EXPRESSIONS AND CLINICAL SIGNIFICANCE OF PSA, ALP AND ASSOCIATED INDICATORS IN SERUM OF PROSTATE CANCER PATIENTS WITH OSSEOUS METASTASIS

ZHAO NI', HUI ZHOU', QING YANG', SONG OU'YANG', WEI LIN'

'Department of urology, the first affiliated hospital of the medical college, shihezi university Shihezi, Xinjiang, P.R.China. 832008 - 2Department of urology, The 3rd hospital of Chengdu, Chengdu Sichuan, P.R.China. 610031 - 3Department of blood transfusion, No.1 Hospital of Jilin University, two, Changchun, Jilin, P.R.China, 130000

ABSTRACT

Objective: To investigate the correlations of ALP, PSA and associated indicators (fPSA, fPSA/tPSA and PSAD) and osseous metastasis in prostate cancer, and the predictive value of these indicators for diagnosis of osseous metastasis of prostate cancer.

Methods: A retrospective study was conducted for 167 prostate cancer patients who were confirmed by needle biopsy of prostate gland or postoperative pathologic examination between September 2014 and August 2017. Osseous metastasis was diagnosed through ECT, X-ray, CT/MRI or bone biopsy, and we analyzed the correlations of ALP, PSA, fPSA, fPSA/tPSA and PSAD with the osseous metastasis of prostate cancer and their diagnostic value for osseous metastasis.

Results: In 183 patients, there were 114 with osseous metastasis (62.3%) and 69 with non-osseous metastasis (37.7%). In the osseous metastasis group, the levels of ALP, PSA and PSAD were significantly higher than those in the non-osseous metastasis group (p<0.01), while the difference in comparison of fPSA/tPSA between two groups showed no statistical significance (p>0.05). In patients with PSA>50 ng/mL, the incidence rate of osseous metastasis was significantly higher than that in those with PSA in concentrations between 20 and 50 ng/mL, 10 and 20 ng/mL and not higher than 10 ng/mL (p<0.05); for patients with ALP larger than 90 U/L, incidence of osseous metastasis was significantly elevated in comparison with that in patients with ALP in concentration not higher than 90 U/L (p<0.05); the rate of osseous metastasis in patients with PSAD>0.4 ng/ml/cm3 was significantly higher than that in those with PSAD≤0.4 ng/ml/cm3. With ALP>90 U/L, PSA>50 ng/mL and PSAD>0.4 ng/ml/cm3 as critical values, we analyzed the predictive values of ALP, PSA, PSAD, PSA+ALP, PSA+PSAD and PSA+PSAD+ALP in diagnosis of osseous metastasis in prostate cancer, and the results revealed that combined application of these indicators is more effective for positive and negative predictions in comparison with the single indicator, and combination of PSA+PSAD+ALP showed optimal outcomes in sensitivity (100%), specificity (79.17%), positive predictive value (91.38%) and negative predictive value (100%).

Conclusion: ALP, PSA and PSAD are the reliable indicators for evaluating the osseous metastasis in prostate cancer patients, while the combination of PSA, PSAD and ALP is conducive to prediction of prostate cancer. PSA<50 ng/mL, PSAD<0.4 ng/ml/cm3 and ALP<90 U/L can help physicians to rule out the osseous metastasis.

Keywords: Prostate cancer, osseous metastasis, prostate specific antigen, prostate-specific antigen density.

DOI: 10.19193/0393-6384_2018_6_279

Received March 30, 2018; Accepted June 20, 2018

Introduction

Prostate cancer (PCa) ranks 3rd only secondary to the bladder cancer and renal cancer in all malignancies in male genitourinary system. With atypical clinical symptoms, PCa shows few symptoms in early stage, and usually evolves into the progression stage when diagnosed. In some severe cases, there are almost 24% to 35% of PCa patients with metastasis at the time of diagnosis, in which osseous metastasis occupies around 70%. Diagnosis of osseous metastasis in PCa is significant for TNM staging, therapeutic protocols and prognosis of PCa. In this paper, with 167 PCa patients as subjects, we retrospectively analyzed the correlations of ALP, PSA and PSAD with the
osseous metastasis in PCa, and, through the combination analysis of indicators, we aimed to identify an optimal combination of indicators for diagnosis of osseous metastasis in PCa in an early stage.

**Data and methods**

**Subjects**

A retrospective study was performed for 277 PCa patients who were admitted to this hospital between September 2014 and August 2017. PCa diagnoses were confirmed through needle biopsy or postoperative pathologic examination. After a total of 94 patients with imperfect data or liver function lesion caused by ALP elevation were excluded, we analyzed the data of 183 patients, including the ALP, PSA and other indicators partly obtained from other 3A hospitals in this city. Among those patients, age ranged from 54 to 91 years old with an average of (73±8.21) years old; through ECT, X-ray, CT/MRI or biopsy, osseous metastasis was identified in 114 patients who were enrolled into the osseous metastasis group, while the remaining subjects were enrolled into the non-osseous metastasis group.

**Methods**

Diagnosis of osseous metastasis was confirmed through ECT, X-ray, CT/MRI or bone biopsy, and the levels of ALP, PSA, fPSA, fPSA/tPSA and PSAD were detected in patients in two groups. In addition, diagnostic values of these indicators were analyzed to figure out their correlations with osseous metastasis and the predictive values.

**Detection indexes**

**ALP**

Velocity method was applied with OLYMPUS AU5400 and AU640 Automatic Biochemical Analyzer and the corresponding reagent provided by OLYMPUS.

**PSA and fPSA**

Micro-particle enzyme immunoassay was carried out with ABBOTT Axsym Analyzer and the corresponding reagent provided by Abbott, and the normal reference value of PSA was set as not higher than 5.0 ng/mL.

**PSA**

Before test, patients were required to sustain the filling of bladder. Abdominal B ultrasonic examination was adopted to examine the cross section and vertical section, and the maximal transverse diameter, anterior-posterior diameter and vertical diameter were recorded, with which we aimed to identify the suspicious lesions or nodes. Measurement of volume was performed in accordance with Terris formula: volume (cm³) = Transverse diameter (cm) × anterior-posterior diameter (cm) × vertical diameter (cm) × 0.52. PSAD = tPSA/Prostate volume (cm³).

**Scanning protocols**

After patients took 99m Tc-MDP for 3 to 6 h, single photon emission computed tomography was performed with Diacam and Symbia T2 of Siemens to investigate the distribution of radioactivity in bones, and the results were verified by professionals.

**Diagnostic criteria of osseous metastasis**

From the images of bone scanning, patients with 2 or more sporadic sites of abnormally concentrated radioactivity or lesion; X-ray or CT/MRI images revealed lesions of bone destruction, and all benign lesions, including bone trauma, infection, arthritis or degenerative changes, were excluded; or the results were confirmed through bone biopsy.

**Statistical methods**

All data were processed by SPSS 15.0 software. Measurement data were presented by mean ± standard deviation (x̄±s), while Mann-Whitney U test was carried out for the intergroup comparison of means. In accordance with the levels of ALP, PSA, fPSA/tPSA and PSAD in serum, data were divided into groups, and chi-square test was performed. p<0.05 suggested that the difference had statistical significance.

**Results**

**ALP, PSA and PSAD in osseous metastasis group and non-osseous metastasis group**

In 167 PCa patients, the rate of osseous metastasis was 62.3% (104/167). Levels of ALP, PSA and PSAD in the osseous metastasis group were significantly higher than those in the non-osseous metastasis group (p<0.05), while differ-
ence in comparison of fPSA/tPSA between two groups showed no statistical significance (p>0.05; Table 1).

**Correlation between PSA and osseous metastasis in PCa**

Stratification analysis was performed by dividing the levels of PSA into following levels: ≤10 ng/mL, >10-20 ng/mL, >20-50 ng/mL and >50 ng/mL. For patients with levels of PSA as described before, incidence rates of osseous metastasis were 6.7%, 11.1%, 38.7% and 86.4%, respectively, and the rates were increased in a concentration-dependent manner. Comparisons between patients with PSA level higher than 50 ng/mL and other levels showed p<0.05, suggesting that the rate of osseous metastasis was significantly elevated for PSA>50 ng/mL (Table 2).

**Correlation of fPSA/tPSA with osseous metastasis in PCa**

With 0.18 of fPSA/tPSA as critical value, we found that there was no statistical significance in difference of the osseous metastasis between two groups (p>0.05; Table 3).

**Correlation of PSAD with osseous metastasis in PCa**

With 0.4 ng/mL/cm$^3$ of PSAD as a critical value, stratification analysis showed that in patients with PSAD>0.4 ng/mL/cm$^3$, the rate of osseous metastasis was significantly higher than that in those with PSAD ≤0.4 ng/mL/cm$^3$ (p<0.01; Table 4).

**Correlation between ALP and osseous metastasis in PCa**

Stratification analysis with 90 U/L of ALP as the critical value revealed that in patients with ALP>90 U/L, the rate of osseous metastasis was significantly higher than that in those with ALP≤90 U/L (p<0.01; Table 5).

**Correlations between combination of ALP, PSA and PSAD and the osseous metastasis in PCa**

According to the results of stratification analysis and with ALP>90 U/L, PSA>50 ng/mL and PSAD>0.4 ng/mL/cm$^3$ as critical values, we analyzed the predictive values of ALP, PSA, PSAD, ALP+PSA, PSA+PSAD and ALP+PSA+PSAD for diagnosis of osseous metastasis in PCa.

We found that PSAD had a higher sensitivity than ALP and PSA but with a poor specificity, while the specificities and positive predictive values were somehow increased in combinations of ALP+PSA and PSA+PSAD; the combination of PSA+PSA+ALP showed optimal outcomes in sensitivity (100%), specificity (79.17%), positive predictive value (91.38%) and negative predictive value (100%), respectively (Table 6).

---

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>ALP (U/L)</th>
<th>PSA (ng/mL)</th>
<th>fPSA/tPSA</th>
<th>PSAD (ng/mL/cm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteosarcoma metastasis group</td>
<td>114</td>
<td>166.0±199.70</td>
<td>808.69±1631.16</td>
<td>0.16±0.14</td>
<td>30.35±72.91</td>
</tr>
<tr>
<td>Non-osteosarcoma metastasis group</td>
<td>69</td>
<td>79.5±36.35*</td>
<td>63.9±155.89*</td>
<td>0.14±0.08</td>
<td>1.83±3.11*</td>
</tr>
</tbody>
</table>

Table 1: Comparisons of indicators between two groups (X±s).
Note: *p<0.05 vs. osteosarcoma metastasis group.

**Correlation of PSA and osseous metastasis in PCa**

Table 2: Comparison of the osseous metastasis among patients with varying levels of PSA in serum [n (%)].
Note: *p<0.05 vs. patients with level of PSA>50 ng/mL; #p<0.05 vs. patients with PSA between 20 and 50 ng/mL.

<table>
<thead>
<tr>
<th>PSA (ng/mL)</th>
<th>N</th>
<th>Osteosarcoma metastasis</th>
<th>Non-osteosarcoma metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>113</td>
<td>98 (86.7%)</td>
<td>15 (13.3%)</td>
</tr>
<tr>
<td>&gt;20-50</td>
<td>34</td>
<td>33 (38.2%)*</td>
<td>21 (61.8%)</td>
</tr>
<tr>
<td>&gt;10-20</td>
<td>20</td>
<td>2 (10%)*#</td>
<td>18 (90%)</td>
</tr>
<tr>
<td>≤10</td>
<td>16</td>
<td>1 (6.3%)*#</td>
<td>15 (93.7%)</td>
</tr>
</tbody>
</table>

**Correlation of fPSA/tPSA with osseous metastasis in PCa**

Table 3: Comparison of the osseous metastasis among patients with different fPSA/tPSA ratios [n (%)].

<table>
<thead>
<tr>
<th>fPSA/tPSA</th>
<th>N</th>
<th>Osteosarcoma metastasis</th>
<th>Non-osteosarcoma metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.18</td>
<td>51</td>
<td>34 (66.6%)</td>
<td>17 (33.4%)</td>
</tr>
<tr>
<td>≤0.18</td>
<td>132</td>
<td>80 (60.6%)</td>
<td>52 (39.4%)</td>
</tr>
</tbody>
</table>

**Correlation of PSAD with osseous metastasis in PCa**

Table 4: Comparison of the osseous metastasis among patients with different PSAD levels [n (%)].

<table>
<thead>
<tr>
<th>PSAD (ng/mL/cm$^3$)</th>
<th>N</th>
<th>Osteosarcoma metastasis</th>
<th>Non-osteosarcoma metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.4</td>
<td>153</td>
<td>110 (71.9%)</td>
<td>43 (28.1%)</td>
</tr>
<tr>
<td>≤0.4</td>
<td>30</td>
<td>3 (10%)*</td>
<td>27 (90%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ALP (U/L)</th>
<th>N</th>
<th>Osteosarcoma metastasis</th>
<th>Non-osteosarcoma metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;90</td>
<td>79</td>
<td>63 (79.8%)</td>
<td>16 (20.2%)</td>
</tr>
<tr>
<td>≤90</td>
<td>104</td>
<td>51 (49%)*</td>
<td>53 (51%)</td>
</tr>
</tbody>
</table>

Table 5: Comparison of the osseous metastasis among patients with different ALP levels [n (%)].

**Correlations between combination of ALP, PSA and PSAD and the osseous metastasis in PCa**

Table 6: The combination of PSA+PSA+ALP showed optimal outcomes in sensitivity (100%), specificity (79.17%), positive predictive value (91.38%) and negative predictive value (100%), respectively.
This method has a higher sensitivity in diagnosis of osseous metastasis in PCa, and can detect almost 95% to 97% of the osseous metastatic lesions. Generally, this method can detect the lesion of osseous metastasis about 3 to 6 months, or even 18 months earlier than X-ray imaging\(^6\). However, it increases the medical expense and also exacerbate the damages of radioactive drugs. Thus, to explore the ALP, PSA and associated indicators is significant for diagnosis of osseous metastasis in PCa.

In 183 PCa patients, there were 114 patients with osseous metastasis, and the rate of osseous metastasis was 62.3%. After patients were divided into the osseous metastasis group and the non-osseous metastasis group, the levels of ALP, PSA and PSAD were elevated obviously in patients with osseous metastasis (p<0.05), while no significant correlation was identified between fPSA/tPSA and osseous metastasis (p>0.05), suggesting that ALP, PSA and PSAD, instead of fPSA/tPSA, are effective indicators in diagnosis of osseous metastasis.

To further discover the correlation between PSA and osseous metastasis in PCa, we carried out stratification analysis by dividing these patients according to the levels of PSA (≤10 ng/mL, >10-20 ng/mL, >20-50 ng/mL and >50 ng/mL) to explore the availability of PSA changes in predicting the osseous metastasis in PCa, which was based on the discovery of Semjonow et al\(^7\) that patients with PSA>50 ng/mL already had extensive osseous metastasis. As is shown in Table 2, positive rate of osseous metastasis was increased against an elevation of PSA, suggesting that a higher PSA may indicate an increasing possibility of osseous metastasis. For PCa patients with PSA>50 ng/mL, a significant increase was identified in positive rate of osseous metastasis (86.7%, p<0.05) with specificity of 77.80%, suggestive of the onset of early osseous metastasis; while among patients with PSA≤10 ng/mL, osseous metastasis was identified in only 1 patient (6.3%); as for those with PSA≤20 ng/mL, 2 patients were diagnosed with osseous metastasis (10%).

These results indicated that osseous metastasis scarcely occurs in patients with PSA<20 ng/mL\(^8\). In terms of fPSA/tPSA, this parameter only shows its potential in identification between PCa and BPH at a critical value of 0.16\(^9\). To further investigate the predictive value of fPSA/tPSA for osseous metastasis, we set 0.18 as the critical value of fPSA/tPSA, and the results showed that the difference in fPSA/tPSA between two groups had no

<table>
<thead>
<tr>
<th>Indicators</th>
<th>n</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP</td>
<td>79</td>
<td>54.79</td>
<td>79.98</td>
<td>79.15</td>
<td>50.56</td>
</tr>
<tr>
<td>PSA</td>
<td>113</td>
<td>85.59</td>
<td>77.8</td>
<td>86.43</td>
<td>76.54</td>
</tr>
<tr>
<td>PSAD</td>
<td>153</td>
<td>97.14</td>
<td>58.08</td>
<td>72.12</td>
<td>88.91</td>
</tr>
<tr>
<td>ALP+PSA</td>
<td>64</td>
<td>84.11</td>
<td>88.39</td>
<td>91.36</td>
<td>79.15</td>
</tr>
<tr>
<td>PSA+PSAD</td>
<td>112</td>
<td>96.76</td>
<td>63.87</td>
<td>87.23</td>
<td>88.44</td>
</tr>
<tr>
<td>ALP+PSA+PSAD</td>
<td>64</td>
<td>100</td>
<td>79.19</td>
<td>91.4</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 6: Predictive values of ALP, PSA, PSAD and combinations of these indicators for diagnosis of osseous metastasis in PCa (%).

Discussion

PSA, a kind of glycoprotein only secreted by prostate epithelium, is characterized by the activity of neutral serine proteinase and a high tissue-specificity, instead of the carcinogen-specificity, and PSA is increased due to prostate hyperplasia and enlargement. However, in PCa tissues, PSA can be elevated significantly due to the excessive growth of tumor cells, damage to the normal structure of prostate gland and an increase in release of PSA from tissues to blood. Similarly, for patients with osseous metastasis, PCa cells migrated to the bones can reproduce enormously, leading to massive secretion of PSA into the blood, and further increases of PSA in serum. Currently, PSA has been regarded as one of the first-line methods in diagnosis of PCa, and also the best indicator in judging the prognosis and clues of osseous metastasis\(^2\).

Decreases of fPSA/tPSA ratio and increase in PSAD are more effective in identification of BPH and malignancy of PCa than PSA\(^1, 4\). Few reports concentrate on the correlations between the indicators, including PSA, fPSA/tPSA and PSAD and osseous metastasis. ALP, a kind of phosphohydrolase widely spread in organs, has a variety of isoenzymes and also an indicator with significance for diagnosis of osseous metastasis in PCa in addition to the lesions in liver and benign lesion of bones\(^3\).

In this paper, we analyzed retrospectively the correlations between ALP, PSA and associated indicators and the predictive values in diagnosis of osseous metastasis in PCa. In clinical practice, osseous metastasis in PCa is mainly diagnosed by the general bone scanning with nuclide, X-ray examination and further CT/MRI. Bone scan with nuclide can reveal the morphology, blood supply and metabolism of bones in different sites, through which location, determination and diagnosis of the lesions can be realized.

This method has a higher sensitivity in diagnosis of osseous metastasis in PCa, and can detect almost 95% to 97% of the osseous metastatic lesions. Generally, this method can detect the lesion of osseous metastasis about 3 to 6 months, or even 18 months earlier than X-ray imaging\(^6\). However, it increases the medical expense and also exacerbate the damages of radioactive drugs. Thus, to explore the ALP, PSA and associated indicators is significant for diagnosis of osseous metastasis in PCa.

In 183 PCa patients, there were 114 patients with osseous metastasis, and the rate of osseous metastasis was 62.3%. After patients were divided into the osseous metastasis group and the non-osseous metastasis group, the levels of ALP, PSA and PSAD were elevated obviously in patients with osseous metastasis (p<0.05), while no significant correlation was identified between fPSA/tPSA and osseous metastasis (p>0.05), suggesting that ALP, PSA and PSAD, instead of fPSA/tPSA, are effective indicators in diagnosis of osseous metastasis.

To further discover the correlation between PSA and osseous metastasis in PCa, we carried out stratification analysis by dividing these patients according to the levels of PSA (≤10 ng/mL, >10–20 ng/mL, >20–50 ng/mL and >50 ng/mL) to explore the availability of PSA changes in predicting the osseous metastasis in PCa, which was based on the discovery of Semjonow et al\(^7\) that patients with PSA>50 ng/mL already had extensive osseous metastasis. As is shown in Table 2, positive rate of osseous metastasis was increased against an elevation of PSA, suggesting that a higher PSA may indicate an increasing possibility of osseous metastasis. For PCa patients with PSA>50 ng/mL, a significant increase was identified in positive rate of osseous metastasis (86.7%, p<0.05) with specificity of 77.80%, suggestive of the onset of early osseous metastasis; while among patients with PSA≤10 ng/mL, osseous metastasis was identified in only 1 patient (6.3%); as for those with PSA≤20 ng/mL, 2 patients were diagnosed with osseous metastasis (10%).

These results indicated that osseous metastasis scarcely occurs in patients with PSA<20 ng/mL\(^8\). In terms of fPSA/tPSA, this parameter only shows its potential in identification between PCa and BPH at a critical value of 0.16\(^9\). To further investigate the predictive value of fPSA/tPSA for osseous metastasis, we set 0.18 as the critical value of fPSA/tPSA, and the results showed that the difference in fPSA/tPSA between two groups had no
Expressions and clinical significance of PSA, ALP and associated indicators in serum of prostate cancer ...

statistical significance (p>0.05), suggesting that fPSA/tPSA has a poor predictive value for diagnosis of osseous metastasis\(^{(10)}\). Besides, in this study, we found that in diagnosis of osseous metastasis in PCa, critical values of PSAD (>0.4 ng/mL/cm\(^3\)) and PSA (50 ng/mL) show promising sensitivity and NPV (11). In this paper, PPV in patients with PSAD>0.4 ng/mL/cm\(^3\) was significantly higher than that in those with PSAD≤0.4 ng/mL/cm\(^3\), indicating that PSAD may serve as an effective indicator for osseous metastasis. Wymenga et al\(^{(12)}\) believed that the level of ALP in serum exceeding 90 U/L and bone pain in PCa patients may suggest the possibility of osseous metastasis. Also, stratification analysis with 90 U/L as the critical value of ALP showed that in patients with ALP>90 U/L, the positive rate of osseous metastasis was significantly elevated, revealing that elevated ALP remains the effective indicator for diagnosis of osseous metastasis of PCa.

In this study, for patients with PSA≤10 ng/ml, only 1 patient with ALP>90 U/L (127 U/L) was still diagnosed with osseous metastasis. Thus, patients with ALP> 90 U/L should undergo bone scanning to minimize the rate of misdiagnosis regardless of the PSA values. For cases with ALP<90 U/L and PSA≤10ng/mL, no osseous metastasis was identified, suggestive of little possibility in osseous metastasis, and patients would not take any regular bone scanning protocols.

Talbot et al\(^{(13)}\) reported that combination of PSA and ALP in serum is conducive to the prediction of osseous metastasis in PCa. In this paper, we analyzed the predictive values of different combinations of indicators for diagnosis of osseous metastasis in PCa, and found that sensitivities of different indicators ranked as follows: PSAD > PSA > ALP; in addition, PSAD had a higher sensitivity and NPV than PSA\(^{(14)}\) but a lower specificity. PSAD with 0.4 ng/mL/cm\(^3\) as a critical value may increase the false positive rate in diagnosis of osseous metastasis. Combination of indicators showed more promising results than single use, and the optimal combination should be ALP+PSA+PSAD with the highest PPV (91.36%) and NPV (100%), indicating that combined application of indicators is more suitable for predicting the osseous metastasis in PCa. In addition, we also found that NPV could reach 100% in cases with ALP<90 U/L, PSA<50 ng/mL and PSAD<0.4 ng/mL/cm\(^3\).

Thus, combined application of three indicators can avoid the regular bone scanning protocols, which can not only reduce the medical expense, but also scarcely increase the misdiagnosis rate of osseous metastasis in PCa. Moreover, patients can be protected from the damages from rays, radioactive matters and intravenous injection of drugs.

In conclusion, ALP, PSA and PSAD are reliable indicators for evaluating the osseous metastasis in PCa patients, and combined application of these indicators has a more practical significance in clinical practice.

References


___

Corresponding author
WEI LIN
Shanghai Changning Maternity & Infant Health Institute
Andrology Department, No. 773, Wuyi Road, Changning District, Shanghai, P.R. China. 200051
Email: shlinwei123@163.com (China)