A Prospective Study on Incidence of Bone Metastases at Various Prostate Specific Antigen Levels in Carcinoma Prostate in South Indian Population

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ABSTRACT

Introduction: Globally prostate cancer is the second most frequently diagnosed cancer in men and the fifth most common cancer overall. Several Indian registries have revealed an increasing trend in the incidence of prostate cancer. Prostate cancer has a tendency to metastasize to bone. On presentation, up to 14% of patients have bone metastasis. Radionuclide bone scanning being the most sensitive method plays an important role in detecting bone metastasis in prostate cancer. The aim of this study is to study the incidence of bone metastases of the south Indian population at various PSA levels in carcinoma prostate and to determine whether the probability of positive bone scan result of newly diagnosed Carcinoma Prostate patients can be predicted by serum PSA level, with an attempt to define a particular PSA level under which the group of patients would have low risk of obtaining a positive bone scan, so that the radiologic procedure can be safely omitted.
Material ans methods: This prospective study was conducted in Department of Urology, at Sri Venkateswara Institute of Medical Sciences, Tirupati from May 2016 to august 2017. All patients who were diagnosed to have carcinoma prostate on TRUS guided biopsy or in TURP chips were subjected to bone scans.
Results: Because of high incidence of bone metastases in south Indian population, it is better to undergo bone scan in newly diagnosed carcinoma prostate even with sr. PSA <20ng/ml.
Conclusion: Because of high incidence of bone metastases in south Indian population, it is better to undergo bone scan in a newly diagnosed carcinoma prostate even with sr. PSA <20ng/ml.

Keywords: Bone scan, Carcinoma Prostate, Prostate Specific Antigen

INTRODUCTION

Globally, prostate cancer is the second most frequently diagnosed cancer in men (13.6% of the total) and the fifth most common cancer overall[1]. Several Indian registries have revealed an increasing trend in the incidence of prostate cancer and the mean annual percentage change has ranged from 0.14-8.6[2]. Serum prostate specific antigen (PSA) based screening is helpful in early diagnosis and staging of prostate cancer[3]. Prostate Specific Antigen (PSA) is the primary parameter used to screen for prostate cancer. PSA is organ specific but not disease specific, its use for prostate cancer screening lacks adequate sensitivity[4]. Serum PSA has been reported to be the single most useful predictor of metastasis detected on radionuclide scanning in patients with prostate cancer[5,6,7].

Prostate cancer has a tendency to metastasize to bone. On presentation, up to 14% of patients have bone metastasis[8]. Radionuclide bone scanning being the most sensitive method plays an important role in detecting bone metastasis in prostate cancer[9,10]. It is more sensitive than skeletal radiography and serum alkaline phosphatase levels, it is good in its accessibility, non-invasiveness, low radiation dose, and above all, its ability to evaluate the entire skeletal system[11]. Because of the high incidence of bone metastases, bone scans (BS) are routinely performed to detect bone metastases and/or to assess the response of a patient's known metastatic bone disease to chemotherapy. Recent European Association of Urology guidelines state that a bone scan may not be indicated in asymptomatic patients with well or moderately differentiated prostate cancer presenting with a serum PSA < 20 ng/ml[12]. However, BS should be considered only if the result is likely to have a strong impact on the management plan.

Prostate cancer exhibits tremendous difference in incidence in different populations worldwide. Asian men typically have a very low incidence and mortality of Carcinoma prostate in contrast to northern European and American populations[13]. The purpose of this study is to determine whether the probability of positive bone scan result of newly diagnosed Carcinoma Prostate patients can be predicted by serum PSA level, with an attempt to define a particular PSA level under which the group of patients would have low risk of obtaining a positive bone scan, so that the radiologic procedure can be safely omitted.

The current research was done to study the incidence of bone metastases of the south Indian population at various PSA levels in carcinoma prostate.

MATERIAL AND METHODS

This prospective study was conducted in the Department of Urology, at Sri Venkateswara Institute of Medical Sciences,

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Age	40- 50	50-60	60-70	70-80	80-90	90-100
No.of Patients	1	13	41	22	8	0
Table-1: Showing age distribution						

<10 PSA		10 TO 20 PSA		20 TO 50 PSA		50 TO100 PSA		>100 PSA	
P=6	N=7	P=5	N=13	P=10	N=7	P=25	N=5	P=6	N=1
P= Positive on bone scan, N= Negative on bone scan									
Table-2: Showing PSA distribution:									

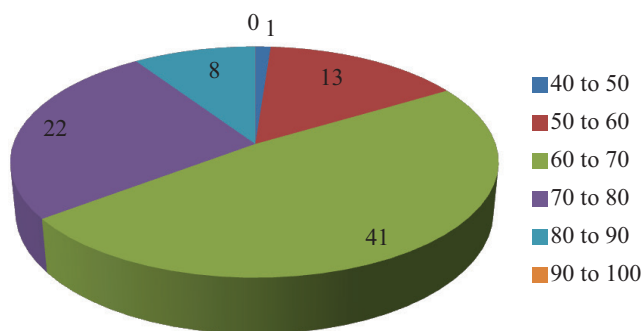| PSA	Postive	Negative	
<20	11	20	31
>20	41	13	54
Total	52	33	85
he P – value was <0.001(significant)			
Table-3: Showing results of Bone scanbelow 20ng/ml PSA			

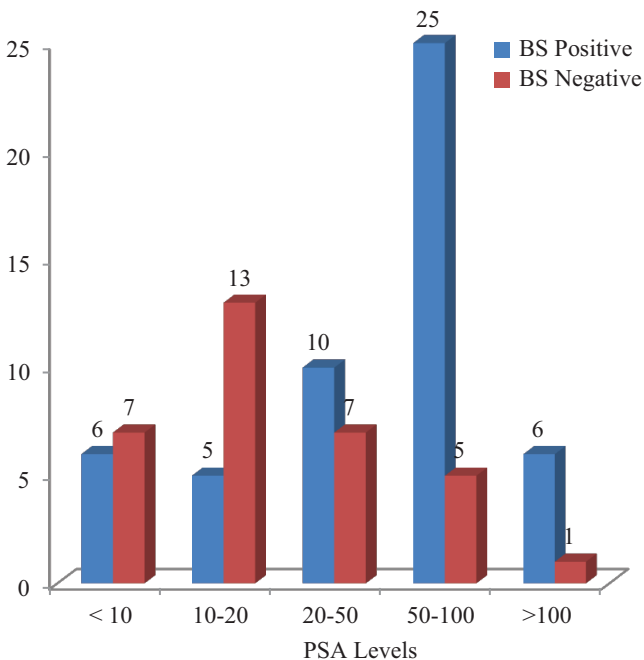**Figure-1:** Pie chart showing the distribution of the patients

Figure-2: Bar diagram showing results of Bone scan (Tc-99m MDP -Methylene diphosphonate)

Tirupati from May 2016 to august 2017

Inclusion criteria
1. Carcinoma prostate patients with all levels of PSA
2. Patients with Post TURP Chips positive for Carcinoma prostate

Exclusion criteria
1. Patients refusing bone scan

Methodology
Patients were presented to urology department with lower urinary tract symptoms evaluated clinically by
1. Digital Rectal Examination (DRE): To assess the size of the prostate, nodules, consistency and tenderness.
2. Urine Routine Examination and Culture and Sensitivity (R/E and C&S)
3. Estimation of Serum PSA: Serum PSA was estimated by ELISA technique using commercial kit- DS- EIA-PSA-TOTAL kit (DSI s.r.l, Saronno (VA)Italy).
4. Ultrasound Abdomen: To assess the size of the Prostate, bladder wall thickness, pre void and Post void residual urine.

On evaluation if patient have abnormal prostate (Nodular enlargement/ hard consistency of prostate) with or without raised PSA and urine C&S showed no growth, patients were subjected to TRUS guided prostate biopsy.

TRUS guidedprostatebiopsy
TRUS guided biopsy was performed by the radiologist. TRUS was performed with the patient in left lateral decubitus position using Siemens Sonoline G40 scanner with an attached 7 MHz bi planar probe. Standard extended 12-core biopsies (6 on each side of midline) were taken. Additional lesion directed biopsies were performed from hypoechoic area. Cores were immediately placed in 10% neutral buffered formalin. Right and left sided biopsy cores sent for pathological examination in separate containers.

If TRUS biopsy revealed carcinoma prostate or TURP chips positive for carcinoma prostate, patients were evaluated with Bone Scan (scintigraphy) for the bony metastases.

BONE scintigraphy
Bone scintigraphy was performed with technetium-99m MDP. The dose of Tc-99m MDP (Methylene diphosphonate) used approximately 20 mCi and the scanning was performed by a dual head camera with high-resolution collimator was used and whole body anterior and posterior planar images were taken. The bone scan was reviewed by Nuclear medicine specialist.

Data analysis
Statistical analyses was done using the Chi-square test, by a statistical software (SPSS, Statistical Package for the Social Sciences, version 11.5.1, Chicago, IL) with differences p value < 0.05 considered significant.

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Observations

Age: Table 1 shows that total 85 patients were included in this study. The minimum age of the patient was 49 years. The maximum age of the patient was 88 years. The mean age of the patients was 68 years

Total No of Patients were 85. Out of 85 patients 52 patients were positive on bone scan. i.e 61.17%. Out of 85 patients 33 patients were negative on bone scan. i.e 38.82% (figure -2). According to PSA levels, patients were divided into 5 groups:

1) In less than 10 PSA value, 13 patients were included
   Out of 13 patients, 6 patients positive on bone scan i.e
   6/13x100 = 46.15%
2) In 10 to 20 PSA value, 18 patients were included.
   Out of 18 patients, 5 patients positive on bone scan i.e
   5/18x100 = 27.77%
3) In 20 to 50 PSA value, 17 patients were included
   Out of 17 patients, 10 patients positive on bone scan i.e
   10/17x100 = 58.82%
4) In 50 to 100 PSA value, 30 patients were included.
   Out of 30 patients 25 patients positive on bone scan i.e
   25/30x100 = 83.33%
5) In >100 PSA value, 7 patients were included.
   Out of 7 patients 6 patients positive on bone scan i.e
   6/7x100= 85.71%

In less than 20 PSA value (0 to 20), total 31 patients were included. Out of 31 patients 11 patients (35.48%) were positive on bone scan and 20 patients were negative (64.52%) on bone scan. In more than 20 PSA value 54 patients were included. Out of 54 patients 41 patients (75.92%) were positive on bone scan and 13 patients (24.07%) were negative on bone scan (table-3).

DISCUSSION

Prostate cancer in India ranks fifth in incidence and fourth in cancer related mortality. It is uniformly lethal in advanced stage. Prostate cancer shows tremendous difference in its incidence in different populations worldwide. Asian men typically have a very low incidence and mortality of carcinoma prostate in contrast to northern European, African and American populations. Screening out patients with advanced disease or bone metastases is essential in order to prevent complications from bone destruction, and to improve the quality of life of these patients. The diagnosis of bone metastasis secondary to prostate cancer significantly alters the patient's treatment. Currently, radionuclide bone scans are the gold standard for detecting osseous metastasis. Detecting bone metastases is essential in predicting prognosis, and identifying or preventing complications incurred by disease progression.

In our study, the incidence of bone metastases in carcinoma prostate was 61.17%. Out of 85 patients 52 patients were positive on bone scan with a rate much higher than that in the reports carried out by researchers in western countries. It could be partly explained by short duration of study with small sample size. There is no population based screening program for carcinoma prostate in India. In our study all cases presented with lower urinary tract symptoms and subsequent

digital rectal examination, PSA and TRUS were done to rule out carcinoma prostate. This might have contributed to the higher incidence of advanced disease, that is, having bone metastases, in those newly diagnosed carcinoma prostate patients. In newly diagnosed cases, the incidence of positive bone scans in patients with PSA lower than 20 ng/ml is low. In our study 11patients (35.48%) out of 31 patients were positive on bone scan with PSA less than 20 ng/ml and 20 patients (64.52%) were negative on bone scan with PSA less than 20 ng/ml. (P value < 0.001).[7,8]

Our study results were similar to NCCN guidelines, which recommends the use of bone scans for patients with a PSA greater than 20 ng/mL, a Gleason score of 8 to 10, clinical stage T3 or T4, or clinical symptoms (National comprehensive Cancer Network, 2009).

According to Chybowski[7] in a group of 521 American subjects with untreated newly diagnosed prostate cancer, bone scan finding showed that bone metastasis did not occur in patients with PSA levels of 15 ng/ml or lower, but it did occur in 1 patient (0.3%) with a PSA level of 15-20 ng/ml. Rhoden et al. studied a group of 214 patients with 35 positive bone scans: only 1 of those was in the group with a PSA lower than20 ng/ml. Such studies led to a recommendation to avoid staging bone scans in patients with PSA lower than20 ng/ml. Many recent studies took 10 ng/ml as a threshold PSA for omitting bone scan, but there is a reluctance to make an absolute recommendation, and bone scan continues to be used by many physicians and urologists in the staging process of the disease.[8-13] Oesterling examined the relations among bone metastases, PSA, pathohistologic differentiation, and local findings in 852 subjects with untreated prostate cancer.[14] The likelihood of bone metastases in men with PSA levels <10 ng/ml was 0.5% (4/852). In those with levels <20 ng/ml, the incidence of bone metastases was only 0.8% (7/852), and of these 7 men, 5 had bone pain. Of the 4 patients in their study with PSA levels of 10 ng/ml or lower, only 1 patient had bone metastasis without bone pain [14]. In another study only 6% out of 490 patients with newly diagnosed CaP had positive bone scan on initial evaluation. Scans were positive in none of the 290 patients with PSA levels below 10 ng/ml, 4 out of 88 (4.5%) with PSA levels between 10 and 20 ng/ml, and 24 of 122 (21%) with PSA levels above 20 ng/ml.[15]

In contrast to the other studies carried out in western countries, a multi-centre retrospective study in Japan has revealed that bone metastasis is common in Japanese patients with newly diagnosed, untreated prostate carcinoma, with an overall positive rate of 24.2% on bone scans.[16] The positive rate is approximately double that reported in the United States and Canada (8.9%). According to Ito et al., of the 303 patients identified to have carcinoma prostate in a mass screening program in 9671 subjects, 36 had bone metastasis. 13 (36%) of the 36 patients had PSA levels of 10 ng/ml or less[17]. The incidence of having positive bone scan in a patient group with low PSA levels is much higher than in the other studies in western countries. It is therefore certain that the behaviour and histopathologic characters of carcinoma prostate are

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different according to the continent, the geographic origin, the race and the ethnic group[18].

Limitations of this study

Our study was short duration of study with small sample size.

The major limitation of this study was the presence or absence of metastases was not proven by tissue biopsy.

CONCLUSION

In our study 11patients (35.48%) out of 31 patients with PSA less than 20 ng/ml were positive on bone scan, which was higher than other studies. i.e it needs further continuation of study with large number. Because of high incidence of bone metastases in south Indian population, it is better to undergo bone scan in a newly diagnosed carcinoma prostate even with sr. PSA <20ng/ml.

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