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EVALUATION OF BONE SCAN INDEX CHANGE OVER TIME ON AUTOMATED CALCULATION IN BONE SCINTIGRAPHY

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Abstract

Objective, bone scintigraphy (bone scan) is useful in detecting metastatic bone lesions through visual assessment of hot spots. A semi quantitative analysis method that evaluates bone scan images has been eagerly anticipated. BONENAVI is software that enables automatic assessment of bone scan index (BSI). BSI is useful for stratifying cancer patients and monitoring their therapeutic response. The purpose of this study was to evaluate the efficacy of BONENAVI in determining BSI and hot spots at different time intervals after radioisotope injection.
Methods, we evaluated 32 patients, including 22 males and 10 females. Ten patients had breast cancer, 20 patients had prostate cancer, and 2 had malignant phaeochromocytoma. Patients were injected with 20 mCi of 99mTc-methylene diphosphonate (99mTc-MDP) and bone scintigraphy was performed at 2, 4, and 6 hours after injection on each patient. The BSI and the number of hot spots were obtained from BONENAVI software. Bone scan images were also visually assessed to exclude false positives due to artifacts. Analyses were performed in all lesions, selected true lesions, segment-based and cancer-type-based. Non-parametric statistical analyses for pairwise multiple group comparison were performed using Friedman test followed with post-hoc analysis.
Results, the BSIs and the number of hot spots were significantly increased with time, with significant differences between each of time points (P< 0.001). Analysis of regional BSI (rBSI) and hot spot number changes of selected 15 true lesions also showed similar increase (P<0.001). In general, the pelvic segment was the most prone to rBSI changes and the chest segment was the most prone to hot spot number changes. Visual assessment showed that BONENAVI diagnosed some typical artifacts as metastases (hot spots).
Conclusion, BONENAVI reading of BSIs and hot spot numbers was highly affected by acquisitiontime. In serial or follow-up examinations (in particular, for monitoring therapeutic efficacy), acquisition time should be fixed for each patient. Cautious interpretation should be made on segments with high physiological uptake. BONENAVI reading was prone to misinterpretation of artifacts. Visual assessment is necessary to rule out this possibility.

Keywords: *Bone Scintigraphy, Bone Scan Index, BONENAVI, computer-assisted diagnostic software*

INTRODUCTION

Bone is the most common cancer metastatic site and has particular clinical importance in breast and prostate cancer because of its prevalence in these diseases[1]. A semi quantitative analysis method that evaluates bone scan images has been eagerly anticipated. Bone Scan Index (BSI) was developed to improve interpretability [2]. BSI has been proven useful for stratifying cancer patients and evaluating their response to treatment[1, 3].Manual calculation of BSI is possible, but it is

a tedious and time-consuming task. Moreover, variation in bone scan image interpretation is substantial [4].

To address this, fully automated computer-assisted diagnosis (CAD) systems based on artificial neural networks (ANNs) have been developed (EXINIbone, EXINI Diagnostic AB)[5, 6]. Since then, BSI quantification have been proven that their clinical value surpasses conventional clinical imaging and that BSIs reflect pathological features[7-9]. To improve its accuracy in specific population, a race-specific training databasesis important[10]. Based on EXINIbone, BONENAVI (Fuji Film RI Pharma Tokyo, Japan) was developed. BONENAVI was later upgraded to include information on gender-specific characteristics [11]. For BSI calculation, the whole body bone scan image is segmented into eight regions. Hotspots are then located, normalized, and quantified by a thresholding algorithm. The ANN values classifies the metastasis detection [7]. rBSI (regional BSI) and rANN (regional ANN) values are also provided for individual lesion analysis. Under the current protocol, bone scan can be routinely performed between 2 to 5 hours after intravenous administration of 740 MBq of ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP;^{99m}Tc energy: 140keV, half-life: 6 hours)[12, 13]. While Saha*et al* recommended 2 to 3 hours, several centers performed acquisition at 4 hours[14].

Scan acquisition time is critical to image quality and may affect patient diagnosis and therapy. A high target-to-nontarget ratio should be obtained to avoid nondiagnostic scans in which pathologic processes cannot be distinguished from background[15].Our previous experience showed that target-to-background ratio was significantly different found between 2 and 3 hours (unpublished data). Studies revealed that from 2 hours to 4 hours, the ratio of tracer uptake compared with contralateral normal bone, as well as bone-to-softtissue ratio, might increase quantitatively[16, 17]. This can, however, be problematic when dealing with accuracy of fully-automated CAD systems. More importantly, even though BONENAVI was trained with a massive multi-center database, the bone scan images in that database were taken at different acquisition times[11]. Those tendencies brought us to investigate the quality of BSI reading by fully automated CAD at several different acquisition times.

In this era of digital and high-definition/high-resolution medical imaging, such consideration is inevitable for further development. Simultaneously, the response criteria for tumors has been rapidly developed within the last several years. Bone scintigraphyis also being considered to be included in workup test list, due to their whole-body scan capability and high specificity for bone metastases[18]. In such situation, accurate quantitative reading of bone scan is essential.

Despite the high potential benefit from accuracy and versatiliy of CAD systems to obtain reproducible and prompt calculation of BSI, there is no standardized protocol detailing optimal acquisition time and use of these CAD software. In the clinical setting, a patient may be initially imaged in one center then referred to another center using a different “standard” acquisition time. A difference in acquisition time may influence the reliability of BSI in evaluating disease progression or therapeutic efficacy. This makes it important to evaluate the reading capability and reading accuracy of BONENAVI at different acquisition times.

In this study we investigated how BONENAVI version 2 reads BSI and lesion number and how the readings differ with acquisition time. As time points, 2 hours, 4 hours and 6 hours after injection were selected to follow the dynamic of ^{99m}Tc-MDP uptake within the clinical range of acquisition time.

METHODOLOGY

Patients,Thirty-two patients (22 males and 10 females) matched with inclusion criteria were involved in this prospective study from July 2014 to February 2015. Twenty patients had prostate cancer, while ten had breast cancer and two had phaeochromocytoma. The patient inclusion criteria were: a) having one or more bone metastatic lesions on previous bone scan confirmed by other diagnostic imaging (CT or MRI), b) being scheduled for bone scan, c) being older than 22 years old, d) having performance status based on The Eastern Cooperative Oncology Group between 0 to 2, and e) having signed informed consent. Patients were excluded if they had one or more of these conditions: a) pregnancy,

lactation, or suspected pregnancy, b) abnormal extra osseous uptake disturbing diagnosis of bone uptake, c) decreased renal function (serum creatinine level >3.0 mg/dL), d) active multiple cancers, e) severe background disease (sepsis, severe diabetes, etc.), or f) considered inappropriate for this study by the medical staff. The ethical committee of our hospital approved this study protocol, and written informed consent was obtained from all participants.

This method with steps : 1). *Bone Scintigraphy,* Each patient was injected intravenously with 740MBq of ^{99m}Tc-MDP (Fujifilm RI Pharma Co. Ltd, Tokyo, Japan) and whole-body scintigraphy was performed at 2, 4, and 6 hours after injection. The scans were performed using a gamma camera at a speed of 11 cm/minute with a low energy high-resolution collimator, 256×1024 matrix and zoom factor of 1. Bone scan images were obtained using two different gamma camera units of the same type and manufacturer (E.CAM, Toshiba, Tokyo, Japan)**.** Raw image data were transferred to a workstation (e.soft, Siemens AG, Erlangen, Germany) for visual assessment by nuclear medicine physicians and further analyzed in a PC with BONENAVI version 2 software installed. 2).

Data analysis, data analysis was performed based on BONENAVI readings of all patients' bone scan images, including BSI, hot spot number and ANN values. In segmental analysis, regional BSI (rBSI) and regional hot spot number were used, which basically are components of BSIs and total hot spot numbers. "Balanced thresholding method" was used for all readings. Pairwise comparison for all lesions were made at 2, 4, and 6 hours after injection. To further analyze the BONENAVI readings on lesions considered real metastatic lesions, individual lesions were compared. In this analysis, it was important to avoid "fused lesions," or several adjacent lesions appearing as one large lesion due to lesion size and partial volume effect.

To avoid this, we selected bone scan images from patients who were Grade 1 (less than 6 hot spots on 2 hours image) on a five-point scale for extent of disease (EOD)(Table 1)[19]. To avoid including false positive lesions, only lesions read as bone metastasis (red dot) having the same position and similar shape (i.e. not fused with adjacent lesions) at all-time points were used. These lesions were considered true lesions, and their rBSIs were subjected to pairwise comparison at group of 2, 4 and 6 hours. Analysis was also performed at the segmental level to describe reading changes in each segment. For this purpose, all lesions read as hot spots at all-time points were included for analysis, regardless of the patient's EOD grade.

In this study, the majority of cases were prostate and breast cancer. Since the bone metastasis lesions of the two malignancies show different pathological behavior[20, 21], and metabolism of ^{99m}Tc-MDP is highly affected by bone turnover [14], analysis of regional BSI (rBSI) and hot spot number changes over time was also performed according to cancer type. 3). ***Statistical Analysis, s***tatistical analyses were performed to compare variables using SPSS statistical software version 22. All obtained data were not normally distributed, therefore for comparison of multiple group, non-parametric Friedman test with Wilcoxon signed-rank test as a post hoc analysis were applied. Statistical significance level of $P < 0.05$ was applied in each test.

RESULTS

Assessment of BONENAVI reading. Patient inclusion was described in Fig. 1. Among 32 patients, four patients (2 prostate cancer and 2 breast cancer patients) were omitted from further quantitative analysis due to abnormal extra-osseous uptake. In these four cases, BONENAVI diagnosed typical artifacts as metastatic lesions, as shown on Fig. 2. BONENAVI detected the bladder as a large hot spot at 2 and 4 hours, but omitted it at 6 hours, resulting in BSI and lesion number changes.

Representative images of BONENAVI readings are shown on Fig. 3. In Fig. 3a, a 55 year-old metastatic prostate cancer patient showed several large hot spots in the pelvis, spine, chest and upper extremity from as early as 2 hours. Interestingly, two large bilateral lesions on the anterior edge of iliac bone (yellow arrow) were read differently by BONENAVI at 2, 4, and 6 hours. Total BSIs increased over time, as well as rBSI, total hot spot number and regional hot spot numbers in the pelvis, thoracic spine and lumbar spine segments. However, BONENAVI correctly excluded urine

accumulation in the bladder at all times. Fig. 3b shows another case of prostate cancer （a 79 year-old male）. Large hot spots were detected in the thoracic spine and pelvis at 2 hours and intensified over time. Several hot spots in the pelvis and left humerus were detected only at 4 hours. The pelvis and lumbar spine have prominent increases in hot spot number. Total BSI and total hotspots were steeply increased. At 6 hours, BONENAVI distinguished normal uptake and active lesions in the lumbar spine and sacro-iliac joint (yellow arrow), which normally have high uptake. In this patient, two injection leakage sites on the left elbow (white arrows) were observed and potentially lead to misinterpretation. At 2 hours, a 2 mm lead plate successfully hid these spots, but they were detected as hot spots at 4 hours. They were outside the segmented field at 6 hours.

Quantitative Analysis. Data from 28 patients (18 prostate cancer, 8 breast cancer, and 2 phaeochromocytoma) were eligible for quantitative analysis. As shown on Fig.4a, BSI distribution changed for each time point with significant increase over time at all points ($P < 0.001$ for all interval pairs). Fig. 4b shows that hot spot number was also significantly increased over time at each time point ($P < 0.001$ for all interval pairs). Individual lesion analysis was performed on lesions from eight patients with low EOD grades (grades 0 and 1). rBSIs from 15 true lesions in these eight patients were evaluated. As described on Fig. 4c, rBSIsfrom these true lesions also showed a distribution similar to overall BSI distribution, with significant increase at each time point ($P < 0.001$ for each interval pair).

Table 2 and Fig. 5 resumed the pairwise comparison among acquisition time groups in each segment for rBSIs and hot spot numbers.All segments showed significant increase of rBSIs at all intervals, except cervical spine, skull and lower extremity (Fig. 5a, Table 2). The pelvic segment showed the most prominent rBSIincrease ($P<0.001$), followed by the chest ($P<0.001$) and lumbar spine ($P<0.001$). Fig. 5b and Table 2 showed that the chestwas the segment most prone to hot spot number change over time ($P <0.001$). All other segments also showed significant hot spot number increases, except the cervical spine ($P=0.135$) and the lower extremity ($P=0.104$). Qualitative analysis was performed in each cancer type (18 prostate cancer and 8 breast cancer patients) based on total rBSI and total hot spot numbers, sincebreast cancer patient number was limited. Generally, the pelvis was the segment most prone to rBSI change over time in both cancer types (Fig. 6a and 6b). Cervical segment in both cancers had the lowest total rBSI and was the segment least prone to rBSI change over time.

In both cancers (Fig. 6c and 6d), the chest segment was far more prone to hot spot number changes compared to other segments, except pelvis in breast cancer, which had increase rates similar to other segments. Inboth prostate and breast cancer, hot spot number barely changed in the cervical spine segment, a finding similar to the tendency of rBSI.

DISCUSSION

BONENAVI has been proven useful for BSI calculation in bone scintigraphy [9, 22, 23].However, in many studies, there is no consensus regarding the optimum acquisition time for the most accurate bone scan interpretation [9]. The only standards available give a wide range from 2 to 5 hours as being acceptable for bone scan image acquisition [12]. In our knowledge, this was the first study to evaluate the reading performance of a CAD software over time for automated BSI calculation.

Our result showed that BSI, rBSI and lesion number were increased significantly over time on BONENAVI reading. Results of our true lesion analysis suggested that BSI increase was affected by rBSI increase. Some segments were also more sensitive than others to rBSI and hot spot number changes over time. Several explanations can be proposed. The first factor for uptake of any radiopharmaceutical is the local blood flow. ^{99m}Tc-MDP itself is exchanged rapidly with extracellular fluid due to its low molecular weight. Immediately after injection, ^{99m}Tc-MDP begins to not only be metabolized by bone but also excreted through kidney. Within the first hour, only 10% of the injected dose remains in the blood, 50% accumulates in bones and more than 30% has undergone kidney filtration. At 3 hours after injection, 45-55% of the ^{99m}Tc-MDP is distributed in the skeleton, 56-59% in urine and 3-5% in blood[13, 21]. By 6 hours, approximately 70% of administered ^{99m}Tc-MDP has been excreted via urine[20]. Since the level of ^{99m}Tc-MDP in the blood becomes practically negligible

within 3 hours, there is high contrast between bone and soft tissue. This is one advantage of ^{99m}Tc-MDP compared to other bone scan agents.

^{99m}Tc-MDP is a bone seeking agent and not tumor specific, thus high bone-to-soft-tissue contrast should be carefully interpreted. Normal uptake in several bones is also relatively high. This is the second factor: the dependency of ^{99m}Tc-MDP on osteoblastic activity. Trabecular bones like the pelvis and spine have more osteoblastic activity compared to tubular and cortical bones (i.e. most other bones in the body). Abnormal uptake in these regions at later hours requires more careful evaluation. A tumor with a very large number of osteoblasts will likely have higher uptake, and the uptake might increase quite soon after injection. Metastatic prostate cancer is one of the most common causes of malignant superscan in bone scintigraphy[20].

Most bone metastases are distributed irregularly in the axial skeleton (spine and pelvis) and rib cage, while less than 10% affect extremities. On the other hand, metastases in the bones of the extremities are commonly seen in lung, prostate and breast cancer[24].Both prostate and breast cancer tend to have similar sites of metastases: spine, ribs, pelvis, and long bones. The important difference is their pathologic behavior. Osteoblastic activity is dominant in prostate cancer, resulting in a sclerotic appearance on X-ray, while an osteolytic or mixed osteoblastic and osteolytic pattern is observed in breast cancer. Since ^{99m}Tc-MDP is highly dependent on osteoblastic activity, it has been long known that bone scans are very useful for metastasis detection on prostate cancer, expands its benefit from tumor grade stratification [19] to bone metabolic biomarker[9]. However, a recent study showed the importance of bone scans and BSI measurements in breast cancer cases for evaluating the risk of skeletal-related events (palsy, pathological fracture, radiation and surgery)[25].

We showed that bone scan image contrast and intensity changed significantly in a relatively short period of time. This finding showed that the influence of acquisition time to rBSI and eventually BSI, could not be ignored. Without standardization of acquisition time for each patient in each bone scan session, accurate interpretation of serial bone scans is not possible, especially for evaluating cancer treatment efficacy. The change of BSI over time was too large and it means that the absolute value of BSI from one patient's study has limited value, if absolute BSI value is compared with that obtained from other study with different acquisition time. This BSI value change depend on binomial cut-off of rANN value which is affected by the acquisition time. Therefore, we can only count on relative change of BSI values between different studies if it is performed in the same patient at fixed acquisition time.

Despite the massive database that has been used to train BONENAVI [11], our findings suggested that re-training might be necessary to further improve accuracy of automatic interpretation. Our finding on true lesions analysis and segmental analysis showed that some regions have higher uptake intensity and also higher rates of BSI and lesion number increase. Particular caution must be made in evaluating the pelvic segment. Compared to other bones, which are predominantly long tubular and of cortical type, pelvic bones are flat, wide and trabecular. Even on normal bone scans, higher activity is detected in trabecular bones compared to cortical bones. The most common sites with high normal uptake in later hours are the sacro-iliac joint and the long anterior edge of the iliac bone, which might resemble large metastatic lesions. In comparison, lesions in the chest segment are smaller and multiple, making this segment more prone than the pelvic segment to hot spot changes over time. Bladder and urinary tracts may present as artifacts in the pelvis and complicate readings. BONENAVI might need additional training with a higher threshold in this particular segment, if possible with specific features to recognize artifacts such as urinary catheters.

This would also likely also apply to the spine, in particular the thoracic to lumbar segments, which have trabecular structures similar to the pelvic bones. In elderly patients, hot spot interpretation in this segment might also be further complicated by a high prevalence of benign abnormal lesions from degenerative processes, which are indistinguishable without further examination[20]. More than a half (57%) of lesions found in the vertebral region were reported to be benign on additional clinical and imaging follow-up[26].

The limitation of this study was the relatively small number of patients. About a hundred patients were eligible during the study period according to our inclusion criteria, however, the long examination protocol and scheduling conflicts with outpatient chemotherapy were the main reasons

why some patients declined to participate. Another limitation was there was no gold standard to determine which lesions were metastatic. Patients in our study had been diagnosed as having bone metastasis from previous bone scans (also confirmed by other diagnostic imaging modalities such as CT or MRI). Due to the patients' advanced stage disease, histopathological confirmation of all bone metastatic lesions would have been impractical, not to mention unethical when there would be no impact on clinical management. In future studies, it would be very interesting to follow the final diagnosis and treatment result to evaluate the diagnostic accuracy of BONENAVI. However, such evaluation is beyond the scope of this study. Evaluation of diagnostic accuracy during treatment monitoring under fixed acquisition time using this software is open for further investigation.

CONCLUSION

BSI increases over time, as well as increases in hot spot numbers, in automated calculation by BONENAVI software were caused by individual increases in rBSIs and hot spot numbers. The pelvic segment was the most prone to such change, followed by the spine and thoracic segments. Since this increase might be related to the natural distribution pattern of ^{99m}Tc-MDP in bone, fixing acquisition time for each patient in each bone scan session should be considered for optimal image interpretation. Ultimately, visual confirmation was required in each scan to rule out the possibility of false positive due to artifacts.

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Conflict Of Interest

The authors declare that they have no conflict of interest.

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