Original Article

Diagnostic Accuracy Of Serum Prostate Specific Antigen And Gleason Score In Determining The Presence Of Skeletal Metastasis In Prostate Cancer Patients: A Pakistani Perspective

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Abstract

Objective: To determine the cut-off values for serum Prostate Specific Antigen (PSA) and Gleason score (GS) for predicting bone metastasis of Prostate cancer.

Methodology: 330 Prostate cancer patients were enrolled in the study. PSA and GS were determined using commercially available ELECSYS® assays in Modular Analytics E170 (Roche Diagnostics) and histopathology respectively. Tc99m methylene diphosphonate (MDP) was used to perform the Bone scans (BS).

Results: BS was positive in 186 (56.4%) patients and negative in 144 (43.6%) patients. Amongst these 186 positive patients, 5 (2.7%) had PSA < 20 ng/ml, and 181 (97.3%) had PSA > 20 ng/ml. Out of the 144 patients with negative BS, 142 (98.6%) had PSA < 20 ng/ml. Only 2 (1.4%) had PSA > 20 ng/ml. Of the 147 patients with PSA < 20 ng/ml, 142 (96.6%) did not have metastases. Of the 183 patients with PSA > 20 ng/ml, 181 (98.9%) had positive BS. Using a cut-off value of 20 ng/ml for PSA, 142 scans would have been unnecessary.

Out of the 186 patients with positive BS, 3 (1.6%) patients had GS < 7, and 183 (98.4%) had GS > 7. Out of the 144 patients with negative BS, 84 (58.3%) had GS < 7, and 60 had GS > 7. Of the 87 patients with GS < 7, 3 (3.4%) patients had a positive BS while 84 (96.6%) patients had a negative BS. Of the 243 patients with GS > 7, 183 (75.3%) had a positive BS while 60 (24.7%) patients had a negative GS. This indicates that a GS > 7 cannot be reliably used to rule in the need for a BS in Prostate cancer patients.

Conclusion: Our study concludes that serum PSA < 20 ng/ml can be safely used to omit a BS. It suggests that Gleason Score < 7 nullifies the need to conduct a BS. However, serum PSA is a more reliable indicator of bone metastases because of better sensitivity and specificity.

Key Words: Bone metastasis, bone scan, Gleason score, prostate cancer, prostate-specific antigen.

Introduction

The prostate is a male exocrine gland that secretes components of the seminal fluid[1]. It is located at the base of the urinary bladder and encircles the urethra. The epithelial cells of the prostate release prostate-specific antigen (PSA). The value of PSA in serum increases in both Benign Prostatic Hyperplasia (BPH) and Prostatic Carcinoma.

According to the World Cancer Research Fund, prostate cancer is the second most common cancer in men by incidence and the fourth most common cancer overall[2]. The prevalence of prostate cancer in Pakistan is relatively low as compared to the Western world but it is still the third most common malignancy in males, comprising almost 7% of all malignant neoplasms[3]. According to a survey, the incidence of prostate cancer is predicted to rise drastically in Asian countries by the year 2040[4]. This merits the need for further research to be conducted in Pakistan in order to improve the management of prostate cancer patients in the future.

Prostate cancer may be asymptomatic in the early stages and often has an indolent course[5]. As it usually arises from the posterior portion of the gland, it often does not produce any urinary symptoms. It can, however, be palpated by Digital Rectal Exam (DRE). It is usually diagnosed on needle biopsy performed to investigate an increased serum PSA. The majority of men with progressive prostate cancer develop metastases, with the bones being the most prevalent metastatic site[6]. Bone metastases may cause intermittent or constant bone pain, bone marrow suppression, leukopenia, hypercalcemia, and pathologic fractures[7]. In addition to this, there are raised serum levels of serum PSA and Alkaline Phosphatase.

Radionuclide imaging of the bony skeleton is currently the most widely used modality to diagnose bone metastases in patients with prostate carcinoma[7]. This procedure, along with being expensive and time-consuming, is a burden on the hospital resources of a developing country like Pakistan and should be avoided where possible.

Multiple research projects suggest that serum PSA and GS are useful predictors of bone metastasis and eliminate the need to perform a bone scan[8, 9, 10, 11, 12].

As various studies conducted in different countries have yielded different results[8, 9, 10, 11, 12, 13, 14], a single, reliable, universal cut-off value cannot be evaluated. The purpose of this research is to determine the appropriate cut-off values of PSA and GS that are significant enough to predict the bony metastasis of cancer.

Materials and Methods

This diagnostic accuracy study was conducted at the Pakistan Institute of Medical Sciences (PIMS), Islamabad from 2018 to 2019. 330 patients with prostate cancer were included in the study. The inclusion criteria were patients diagnosed with prostate cancer, and on whom a bone scan to detect osseous metastasis was performed. The exclusion criteria consisted of patients who received hormonal or other therapy before PSA measurement and patients for whom serum PSA levels were unavailable. Serum PSA, Gleason Score, and ages were evaluated for the remainder of the patients in the sample. Tc99m methylene diphosphonate (MDP) was used to perform the bone scan (BS) and the scans were evaluated by experienced nuclear medicine radiologists. Serum PSA levels were measured in the laboratory as nanograms of PSA per milliliter (ng/ml) of blood. Total PSA concentration was measured using commercially available ELECSYS® assays in Modular Analytics E170 (Roche Diagnostics). The normal serum PSA value in the lab is considered to be 0.3-3.9 ng/ml. Gleason's grading system was used to grade the tumors after biopsy and they were given a Gleason Score (GS) based on their cellular histology after being analyzed by histopathologists. Quantitative variables were analyzed using mean and standard deviation. Qualitative variables were analyzed using frequency and percentages.

Results

Out of the total 330 patients (mean age 74 years; range 61-84 years) included in the sample, BS was positive for metastasis in 186 (56.4%) patients and negative in 144 (43.6%) patients.

Amongst these 186 positive patients, 5 (2.7%) had PSA < 20 ng/ml, 174 (93.5%) had PSA between 20 and 90 ng/ml, and 9 (4.8%) had PSA > 90 ng/ml.

Out of the 144 patients with negative BS, 142 (98.6%) had PSA < 20ng/ml. Only 2 (1.4%) had PSA in the range of 20 and 90 ng/ml, while none had PSA > 90 ng/ml.

Of the 147 patients with PSA < 20 ng/ml, 142 (96.6%) did not have any skeletal metastases. Of the 183 patients with PSA > 20 ng/ml, 181 (98.9%) had positive bone scans. Using a cut-off value of 20 ng/ml of serum PSA, 142 unnecessary scans would have been avoided.

The sensitivity of using a PSA level of 20 ng/ml as a cut-off value to determine the need for the bone scan is 97.3%. The specificity of the same cut-off value is 98.6%. The positive predictive value of a positive BS with a PSA > 20 ng/ml is 0.989. The negative predictive value of having a negative BS with a PSA < 20 ng/ml is 0.966. This data suggests that according to the present study, a PSA value of 20 ng/ml can be used as an effective cut-off when assessing the need for a bone scan in patients with prostate cancer.

		Bone Scan		
		Positive	Negative	Total
Gleason Score	<7	3	84	87
	7 to 9	160	60	220
	>9	23	0	23
	Total	186	144	330

		Bone Scan		
		Positive	Negative	Total
Serum PSA	<20	5	142	147
	20 to 90	174	2	176
	>90	7	0	7
	Total	186	144	330

		Bone Scan		*Predictive value*		*Total*
		Positive	Negative			
Serum PSA	>20	181	2	0.989	PPV	183
	<20	5	142	0.966	NPV	147
Sensitivity and Specificity		Sensitivity	Specificity			
		97.3%	98.6%			
Total		186	144			

Out of the 186 patients with positive bone scans, 3 (1.6%) patients had GS < 7, 160 (86.0%) patients had GS between 7 and 9, and 23 (12.4%) patients had GS > 9.

Out of the 144 patients with negative BS, 84 (58.3%) had GS < 7, 60 (41.7%) had GS between 7 and 9, and none of the patients had a GS more than 9.

Of the 87 patients with GS < 7, 3 (3.4%) patients had a positive BS while 84 (96.6%) patients had a negative BS. Of the 243 patients with GS > 7, 183 (75.3%) had a positive BS while 60 (24.7%) patients had a negative GS.

The sensitivity of using a GS value of 7 as a cut-off is 98.4%. However, the specificity of the same value as a cut-off is 58.3%. The positive predictive value of GS > 7 is 0.753. The negative predictive value of GS <7 is 0.966. These results indicate that a GS > 7 cannot be reliably used to rule out the need for a BS in patients with Prostate cancer.

		Bone Scan		*Predictive value*		*Total*
		Positive	Negative			
Gleason Score	>7	183	60	0.753	PPV	243
	<7	3	84	0.966	NPV	87
Sensitivity and Specificity		Sensitivity	Specificity			
		98.4%	58.3%			
Total		186	144			

Discussion

Bone scan (BS) is a very well-established parameter in the diagnosis of skeletal metastases in prostate cancer. However, resources and the time of hospital staff can be better utilized if BS is done only for selective patients. Thus, many studies have been carried out to determine reliable cut-off values for serum PSA and GS to include or exclude a BS.

Cut-off values of PSA and Gleason scores have been suggested below and there is minimal risk of metastasis to the lumbar spine. This would rule out the need for bone scintigraphy. Studies in different settings have yielded different results. A review of the present literature suggests that patients with PSA ≤20 ng/ml are very unlikely to have metastasis[8]. Many other studies have reported the same cut-off value[9]. However, Zaman et al (2011) reported that a significant number of patients with PSA below 20 ng/ml had bone metastasis[10]. These findings are supported by other studies.

Articles regarding GS suggest that a bone scan is not necessary for a Gleason score of 7 or less[8]. This finding is supported by another study which stated that a bone scan can be omitted if GS < 8[11]. In contrast to this, a further review of the literature suggests that a GS of less than 8 still merits a bone scan[10]. A similar study found that bone scans should be done even for GS ≤ 6[12].

In this study, it has been shown that 96.6% of patients coming to the PIMS outpatient department with serum PSA less than 20 ng/ml had a negative BS. In contrast, when PSA values greater than 20 ng/ml were considered, 98.9% of patients had a positive BS. This shows that a serum PSA of 20 ng/ml is a reliable cut-off value to exclude BS in patients.

These findings are supported by other studies that have been conducted[8, 9]. Yin et al. (2017)[8] also reported a cut-off value for PSA of 20 ng/ml. Another study also reported the same result and stated that serum PSA < 20 ng/ml has a high PPV to rule out skeletal metastasis[9]. Thus, using this cut-off can save healthcare facilities from unnecessary diagnostic testing. This will eventually lead to a decrease in both the total cost of providing healthcare services and inconvenience to the patients.

In contrast to our findings, a study conducted in Pakistan yielded a different result[10]. It reports that there is a significant cause of positive BS in the local population with PSA < 20 ng/ml, and that BS should not be excluded from this cut-off value. This can be explained by the fact that there was referral bias in the study population as only symptomatic patients were selected. It was not selected via a population screening method. This study also utilized two different nuclear medicine sections which might possibly alter the results due to intrinsic differences in the machinery. Another study suggested that the optimal cut-off value for PSA is 29.16 ng/ml[13]. Ling-Huei et al. suggested that the optimal value for PSA cut-off is 13 ng/ml[14].

The present study yields a sensitivity and specificity of 97.3% and 98.6% respectively for a PSA value of 20 ng/ml. For this value of PSA, a study in a different setting yielded sensitivity and specificity values of 78.8% and 82.7% respectively[13]. An additional study revealed sensitivity and specificity values of 92.98% and 86.36% respectively for a PSA value of 20 ng/ml[14]. Both of these studies suggested a different PSA value which gave optimal values of sensitivity and specificity.

In addition to serum PSA, our study considered the use of GS for predicting the incidence of bone metastasis. Of the 87 patients with GS < 7, only 3 (3.4%) patients had a positive BS while 84 (96.6%) patients had a negative BS. Of the 243 patients with GS > 7, 183 (75.3%) had a positive BS while 60 (24.7%)

patients had a negative GS. This suggests that a GS < 7 can effectively rule out the need for a BS. This is supported by other studies[8,11]. They report that performing a BS for these values is of limited clinical importance. A NPV of 100% has been reported for GS ≤ 7[11].

A further review of literature reveals conflicting results regarding the cut-off value for GS. It has been reported that GS values of 7 still have a significant number of positive BS[10]. One study even reported that a GS score of ≤ 6 did not rule out the need for a BS because there were a small percentage of patients with positive BS[12]. This suggests that further studies need to be conducted on this subject.

In light of the above information, it can be reasoned that serum PSA is a better predictor for bone metastasis than GS.

Conclusion

In conclusion, our study reports that serum PSA < 20 ng/ml can be safely used to omit a bone scan. It also suggests that Gleason Score < 7 nullifies the need to conduct a bone scan. However, serum PSA is a better and more reliable indicator of bone metastases as it has better sensitivity and specificity values as compared to GS. If these results are applied in hospitals all over the country, we can significantly reduce the burden on our resources and prevent unnecessary, low-yield diagnostic tests from being carried out.

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