Original Article

Correlation between Serum Prostate Specific Antigen levels with Incidence of Bone Metastases in Newly Diagnosed Prostate Cancer Patients in Indian Population

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Abstract
Introduction: *Prostate cancer is second most frequently diagnosed cancer of men and bone is the commonest site of metastasis in them. There is lack of consensus for the selection criteria for bone scan in low risk patients. Western guidelines do not recommend use of bone scan in asymptomatic patients and in low PSA values. We try to correlate the PSA value with bone metastases through bone scan in Indian population.*
Material and Methods: *89 males of histologically proven carcinoma prostate over the period of 15 months, from March 2014 to May 2015 were included in the study. The patients were stratified into 3 groups according to their PSA level: the first group of patients had PSA level ranging from 0 - 10 ng/ml (n = 32), the second group had PSA level ranging from 10.1 - 20 ng/ml (n= 9), the third group had PSA levels > 20 ng/ml (n = 48).*
Results: *The incidence of osseous metastases proven by bone scintigraphy was found to be 25% (8 out of 32) for PSA level 0 - 10 ng/ml, to 22.2 % (2 out of 9) for PSA level 10.1-20 and 68.7% (33 out of 48) for PSA level > 20 ng/ml (P < 0.001). The incidence of bone metastases < 20ng/ml is 21.73 % (10/46) (table-3). All*

patients (n=17) with PSA value>100 ng/ml were having bone metastases.
Conclusion: *The correlation between PSA value and both presence and metastases confirms the usefulness of bone scan scintigraphy in prostate cancer staging. Bone scan should be part of initial evaluation in all patients irrespective of serum PSA value as even patients with PSA values< 20 ng/ml are presenting with bone metastases.There should not be any minimal threshold limit of PSA for referring patients to bone scan.*

Introduction

Prostate cancer is second most frequently diagnosed cancer of men after lung cancer. [1] Almost 75%, of registered prostate cancer cases occur in developed countries, the highest in Northern America and Europe region and the lowest rate in South-East Asia Region (8.3 per 100,000) [2]. However, there is rapid increase in prostate cancer incidence and mortality in Asian countries due to more westernized lifestyle. The proportion of advanced stage prostate cancer patients is also high [3].

Bone Metastasis is the commonest metastasis site of prostate cancer (90%) and it precedes lung and liver [4]. Bone metastasis occurs in up to 14% cases at presentation and around 80-85% in advanced stage [5]. Planar Bone Scan (BS) is very sensitive method (72-77%) to detect bone metastases and currently the investigation of choice [6]. Many studies have confirmed that incidence of bone metastases correlates positively with staging of the tumour, PSA (Prostate-specific antigen) and Gleason Score (GS). However, there is still a lack of consensus about the selection criteria for bone scan in low risk patients and the cut-off value for PSA and GS. Though, European Association of Urology (EAU), American Urological Association (AUA) and American Joint Committee on Cancer (AJCC) had recommended similar indication for BS, which were: GS>7, PSA level>20 ng/ml and presence of bony symptoms, based on studies in western countries [7].

Overuse of radiographic imaging in patients with prostate cancer (CaP) who are unlikely to have metastatic disease is costly and can lead to patient harm from unnecessary procedures. However, underuse of imaging can lead to undiagnosed metastatic disease, resulting in aggressive treatments in patients with incurable disease. The National Comprehensive Cancer Network (NCCN) recommends bone scans and computed tomography (CT) or magnetic resonance imaging (MRI) during initial work-up of selected patients with intermediate- or high-risk (CaP). The study was done to assess the proportion of patients who received bone scan work-up discordant with NCCN and various other western guidelines.

Material and Methods

This study was a prospective observational study of patients diagnosed with prostate cancer at Army Hospital (Research & Referral), Delhi Cantt, which is a tertiary care hospital during the period of Mar 2014 to May 2015. A detailed history was taken of each patient and explained about the bone scan procedure to be carried out, duly approved by Institutional Ethical Committee. Recorded data was PSA value, histopathological examination of prostate's tissue, and bone scan result. Bone scintigraphy was performed with technetium-99m–labeled diphosphonate (MDP) Imaging was typically performed 2–5 hours after intravenous administration of 925-1110 MBq (25–30 mCi) of Tc-99m–labeled diphosphonates (as per Society of Nuclear Medicine Procedure Guideline, version 3.0, approved June 20, 2003) for bone scintigraphy. Dual head Gamma Camera SPECT Symbia T6 (Siemens, Germany) SPECT/CT equipped with a low-energy, high-resolution collimator. Additional anterior and posterior whole-body and SPECT/CT images are often obtained as needed. The time interval between PSA determination and bone scan was within 30 days. PSA value was measured using the sandwich electrochemiluminescent immune-assay technique in BECKMAN COULTER (Reference value- < 4 ng/dl).

All newly diagnosed patients of carcinoma prostate were included in the study. A total of 89

males of histologically proven carcinoma prostate over the period of 15 months, from March 2014 to May 2015 were included in the study.

Following patients were excluded:

- Patients unable to lie supine for bone scan imaging
- Failure to obtain informed consent
- Patients with dual malignancy
- Patients having previous therapy for prostatic diseases, including androgen ablation therapy, radiation therapy on prostate or prostate surgery were excluded from the study.

The outcome of the results (PSA value and bone scan result) was tabulated and analysed to assess the correlation between serum PSA value and bone metastases in bone scan. PSA value in the study was divided into 3 categories: <10 ng/ml, 10 - 20 ng/ml, >20 ng/ml. Statistical analyses were performed using the Chi square test, by statistical software (SPSS, Statistical Package for the Social Sciences, version 11.5.1) with differences at P < 0.05 considered significant.

Results

89 patients aged 50 to 95 years, with a mean age of 71.4 + 8.3 years and mean PSA of 62.6 + 120.9 ng/ml (median = 25.2 ng/ml, range from 0.008 to 995 ng/ml) were included in the study. All 89 cases were histologically proven adenocarcinoma. Bone metastases were identified in 43 patients out of 89 patients as shown in table-1. Table-2 shows mean and median age as well as mean and median PSA values for both groups having bone metastases and without metastases.

The patients were stratified into 3 groups according to their PSA level: the first group of patients had PSA level ranging from 0 - 10 ng/ml (n = 32), the second group had PSA level ranging from 10.1 - 20 ng/ml (n= 9), the third group had PSA levels > 20 ng/ml (n = 48). Stratification of patients has been described in table -3. The incidence of osseous metastases proven by bone scintigrams was found to be 25% (8 out of 32) for

PSA level 0 - 10 ng/ml, to 22.2 % (2 out of 9) for PSA level 10.1-20 and 68.7% (33 out of 48) for PSA level > 20 ng/ml (P < 0.001). The incidence of bone metastases < 20ng/ml is 21.73 % (10/46) (table-3). All patients (n=17) with PSA value>100 ng/ml were having bone metastases.

Receiver operating characteristic (ROC) curve for accuracy of PSA for diagnosing bone metastasis on bone scan shows an area under curve 0.787 with significant p value (<0.05). The sensitivity and specificity of PSA at a cut-off 5.4 ng/ml was 88.4% and 43.5%, at 10 ng/ml was 83.7% and 52.2 %, at 15 ng/ml was 81.4 % and 63%, at19.3 ng/ml was 79.1% and 67.4% respectively (figure-1). They found that PSA was good for predicting the results of a radionuclide bone scan when receiver operating characteristic (ROC) curves were used.

Logistic regression analysis with presence and absence of metastasis as dependent variable and PSA as independent continuous variable was performed. The model was found to be significant at p value <0.005 (Chi square = 27.8). The model depicts that for each unit increase in PSA level there is approximately 2.7 times more chances of metastasis.

At very high PSA values (>100ng/ml), all 17 patients were having bone metastases

Table: 1

N	Bone scan positive for mets	Bone scan negative for mets
89	43	46

Table-2

Scintigraphy result	PSA (mean)ng/ml ± SD	Age (mean) yrs ± SD
Bone metastases present (BM+)	106.9 ± 160.8 (median =56.3, range 0.01 - 995)	69.2 ± 7.9
Bone metastases absent (BM-)	21.05 ± 28.34 (median =8.7, range 0.008 – 100)	73.4 ± 8.3

Table-3

PSA level (ng/ml)	Bone scan positive for BM	Bone scan negative for BM	TOTAL	p value using Chi square test
0-10	8 (25%)	24 (75%)	32 (100%)	<0.001
11-20	2 (22.2%)	7 (77.8%)	9 (100%)	
>20	33 (68.7%)	15 (31.3%)	48 (100%)	
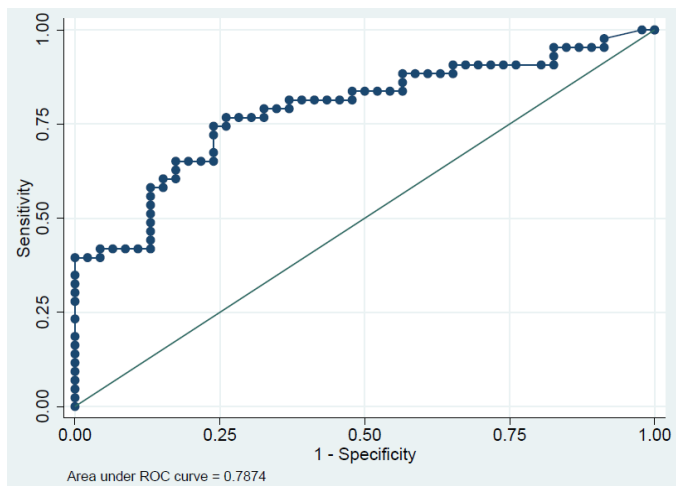
Figure-1: ROC curve analysis for PSA values.

Discussion

The diagnosis of bony metastasis secondary to prostate cancer significantly alters patient treatment. Currently radionuclide bone scans are the gold standard for detecting osseous metastasis. An ongoing debate surrounds the optimal PSA for recommending a bone scan for non metastatic prostate carcinomas. Detecting patients with bone metastases is essential in predicting prognosis, and identifying or preventing complications incurred by disease progression. However, if every patient newly diagnosed with prostate carcinoma is offered bone scintigraphy as the baseline staging investigation, the increase in incidence would imply a growing burden on the health care system. It is therefore important to seek a balance between cost and benefit, and to develop an algorithm for the indication of a baseline bane scintigraphy.

The incidence of bone metastasis in newly diagnosed prostate carcinoma in this study is significantly high (48.3%) comparable to other studies (0.8-50%) [6]. Even it was still higher compared to the other adjoining Asian nations, such as Pakistan (33%) , Japan (11.8%), China (33%), Indonesia(36.8%) (Table-4). This high number of BM could be due to several causes: most of patients come with advance stages.

Table-4 Various Asian studies

Country	(Study)	Number of patients	PSA (ng/ml)	BM+ No. (%)
Pakistan	(Zaman et al., 2011) (8)	204	<20	15/119 (12.6%)
Japan	(Ito et al., 2000) (9)	303	<10	13/36 (36.1%)
China	(Yang et al., 2009) (10)	77	<20	5/26 (19.2%)
Indonesia	(I Putu Gde Sanjaya et al 2013) (11)	358	<20 <10	25/90 (27.7%) 10/42 (23.8 %)

It grossly differs with reported American (14%) [12] and Italian (2.5%) studies [13]. These published facts point towards an altered behaviour of prostate carcinoma in Asian population and this aspect needs to be further investigation.

PSA correlated positively with the incidence of a positive bone scan, with a coefficient of p < 0.0001 using Chi square test. However, age was not a predictor for bone metastasis (p value 0.7559) as reported in literature as well [14].

Our gathered data from performed bone scans support previously published studies demonstr-ating the close relationship between serum PSA level and bone scan positivity [15-17]. In our study, working with a broad range of PSA values at the time of diagnosis, we confirmed the existence of a correlation between PSA values with positive bone scan results and the number of metastases present.

All 17 patients with serum PSA >100ng/ml had multiple skeletal metastases. Another important fact which draws our attention is significantly increased incidence of bone metastasis in patients with PSA < 20 ng/ml. This is in contradiction to many published studies showing high negative predictive value of low PSA (<20 ng/ml) [18]. Furthermore, as per recommendations of Euro-pean Association of Urologist (EAU), American Urological Association (AUA) and American Joint Commission on Cancer (AJCC), staging bone scan may not be indicated in patients with PSA < 20 ng/ml and GS < 8, in the absence of

bony symptoms. However in our study sample, if bone scan were omitted for patients having PSA < 20 ng/ml , 23.25 % (10/43) would have missed the diagnosis of metastatic bone disease. Ito et al (2000) [14] have reported an incidence of 36% (13/36 patients) of bony metastasis with PSA ≤ 10 ng/ml in Japanese mass screening program. Another study from China by Yang et al (2009) revealed bony metastases in 19% (5/26 patients) of patients with PSA < 20 ng/ml. These facts from studies upon Asian population again point towards an aggressive behavior of prostate carcinoma in Asians as compared to Caucasians.

Indian studies, however, in contrast to other Asian studies, had shown low incidences of bone metastases <20ng/ml as follows (as per table no-4). Some other Asian studies like Liu et al [65] also mentioned that for patients with PSA≤10 ng/ml or simultaneously PSA≤50 ng/ml and Gleason score≤7 and clinical stage≤T2, bone scan is not necessary. This is in accordance with EAU guidelines. In my study incidence of bone metastases is 23.25 % below 20 ng/ml of PSA, henceforth a recommendation of not to follow western guidelines for initial evaluation in atleast Indian scenario and bone scan should also be done in all asymptomatic patients irrespective of PSA value.

Table-5: Various Indian studies

(Study-year)	Total number of patients	PSA value (ng/ml)	Bone metastases (BM + %)
(Koramadai Karuppusamy Kamaleshwaran et al 2012)-(19)	322	<20	2/113 (1.8%)
(Kanthilatha Pai et al jan 2015)(20)	72	<20	0
(Oomen et al) (1994) (21)	48	Normal PSA	3/26 (11.5%)

Prostate cancer remains disease of old age. In the study, mean age of presentation (71 ±8.3 years) matches data provided by UK national statistics (22-25) which shows incidences in UK between 2009 and 2011, an average of 36% of cases were diagnosed in men aged 75 years and over, and only 1% were diagnosed in the under-50s.

The major limitation in the study is that only PSA values, not Gleason score and grade of tumour, were included. Gleason scores have been suggested by many authors as useful predictors of positive bone scans . It has been stated that the risk of a positive bone scan increases with advanced stages and higher grades of prostate cancer. As a result of the introduction and wide usage of PSA as a readily-available tumor marker for prostate cancer, the majority of patients now have low serum PSA levels. Most patients referred for a bone scan by urologists or oncologists did not have any information in their medical history regarding local advance of the disease. These data could provide us with additional information regarding the influence of local advance, in addition to Gleason score results, on the presence of metastatic bone disease.

Bone scans have also been an important tool in monitoring disease progression after definitive therapy. However, the same controversy exists about the optimal post-treatment PSA at which to recommend this test. To date only small series have been published which correlate the prevalence of bone metastases with PSA after local therapy.

Conclusion

Working with a broad range of PSA values at the time of diagnosis, the study concluded the existence of a correlation between both PSA values with positive bone scan results. The correlation between PSA value and presence of skeletal metastases confirms the usefulness of bone scan scintigraphy in prostate cancer staging. Incidences of bone metastases in newly diagnosed Indian population is more than compared to western population. Incidence rate is matching with result of many Asian studies done in the past.

PSA is independent predictors for bony metastasis.

Carcinoma prostate continues to be disease of old age group (>70 yrs). In view of possible aggressive behaviour of prostate carcinoma in local population, one must be careful in adopting Western guidelines for using bone scan in newly diagnosed Asian males with carcinoma prostate having PSA ≤ 20 ng/ml. The correlation between PSA value and both presence and metastases confirms the usefulness of bone scan scintigraphy in prostate cancer staging. Bone scan should be part of initial evaluation in all patients irrespective of serum PSA value as even patients with PSA values< 20 ng/ml are presenting with bone metastases. There should not be any minimal threshold limit of PSA for referring patients to bone scan.

Acknowledgments

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25. Data were provided by the Northern Ireland Cancer Registry on request, June 2013. Similar data can be found here:http://www.qub.ac.uk/research-centres/nicr/CancerData/OnlineStatistics/(link is external).