ORIGINAL ARTICLE

Correlation of Serum Prostate Specific Antigen and Gleason Grade with Bone Metastases in Patients with Prostate Cancer; An Experience at a Tertiary Care Hospital

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Abstract

Background: Prostate cancer (PCa) is the second most frequent cancer in the world and its incidence in Asian countries is on the rise. A lot of research work has been done in the Western world for the better understanding and treatment of the disease but the Western data may not be relevant to the data from Asian countries.

Objective: To find out the association of serum prostate-specific antigen level and Gleason grade to the incidence of positive bone scan disease in our prostate cancer patient population.

Methods: A four-year retrospective study that comprised 32 Prostate cancer (PCa) patients who were seen at The Indus Hospital and Health Network (IHHN) from October 2017 to December 2021. Recorded data were serum PSA value, histopathological examination of prostate tissue, and bone scan results. Histopathological examination of PCa was confirmed on biopsy with well-documented Gleason grade groups and scores.

Results: Thirty-two patients with prostate cancer with a median age of 72.5 years (68-76.7), median PSA was 74 (12.4-100) ng/mL, and median GS was 9 (7-9) were included. Patients were segregated into four groups following their serum PSA levels ranging from ≤10 ng/ml (n=7; 21.8%), >10-≤20 ng/ml (n=4; 12.5%), > 20-≤100 ng/ml (n=14; 43.7%) and >100 ng/ml (n=7; 21.8%). Levels of PSA showed a significant association with BM (p=0.002). Similarly, in cancers with low Gleason grade, no bone metastasis was found (p=0.02).

Conclusion: Raised PSA and high Gleason grade are associated with increased occurrence of bone metastasis in patients with carcinoma of the prostate and can be used as predictors of disease severity and progression.

Keywords: *Prostate-specific antigen, bone metastasis, core needle biopsy, gleason grade.*

INTRODUCTION

Prostate cancer (PCa) is the second most frequent cancer in men and the fifth leading cancer-related cause of mortality globally [1, 2]. An estimated 18.1 million new cancer cases and 9.6 million cancer mortality were reported in 2018 [3, 4]. Almost 75% of recorded PCa cases occur in industrialized countries, with Northern America and Europe having the highest rates and South-East Asia having the lowest (8.3 per 100,000). It was believed to be a disease of the developed world until recently when a swift increase in the incidence and mortality has been seen in Asian countries which is believed to be due to adaptation of a more westernized standard of living and a high percentage of advanced stage cancer at the time of diagnosis [4]. The exact incidence of PCa in Pakistan is not known but based on some regional research and registries the estimated prevalence is around 7%. Nevertheless, with the overall rise of incidence in the developing world and increased awareness of disease screening and registration in our region, the actual prevalence can safely be expected to be much higher than the reported figures [5].

An early diagnosis of cancer of prostate decreases cancer-specific mortality by 20% [6]. Serum Prostate Specific Antigen (PSA) is widely utilized as a screening, diagnostic, and prognostic marker of PCa [5]. Higher levels of serum prostate-specific antigen (PSA > 4 mg/dl) have a reported sensitivity of 66% in diagnosing PCa [5, 7, 8]. PSA is a continuous parameter, with more elevated levels demonstrating a more prominent probability of malignant growth with a higher grade and higher chances of metastasis [9-11]. Bone is the first and the commonest site of prostate cancer metastasis (90%) preceding the lung and liver [12, 13]. However, recent data emerging from Asian countries is reporting a higher incidence of positive bone scans in patients with low serum PSA contrasting with the Western data [11].

Like all malignancies, histological type, grade, and stage of PCa is crucial in planning treatment strategies and forecasting prognosis. The Gleason grading system was developed in 1970 as a result of a prospective randomized study conducted by the Veterans Administration of the United States in which Dr. Donald Gleason summarized

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Table 1: International Society of Urological Pathology 2014 grade (group) system.

Gleason score	ISUP grade
2-6	1
7 (3+4)	2
7 (4+3)	3
8 (4+4 or 3+5 or 5+3)	4
9-10	5

the histopathologic grades of prostate adenocarcinoma and correlated them with clinical evidence including staging and prognosis. The WHO embraced the Gleason grading system in the PCa classification of 2004 and it is now one of the key factors, together with PSA and clinical staging, in the treatment decision of prostate cancer patients. In the original Gleason grading system, 5 Gleason grades, grade 1 representing the best differentiated and Gleason 5 the least differentiated on tumor architecture, were distinguished [14]. The Gleason grade of the most predominant pattern (primary) plus the second most common pattern (secondary) in the biopsy tissue make the Gleason score. In 2005 and subsequently 2014 International Society of Urology Pathology (ISUP) modified the Gleason Score (GS) by eliminating the "well-differentiated" Gleason grades 1 and 2. This modified Gleason scoring system, also known as the ISUP grade, is now routinely used for grading prostate carcinoma (**Table 1**). ISUP grade 3 or more is generally considered high for metastasis and warrants detailed radiological investigation for the distant spread of disease in patients with prostate cancer. However, a risk of metastasis exists, even with a low Gleason grade [15].

The PSA level, tumor stage, and ISUP grade are often used to predict the probability of prostate cancer spread.

We conducted this retrospective study to find out the association of serum PSA level and Gleason grade to the incidence of bone scan-positive disease in our prostate cancer patient population.

METHODOLOGY

This was a four-year retrospective study that comprised of 32 PCa patients who were seen at The Indus Hospital and Health Network (IHHN) from October 2017 to December 2021. The data was gathered from the patient's medical records. Serum PSA value, histopathological examination of prostate tissue, and bone scan result were recorded for all patients and those lacking any of the three aforementioned investigations were excluded from the study. The histopathological examination of PCa was confirmed on Core Needle Biopsy (CNB) and Transurethral Resection of the Prostate (TURP). The Gleason score (sum of primary and secondary pattern) and Gleason grade (as per the ISUP grading system mentioned above) as reported by the histopathologist were noted. The patients in whom the aforementioned data was not available were excluded from the study.

STATISTICAL ANALYSIS

The data was entered into Microsoft Excel and analyzed with the Statistical Package for Social Sciences (SPSS) Version 23.0 software. For categorical variables, frequency with percentages was calculated while median and interquartile ranges (IQR) were calculated for numerical data due to not normal distribution of the data (assessed *via* the Shapiro-Wilk test). The Age Standardized Incidence Rate (ASIR) was calculated using the Segi World Standard, applying the direct method of age-standardization, and presented per 100,000 population. Receiver operating characteristic (ROC) analysis was performed to assess the diagnostic accuracy of serum PSA and GG for bone metastases. Sensitivity and specificity were calculated. The Kruskal-Wallis test was applied to determine the statistical difference between GS with serum PSA levels. The association of grade groups and Bone Metastases (BM) with serum PSA levels was evaluated using the Chi-Squared/Fisher's-Exact test (as per need). The level of statistical significance was set at <0.05.

RESULTS

As per the inclusion criteria, a total of 32 patients with prostate cancer were enrolled in the study. The median age of the patients was 72.5 years (68-76.7), the median PSA was 74 (12.4-100) ng/mL, and the median GS was 9 (7-9). Gleason grades were divided into 5 Grade groups (GG): GG-1 (5/32; 15.6%), GG-2 (1/32; 3.1%), GG-3 (3/32; 9.4%), GG-4 (9/32; 28.1%) and GG-5 (14/32; 43.8%). Bone scan was positive for metastasis in 15 (46.9%) patients while 17 (53.1%) were negative (**Table 2**). It was also noted that the levels of serum PSA rose with increasing age as depicted in **Fig.** (**1**).

Table **3** shows the frequencies of different levels of GS. GS-9 was found to be the most dominant while the least common was GS-10.

Patients were segregated into four groups in accordance to their serum PSA levels ranging from ≤10 ng/ml (n=7; 21.8%), >10-≤20 ng/ml (n=4; 12.5%), > 20-≤100 ng/ml (n=14; 43.7%) and >100 ng/ml (n=7; 21.8%). Bone metastases (BM) were analyzed per subgroup of serum

Table 2: Baseline characteristics of prostatic carcinoma patients (n=32).

Characteristics		Median (Interquartile Range)
Age in years		72.5 (68-76.7)
PSA		74 (12.4-100)
Gleason Score		9 (7-9)
		n (%)
Grade Groups	GG1	5 (15.6)
	GG2	1 (3.1)
	GG3	3 (9.4)
	GG4	9 (28.1)
	GG5	14 (43.8)
Bone Metastases	Positive	15 (46.9)
	Negative	17 (53.1)

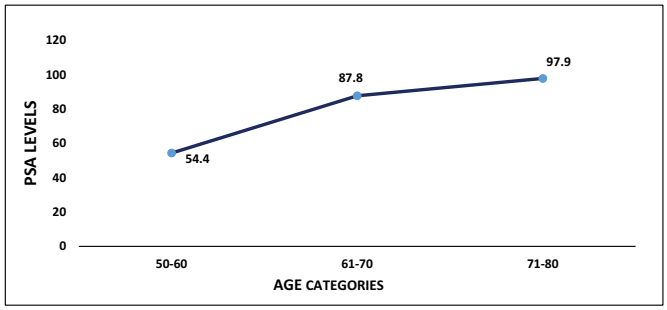

Fig. (1): Age categories and serum PSA levels.

Table 3: Levels of Gleason scores.

Gleason Scores	Frequency (n)	Percentages (%)
6	5	15.6
7	6	18.8
8	4	12.5
9	16	50.0
10	1	3.1

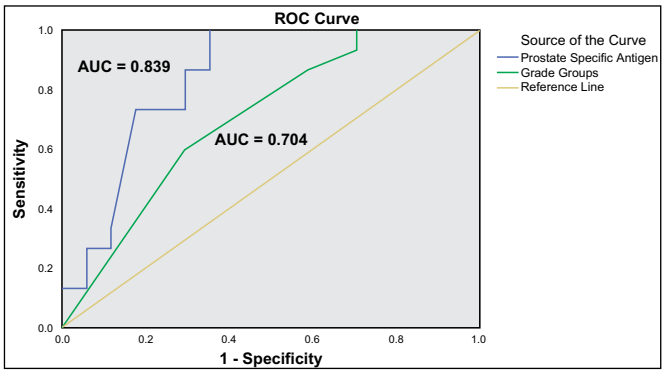

Fig. (2): Receiver Operating Curves (ROC) Analysis of Serum Prostate Specific Antigen (PSA) and Grade Groups (GG) for Bone Metastasis in Patients with Prostate Cancer.

PSA. Around 66.6% (3/4) of patients in PSA group 3 (20-100 ng/ml) had positive BM, whereas 33.3% (1/4) in PSA group 4 (>100ng/ml) had BM positive showing a significant association (p=0.002) (**Table 4**).

The most common Gleason grade group in our study population was GG-5 (n=14; 43.7%). While, GG-4 (n=9; 28.1%), GG-3 (n= 3; 9.3%), GG-2(n=1; 3.1%) and remaining (n=5; 15.6%) were GG-1. Approximately 60% of the patients having grade 5 had positive BM.

Table 5: Association between grade groups and bone metastasis.

Bone Metastasis (BM)			
Grade Groups (GG)	**Positive BM (n=15)**	**Negative BM (n=17)**	**P-value**
GG1	0	5 (29.4%)	0.02*
GG2	1 (6.7%)	0	0.29
GG3	1 (6.7%)	2 (11.8%)	0.08
GG4	4 (26.7%)	5 (29.4%)	0.16
GG5	9 (60.0%)	5 (29.4%)	0.30

whereas, grade 1 tumors are found to be negative for BM (**Table 5**).

We also compared the accuracy of serum PSA for diagnosing bone metastases; the area under the curve (AUC) of serum PSA was found to be (0.839, 95% CI: 0.696-0.982; p-value 0.001*). At ≥54.75 ng/ml the maximum sensitivity of serum PSA with BM was 86.7%, specificity was 78 % (**Fig. 2**).

We also compared the accuracy of GG for diagnosing bone metastases; the area under the curve (AUC) of GG was found to be (0.704, 95% CI: 0.523-0.885; p-value 0.050*). At ≥ 4.5 the maximum sensitivity of GG with BM was 60 %, specificity was 70.6 % (**Fig. 2**).

DISCUSSION

Prostate Adenocarcinoma is a malignancy in middle-aged and elderly men, and it is uncommon in males under the age of 50 years [16]. Approximately 99% of PCa is diagnosed after 50 years of age [17]. In Pakistan, the incidence of PCa is 2.6% *i.e.* comparatively low in comparison to other Asian countries, and ranked thirteenth in the list of all malignancies while ranked fourth among males. According to Globocan 2020, the Age Standardized Incidence rate (ASIR) in Pakistan was 6.3 per 100,000 [18]. However, our study shows an ASIR of 6.4 per 100,000.

Our study population with PCa aged between 65-80 years and when correlated with the PSA levels a rising trend in PSA was noted with increasing age although this could not be statistically proven to be significant. Similarly, Mehnaz *et al.* [5] and Hanif *et al.* [19] also show rising trends in the 60-69 age group. Dijkman *et al.*

Table 4: Association of PSA levels with age, bone metastases, and histological grade.

Serum PSA Levels					
Parameters	**≤ 10 (n=7)**	**>10 - ≤20 (n=4)**	**>20- ≤100 (n=14)**	**>100 (n=7)**	**P-values**
Age, Median (IQR)	73 (60-78)	79 (76-80)	69 (68-72)	74 (66.5-75.5)	0.031a
Gleason Score	7 (6-9.5)	6 (6-7)	8 (7-8.5)	9 (8-9)	0.071a
G1	4 (57.1%)	1 (25%)	0	0	0.004*b
G2	0	0	0	1 (14.3%)	0.297b
G3	1 (14.3%)	1 (25%)	1 (7.1%)	0	0.541b
G4	0	1 (25%)	6 (42.9%)	2 (28.6%)	0.235b
G5	2 (28.6%)	1 (25%)	7 (50.0%)	4 (57.1%)	0.581b
Positive BM	0	0	10	5	0.002*b
Negative BM	7	4	4	2	

a = Kruskal Wallis Test, b = Chi Square Test, c= Fisher's Exact Test.

reported that PCa is a severe age-related malignancy that affects 50% of patients aged 61-70 years. The median age of patients reported in our study was 72.50 years. A similar median age has been stated in studies conducted in Japan and Jamaica [20, 21].

The role of serum PSA is well-established in prostate carcinoma. There is no optimal PSA threshold that could confirm the harboring of PCa and even a PSA of 0.5 ng/ml carries a 6.6% risk of PCa [22]. However, levels > 4ng/ml are generally considered to be abnormal. In our study, 21.8% (7/32) of patients with PCa had PSA < 10 ng/dl and 12.5% with PSA < 20 ng/dl (**Table 4**). On correlating PSA levels to bone metastasis we found a high PSA to be positively associated with bone metastases (BM) and no BM was seen in PSA reported below 20 ng/dl. This difference was shown to be statistically significant. In a meta-analysis of 23 different series the mean for a metastatic PCa was 2.3% in patients with PSA levels < 10 ng/ml, 5.3% in patients with PSA levels between 10.1 and 19.9 ng/ml, and 16.2% in patients with PSA levels of 20-49.9 ng/ml [23]. Studies have shown a high negative predictive value of low PSA (<20 ng/ml) and as PSA rises to> 10.0 ng/ml, the risk of cancer increases significantly. A PSA level of 10ng/ml is regarded as a cutoff threshold for the bone scan [22]. The Gleason grading system is recommended for use in all prostate specimens containing adenocarcinoma, except those showing treatment effects, usually in the setting of hormonal ablation and radiation therapy. The primary and secondary grades should be reported in addition to the Gleason score, that is, the Gleason score is 7(3+4) or 7(4+3). The Gleason score is the sum of the primary (most predominant in terms of surface area of involvement) Gleason grade and the secondary (second most predominant) Gleason grade. If no secondary Gleason grade exists, the primary Gleason grade is doubled to determine a Gleason score. The Gleason grading system is considered the standard for histological grading and reporting of PCa. Contemporary Gleason scores can be grouped into 5 prognostic categories, Grade groups 1-5. This grade grouping has also been subsequently validated by other independent studies in surgical cohorts showing a significant correlation with outcome. The new grade grouping has been endorsed by ISUP, GUPS, and the 2016 WHO classification. The grade group is also referred to as ISUP grade or WHO grade in other publications and should be reported in parallel with the Gleason score [15].

In our study, biopsy proven total GS-6 was found in 5 (15.6%), GS-7 in 6 (18.8%), GS-8 in 4 (12.5%), GS-9 in 16 (50%) and GS-10 in 1 (3.1%) patients respectively (**Table 3**). GS-9 was the most frequent finding which reflects poorly differentiated condition with worse prognosis. Another study from Nigeria also reported that their most of the PCa patients fall in GS-8 and 10 [2] Pierorazio and Taimoor *et al.* showed that a higher level of serum PSA is associated with poorly differentiated histopathology (GS>7). Serum PSA and total GS in our study are moderately correlated and statistically significant (r=0.383, p=0.037). Gleason GG-4 and GG-5 were the most common in our study. A comparative study by Abubakar *et al.* showed similar results [24]. These findings give an evidence that serum PSA is one of the strongest variable in the evaluation of PCa whereas, in combination with GS and grade can efficiently describe clinical prognosis of patients.

Sharma *et al.* shows an area under curve 0.787 with significant p value (<0.05) for accuracy of PSA for diagnosing bone metastasis on bone scan which is similar to our study AUC 0.839 p-value (<0.05) [25]. Similarly, Maseeh uz Zaman *et al.*, reported serum PSA AUCs of 0.803 [11]. It means that PSA is a good predictor of BM when ROC curves are used.

Of the total, 60% of our bone metastasis positive population has GG5 (**Table 5**). Two other studies reported that a major Gleason pattern of 4 was found to be a significant indicator of positive bone scan[10, 26]. Our study reported the incidence of BM to be 46.9%. Comparative incidence of BM was reported in various Asian studies (30%-60%). Significant association was found between BM and serum PSA levels in our study (p=0.002*). Comparative studies conducted at Bangladesh and India also reported a significant association [10, 27].

A major limitation of this study is its small sample size. As our center does not have radiation oncology services, the referral of Ca prostate patients to us is selective. However, our results are in concordance with similar local and international studies with large sample size. It is a retrospective study and most of the patients were already diagnosed and under treatment which may have affected the available parameters under analysis.

CONCLUSION

This study concludes that raised PSA and high Gleason grade are positively associated with the occurrence of bone metastasis in patients with carcinoma of the prostate and can be used as predictors of disease severity and progression. An important point to note is that our patient population had high Gleason scores at the time of presentation. This could be a geographic variability of the disease or because of a delay in diagnosis as there is still a lack of disease awareness and early screening in our region. We also found that a high Gleason grade can be present even with a low PSA level. This is not proven statistically significant because of our limited study sample but we may find similar results on a larger sample size.

ETHICAL APPROVAL

Ethical exemption was obtained from the Institutional Review Committee of, Indus Hospital, Karachi (REF letter No. IHHN_IRB_2022_05_003). All procedures performed in studies involving human participants were

following the ethical standards of the institutional and/or national research committee and with the Helsinki Declaration.

CONSENT FOR PUBLICATION

Written informed consent was taken from the participants.

AVAILABILITY OF DATA

The data set may be acquired from the corresponding author upon a reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Declared none.

AUTHORS' CONTRIBUTION

NY: study concept and designing, critical reviewing. BJ: result interpretation, manuscript drafting, critical review and revision of initial draft, MF: result analysis and interpretation, manuscript drafting, KA: critical review and revision of initial draft, AH: critical review and revision of initial draft, SJ: critical review and revision of initial draft.

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