Original Article

Histopathology, pharmacotherapy, and predictors of prostatic malignancy in elderly male patients with raised prostate-specific antigen levels – A prospective study

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Abstract

Background: Prostate cancer is the second most common cancer among adult men in the world, and the diagnosis requires biopsy. Prostate-specific antigen (PSA) test along with digital rectal examination (DRE) increases the detection rate of prostate cancer than DRE alone. The objective of this study was to correlate serum PSA level with histopathological diagnosis, identify the predictors of malignancy, and describe the pharmacotherapy of patients with serum PSA levels >4 ng/ml.

Materials and Methods: This was a hospital-based observational study done among patients who presented with lower urinary tract symptoms and PSA levels >4 ng/ml who were planned to undergo prostatic biopsy. DRE followed by transrectal ultrasound (TRUS) assessment and guided sextant (6-core) prostatic biopsy was performed.

Results: One hundred and four patients were screened and 87 were included. Nineteen patients were diagnosed with malignancy, and among them, eight had bone metastasis. Spearman's correlation coefficient between PSA and malignancy was 0.449 ($P \leq 0.001$). Multivariate analysis suggested that the factors (adjusted odds ratio; 95% confidence interval; *P* value) such as increasing age (1.127; 1.013, 1.253; 0.027), nodular prostate (22.668; 4.655, 110.377; $P < 0.001$), and PSA (1.034; 1.004, 1.064; 0.024) were significant predictors of prostate cancer. All patients with benign prostatic hyperplasia were advised a combination therapy with 5-alpha reductase inhibitor and selective alpha-1 receptor antagonist while those with malignancy were prescribed androgen deprivation therapy with antiosteoporosis therapy.

Conclusion: In elderly patients with raised PSA levels or suspicious DRE findings, TRUS-guided prostate is recommended to rule out malignancy and plan appropriate management.

Keywords: Benign prostatic hyperplasia, prostate biopsy, prostate cancer, prostate-specific antigen

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INTRODUCTION

Considerable changes have occurred in the epidemiology of prostate cancer since the widespread availability of prostate specific antigen (PSA) in the early 1990s. In the pre-PSA era, autopsy studies indicated a cancer prevalence rate quite distinct from that of living men.

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This gap is now closing in populations in which PSA testing is widespread.[1] A thorough understanding of these PSA-induced changes is necessary to understand current epidemiologic data as PSA-driven biopsies constitute one of the most important part in the diagnosis of prostate cancer.[2] Prostatitis, benign prostatic hyperplasia (BPH), and prostate cancer are common diseases of the prostate. Prostatitis can be easily diagnosed clinically and is treated with antibiotics. However, BPH and prostate cancer are major public health issues; diagnosis and differentiation of these two conditions is very difficult without invasive procedures.[3] Prostate cancer can lead to lower urinary tract symptoms (LUTS) by producing bladder outflow obstruction similar to (BPH) and it commonly coexists with BPH.[2] A PSA test and digital rectal examination (DRE) increase the detection rate of prostate cancer over DRE alone. Therefore, measurement of the serum PSA value should be performed in patients in whom the identification of cancer would clearly alter the management.[4] A diagnosis of prostate cancer is highly dependent on the frequency and extent of prostatic tissue sampling. Other issues have also changed in recent years; these include the threshold for PSA-driven biopsies, the number of core samples obtained when biopsies are performed, and the number of repetitive biopsies in men with a prior negative biopsy.[5] Hence, the focus of our study was to correlate serum PSA level with histopathological diagnosis following prostatic biopsy, identify the predictors of malignancy and describe the pharmacotherapy of patients with raised serum PSA levels (i.e., >4 ng/ml).

MATERIALS AND METHODS

This was a prospective hospital based observational study done among patients who presented with LUTS and raised PSA levels to a tertiary care teaching hospital who were planned to undergo prostatic biopsy. The study period was for a period of 2 years from July 2012 to June 2014 and all patients who fulfilled the eligibility criteria were included. All consenting adult male patients 50 years of age and above presenting with LUTS and a serum PSA of >4 ng/ml were included in the study. Patients who were not willing for prostatic biopsy, those already on 5-alpha reductase inhibitors, and those with painful anal conditions were excluded. After obtaining consent, DRE was done with patient in the left lateral position ensuring that the right knee is bent up toward the chest. Particular attention was paid to the anal tone as a very tight sphincter may render the procedure painful. Precaution was also taken to exclude the presence of anal pathology such as fissures and rectal tumors. A circumferential examination of the rectum was undertaken which was followed by examination of the prostate for its symmetry, size, the presence of nodules or tenderness and pain. DRE was followed by transrectal ultrasound (TRUS) guided sextant (6-core) prostatic biopsy. 7.5MHz probe covered with a condom and a needle guide attached to it was used. Once the probe was introduced and the prostate visualized, a traditional sextant biopsy done using tru-cut biopsy gun with 16/18G needles under local anesthesia was performed. 6 core biopsies (2– Apex [right and left], 2– middle [right and left] and 2– base [right and left]) were taken from peripheral zone as far as possible. Additional biopsy cores were taken if there were suspicious findings on DRE or TRUS. These core biopsies were sent to the laboratory for histopathology in separate labeled pots. Rectal pack was kept for 10 min and then removed. Postprocedure, the patient was sent home on oral ciprofloxacin 500 mg and tinidazole 500 mg twice daily for 5 days and oral paracetamol 500 mg three times daily for 3 days. Depending on the histopathological report and severity of symptoms further treatment was advised as per the existing treatment protocols. Before doing TRUS, the size of prostate and postvoid residual (PVR) urine volume were assessed using transabdominal ultrasound. The study procedures were done in accordance to the Declaration of Helsinki and was approved by the institutional Ethics committee.

Data were entered into Epi Info Version 7 (Centers of Disease Control and Prevention, Atlanta, GA, USA, 2011) and analyses were performed using SPSS Statistics for Windows Version 20.0 (IBM Corp., Armonk, NY, USA, 2011). Demographic characteristics were summarized using descriptive statistics. The correlation and association between PSA value and the histopathology result was analyzed using Spearman's correlation and simple regression, respectively. Factors hypothesized to predict malignancy such as Gleason's score, DRE findings, ultrasound findings, International Prostate Symptom Score (IPSS), and likewise were analyzed using simple regression. Those predictors whose P value was <0.2 were subjected to binary logistic regression. Statistical significance was set at a $P < 0.05$.

The IPSS consists of 7 items in total which are 3 storage symptoms (frequency, urgency, and nocturia), 3 voiding symptoms (intermittency, slow stream, and straining to void) and one postmicturition symptom (feeling of incomplete emptying). The score attainable is between 0 and 35 and is classified as mild (0–7), moderate (8–19) or severely (20–35) symptomatic.[6] Gleason scores range from 2 to 10, with 2 representing the most well-differentiated tumors and 10 the least-differentiated

tumors. Prostate cancers with a Gleason score ≤6 usually have good prognoses.[7] Prostate gland enlargement was graded using DRE where it was classified as Grade I (approximately 20 g): normal prostate which is flat or slightly rounded surface, median sulcus usually unnoticed or shallow, superficial depth of lateral sulci, with approximately one fingertip length anteroposteriorly, and one fingertip mediolaterally; Grade II (approximately 40 g) which is bilobar rounded surface, well-delimitated median sulcus, superficial/intermediary depth of lateral sulci, with approximately two fingertips of length anteroposteriorly, and one/one and a half fingertip mediolaterally (above), or one fingertip length anteroposteriorly, and two fingertips mediolaterally (below); Grade III (approximately 60 g) which is rounded surface, complete obliteration of the median sulcus, intermediary/deep depth of lateral sulci, with two finger tips anteroposteriorly, and two fingertips mediolaterally; and Grade IV (approximately 80 g or greater) which is rounded surface, complete obliteration of the median sulcus, deep depth of lateral sulci, with no accessibility of the upper limits of the prostate to the tip of the examining finger.[8] It was also graded using ultrasound as per Aguirre *et al*. into Grades I (21–30 cc), II (31–50 cc), III (51–80 cc), and IV (>80 cc).[9]

RESULTS

One hundred and four patients were screened for eligibility and 87 were finally included. The reasons for exclusion were those individuals who did not provide consent (n = 11), those on 5-alpha reductase inhibitors (n = 5) and concomitant anal fissure (n = 1). 68 patients (78.16%) were diagnosed with BPH and the remaining 19 patients (21.84%) were diagnosed with malignant prostate, all of subtype – adenocarcinoma. The demographic and clinical characteristics of the patients are listed in Tables 1 and 2. The mean (standard deviation [SD]) age of patients diagnosed with BPH and malignancy were 67.57 (7.59) and 73.32 (8.44), respectively. A total of 41 patients had at least one of the comorbidities, namely diabetes mellitus, hypertension, coronary artery disease, or chronic kidney disease of which 29 patients belonged to the benign group. The mean (SD) of PSA in the benign group was 17.22 (20.39) and that for malignant group was 35.42 (22.18).

Factors such as age, number of co-morbidities, grade and feel of prostate on DRE, IPSS, prostate size in ultrasonography, PVR and PSA were subjected to univariate analysis using simple regression. Increasing age (P = 0.009),

Table 1: Demographic and clinical characteristics of patients (discrete variables)

Variable	Benign (row percentage), (n=68)	Malignant (row percentage) (n=17)	Total (column percentage) (n=87)
Age (years)			
50-60	16 (94.12)	1 (5.88)	17 (19.54)
61-70	28 (84.85)	5 (15.15)	33 (37.93)
71-80	20 (68.97)	9 (31.03)	29 (33.33)
>80	4 (50.00)	4 (50.00)	8 (9.20)
Presence of other comorbidities			
Diabetes mellitus	17 (85.00)	3 (15.00)	20 (22.99)
Hypertension	25 (71.43)	10 (28.57)	35 (40.23)
CAD	10 (55.56)	8 (44.44)	18 (20.69)
CKD	0 (0.00)	1 (100.00)	1 (1.15)
Prostate grade on DRE			
I	0 (0.00)	0 (0.00)	0 (0.00)
II	43 (78.18)	12 (21.82)	55 (63.22)
III	25 (78.13)	7 (21.87)	32 (36.78)
Feel of prostate on DRE			
Nodular	6 (30.00)	14 (70.00)	20 (22.99)
Smooth	62 (92.54)	5 (7.46)	67 (77.01)
Mortality	0 (0.00)	4 (100.00)	4 (4.60)

CAD: Coronary artery disease, CKD: Chronic kidney disease, DRE: Digital rectal examination

Table 2: Demographic and clinical characteristics of patients (continuous variables)

Variable	Mean (SD)			Median (IQR)		
	Benign (n=68)	Malignant (n=19)	Total (n=87)	Benign (n=68)	Malignant (n=19)	Total (n=87)
Age*	67.57 (7.60)	73.32 (8.45)	68.83 (8.10)	67.00 (12.50)	74.00 (11.00)	68.00 (12.00)
IPSS#	16.35 (1.79)	16.11 (1.88)	16.30 (1.81)	17.00 (2.75)	16.00 (3.00)	17.00 (3.00)
Prostate size in USG	82.47 (31.97)	78.58 (27.81)	81.62 (30.99)	79.00 (43.00)	74.00 (34.00)	79.00 (43.00)
PVR#	44.69 (31.53)	62.61 (27.86)	48.44 (31.50)	45.00 (61.00)	75.00 (35.00)	55.00 (60.25)
PSA#	17.22 (20.39)	35.42 (22.18)	21.20 (22.00)	10.00 (14.00)	32.00 (31.00)	12.00 (21.00)

*Normally distributed in all 3 categories as assessed by Shapiro-Wilk test, #Normally distributed under malignant category only as assessed by Shapiro-Wilk test. IPSS: International Prostate Symptom Score, USG: Ultrasonography, PVR: Postvoid residual volume, PSA: Prostate-specific antigen, SD: Standard deviation, IQR: Interquartile range

nodular prostate ($P < 0.001$), PVR ($P = 0.037$), and PSA ($P = 0.009$) which were significant in univariate analysis were subjected to binary logistic regression along with the factor, number of comorbidities as its P value was <0.2. The results of the univariate and multivariate analysis are presented in Table 3. The factors (adjusted odds ratio; 95% confidence interval; P value) such as increasing age (1.127; 1.013, 1.253; 0.027), nodular prostate (22.668; 4.655, 110.377; $P < 0.001$), and PSA (1.034; 1.004, 1.064; 0.024) continued to remain significant after multivariate analysis.

The clinical characteristics of malignant disease are depicted in Table 4. 61.54% of those with a Gleason's score >6 were diagnosed with metastatic disease and all patients with Gleason's score ≤6 had nonmetastatic disease which was statistically significant ($P = 0.036$). During the study period, we encountered 4 mortality all of them from the malignant group with metastatic disease. With regards to the Pharmacotherapy, all patients with BPH were advised a combination therapy with 5-alpha reductase inhibitor and selective alpha-1 receptor antagonist. All the patients who were taking 5-alpha reductase inhibitor were on Dutasteride. However, with regards to selective alpha-1 receptor antagonist 41.18% ($n = 28$) were on tamsulosin while the others (58.82%, $n = 40$) were advised alfuzosin. Among those with malignancy, 12 patients were on a combination therapy with bicalutamide, a testosterone receptor antagonist and denosumab, a monoclonal antibody that inhibits receptor activator of nuclear factor kappa-B ligand thereby preventing osteoclast formation. The remaining 7 patients with malignancy were put on leuprolide which is an injectable gonadotropin-releasing hormone (GnRH) analog.

DISCUSSION

Prostatic cancer is the second most common cancer among adult men in the world whose diagnosis requires obtaining cancerous tissue from the prostate gland with biopsy.[10] The advent of trans rectal ultrasound has revolutionized prostate biopsy techniques and the sextant prostate biopsy introduced by Hodge *et al*. has been the gold standard for diagnosing prostate cancer.[11] The absolute indications for prostate biopsy include serum PSA >4 ng/ml, abnormal DRE and presence of high-grade prostate *in situ* neoplasia (PIN) or cellular atypia on previous biopsy.[1,12] At present, preoperative serum PSA, Gleason score from biopsy, and clinical stage are the most common parameters used to predict the pathological outcome, prognosticate, or choose a definitive treatment in patients with prostate cancer.[13] In our study out of 87 patients who underwent prostatic biopsy (TRUS guided), 68 (78.16%) patients were found to have BPH and 19 (21.84%) patients were found to have prostatic adenocarcinoma. These results were nearly comparable with the studies conducted by Rukhsana Akhter *et al*. from Srinagar, India reported who in the year 2014 reported that out of 60 patients, 15% had adenocarcinoma, 6.6% of PIN and the rest BPH[14] while Gupta *et al*. from New Delhi have reported in the year 2015, 24% of 142 men to have adenocarcinoma.[15]

We report that increasing age, nodular prostate, and raised PSA to be significant predictors of malignancy after multivariate analysis. As per our results, with increase in age by 1 year, there is an increased-odds of around 13% to have prostatic malignancy and this is probably due to the increased duration of exposure of the prostates to the androgens. Our results are comparable with other studies such as those conducted by Anderson-Jackson *et al*.[16] and Wadgaonkar *et al*.[17] in which 43.45% and 41.7% of the patients with malignancy respectively were in the age group between 70 and 79 years. Nodular feel in DRE is the next factor which is significantly associated with malignancy and there is a 22 times increased chance of it being malignant. Similar findings have been reported in another study by Porter *et al*. where 53.3% with abnormal DRE findings had malignancy when compared to 28.8% who did not have malignancy despite abnormal DRE and the difference was statistically significant ($P < 0.01$).[18] The association between nodularity of the prostate and prostate cancer is probably because malignancy starts

Table 3: Factors predicting prostatic malignancy

Risk factors	Univariate analysis		Multivariate analysis	
	OR	P	aOR (95% CI)	P
Increasing age	1.096	0.009	1.127 (1.013-1.253)	0.027
Number of comorbidities	1.531	0.117	1.381 (0.617-3.090)	0.432
Prostate grade on DRE	1.003	0.995	Not included in analysis	
Nodular feel of prostate on DRE	28.93	<0.001	22.668 (4.655-110.377)	<0.001
IPSS	0.926	0.595	Not included in analysis	
Prostate size in USG	0.627	0.996	Not included in analysis	
PVR	1.020	0.037	1.021 (0.995-1.048)	0.109
PSA*	1.036	0.009	1.034 (1.004-1.064)	0.024

*Spearman's correlation coefficient $R=0.449$ ($P<0.001$ for two-tailed). OR: Odds ratio, aOR: Adjusted odds ratio, CI: Confidence interval, DRE: Digital rectal examination, IPSS: International Prostate Symptom Score, USG: Ultrasonography, PVR: Postvoid residual volume, PSA: Prostate-specific antigen

Table 4: Clinical characteristics of malignant disease

Variable	Metastatic disease (row percentage) (*n*=8)	Nonmetastatic disease (row percentage) (*n*=11)	Total (column percentage) (*n*=19)
Gleason's score			
≤6	0 (0.00)	6 (100.00)	6 (31.58)
>6	8 (61.54)	5 (38.46)	13 (68.42)
Mortality			
Yes	4 (100.00)	0 (0.00)	4 (21.05)
No	4 (26.67)	11 (73.33)	15 (78.95)

as dysplastic changes at focal areas in peripheral zone of the prostate whereas BPH is a diffuse enlargement predominantly of the median lobe.[19] The third predictor that we have reported as significant is PSA levels. With every unit rise in PSA, there is a 3% increased chance of the prostate having malignancy and there is a fair positive correlation between PSA and occurrence of malignancy. This finding is also comparable with the other studies such as the one conducted by Porter *et al*. where there was a significant association between elevated serum PSA and prostate cancer ($P < 0.0001$) and a hazards ratio of 5.225.[18] Since PSA being a protease produced by the prostatic cells, it will be elevated more in malignancies rather than BPH as there is uncontrolled proliferation in cancer.[20] We did not find any significant association between the number of comorbidities and malignancy because none of the comorbidities have a definite role influencing the metabolism of androgens. Similarly, there was no association between IPSS and malignancy because the prostate size and grade which determines the severity of symptoms is similar in both groups with no significant difference and also the main clinical sign behind both the conditions is prostatic enlargement. Villeda-Sandoval *et al*. have also reported similar findings with regard to comorbidities and IPSS in their association with prostatic malignancy.[21] PVR is once again not significantly different between the two groups as the mean size of prostate in both groups are similar.

With regard to the patient outcomes, we report that of the 19 patients with malignancy, 8 patients had bone metastasis. This is in line with findings from previous studies where it is reported that bone metastasis precedes lung and liver metastasis in patients with prostate malignancy.[22] We also report that the Gleason's score is predictive of metastasis, and this is due to the fact that Gleason's score is based on differentiation of the tumors and those with a score >6 are poorly differentiated tumors which are in turn highly aggressive. These results are in line with the findings of Sanjaya *et al*. in which among 358 patients of carcinoma prostate, 192 (53.6%) of them had bone metastasis and in that 192 patients, 170 (88.54% of 192) had Gleason score more than 6 signifying poor prognosis.[23] In our study however, we could not do inferential statistics on mortality rates as the mortality rate was very low probably because of a smaller sample size and a shorter follow-up duration.

As per the clinical guidelines of American Urological Association, any patient diagnosed with BPH is prescribed an alpha 1 receptor selective blocker (such as tamsulosin, aflusozin, and doxazosin) or 5-alpha reductase inhibitors (such as finasteride, and dutasteride) or a combination of both.[24] Thus, all our patients are on a combination therapy of these agents. Those patients diagnosed with malignancy were either on a antiandrogen bicautamide or GnRH analogue leuprolide. This is as per the various guidelines in place where medical management is through androgen deprivation therapy. Androgen deprivation can lead to osteoporosis and as per the guidelines, the patients have advised used of calcium supplementation, bisphosphonates, or denosumab which is a monoclonal anti-osteoporotic antibody and our patients.[25]

CONCLUSION

Based on our study results, for elderly patients with raised PSA levels or suspicious DRE findings, we recommend TRUS guided prostate. The commonest pathology encountered in the prostates studied were BPH (78.16%) and adenocarcinoma of prostate (21.84%). We also report that there is increased incidence of bony metastasis at diagnosis if the Gleason score of the prostate biopsy specimen is >6 which emphasize that it is an important prognostic factor for prostatic malignancy. As per the existing clinical guidelines, our patients with BPH were on a combination therapy with 5-alpha reductase inhibitors and selective alpha-1 receptor blockers while those with prostatic malignancy were advised androgen deprivation therapy with anti-osteoporotic agents. One limitation of our study was that the follow-up duration was shorter, and hence, the number of outcome events was less making it difficult to do statistical analysis. Hence, we recommend a much larger study with adequate sample size and longer follow-up duration to confirm the findings of our study.

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Conflicts of interest
There are no conflicts of interest.

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