RESEARCH ARTICLE

Retrospective Study of Predictors of Bone Metastasis in Prostate Cancer Cases

Christopher Chee Kong Ho1*, Poh Keat Seong1, Zulkifli Md Zainuddin1, Mohd Rizal Abdul Manaf2, Muhilan Parameswaran3, Azad HA Razack3

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 those 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=2.718/1+2.718x. 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

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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 Department of Surgery, Universiti Malaya, Kuala Lumpur, Malaysia. *For correspondence: chrisckho2002@yahoo.com

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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 50-91 years). 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.

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.

<table>
<thead>
<tr>
<th>References</th>
<th>Origin of Study</th>
<th>Year of Study</th>
<th>No of patients</th>
<th>Positive bone scan, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chybowski et al.</td>
<td>USA</td>
<td>1991</td>
<td>521</td>
<td>71 (0.14)</td>
</tr>
<tr>
<td>Oesterling et al.</td>
<td>USA</td>
<td>1993</td>
<td>852</td>
<td>7 (0.8)</td>
</tr>
<tr>
<td>Rudoni et al.</td>
<td>Germany</td>
<td>1995</td>
<td>118</td>
<td>54 (45.8)</td>
</tr>
<tr>
<td>Gleave et al.</td>
<td>Canada</td>
<td>1996</td>
<td>490</td>
<td>28 (6.0)</td>
</tr>
<tr>
<td>Kemp et al.</td>
<td>UK</td>
<td>1997</td>
<td>998</td>
<td>26 (26.5)</td>
</tr>
<tr>
<td>Lin et al.</td>
<td>USA</td>
<td>1999</td>
<td>270</td>
<td>24 (8.9)</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>USA</td>
<td>2000</td>
<td>631</td>
<td>88 (14.0)</td>
</tr>
<tr>
<td>Wolff et al.</td>
<td>Germany</td>
<td>2000</td>
<td>359</td>
<td>40 (11.2)</td>
</tr>
<tr>
<td>Kosuda et al.</td>
<td>Japan</td>
<td>2002</td>
<td>1000</td>
<td>222 (22.2)</td>
</tr>
<tr>
<td>Salonia et al.</td>
<td>Italy</td>
<td>2006</td>
<td>1242</td>
<td>31 (2.5)</td>
</tr>
<tr>
<td>Huang et al.</td>
<td>Chinese Taipei</td>
<td>2006</td>
<td>342</td>
<td>97 (28.4)</td>
</tr>
<tr>
<td>Hirobe et al.</td>
<td>Japan</td>
<td>2007</td>
<td>366</td>
<td>28 (7.7)</td>
</tr>
<tr>
<td>Current study</td>
<td>Malaysia</td>
<td>2011</td>
<td>258</td>
<td>90 (34.9)</td>
</tr>
</tbody>
</table>

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+2.718

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 can 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...
Christopher Chee Kong Ho et al echoed by Lai et al. (2011) who suggested that the risk of having positive bone scans is 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 phosphatase (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.

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