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Prevalence of Incidental Prostate Carcinoma among Patients Undergoing Turp for Benign Prostatic Enlargement

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Abstract

Background

Incidental prostate cancer is detected by histological examination of resected biopsy tissue that has been previously diagnosed as benign. It has the potential for progressing to become a disease necessitating active treatment. There is paucity of data on detection of incidental prostate cancer in Tanzania. A study done in northern Tanzania among the urban public sector revealed an alarming detection rate of 21.71%. We aimed to establish the prevalence of incidental prostate cancer among men surgically treated for benign prostate enlargement with considered normal range of prostate specific antigen.

Methods

This was a retrospective hospital-based cross-sectional study conducted to establish the prevalence of incidental prostate cancer among men who underwent transurethral resection of prostate with considered normal range of prostate-specific antigen from 2010 to 2019 at Aga Khan Hospital Dar es salaam, Tanzania. To find the prevalence of incidental prostate cancer with 95% confidence level, 5% tolerable error, minimum of 195 participants' data was reviewed, and factors associated with incidental prostate carcinoma were evaluated by binary regression analysis.

Results

Total of 195 men were included in the study. The prevalence of incidental prostate cancer among men with prostate-specific antigen levels of less than 5.5ng/mL was 7.2% (95% CI, 4.0 to 11.8%). More than half of the patients had high-grade cancer and three quarters had T1b histological subtype making up the clinically significant category. For every 1-year increase in age from age of 65 years, risk of incidental prostate cancer increased by 1.6 (95% CI, 1.054 to 23.38; P<0.05) and for every unit increase in prostate specific antigen, incidental prostate cancer increased by 2.2 (95% CI, 1.953 to 42.28; P<0.05).

Conclusion

The Incidental prostate cancer detection rate of 7.2% in our settings is within the range found internationally.

Key Words: *Incidental prostate cancer, Prevalence of incidental prostate cancer, Prostate specific antigen, Sub-Saharan Africa.*

Background

Prostate cancer is one of the commonest cancers in men worldwide, with an estimated 1,600,000 cases and 366,000 deaths annually (1). It is rated the second most diagnosed cancer and a sixth leading cause of cancer deaths among men globally. In sub-Saharan Africa (SSA) alone, it is estimated that disability-adjusted life years (DALYs) from prostate cancer increased and doubled in two consecutive decades, and deaths also increased twice over the same period mortality is mainly due to late presentation to health facility with advanced stage of the disease (2 - 4).

Incidental prostate carcinoma (IPCa) is defined as prostate "cancer which lacks apparent neoplastic symptoms or cancer which is unusually detected by histology examination of resected biopsy tissue that had been previously diagnosed as benign" as is the case for patients who undergo trans-urethral resection of prostate (TURP) for benign prostatic enlargement (BPE) (5). These tumors are also referred to as clinically in-apparent tumor or non-palpable clinically (T1a/b). Clinical T1a is one which is found in less than 5% of resected prostate tissue while T1b is found in more than 5% of resected prostate tissue. T1b is more aggressive compared to T1a with different prognoses and associated management recommendations.

Factors such as the use of pharmacological therapy for voiding symptoms resulting in delayed surgical management of BPE, minimally invasive and ablative treatments of BPE that may not allow for histological analysis of BPE tissue resected, and widespread testing of PSA so as to potentially differentiate those who may benefit from further search for prostate cancer among patients with urinary symptoms have affected the diagnostic trend of IPCa, which ideally should not be suspected pre operatively (6). Multiple studies have established that in the era prior to the wide-scale PSA testing the incidence of IPCa was found in 10 - 31% for the patient who underwent surgical treatment for the benign prostate disease compared to post PSA testing era whereby the trends in incidence of IPCa has significantly decreased and ranges between 1.4 to 13% (7).

The clinical significance of IPCa has remained a dynamic and debatable matter. Some cohort studies among men who were diagnosed with IPCa showed a significant cancer specific mortality during the last three decades and so this finding supported the notion that IPCa is a clinically significant disease and requires management recommendations to potentially avoid progression to prostate carcinoma (8).

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In attempts to better determine which subset of IPCa is in fact clinically significant, PSA and Gleason Scoring system have been proposed and evaluated. Higher Gleason scores have been associated with poor prognostic factor for both clinical behavior of tumor and treatment outcome(10). PSA generally increases as the tumor volume increase and is a better predictor of cancer than DRE or TRUS. In most settings, PSA value ≤ 5 ng/mL is considered normal and potentially excludes prostate cancer, however this is not the case for incidental prostate cancer (5, 8). The lower cut off PSA for detecting clinically IPCa, or it's clinically significant variant is not established, as prostate cancers smaller than 1.0 cm^3 will not cause an elevation of PSA above 5 ng/ml PSA and of further clinical concern, biopsy-detected prostate cancer including high-grade cancer (with high Gleason score), is not rare below this cut off (9).

Advancing age has been shown to have an association with clinically significant IPCa. A 10-year prospective cohort study among men who underwent TURP for BPH found 63.4% of men had clinically significant IPCa i.e T1b, tumor with GS≥7, observed predominantly among men ≥ 75 years of age. Another systematic review of autopsy study showed more variation in prevalence, but established its increase with each decade of life starting from the 6^{th} (7, 11). In Tanzania, prostate cancer has been reported to be the most common cancer among men, with incidence of 3,434 cases per year, reports of WHO cancer registry in 2012. A study conducted in northern, Tanzania among men who underwent TURP for probable benign prostatic enlargement, found an alarming prevalence of 21% of IPCa (12). However, in this study, men with high PSA values above 5.5 ng/ml were also included and probably explains why the prevalence of IPCa was high.

The current study aimed to establish the prevalence of the IPCa among men with PSA levels of less than 5.5 ng/ml who underwent TURP for BPE along with its associated factors.In consideration of several benign modifiable factors (catheterization, DRE, acute urine retention) and nonmodifiable (age specific reference PSA range) this have accounted the adoption of upper cutoff of 5.5 ng/ml, this cut off have positive predictive value of 25% with nearly 75% chances of organ confined prostate cancer. The findings of this study may provide evidence that will assist in establishing the low cut off value for the normal PSA level in our setting.

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Methodology

Design and setting of the study

This was a retrospective hospital-based cross-sectional study conducted at Agha Khan Hospital Dar-es-salaam, Tanzania between October 2010 and September 2019. The study was set in a private teaching hospital providing Uro-Surgical subspecialty services with the team of urologists performing 35-40 TURP per year.

Study population & data collection

All patients who underwent TURP for BPE with PSA levels of less than 5.5 ng/ml. were included in the study. Routinely all patients who were selected for TURP were either failed trial of acute urine retention or poorly progressed despite being on medication for BPE (alpha blockers and 5 alpha reductase inhibitors) for a certain period of time. These patients underwent initial clinical assessment of lower urinary tracts symptoms and self-assessment with International Prostate Symptom Score (IPSS) and physical exam DRE, then investigations such as renal function test (RFT), complete blood count (CBC), urinalysis and uroflowmetry were done to rule out infectious complications of BOO and neurologic dysfunction of bladder. The prostate was then assessed by kidney-ureter-bladder ultrasound. Prostate volume, echogenicity pattern, and post-void urine residue volume were documented. The serum PSA level was then measured. After proper evaluation, the patients meeting the indication for surgical intervention underwent TURP. Prostatic chips were analyzed and reported by consultant anatomical pathologist, and 10% of samples were randomly reviewed by another consultant anatomical pathologist for quality assurance measures set by the laboratory.

Sample size

A formula of Kish & Lisle (1965) was used to calculate the sample size. Minimum number of participants required for the study was 195 patients, This sample size of 195 patients was considered able to pick 15% prevalence of IPCa with 80% power, and type 1 error of 5% at 95% confidence interval (9).

Study Analysis

Data were entered, cleaned and analyzed with SPSS v25 statistical package. PSA results were grouped into two categories 0-2.5 and 2.6 to 5.5 ng/ml. Since most of the variables are categorical, they have been analyzed in proportions and percentages.

Descriptive analysis of demographic characteristics were done and presented as percentages while the categorical and continuous were analyzed and presented as means and medians. Comparisons between population groups among those with IPCa and those without were done using chi square test. P-value of less than 0.05 was considered statistically significant. Binary logistic regression was used to calculate odds ratio with 95% confidence interval (CI) to identify factors associated with incidental detection of prostate cancer. The performance of PSA in detecting IPCa was assessed by the area under the receiver operating characteristics (ROC) curve. The AUC of 0.7 to 0.8 was considered fair, 0.8 to 0.9 is good and above 0.9 is excellent.

Ethical consideration

This study was conducted after approval and permission from AKU ethical research committee with reference number AKU/2019/304/fb. Further permission from the hospital was sought and obtained from the Medical director's office.

Results

Total number of 294 men underwent TURP during the study period of which 23 underwent channel TURP, 76 had PSA above 5.5ng/ml and hence were excluded from the study leaving 195 eligible patients.

Table 1 summarizes demographic and clinical characteristics of the participants. Most participants 143 (73%) were of African ethnicity. Age was normally distributed with mean age of 66.17 (SD 9.63) years, more than half 108/195 (55%) falling between 66 – 93 years. Majority had a clinical grade III (92.3%) prostate size. Mean prostate volume estimated by USS was 54.01 (SD 5.33) grams. In consideration of age-specific-PSA-reference-range, our study included upper PSA cutoff of 5.5 ng/mL, which is somewhat above the International recommended value of 4 ng/mL, this aimed to enable the study to detect any association of Age and risk of prostate cancer, since both PSA and risk of cancer increases with age. Mean values of PSA and their respective PSA-density were 2.35±1.5ng/ml and 0.0434±0.029 ng/ml^2 respectively. Positive correlation between age and prostate volume was found ($r=0.19$, $p<0.05$). In the present study, the prevalence of incidental prostate cancer among men with PSA levels of less than 5.5ng/mL who underwent TURP for BPE was 7.2% (Table 1). Mean age was 71.5 (SD 8.14) years in IPCa compared to 65.76 (SD 9.6) years among

men with BPE, approximately five-year difference was observed, and this difference was statistically significant (p <0.05) (figure 1).

Table 1: Participant's Baseline Demographic & Clinical Characteristics

	FREQUENCY (%)
Mean age - 66.17 (sd 9.63)	
Groups	
< 60	60 (30.8)
61 – 65	27 (13.8)
66 – 70	50 (25.6)
71 – 75	30 (15.4)
> 76 s	28 (14.4)
Ethnicity	
Africans	143 (73)
Non-Africans	52 (27)
PSA range	
0- 2.5 ng/ml	113 (57.9)
2.6- 5.5 ng/ml	82 (42.1)
Prostate size	
II (40.54 ± 7.69 ml)	15 (7.7)
III (61.08 ± 11.90 ml)	180 (92.3)
Histology	
Bph	181 (92.8)
Ipca	14 (7.2)
Tumor size	
T1a (≤ 5%)	3 (21)
T1b (>5%)	10 (71)
Not known	1 (1)
Gleason score	
Grade 1	3 (21)
Grade 2	5 (36)
Grade 3	6 (43)

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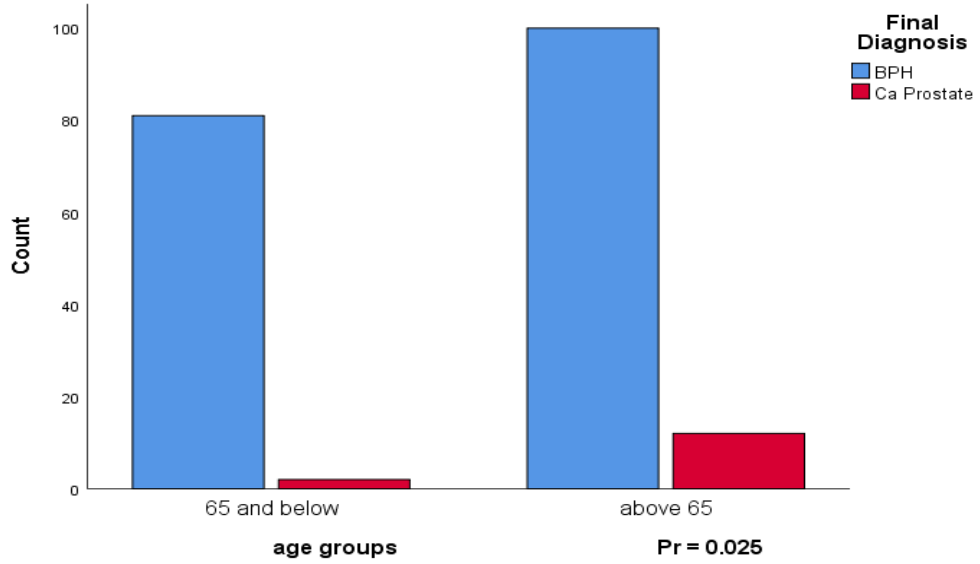

Figure 1. Distribution of IPCa by cutoff age of 65 years

Figure 2 summarizes distribution of tumor percentage by cutoff age of 65 years. Among men with IPCa, 10 (71%) patients had T1b disease, predominantly among those were above 65yrs, ($p<0.05$).

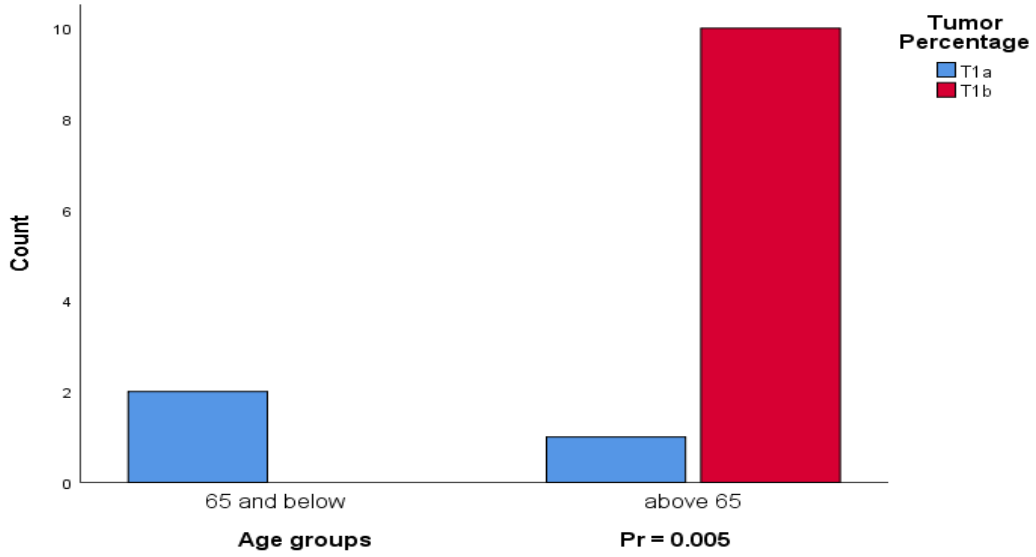

Figure 2. Distribution of Tumor percentage by cutoff age of 65

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The mean PSA was higher in men with IPCa compared to men with BPH with positive association in linear regression analysis (f (1,193) 0.879, p<0.05), The histological tendency of poorly differentiated IPCa was shown to increase with the PSA increase (Figure 3). The mean PSA density was higher among men with IPCa (0.0524± 0.017) compared to those with BPH (0.0427± 0.03) however, this association was not statistically significant (r= -0.044, p>0.05).

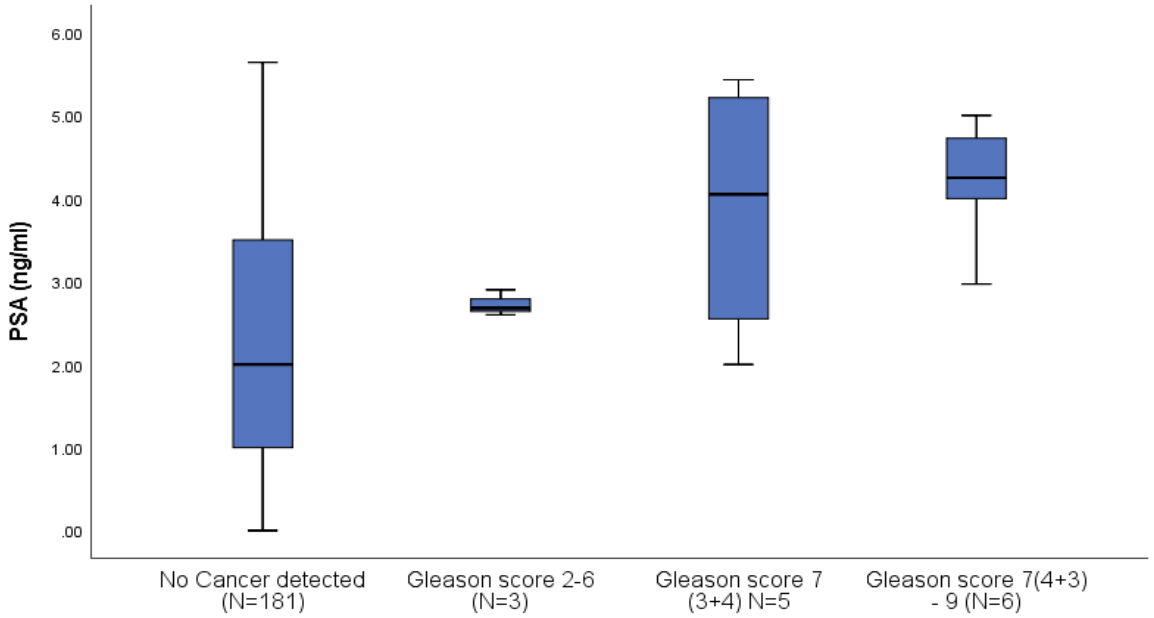

Figure 3. Boxplot displaying distribution of prostate values according to the Gleason-score

The black horizontal lines within the boxes denote the medians PSA values, and the distribution span of the box is between 25th and 75th percentiles. The vertical lines above and below each box indicate the range of the distribution. The width of the box is proportional to the number of men within the specific Gleason score range.

Table 2 summarizes factors associated with IPCa. Bivariate analysis, the odds of diagnosing IPCa was independently associated with the Age and PSA. Multivariate logistic regression model for Age and PSA was then performed (AOR = 3.67, 95% CI 1.05 to 6.01, P = 0.045) and (AOR = 1.18, 95% CI 0.37 to 3.45, P = 0.043) respectively. For every 1-year increase in age from age of 76 years, risk of IPCa increased by 3.67 (P<0.05). and for every unit

increment of PSA value from 2.5ng/ml the risk of IPCa was observed to be 1.18 (P<0.05). Prostate size and ethnicity did not have statistically significant association with IPCa.

Table 2: Factors associated to incidental prostate carcinoma

Factors		IPCa		Un-adjusted		Adjusted
		NO	YES	OR (95%CI)	p-val	OR (95%CI) p-val
Age groups (years)	≤ 60	60 (100)	0 (0)	.00	0.019	
	61 – 65	25 (92.6)	2 (7.4)	0.34 (0.06-2.01)		
	66 – 70	44 (88)	6 (12)	0.62 (1.17-2.08)		
	71 – 75	29 (96.7)	1 (3.3)	0.91(0.07-1.47)		
	≥76	23 (82.1)	5 (17.9)	4.91 (0.7-1.4)		3.67 (1.05-2.01) 0.045
PSA Levels (ng/ml)	0 - 2.5	111	70		0.004	
	2.6- 5.5	2	12	2.13 (1.8- 14.1)		1.18 (0.37-3.45) 0.043
Prostate size	Grade II	15 (100)	0 (0)		0.26	
	Grade III	166 (93.2)	14 (7.8)	1.27 (0.02-0.18)		
Ethnic groups	African	136 (92.5)	11 (7.5)		0.77	
	Non-African	45 (93.7)	3 (6.3)	0.83 (0.09-0.14)		

The prevalence of IPCa increased from 14% for PSA value less than 2.5ng/ml compared of IPCa prevalence of 86% for PSA values of 2.6ng/ml to 5.5ng/ml. ROC was conducted for this PSA range to determine if there is an optimal cut-off value with sufficient diagnostic accuracy to detect IPCa. PSA had shown fair diagnostic performance in diagnosing IPCa with (AUC of 73.3% 95% CI 0.642 to 0.824 P = 0.04). The best cutoff of 2.5ng/ml had shown a sensitivity of 92.9% and specificity of 60.8% (figure 4).

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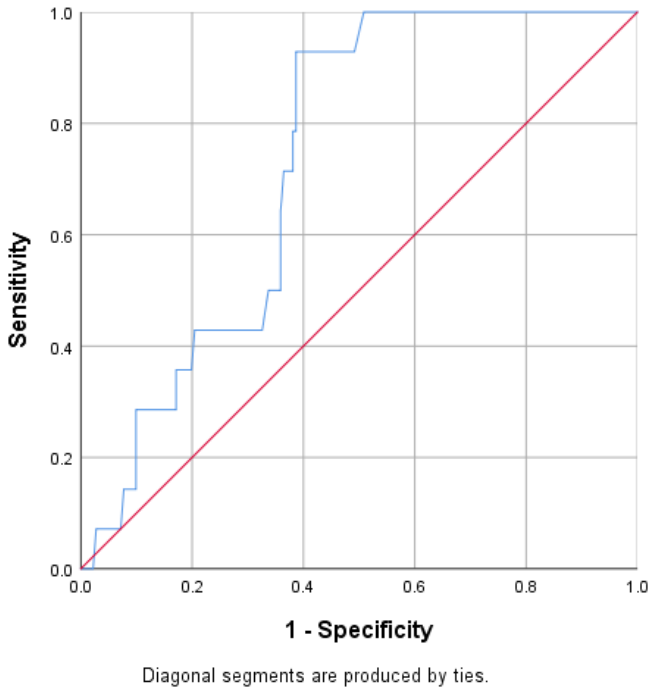

Figure 4. ROC curve for PSA diagnostic performance of IPCa

ROC was performed for serum PSA (total number of patients 195; 14 patients had incidental prostate cancer).

Discussion

This study revealed an incidental prostate carcinoma rate of 7.2 percent among men undergoing TURP for BPE. This prevalence was much less compared to the alarming prevalence of recently published study in Northern Tanzania which was 21% (12). There was a difference in patient populations as this study only included men with considered normal PSA as opposed to those in the previous study. This prevalence was similar to other studies determining prevalence of IPCa in the PSA use era, with even lower prevalence reported in America of 1.4%, 6.2% was reported in the in Brazil, and in Croatia 2018 reported detection rate of 6.34% (6, 7, 13).

In the present study, age greater 65 years was statistically significantly associated with IPCa. This result was similar to the results reported by Bright et al, whereby age was the only predictor of IPCa. In that study men with IPCa had a mean age of 76 years, which was 5 years older compare to BPH group (13). The difference between those with IPCa and

those with BPE was about 5 years in this study. Similar results were observed in the study conducted earlier in Tanzania by Gunda et al, whereby age of greater than 65 years was associated with incidental prostate cancer (12). Di Silverio et al established in their study that IPCa increased with each decade of age from 6th to 9th decade (14). This linear relationship between age and IPCa was also observed in this study. The mean PSA in men with IPCa was statistically significantly higher compared to BPH group. In a study by Tombal et al, comparing IPCa in pre and post PSA use era, a drop of 18% prevalence of IPCa was attributed to PSA use (15), Jones et al, showed 9.7 % drop in IPCa prevalence that was attributed to PSA use. In contrast, Antunez did not find this association (16-18). With this low, but potentially significant IPCa detection rate among men with a considered normal range of PSA, it is difficult to propose an optimal PSA cut-off value in our setting.

African ethnicity did not show significant association to the IPCa in our study. There are conflicting results in literature that evaluated ethnicity to prevalence of IPCa. Our results add to the argument that the association may not be present, however our study was not adequately powered to determine this association (17). Prostate volume did not have statistically significant association with IPCa in our study. There are recommendations of using PSA derivatives that may incorporate PSA and prostate indices such as PSA density to better establish clinically relevant associations(19).

The rate of IPCa detection in our setting is evidence that 7.2% of men treated for BPE have a potential chance of developing an advance stage of prostate cancer. T1a disease is not a dismissible disease, it needs an active surveillance and definitive staging as 16% of T1a progress to a stage that requires active treatment (20). The lower rates of IPCa in the present study compared to the other study in North Tanzania, has further established the role of PSA screening of men presenting with bladder outlet obstruction.

Conclusion

The IPCa detection rate of 7.2% among men undergoing TURP for BPE in our settings is within the internationals range of IPCa prevalence in this PSA-use era. All patients with bladder outlet obstruction symptoms from suspected benign prostatic enlargement treated medically or surgically (TURP) should be informed of 7.2% chance of IPCa. However, this detection rate is not high enough to propose fundamental changes in a current PCa diagnostic approach, mass education and focused group PSA screening of men at age of 60 years is advised.

Recommendation

To address the overdiagnoses/overtreatment of clinically insignificant IPCa, more studies should focus on developing serum/tissue prognostic biomarkers that can differentiate clinically significant IPCa from insignificant tumor.

Competing interests

The authors declare no competing interests.

Authors' contributions

IHM author and primary researcher, MKN helped in write-up, reviewed the Manuscript, AA Co- supervisor and reviewed the manuscript, AN Reviewed the manuscript, PA Methodology supervisor and reviewed the article and AAZ Primary supervisor and reviewed the manuscript.

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List of Abbreviation

BOO	Bladder Outlet Obstruction
BPE	Benign prostatic Enlargement
BPH	Benign Prostate Hyperplasia
DALY's	Disability-Adjusted Life Years
DRE	Digital Rectal Prostate
GS	Gleason Score
IHME	Institute of Health Metrics
IPCa	Incidental Prostate Carcinoma
IPSS	International Prostate-Specific Systems
ISUP	International Society for Urological Pathology
PCa	Prostate Carcinoma
PSA	Prostate Specific Antigen
PVR	POST-VOID RESIDUE
QoL	Quality of life
SSA	Sub-Saharan Africa

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