Diagnostic utility of the computer-aided diagnosis system for detection of bone metastasis on whole-body bone scan in breast cancer patients

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Aims and objectives

Patients with advanced breast cancer frequently develop bone metastasis, and the extent of the disease significantly affects overall survival [1]. Bone metastasis also causes skeletal-related events (SREs), including pain, bone fractures, spinal cord compression, and hypercalcemia. SREs significantly impair patients’ quality of life. Zoledronic acid and other bisphosphonates have been recognized to reduce the frequency of SREs and prolong a survival period in breast cancer patients with bone metastasis. Early diagnosis of bone metastasis is important in order to choose an appropriate treatment.

Bone scanning is one of the effective diagnostic tools for whole-body examinations. It is used to evaluate the extent of the metastatic spread involving bone tissues for both staging and follow-up [1, 2]. However, the interpretation of bone scans is a difficult pattern-recognition task that requires extensive experience [3]. Since non-neoplastic diseases can also exhibit abnormal imaging findings, a number of differential diagnoses and error sources should be considered [4]. Therefore, physicians are facing an increasing workload but must still manage to read the diagnostic images carefully and avoid errors in interpretation that may otherwise lead to serious mistakes in the treatment of patients [3].

In this study, we examined the diagnostic ability of the computer-aided diagnosis (CAD) system (Viewer for Standardized Bone Scintigraphies; VSBONE) for detection of interval changes in successive whole-body bone scans and compared it with conventional planar image (PI) for detection of bone metastases in breast cancer patients.
Methods and materials

Patients

Between January 2004 and August 2014, 661 women with breast cancer underwent whole-body bone scans at our institution and 240 patients underwent successive whole-body bone scans. Among them, 43 patients (median, 57 years; range, 37-79) who had undergone magnetic resonance images (MRI) within 3 months (median 19 days; range, 0-75) from the second whole-body bone scans were included in this study and a total of 604 bones (578 regions of the spine and pelvis, 3 regions of the sternum and ribs, 19 regions of the upper extremities and 4 regions of the lower extremities) were analyzed in this study.

Bone scan

Patients underwent whole-body bone scans approximately 3 hours after the intravenous injection of 740 MBq technetium-99m-hydroxymethylene diphosphonate (Tc99m-HMDP; Nihon Medi-Physics Co., Ltd., Tokyo, Japan). Whole-body images (anterior and posterior views, scan speed 20cm/min, matrix 256 x 1024 or 768 x 512) were obtained with a gamma camera (e.cam; Siemens, Forchheim, Germany or Bright View X with XCT; Philips, Best, Netherland) equipped with low-energy high-resolution parallel hole collimators. Energy discrimination was provided by a 20% window centered on the 140 keV of Tc99m. Planar images of the entire skeleton in the anterior and posterior positions were acquired. No single photon emission computed tomography (SPECT) was used in this analysis.

Initial bone scans were performed as a part of standard staging protocols after the diagnosis of breast cancer or to screen for pain symptoms. Second bone scans were performed to assess the changes of known metastasis or to screen for newly emerged pain symptoms or increase of tumor markers (cancer antigen 15-3 or carcinoembryonic antigen). The interval between the initial scan and secondary scan was 1-89 month (median 23 month).

Diagnostic supporting software analysis

We used a special diagnostic supporting software, VSBONE version 2 (Nihon Medi-Physics) for the analysis of bone scans. To detect interval changes on successive whole-body bone scans, the gray scale of each image was normalized first, and then the size, orientation and gray scale of a previous image were adjusted to match those of second images (Fig. 1) [5]. Planer images of the entire skeleton in the anterior and posterior positions were acquired.
MR imaging and criteria for bone metastasis

MR imaging was performed with 1.5 or 3.0 tesla scanners using standard techniques with T1, T2-weighted images (T1WI, T2WI) and fat suppressed T2WI; short-tau inversion recovery (STIR), spectral presaturation with inversion recovery (SPIR) or spectral attenuated inversion recovery (SPAIR) sequences. The criteria for the MRI diagnosis of metastasis were the presence of a well defined focus of low signals on both the T1WI and T2WI and/or high signal intensity on fat suppressed T2WI.

Image Analysis

The PI and VSBONE images were interpreted separately by two independent radiologists to diagnose bone metastases. Two radiologists with 6- and 14-year experience who were fully blinded to any clinical information undertook two reading sessions on PI and VSBONE. The two sessions were performed at least 4 weeks apart. The readers were free to use tools such as zooming and adjusting window width and/or level during PI reading. Referring to each initial bone scan image, the second scan was assessed qualitatively for a change of lesions present on the initial scan and for the presence of new lesions. Every site with abnormal uptake of 99mTc-HMDP was recorded by region as positive or negative for metastatic involvement. Scans were categorized as negative if scintigraphic abnormalities were considered typical for benign lesions (e.g. adjacent rib fractures, joint-based uptake and typical arthritic or degenerative change). MR diagnosis of metastasis was made blindy by two radiologists with 17- and 8- year experience in consensus for all 43 patients and used as the gold standard for the presence or absence of bone metastasis.

Statistical Analysis

To compare the sensitivity and specificity of PI and VSBONE for determining the presence of metastatic involvement by bones, the McNemar test was performed. Interobserver agreement was calculated by using kappa statistics. Kappa scores of 0.41-0.60, 0.61-0.80, and greater than 0.80 were regarded to be indicative of moderate, good, and excellent agreement, respectively [6].
Fig. 1: Imaging procedures of Viewer for Standardized Bone Scintigraphies (VSBONE). The gray scale of the initial and second original raw image data are normalized first, and then the size, orientation and gray scale of the initial image are adjusted by using the second image as a reference.
Results

Bone metastases were confirmed in 362 regions based on the MR diagnosis (Table 1). For reviewer 1, the sensitivities of PI and VSBONE were 40% and 48%, respectively, and the specificities were 98% and 96%, respectively (Table 2). For reviewer 2, they were 35, 44, 98 and 96%, respectively. There were significant differences (P<0.001) between PI and VSBONE for both reviewers.

Kappa scores for agreement between reviewers were 0.58 for PI and 0.66 for VSBONE. Agreement could therefore be considered moderate for PI and good for VSBONE.

Figure 2 shows a 60-year-old breast cancer patient. On initial bone scan images, there were no abnormal uptakes. Seven years and 6 month after the initial scan, she complained neck pain, lumbago and coxalgia. She underwent a second bone scintigraphy. Reviewer 1 interpreted as metastases in C1, T10, 11, L3, 4 and C1, T9-11, L3, 4 on PI and VSBONE, respectively. Reviewer 2 interpreted as metastases in T11, L3, 4 and T9, 11, L3, 4 on PI and VSBONE, respectively. Reviewer 2 diagnosed a hot spot in C1 lesion as a joint-based uptake or degenerative change. On MRI, the metastatic lesions of C1, 6, T1, 3, 6, 7, 9-11, L1 and L3-5 were confirmed (Fig.3).
<table>
<thead>
<tr>
<th>Bone segments</th>
<th>Bone segments with metastases (no.)</th>
</tr>
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<tbody>
<tr>
<td>Cervical spine</td>
<td>53</td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>188</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>92</td>
</tr>
<tr>
<td>Sacrum with coccyx</td>
<td>19</td>
</tr>
<tr>
<td>Pelvis</td>
<td>6</td>
</tr>
<tr>
<td>Upper extremities</td>
<td>1</td>
</tr>
<tr>
<td>Lower extremities</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>362</td>
</tr>
</tbody>
</table>

**Table 1:** Incidence of Bone Metastases in Bone Segments

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Table 2: Results of comparison of each images

<table>
<thead>
<tr>
<th></th>
<th>No. (%) of cases</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Planar Image</td>
<td>VSBONE</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td><strong>Reviewer 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>145/362 (40)</td>
<td>174/362 (48)</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>238/242 (98)</td>
<td>232/242 (96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Reviewer 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>126/362 (35)</td>
<td>160/232 (44)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>236/242 (98)</td>
<td>235/242 (96)</td>
<td></td>
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</table>
Fig. 2: A 60-year-old female who had undergone left mastectomy 20 years before. The initial bone scan was performed for screening. This patient complained neck pain, lumbago and coxalgia, for which second scintigraphies were performed seven years and 6 months after the initial scan. (a) The initial planar Tc-99m HMDP bone scan images (PI) showed no obvious metastatic lesion. The second PI showed three obvious foci of uptake. The lesions at the level of T11, L3 and 4 were interpreted as metastases by both of the reviewers. The lesions at the level of C1 and T10 showed equivocal uptake. One reviewer interpreted them as metastases and the other did not. (b) The initial bone scan processed by VSBONE showed no obvious metastatic lesions. The second VSBONE images show four obvious foci of uptake. The lesions at T11, L3 and 4 were interpreted as metastases by both of the reviewers. The lesions at C1 were interpreted as metastases and benign lesion by reviewer1 and reviewer 2, respectively. The lesions at T9 and
10 show equivocal uptake. The lesion at T9 was interpreted as metastasis by both of
the reviewers. The lesions at T10 were interpreted as metastasis and benign lesion by
reviewer1 and reviewer 2, respectively.

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**Fig. 3:** T1-weighted sagittal images showed low signal-intensity mass lesions in C1, C6,
T1,3, 6, 7, T9-11, L1 and L3-5, corresponding to a bone metastasis (partly not shown).

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Conclusion

There was significant difference between PI and VSBONE for detection of bone metastases in breast cancer patients. Although further improvement would be necessary for reducing the number of false negative diagnoses, the CAD scheme for detection of interval changes by use of the temporal subtraction technique would be useful in assisting radiologists' interpretation on successive bone scan images.
References


