Study of the Usefulness of Bone Scan Index Calculated From 99m-Technetium-Hydroxymethylene Diphosphonate (99mTc-HMDP) Bone Scintigraphy for Bone Metastases from Prostate Cancer Using Deep Learning Algorithms

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Study of the usefulness of bone scan index calculated from 99m-technetium-hydroxymethylene diphosphonate (99mTc-HMDP) bone scintigraphy for bone metastases from prostate cancer using deep learning algorithms

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Abstract

Aim

We developed a method in collaboration with the Tokyo University of Agriculture and Technology to calculate bone scan index (BSI) employing deep learning algorithms with bone scintigraphy images using $^{99m}$technetium-hydroxymethylene diphosphonate ($^{99m}$Tc-HMDP). We used a convolutional neural network (CNN) enabling the simultaneous processing of anterior and posterior bone scintigraphy images named CNNapis.

Background

BSI calculated from bone scintigraphy using $^{99m}$technetium-methylene diphosphonate ($^{99m}$Tc-MDP) is used as a quantitative indicator of metastatic bone involvement in bone metastasis diagnosis, therapeutic effect assessment, and prognosis prediction. However, the BONE NAVI, which calculates BSI, only supports bone scintigraphy using $^{99m}$Tc-MDP.

Objective

The purpose of this study is to investigate the usefulness of the BSI calculated by CNNapis as bone imaging and bone metabolic biomarkers in patients with bone metastases from prostate cancer.
Method

At our hospital, 121 bone scintigraphy scans using $^{99m}$Tc–HMDP were performed and analyzed to examine bone metastases from prostate cancer, revealing the abnormal accumulation of radioisotope (RI) at bone metastasis sites. Blood tests for serum prostate-specific antigen (PSA) and alkaline phosphatase (ALP) were performed concurrently. BSI values calculated by CNNapis were used to quantify the metastatic bone tumor involvement. Correlations between BSI and PSA and between BSI and ALP were calculated. Subjects were divided into four groups by BSI values (Group 1, 0 to <1; Group 2, 1 to <3; Group 3, 3 to <10; Group 4, >10), and the PSA and ALP values in each group were statistically compared.

Result

Patients diagnosed with bone metastases after bone scintigraphy were also diagnosed with bone metastases using CNNapis. BSI corresponding to the range of abnormal RI accumulation was calculated. PSA and BSI ($r = 0.2791$) and ALP and BSI ($r = 0.6814$) correlated positively. Significant intergroup differences in PSA between Groups 1 and 2, Groups 1 and 4,
Groups 2 and 3, and Groups 3 and 4 and in ALP between Groups 1 and 4, Groups 2 and 4, and Groups 3 and 4 were found.

Conclusion

BSI calculated using CNNapis correlated with ALP and PSA values and is useful as bone imaging and bone metabolic biomarkers, indicative of the activity and spread of bone metastases from prostate cancer.

Keywords

BSI, $^{99m}$Technetium-hydroxymethylene diphosphonate, PSA,
Prostate cancer, Bone metastases, convolutional neural network,

Running header

Usefulness of bone scan index calculated from $^{99m}$Tc–HMDP bone scintigraphy using deep learning algorithms
Introduction

Bone scintigraphy is widely used to examine bone metastases from malignant diseases, including prostate cancer. The extent of disease (EOD) is known as a method of classifying the extent of bone metastases from prostate cancer [1]. However, in most patients with multiple bone metastases, the EOD from visual assessment does not accurately evaluate the extent of metastatic bone tumor involvement and response to treatment [2]. Therefore, in 1997, Erdi et al. at the Memorial Sloan Kettering Cancer Center in the United States proposed the bone scan index (BSI), a quantitative indicator for calculating the percentage of the composition ratio of abnormal uptake of radioisotope (RI) accumulated in bone tumor lesions, including bone metastases, relative to that of the entire skeleton [3]. In 2008, Sadik et al. developed software to automatically calculate the BSI using an artificial neural network, and this software was placed on the market by EXINI Diagnostics, Sweden [4, 5]. Currently, the BSI calculated from bone scintigraphy using $^{99m}$technetium-methylene diphosphonate ($^{99m}$Tc–MDP) has been recognized as an
imaging biomarker that is useful in the diagnosis of bone metastases, assessment of therapeutic effects, and prediction of prognosis [6, 7]. Fig. 1 shows the structural formula of $^{99m}$Tc-MDP. However, BSI can be calculated only for bone scintigraphy using $^{99m}$Tc-MDP at this time. BSI cannot be calculated by bone scintigraphy using $^{99m}$ technetium-hydroxymethylene diphosphonate ($^{99m}$Tc-HMDP). It is considered useful to calculate BSI from bone scintigraphy using $^{99m}$Tc-HMDP.

Together with the Tokyo University of Agriculture and Technology, we have been exploring a new algorithm to calculate BSI from bone scintigraphy using $^{99m}$Tc-HMDP. $^{99m}$Tc-HMDP exists as a chelate compound composed of methane-1-hydroxy-1,1-diphosphonic acid disodium (Fig. 2a) and technetium oxide ion as a chemical structure shown in Fig. 2b.

In the present study, we focused on a deep learning algorithm suitable for image analysis and determined a method using a convolutional neural network (CNN) to process bone scintigraphy [8]. This CNN is characterized by the feature of processing anterior and posterior bone scintigraphy images simultaneously and was thus named CNNapis. CNNapis, which we developed, uses a CNN to recognize the skeletal anatomy and a CNN to
detect abnormal RI accumulation. The candidate algorithms for CNNapis were the Multi Atlas method, U-Net and Butterfly-Net. In order to examine the algorithm corresponding to CNNapis, we conducted comparative study using Butterfly-Net, Multi Atlas method and U-Net. Butterfly-Net has an average accuracy of 3.9 points higher than the Multi Atlas method for bone anatomy recognition, and the processing speed is 300 times faster. The processing speed of Butterfly-Net is comparable to that of U-Net, but errors are reduced by 10 to 20% in highly integrated detection. As these reasons, Butterfly-Net was applied to CNNapis. For deep learning, $^{99m}$Tc-HMDP bone scintigraphy images were adopted as training data. The CNN that learned from those training data then analyzed the bone scintigraphy scans and calculated the BSI. The objective of our study was to investigate the usefulness of the BSI calculated by CNNapis as bone imaging and bone metabolic biomarkers for bone metastases.

Material and methods

1. Patients
During the period from May 2017 to May 2019 at our hospital, 451 bone scintigraphy scans using $^{99m}$Tc-HMDP were performed to examine for bone metastases from prostate cancer. Of the 451 bone scintigraphy scans, 121 scans, as well as computed tomography or MRI scans, established a diagnosis of bone metastases. All 121 scans were included in the study. The 121 scans were performed in 70 patients whose serum prostate-specific antigen (PSA) and alkaline phosphatase (ALP) levels were measured within 2 weeks following bone scintigraphy. Patient ages ranged from 51 to 94 years with a mean age of 73.9 years. Gleason scores were measured in 64 patients, ranging from 6 to 10 with a mean score of 8.46. Patient characteristics are shown in Table 1. Of the 70 patients, 12 were previously untreated patients. Other than bone metastases, intrapelvic lymph node metastases were found in 16 patients; intrapelvic lymph node and lung metastases were found in one patient; lung metastases were found in one patient; and intrapelvic lymph node, lung, and liver metastases were found in one patient. This was a retrospective study and the results of routine laboratory tests were used as clinical data.
We obtained written informed consent from all the participants in accordance with the Code of Ethics of the World Medical Association. All procedures performed in this study were in accordance with the ethical standards of our institutional research committee and with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

This is a retrospective study that uses basic patient information, blood test date and nuclear medicine imaging data. Follows the Helsinki Declaration of 1975, revised in 1983 (Declaration of Helsinki: ethical principles for medical research involving human subjects).

Patients' human rights are respected. It is possible to refuse to participate in this study, and even if the patient declines to participate in the study, the patient will not suffer any disadvantages related to medical treatment.

This study has been approved by the Ethics Committee sponsored by the Graduate School of Medicine, Osaka City University, under the name of “Validation of an automated diagnostic system for abnormal accumulation sites in nuclear medicine images, certification number 2019-40”.

2. Blood tests

Serum PSA and ALP levels were measured. Normal ranges were 0–4.0 ng/mL for PSA and 106–322 U/L for ALP in our hospital.

3. Bone scintigraphy

The whole-body anterior and posterior bone scan images were acquired within 3 to 5 hours of intravenous injection of 740 MBq $^{99m}$Tc-HMDP. The imaging devices employed were an ADAC Forte and Phillips Bright view X equipped with low-energy high-resolution collimators. The imaging parameters of the Forte were a scan speed of 20 cm/min, $1024 \times 1024$ matrix, and a 140-keV photopeak with a 20% window. Those of the Bright view X were a scan speed of 20 cm/min, $1024 \times 512$ matrix, and a 140-keV photopeak with a 20% window.

4. Deep Learning

CNNapis utilizes two CNNs that learned from training data for deep learning [8]. One of the CNNs performs a skeletal anatomy recognition
process using the bone scintigraphy images. The other CNN detects abnormal RI accumulation. The BSI can be calculated by combining the two results.

4.1. Anatomical structure recognition process

The BSI was calculated at 12 sites: skull, sternum, cervical vertebrae, thoracic vertebrae, lumbar vertebrae, sacra, clavicles, scapulae, humeri, ribs, pelvis, and femurs [9].

The bone scintigraphy to be processed is applied to 12 skeletal atlas images by deep learning, and the fitted image is subjected abnormal accumulation detection processing as explained in chapter 4.2.

The CNN for the skeletal anatomy recognition process was prepared using the training data obtained by identifying anatomical location information from the bone scintigraphy images of 246 Japanese subjects with no skeletal abnormalities taken at Osaka City University Hospital.

4.2. Process for detecting abnormal RI accumulations
The sites of abnormal RI accumulations were classified into the following three groups: (1) abnormal RI accumulation in bone metastases, (2) increased RI accumulation in non-bone metastases such as areas affected by arthrosis or showing a post-traumatic change, and (3) non-specific RI distribution not indicating RI accumulation in bones (e.g., distribution of RI accumulated in the bladder/kidneys, adherence of RI excreted in the urine to the skin, leakage of the injection of a radioactive tracer for bone scintigraphy). Among bone scintigraphy data from 896 Japanese patients provided by five institutions in Japan (The Jikei University Hospital, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Gunma Prefectural Cancer Center, Niigata Cancer Center Hospital, and Osaka City University Hospital), those confirmed as abnormal RI accumulations in bone metastases by nuclear medicine specialists were employed as training data to prepare a CNN for abnormal RI accumulation detection.

5. Calculation of BSI
BSI is an index of the area of bone metastases expressed as a percentage of the area of the entire skeleton. In metastases to the femur, vertebral bone, and pelvic bone, tumor spread not only to the bone cortex but also to the bone marrow is frequently observed. When calculating the extent of metastatic bone tumor involvement, it is considered necessary to adjust the bone weight in consideration of the bone marrow thickness, as well as the bone area obtained from anterior and posterior views. In calculating BSI, we corrected the proportional weight of the target bone to the total skeletal mass using the standard proportional weights of the bones [10]. In addition, for the skull and ribs, in which different sites are evaluated in the anterior and posterior images, a correction coefficient reflecting the regional proportion of the total skeletal mass was calculated for both the anterior and posterior regions. In addition, in the right and left regions and for the ribs, corrections of the bone areas in the anatomical recognition region were made. Based on these corrections, the regional bone scan index (rBSI) in each of the 20 regions was calculated using formula (1). The BSI of the target
patient is calculated using formula (2) as the sum of the rBSI of each region.

rBSI calculation formula (1)

\[
\text{rBSI} = \frac{\text{Area of the abnormal RI accumulation \ (pixels)}}{\text{Area of the anatomical region in which the abnormal accumulation is located \ (pixels)} \times \text{correction coefficient of the bone area \ (pixels)}}
\times \text{Area of the anatomical region in which the abnormal accumulation is located \ (pixels)} \times \text{Standard proportional weight of the bone} \times \text{Correction coefficient reflecting the regional proportion of total skeletal mass}
\]

BSI calculation formula (2)

\[
\text{BSI \ [%]} = \sum_{i=1}^{n} \text{rBSI}(i)
\]

For analysis using CNNapis, the Digital Imaging and Communications in Medicine (DICOM) data of the anterior and posterior views of the whole-body image of the target bone scintigraphy were used. The regions assessed as bone metastases are displayed as hot spot (HS) in red, while those assessed as non-bone metastases are displayed in blue (Fig.3) [11]. On the Fig.3, BSI was 10.01% and the HS was 48. The results of the analysis of the previous test are also displayed. The previous bone
scintigraphy and BSI in this patient showed that the number of HS was 0 and no bone metastases were observed. Leakage of subcutaneous injection of $^{99m}$Tc-HMDP and RI distribution to the bladder and kidneys are not recognized as abnormal accumulations. These ratings were modified as necessary to calculate the BSI. In addition, multiple tests can be analyzed to show changes over time (Fig. 4) [11]. The results of the analysis of each bone scintigraphy scan are shown in graphs and tables on Fig. 4.

6. Data analysis

The 121 scans were analyzed using CNNapis to calculate BSI. BSI and PSA, and BSI and ALP were compared for each subject to examine for correlations. Based on the BSI values obtained, subjects were divided into four groups: Group 1, BSI values from 0 to $<1$; Group 2, BSI values from 1 to $<3$; Group 3, BSI values from 3 to $<10$; and Group 4, BSI values $>10$. PSA and ALP values were compared between the groups.

7. Statistical analysis
A statistical software package (JMP SAS Institute., Cary, NC, USA) was used for all statistical analyses. “Linear fit” was performed to analyze relationships between BSI and PSA and between BSI and ALP in all subjects. The ALP and PSA values among the groups classified according to BSI values were compared for each pair using Student's t-test.

Results

PSA (median 166.16 ng/mL, range 0.003–2342 ng/mL) and ALP levels (median 691.196 U/L, range 82–11838 U/L) were measured in all patients. A correlation (r = 0.279, p = 0.0019) was observed between BSI and PSA (Fig. 5). BSI and ALP showed a strong correlation (r = 0.6814 and p < 0.0001) (Fig. 6). As a result of calculating BSI, 39 scans were classified in Group 1, 32 scans in Group 2, 30 scans in Group 3, and 19 in Group 4. Fig. 7 shows the results of the intergroup comparisons of PSA. Significant differences were observed between Groups 4 and 1 (p = 0.0007), Groups 4 and 3 (p = 0.0058), Groups 2 and 1 (p = 0.0052), and Groups 2 and 3 (p = 0.035). There was no significant difference between Groups 4 and 2 or Groups 3 and 1. Intergroup comparisons of ALP showed a significant
difference between Groups 4 and 1, Groups 4 and 2, and Groups 4 and 3 (p < 0.0001) (Fig. 8).

Discussion

Bone metabolic markers, which are indicators of bone metabolism, indicate bone remodeling and osteoclast and osteoblast turnover [3]. Osteoblastic bone metastases are common bone metastases in prostate cancer [12]. In bone scintigraphy, a radioactive tracer is administered and accumulates after administration owing to the binding of the tracer to hydroxyapatite crystals at sites of active bone formation, such as osteoblastic lesions. This allows bone scintigraphy to facilitate whole-body bone scans and makes it the first choice for investigation of bone metastases in patients with prostate cancer. Alongside pyridinoline cross-linked carboxyterminal telopeptide of type 1 collagen (1-CTP) and bone alkaline phosphatase (BAP), BSI from 99mTc-MDP bone scintigraphy has become an index used for the diagnosis of bone metastases, assessment of therapeutic effects, and prediction of prognosis in cancers, including prostate and breast cancers [13,14].
In Japan, about 30,000 bone scintigraphy are performed annually, of which about 50% are bone scintigraphy using $^{99m}$Tc-HMDP. It is clinically very useful to be able to calculate BSI for these bone scintigraphies. In order to determine whether BSI from $^{99m}$Tc-HMDP bone scintigraphy is useful as a bone imaging biomarker and bone metabolic biomarker for bone metastases from prostate cancer, the relationships between BSI and PSA and between BSI and ALP were examined for all cases. The results showed a statistical correlation between PSA and BSI. Consistent with a study showing that BSI from $^{99m}$Tc-MDP bone scintigraphy is useful in determining the therapeutic response to chemotherapy for bone metastases from prostate cancer, this study suggests that BSI calculated by CNNapis may also be useful as a bone imaging biomarker for bone metastases from prostate cancer [14]. In our study, ALP, which is useful for the clinical evaluation of bone metastases from prostate and breast cancers, was used as an index of bone metabolic markers [15,16]. This study showed a stronger correlation between ALP and BSI than between PSA and BSI. This study suggests the possibility that BSI calculated using CNNapis can be substituted as a bone metabolic biomarker, similar to findings from a
study showing that response evaluation based on BSI was useful for bone metastases from breast cancer and another that showed that BSI values before and after chemotherapy for bone metastases from prostate cancer correlated with the bone metabolic markers of BAP and 1CTP [6,16].

In order to demonstrate that BSI calculated using CNNapis is useful as a quantitative evaluation according to the progression of bone metastases, subjects were divided into four groups according to BSI values as with previous studies, and a paired comparison test was performed for each group based on the respective PSA and ALP values [6,17]. For both PSA and ALP, significant differences were observed between Group 1 with the lowest BSI and Group 4 with the highest BSI. A significant difference was also observed between Group 3 and Group 4. PSA is also affected by relapse of the primary lesion and exacerbation of other metastatic lesions, and the results of the comparisons of PSA and ALP between the high- and low-BSI groups are thought to suggest that BSI calculated by CNNapis may be useful as a quantitative evaluation of the progression of bone metastases.
Conclusion

The BSI values calculated by CNNapis, which we developed, showed correlations with PSA and ALP. Significant differences in PSA and ALP were observed between the groups classified according to their BSI values. It has been suggested that BSI calculated by CNNapis is useful as bone imaging and bone metabolic biomarkers and may reflect the activity and spread of bone metastases from prostate cancer.
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### Table 1

**Patient characteristics**

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<td>Gleason score (mean, range)</td>
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<td>3 were unexamined and 3 were unknown</td>
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<td>Number of Patients</td>
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<tr>
<td>With only bone metastasis</td>
<td>51</td>
</tr>
<tr>
<td>With bone and other metastasis</td>
<td>19</td>
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Fig. 1

The structural formula of $^{99m}$Tc-MDP.

[Diagram of the structural formula of $^{99m}$Tc-MDP]
Fig. 2a, b

$^{99m}$Tc-HMDP exists as a chelate compound composed of methane-1-hydroxy-1,1-diphosphonic acid disodium (Fig. 2a) and technetium oxide (Fig. 2b).

Fig. 2a
Fig. 3

A: Bone Scintigraphy, B: Results of analyzed bone scintigraphy

A case of bone metastases from prostate cancer is shown.
Fig. 4

A: Results of analyzed bone scintigraphy

B: Graphs and Tables of BSI and number of HS
Fig. 5

The correlation coefficients between BSI and PSA
Fig. 6

The correlation coefficients between BSI and ALP
Correlations for PSA between the groups classified by BSI. BSI values:

Group 1, 0 to <1; Group 2, 1 to <3; Group 3, 3 to <10; and Group 4, >10.

* p<0.01
** p<0.05
Correlations for ALP between the groups classified by BSI values:

Group 1, 0 to <1; Group 2, 1 to <3; Group 3, 3 to <10; and Group 4, >10.
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Conflict of interest

The authors have a financial conflict of interest to disclose concerning the study.

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The author is not funded by public institutions.

There is no grant number for Medi-Physics companies and grants.
Fig. 1
Fig. 2a

\[
\begin{align*}
\text{NaO} & \quad \text{OH} & \quad \text{ONa} \\
\hspace{1cm} \text{O}=\text{P} & \quad \text{C} & \quad \text{P}=\text{O} \\
\text{HO} & \quad \text{H} & \quad \text{OH}
\end{align*}
\]
Fig. 2b
Fig. 3
Fig. 4
Fig. 7

A box plot showing PSA levels across different groups. Group 1 has the lowest PSA levels, followed by Group 2, then Group 3, and Group 4 has the highest. There are significant differences between Group 1 and Group 4, with Group 4 having a significantly higher PSA level. The symbols * and ** indicate statistical significance, with * p<0.01 and ** p<0.05.
Fig. 8

* p<0.01
**Table 1**

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