Predictors of bone metastasis in pre-treatment staging of asymptomatic treatment-naive patients with prostate cancer

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Abstract

Background: There is no general consensus on the optimal criteria for the application of bone scintigraphy in screening of bone metastasis in patients with prostate cancer. Our study was conducted to assess the value of bone scan for pre-treatment staging of asymptomatic treatment-naive patients with prostate cancer.

Methods: A total of 203 consecutive asymptomatic and treatment-naive patients with prostate cancer (age: 67.6 ± 6.4 years) who were referred to our department for whole body bone scintigraphy were enrolled in the study. Three hours after intravenous injection of 20 mCi 99mTc-MDP, all patients underwent whole body bone scanning using a single head gamma camera. The planar images were supplemented with SPECT as needed for questionable abnormalities or those having uncertain location on planar images.

Results: The mean serum PSA levels, serum alkaline phosphatase (ALP) and Gleason score (GS) were 42.41 ± 37.1 ng/ml, 223.9 ± 129.9 IU/L and 6.7 ± 1.1, respectively. A total of 55 cases (27.1%) out of 203 patients had bone metastases.

The univariate analysis showed that serum PSA levels, GS and ALP were all significant predictors of bone metastases. However, only serum PSA and ALP levels were found to be independent predictors of bone metastasis in the multivariate logistic regression analysis. The combination of PSA and ALP (in which patients with either elevated PSA >20 ng/ml or elevated ALP were considered as positive) had the best screening value, with 98.2% sensitivity and 48.6% specificity.

Conclusion: Serum ALP screening can be employed as a tool to detect the subgroup of patients who are at high risk of bone metastases, while having a PSA of <20 ng/ml. 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.

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Predictores de metástasis óseas en la estadificación pre-tratamiento de pacientes asintomáticos con cáncer de próstata

Resumen

Introducción: No existe un consenso general en cuanto a los criterios óptimos para la utilización de la gammagrafía ósea para la detección de metástasis óseas en pacientes con cáncer de próstata. El objetivo de nuestro estudio fue determinar el valor de la gammagrafía ósea para la estadificación pretratamiento de pacientes con cáncer de próstata.

Métodos: Se incluyeron de forma consecutiva en el estudio 203 pacientes con cáncer de próstata, asintomáticos y sin tratamiento previo (edad: 67.6 ± 6.4 años) que fueron derivados a nuestro departamento para la realización de una gammagrafía ósea. A las 3 h de la inyección intravenosa de 20 mCi 99mTc-MDP se realizó la gammagrafía ósea con rastreo corporal total utilizando una gammacámara de un solo cabezal. Las imágenes planares fueron complementadas con una SPECT en caso necesario ante anormalidades que fueran cuestionadas o de localización incierta en la imagen planar.

Resultados: Los niveles de PSA en suero, fosfatasa alcalina (FAL) en suero y escala de Gleason fueron de 42.41 ± 37.1, 223.9 ± 129.9 y 6.7 ± 1.1, respectivamente. De los 203 pacientes, 55 casos (27,1%) tuvieron metástasis óseas.

El análisis univariable mostró que los niveles de PSA, escala de Gleason y FAL fueron todos predictores significativos para metástasis óseas, aunque en el análisis de regresión logística multivariable solo el PSA y la FAL fueron predictores independientes de la metástasis ósea. La combinación de PSA y FAL (en donde los pacientes con PSA elevado (> 20 ng/ml) o FAL elevada eran considerados como positivos) tuvo el mejor valor de detección con sensibilidad de 98,2% y especificidad de 48,6%.

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Introduction

Prostate cancer is the second leading cause of cancer related death among men.\(^1\) The appropriate treatment planning for these patients requires accurate staging of the disease, on which there is no universal consensus yet.\(^2\)-\(^4\) It is widely accepted that bone scan has a higher accuracy than skeletal radiography or serum alkaline phosphatase (ALP) regarding staging of the disease and detection of bone metastases.\(^5\)-\(^7\) So, until a decade ago, bone scan was a part of routine work up for newly diagnosed prostate cancer patients.\(^5\) However, bone scan, although still a useful modality, has been replaced widely by the readily available prostatic specific antigen (PSA) testing.\(^1\) Accordingly, referral of prostate cancer patients for bone scan has been done more selectively and those patients with minimal risk of bone metastases have been excluded from scintigraphic investigation. Such a referral modification can be explained by the physicians' effort to reduce cost and radiation burden of unnecessary and low yield testing.\(^1\) However, PSA testing lacks both the sensitivity and specificity to accurately detect bone metastasis.\(^4\)

Although both the American Urological Association (AUA) and the American College of Radiology (ACR) recommend application of bone scan in high-risk patients,\(^1,5,6\) based on the AUA's best practice statement, there is no room for a bone scan in an asymptomatic patient with localized disease and a PSA of $<20$ ng/ml.\(^1,5\) Guideline of the ACR, on the other hand, is more conservative and recommends application of bone scans as an integral part of patients' work-up, unless the PSA is $<10$ ng/ml.\(^1,6\) European Association of Urology (EAU) states that the best tool to screen skeletal metastasis is a bone scan; however, it may not be a necessary investigation in asymptomatic patients with well- or moderately differentiated tumors and the serum PSA level of $<20$ ng/ml.\(^7\) The guideline released by National Comprehensive Cancer Network (NCCN) supports application of bone scan for symptomatic patients and/or those with a life expectancy of $>5$ years and patients with T1 to T2 disease whose PSA level is $>20$ ng/ml or a Gleason score (GS) $\geq 8$.\(^8\) These disagreements partly originate from current discrepancies in the appropriate criteria to select patients for whole body bone scan screening and lack of clarification on the definition of high risk patient.\(^9\) Therefore, some authors believe that the recent drop in the utilization of bone scan in the work up of patients with prostate cancer is not justified by appropriate supportive evidence\(^1,3\) and has raised concerns that patients at highest risk might not be appropriately evaluated.\(^1\)

Our study was conducted to assess the value of bone scan for pre-treatment staging of asymptomatic treatment-naïve patients with prostate cancer.

Patients and methods

The study was done from May 2009 to February 2012. All consecutive patients with prostate cancer who were referred to our nuclear medicine department for a whole body bone survey were evaluated for possible inclusion in the study. Of this population, just those who were asymptomatic and treatment naïve were included in the study. Any kind of treatment (e.g. prostatectomy, anti-hormone therapy, or radiotherapy) was considered as the exclusion criteria. Serum PSA level and serum ALP during four weeks before or after bone scan was recorded for each patient. GS was recorded as provided by prostate biopsy. All patients gave informed consent to participate in the study. The study was approved by the committee on ethics, Isfahan University of Medical Sciences.

Imaging procedure

A commercial MDP kit [Iranian Atomic Energy Organization (IAEO), Tehran, Iran] was used. All labeling and quality control procedures were done according to the manufacturer's instruction. Three hours after intravenous injection of $20$ mCi$^{99m}$Tc-MDP, all patients underwent whole body bone scanning using a single head gamma camera (Scintron, Orbiter, US). The planar imaging supplemented with SPECT as needed for abnormalities that were questionable or of uncertain location on planar images. All bone scans were reported by an expert nuclear medicine physician. If the diagnosis of bone metastases was suspected, then additional imaging studies with computed tomography (CT) scanning or magnetic resonance imaging (MRI) were undertaken to confirm the final diagnosis.

Statistical analysis

The proportion of positive bone metastases were assessed according to patients' age, PSA level at the time of bone scanning, and Gleason score. Fisher's probability exact test was employed to compare the categorical parameters. Mann–Whitney's U-test was employed to compare the continuous parameters. Univariate and multivariate logistic regression analyses were done to evaluate predictors of bone metastasis. All the statistical analyses were performed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). A $P$ value of $<0.05$ was considered statistically significant.

Results

A total of 203 patients (age: $67.6 \pm 6.4$ years) were included in the final analysis. The mean serum PSA level, serum ALP and GS were $42.41 \pm 37.1$ ng/ml, $223.9 \pm 129.9$ IU/L and $6.7 \pm 1.1$, respectively. Out of 203 patients, 55 cases ($27.1\%$) had bone metastases. \(\) Table 1 elucidates the relationship between different ranges of serum PSA, presence of bone metastasis in bone scan, GS and ALP. Serum ALP level was significantly different between patients with and without metastasis, in all ranges of serum PSA (all $P$ values $<0.01$). The means of GS and quantitative PSA value were not significantly different among patients with and without metastasis status, except mean GS in the PSA range 20–50 ng/ml.

Univariate analysis showed serum PSA level, GS and ALP are all significant predictors of bone metastases (Table 2). However, in multivariate logistic regression analysis just quantitative serum PSA and ALP levels were found to be independent predictors of bone metastasis (Table 2).

Accuracy of PSA, ALP and GS for diagnosing bone metastases had examined using Receiver operating characteristic (ROC) curve (Fig. 1). The difference between AUC of PSA and ALP was not significant ($P$ value: 0.23), but both of them had significantly higher AUC than GS (both $P$ values $<0.05$). The combination of PSA and ALP (in which patients with either of elevated PSA $>20$ ng/ml) OR elevated ALP were considered as positive) had the best screening value, with
In Positive

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Table 1
The relationship between different levels of serum PSA with GS and ALP.

<table>
<thead>
<tr>
<th>Serum PSA level</th>
<th>Metastasis</th>
<th>Number of patients (%)</th>
<th>GS</th>
<th>P value</th>
<th>ALP</th>
<th>P value</th>
<th>Quantitative PSA value (ng/ml)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>Positive</td>
<td>6 (7.3%)</td>
<td>6.7 ± 0.5</td>
<td>0.09</td>
<td>345.3 ± 109.9</td>
<td>0.01</td>
<td>145 ± 5.7</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>76 (92.7%)</td>
<td>6.1 ± 1.0</td>
<td></td>
<td>168 ± 61.3</td>
<td></td>
<td>117.7 ± 5.1</td>
<td></td>
</tr>
<tr>
<td>≥ 20–50</td>
<td>Positive</td>
<td>14 (23.3%)</td>
<td>7.1 ± 1.0</td>
<td>0.04</td>
<td>322 ± 146.2</td>
<td>0.01</td>
<td>181.3 ± 75.1</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>46 (76.7%)</td>
<td>6.5 ± 0.9</td>
<td></td>
<td>181 ± 75.1</td>
<td></td>
<td>342.2 ± 7.9</td>
<td></td>
</tr>
<tr>
<td>≥ 50</td>
<td>Positive</td>
<td>35 (57.4%)</td>
<td>7.5 ± 0.9</td>
<td>0.51</td>
<td>365 ± 183.7</td>
<td>0.01</td>
<td>95.2 ± 32.3</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>26 (42.6%)</td>
<td>7.4 ± 0.9</td>
<td></td>
<td>186 ± 66.6</td>
<td></td>
<td>84.3 ± 23.7</td>
<td></td>
</tr>
</tbody>
</table>

A continuous quantitative value in ng/ml.

A dichotomous variable, with the patients divided into two groups of GS < 8 and GS ≥ 8.

Table 2
Predictors of bone metastasis in univariate and multivariate analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>OR</th>
<th>P value</th>
<th>Coefficient</th>
<th>SE</th>
<th>OR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>−0.01</td>
<td>0.03</td>
<td>0.99</td>
<td>0.73</td>
<td>−0.07</td>
<td>0.04</td>
<td>0.93</td>
<td>0.08</td>
</tr>
<tr>
<td>PSA</td>
<td>1.02</td>
<td>1.02</td>
<td>1.02</td>
<td>0.001</td>
<td>0.02</td>
<td>0.01</td>
<td>1.02</td>
<td>0.001</td>
</tr>
<tr>
<td>GS (quantitative value×)</td>
<td>0.87</td>
<td>0.18</td>
<td>2.40</td>
<td>0.001</td>
<td>0.32</td>
<td>0.28</td>
<td>1.37</td>
<td>0.25</td>
</tr>
<tr>
<td>GS (dichotomous$^d$)</td>
<td>1.62</td>
<td>0.36</td>
<td>5.04</td>
<td>0.001</td>
<td>0.73</td>
<td>0.59</td>
<td>2.08</td>
<td>0.22</td>
</tr>
<tr>
<td>ALP</td>
<td>0.02</td>
<td>0.003</td>
<td>1.02</td>
<td>0.001</td>
<td>0.02</td>
<td>0.003</td>
<td>1.02</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Fig. 1. Receiver Operating Characteristic (ROC) curves for PSA, ALP, and GS. The area under the curve [standard error (SE): 95% CI] for PSA, ALP, and GS are 0.81 (0.03: 0.76–0.88), 0.87 (0.03: 0.80–0.93), and 0.73 (0.04: 0.65–0.80), respectively. (a) Sensitivity and specificity of PSA for detection of bone metastasis at the best cut-point (33 ng/ml) was 83.6% and 69.6%, respectively. (b) Sensitivity and specificity of ALP for detection of bone metastasis at the best cut-point (286 IU/L) was 72.7% and 91.9%, respectively. (c) Sensitivity and specificity of GS for detection of bone metastasis at the best cut-point (6) was 80% and 51.4%, respectively.

sensitivity of 98.2% and specificity of 48.6%. Among those patients with serum PSA level less than 20 ng/ml and metastasis on bone scan, five patients had serum PSA levels between 10 and 20 ng/ml and just two patients had values of <10 ng/ml.

Discussion

Regarding the emergence of PSA testing, the proportion of low-risk patients has increased and the majority of prostate cancer patients do not show bone metastasis at the time of diagnosis. However, bone metastasis is the most unfavorable prognostic factor in these patients, and therefore, bone scintigraphy is still widely employed at the initial staging, even in asymptomatic patients with low stage and low PSA level.4 This trend among oncologists and urologists explain why we encounter a high number of referrals of asymptomatic prostate cancer patients to our department for a whole body bone investigation. Ritenour et al. reported the same issue in their patient population,7 which means a worldwide trend to refer patients for imaging staging of the disease, irrespective of patients’ risk estimate. Such a strategy will pose patients at increased risk of receiving unnecessary radiation burden and diagnostic expenses. Therefore, a more systematic patient selection approach for imaging staging is strongly recommended, which may lead to a significant reduction of superfluous costs for the health care system,8 as well as reduction of patients’ radiation.

It has been reported that the detection rate of bone metastases in newly diagnosed prostate cancer is influenced by three major factors, including PSA, stage and grade.14-16 In our study, PSA was found to be a significant predictor of bone metastasis, but it was not the case for GS. On the other hand, we found ALP as an independent marker of bone metastasis.

PSA, as a screening tool

In our study, the incidence of bone metastases in patients with a PSA <20 ng/ml was reasonably low. The 7.3% rate of bone metastasis in our patient population is consistent with the review of Katana et al. on the available reports, who stated that the incidence of bone metastasis in patients with a PSA level of less than 20 ng/ml ranges from 0.03 to 11.1%. Therefore, a bone scan can be spared for these patients at their initial staging, a conclusion which is supported by Tanaka et al.10; however, serum ALP screening can be employed as a tool to detect the subgroup of patients who are at increase risk of bone metastasis while having a PSA of <20 ng/ml (Table 1).

ALP

The main concern about the application of ALP as a screening tool for bone metastasis is the low specificity of the test. A report from Columbia showed a sensitivity of 83.8%, specificity of 78%, positive predictive value of 60% and negative predictive value of
92% for ALP in the detection of bone metastasis. However, in our study the specificity of test was at the level of >90%, which makes it more trustworthy. Regarding the acceptable sensitivity and the low cost of the test, it can be safely included in the screening approach to these patients. So for patients with a PSA <20 ng/ml, we recommend a bone scan, if the ALP is abnormal. The combination of PSA and ALP can be used to improve the predictability of bone metastasis in newly diagnosed patients with prostate cancer, without compromising the staging accuracy.

**GS, as a screening tool**

Kosuda et al. reported that bone scan can be omitted for patients with GS ≤ 6. On the other hand, the guideline by NCCN recommends that for patients with GS ≥ 8, a bone scan is appropriate. However, based on our study findings, GS is not a significant predictor of bone metastasis, and trusting to GS alone at its best cut off point (=6) can lead to missing at least 20% of patients with bone metastasis (Fig. 1). This can be partly explained by the discrepancies in the report of GS between pathologists.

**Conclusion**

Both the PSA level at diagnosis and serum ALP are important predictors of bone metastasis. Although the incidence of bone metastasis in patients with a PSA <20 ng/ml is low, to spare a bone scan at the initial staging of prostate cancer, adding serum ALP level in decision making may decrease the odds of missing patients with bone metastasis.

**Conflict of interest**

The authors declare that they have no conflict of interest.

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8. NCCN Clinical Practice Guidelines in Oncology/PM, Prostate Cancer Early Detection V.2.2010. www.nccn.org


