RESEARCH ARTICLE

Retrospective Study of Predictors of Bone Metastasis in Prostate Cancer Cases

Christopher Chee Kong Ho[1]*, Poh Keat Seong[1], Zulkifli Md Zainuddin[1], Mohd Rizal Abdul Manaf[2], Muhilan Parameswaran[3], Azad HA Razack[3]

Abstract

Introduction: The purpose of this study was to identify clinical profiles of patients with low risk of having bone metastases, for which bone scanning could be safely eliminated. Materials and Methods: This retrospective cross sectional study looked at prostate cancer patients seen in the Urology Departments in 2 tertiary centres over the 11 year period starting from January 2000 to May 2011. Patient demographic data, levels of PSA at diagnosis, Gleason score for the biopsy core, T-staging as well as the lymph node status were recorded and analysed. Results: 258 men were included. The mean age of those 90 men (34.9%) with bone metastasis was 69.2±7.3 years. . Logistic regression found that PSA level (P=0.000) at diagnosis and patient's nodal-stage (P=0.02) were the only two independent variables able to predict the probability of bone metastasis among the newly diagnosed prostate cancer patients. Among thowse with a low PSA level less than 20ng/ml, and less than 10ng/ml, bone metastasis were detected in 10.3% (12 out of 117) and 9.7% (7 out of 72), respectively. However, by combining PSA level of 10ng/ml or lower, and nodal negative as the two criteria to predict negative bone scan, a relatively high negative predictive value of 93.8% was obtained. The probability of bone metastasis in prostate cancer can be calculated with this formula: -1.069+0.007(PSA value, ng/ml)+1.021(Nodal status, 0 or 1)=x Probability of bone metastasis=2.718^x/1+2.718^x. Conclusion: Newly diagnosed prostate cancer patients with a PSA level of 10ng/ml or lower and negative nodes have a very low risk of bone metastasis (negative predictive value 93.8%) and therefore bone scans may not be necessary.

Keywords: Prostate cancer - bone metastasis - bone scan - prostate specific antigen - gleason score

Asian Pacific J Cancer Prev, **14 (5)**, 3289-3292

Introduction

Advanced prostate cancer can metastasize to various sites of the body like bone, distant lymph nodes, lungs, liver, brain and skin (Heidenreich et al., 2008). The most frequent sites of metastasis are lymph nodes and bone. Ninety percent of patients who die of prostate cancer harbour bone metastases (Gomez et al., 2004). Of those patients dying from prostate cancer, the rate of skeletal involvement ranges between 85% and 100% (Carlin and Andriole, 2000; Groot et al., 2003). Studies have shown that roughly 50% of patients with bone metastases will die within 30-35 months after diagnosis (Carlin and Andriole, 2000; Rigaud et al., 2002; Groot et al., 2003).

Bone scintigraphy/scan [technetium Tc 99m methylene diphosphonate (Tc 99m MDP)] has been used routinely in newly diagnosed prostate cancer patient to detect prostate cancer bone metastases (Thurairaja et al., 2004). However, bone scan is rather time-consuming, costly and exposing patient to more radiation (Oesterling et al., 1993; Thurairaja et al., 2004). Some authors have discouraged the routine use of bone scan for primary staging in all patients with newly diagnosed prostate cancer and suggested that bone scan should be done only in selective high risk patients (Oesterling et al., 1993; Lee et al., 2000; Abuzallouf et al., 2004; Hirobe et al., 2007). However, in another study, it has been suggested that bone scan should be used in all patients as there is a lack of reliable marker to identify high risk patients (Wolff et al., 2000).

The purpose of the present study was to determine the relationship between bone metastasis and clinical or pathological variables, including the serum PSA level at diagnosis, Gleason score, T-staging and lymph node status in patients with newly diagnosed prostate cancer. With the evaluation, we hope to identify the clinical profile of patients with low risk of having bone metastases, for which bone scanning could be safely eliminated. By doing selective bone scan only for high risk prostate cancer patients, it is hoped that the national health care cost can be reduced and the long waiting period of a bone scan be prevented.

Materials and Methods

This was a retrospective cross sectional study involving all prostate cancer patients who presented to the Urology

*[1]Urology Unit, Department of Surgery, [2]Department of Community Health, Universiti Kebangsaan Malaysia Medical Centre, [3]Department of Surgery, Universiti Malaya, Kuala Lumpur, Malaysia *For correspondence: chriskho2002@yahoo.com*

Departments in Universiti Kebangsaan Malaysia Medical Center (UKMMC) and Universiti Malaya Medical Center (UMMC) for the past 11 years, starting from January 2000 to May 2011.

Data collected include demography, PSA at diagnosis, the Gleason score of the biopsy core, T-staging as well as the lymph node status of the tumour. The T-staging (T) and lymph node status (N) was based on the pre-treatment staging CT or MRI abdomen/pelvis assessment.

Patients who presented to the urology department of UKMMC and UMMC, with confirmed histological diagnosis of prostatic carcinoma, from year January 2000-May 2011 were included in this study. Exclusion criteria were any other preexisting malignancy which may predispose them to bone metastasis, prostate cancer patients who had presented with acute urinary obstruction and had emergency prostate resection for relief of the obstruction, and patients who had pretreatment with antiandrogen/5- alpha reductase inhibitor.

The ethical approval for this study was obtained from the UKMMC/UMMC ethics committee (FF-077-2011). The data were analyzed using IBM SPSS software version 19. Level of significance was fixed at 0.05. Chi-squared, t-test and logistic regression was used for statistical analysis of significance.

Results

A total of 281 patients with newly diagnosed prostate cancer during the study period were identified from both UKMMC and UMMC. Out of these numbers, 258 patients who had fulfilled the criteria of the study were included into the study. Most of the excluded patients were due to incomplete data.

The median age was 69.2 years (range 50-91years). Among the study population, majority of the patients were Chinese (57.4%), followed by Malay (31.4%) and Indian (8.1%).

93 out of 258 patients included (36%) were found to have distant metastasis upon diagnosis of prostate cancer. Among those who have no distant metastasis, most (31%) were diagnosed at the stage of T2N0M0. Table 1 shows the clinical staging of newly diagnosed prostate cancer patients.

Bone was the most common site of metastasis among prostate cancer patients, where it was found in 90 out of 258 patients (34.9%). Only three patients were noted to have lung metastasis instead of bone metastasis in this study. Only about half of the newly diagnosed prostate cancer patients (52.7%) had localized disease without any nodal or distant metastasis at diagnosis.

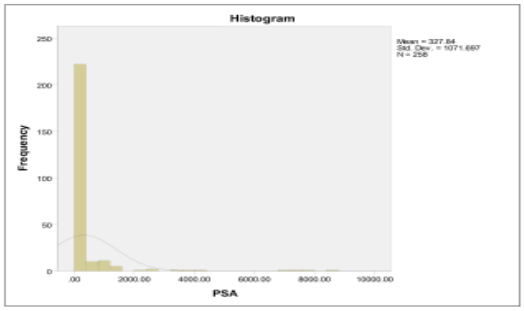

Figure 1. PSA Level of Prostate Cancer with Bone Metastasis. (Median PSA 27.5ng/ml)

Table 1. Clinical Staging at Diagnosis

	No. (%)
Clinical Staging (TNM Staging) at diagnosis	
Total Number of Patients	258
T1N0M0	3 (1.2)
T2N0M0	80 (31.0)
T3/T4N0M0	53 (20.5)
Any T, N1, M0	29 (11.2)
Any T, any N, M1	93 (36.0)*

*3 patients have lung metastasis

Table 2. Relationship between Bone Metastasis with Clinical/pathological Variables

Clinical/Pathological Variables		Total (%)	Bone metastasis Yes n (%)	No n (%)	P-value
Number of patients		258 (100)	90 (34.9)	168 (65.1)	
Gleason score	≤5	60 (23.3)	14	46	
	6	44 (17.1)	09	35	0.016
	7	76 (29.5)	26	50	
	8	25 (9.7)	15	10	
	≥9	53 (20.5)	26	27	
T-stage	T1	005 (01.9)	02	03	
	T2	104 (40.3)	18	86	0.00
	T3/4	149 (57.8)	70	79	
Lymph node status	N0	173 (67.1)	36	137	0.00
	N1	085 (32.9)	54	31	
Serum PSA level, ng/ml	≤10	72 (27.9)	07	65	
	10.1-20	45 (17.4)	05	40	0.00
	20.1-50	44 (17.1)	10	34	
	≥50	97 (37.6)	68	29	

Table 3. Relationship of Bone Metastasis and Age of Patients

		Number	Mean (Years)	Std. Deviation	Std. Error Mean
Age	No Bone Metastasis	168	69.32	7.131	0.550
	Bone Metastasis	90	68.92	7.515	0.792

Table 2 shows the comparison between the groups of patients who had bone metastasis at diagnosis with those who did not have bone metastasis based on several clinical and pathological variables such as T stage, N stage, Gleason score, PSA level at diagnosis, as well as the age of patients at diagnosis. It was found that there was a significant difference between those with or without bone metastasis in terms of Gleason score, T-stage, lymph node status and serum PSA.

Overall, patients with bone metastasis were diagnosed at the mean age of 69.2±7.3 years. Table 3 shows that there was no significant age difference between the group with bone metastasis and those without (P=0.679).

The results also showed that among the newly diagnosed prostate cancer patients, parameters like patients' T-stage, N-stage, Gleason score as well PSA level at diagnosis were significantly different between those with bone metastasis and those without bone metastasis.

These variables were grouped and analysed together to look for the independent variables that may help in predicting the probability of bone metastasis among the newly diagnosed prostate cancer patients. By using logistic regression method, it was found that PSA level (P=0.000)

Table 4. Studies Addressing Incidence of Positive Bone Scan Among Prostate Cancer Patients.

References	Origin of Study	Year of Study	No of patients	Positive bone scan, n (%)
Chybowski et al.	USA	1991	521	71 (0.14)
Oesterling et al.	USA	1993	852	7 (0.8)
Rudoni et al.	Germany	1995	118	54 (45.8)
Gleave et al.	Canada	1996	490	28 (6.0)
Kemp et al.	UK	1997	098	26 (26.5)
Lin et al.	USA	1999	270	24 (8.9)
Lee et al.	USA	2000	631	88 (14.0)
Wolff et al.	Germany	2000	359	40 (11.2)
Kosuda et al.	Japan	2002	1000	222 (22.2)
Salonia et al.	Italy	2006	1242	31 (2.5)
Huang et al.	Chinese Taipei	2006	342	97 (28.4)
Hirobe et al.	Japan	2007	366	28 (7.7)
Current study	Malaysia	2011	258	90 (34.9)

at diagnosis and patient's N-stage (P=0.02) are the only two independent variables that can predict the probability of bone metastasis among the newly diagnosed prostate cancer patients.

Among the prostate cancer patients with a low PSA level of less than 20ng/ml, and less than 10ng/ml, bone metastasis were detected in 10.3% (12 out of 117) and 9.7% (7 out of 72) of them respectively. However, by combining PSA level of 10ng/ml or lower, and nodal negative as the two criteria to predict negative bone scan, we are able to achieve a relatively higher negative predictive value of 93.8%. This relation can be expressed as a formula as shown below; **-1.069+0.007(PSA value, ng/ml)+1.021(Nodal status, 0 or 1)=x, Probability of bone metastasis = $2.718^x/1+2.718^x$**

Discussion

In our study, bone metastasis was found in 34.9% of the 258 prostate cancer patients. This figure is considered relatively high compared to most of recent studies (Table 4). This higher proportion probably reflects the lack of prostate cancer screening programme and public awareness in Malaysia leading to a higher rate of patients being diagnosed at a more advanced stage

AUA and EUA had set guidelines to perform bone scan selectively among the newly diagnosed prostate cancer patients based on the results of previous studies. The European Association of Urology (EAU) (Heidenreich et al., 2008), the American Urological Association (AUA) (Thompson et al., 2007) have both updated their guidelines to indicate the need for bone scans only in patients with certain unfavourable prostate cancer characteristics.

AUA guideline stated that routine use of bone scanning may not be required for staging asymptomatic patients who have clinically localized disease that is newly diagnosed, when their PSA is equal to, or less than 20ng/ml (Thompson et al., 2007). EAU guideline for prostate cancer suggested that bone scan may not be indicated in asymptomatic patients, if the serum PSA level is less than 20ng/ml in the presence of well or moderately differentiated tumours (Heidenreich et al., 2008).

Both guidelines used PSA level of 20ng/ml and below as part of the cut off point to omit bone scan. In our study, we found that 12 out of 117 patients with a PSA level of 20ng/ml or less were found to have positive bone scan. As a result, if PSA of 20ng/ml or less were used as a cut off point to omit the bone scan, 12 patients with bone metastasis would be missed from our study population (86.7% negative predictive value).

Our study showed a much lower negative predictive value for PSA level when compared to another study done previously by Chybowski et al. (1991) where bone metastasis was detected in only one out of 307 patients with PSA level of 20 ng/ml or less (negative predictive value of 99.7%). Similarly, another study by Oesterling et al. (1993) found that, 0.8% had abnormal findings on bone scans when their PSA level is equal or below 20ng/ml. In our study, 13.3% of our prostate cancer patients were found to have bone metastasis despite having low PSA level of less than 20ng/ml. Based on this, we think that the guidelines from EAU and AUA may not be suitable for our region and population especially when we found such a high percentage of patients with bone metastasis when their PSA level at diagnosis was lower than 20ng/ml. Similar findings were found in Pakistan, where there was an overall increased incidence of bone metastasis in newly diagnosed patients with prostate cancer and even at serum PSA level≤20 ng/ml and Gleason score <8 (Zaman et al., 2011). In Korea, 27 men (4.6%) with serum PSA between 10 and 20 ng/mL, 29/579 men (5.0%) with GS≤7, and 21/83 (25.3%) with serum PSA≤20 ng/mL and Gleason score (GS)≤7 had positive bone scans (Lee et al., 2012).

Similarly, there are reports that discourage the routine use of a bone scan when the serum PSA level is only <10 ng/mL. A recent review article recommended the use of bone scan for prostate cancer patients only when the PSA level is greater than 10 ng/ml (Hricak et al., 2007). This is supported by another multicenter study done in Japan in year 2002 where positive bone scans were found in four (1.3%) of 300 patients whose PSA concentrations were equal to or less than 10 ng/ml (Kosuda et al,. 2002). The similar study also suggested that bone scan be omitted in patients with Gleason score of 6 or lower. Besides PSA level less than 10ng/ml, Hirobe et al. (2007) also recommended to omit bone scan in patients with PSA level between 10-20ng/ml, when they are T1 disease and having a Gleason score of 6 or lower.

In our study, there are 72 prostate cancer patients diagnosed with a low PSA level of 10ng/ml or less. Using the recommendation by the previously mentioned Japanese authors, we found that if we omitted bone scan on those 72 patients, bone metastasis would be missed in 7 patients in our series (negative predictive value of 90.3%). In other words, nearly 8% of prostate cancer patients with bone metastasis in our series (7 out of 90 patients with bone metastasis) have a PSA level lower than, or equal to 10ng/ml. Our finding was found to be consistent with a Taiwanese paper which found that in 9.37% of patients with bone metastasis, PSA level was only 10ng/ml or lower (Huang. et al. 2006). This showed that we cannot exclude bone metastasis totally when the PSA level is lower than 10ng/ml although the probability of bone metastasis in this group of patients is low. This is

echoed by Lai et al. (2011) who suggested that The risk of having positive bone scanis so low that it is not required for patients with PSA level less than 10 ng/ml.

Moslehi et al. (2013) suggested using serum alkaline phospatase (ALP) screening as a tool to detect the subgroup of patients who are at high risk of bone metastases, while having a PSA of <20ng/ml. In fact, the authors concluded that the combination of PSA and ALP can be used to improve predictability of bone metastasis in newly diagnosed patients with prostate cancer, without affecting staging accuracy. This was however not assessed in our retrospective study as we did not routinely do serum ALP for our patients.

In our study, only PSA level (P=0.000), and nodal status (P=0.02) are proven to be the two independent variables in predicting bone metastasis in newly diagnosed prostate cancer patients. The relation of PSA level, nodal status and probability of bone metastasis can be expressed as **-1.069+0.007(PSA value, ng/ml)+1.021(Nodal status, 0 or 1)=x, Probability of bone metastasis=2.718^x/1+2.718^x**

If we included either PSA level of 10ng/ml or lower, and nodal negative as the 2 criteria to omit bone scan in our newly diagnosed prostate cancer patients, there would still be 4 out of 90 (4.4%) bone metastases missed in our series. However, by combining these 2 criteria, we are able to achieve a relatively higher negative predictive value of 93.8% to predict negative bone scan.

In conclusion, newly diagnosed prostate cancer patients with PSA level of 10ng/ml or lower and negative nodes have a very low risk of bone metastasis (negative predictive value 93.8%) and therefore bone scan may not be necessary.

Acknowledgements

We would like to thank Dr Muhilan, Prof Azad, Dr Praveen, Dr Goh Eng Hong, Dr Tan Guan Hee, Dr Badrulhisham and Staff Nurse Azlina for their assistance in helping with this study.

References

Abuzallouf S, Dayes I, Lukka H (2004). Baseline staging of newly diagnosed prostate cancer: a summary of the literature. *J Urol*, **171**, 2122-7.

Carlin BI, Andriole GL (2000). The natural history, skeletal complications, and management of bone metastases in patients with prostate carcinoma. *Cancer*, **88**, 2989-94.

Chybowski FM, Keller JJ, Bergstralh EJ, JOesterling JE (1991). Predicting radionuclide bone scan findings in patients with newly diagnosed, untreated prostate cancer: prostate specific antigen is superior to all other clinical parameters. *J Urol*, **145**, 313-8.

Gleave M, Coupland D, Drachenberg D, et al (1996). Ability of serum prostate-specific antigen levels to predict normal bone scans in patients with newly diagnosed prostate cancer. *Urolog*, **47**, 708-12.

Gomez P, Manoharan M, Kim SS, Soloway MS (2004). Radionuclide bone scintigraphy in patients with biochemical recurrence after radical prostatectomy: when is it indicated? *BJU Int*, **94**, 299-302.

Groot MT, Boeken Kruger CG, Pelger RC, Uyl-de Groot CA (2003). Costs of prostate cancer, metastatic to the bone, in the Netherlands. *Eur Urol*, **43**, 226-32.

Heidenreich A, Aus G, Bolla M, et al (2008). EAU guidelines on prostate cancer. *Eur Urol*, **53**, 68-80.

Hirobe M, Takahashi A, Hisasue S, et al (2007). Bone scanning--who needs it among patients with newly diagnosed prostate cancer? *Jpn J Clin Oncol*, **37**, 788-92.

Hricak H, Choyke PL, Eberhardt SC, Leibel SA, Scardino PT (2007). Imaging prostate cancer: A multidisciplinary perspective. *Radiology*, **243**, 28-53.

Huang CY, Hsu HC, Chang CH, Tseng KF, Fong YC (2006). Prostate Cancer with Bone Metastases: A Clinical Profile. *Mid Taiwan J Med*, **11**, 82-9.

Kemp PM, Maguire GA, Bird NJ (1997). Which patients with prostatic carcinoma require a staging bone scan? *Br J Urol*, **79**, 611-4.

Kosuda S, Yoshimura I, Aizawa T, et al (2002). Can initial prostate specific antigen determinations eliminate the need for bone scans in patients with newly diagnosed prostate carcinoma? A multicenter retrospective study in Japan. *Cancer*, **94**, 964-72.

Lai MH, Luk WH, Chan JC (2011). Predicting bone scan findings using sPSA in patients newly diagnosed of prostate cancer: feasibility in Asian population. *Urol Oncol*, **29**, 275-9.

Lee SH, Chung MS, Park KK, et al (2012). Is it suitable to eliminate bone scan for prostate cancer patients with PSA≤20 ng/mL? *World J Urol*, **30**, 265-9.

Lee N, Fawaaz R, Olsson CA, et al (2000). Which patients with newly diagnosed prostate cancer need a radionuclide bone scan? An analysis based on 631 patients. *Int J Radiat Oncol Biol Phys*, **48**, 1443-6.

Lin K, Szabo Z, Chin BB, Civelek AC (1999). The value of a baseline bone scan in patients with newly diagnosed prostate cancer. *Clin Nucl Med*, **24**, 579-82.

Moslehi M, Cheki M, Salehi-Marzijarani M, Amuchastegui T, Gholamrezanezhad A (2013). Predictors of bone metastasis in pre-treatment staging of asymptomatic treatment-naïve patients with prostate cancer. *Rev Esp Med Nucl Imagen Mol*, [Epub ahead of print].

Oesterling JE, Martin SK, Bergstralh EJ, Lowe FC (1993). The use of prostate-specific antigen in staging patients with newly diagnosed prostate cancer. *JAMA*, **269**, 57-60.

Rigaud J, Tiguert R, Normand LL, et al (2002). Prognostic value of bone scan in patients with metastatic prostate cancer treated initially with androgen deprivation therapy. *J Urol*, **168**, 1423-6.

Rudoni M, Antonini G, Favr M, et al (1995). The clinical value of prostate-specific antigen and bone scintigraphy in the staging of patients with newly diagnosed, pathologically proven prostate cancer. *Eur J Nucl Med*, **22**, 207-11.

Salonia A, Gallina A, Camerota TC, et al (2006). Bone metastases are infrequent in patients with newly diagnosed prostate cancer: analysis of their clinical and pathologic features. *Urology*, **68**, 362-6.

Thompson I, Thrasher JB, Aus G, et al (2007). Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol*, **177**, 2106-31.

Thurairaja R, McFarlane J, Traill Z, Persad R (2004). State-of-the-art approaches to detecting early bone metastasis in prostate cancer. *BJU Int*, **94**, 268-71.

Wolff JM, Borchers ZH, Wildberger J, Buell U, Jakse G (2000). Is prostate-specific antigen a reliable marker of bone metastasis in patients with newly diagnosed cancer of the prostate? *Eur Urol*, **33**, 376-81.

Zaman MU, Fatima N, Sajjad Z (2011). 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? *Asian Pac J Cancer Prev*, **12**, 1529-32.