Relationship Between Bone Scintigraphy Results and Gleason Scores and Prostate-Specific Antigen Levels

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Abstract

Introduction: We aimed to determine the relationship between bone scintigraphy results and Gleason score (GS) and prostate-specific antigen (PSA) levels in the detection of bone metastases in patients diagnosed with prostate cancer. Further, the predictive values of PSA levels and GSs were determined using bone scintigraphy.

Methods: Seventy-three patients diagnosed with prostate cancer and who underwent bone scintigraphy for staging at our department between 2013 and 2015 were enrolled. The records of these patients were retrospectively reviewed for determining bone scintigraphy results, GSs, and PSA levels. The patients were grouped based on PSA levels, GSs, and bone scan results, and the relationship between bone scintigraphy results and PSA levels and GSs was examined.

Results: Based on bone scintigraphy results, 39.7% of the patients had bone metastases. When GSs and PSA levels were independently considered, bone metastases were found significantly more often in patients with PSA levels of >20 ng/mL and GSs of ≥8. When GSs and PSA levels were combined, bone metastases were found significantly less often in patients with PSA levels of ≤20 ng/mL and GSs of ≤6.

Conclusion: The combination of GS and PSA levels may be helpful for the necessity of bone scintigraphy in patients with prostate cancer, but it should be noted that it is also important to conduct a patient-specific assessment using bone scintigraphy in patients with prostate cancer.

Keywords: Prostate cancer, bone scintigraphy, gleason score, prostate-specific antigen

Introduction

Prostate cancer (PCa) is the most common non-cutaneous cancer in men, especially in the U.S. and European countries, although it is seen at various frequencies depending on genetic and regional differences (1, 2). Because the surgical treatment is the most effective method for localized PCa, accurate staging in patients is very important in terms of treatment and therefore survival morbidity. The most common distant metastasis in PCa is bone metastases, and the majority of them have osteoblastic characteristics, and they can be detected with high accuracy through the whole-body bone scintigraphy with the technetium 99 m-methylene diphosphonate (Tc99m-MDP). Although scintigraphic method has advantages such as high sensitivity and a full body scanning in one step; due to their low specificity and cost disadvantages, there is still no clear consensus in all countries to use it in staging before the treatment in newly diagnosed patients with prostate cancer. If the prostate-specific antigen (PSA) is ≤20 ng/mL, the Gleason score (GS) is ≤7, and the patient has no additional complaint, there is no need for scintigraphic imaging for bone metastasis according to the guidelines of prostate cancer of the American and European Urology associations; however the prostate cancer guideline of the Japanese Urology Association does not accept this view (3-5). While the National Comprehensive Cancer Network (NCNN) recommends bone scintigraphy in clinical T3, T4 stage patients or in patients with bone symptoms, it has the opinion that bone scintigraphy should be performed if the PSA value is above 10 ng/mL or GS value is 8 or above in patients with the stage of T1 or T2 (6). As can be understood from these, it is controversial in which cases bone scintigraphy should be used in patients with PCa diagnosis.

We aimed to reveal the relationship between bone scintigraphy results and the levels of GS and PSA in terms of the determination of metastasis in patients with PCa and to provide information about the necessity of using bone scintigraphy according to the results obtained.

Methods

In our study, scintigraphic images and file records (anamnesis, physical examination, PSA, GS, and radiological examination results, if any) of male patients who were histopathologically diagnosed with PCa and who came to our hospital’s nuclear medicine department for whole-body bone scin-
tigraphy in order to have a bone metastasis scan between March 2013 and January 2016 were examined retrospectively. Patients who were included in the study prior to bone scintigraphy were informed and their informed consents were received. Ethics committee approval was obtained from the medical faculty of our university. Patients were included in the study if the period between their histopathological diagnosis and the whole-body bone scintigraphy was 1 month. The patients who were assessed as suspicious in terms of the results of the whole-body bone scintigraphy, the patients with other known or suspected malignancies, the patients with a history of trauma/accident/fracture up to 6 months before, and the patients receiving hormonotherapy were not included in the study. Considering these criteria, a total of 73 male patients were included in the study. Whole-body bone scintigraphy imaging was performed 2–4 hours after 740 Mega Becquerel (MBq) Tc99 m-MDP intravenous injection by providing a good hydration with a dual-detector Gamma camera device (Symbia E; Siemens Medical Solutions, IL, USA) using low-energy, high-resolution collimators (LEHR). In terms of metastasis in bone scintigraphy, the patients were divided into two groups as “those with no bone metastasis (BM−)" and “those with bone metastasis (BM+).” PSA 0.4 ng/dl was accepted as the normal value range. According to PSA values, the patients were divided into four groups as PSA-I: 0–≤10 ng/mL; PSA-II: >10–≤20 ng/mL; PSA-III: 20–≤100 ng/mL, and PSA-IV: >100 ng/mL. According to the results of GS, they were grouped into GS-I (those with GS≤6), GS-II (those with GS=7), and GS-III (those with GS ≥ 8).

Statistical analysis

Analysis of the data was performed using PASW® Statistics 18 software (SPSS Inc., Chicago, IL, USA). As descriptive statistical methods, number, percentage, and mean±standard deviation were used for the categorical data, and the mean±standard deviation values were used for the age in the evaluation of the data. In the groups determined according to PSA and GS values, the incidence of bone metastasis was compared using the Student t test and Chi-square test. Statistically, p<0.05 was considered significant.

Results

For the 73 male patients we included in our study, the mean age was 51–82 years (mean: 65.6±10.1 y), the PSA value ranged from 5 to 278 ng/mL (mean: 48.6±14.7 ng/mL), and the GS value ranged from 3 to 10 (mean: 6.7±0.8).

According to the bone scintigraphy, while 29 patients (39.7%) had bone metastasis, no bone metastasis was found in 44 (60.2%) patients. The mean age of the group without bone metastasis (BM−) was 63.3±9.7 y and the mean age of the group with bone metastasis (BM+) was 66.1±11.2 y; there was no statistically significant difference between the two groups in terms of age (p=0.76).

When the whole study group was examined according to PSA levels, there were six patients in the first group (PSA: 0–≤10 ng/mL), 17 patients in the second group (PSA-II: >10–≤20 ng/mL), 39 patients in the third group (PSA-III: >20–≤100 ng/mL), and 11 patients in the fourth group (PSA-IV: >100 ng/mL).

When PSA levels were examined separately in patients with BM− and BM+, six of the patients with BM− were found in group 1, 13 in group 2, 23 in group 3, and 2 in group 4; and of the patients with BM+, 4 were in group 2, 16 were in group 3, and 9 were in group 4. As noted in the results, no bone metastasis was observed in any of the 6 patients in Group 1 with a PSA level of less than 10 ng/mL. The rates of bone metastasis in patients that were divided into four groups according to PSA levels are shown in Table 1.

The distribution of PSA values in groups with and without bone metastasis: When evaluated separately for the other three groups (group 2, group 3, and group 4), no statistically significant difference was observed (p=0.06 for group 2, p=0.19 for group 3, p=0.21 for group 4).

When the presence of bone metastasis was assessed after the PSA level was grouped as 0–≤20 and >20 ng/mL, bone metastasis was statistically significantly higher in the group with 20 ng/mL (p=0.008). The incidence of bone metastases in patients divided into two groups according to PSA levels is shown in Table 2.

When all patients were examined according to GS values, 34 patients were in GS-I group (those with GS≤6), 18 patients in GS-II group (those with GS=7), and 21 patients in GS-III group (those with GS>7). When GS values were examined separately in patients with BM− and BM+: While 29 of the patients with BM− were in GS-I group, 10 in GS-II group, and 5 in GS-III group; of the patients with BM+, 5 were in GS-I group, 8 in GS-II group, and 16 were in GS-III group. When GS values were assessed for each group in terms of bone metastasis: While the difference that was observed in GS-I and GS-III was statistically significant (p<0.0001), the difference in GS-II was not statistically significant (p=0.63). The incidence of bone metastasis in patients who were separated into three groups according to GS values is shown in Table 3.

By combining the PSA and GS values, the patients were again classified as: those with PSA >20 ng/mL and GS≤6 (combined group 1), those with PSA>20 ng/mL and GS>6 (combined group 2), those

| Table 1. Bone metastasis prevalence rates in patients who were divided into four groups according to PSA levels |
|---------------|------------------|------------------|------------------|------------------|
| Group (PSA: 0–≤20 ng/mL) | First group | Second group | Third group | Fourth group |
| BM+(n: 29) | 0 (0%) | 4 (5.5%) | 16 (21.9%) | 9 (12.3%) |
| BM -(n: 44) | 6 (13.6%) | 17 (38.6%) | 23 (52.3%) | 2 (4.6%) |
| Total (n: 73) | 6 (8.2%) | 23 (31.5%) | 39 (53.4%) | 11 (15.1%) |
| n: number of patients; PSA: prostate specific antigen; BM+: there is bone metastasis; BM−: there is no bone metastasis; ng / ml: nanogram / milliliter |

| Table 2. Bone metastasis prevalence rates in patients who were divided into two groups according to PSA levels |
|---------------|------------------|------------------|
| Grup (PSA: 0–≤20 ng/mL) | 1. grup | 2. grup |
| BM+(n: 29) | 4 (5.5%) | 25 (34.2%) |
| BM -(n: 44) | 19 (26.0%) | 25 (34.2%) |
| Total (n: 73) | 23 (31.5%) | 50 (68.5%) |
| n: number of patients; PSA: prostate specific antigen; BM+: there is bone metastasis; BM−: there is no bone metastasis; ng / ml: nanogram / milliliter |
Table 3. Bone metastasis prevalence rates in patients who were divided into three groups according to GS values

<table>
<thead>
<tr>
<th>Group</th>
<th>GS-I (GS ≤ 6)</th>
<th>GS-II (GS = 7)</th>
<th>GS-III (GS ≥ 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM+ (n: 29)</td>
<td>5 (6.8%)</td>
<td>8 (10.9%)</td>
<td>16 (21.9%)</td>
</tr>
<tr>
<td>BM- (n: 44)</td>
<td>29 (39.7%)</td>
<td>10 (13.7%)</td>
<td>5 (6.9%)</td>
</tr>
<tr>
<td>Total (n: 73)</td>
<td>34 (46.5%)</td>
<td>18 (24.6%)</td>
<td>21 (28.8%)</td>
</tr>
</tbody>
</table>

n: number of patients; GS: Gleason score; BM+: there is bone metastasis; BM-: There is no bone metastasis

Table 4. Bone metastasis prevalence rates in groups in which PSA and GS values were combined

<table>
<thead>
<tr>
<th>Group</th>
<th>Combined group 1</th>
<th>Combined group 2</th>
<th>Combined group 3</th>
<th>Combined group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM+ (n: 29)</td>
<td>6 (8.2%)</td>
<td>15 (20.6%)</td>
<td>3 (4.1%)</td>
<td>5 (6.9%)</td>
</tr>
<tr>
<td>BM- (n: 44)</td>
<td>4 (5.5%)</td>
<td>2 (2.7%)</td>
<td>29 (39.7%)</td>
<td>9 (12.3%)</td>
</tr>
<tr>
<td>Total (n: 73)</td>
<td>10 (13.7%)</td>
<td>17 (23.3%)</td>
<td>32 (43.8%)</td>
<td>14 (19.2%)</td>
</tr>
</tbody>
</table>

n: number of patients; PSA: prostate specific antigen; GS: Gleason score; BM+: there is a bone metastasis; BM-: there is no bone metastasis

Figure 1. BM+: there is bone metastasis; BM-: there is no bone metastasis; Combined group 1: patients with PSA value >20 ng/mL and GS ≤ 6; Combined group 2: patients with PSA value >20 ng/mL and GS > 6; Combined group 3: patients with PSA value ≤20 ng/mL and GS value ≤6; Combined group 4: patients with PSA value ≤20 ng/mL and GS value >6

Discussion

PCa is one of the most common malignancies in males worldwide, although the incidence varies depending on regional and genetic differences. As is the case with other malignancies, in the treatment of PCa, it is also important to be able to make a correct staging of the disease.

It is a known fact that distant metastases of PCa occur most commonly in bones and generally have osteoblastic characteristics. Tc99m-MDP full-body bone scintigraphy is used extensively in the detection of bone metastases of PCa because it has a high sensitivity and enables the scan of the whole body in one step. Although osteolytic metastases in PCa are not seen frequently, it is important to remember that the sensitivity of Tc99m-MDP whole-body bone scintigraphy is low to show osteolytic bone metastases. Hybrid imaging systems such as single-photon emission computed tomography (SPECT)/CT, developed by adding CT technique to conventional gamma cameras, provide additional contributions to the detection of lesions. In addition, many studies have shown that 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging has higher sensitivity, specificity, and accuracy rates in the detection of osteolytic metastases. There are also studies showing that 68gallium-prostate-specific membrane antigen (68Ga-PSMA)-PET/CT imaging, which has been widely used in our country in recent years, is superior to bone scintigraphy in detecting bone metastases (osteoblastic osteolytic). Even though we could not use these methods in our study, we aimed to increase the diagnostic accuracy of bone scintigraphy by not involving patients suspected of bone metastasis.

Bone metastasis was detected in 39.7% of the patients included in our study; while it is similar to the results obtained in some studies in Asian countries (7, 8), it is higher than some studies done in America and Europe (9, 10). Although these studies are thought to be different from each other and from our study in terms of design and evaluation parameters, and thus the results may differ, our findings are consistent with the fact that bone metastases of PCa are more frequently encountered in Asian societies (although seen less frequently than in Europe).

The detection of the presence of bone metastases is crucial because it leads to changes in the form of treatment and in the survival morbidity rates of patients. Although there are many studies conducted with different cutoff values in which PSA levels, GS values, and the combination of these two parameters are used in order to predict bone metastases, there are different guidelines for communities and countries for the investigation of bone metastases.

When we assessed the presence of bone metastasis according to PSA levels in our study, while no bone metastases were detected in patients with a PSA level of less than ≤10 ng/mL, bone metastasis was found in patients with a PSA level of 10–20 ng/mL at a rate of 15.4%, and these values are similar to the study of Janane et al. (11). When we assessed the presence of bone metastasis according to PSA levels in our study, while no bone metastases were detected in patients with a PSA level of less than ≤10 ng/mL, bone metastasis was found in patients with a PSA level of >10–20 ng/mL at a rate of 5.5%, and these values are similar to the study of Janane et al. (11). When the presence of bone metastasis was assessed by grouping the PSA levels as 0–≤20 and >20 ng/mL, the incidence of bone metastasis was statistically significantly higher in the group with >20 ng/mL. These values were, respectively, 5.5% and 34.2% and this was found consistent with the studies conducted by determining

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the cutoff value of the PSA level as 20 ng/mL (8, 12). In the study conducted by Zaman et al. (7), it was reported that the incidence of bone metastasis was higher in patients with a PSA level below 20 ng/mL.

As is seen, PSA levels are a decisive parameter for bone metastases, but it is not clear what the cutoff value should be. However, according to our study, we can say that PSA levels below 10 ng/mL do not pose a significant risk for bone metastasis and do not require bone scintigraphy, which also supports many other studies (8, 13-15).

However, it should not be forgotten that considering PSA levels alone is not enough to predict bone metastasis. It has been reported in the NCCN prostate cancer guidelines that clinical staging and GS values could also be used for the indication of metastasis scan with bone scintigraphy. Although there is accepted information that GS values are deterministic about capsular invasion and lymph node metastasis, its decisive role in predicting bone metastasis is not clear. In this regard; when we examined the GS values in our study, they were found as ≤6 in 5 of 29 (17%, 2) patients with bone metastases, as 7 in 8 of the 29 (27.6%) of them, and >8 in 16 of 29 (55.2%). These results suggest that the incidence of bone metastasis is very high in patients with a GS >6 and bone scintigraphy should be performed, and they are compatible with other studies (16, 17). On the other hand, when we examine our study which is based on the studies and guidelines suggesting that bone scintigraphy is appropriate for patients with GS≥8, it is understood that 44.9% (13/29) of patients with bone metastasis can be missed out.

In addition to the studies in which PSA and GS values are separately assessed to predict bone metastasis in PCa, there is also a number of studies in the literature in which both parameters are combined and the evaluation is made in this way, which is suggested to be more useful in predicting bone metastases (7, 18, 19).

When we investigated our study by combining PSA (>20 and ≤20 ng/mL) and GS (≥6 and ≤6) values (these values were determined in the direction of the previous studies and European and American prostate cancer guidelines by taking into account the values of patients in our study group), while the bone metastasis was found as the highest in the group (combined group 2) with PSA value >20 ng/mL and GS>6, it was found as the lowest in the group (combined group 3) with PSA value ≤20 ng/mL and GS≤6. When these ratios were compared according to the patients with bone metastasis and to the whole group, they were 51.7% (15 of 29), 20.6% (15 of 73), 10.3% (3 of 29), 4.1% (3 of 73), respectively, for the combined group 2 and combined group 3.

While the rate of those with and without bone metastasis was found as 4.1% and 39.7% in the combined group 2 with PSA ≤20 ng/mL and GS≥6, when we compared PSA and GS values by examining separately, the rate of those with and without bone metastasis was found to be 5.5% and 26.0% according to only PSA value ≤20 ng/mL, and the rate of those with and without metastasis was found to be 12.3% and 45.2% according to only GS value ≤6.

In accordance with these results, it has been suggested that the grouping as PSA≤20 ng/mL and GS≥6 would be a more useful method to distinguish between those with and without bone metastasis than in the method in which both parameters are separately evaluated, and therefore it would be more appropriate to determine the indications for bone scintigraphy according to these parameters especially in asymptomatic patients in terms of cost and accessibility factors. On the other hand, apart from the data we have obtained; factors such as the necessity of modifying these combined values on the basis of community, the possibility of bone metastases beyond these ranges of values even though it is low, the difficulty in the follow-up of socioeconomic-based patients as in our country, and the advantage of a baseline study in the follow-up of patients require bone scintigraphy in patients diagnosed with PCa.

The basic restrictive elements of our study are that it was a retrospective and single-centered study, that the number of cases was limited, that the diagnosis of bone metastasis could not be confirmed by histopathologic or other radiological methods but only by scintigraphy, that the imaging was performed with a conventional gamma camera (hybrid systems with higher diagnostic accuracy such as SPECT/CT could not be used), and that the other laboratory findings [alkaline phosphatase (ALP), calcium level] associated with bone metastasis could not be examined. But despite these limitations, we have found that the results we obtained are mostly compatible with the literature.

**Conclusion**

We believe that evaluating through the combination of PSA and GS levels may be useful in predicting PCa’s bone metastases and in determining the necessity of using bone scintigraphy, especially in asymptomatic patients. However, it should be kept in mind that it is also important to make patient-based evaluation because of the insufficiency of these parameters in predicting, the high incidence of bone metastases in PCa and the difficulties in the follow-up of the patients newly diagnosed with PCa.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Namık Kemal University School of Medicine.

**Informed Consent:** Informed consent was not received because data analysis for this study was taken retrospectively.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** No conflict of interest was declared by the author.

**Financial Disclosure:** The author declared that this study has received no financial support.

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