RESEARCH COMMUNICATION

Metastasis on Bone Scan With Low Prostate Specific Antigen (≤ 20 ng/ml) and Gleason's Score (< 8) in Newly Diagnosed Pakistani Males with Prostate Cancer: Should We Follow Western Guidelines?

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Abstract

Aim: To find out diagnostic correlation of prostate specific antigen (PSA) and Gleason's score (GS) with bone metastasis (BM) in newly diagnosed prostate cancer (PC) patients in Pakistan. Materials and Methods: This retrospective study included 204 newly diagnosed PC patients who were referred for BS for staging. Results: The mean age, mean PSA and incidence of BM on BS were 71 ± 09 years, 111.01 ± 58.45 ng/ml and 67/204 (33%), respectively. The mean GS of the studied population was 7 ±1. According to PSA levels, patients were divided into 5 groups: < 10 ng/ml (77/204), > 10 - ≤ 20 ng/ml (42/204), > 20 - ≤ 50 ng/ml (22/204), > 50 - ≤ 100 (25/204) and > 100 ng/ml (38/204). The incidence of positive BS (%) for BM and mean GS (score ± SD) for each group were 14%, 7 ±1; 10%, 6±1; 32%, 7 ±1; 56%, 8 ±1 and 82%, 8 ±1 respectively (significant p value). PSA and GS were statistically significant predictors of BM on BS and their predictive value was additive (p < 0.0001). Age was not a predictive factor (non-significant p value). Sensitivity and specificity of PSA at a cut-off 48 ng/ml were 68.3% and 86.1% respectively, while GS at a cut-off >6 was more sensitive (88.9%) and less specific (56.2%) for diagnosing BM. Conclusions: (1) There is an overall increased incidence of BM in newly diagnosed patients with PC and even at serum PSA level ≤ 20 ng/ml and GS < 8; (2) PSA and GS are independent predictors for BM but age is not; (3) in view of possible aggressive behavior of PC in local population, one must be careful in adopting Western guidelines for using BS in newly diagnosed Asian males with PC having PSA ≤ 20 ng/ml and GS < 8.

Keywords: Prostate specific antigen - Gleason's score - bone metastasis - prostate cancer - bone scan

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Introduction

Colorectal cancer PC is currently the most common malignancy diagnosed in American and British males (Jemal et al., 2009, UK. CR Prostate Cancer Statistics cited on 20.5.2010). In European Union, PC constitutes about 13% of all malignancies diagnosed in male but unfortunately its magnitude in Pakistan is not clearly known (Khan et al., 2008). However, according to Karachi Cancer Registry, PC is the 6th commonest male cancer in Pakistan (Bhurgi et al., 2000). It has the second highest cancer mortality in males in USA and UK (Kemp et al., 1997; Jemal et al., 2009). Interestingly there is a wide geographical variation in incidence of PC as its incidence and mortality is strikingly lower in Asian population (Fakras et al., 2000).

Identification of bone metastasis, which is present in up to 14% cases at presentation (Pal et al., 2008) and about 80-85% in later phase (Lin et al., 1999), essential for staging, choice of therapy and prognosis. Bone scanning is the routine staging procedure in newly diagnosed PC and it is more sensitive than conventional X-ray for detecting bony metastasis. Sensitivity of planar bone scan for the detection of bone metastasis is 72–77% in adults (Sadik et al., 2008) and is currently the investigation of choice. However, it lacks diagnostic specificity with indeterminate results often prompting the need for further imaging.

Serum prostate specific antigen (PSA) was first isolated in 1979 (Wang et al., 1979) and is derived from acinar and ductal epithelial cells of normal, hyperplastic and malignant prostate tissue (Kemp et al., 1997). PSA assay has been suggested as an accurate mean of monitoring prostate cancer patients before treatment and during follow-up (Oommen et al., 1994). Serum PSA correlates well with positive bone scan (having bone metastasis) and various studies have demonstrated a low risk of a positive bone in newly diagnosed patients with a low PSA level (Ayyathurai et al., 2006; Pal et al., 2008). However, there are reports which revealed higher incidence of positive bone scan with low PSA in mass population screening

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in Asians as compared with Western data (Kosuda et al. 2002).

The Gleason's scoring (GS) system is currently the most widely utilized histologic grading system for PC and is a powerful predictor of cancer behavior (Gleason DF and Mellinger GT 1974). The prognostic value of GS for predicting biochemical failure, systemic recurrence and overall survival is considered high (Tollefson et al., 2006). Patients with well differentiated tumors (GS 2 to 6) generally have a favorable prognosis while high grade tumors (GS 7 to 10) are associated with higher mortality rate (Blute et al., 2001).

The aim of this study was to find out the diagnostic correlation of serum PSA and GS with bone metastasis on bone scan in newly diagnosed PC patients in local population.

Materials and Methods

This is a retrospective study which included 204 newly diagnosed patients with PC who were referred for bone scan for staging to Nuclear Medicine Sections of The Aga Khan University Hospital (157/204) and Karachi Institute of Radiotherapy and Nuclear Medicine (47/204), Karachi from January 2006 till January 2011. Inclusion criteria were hispatopathological diagnosis of PC, staging bone scan and PSA were performed with 4 weeks of each other, unequivocal bone scan (or equivocal findings confirmed by other imaging modalities) and no treatment before bone scan and PSA measurement.

Whole body bone scanning was performed with 20-25 mCi of Tcehnetium-99m labeled Methylene Diphosphonate (Tc-99m MDP) injected intravenously and images were acquired 3-4 hours after under digital gamma cameras (Double head ECAM Siemens, Single Head ECAM Siemens and GCA 7200 Toshiba). Bone scans were interpreted by qualified nuclear physicians. Total PSA was measured by using IMMULITE® system (Diagnostic Products Corporation 5700 West 96th Street Los Angeles, CA) in a single laboratory. All biopsy specimens were fixed in10% buffered formalin and using standard procedure stained with Hematoxylin and Eosin. The tumors were graded according to the Gleason's grading system (Gleason DF and Mellinger GT 1974). GS 2-4, 5-7 and 8-10 were grouped as well differentiated (GS-I), moderately differentiated (GS-II) and poorly differentiated (GS-III).

Data were analyzed by using the MedCalc statistical software version 11.3.10 and SPSS software version 10. Chi-square test was used for the comparison of proportions. Logistic regression analysis was used for the multivariate analysis. For all statistical comparisons, significance was defined as $P < 0.05$.

Results

The mean age of studied 204 patients was 71± 09 years, mean serum PSA value was 111.0± 58.5 ng/ml and the incidence of bone metastasis evident on bone scan was 67/204 (33%). The mean GS of studied population was 7±1 while incidence of well differentiated tumor (GS-I: < 5), moderately differentiated (GS-II: ≥ 5 - < 8) and poorly differentiated tumors (GS-III: ≥ 8) were 01%, 71% and 28% respectively. The p value was statistically significant for all above variables.

Table 1. Incidence of Bone Metastasis in Patients with Different Levels of Prostatic Specific Antigen

PSA level (ng/ml)	No.	Mets +ve[1]	Mets -ve[1]	Bone Mets+ve PSA	GS
≤10	77	11 (14%)*	66 (86%)	5.4±2.8	7±1
>10- ≤20	42	04 (10%)*	38 (90%)	13.9±3.7	6±1
>20- ≤50	22	07 (32%)*	15 (68%)	35.4±10.9	7±1
>50- ≤100	25	14 (56%)*	11 (44%)	72.7±17.3	8±1
>100	38	31 (82%)*	07 (18%)	543.3±938.2	8±1

[1]Bone scan; Mets, Metastasis; PSA, Prostate Specific Antigen; GS, Gleason's Score; *p<0.0001

Table 2. Bone Metastasis in Correlation with Age, Pathological Grading and PSA Level

Bone Metastasis Vs variables	Logistic regression $\chi 2$	Area Under the ROC Curve (95%CI)	P value
Age+PSA+GS	73.8	0.857 (0.801-0.902)	<0.0001
	Coefficient+SE	OR (95%CI)	P value
Age	-0.006+0.021	0.994 (0954-1.035)	0.7559
GS	0.824+0.175	2.279 (1.617-3.212)	<0.0001
PSA level	0.009+0.002	1.009 (1.005-1.014)	<0.0001

PSA, Prostate Specific Antigen; GS, Gleason's Score; ROC, Receiver Operator CharacteristicsCI=Confidence Interval SE, Standard Error, OR, Odds Ratio

According to serum PSA levels, patients were divided into 5 groups: < 10 ng/ml (77 patients), > 10 - ≤ 20 ng/ml (42 patients), > 20 - ≤ 50 ng/ml (22 patients), > 50 - ≤ 100 (25 patients) and > 100 ng/ml (38 patients). The incidence of positive bone scan (%) for bone metastases and mean GS (score ± SD) for each group were 14%, 7 ±1; 10%, 6±1; 32%, 7 ±1; 56%, 8 ±1 and 82%, 8 ±1 respectively (significant p value for bone metastases in each category). Mean GS in each class ranged from 6 to 8 ±1 (higher for PSA > 50 ng/ml) (Table 1).

Sequential logistic regression with bony metastasis on bone scan as the dependent variable and age, log PSA and GS as independent variables was carried out to determine whether PSA and Gleason scores were additive. In the final

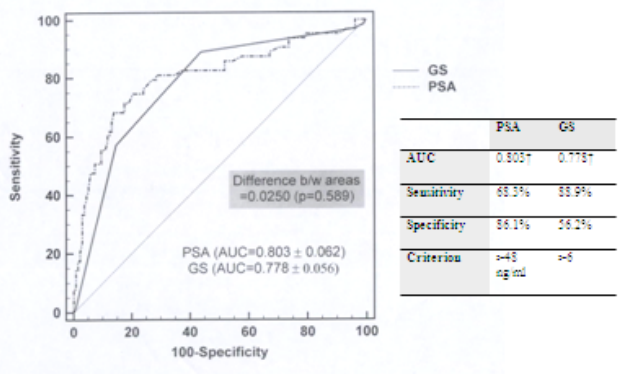

Figure 1. Receiver Operating Curves (ROC) Analysis of Prostate Specific Antigen (PSA) and Gleasons Scores (GS) for Bone Metastasis in Patients with Prostate Cancer

model both log PSA and GS were statistically significant predictors of bone metastasis on bone scan and their predictive value was additive (p<0.0001). Age was not a predictive factor (non-significant p value) (Table 2).

Receiver operating characteristic (ROC) curve for accuracy of PSA and GS for diagnosing bone metastasis on bone scan has an area under curve 0.803 and 0.778 respectively and a difference of 0.0250 (p value non-significant). The sensitivity and specificity of PSA at a cut-off 48 ng/ml was 68.3% and 86.1% respectively, while GS at a cut-off >6 was more sensitive (88.9%) and less specific (56.2%) for diagnosing bone metastasis (Figure 1).

Discussion

The incidence of bone metastasis in newly diagnosed PC in this study is significantly high (33%) as compared with reported American (14%) (Pal et al., 2008) and Italian (2.5%) (Salonia et al., 2006) studies. The reason for this may be the referral bias as we have included patients who presented with urological symptoms and not a true screening population. Second plausible explanation is higher incidence of moderately differentiated (GS > 4 and ≤ 7) and poorly differentiated tumors (GS ≥ 8) in the studied cohort. A multi-center retrospective study in Japan has revealed an incidence of positive bone scan in 22% of recently diagnosed PC patients (Kosuda et al., 2002). Similarly a recently published study from Hong Kong, China has shown an incidence of positive bone scan of 29.3% (Lai et al., 2009). These published facts point towards an altered behavior of PC in Asian population and this aspect needs to be further investigated.

Another important fact which draws our attention is significantly increased incidence of bone metastasis in patients with PSA < 20 ng/ml and mean GS < 8. This is in contradiction to many published studies showing high negative predictive value of low PSA (<20 ng/ml) (Lai et al., 2009; Mcarthur et al., 2011). Furthermore, as per recommendations of European Association of Urologist (EAU) (Heidnreich A et al., 2009), American Urological Association (AUA) and American Joint Commission on Cancer (AJCC) (Briganti et al., 2010), 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 and GS < 8, 13% (15/119) would have missed the diagnosis of metastatic bone disease. Ito et al (2000) 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 PC in Asians as compared to Caucasians (71% patients in our study had moderately differentiated PC i.e. GS 5, 6, 7 and 28% had poorly differentiated PC, i.e. >7). Furthermore, it seems imperative to use bone scan in primary staging even in patients with PSA < 20 ng/ml and GS < 8, contradictory to international guidelines, to avoid under-staging in significant number of patients. In view of these findings, a large multi centre study is deeming required to ascertain the behavior of PC and applicability of Western guidelines in Asians males with PC.

The result also shows higher level of PSA (>50 ng/ml) is associated with poorly differentiated histopathology (GS >7) and this is a well documented fact (Pierorazio et al., 2009). In this study PSA and GS are independent predictors of bone metastasis and this is in accordance to published studies (Paryin et al., 1990; Ayyathurai et al., 2006; McArthur et al., 2011). However, age was not a predictor for bone metastasis (p value 0.7559) as reported in literature as well (Mcarthur et al., 2011).

The major limitation of our study is its retrospective design and biased recruitment of symptomatic patients and not from population based screening program. Another limitation is performance of bone scan at two different nuclear medicine sections which may raise issue of standardization as far as acquisition and reporting of the procedure. However, the reporting nuclear medicine physicians at two Centers were having at least more than 5 years experience of reporting such procedures.

Conclusion: We conclude that (1) there is an overall increased incidence of bony metastasis in newly diagnosed patients with PC and even at serum PSA level ≤ 20 ng/ml and GS < 8; (2) PSA and GS are independent predictors for bony metastasis but age is not; (3) in view of possible aggressive behavior of PC in local population, one must be careful in adopting Western guidelines for using bone scan in newly diagnosed Asian males with PC having PSA ≤ 20 ng/ml and GS < 8.

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