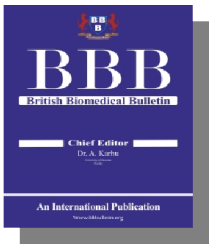
Journal Home Page www.bbbulletin.org

BRITISH BIOMEDICAL BULLETIN




Original

# Diagnostic Correlation between Serum PSA, Gleason Score and Bone Scan Results in Prostatic Cancer Patients with Bone Metastasis

**Kanthilatha Pai[1], Gauri Salgaonkar*[1], Ranjini Kudva[1] and Padmaraj Hegde[2]**

*[1]Dept of Pathology, Kasturba Medical College, Manipal University, Karnataka, India*
*[2]Dept of Urology, Kasturba Medical College, Manipal University, Karnataka, India*

A R T I C L E  I N F O

Received 17 Dec. 2014
Received in revised form 30 Dec. 2014
Accepted 04 Jan. 2015

***Keywords***:
Serum PSA,
Bone Scan,
Prostatic Cancer Patients,
Bone Metastasis,
Scintigraphy.

**Corresponding author: Dr. Gauri Salgaonkar,** Dept of Pathology, Kasturba Medical College, Manipal University, Karnataka, India.
**E-mail address:** dcgauri2477@gmail.com

A B S T R A C T

**Aim:** To analyse the association between serum PSA, Gleason score and bone scan results in patients with a diagnosis of prostatic carcinoma. **Materials and Methods:** A three years retrospective study of patients diagnosed with prostatic adenocarcinoma were reviewed to collect information about age, clinical symptoms, digital rectal examination findings, serum prostate specific antigen (PSA), Gleason score on biopsy and bone isotope scan results. We analysed the association between these clinical, pathological and radiological parameters in patients with a diagnosis of prostatic adenocarcinoma. **Results:** Of the 123 patients diagnosed with prostatic cancer during the 3 year study period, 72 patients with complete data were included in the study. Of the 72 patients, 15 (20.83%) presented positive scintigraphic examinations for the presence of bone metastasis. All patients who had bone metastasis on scintigraphy had PSA value of > 20 ng/mL, and in only 1 patient (0.46%) with bone metastasis PSA concentration was < 50ng/mL. There was no statistical significant correlation between PSA level and tumor grading by Gleason score and also between Gleason score and bone metastasis. Statistical analysis was performed using Chi-square (Fisher exact) test and a value of <0.05 was considered statistically significant. **Conclusion:** Evaluation for bone metastasis in patients with prostatic carcinoma is indicated when PSA levels are above 20ng/ml, because all patients with metastasis had a value when a PSA cut-off of >20ng/ml was considered. Though poorly differentiated prostatic carcinomas (Gleason score > 7) are known to be associated with poor prognosis with high likelihood of bone metastasis and higher serum PSA values, we did not see such association in our study.

## Introduction

Prostate cancer occupies a prominent place among malignant neoplasia of the genitourinary tract, and currently represents the most common neoplasia, being the second most frequent cause of death by cancer in men.[1] It is a silent disease until it is quite advanced in its evolution.

Consequently, digital rectal examination (DRE) and or prostate specific antigen (PSA) can help in detecting the disease. Most cases of prostate cancer are indolent and rarely fatal, at least for 5-10 years after diagnosis. It is established that higher the values of PSA are, the bigger is the volume of tumor existing in the patient, suggesting also a relation that is directly proportional to the tumor stage.[2] Besides PSA, prostatic acid phosphatase, alkaline phosphatase, tumor ploidy, Gleason score, ultrasonography, computer tomography, magnetic resonance imaging, and bone scintigraphy are useful in the work-up of patients with prostate neoplasia.[3]

The grading of prostatic carcinoma by Gleason score is a good predictor of the pace of disease. Patients with well differentiated tumors (Gleason score 2 to 6) generally have a favorable prognosis while high grade tumors (Gleason score 7 to 10) are associated with higher mortality rate.[4] Early prostate cancer remains localized to the prostate gland whereas advanced cancer can spread into distant organs like, bone, lungs or liver. Metastatic prostate cancer commonly spreads into bones and often causes back pain, which can sometimes be the first symptom of this cancer. Autopsies have revealed that 80% of advanced prostate cancer is accompanied by the development of skeletal metastases.[5] The American Urology Association (AUA) and the European Association of Urology guidelines for prostatic carcinoma suggest that bone scan may not be indicated in patients with a PSA level of <20 ng/ml or less, who have well differentiated prostatic cancer.[6,7] However, there are reports which revealed higher incidence of positive bone scan with low PSA in mass population screening in Asians as compared with Western data.[8]

The objective of the present study is to evaluatein patients with diagnosis of prostate cancer, the relationship between serum concentration of PSA, histological grading by Gleason score and the presence of bone metastasis by scintigraphy. This evaluation could give insight into the clinical profiles of patients for whom bone scanning could be eliminated due to a low probability of bone metastasis.

## Materials and methods

From Jan 2008-Dec 2010, a total of 123 patients were diagnosed with prostatic carcinoma in Kasturba Hospital Manipal, of which 72 patients were included in the study as the others had incomplete data. The diagnosis of prostate carcinoma was established through prostate biopsy guided by trans-rectal ultrasonography or in the material of prostate transurethral resection performed for presumable benign prostatic hyperplasia. The serum concentration of PSA was determined by the Tandem-R PSA, monoclonal immuno-radiometric assay with the normal range set between 0 and 4.0 ng/ml. The Gleason score was given by surgical pathologists in the Department of Pathology of the university hospital according to the Gleason grading system. Presence of adenocarcinoma was diagnosed according to the criteria of Mostofi& Price.[9] The diagnosis was based on invasion or architectural disturbance. Histological grading was performed according to the Gleason system.[10] Prostatic carcinomas with final score < 7 were considered low-grade; and, with final score ≥ 7 were considered

high-grade.[11] Bone scans were done for evaluation of bone metastases in the Diagnostic Radiology department of the hospital according to the standard procedures. Patients were intravenously given555 MBq Technetium-99m (99mTc) methylene diphosphonate.

For statistical analysis, chi square (Fisher exact) test was used, considering $p < 0.05$ as statistically significant.

## Results

Of the total of 123 patients who were diagnosed with prostatic cancer during the 3 year study, 72 had a complete retrospective data collection and were entered into the study. The median age of the patients was 69.5 years (Age range from 49-78 years). Demographic and clinical data are shown in Table-1. 4.16% of the patients were asymptomatic and were diagnosed during work-up for elevated PSA levels during screening. 39 patients (54.16 %) had hard irregular prostate on DRE, while others had normal findings. 53 patients (73.61 %) out of the 72 patient shad an elevated PSA level above 4ng/ml. The elevated PSA in these patients ranged from 15.1 to >1000ng/ml.

A total of 15 patients (20.83 %) had positive bone scan suggestive of metastasis. 14 patients had clinical symptoms suggestive of bone metastasis, of which 13patients had bone pain and tenderness, and one patient had pathologic fracture. All patients with bone symptoms also had obstructive urinary symptoms. 1 patient with no clinical symptoms suggesting metastases, was detected on radiological examination. The relationship between PSA level and bone scan results are shown in Table 2. Among 15 patients who had a positive bone scan suggestive of metastases, the PSA level was above a cut-off of 20ng/ml and only 1 patient had lower PSA level when a cut-off of 50ng/ml was taken into consideration. [Table 3].

16 patients (22.23 %) were categorized as low Gleason score between 2-6 while 56 patients (77.77 %) had a high Gleason score between 7-10 reported on histopathological examination. The relationship between PSA levels and Gleason score is shown in Table 4. There was no significant correlation between PSA levels and Gleason score (p value=0.221).

Of the 56 patients with high Gleason score, 44 (78.57 %) were negative for bone metastasis and 12 patients (21.43 %) revealed metastasis on bone scan, while in 16 patients with low Gleason score, 13 patients (81.25 %), were negative and 3 patients were positive (18.75 %) respectively for bone metastasis, suggesting no significant correlation between high Gleason score and bone metastasis. Table 5 shows the relationship between Gleason score and bone metastasis.

## Discussion

Serum concentrations of PSA have been widely used for early detection of prostate cancer, and PSA has been described as the best circulating tumour marker in oncology.[12,13] It is widely used in clinical practice for the diagnosis, staging, and monitoring of prostate cancer. The traditional cut-off for an abnormal PSA level in the major screening studies has been 4.0 ng/mL.[14] However, when screening a population with a relatively low prevalence of prostate cancer as in Asian population, extremely high validity must be achieved. According to our study, 53 out of 72 patients with diagnosis of prostatic carcinoma had elevated PSA value, with a sensitivity of 73.61 %, and this was slightly higher than the sensitivity of digital rectal examination which was 54.16 % in predicting diagnosis of prostatic carcinoma. The study by Part in *et al* on a large series of prostatic carcinoma reported sensitivity of 52 % and a specificity of 81 % for the prediction by DRE alone.[2]

The American Cancer Society systematically reviewed the literature assessing PSA performance. In a pooled analysis, the estimated sensitivity of a PSA cutoff of 4.0 ng/mL was 21 % for detecting prostate cancer and specificity was 91 percent.[15]

Although serum PSA is not specific for prostate cancer, the concentration of serum PSA does correlate with pathologic stage and tumor volume. Chybowski *et al* documented that the PSA level was correlated with the risk of bone metastasis in 521 patients randomly selected. They suggested that the PSA concentration was the best predictor for bone metastases among other clinical and pathological parameters.[16] In their study, only one patient had bone metastases among 307 with PSA concentration of 20 ng/ml or less, indicating that the negative predictive value was 99.7%. In our study among 15 patients who had bone metastases, all patients had PSA level more than 20ng/ml, and 1 patient had a PSA value < 50ng/ml. Several studies have raised the question of whether a staging bone scan could be omitted for patients with PSA concentrations of 20 ng/ml or less. Partin *et al* noted that 80% of men with PSA levels higher than 20.0 ng/mL had extra prostatic disease. Oommen *et al* contra-indicate bone scintigraphy in asymptomatic patients with PSA < 10 ng/mL because cost benefit is not worth.[17] The prognostic value of any clinical criterion when used alone to predict tumor extent is limited for an individual patient. However, staging accuracy is substantially enhanced by using the combination of local disease extent on DRE (T stage), serum PSA level, and Gleason score from prostate biopsy specimen. Of the many histologic grading systems introduced to help predict pathologic stage and prognosis for prostate cancer, the most commonly used is the Gleason system, which correlates directly with pathologic extent of disease. To this end, a nomogram (namely, the Partin Tables) based on these preoperative parameters has been constructed. The Partin Tables, which are the result of a single-institutional study of men undergoing radical prostatectomy relating pathologic stage to clinical stage, demonstrate that PSA and biopsy Gleason score exhibit independent predictive significance in multivariate analysis Therefore, using the Partin Tables, it is possible to accurately predict, those that are likely to be at a high risk for disease recurrence (i.e., Gleason score 8-10 and serum PSA >20 ng/ml).[18] Higher level of PSA (>50 ng/ml) is associated with poorly differentiated histopathology (GS >7) and this is a well-documented fact.[19] In univariate analyses, Gleason scores >7 were also associated with shorter bone metastasis-freesurvival.[20]

Although higher grade cancer produces less PSA per cell as compared to lower grade tumors, overall, poorly differentiated tumors are associated with higher PSA levels as these tumors tend to be larger and of more advanced stage.[21] However, in our study there was no significant correlation between tumor grade by Gleason score and pre-operative levels of PSA.

Bone scintigraphy using the radioisotope Technetium (99 mTc) methylene diphosphate is a sensitive method for evaluating the skeleton in bone metastasis diagnosis, being superior to conventional radiological study and to the serum levels of prostatic alkaline phosphatase. This examination presents high sensitivity with low rate of false negatives. A large proportion of individuals with metastasis detected in scintigraphy can be asymptomatic.[16] We found that 1 of the 15 patients were clinically asymptomatic and had undergone bone scan because of very high PSA levels (>1000ng/ml). Table 6

compares our results of PSA, Gleason score and bone metastasis with other studies.

**Conclusion**

We conclude that:

(1) There was no evidence of bone metastasis in newly diagnosed patients with prostatic carcinoma when a serum PSA level was < 20 ng/ml.

(2) There was no statistically significant relationship between preoperative prostate specific antigen and biopsy Gleason score.

(3) High Gleason score was not a predictor for bone metastasis .However, important limitation of the present study is its relatively small study population and few patients with bone metastases.

**References**


1. Wymenga LF, Boomsma JH, Groenier K, Piers DA, Mensink HJ. Routine bone scans in patients with prostate cancer related to serum prostate-specific antigen an alkaline phosphatase. *BJU Int*. 2001; 88:226-30.
2. Partin AW, Yoo J, Carter HB, Pearson JD, Chan DW, Epstein Jr, *et al*.: The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. *J Urol*. 1993; 150:110-4.
3. Oesterling JE. Using PSA to eliminate the staging radionuclide bone scan. *Urol Clin North Am*. 1993; 20: 705-11.
4. Blute ML, Bergstralh EJ, Iocca A, Scherer B, Zincke H. Use of Gleason score, prostate specific antigen, seminal vesicle and margin status to predict biochemical failure after radical prostatectomy. *J Urol*. 2001; 165, 119-25
5. Galasko CS. Skeletal metastases. *Clin Orthop Relat Res*. 1968; 210:18-30.
6. Thompson I, Thrasher JB, Aus G, Burnett AL, Canby-Hagino ED, Cookson MS *et al* Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol*. 2007; 177(6):2106-31.
7. Heidenreich A, Aus G, Bolla M, Joniau S, Matveev VB, Schmid HP *et al*. EAU guidelines on prostate cancer. *Eur Urol*. 2008; 53(1):68-80.
8. Kosuda S, Yoshimura I, Aizawa T, Koizumi K, Akakura K, Kuyama J*et al*. Can initial prostate specific antigen determinations eliminate the need for bone scans in patients with newly diagnosed prostate carcinoma? *Cancer*. 200; 94, 964-72.
9. Mostofi, FK, Price EB. Tumors of the Male Genital System, Atlas of Tumor Pathology, Second Series, Fascicle 8. Washington DC, *Armed Forces Institute of Pathology*. 1973; pp. 202-1
10. Gleason DF, Mellinger GT. Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. *J Urol*. 1974; 111:58-64.
11. Gleason DF: Histologic grading of prostate cancer: a perspective. *Hum Pathol*. 1992; 23: 273-9.
12. Ross KS, Carter HB, Pearson JD, Guess HA. Comparative efficiency of prostate-specific antigen screening strategies for prostate cancer detection. *JAMA*. 2000; 284:1399-405.
13. Yao SL, Lu-Yao G. Interval after prostate specific antigen testing and subsequent risk of incurable prostate cancer. *J Urol.* 2001; 166:861-5.
14. Brawer MK, Chetner MP, Beatie J, *et al*. Screening for prostatic carcinoma with prostate specific antigen. *J Urol*. 1992; 147:841.
15. Wolf AM, Wender RC, Etzioni RB, Thompson IM, D'Amico AV, Volk RJ. American Cancer Society guideline for the early detection of prostate cancer: update 2010. *CA Cancer J Clin*. 2010; 60:70-98.
16. Chybowski FM, Larson Keller JJ, Bergstralh EJ, Oestering JE. Predicting radionuclide bone scan finding in patients with newly diagnosed, untreated prostate cancer: prostate specific antigen is superior to all other clinical parameters. *J Urol*. 1991; 145:313–18.
17. Oommen R, Geethanjali FS, Gopalakrishnan G, Chacko N, Jhon S, Kanagasabathy AS, *et al*.: Correlation of serum prostate specific antigen levels and bone scintigraphy in

carcinoma prostate. *Br J Radiol*. 1994; 67: 469-71.
18. Partin AW, Mangold LA, Lamm DM, Walsh PC, Epstein JI, Pearson JD: Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. *Urology*. 2001; 58:843-8.
19. Pierorazio P, Desai M, McCann T, Benson M, McKiernan J. The relationship between preoperative prostate specific antigen and biopsy Gleason sum in men undergoing radical retopubic prostatectomy: a novel assessment of traditional predictors of outcome. *BJU Int*. 2009; 103, 38-42.
20. Smith MR, Kabbinavar F, Saad F, Hussain A, Gittelman MC, Bilhartz DL. Natural history of rising serum prostate-specific antigen in men with castrate non metastatic prostate cancer. *J Clin Oncol*. 2005; 23: 2918–25.
21. Partin AW, Carter HB, Chan DW, Epstein JI, Oesterling JE, Rock RC *et al*.: Prostate specific antigen in the staging of localized prostate cancer: influence of tumor differentiation, tumor volume and benign hyperplasia. *J Urol*. 1990; 143:747-52.

**Table 1.** Clinical variables in patients with prostatic carcinoma

| Total number of patients = 72 | No of patients | % of patients |
|---|---|---|
| Symptoms | | |
| Asymptomatic | 3 | 4.16 |
| Lower urinary tract symptoms | 55 | 19.44 |
| Lower urinary tract symptoms + Suggestive of Bone Metastases | 14 | 76.38 |
| Per Rectal Examination | | |
| Abnormal rectal examination | 39 | 54.16 |
| Normal rectal examination | 33 | 45.84 |
| PSA Levels | | |
| > 4ng/mL | 53 | 73.61 |
| < 4ng/ml | 19 | 26.39 |

**Table 2.** Relationship between serum PSA levels and bone scan results

| Serum PSA | Total | Negative bone scan | Positive bone scan |
|---|---|---|---|
| <10ng/mL | 19 | 19 | 0 |
| 10.1-20ng/mL | 2 | 2 | 0 |
| 20.1-50ng/mL | 18 | 17 | 1 |
| >50ng/mL | 33 | 19 | 14 |

**Table 3.** Relationship between serum PSA levels and tumor grade by Gleason score

| Serum PSA | Total | Low Gleason score (2-6) | High Gleason score (7-10) |
|---|---|---|---|
| <10ng/mL | 19 | 5 | 14 |
| 10.1-20ng/mL | 2 | 1 | 1 |
| 20.1-50ng/mL | 18 | 3 | 15 |
| >50ng/mL | 33 | 7 | 26 |

**Table 4.** Relationship between prostate specific antigen (PSA) concentration with a cut-off point of 50 ng/mL and presence of bone metastasis in scintigraphy for patients with prostate cancer

| Serum PSA | Total | Negative bone scan | Positive bone scan | P value |
|---|---|---|---|---|
| <50ng/mL | 39 | 38 | 1 | <0.001 |
| >50ng/mL | 33 | 19 | 14 | |

**Table 5.** Relationship between Gleason score and presence of bone metastasis in scintigraphy for patients with prostate cancer

| Gleason score | Total | Negative bone scan | Positive bone scan | P value |
|---|---|---|---|---|
| Low Gleason score | 16 | 13 | 3 | 1.000 |
| High Gleason score | 56 | 44 | 12 | |

**Table 6.** Comparison of incidence rates of bone metastasis by Tc99m, and other findings in prostatic adenocarcinoma with other studies

| Authors, Year | Incidence | Findings |
|---|---|---|
| Osterling *et al*, 1993 | 0.8% | A bone scan is not necessary in patients with PSA <10 ng/ml and no skeletal symptoms |
| H osuda *et al*, 2002 | 22.2% | Bone scans can be eliminated in newly diagnosed prostatic cancer patients with PSA <10ng/ml, Gleason grade <2 or Gleason score <6 |
| Huang *et al*, 2006 | 34.2% | Bone metastases cannot be ruled out in patients with PSA <10ng/ml |
| Lai *et al*, 2011 | 29.3% | No statistically significant relationship between Gleason score, PSA and bone scan results |
| Jaukovic *et al*, 2011 | 19.35% | Bone scans are not needed in Gleason score <6 and PSA <10ng/ml |
| Janane *et al*, 2012 | 29.3% | No significant correlation between PSA and bone scan |
| Our study | 20.83% | No bone scan needed when PSA cut-off <20ng/ml. No statistically significant correlation between Gleason score and bone metastasis, and Gleason score and serum PSA values. |