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Prevalence and factors associated to incidental prostate carcinoma among patients undergoing turp for benign prostatic enlargement.

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PREVALENCE AND FACTORS ASSOCIATED TO INCIDENTAL PROSTATE CARCINOMA AMONG PATIENTS UNDERGOING TURP FOR BENIGN PROSTATIC ENLARGEMENT

BY

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ABSTRACT

Background: Prostate carcinoma carries higher morbidity and mortality when diagnosed late. Prostate cancer screening is of paramount, however there are no specific clinical signs for early stage prostate cancer. As an independent variable, prostate-specific antigen is an established predictor of cancer.

Incidental prostate cancer is detected by histological examination of resected biopsy tissue that had been previously diagnosed as benign.

In the current PSA-use era the prevalence of incidental prostate cancer ranges from 1.4 to 13%. The prevalence in Tanzania as published by Gunda et al was 21.71%. This is alarmingly high. However, in his study, patients with high prostate-specific antigen were included.

Objective: To determine the prevalence of incidental prostate carcinoma among patient undergoing trans-urethral resection of prostate for benign prostate enlargement with prostate-specific antigen less than 5.5 ng/ml.

Methods: A retrospective hospital-based cross-sectional study was 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 in Dar es salaam, Tanzania. Minimum of 195 participants were reviewed, and factors associated with incidental prostate carcinoma were evaluated by binary regression analysis.

Results: A 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%. 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 one year increase in age from 76 years,

the risk of incidental prostate cancer increased by 1.6, and for every unit increase in prostate specific antigen, incidental prostate cancer increased by 2.2.

Conclusion: The Incidental prostate cancer detection rate of 7.2% in our settings is within the Internationals range. Factors associated, were prostate-specific antigen levels and Age. 3.6% of all patient had high grade cancer with potential chance of progressing to an advance stage of prostate cancer

LIST OF TERMS OF ABBREVIATIONS AND SYMBOLS USED

BOO - BLADDER OUTLET OBSTRUCTION

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

ISUP - INTERNATIONAL SOCIETY FOR UROLOGICAL PATHOLOGY

QOL - QUALITY OF LIFE

QUALYS - QOL-ADJUSTED GAIN IN LIFE YEARS

SSA - SUB-SAHARAN AFRICA

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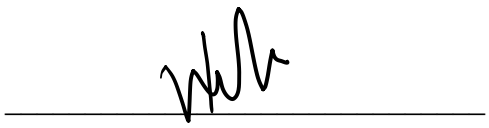
DECLARATION

I declare this dissertation does not in cooperate without acknowledgment any material previously submitted for a degree or diploma in any university and that to the best of my knowledge it does not contain any material previously published or written by another person except where due reference has been made in the text

The editorial assistance provided to me has in no way added to the substance of my dissertation which is the product of my own research endeavors.



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OPERATIONAL DEFINITION OF TERMS

Incidental prostate cancer: Incidental prostate cancer (IPCa) is defined as symptom-free cancer unexpectedly discovered upon microscopic examination of resected tissue.

Prevalence of incidental prostate: Refers to the proportion of individuals with incidental prostate cancer to the total number of patients who underwent TURP for presumed BPE at a given point.

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1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

Prostate cancer is one of the commonest cancers in men worldwide, with an estimated 1,600,000 cases and 366,000 death annually (1). It is rated the second most diagnosed cancer and a sixth leading cause of cancer deaths among men globally.

African ethnicity has been shown to have a significant association to prostate cancer (2), with genetic predisposition hypothesized (3). In the west where disease burden is well established, a disproportionately high incidence and subsequent mortality rate of prostate cancer was shown among African American men (4) (5).

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 (6, 7). In this region PCa incidence and mortality rates are lower in northern Africa at 10.6 and 7.0 per 100,000, compared to the average rates in SSA with 34.3 and 22.1 per 100,000, respectively (8). Mortality is mainly due to late presentation to health facility hence advanced stage of the disease (9).

Prostate cancer (PCa) is suspected based on voiding clinical symptoms with associated malignancy stigmata and digital rectal examination (DRE) of the suspicious prostate. The diagnosis is confirmed by histological verification of adenocarcinoma (10).

To diagnose the disease in the early stage, Prostate cancer screening define as systematic examination of men at risk of PCa who are asymptomatic, normally instituted by health National/Regional facility (10). In a similar manner to PCa screening, early detection of prostate cancer or opportunistic testing is done on the ad hoc basis consisting of individual case findings, which are initiated by the man being tested or initiated test by his physician (10). The co-primary objectives of both strategies are a reduction in mortality related to PCa, and at least, a maintained quality of life (QoL) as expressed by QoL-adjusted gain in life years (QUALYs) (11).

There is no specific clinical symptoms or signs for detection of early stage of PCa. As an independent variable, PSA has been the most widely used test and has been an established better predictor of cancer than either DRE or trans-rectal USS (12). Targeted PSA screening has been shown to improve early identification of patients who can benefit from biopsy and early treatment.

Incidental prostate carcinoma (IPCa) is defined as "cancer which lacks apparent neoplastic symptoms. This is a 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) (13).

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.

Factors such as the use of pharmacological therapy for voiding symptoms (14), minimally invasive treatments such as the use of laser/electrical ablation of adenoma (15), and widespread testing of PSA among patients with BPH affect the diagnostic trend of IPCa (16).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 (3), compared to post PSA testing era whereby incidence of IPCa specimen has significantly decreased and ranges between 1.4 to 13% (16-18)

Whether histological diagnosis of IPCa during TURP performed for BPE is of clinical significance has remained a dynamic and debatable matter. In one study which assessed the outcome of patients who were incidentally diagnosed with IPCa showed a significant number of men died from cancer specific mortality during the last three decades (19) and so this finding supported the clinical significance of incidental prostate carcinoma.

Currently the most used definition of clinically significant incidental prostate cancer is an incidental prostate cancer, found in more than 5% of resected tissue (T1b) with a Gleason score (GS) of more than 7. At this threshold, it was shown in a study involving 240 men who underwent TURP with T1a-b, Nx, M0 disease with follow up of more than 20 years that patients with T1b were 2.5 more likely to die of PCa compared to T1a. Furthermore GS>7, nuclear grade were also significant independent predictors of prostate cancer death (20). Study conducted by Roy et al, revealed 16% progression rate of among T1a disease concluding it is not a dismissible disease (21).

IPCa cannot be reliably identified. In attempts to determine this, PSA and Gleason Scoring system have been proposed and evaluated.

Higher levels of PSA have been shown to be effective in screening for PCa. PSA was also assessed to determine its performance in detection of IPCa. PSA generally increases as the tumor volume increase (22). In the most settings, PSA value ≤ 4ng/mL is considered normal (23). Non-palpable prostate cancers smaller than 1.0 cm^3 will not cause an elevation of considered normal PSA range. It is estimated that approximately 25 percent of cancers detected by PSA screening were too small to have accounted for the PSA rise that prompted a biopsy (24).

The accurate determination of considered normal PSA testing has been challenged because most men with normal PSA values will not undergo biopsy unless their DRE is abnormal and this will potentially detect higher stage PCa as opposed to clinically significant IPCa. Of further clinical concern biopsy-detected prostate cancer including high-grade cancer, is not rare below considered normal PSA level of less than 4 ng/mL (23).

As an independent variable, PSA is a better predictor of cancer than either DRE or trans-rectal USS (12). In the autopsy study which involved men whom untimely died from trauma, showed 31% prevalence of PCa in their autopsy analysis, Prostate Cancer Prevention Trial elucidated the finding that most men with considered normal PSA levels have PCa identified during biopsy performed without clinical indication (25). Hence the lower cut off of PSA for detecting clinically significant IPCa is not yet uniformly established.

Table 1. The table below shows the risk of IPCa in relation to low PSA values (25).

PSA LEVEL (ng/mL)	RISK OF IPCa (%)	RISK OF GLEASON≥7 PCa (%)
0.0 – 0.5	6.6	0.8
0.6 – 1.0	10.1	1.0
1.1 – 2.0	17.0	2.0
2.1 – 3.0	23.9	4.6
3.1 – 4.0	26.9	6.7

Relying on PSA derivatives such as PSA density in prediction of IPCa has been shown to have relatively higher PPV compared to total PSA alone. Study on PSA derivatives conducted by Froehner et al has shown that diagnostic value of PSA is increased by its derivatives, leading to

decrease of unnecessary biopsies prior TURP (26). PSA density has been also shown to be a strong clinical parameter in predicting the progress of IPCa (27).

Advancing age has also been shown to have an association with clinically significant IPCa. A prospective cohort study among men who underwent TURP for BPH which was conducted from Jan.1997 to Dec.2017 found 168/265 (63.4%) patients had clinically significant IPCa. The clinically significant prostate cancer was defined as T1b, tumor with GS≥7. The findings was predominantly observed among elderly men age 75 years and above (18). A systemic review of IPCa prevalence among 29 autopsy studies has shown the substantial variation of prevalence between population but established that prevalence increases with each decade of age (28).

Ethnic descent has also been proposed to have an association to IPCa. The prevalence of IPCa among Caucasian and Asian men who died from causes other than PCa was 23.1% and 51.4% respectively in that study (29). The study conducted by Rebbeck et al, showed that the African race had relative higher incidence and mortality rate (30).

In Africa, there have been reports of low utilization of both PSA and DRE well below 15% of those at risk (31). Targeted PSA screening has been shown to improve early identification of patients who can benefit from biopsy and early treatment (32).

In Tanzania, prostate cancer has been reported as the most common cancer among men, with incidence of 3,434 cases per year, reports of WHO cancer registry in 2012 (33). A study conducted in northern, Tanzania among men who underwent TURP for probable benign prostatic enlargement, found prevalence 21%, and a positive correlation of increasing age and high PSA values (34). However, in this study, men with high PSA values (above what is considered normal) were include, and probably explain why the prevalence of IPCa was high.

This study aimed to establish the prevalence of the IPCa among men with considered normal PSA levels who underwent TURP for BPE along with its associated factors. The findings of this study will provide evidence that will assist in establishing the low cut off value for the normal PSA level in our setting.

1.2 JUSTIFICATION OF THE STUDY

The prevalence of IPCa among pts undergoing TURP for BPE ranges from 1.4% to 13%.(Otto et al 2014, Jones et al 2008, Pirsa et al 2018, Antunes et al 2006). The prevalence of IPCa in Tanzania as published by Gunda et al was 21.71%. This finding was alarmingly high, as about one quatre of those undergoing TURP for BPE have IPCa with potential for progression (Gunda D, et al 2018). However, in his study, patients with high PSA were included who would have benefited from further evaluation for PCa.

1.3 STUDY QUESTIONS

What is the prevalence of IPCa among men with normal PSA levels undergoing TURP for BPE?

What is the distribution of IPCa in the PSA range of 0 to 5.5ng/ml?

Association of PSA with Gleason score?

1.4 OBJECTIVES

1.4.1 Primary Objective

To determine the prevalence of incidental prostate carcinoma among patient undergoing TURP for benign prostate enlargement

1.4.2 Secondary Objectives

- To determine the proportion of IPCa among men with PSA ≤2.5
- To determine the proportion of IPCa among men with PSA ≥2.6 to 5.5.
- To determine the proportion of IPCa with Gleason score of ≥7.
- To determine if there is an association IPCa with patients' age and ethnicity.

2.0 MATERIALS AND METHODS

2.1 STUDY DESIGN

This was a retrospective hospital-based cross-sectional study.

2.1.1 STUDY SETTING

The study was conducted at Aga Khan University Hospital Dar es Salaam. This is the private, teaching hospital with a bed capacity of 176 inpatient beds. It also has uro-surgical subspecialty with the team of well-experienced urologists. The operating theatre has all standard instruments required for TURP, with an average of 35-40 TURP are performed every year.

The patients that arrive at Aga Khan University Hospital are self-referral, and some are referred from peripheral clinics distributed in different parts of Tanzania. Routinely patients with BOO will undergo initial clinical assessment consisting of the International Prostate Symptom Score (IPSS) and physical exam DRE, then investigation such as renal function test (RFT), complete blood count (CBC), urinalysis and uroflowmetry are done to rule out infectious complications of BOO, and neurologic dysfunction of bladder. The prostate is then next assessed by kidney-ureter-bladder ultrasound. Prostate volume, echogenicity pattern, and post-void urine residue volume is documented. The serum PSA level is then measured. After proper evaluation, the patients meeting the indication for surgical intervention will undergo TURP. All prostatic chips biopsies were kept in formalin bottles, paraffin-embedded blocks and were stained by hematoxylin and eosin (H&E).

The prostatic chips for histological evaluation was done for all patients who underwent TURP for BPE with PSA level below 5.5ng/mL as is routine for the hospital and were interpreted by Dr. O, consultant anatomical pathologist, with 10% of samples randomly reviewed by Dr. C, consultant anatomical pathologists for quality assurance measures set by the lab.

2.1.2 STUDY POPULATION

All patients who underwent TURP in Oct.2010 – Sep.2019 for presumed BPH were included in this study.

2.1.2.1 INCLUSION CRITERIA

All men who underwent TURP between Oct.2010 to Sep.2019.

2.1.2.1 EXCLUSION CRITERIA

All men who underwent TURP with PSA level above 5.5ng/mL.

All men who underwent channel TURP between Oct.2010 to Sep.2019.

2.2.3 RESEARCH TOOL

During the study, a data abstraction tool consisting of the relevant variables that address the objectives of the study, was used to collect information from each medical records and histology forms.

2.2 DATA COLLECTION

Data were collected retrospectively. Relevant data from charts of all patients who underwent TURP were extracted into a data abstraction tool

The first section composed of demographic factors including age and ethnicity both this are independent variable. Age groups were coded as categorical ordinal values, while ethnicity was coded as nominal data, two groups (Africans and Non-Africans) were developed.

Data from investigations including USS prostate volume and PSA levels were collected. These variables were defined as dependent variable, and were coded as categorical data. Histological reports of prostatic chips resected were reviewed and coded as nominal categorical data. In instances where PCa was found, histological findings consisting of histological type, Gleason-scores and tumor quantitation was recorded.

2.3 DATA MANAGEMENT

Data abstraction from patient charts and histology results were safely stored in locker with access to only investigator during data entry and coding. The data coding and entry were done using SPSS electronic template.

The filled data abstraction tools will be archived by the university. Future use of this data will require university ethical clearance or bodies responsible.

2.3.1 DATA 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.

Prevalence of IPCa has been determined as proportional of positive histology results to a total of all TURP samples collected. Comparisons between population groups among those with IPCa and those without was done.

2.3.2 STATISTICAL TEST

Descriptive statistics of demographic and investigation findings will be used to describe population groups between those with IPCa and those without.

Comparisons and associations between categorical variables will be analyzed using Chi square test. The level of statistical significance will be at a p value of less than 0.05.

Odds ratios and 95% CI will be used to determine the association of these factors individually associated with IPCa from binary logistic regression. A model will be developed to determine which factors are strongly associated with IPCa. Level of significance will be set at a p-value of less than 0.05.

Correlations coefficients were determined and a p-value of less than 0.05 was considered statistically significant. Pearson's correlation was used for normally distributed variables and Spearman's correlation was used for non-normally distributed variables.

2.3.3 SAMPLE SIZE DETERMINATION

The study included all patients who met the inclusion and exclusion criteria from Oct.2010 – Sep.2019.

A formula of Kish & Lisle (1965) was used to calculate the sample size.

$n = z^2 p (1-p) / d^2$.

Where: z = Z score for 95% confidence interval = 1.96,

p = prevalence,

d = tolerable error =5%.

A proportion of 15% was used as proportion of IPCA in study by Thompson et al 2004 (25).

Minimum patient of 195 patients required.

2.4 ETHICAL CONSIDERATION

This study was conducted following universally acceptable ethical principles and guidelines for conducting health research in Tanzania. The study did not engage human participants. The records of all patients who underwent TURP in Oct.2010 – Sep.2019 for presumed BPH was included in this study. The written permission to access and collect the data was sought and granted from the medical director's office and subsequently from the head of general surgery unit at Aga Khan University Hospital Dar es Salaam. This study has strictly observed confidentiality, patients' information such as names was not used. The study has followed all rules-abiding to medical records facility.

Permission to conduct the study was sought and granted by the Aga Khan University Ethics Review Board and NIMR.

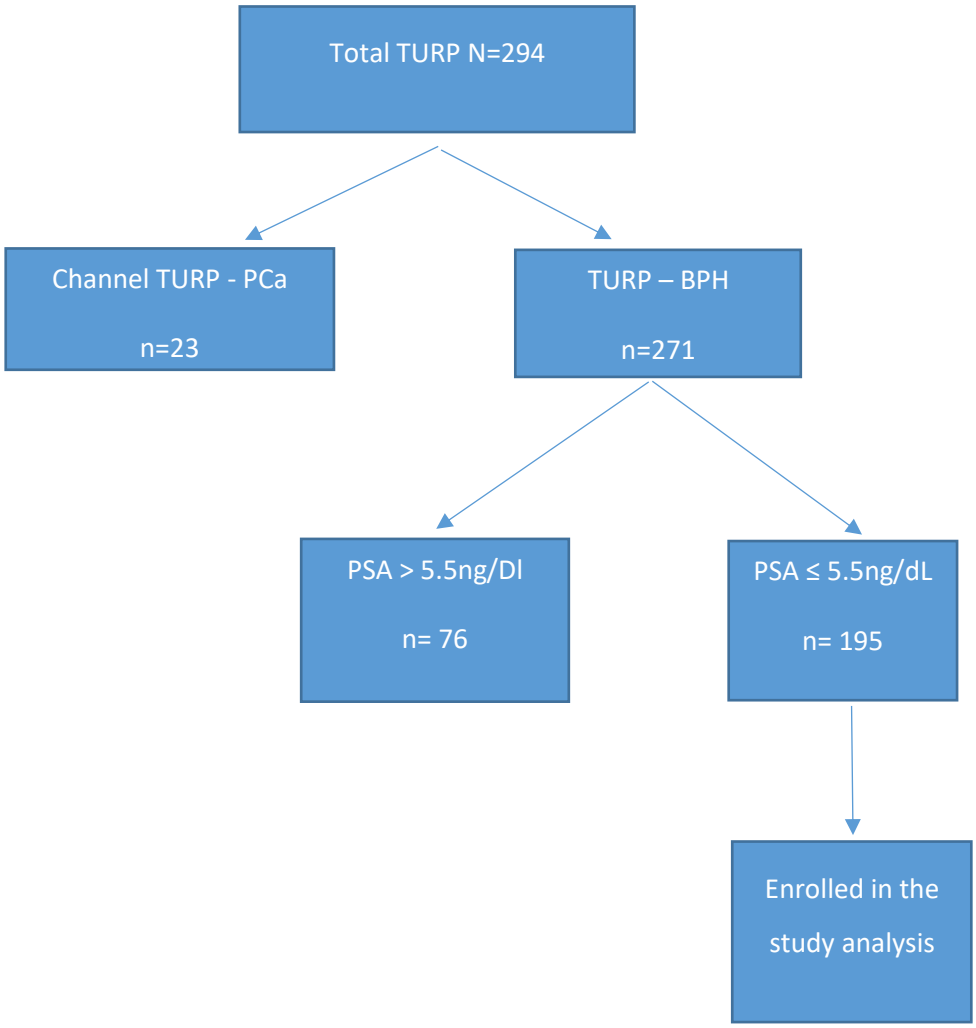
2.5.3 SIGNIFICANCE OF THE STUDY

The study aimed to highlight the burden of IPCa among patient undergoing TURP for BPE and ascertain its clinical correlates. In so doing the study aimed to publish the results as they stand as the immediate strategically remedy to proper cancer care in our setting.

3.0 RESULTS

Total number of 294 men underwent TURP in the study period. Total of 195 men who met the inclusion criteria, were analyzed in this study, figure 1.

Figure 1. flow chart for enrollment of patients' data.



Most participants 143 (73%) were of African ethnicity and non-Africans were 52 (27%). The age of participants was normally distributed with mean age of 66.17 (SD 9.63) years. More than half

of them 108/195 (55%) falling between (66 – 93 years). Majority had a clinical grade III 180/195 (92.3%) prostate size. Mean prostate volume estimated by USS was 54.01 (SD 5.33) Gram.

Table 1. Participant's baseline demographic & clinical characteristics

	FREQUENCY	PERCENTAGE (%)
Age groups		
Less than 60 years	60	30.8
61- 65 years	27	13.8
66- 70 years	50	25.6
71- 75 years	30	15.4
Greater than 76 years	28	14.4
Ethnicity		
AFRICANS	143	73
NON-AFRICANS	52	27

Table 2. Participants' clinical characteristics

PSA range		
0- 2.5 ng/ml	113	57.9
2.6- 5.5 ng/ml	82	42.1
Prostate size (in grades)		
II (40.54 ± 7.69 ml)	15	7.7
III (61.08 ± 11.90 ml)	180	92.3

Prostate indices;

The PSA and their respective PSA-density were normally distributed, with mean (SD) values of 2.35±1.5 ng/ml and 0.0434±0.029 ng/ml^2 respectively. 58% of all PSA fell between 0 – 2.5ng/ml. No positive correlation between age and PSA ($r=-.014$, $p>0.05$) was found. Positive correlation between age and prostate volume was found ($r=0.19$, $p<0.05$).

Table 3. Tumor characteristics

	FREQUENCY	PERCENTAGE %
Incidental Prostate Ca		
Yes	14	7.2%
No	181	92.8%
Tumor Size		
T1a	3	21%
T1b	10	71%
Not known	1	8%
ISUP Score		
Grade 1	7	50%
Grade 2	3	21%
Grade 3	2	14.5%
Grade 4	2	14.5%

Incidental prostate cancer;

Histological analysis revealed- 92.8% had BPE and a 7.2% had prostate carcinoma. In the present study, the prevalence of incidental prostate cancer among men with PSA levels of less than 5.5ng/mL was 7.2% (95% CI). Table 2 summarizes the characteristics of incidental prostate ca. Mean age is 71.5(SD 8.14) in IPCa compare to 65.76 (SD 9.6) among men with BPE, this difference was statistically difference ($x^2 = 11.8$, $p < 0.05$)

The mean (±SD) PSA value is 3.01±0.99 ng/ml among 14 men with IPCA compared to 2.29 ± 1.57ng/ml among 181 men with BPH. Figure 1 shows the distribution of PSA levels in the BPH and IPCa groups.

PSA had positive association with IPCA. This was analyzed by means of linear regression f(1,193)=0.879, p=0.001. Mean prostate volume estimated by USS was 54.01 (SD 5.33) Gram.

The mean ratio of the PSA level to the prostate volume was slightly higher among men with IPCa (0.0524± 0.017) than among men with BPH (0.0427± 0.03), however, the association was not statistically significant (r= -.044, p=0.545).

Total of 10 (71%) patients had T1b disease, predominantly among those above 65yrs, ($p<0.05$)

Half of incidental prostate Ca were high grade cancers (GS ≥7). The relationship of PSA and GS is summarized figure 1. There was no association between age and high-grade tumor (($x^2= 13.9$, $p>0.05$).

Table 4. Factors associated to incidental prostate carcinoma

		Incidental Prostate Carcinoma				
		NO	**YES**	**X^2**	**df**	**p-value**
AGE GROUPS (years)	≤60	60 (100)	0 (0)	11.83	4	0.019
	61-65	25 (92.6)	2 (7.4)			
	66-70	44 (88)	6 (12)			
	71-75	29 (96.7)	1 (3.3)			
	≥76	23 (82.1)	5 (17.9)			
PSA Levels (ng/ml)	0-2.5	111	70	11.80	1	0.001
	2.6-5.5	2	12			
Prostate size	Grade II	15 (100)	0 (0)	1.257	1	0.26
	Grade III	166 (93.2)	14 (7.8)			
Ethnic groups	African	136 (92.5)	11 (7.5)	0.83	1	0.77
	Non-African	45 (93.7)	3 (6.3)			

A logistic regression analysis to investigate the risk factors of IPCa was conducted. The predictors variables such as (Age, PSA, Prostate size and ethnicity) were tested a priori to verify there was no violation of the assumption of the linearity of the logit. The predictors (Age and PSA) in logistic regression analysis were found to contribute to the model and were summarized in the table 4. Age has significant effect on risks for IPCa with (OR for IPCa, 1.6 per unit increase in age, 95 percent confidence interval, 1.054 to 23.38; $P<0.043$) and PSA level had (odds ratio for IPCa, 2.2 per unit increase in PSA, 95 percent confidence interval, 1.953 to 42.28; $P<0.005$), respectively. The rest of the factors had no association for IPCa.

Table 5. Multivariate binary regression analysis IPCa

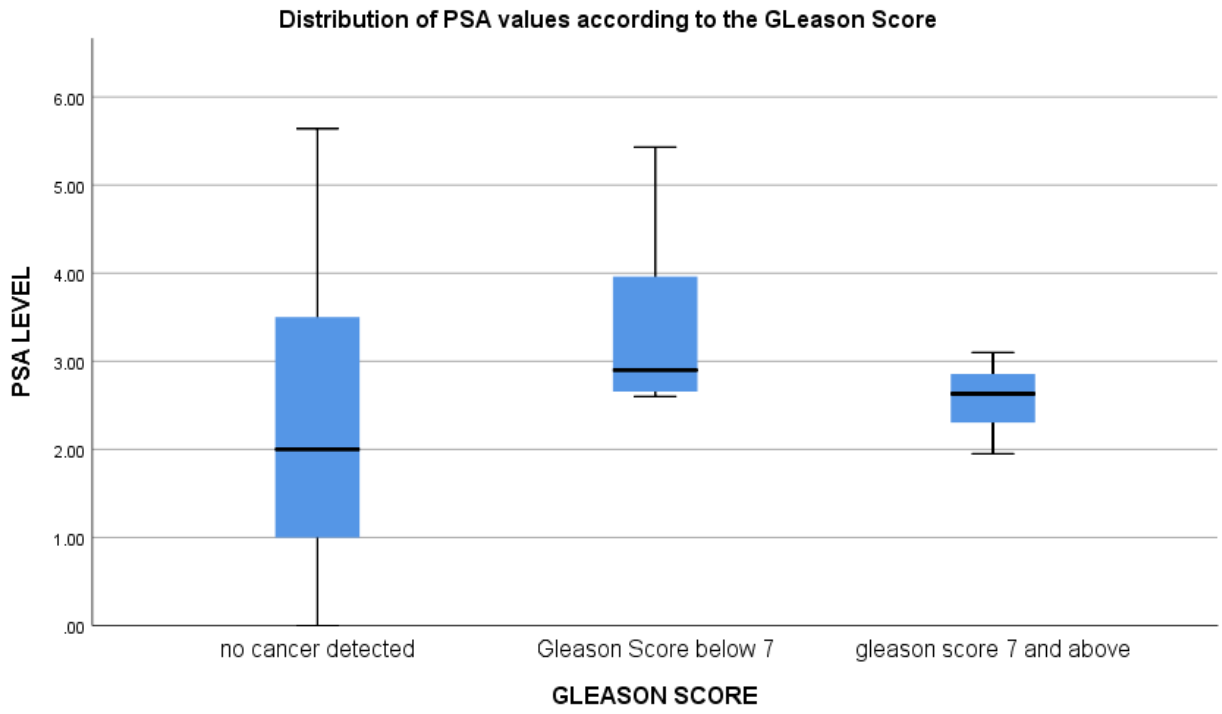
	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
PSA	2.207	.784	7.913	1	.005	9.086	1.953	42.280
AGE	1.602	.791	4.107	1	.043	4.964	1.054	23.383
PROSTATE SIZE	18.736	10048.2	.000	1	.999	137070	.000	
ETHNICITY	0.193	0.674	0.082	1	0.77	1.213	0.324	4.543
Constant	-8.940	2.067	18.711	1	.000	.000		

The prevalence of incidental prostate cancer 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 as summarized in table 5. ROC was conducted for PSA value less than 5.5ng/ml to determine if there is an optimal cut-off value with sufficient diagnostic accuracy to detect IPCa. The AUC was 65%, concluding luck of sufficient diagnostic utility, figure 2.

Table 6. Relationship of PSA levels to the prevalence of prostate cancer among 195 patients

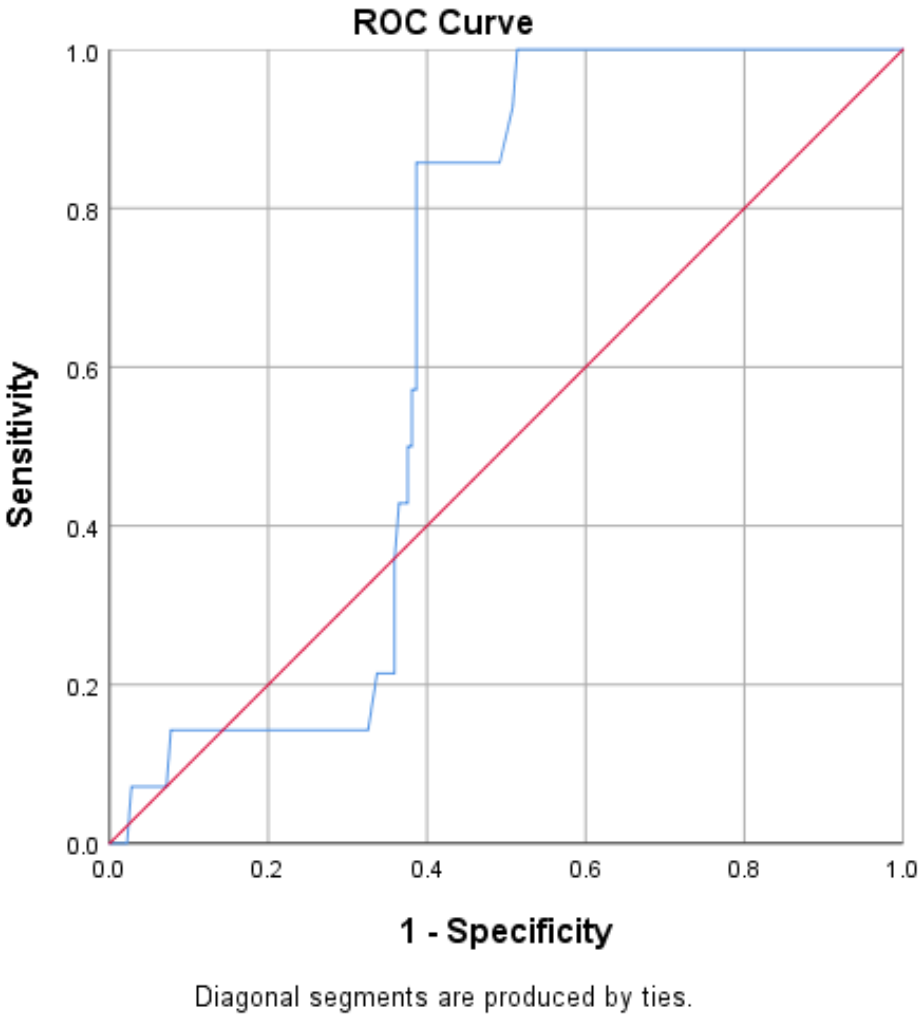
PSA LEVEL	NO. OF MEN	MEN WITH ICPA	HIGH GRADE CANCER
≤2.5ng/mL	113	2 (14%)	4
≥2.6ng/mL	82	12 (86%)	3

Figure 2. Boxplot displaying distribution of prostate values according to the Gleason-score.



The black horizontal lines within the boxes denote the medians, 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.

Figure 3. ROC curve for diagnostic performance of PSA values.



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

4.0 DISCUSSION

This study showed an incidental prostate carcinoma rate of 7.2 percent among men undergoing TURP for BPE. This prevalence was much less compared to the prevalence of recently published study in Northern Tanzania which was 21% (34). There was a difference in patient population as this study only included men with considered normal PSA as opposed to the above study by Gunda et al.

This prevalence was similar to other studies comparing prevalence of IPCa in the PSA use era, with even lower prevalence reported by Otto et al of 1.4%, the prevalence 6.2% was reported in the study conducted in Brazil, the study by Pirsa et al in 2018 reported detection rate of 6.34% (16-18).

The lower prevalence of IPCa in this study is most likely a result of PSA usage. Similar results were reported by several American studies, which compares the prevalence of IPCa among men in 1980's and 1990's and found a significant decrease on detection rates, from 14.6 to 6.7 and 11.8 to 6.5 in population of thousand white and thousand black men, respectively(35). These findings were attributed to adoption of routine PSA measurement.

In the present study IPCa had clinically significant association to Age. Age >65 years was significantly associated with IPCa (p=0.043). this results was similar to the results reported by Bright et al, whereby age was the only predictor of IPCa, the mean age in the study was 76 years among IPCa group, which was 5 years older compare to BPH group (17), similar results was observed by Gunda et al, elderly male (≥65 years) had increased risk of prostate cancer with (p=0.005) (34). The increasing trend of IPCa with age was well established in the study conducted by Di Silverio et al, whereby IPCa increased with each decade of age from 6^{th} to 9^{th} decade (36).

PSA level in the present study had an association to IPCa. The mean PSA in IPCa and BPH groups were found to be 3ng/ml and 2.3ng/ml respectively, this was a significant association. This result was also comparable to the number of studies which compared the detection rate of IPCa in PSA use era to pre-PSA use era, the study conducted by, Tombal et al showed drop of 18% prevalence of IPCa (27% to 9%), accounting the difference to PSA use (37). Another study conducted by Jones et al, showed that the prevalence IPCa among 700 men who underwent TURP, decreased from 14.9% to 5.2% in PSA-use era compare to non-PSA use. Contrast results of PSA use was reported by Antunez et al, PSA had no association (38). Some studies have highlighted the

challenges arising on PSA false positive's values leading to overtreatment and associated overtreatment-related complications (39, 40). PSA has to be interpreted with caution as the marker is not a cancer specific but rather a prostate-tissue specific. With this low rate but potentially significant IPCa detection among men with a considered normal range of PSA, it is difficult to propose an optimal PSA cut-off values in our setting. We propose even larger scale follow up studies, to ascertain this dramatic association.

African ethnicity did not show any significant association to the IPCa. This result is contrast to the study conducted by Thompson et al, who showed a significant association in Black race and IPCa, however this study failed to adequately establish an association between these factors due to inadequate numbers (25). The current high incidence rate and mortality rate within African ethnicity is probably the result of knowledge of pattern of screening, the study by Mariotto et al, which had 45% and 43% white and black men respective, found no racial difference in PSA testing (41). The study on knowledge, perceived risk of prostate screening in Dar es salaam Tanzania also found low utilization of prostate screening services due to poor socio-economical and low knowledge factors (42).

Prostate volume estimated by TRUS was found to have positive correlation with the age, however it was not significantly associated with IPCa. The study by Antunes had similar results where by mean prostate volume of 72±28.8 grams in IPCa group was statistically insignificant risk of IPCa p=0.179. PSA volume increased proportionally to increase in age, prostate volume has been incorporated in PSA derivatives, in order to increase the positive predictive value of PSA. Study by Froehner et al showed that PSA density, reduced the rate of unnecessary prostate biopsy prior TURP (26).

Half of patient had a high-grade prostate cancer, GS≥7 and T1b disease, there was significant association GS to the PSA (p=0.02). It was also observed that 71% of men had a T1b disease, this finding was again observed in the age of 65 years and above, these results were comparable to several other studies (34, 43).

This rate of IPCa in our setting is an evidence that there is unknown number of men treated for BPE who have a potential chance of developing an advance stage of prostate cancer. The study done by Roy et al, has shown that T1a disease is not a dismissible disease, it needs an active surveillance and definitive staging, the study showed 16% of T1a progress to a stage that requires

active treatment (21). The medical advancement, has led to a significant number of patients being pharmacologically treated for bladder outlet obstruction. This approach hinders the availability of tissue biopsy for histological analysis of this small but significant spectrum of prostate cancer. In the present study, clinically significant IPCa i.e. GS≥7, was found in half of all cases. To counteract the overtreatment imbalance as a result of PSA screening and Age simultaneously should be adopted in clinical judgement, 60 years and PSA above 5.5ng/ml should be used to decide if the prostate biopsy should be taken.

The lower rates of IPCa in the present study compare to the other study in North Tanzania, has just signify the role of PSA screening of men presenting with bladder outlet obstruction. PSA combined with older age (>65) with urinary obstructive symptoms, warrants TRUS biopsy. In our facility channel-TURP were done among men with advanced stage PCa.

4.1 CONCLUSION

The IPCa detection rate of 7.3% among men undergoing TURP for BPE in our settings is within the Internationals range of IPCa prevalence in this PSA-use era.

This prevalence of IPCa in our setting is an evidence that there is unknown number of men treated for BPE who have potential chances of developing an advance stage of prostate cancer.

However, this detection rate is not high enough to propose fundamental changes in PCa diagnostic approach.

4.2 LIMITATION

This study was not powered to elicit the risk factors, hence the wide range of confidence interval observed in the statistically significant associated factors.

This being a retrospective study, has caused challenges of adequacy assessment of participants information, due to documentation issues, such as family Hx of Prostate Ca which was not uniformly documented.

4.3 RECOMMENDATION

All patient with bladder outlet obstruction symptoms treated medically or surgically (TURP) should be informed of 7.2% chance of IPCa.

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

REFERENCES

1. Global Burden of Disease Cancer C, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2017;3(4):524-48.
2. Kheirandish P, Chinegwundoh F. Ethnic differences in prostate cancer. Br J Cancer. 2011;105(4):481-5.
3. Panz VR, Joffe BI, Spitz I, Lindenberg T, Farkas A, Haffejee M. Tandem CAG repeats of the androgen receptor gene and prostate cancer risk in black and white men. Endocrine. 2001;15(2):213-6.
4. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-403.
5. Rebbeck TR, Devesa SS, Chang BL, Bunker CH, Cheng I, Cooney K, et al. Global patterns of prostate cancer incidence, aggressiveness, and mortality in men of african descent. Prostate Cancer. 2013;2013:560857.
6. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128.
7. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197-223.
8. Adeloye D, David RA, Aderemi AV, Iseolorunkanmi A, Oyedokun A, Iweala EE, et al. An Estimate of the Incidence of Prostate Cancer in Africa: A Systematic Review and Meta-Analysis. PLoS One. 2016;11(4):e0153496.

9. Nakandi H, Kirabo M, Semugabo C, Kittengo A, Kitayimbwa P, Kalungi S, et al. Knowledge, attitudes and practices of Ugandan men regarding prostate cancer. Afr J Urol. 2013;19(4):165-70.
10. <EAU-ESUR-ESTRO-SIOG-Guidelines-on-Prostate-Can.pdf>.
11. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol. 2006;24(14):2137-50.
12. Catalona WJ, Richie JP, deKernion JB, Ahmann FR, Ratliff TL, Dalkin BL, et al. Comparison of prostate specific antigen concentration versus prostate specific antigen density in the early detection of prostate cancer: receiver operating characteristic curves. J Urol. 1994;152(6 Pt 1):2031-6.
13. Abedi AR, Fallah-Karkan M, Allameh F, Ranjbar A, Shadmehr A. Incidental prostate cancer: a 10-year review of a tertiary center, Tehran, Iran. Res Rep Urol. 2018;10:1-6.
14. Lu-Yao GL, Barry MJ, Chang CH, Wasson JH, Wennberg JE. Transurethral resection of the prostate among Medicare beneficiaries in the United States: time trends and outcomes. Prostate Patient Outcomes Research Team (PORT). Urology. 1994;44(5):692-8; discussion 8-9.
15. Yu X, Elliott SP, Wilt TJ, McBean AM. Practice patterns in benign prostatic hyperplasia surgical therapy: the dramatic increase in minimally invasive technologies. J Urol. 2008;180(1):241-5; discussion 5.
16. Otto B, Barbieri C, Lee R, Te AE, Kaplan SA, Robinson B, et al. Incidental prostate cancer in transurethral resection of the prostate specimens in the modern era. Adv Urol. 2014;2014:627290.
17. Bright EA, Manuel C, Goddard JC, Khan MA. Incidence and factors predicting the detection of prostate cancer after transurethral resection of the prostate for clinically benign disease. Urol Int. 2009;83(2):171-4.
18. Pirsa M, Pezelj I, Knezevic M, Spajic B, Tomaskovic I, Reljic A, et al. Incidental Prostate Cancer in Patients Treated for Benign Prostate Hyperplasia in the Period of 21 Years. Acta Clin Croat. 2018;57(Suppl 1):71-6.

19. Andren O, Garmo H, Mucci L, Andersson SO, Johansson JE, Fall K. Incidence and mortality of incidental prostate cancer: a Swedish register-based study. Br J Cancer. 2009;100(1):170-3.
20. Andrén O, Fall K, Franzén L, Andersson S-O, Johansson J-E, Rubin MA. How Well Does the Gleason Score Predict Prostate Cancer Death? A 20-Year Followup of a Population Based Cohort in Sweden. Journal of Urology. 2006;175(4):1337-40.
21. Roy CR, 2nd, Horne D, Raife M, Pienkos E. Incidental carcinoma of prostate, Long-term follow-up. Urology. 1990;36(3):210-3.
22. <sect_23_prostate.pdf>.
23. Punglia RS, D'Amico AV, Catalona WJ, Roehl KA, Kuntz KM. Effect of verification bias on screening for prostate cancer by measurement of prostate-specific antigen. N Engl J Med. 2003;349(4):335-42.
24. <EAU-ESUR-ESTRO-SIOG-Guidelines-on-Prostate-Cancer-large-text-V2.pdf>.
25. Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. N Engl J Med. 2004;350(22):2239-46.
26. Froehner M, Buck LM, Koch R, Hakenberg OW, Wirth MP. Derivatives of prostate-specific antigen as predictors of incidental prostate cancer. BJU Int. 2009;104(1):25-8.
27. Herden J, Ernstmann N, Schnell D, Weissbach L. [The HAROW study: an example of outcomes research: a prospective, non-interventional study comparing treatment options in localized prostate cancer]. Urologe A. 2014;53(12):1743-52.
28. Bell KJ, Del Mar C, Wright G, Dickinson J, Glasziou P. Prevalence of incidental prostate cancer: A systematic review of autopsy studies. Int J Cancer. 2015;137(7):1749-57.
29. Zlotta AR, Egawa S, Pushkar D, Govorov A, Kimura T, Kido M, et al. Prevalence of prostate cancer on autopsy: cross-sectional study on unscreened Caucasian and Asian men. J Natl Cancer Inst. 2013;105(14):1050-8.
30. Rebbeck TR, Haas GP. Temporal trends and racial disparities in global prostate cancer prevalence. Can J Urol. 2014;21(5):7496-506.
31. Ajape AA, Babata A, Abiola OO. Knowledge of prostate cancer screening among native African urban population in Nigeria. Nig Q J Hosp Med. 2010;20(2):94-6.

32. Draisma G, Boer R, Otto SJ, van der Cruijsen IW, Damhuis RA, Schroder FH, et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst. 2003;95(12):868-78.
33. WHO. WHO; UNITED REPUBLIC OF TANZANIA CANCER COUNTRY PROFILE, WH. WHO. 2014:1.
34. Gunda D, Kido I, Kilonzo S, Nkandala I, Igenge J, Mpondo B. Prevalence and associated factors of incidentally diagnosed prostatic carcinoma among patients who had transurethral prostatectomy in Tanzania: a retrospective study. Ethiopian Journal of Health Sciences. 2018;28(1).
35. Wasson JH, Bubolz TA, Lu-Yao GL, Walker-Corkery E, Hammond CS, Barry MJ. Transurethral resection of the prostate among medicare beneficiaries: 1984 to 1997. For the Patient Outcomes Research Team for Prostatic Diseases. J Urol. 2000;164(4):1212-5.
36. Di Silverio F, Gentile V, De Matteis A, Mariotti G, Giuseppe V, Luigi PA, et al. Distribution of inflammation, pre-malignant lesions, incidental carcinoma in histologically confirmed benign prostatic hyperplasia: a retrospective analysis. Eur Urol. 2003;43(2):164-75.
37. Tombal B, De Viscchер L, Cosyns JP, Lorge F, Opsomer R, Wese FX, et al. Assessing the risk of unsuspected prostate cancer in patients with benign prostatic hypertrophy: a 13-year retrospective study of the incidence and natural history of T1a-T1b prostate cancers. BJU Int. 1999;84(9):1015-20.
38. Antunes AA, Freire Gde C, Aiello Filho D, Cury J, Srougi M. Analysis of the risk factors for incidental carcinoma of the prostate in patients with benign prostatic hyperplasia. Clinics (Sao Paulo). 2006;61(6):545-50.
39. Andriole GL, Jr. PSA screening and prostate cancer risk reduction. Urol Oncol. 2012;30(6):936-7.
40. Sandhu GS, Andriole GL. Overdiagnosis of prostate cancer. J Natl Cancer Inst Monogr. 2012;2012(45):146-51.
41. Mariotto AB, Etzioni R, Krapcho M, Feuer EJ. Reconstructing PSA testing patterns between black and white men in the US from Medicare claims and the National Health Interview Survey. Cancer. 2007;109(9):1877-86.

42. Bugoye FC, Leyna GH, Moen K, Mmbaga EJ. Knowledge, Perceived Risk and Utilization of Prostate Cancer Screening Services among Men in Dar Es Salaam, Tanzania. Prostate Cancer. 2019;2019:2463048.
43. Perera M, Lawrentschuk N, Perera N, Bolton D, Clouston D. Incidental prostate cancer in transurethral resection of prostate specimens in men aged up to 65 years. Prostate Int. 2016;4(1):11-4.

Appendix

DATA ABSTRACTION TOOL

Patients' demographic data

MRNo…….

Age……..

Ethnicity/Race…….

Laboratory Data

Serum PSA levels……

Radiological data

KUB-USS volume of prostate ……

Histological Data

Adenocarcinoma Yes …….

No …….

If the above is Yes ;

Histopathological type of carcinoma…….

Histological grade

Primary (predominant) Gleason grade …….

Secondary Gleason grade …….

Global Gleason score/ISUP 2014 grade ……...

Approximate percentage of Gleason grade 4 or 5 …….

Tumor quantitation percentage of prostate involved Size/volume of dominant tumour nodue)

T1a (tumor ≤ 5%)……

T1b (tumor≥5%) …….