 and 70.0 years respectively (Range: 43 – 99 years, SD = 10.85).

Table 1 shows the age groups of the study subjects. Majority of the patients, (n = 77, 36.5%) were between 61 and 70 years. Patients with age between 41 and 50 years, were only 7.6% (n = 16).

Table 1: Distribution of the subjects by age groups

Age group (Years)	No of caese (N)	Percentage (%)
41 - 50	16	7.6
51 - 60	28	13.3
61 - 70	77	36.5
71 - 80	60	28.4
81 - 90	26	12.3
91 - 100	4	1.9
Total	211	100

The median pre-treatment total prostate specific antigen (TPSA) were 294.44 ng/ml and 40.00 ng/ml respectively (Range: 2.3 – 2456.50 ng/ml, SD = 561.44). Figure 1 shows total PSA categorization of the cases. Most of the patients had pre-treatment TPSA>4.0ng/ml (n = 175, 82.9%) and few of them, (n = 36, 17.1%) had TPSA ≤4.0ng/ml



Only 17.1% of the patients in this study had serum total PSA ≤ 4.0 ng/ml.

Table 2 shows the clinical features of the patients included in this study which were varying from mild to severe and alarming ones. Majority of the patients in this study had lower urinary tract symptoms (LUTS) at initial presentation. Incomplete voiding of urine was the most common clinical feature (n = 92, 43.6%) followed by back pain (n = 40, 19.0%) which presented as mild to severe pain. Of all the cases studied, a significant number of patients, (n = 25, 11.8%) had missing clinical features in either the laboratory request forms or patients' files.

Table 2: Clinical characteristic features of the subjects

Clinical feature	No of cases (N)	Percentage (%)
Incomplete voiding	92	43.6
Back pain	40	19.0
Increased frequency of urination	29	13.7
Haematuria	20	9.5
Lower limbs weakness	15	7.1
Spinal cord compression	20	9.5
Paraplegia	16	7.6
Nocturia	21	14.2
Others	31	14.7
Missing	25	11.8

Figure 2 shows the clinical stages of the cases at diagnosis. Of all the 211 patients studied, most of them, (n = 130, 61.2%)were diagnosed at advanced stage (stage III and IV). Only (n = 30,

14.2%) of all the cases had stage I at the time of initial diagnosis

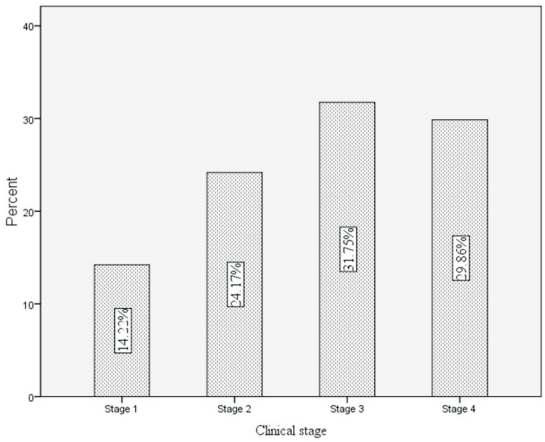


Figure 2: Distribution of the subjects by clinical stages. Most of the patients had advanced clinical stages and only 14.2% of all the cases had clinical stage I.

Figure 3shows extraprostatic extension (EPE) of PCa which was assessed based on the information provided in both the laboratory request forms and some of the patients' files. Regarding EPE among patients for this study, it was found that,(n = 82, 38.9%) of all the cases had PCa confined to the prostate organ whereas (n = 67, 31.8%) and (n = 62, 29.4%) had locally advanced and completely metastatic PCa respectively. Therefore, in this study, it was found that, 61.2% of the cases had advanced PCa. The commonest area of distant metastasis of the tumour in this study was the vertebral column bone followed by urinary bladder.

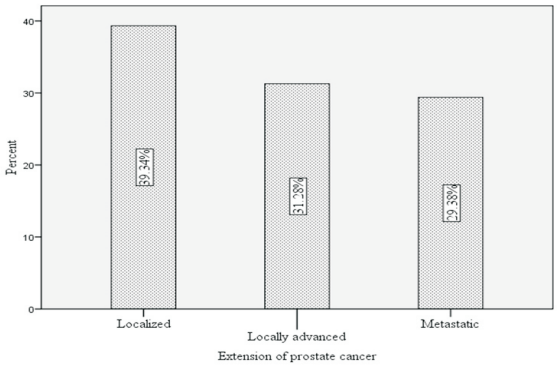


Figure 3: Distribution of the subjects by spreading of prostate cancer. More than half of the patients had PCa spreading outside the capsule.

Figure 4 shows grading of PCa in this study which was done using Gleason score system. The mean and median Gleason score were 7.2 and 7.0 respectively (Range: 5 – 10, SD = 1.27). Majority of the patients had high tumourgrade (poorly differentiated) of PCa (n = 94, 44.6%) and (n = 66, 31.3%) of the cases had lowtumour grade (well differentiated).

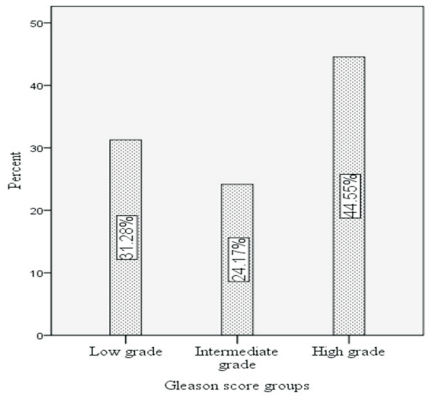


Figure 4: Gleason score grade groups of the subjects.Most of cases in this study had Gleason score ≥ 8.

Figure 5 shows risk stratification of the patients which was done using the most popular system, D'Amico classification. Majority of the patients were in high risk group (HRG), (n = 101, 47.9%). Patients with intermediate and low risk groups were (n = 69, 32.7%) and (n = 41, 19.4%) respectively.

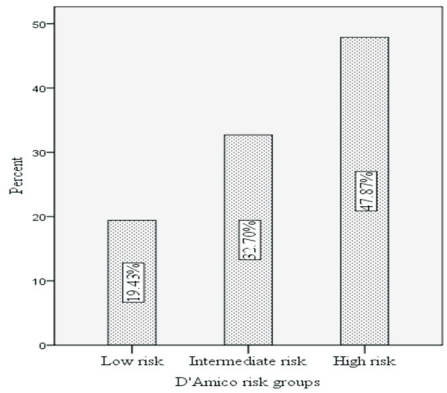


Figure 5: Distribution of the subjects by D'Amico classification of risk groups. Only 19.4% of all the patients studied were in low risk group.

Table 3 shows other histopathological characteristics which were evaluated in this study. Of the specimens submitted for histopathological evaluation, it was found that majority of them, (n = 119, 56.4%) were needle cores. Both surgical margins and seminal vesicle involvement were also evaluated in (n = 61, 28.9%) of all the 211 who had localized PCa and underwent RP surgical treatment. PSM and SVI were found in (n = 22, 36.0%) and (n = 27, 44.3%) respectively.

LVI was positive in (n = 64, 30.3%) cases and PNI was positive in(n = 48, 22.7%) cases.

Table 3: Other histopathological characteristics evaluated

Characteristics		No. of cases (N)	Percentage (%)
Biopsy	Cores	119	56.4
	TURP	54	25.6
	RP	58	27.5
LVI	Positive	64	30.3
	Negative	147	69.7
PNI	Positive	48	22.7
	Negative	168	77.3
SVI	Positive	20	32.8
	Negative	41	67.2
PSM	Positive	22	36.1
	Negative	39	63.9

TURP- Transurethral prostatectomy.

DISCUSSION

This study retrospectively investigated the clinical and histopathological profile of 211 patients who were diagnosed with PCa on histological biopsies. The median age at diagnosis of the patients in this study was keeping in line with findings from many studies done in both developing and developed countries. In 2005, Gondos and associates reported a median age of 70 years of patients with PCa in Uganda.[9] In another study done in USA, similar median age was found.[10] However, a slightly higher median age of 73.6 years was reported in Japan by Ukawa *et al*.[11] The mean age at diagnosis was also almost close to many findings.[12,13] In most of published works, the mean age for patients with PCa is between 68 and 74 years of which the mean age of the patients in this study (69.4 years) was within the interval.[8,11,12,13] The similarity in both mean and median age in patients with PCa in most of studies from different settings globally, indicates that, Pca commonly occurs at advanced age in general regardless of the race and geographical location globally, although they are some minor differences whereby in other settings, the mean age at diagnosis of PCa is slightly lower compared to most of the settings.

The mean preoperative total prostate specific antigen (TPSA) in this study was as higher as what has been documented in large number of studies done in developing countries even thoughit was not exactly similar.[14,15,16] Studies have shown that, patients with PCa in developed countries have lower PSA at baseline. In 2012, Kryvenko *et al* found that the mean PSA among the 345 patients with PCa was 26.8 ng/ml.[17] Likewise in the report of 2007 of the Scandinavian study group of PCa, it was found that the mean PSA was 12.0 ng/ml.[18] The existing difference in baseline preoperative PSA between developed and the developing countries is that, in developed countries, there is a high uptake of PCa screening by PSA testing which is done objectively unlike in the developing countries but also being black is another factor attributed to high PSA.[19]

Regarding the clinical features of patients in this study, the findings were in agreement with other findings in the literature. Studies point out that, most of patients with PCa tend to present with LUTS despite that this feature is lacking specificity. In the study done in Cameroon in 2018, it was found that majority of patients with PCa had features of incomplete voiding of urine (n = 153, 18.8%) of all the 814 that were included in the study.[20]This proportion was lower than what was found in the current study (n = 92, 43.6%). A very high proportion of urine obstruction was also found

among patients with PCa in Uganda in the study done by Okuku *et al* 2016 in which (n =131, 73.0%) had urine obstruction, which is higher than what was found in this study.[6] The findings of patients with incomplete voiding of urine in this study was almost similar to what was reported by Yongolo in Tanzania in 2004 whereby (n = 86, 43.6%) of all the 209 cases studied had incomplete voiding of urine.[21] Tindall *et al* in 2014in South Africa found that inability to pass urine was the dominating complaint (n = 665, 72.3%) out of all 920 cases.[13]In a study done in Port Harcourt, Nigeria, it was found that all the 206 patients with PCa studied had LUTS.[22] LUTS although is not specific for PCa, however, it has been found to be associated with PCa and especially the indolent type.[22,23] Therefore, men presenting with LUTS having age 40+ at the same time, ought to be subjected under rigorous screening tests for PCa including serum PSA, digital rectal examination (DRE) and ultrasound.[24] This helps to detect PCa or excluding it knowing that there other many conditions that can also present clinically with LUTS.

As it is common for cancer patients in developing countries to seek medical intervention at late stage; most of patients in this study were diagnosed already at advanced clinical stage. This observation is in keeping with findings from many studies done in developing countries. For example, Okuku *et al* 2016 in Uganda found that (n = 136, 9%) of the patients included in the study had clinical stage IV at initial presentation. This is one of the highest percentage recorded in the literature.[6] Ekwere *et al* in Calabar, Nigeria found that (n = 118, 84.9%) of the PCa patients studied had clinical stage III and IV.[25] To show that the problem of patients being diagnosed with advanced PCa as it is normally for other cancers in developing countries is like a rule of thumb, Odubanjo and associates from Nigeria, reported a rate of 47.5% of patients with PCa who were found to have clinical stage III and IV at diagnosis.[6,26] The opposite picture on clinical stages of patients with PCa is seen in developed countries. Majority of patients with PCa in developed countries have low clinical stage at diagnosis. In the study done by Winter *et al* in 2017 to compare the trends in clinical stage among patients with PCa between Germany and USA, it was found that, patients with clinical stage III and IV were 9.5% and 4.5% for Germany and USA respectively.[27] The main reason for patients with PCa in developed countries to have advanced clinical stage at diagnosis is that the uptake of screening for PCa is very low as well as poor health seeking behaviour together with low socio-economic status (SES) are the dragging forces for delayed diagnosis.

The high Gleason score in majority of patients in this study is in line with what was found by Okolo *et al* 2008, Nakandi *et al* and Jalloh *et al*.[16,28,29] These studies reported that patients with PCa in the sub-Saharan countries have high grade Gleason score unlike those in the developed countries. In 2016, Rugwizangoga*et al* reported that, 34.6% of the patients with PCa in Tanzania had high grade Gleason score.[16]Patients with PCa in developed countries are diagnosed while still at low clinical stage and most of the patients tend to have low Gleason score. Pedro *et al* in Portugal, reported that 90.0% of the 429 patients with PCa had Gleason score 6 and the remaining 10.0% had Gleason score 7.[30] The high Gleason score for patients with PCa in developing countries is reflected by advanced clinical stage and also raised PSA at initial presentation in the health facilities.

Studies have shown that there are features, such as positive surgical margins (PSM), seminal vesicle invasion (SVI), lymphatic vessel invasion (LVI) and perineural invasion (PNI), are associated with biochemical failure in PCa patients. The proportion of patients with positive LVI in this study was higher than the proportion of PCa patients reported by Baydar *et al* in Turkey and Brooks *et al* in USA of 15.5% and 11.0% respectively.[31,32] Huang *et al* and Jeon *et al* also found a low rate of PCa patients in their studies.[33,34] Kang *et al* in Korea reported a rate of 69.3% of patients with PCa having PNI which is higher than the 22.7% found in this study.[35] In the study done by Jeon *et al* found 42.0% of PCa

patients which is also higher than the rate of PNI positive cases in the current series. What can be observed when the biological behaviour of PCa in involving the vascular system and neural system is that PCa tend to spread to nerves more frequently than involving vascular structures.

Wide variations in the incidence of positive surgical margins (11-48.0%) have been reported at the time of radical prostatectomy (RP).[36] Positive surgical margins (PSM) in this study was 36. 0%, which is in agreement with the range seen in most of the published articles. Kyei *et al* in Ghana reported a PSM rate of 15.0% of patients with PCa in their study, lower than what was found in the current study.[37]In another study done by Makoto *et al* in Japan, it was found that, PSM was present in 27.1%, slightly lower than what was found in the current study.[38] This can be explained by the reason that adult men in Japan have very good uptake of PCa screening compared to those in Uganda. Seminal vesicle invasion (SVI) carries a great role because of being used as one of the histopathological predictors of biochemical recurrence of PCa. For this reason, it is associated with poor survival. The proportion of cases with SVI in this study was higher than what was reported in the series of Marcello *et al* (n = 109, 27.3%), Billis *et al* (n= 34, 12.9%) and Parra *et al* (n = 20, 7.0%).[39,40,41]

Pre-treatment risk stratification of patients with PCa has been found to be of paramount importance in management and selection of patients aiming at improving prognosis. D'Amico risk classification system for patients with PCa which was established in1998, has been used extensively in risk grouping of PCa patients. The large percentage (47.9%) of patients with high risk group (HRG) classification in this study was very close to 46.5% which was found by Gabriele *et al* but slightly lower than the 50.8% that was reported by Hosein *et al*.[42,43]

CONCLUSIONS

The majority of patients with PCa in Uganda clinically present with lower urinary tract symptoms, raised total PSA and advanced clinical stage. Histopathologically, most of the patients have high Gleason score and a significant number of those undergoing retropubic radical prostatectomy at surgery are more likely to end up with poor prognosis because quite a large number of them carry the predictors of biochemical recurrence such as PSM, SVI, LVI and PNI.

Data Availability statement

All data used in preparation of this paper can be obtained from the author upon request.

Conflict of interest

The author has no conflict of interest to disclose.

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