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A Retrospective Study of Patients with Castrate Resistant Prostate Cancer at Muhimbili National Hospital, Tanzania

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Abstract

Background
Prostate cancer (PC) is a common health problem among men globally with high incidence and mortality. The mortality following PC is associated with advanced disease progressing to castrate resistance following androgen ablation therapies. While advances to address castrate resistant prostatic cancer (CRPC) have shown good results, the burden of castrate resistant cancer in Tanzania has remained unknown hence our patients cannot benefit from such advances. This study therefore aimed to determine the magnitude and clinical presentation among patients with a diagnosis of castrate resistant cancer at Muhimbili National Hospital in 2018-2019.

Methods
This was a retrospective descriptive hospital based study carried out at Muhimbili National Hospital. Patients who were treated with androgen blockade, had evidence of attainment of castrate levels of testosterone with a diagnosis of castrate resistant prostate cancer were identified. Information regarding primary prostatic cancer treatment, clinical disease progression symptoms, and age of the patients were collected. Descriptive statistics were prepared and summarized as tables and figures.

Results
We recruited 293 patients with prostate cancer treated by androgen deprivation therapy. Bilateral orchiectomy was the most common treatment modality offered for advanced PC. Castrate levels of testosterone were achieved in 189 (95.5%) of the patients who had testosterone levels checked. Ninety-Six (50.8%) had met the criteria for diagnosis of castrate resistant prostate cancer with mean age of 71.23±4.2 years. Patients presented with lower urinary tract symptoms and metastatic features. Most of the patients had a poorly differentiated histology with prostate specific antigen (PSA) over 100ng/l. Only 13.5% of the patients had spine magnetic resonance imaging (MRI) for their work up.

Conclusion and recommendation
Half of patients treated for advanced PC at MNH will progress to castrate resistance following androgen deprivation therapy. More studies are needed to understand the predictors of CRPC and related treatment strategies.

Key words: Castrate Resistant Prostate cancer, androgen deprivation therapy, advanced prostate cancer

Background

Prostate cancer (PC) is now the second most frequent cancer and fifth cause of cancer related mortality globally which contributes to 1.3 million cases and 359,000 deaths (1). This makes PC to be of significant public health concern to health practitioners and policy makers across the globe. The outcome of PC among patients with advanced disease has been improving owing to better understanding of its biology and improvements in therapeutics (2). In Tanzania, PC is the most prevalent cancer among men and only second to cervical cancer in prevalence nationwide (3).

Despite good initial response to androgen deprivation therapy (ADT) as evidenced by dropping in the levels of PSA after treatment, a good number of patients will show features of disease progression despite castration after duration of 18 – 24 months (4).
The mechanism of transition from castration-sensitive prostate cancer to castration resistant disease is still not fully understood. It has been observed recently that androgen receptors remain active and continue to drive PC progression in spite of having castrate levels of testosterone (5, 6). The existence of other biologic pathways independent of androgen signaling has also been reported to lead to CRPC. In the light of this, new strategies have been developed for this sub set of PC patients that progress to CRPC. For this reason, practicing PC physicians need to understand the magnitude of patients who develop CRPC in their practice.

The Prostate Cancer Working Group (PCWG) defined CRPC as a continuum on the basis of whether metastases are detectable (clinically or by imaging) and whether serum testosterone is in the castrate range because of a surgical orchiectomy or medical therapy (7). CRPC carries worse prognosis, especially when associated with metastatic disease. Over the past 10 years CRPC has been widely studied indicating its global burden especially related to the cost of caring for patients. In Africa, and specifically in Tanzania, the burden of CRPC is unknown hence its cost burden cannot be assessed. In Tanzania little is documented on CRPC and PC in general. Therefore, this study aimed at detailing the patient characteristics and burden of CRPC in the country.

Methodology

A retrospective hospital based descriptive study, involving chart review, was carried out at Muhimbili National Hospital (MNH) between 2018 and 2019. MNH receives patients with PC at various stages from the whole country. The hospital has capacity to diagnose and treat PC, collaborating with a sister institution (Ocean Road Cancer Institute) specializing in cancer care. PC is diagnosed by digital rectal examination, and finger guided tru cut biopsy followed by histological evaluation. Records for both histology and case notes are kept in the pathology registry and records department. Ethical approval to carry out the study was obtained from Muhimbili University of Health and Allied Sciences IRB and permission to access patients' records was granted by the MNH Education, Research and Consultancy Bureau.

The study included patients who had a diagnosis of PC and treated by ADT (medical or surgical). Surgical androgen deprivation was by bilateral orchiectomy while medical androgen deprivation was by Goserelin 3.6mg subcutaneously every 28th day, Bicalutamide 50mg daily for 2 weeks: patient then continues with Goserelin monotherapy. Testosterone levels were checked at three months to establish attainment of castrate levels, ≥0.7nmol/L. Patients with castrate resistance were considered at three months if: PSA levels remained high or continued to rise; clinical or radiological features of disease progression or onset of new symptoms related to PC. Patients who did not have testosterone levels and those who did not achieve castrate levels of testosterone were excluded from the study.

We identified medical registration numbers of patients with histological diagnosis of PC from the hospital central pathology laboratory registry. Their case notes were traced from the hospitals' records department. A structured data collection tool was used by a trained data extractor, and the following variables were extracted: patients' age, clinical presentation at follow up, Gleason score, investigations done, PSA level (at baseline and at three months), any co-morbidities and clinical presentation.

The collected data was checked for completeness and entered into Statistical Package for Social Scientists (SPSS) version 23 for analysis. Continuous variables were summarized as means with standard deviations while categorical variables were summarized as frequency with percentages. Magnitude of CRPC was considered as proportion of patients with CRPC to total patients who attained castrate levels of testosterone. Bar charts and tables have been used to summarize results as presented in the subsequent section.

Results

Figure 1 below represents the flow chart of patient's recruitment into the study. A total of 293 patients were treated for PC by androgen deprivation therapy (surgical and/or medical) at MNH between 2018/2019 of which 95 patients did not have testosterone levels hence were excluded. Of the remaining 198 patients with testosterone levels documented, 189 had reached castrate levels of which 96(50.8%) met the criteria for the diagnoses of CRPC and hence included in the study. The mean age of CRPC patients was 71.23±4.2 (63 – 94) years.

All patients with CRPC had histology results of prostate adenocarcinoma. The most common reported Gleason score was 9 for 40(41%) patients, which signify poorly differentiated prostate cancer. All patients had a baseline PSA of more than 50ng/mL and majority had a baseline PSA of more than 100ng/ml. The most common imaging done in these patients was Abdominal Pelvic Ultrasound with only 13.5% having a spine magnetic resonance imaging (MRI). Most patients, who developed CRPC, were primarily treated by bilateral sub-capsular orchiectomy. [Table 1]

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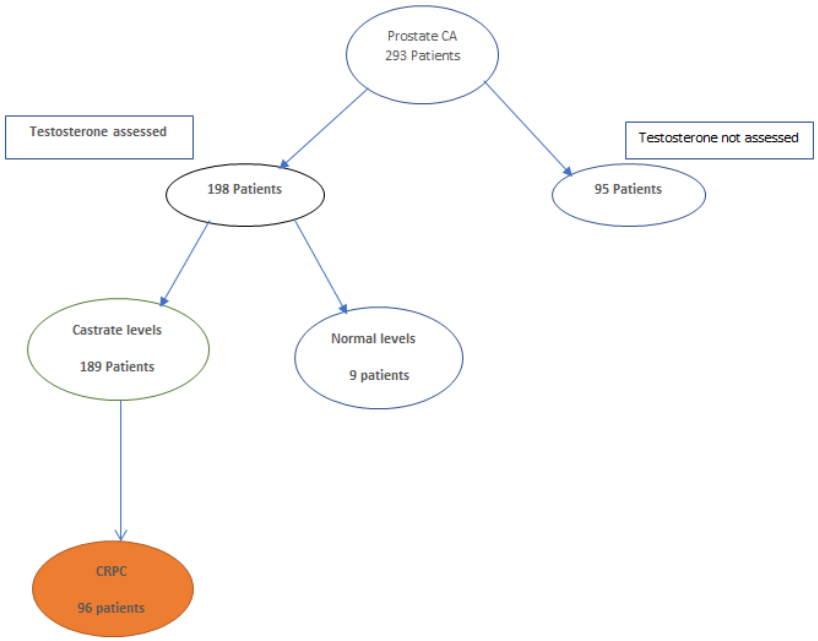
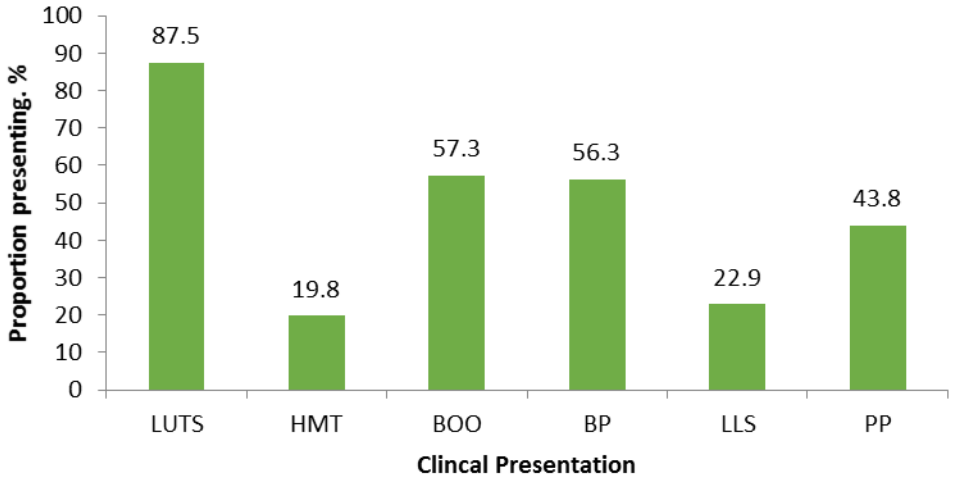


Figure 1: Flow chart showing how 96 patients with CRPC were recruited into the study from patients managed for PC at MNH in 2018/2019

Table 1: Baseline characteristics, investigations and primary treatment of patients with prostate cancer who developed castrate resistance

Variable	Proportion, (%)
Gleason score	
7	31 (32.3)
8	24 (25)
9	40 (41.6)
10	1 (1.1)
PSA (ng/ml)	
50 – 75	15 (15.6)
75 – 100	34 (35.4)
> 100	47 (49)
Radiological investigations	
Ultrasonography of AP	62 (64.6)
Lumbar-sacral X-ray	49 (51)
Chest x-ray	32 (33.3)
MRI of spine	13 (13.5)
Treatment modality	
Bilateral sub-capsular orchiectomy	53 (55.2)
Medical Androgen Deprivation	17 (17.7)
Both	26 (27.1)

Figure 2 below represents clinical presentation among patients who developed CRPC of which lower urinary tract symptoms were the most frequent symptoms reported by 87.5% of the patients, followed by urinary bladder obstruction and back pain in 57.3% and 56.3% respectively. Additionally, 43.8% presented with paraplegia. Majority of patients with CRPC had clinical progression or development of new PC related symptoms.



Key: LUTS – Lower urinary Tract Symptoms; HMT – Hematuria; BOO – Urinary Bladder Outlet obstruction; BP – back pain; LLS – Lower Limb swelling; PP – paraplegia.

Figure 2: Bar chart showing clinical presentation among patients presenting with CRPC at MNH.

Discussion

We conducted this descriptive study to characterize our management practices of patients presenting with advanced PC at MNH. This study aimed to determine the magnitude of CRPC and outline shortcomings in the management of patients with advanced PC. It is the first such study in Tanzania and has provided insight on areas that need improvement given the high prevalence of PC in our population. The findings from this study are likely to be representative of the general picture of the scope of CRPC and our local management practices.

CRPC is a dilemma in low income countries given the morbidity and the cost needed to manage such patients. Patients in sub-Saharan Africa have already been shown to have poor access to active treatment of their CRPC (8). Prostate cancer commonly presents at an advanced stage and in incurable forms among African men (9 - 11). This late stage at presentation is probably due to a weak health system in the country with scarcity of skilled human resources for health. In our study patients with advanced PC initially responded to castration therapy before developing CRPC. A similar observation has been reported elsewhere in Africa (12). We report a high magnitude of CRPC with half of patients treated for advanced PC by androgen deprivation. This is similar to that reported from Nigerian men (8). It is important to identify patients with CRPC since currently there are targeted

therapeutics which can improve both survival and quality of life (*13, 14*). While healthcare systems in similar settings cannot cope with screening for PC, it is important to detect which patients with PC will progress to CRPC when in advanced stage for clinical trials.

Androgen deprivation by bilateral orchiectomy is commonly practiced in our setting, which would possibly suggest that it is acceptable. However, we lack objective evidence on its acceptability by patients, a gap that warrants studies in this area. Bilateral orchiectomy has proven to be a very effective androgen deprivation strategy in settings with scarce resources. It can be advocated for widespread use in our settings along with early diagnosis strategies. There is realization that intracrine/paracrine androgen production plays a significant role in the resistance of PC cells to testosterone-suppression therapy (15). Whether a castration strategy, medical versus surgical, is important in the development of CRPC needs to be studied in this setting. Being in a public health care setting, few patients as we saw in this study will be able to afford medical androgen deprivation. The most important thing is to ensure that castrate levels have been achieved by any of the strategies by checking for testosterone levels, typically at or less than 0.7nmol/L. This should be done for all patients who demonstrate disease progression (new symptoms or progression of pre-existing symptoms or rising PSA levels) before declaring CRPC. A diagnosis of CRPC cannot be reliably made before realization of attainment of castrate levels of testosterone: it should therefore be a practice to have all patients check testosterone levels during routine follow up visits in Urology clinics.

Even though this study did not assess the treatment strategies offered, it should be noted that algorithms for such patients have been developed and used extensively in other settings. But as cancer services are covered by government, it is important to do cost benefit analysis of what it would take to aggressively treat CRPC in such a fragile health care system with rampant out of pocket payment. Radiotherapy and chemotherapeutics are largely “free” of payment by patients but only when available. We therefore propose to review the current treatment strategies in patients with advanced PC and propose way forward.

Management strategies for patients with CRPC differ according to the type of presentation: biochemical without evidence of disease versus metastatic presentation. Most of our patients had progression with evidence of disease hence fall in the mCRPC which requires additional management strategies including: secondary hormonal manipulation, chemotherapy, radiotherapy and immunotherapy. Patients need to be assigned one of the six classes for better treatment outcomes as outlined by America Urology Association (16- 17). It is important to properly investigate patients with suspected CRPC to properly assign a treatment outline. Investigation offered were only proportionately done by patients, hence uniformity in working up was evidently lacking. This will not allow uniform assignment of cases as CRPC only represents a continuum of challenges in patients with advanced PC.

While the findings from this study are impressive by exposing the magnitude of CRPC among our patients, it has the retrospective set back of not being able to capture all the related variables needed to discuss this topic in details. There is a need to establish a PC working group at MNH and later roll it out to the entire country to standardize management strategies for PC patients since more than half will develop CRPC and bring challenges in care. Outcome data and their predictors are also lacking and not routinely collected.

Conclusion

CRPC is common among patients treated by ADT at MNH where by it was diagnosed in more than half of the patients. Disease progression was the main presenting symptom among patients with CRPC. Furthermore, most patients had persistently high or rising levels of PSA at initial diagnosis. More studies, preferably of prospective design, are needed to understand the predictors of CRPC and related treatment strategies.

Competing interests

The authors declare no competing interests.

Authors' contributions

NEK Collected data, performed data analysis and wrote the report. OVN wrote a proposal, participated in the study design, and performed data analysis and manuscript preparation. LOA, FAM, CAM, MA, MM, GFM participated in manuscript preparation.

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List of Abbreviation

ADT	Androgen Deprivation Therapy
CRPC	Castrate Resistant Prostate Cancer
MNH	Muhimbili National Hospital
M CRPC	Metastatic Castrate Resistant Prostate Cancer
MRI	Magnetic Resonant Imaging
PC	Prostate cancer
PSA	Prostate Specific Antigen
PCWG	Prostate cancer Working Group
SPSS	Statistical Package for Social Scientists

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