Clinical Study

ASJ Asian Spine J. 2024;18(3): 398-406
https://doi.org/10.31616/asj.2022.0451
PISSN 1976-1902 • eISSN 1976-7846

Correlation between the maximum standard uptake value and mean Hounsfield unit on single-photon emission computed tomography-computed tomography to discriminate benign and metastatic lesions among patients with breast cancer

S. Thadchaiani Saminathan[1], Wan Aireene Wan Ahmed[1], Norazlina Mat Nawi[2], Nashrulhaq Tagiling[2], Ilyana Aziz[2], Yusri Udin[2], Mohd Fazrin Mohd Rohani[3], Wan Mohd Nazlee Wan Zainon[4], Mohammad Khairul Azhar Abdul Razab[5]

[1]Department of Radiology, School of Medical Sciences, Universiti Sains Malaysia, Kota Bharu, Malaysia
[2]Department of Nuclear Medicine, Radiotherapy and Oncology, School of Medical Sciences, Universiti Sains Malaysia, Kota Bharu, Malaysia
[3]Department of Nuclear Medicine, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia
[4]Department of Family Medicine, Hospital Universiti Sains Malaysia, Kota Bharu, Malaysia
[5]Medical Radiation Program, School of Health Sciences, Universiti Sains Malaysia, Kota Bharu, Malaysia

Received Oct 16, 2023; **Revised** Feb 2, 2024; Accepted Feb 26, 2024
Corresponding author: Norazlina Mat Nawi
Department of Nuclear Medicine, Radiotherapy and Oncology, School of Medical Sciences, 16150 Kota Bharu, Kelantan, Malaysia
Tel: +60-97676669, **Fax:** +60-97676691, **E-mail:** norazlina@usm.my

Study Design: Retrospective study.
Purpose: To compare and correlate technetium-99m methylene diphosphonate uptake between benign and metastatic bone lesions using semiquantitative analysis of maximum standard uptake value (SUVmax) and mean Hounsfield unit (HU) in single-photon emission computed tomography-computed tomography (SPECT-CT).
Overview of Literature: Qualitative interpretation of metastatic bone lesions in breast cancer on bone scintigraphy is often complicated by coexisting benign lesions.
Methods: In total, 185 lesions were identified on bone and SPECT-CT scans from 32 patients. Lesions were classified as metastatic (109 sclerotic lesions) and benign (76 lesions) morphologically on low-dose CT. Semiquantitative analysis using SUVmax and mean HU was performed on the lesions and compared. To discriminate benign and metastatic lesions, the correlation between SUVmax and mean HU was determined using the intraclass correlation coefficients.
Results: The SUVmax was higher in metastatic lesions (20.66±14.36) but lower in benign lesions (10.18±12.79) (p<0.001). The mean HU was lower in metastatic lesions (166.62±202.02) but higher in benign lesions (517.65±192.8) (p<0.001). A weak negative correlation was found between the SUVmax and the mean HU for benign lesions, and a weak positive correlation was noted between the SUVmax and the mean HU on malignant lesions with no statistical significance (p=0.394 and 0.312, respectively). The cutoff values obtained were 10.8 for SUVmax (82.6% sensitivity and 84.2% specificity) and 240.86 for the mean HU (98.7% sensitivity and 88.1% specificity) in differentiating benign from malignant bone lesions.
Conclusions: Semiquantitative assessment using SUVmax and HU can complement qualitative analysis. Metastatic lesions had higher SUVmax but lower mean HU than benign lesions, whereas benign lesions demonstrated higher mean HU but lower SUVmax. A weak correlation was found between the SUVmax and the mean HU on malignant and benign lesions. Cutoff values of 10.8 for the SUVmax and 240.86 for the mean HU may differentiate bone metastases from benign lesions.

Keywords: Breast neoplasms; Bone metastasis; Single-photon emission computed tomography; Standardized uptake value maximum; Hounsfield unit

Introduction

Breast cancer is the most common malignancy among women worldwide, accounting for about 25.1% of all cancers [1]. Approximately 1,671,149 new cases and 521,907 deaths related to breast cancer were documented globally in 2012 [1]. The incidence of breast cancer in Asia has rapidly increased in recent years because of various factors, such as lifestyle changes, socioeconomic status, and an increase in disease detection from a good healthcare system. In Malaysia, the International Agency for Research in Cancer (GLOBOCAN) in 2012 estimated that the age-standardized rate of breast cancer was 38.7 per 100,000, with 5,410 new cases [2]. Breast cancer-related mortality ranked second-most in Malaysia [3].

Bone metastasis was found in 60% of patients who died from breast cancer [4]. Metastatic breast cancer is associated with widespread skeletal involvement in up to 85% of patients, with a median survival period of 24 months [4]. Some debilitating complications related to metastatic bone disease include pathologic fractures, bone pain, spinal cord compression, and hypercalcemia. In Malaysia, with the rising cases of breast cancer associated with high morbidity and mortality rates, bone metastasis must be accurately detected. The accuracy of bone metastasis detection ensures correct staging and rapid therapy initiation, which may extend the life span of these patients.

Bone scintigraphy, also known as bone scan, is the most sensitive, noninvasive imaging modality to detect bone metastasis [5]. It is highly sensitive, readily available, and affordable [6]. It involves the administration of a radiopharmaceutical agent that accumulates in the skeletal system because of changes in bone vascularity or osteoblastic activity [5]. However, the interpretation of bone scans is often complicated by coexisting benign conditions such as osteochondrosis, spondyloarthropathy, collectively known as degenerative diseases, and bony islands, which also demonstrate increased tracer uptake [5]. This issue may cause false-positive findings [7]. Moreover, distinguishing between metastatic and benign bone lesions, particularly in the spine, is often difficult because they often coexist in patients with breast cancer.

With the introduction of hybrid imaging such as single-photon emission computed tomography-computed tomography (SPECT-CT), the specificity of bone scans has improved [5,8,9]. It provides morphological (low-dose CT) and functional or metabolic (SPECT) information on the detected lesions. It can detect 20%–50% more lesions [10] and has higher sensitivity and specificity [11]. In current practice, a metastatic and benign bony lesion is distinguished on SPECT-CT by eyeballing the characteristics of the lesion and its localization, known as the qualitative method, which is subjective and interpreter-dependent [12].

To the best of our knowledge, available data on semiquantitative measurement using SPECT standardized uptake value maximum (SUVmax) and Hounsfield unit (HU) in discriminating benign and metastatic bone lesions are limited. Its clinical utility is not well established, and it is not widely used in clinical practice. Thus, this study aimed to conduct a semiquantitative analysis using the SUVmax and mean HU to distinguish between a metastatic and benign bone lesion in patients with breast cancer. The results may assist in the patient's diagnosis, particularly for an indeterminate or suspicious bony lesion on SPECT-CT.

Materials and Methods

This study was conducted in compliance with the principles of the Declaration of Helsinki and was approved by the Human Research Ethics Committee of Universiti Sains Malaysia (JEPeM code: USM/JEPeM/19120954). Informed consent was waived in view of the retrospective study design.

Bone scintigraphy with SPECT-CT

Patients with breast cancer who underwent bone scintigraphy and SPECT-CT and met the inclusion and exclusion criteria were included. The inclusion criteria were as follows: patients with histologically confirmed breast cancer, irrespective of subtypes, bone lesions detected on both bone scan and SPECT-CT. Conversely, the exclusion criteria were as follows: compression fractures, metabolic bone diseases, ankylosing spondylitis, and bone infections.

Patient information

Personal and clinical details of the patients were obtained from preexisting records in the nuclear medicine clinic. The information was collected by the doctor in charge of the clinic from patients who required whole-body bone scintigraphy (WBBS). The patient's age, height, weight, and clinical data such as diagnosis, date of the bone scan, history of trauma, osteoarthritis, or recent bone surgery, were collected.

SPECT-CT

Standard SPECT was conducted based on the following parameters: 15 seconds per frame, step-and-shoot acquisition, and 64 projections with 180° rotation for each camera head. A 128×128 matrix was used. Low-dose CT was performed immediately before or after SPECT (CT was conducted for anatomical localization, attenuation correction, and calculation of SPECT SUV) without changing the patient's position. The parameters used for low-dose CT were as follows: 30–100 mAs, 120 kV, slice thickness of 1.25 mm, and pitch of 1.75.

Image reconstruction

Planar WBBS images did not require processing. SPECT-CT image fusion and reconstruction were performed on a Xeleris Functional Imaging Workstation (Xeleris 3.1) using GE Evolution Bone (GE HealthCare, Chicago, IL, USA). The SPECT SUVmax was determined using GE's QMetrix software (GE HealthCare), which considered the initial activity of radiopharmaceuticals, time of injection, residual activity in the syringe, activity injected, and timing of SPECT-CT.

Image interpretation

Images were interpreted at workstations (GE Xeleris 3.1) using fusion software, which provided whole-body imaging and multiplanar reformatted SPECT and CT. The technetium-99m methylene diphosphonate (99mTc-MDP) bone scan and SPECT-CT were interpreted by a nuclear medicine physician and a radiologist concurrently.

The qualitative analysis of bone areas with increased radiotracer uptake was categorized into metastasis (M1), benign lesion (M0), and equivocal (Me). Each radiotracer uptake were correlated anatomically on low-dose CT as a standard of reference. Lesions were categorized as bone metastases (M1) if the increased tracer uptake correlated with sclerotic changes on low-dose CT images. Benign lesions were classified into the M0 group if the increased tracer uptake correlated with the facet joints, endplates, within osteophytes, and around the joints on low-dose CT images. If the tracer uptake did not correlate with any CT abnormality, the lesion was categorized as equivocal (Me). Metastatic lesions were identified in the skull, thorax, abdomen, pelvis, and lower limbs. However, only spine lesions, which included 12 in the cervical, 62 in the thoracic, 25 in the lumbar, and 10 in the sacral spine, were analyzed in the study. Likewise, benign lesions were collected predominantly from the facet joints, endplates, and costovertebral joints encompassing two lesions in the cervical, 45 in the thoracic, and 29 in the lumbar vertebrae.

Then, a semiquantitative assessment was performed. The SUVmax on SPECT and the mean HU on low-dose CT were calculated from drawing the volume of interest (VOI) over sites of increased tracer uptake in the skeleton. The principal investigator measured all the VOIs independently. Then, two specialists, one radiologist and one nuclear medicine physician, each with 6 years of experience in their respective fields, measured the VOI independently. The principal investigator compared three sets of data.

The reliability of VOI delineation was assessed using the intraclass correlation coefficient (ICC), a widely used descriptive statistic to assess reliability across raters for quantitative data. Reliability measures the consistency of a set of measurements, that is, a test is considered reliable if the same results were obtained repeatedly using a similar methodology. In addition, all interpreters were given adequate training in drawing the VOI to reduce biases.

The SUVmax and mean HU were calculated only on lesions labeled as M0 (benign) and M1 (metastatic) because these were confirmed by the qualitative method and measurements are more accurate. However, lesions labeled as Me (inconclusive) were excluded because its inclusion may lead to misinterpretation (since a biopsy was not taken). The patient's reconstructed values were normalized based on decay corrected to the time of injection to control fluctuations at the start time of acquisition. The final quantitative tracer concentrations are defined with respect to the injection time. The SUV was calculated based on the equation by Cachovan et al. [13].

$$SUV_{bw} = \text{regional activity concentration} \times \text{weight} / \text{injected activity}$$

The calculation of the SUV based on bodyweight (bw) showed the lowest coefficient of variations compared with lean body weight (lbw) and body surface area. The data obtained were analyzed using research instruments that included data on measured injection activity, time of measurement, time of injection, scan images, SUVmax, and mean HU values obtained from the computational analysis (Fig. 1).

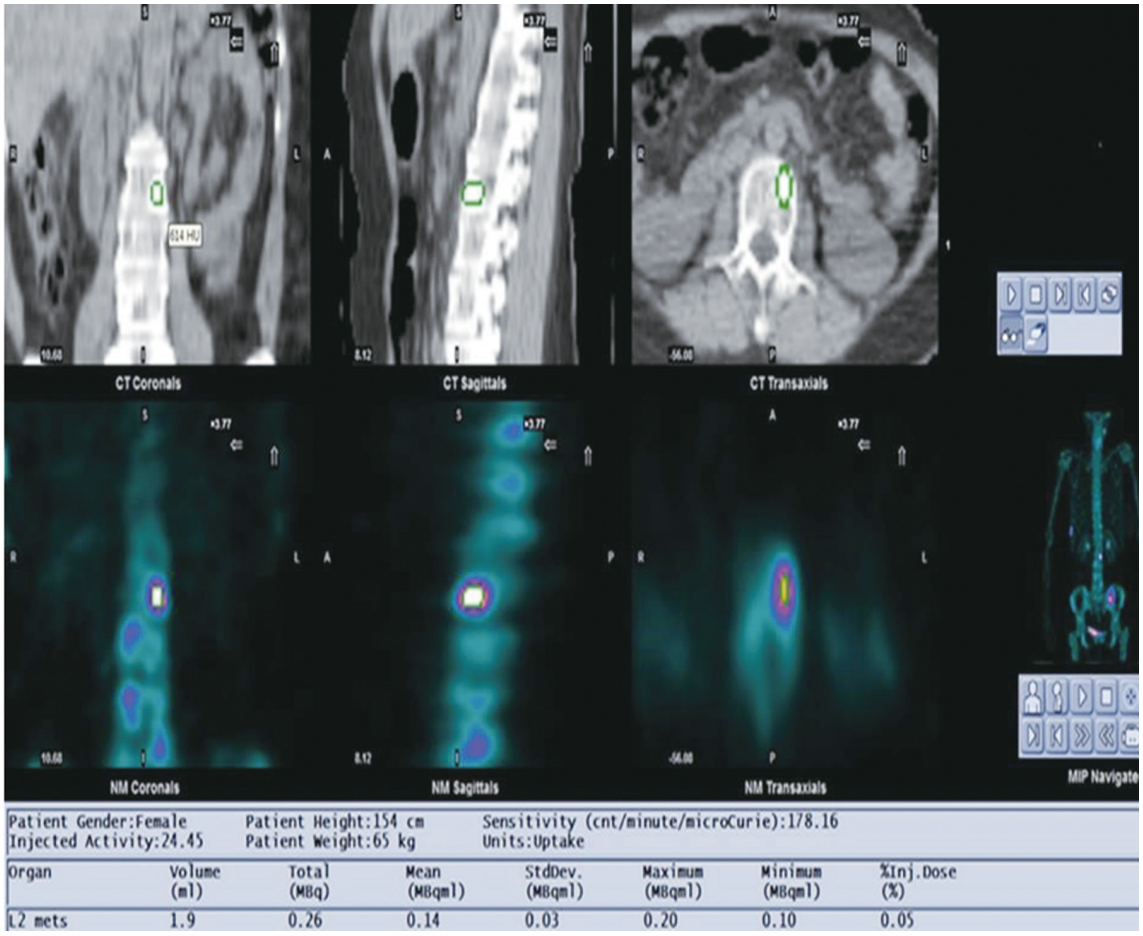

Fig. 1. Image analysis quantifying L2 vertebral sclerotic metastatic lesion using standardized uptake value maximum (SUVmax) and Hounsfield unit (HU) with the QMetrix software on GE's Xeleris 3.1 workstation (GE HealthCare, Chicago, IL, USA). The topmost figure is an image of low-dose computed tomography (CT), and below is image of single-photon emission computed tomography (SPECT). SUVmax on SPECT and mean HU on CT were calculated from drawing volume of interest over sites of increased tracer uptake in the skeleton.

Statistical analysis

Statistical analysis was performed using the IBM SPSS ver. 26.0 (IBM Corp., Armonk, NY, USA). Demographics and profiling of patients were summarized using descriptive studies. The mean and standard deviation are used to describe numerical variables. Independent *t*-tests and correlation were used to compare the SUVmax and mean HU between metastatic and benign bone lesions. The SUVmax and mean HU values for lesions in both the metastatic and benign groups were fitted to the logistic regression model.

Results

A total of 185 lesions were identified in the bone and SPECT-CT scans from 32 patients (mean age, 48.53±9.87 years). Seventy-six were benign bone lesions, and 109 were sclerotic metastatic bone lesions. For benign lesions, patients were mostly 40–70 years old, with a mean age of 53.36±9.26 years. A younger mean age was recorded at 46.00±9.41 years for malignant lesions.

Comparison of the SUVmax between benign and malignant bone lesions

The SUVmax for benign bone lesions ranged from 10.18±12.79, and a higher value was observed for malignant bone lesions at 20.66±14.36. The independent t-test showed a significant mean difference between benign and malignant bone lesions for SUVmax with a *p*-value of <0.001 (Table 1).

Comparison of the mean HU between benign and malignant bone lesions

The mean HU was higher in benign bone lesions at

Table 1. Comparison of SUVmax and mean HU between benign and malignant bone lesions

Characteristic	Benign	Malignant	*t*-stat	*p*-value
SUVmax	10.18±12.79	20.66±14.36	5.104	<0.001
Mean HU	517.65±192.82	166.62±202.02	-11.945	<0.001

Values are presented as mean±standard deviation.
SUVmax, standardized uptake value maximum; HU, Hounsfield unit.

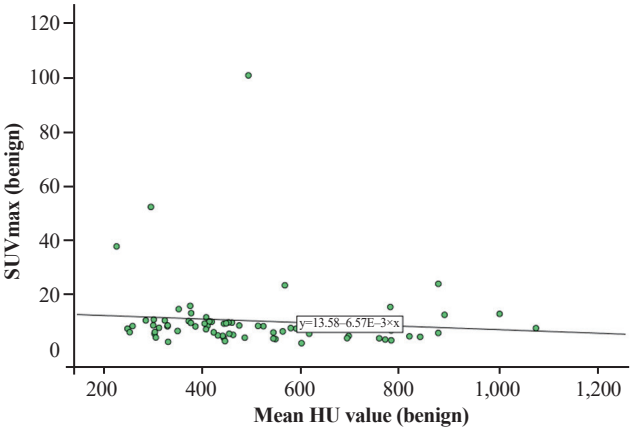

Fig. 2. Correlation plot of standardized uptake value maximum (SUVmax) and mean Hounsfield unit (HU) on benign bone lesions.

517.65±192.82, whereas it ranged from 166.62±202.02 in malignant bone lesions. Therefore, benign bone lesions have higher mean HU than malignant bone lesions. The independent *t*-test revealed a significant mean difference in the mean HU between benign and malignant bone lesions (p<0.001) (Table 1).

Correlation of the SUVmax and mean HU on benign bone lesions

Pearson correlation analysis recorded a weak negative correlation between the SUVmax and mean HU on benign bone lesions (Fig. 2). No statistical significance was recorded, with a *p*-value of 0.394.

Correlation of the SUVmax and mean HU on malignant bone lesions

Pearson correlation analysis recorded a weak positive correlation between the SUVmax and mean HU on malignant bone lesions (Fig. 3). No statistical significance was recorded with a *p*-value of 0.312.

Cutoff values of the SUVmax and mean HU in differentiating malignant and benign bone lesions

The receiver operating characteristic (ROC) curve was

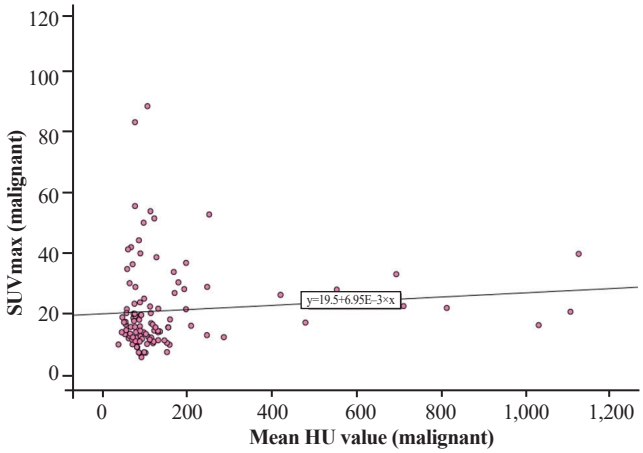

Fig. 3. Correlation plot between standardized uptake value maximum (SUVmax) and mean Hounsfield unit (HU) on malignant bone lesions.

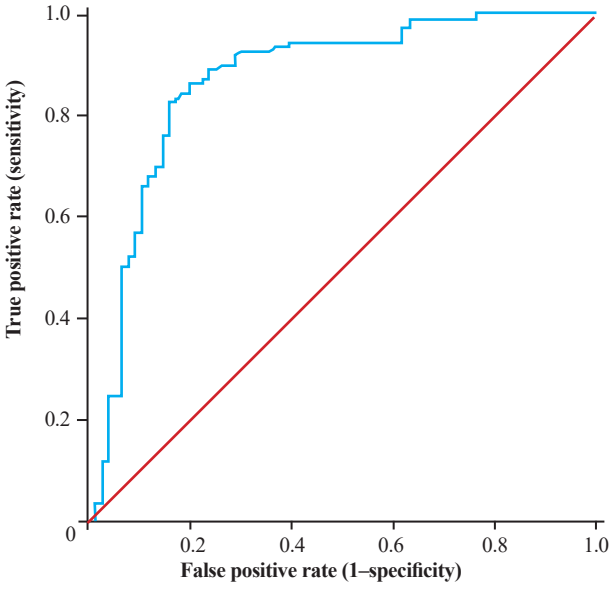

Fig. 4. Receiver operating characteristic (ROC) curve to differentiate between malignant and benign bone lesions using standardized uptake value maximum; the area under the ROC curve is 0.870 (95% confidence interval, 0.812–0.927).

made to assess for the diagnostic accuracy of the SUVmax and mean HU to delineate malignant from benign bone lesions. The analysis of the ROC curve for SUVmax (Fig. 4) showed a very good area under the ROC curve (AUC) with a value of 0.870 (95% confidence interval [CI], 0.812–0.927). The cutoff SUVmax of 10.8 was found to have the best value in differentiating malignant from benign bone lesions with a sensitivity and specificity of 82.6% and 84.2%, respectively. In addition, the ROC curve analysis for the mean HU showed an excellent AUC at 0.933 (95% CI, 0.891–0.976) and a cutoff value of <240.86 (sensitivity of 98.7% and specificity of 88.1%) favoring malignant rather than benign bone lesions (Fig. 5).

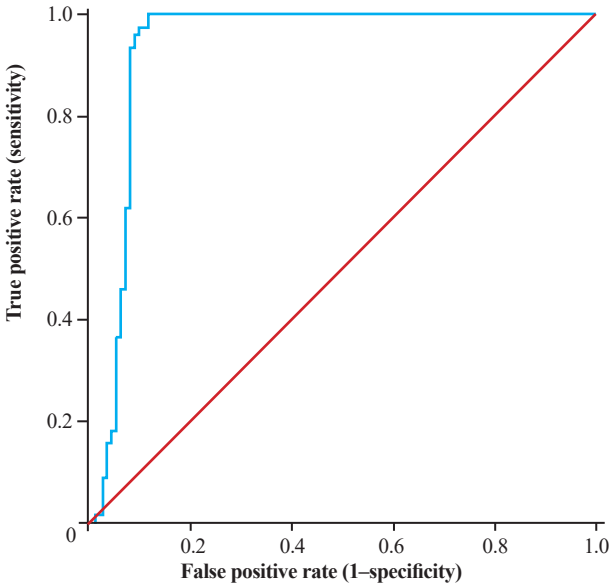

Fig. 5. Receiver operating characteristic (ROC) curve to differentiate between benign and malignant bone lesions with mean Hounsfield unit; the area under the ROC curve is 0.933 (95% confidence interval, 0.891–0.976).

Discussion

The bone is the most common site of distant metastases in patients with breast cancer, in with 69% of patients who died from breast cancer have bone metastases. In contrast, 85% had widespread skeletal involvement [4]. Breast cancer metastasizes predominantly to the vertebrae and pelvis, followed by the ribs, skull, and femur, depending on the degree of vascularization and marrow content. Metastatic bone lesions included lytic, sclerotic, or mixed types. This study focused only on sclerotic lesions because metastatic lesions in breast cancer are predominantly sclerotic. Moreover, only sclerotic bone lesions have higher or positive radiotracer uptake than lytic lesions, which have minimal or no uptake; thus, a quantitative evaluation was impossible.

Metastatic diseases have many debilitating complications, such as bone pain, hypercalcemia, spinal cord compression, and pathologic fracture. Apart from the complications, the treatment of metastatic breast cancer has significant implications including the costs of systemic therapies such as endocrine therapy, chemotherapy, bisphosphonates, monoclonal antibodies, imaging, hospital admission costs for fractures, hypercalcemia or cord compression, and costs of palliative radiotherapy.

Patients with focal diseases are subjected to radical treatment, whereas those with distant spread require systemic therapy [9]. Thus, accurate detection of bone metastases is imperative to ensure correct staging, rapid treatment initiation, and reduce associated morbidity and mortality among patients with breast cancer. A biopsy can determine the definitive nature of a bone lesion. However, obtaining a biopsy from each bone lesion in patients with symptomatic breast cancer is not standard practice in our center or practical because of the multiplicity of lesions. It is invasive and is associated with complications such as infections, hematoma, and organ damage. Moreover, a biopsy on a sclerotic bone lesion is challenging because it is usually scant, inadequate for analysis, and lacks standard protocols [14]. In indeterminate bone lesions evaluated by SPECT-CT scan, apart from bone biopsy, follow-up imaging, correlation with other imaging modalities such as magnetic resonance imaging and positron emission tomography–computed tomography (PET-CT) as well as clinical follow-up, were used to achieve a conclusive diagnosis [9].

Planar bone scintigraphy, or bone scan, provides adequate sensitivity and remains a vital diagnostic tool [14]. It has been the most sensitive and established imaging modality to detect bone metastasis for >30 years in nuclear medicine practice [5]. It is widely available and cost effective. A bone scan helps identify abnormal radiotracer uptake of the skeletal system in patients with symptomatic cancer. 99mTc-MDP is the radiopharmaceutical most used in bone scans. It binds to the bone by chemisorption. Its uptake in the bone indicates an increase in bone turnover caused by changes in bone vascularization, such as in metastasis. If focal abnormalities are found on bone scans, SPECT-CT is performed, which provides both metabolic or functional (SPECT) and morphological (low-dose CT) information, thus enhancing the specificity of bone scans [5]. No further imaging is required if the bone scan is negative.

The pattern and location of radiotracer uptake on SPECT-CT help determine the nature of bone lesions. Metastatic lesions typically involve the posterior part of the vertebral body, whole vertebra, and pedicle, which often correlates with lytic, sclerotic, or mixed lytic–sclerotic lesions on low-dose CT. However, radiotracer uptake can also take place in benign bone lesions. Benign lesions include hemangiomas, osteoid osteomas, bony islands, and degenerative lesions (osteochondrosis, spondylopathy, and spondylarthrosis) [5]. Distinguishing between metastatic and benign bone lesions is often difficult, particularly in the spine, both of which often coexist in patients with breast cancer [15]. If the radiotracer uptake does not correlate with any CT abnormalities, these bone lesions are

classified as indeterminate or equivocal. In this case, quantitative analysis becomes useful, in addition to the traditional qualitative or eyeballing method.

Quantitative SPECT (QSPECT) was introduced in nuclear medicine in the 1990s [13]. It was predicted that SPECT tracer concentration quantification would enter the clinical arena soon. However, only a few approaches to QSPECT have been reported in clinical practice [13] because of the lack of commercially available systems supporting QSPECT along with complex scatter correction [16]. The quantification of SPECT-based radiotracer 99mTc-MDP uptake is a process of calculating the osseous radioactivity concentration expressed as SUV [17]. SUVs can be divided into the SUVmax, peak standard uptake value, and mean standard uptake value. The SUVmax is described as the ratio of radioactivity concentration at a point in time to the injected dose of radioactivity in MBq per kg patient's weight. The SUVmax was used in this study because it is the most accessible and easily measured bone SUV parameter and serves as an excellent osteoblastic biomarker in daily clinical practice [18]. Furthermore, the SUVmax is reproducible and independent of the interest size volume [15,17].

Semiquantitative evaluation of the radiotracer uptake using SUV is widely used in PET-based imaging such as 18F-fluorodeoxyglucose PET-CT [19] because it is an inherently quantitative imaging modality [18]. However, the clinical utility of SUVs in SPECT-based radiotracers is not well established or experimented [20]. PET and SPECT SUVs show minimal variations; thus, further exploration of QSPECT was proposed using SUVs [20]. Moreover, compared with PET-CT, SPECT-CT is superior in terms of cheaper cost and better availability in most centers. The SUVmax taken from the vertebrae was commensurable between PET and SPECT-CT, although the technology varies.

Based on the studies, aforementioned evidence, and the qualitative method, previous studies examined QSPECT and QCT separately. This study explored the semiquantitative evaluation of bone lesions using SPECT-CT SUVmax (SPECT) and mean HU (CT). A total of 185 lesions were collected for analysis, from which 109 were sclerotic metastatic lesions and 76 were benign lesions. Similarly, the mean HU values of metastatic and benign bone lesions were calculated separately. The SUVmax and mean HU for benign and malignant lesions were further compared. Then, a correlation between the SUVmax and mean HU values in differentiating sclerotic metastatic and benign bone lesions was analyzed. The reliability of VOI delineation was assessed using ICC. It is a widely used descriptive statistic to assess reliability across raters for quantitative data. Reliability measures the consistency of a set of measurements. We used up to 10 lesions and produced validation data between three radiologists. The ICC between the three radiologists was 0.992, which indicates a good reliability of 99.2%. To reduce biases, all interpreters were given adequate training in drawing the ROI by an experienced nuclear medicine physician.

SUVs of bone metastases were greater than that of degenerative changes in patients with prostate cancer [15,18,21], breast cancer [22], lung cancer [23], and a combination of both prostate and breast cancer [24,25]. Their findings were similar to ours where the mean SUVmax was significantly higher at 20.66±14.36 for malignant bone lesions than 10.18±12.79 for benign lesions. In this study, the mean SUVmax for benign lesions was within the range of other publications, that is from 6.99±2.58 [25] to 16.73±6.74 [18]. Nonetheless, the mean SUVmax for malignant lesions in this study was lower at 20.66±14.36 than those with published data that ranged from 23.85±14.34 [23] to 40.90±33.46 [18]. Similarly, in the present study, the cutoff value in differentiating malignant from benign lesions was also low at 10.8 with 82.6% sensitivity and 84.2% specificity in contrast to other studies that demonstrate a higher cutoff ranging from 11.10 [23] to 20.0 [15]. This in our opinion could be related to our small sample size, different types of cancers evaluated, the inclusion of extraspinal bone lesions in other studies [21-23], and the mean age of our patients in which was the youngest at 48.53±9.87 years old compared with the rest that ranges from 58.38±9.92 [23] to 74±10 years [21]. Benign degenerative bone lesions will be more apparent in the older population, contributing to a higher SUVmax, than in younger patients.

In addition to quantitative SUV, QCT was also explored using mean HU calculation on malignant and benign lesions. The mean HU value obtained was 166.62±202.02 for malignant lesions, which was significantly lower than that for benign lesions at 517.65±192.82, and the cutoff value of <240.86 indicated a malignant bone lesion with 98.7% sensitivity and 88.1% specificity. To the best of our knowledge, only one study has examined QCT, which showed significantly lower mean HU for osteoblastic bone metastases than for enostosis, a non-cancerous bony abnormality characterized by a localized region of compact mature cortical bone found within the cancellous bone [26]. However, the value obtained by Ulano et al. [26]

was higher than our value, with mean HU attenuation values of 654±176 HU for osteoblastic metastases and 1,190±239 HU for enostoses, and the cutoff threshold value of <885 HU (95% sensitivity and 96% specificity) indicated metastatic lesion as the favored diagnosis. The difference in the results obtained when compared with our study was caused by certain factors, for example, nearly all patients in their study underwent contrast-enhanced CT [26], their study population had a mixture of tumor types, which included breast, prostate, transitional cell, and ovarian carcinoma, and their study did not assess the mean HU of degenerative bone lesions. On the contrary, we used non-contrasted CT, included only patients with breast cancer, and did not include enostoses in the mean HU evaluation because it rarely exhibits tracer uptake on bone scintigraphy [26].

The study also analyzed the correlation between the SUVmax and HU in discriminating metastatic and benign bone lesions. Although a previous study stated a significant physiological correlation between these two variables in healthy vertebrae and proposed further study on degenerative and metastatic lesions [13], the present study found only a weak negative correlation for benign bone lesions and a weak positive correlation in malignant lesions between the SUVmax and mean HU, which was not statistically significant. This, in our opinion, could be related to the small sample size. This study has valuable effects on patients and the healthcare system in Malaysia and internationally. It allows for the accurate detection of metastatic bone lesions and their correct management, ensuring a better prognosis for patients with breast cancer. This study also serves as a reporting aid among radiologists and nuclear medicine physicians.

Conclusions

In addition to the traditional qualitative method, the semiquantitative analysis using SPECT-CT SUVmax and mean HU is reliable in differentiating sclerotic metastatic and benign bone lesions among patients with breast cancer. Metastatic lesions have higher SUVmax and lower mean HU values, whereas benign lesions demonstrate higher mean HU and lower SUVmax comparatively. A weak correlation with no statistical significance exists between the SUVmax and mean HU on benign and malignant lesions. In this study, the proposed cutoff values to differentiate between malignant and benign lesions are 10.8 for the SUVmax and 240.86 for mean HU.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Funding

This research was funded by short-term research grant of the Universiti Sains Malaysia (304/PPSG/631534) and was also supported by the Fundamental Research Grant Scheme, Ministry of Higher Education, Malaysia (FRGS/1/2020/ SKK08/USM/02/1).

ORCID

S. Thadchaiani Saminathan: https://orcid.org/0000-0002-7198-2764; Wan Aireene Wan Ahmed: https://orcid.org/0000-0002-9976-1509; Norazlina Mat Nawi: https://orcid.org/0000-0002-0476-1398; Nashrulhaq Tagiling: https://orcid.org/0000-0003-3850-7563; Ilyana Aziz: https://orcid.org/0009-0009-9685-5735; Yusri Udin: https://orcid.org/0009-0006-4686-5917; Mohd Fazrin Mohd Rohani: https://orcid.org/0000-0002-8450-0170; Wan Mohd Nazlee Wan Zainon: https://orcid.org/0000-0001-6257-0162; Mohammad Khairul Azhar Abdul Razab: https://orcid.org/0000-0001-5788-8176

Author Contributions

Conceptualization: STS, NMN; data curation: YU; formal analysis: STS; methodology: STS; software: STS, UY, MFMR; supervision: WAWA, NMN; writing–original draft: STS, WAWA, MFMR, NMN; writing–review and editing: WAWA, NMN, NT, IA, WMNWZ, MKAAR; and final approval of the manuscript: all authors.

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