

# Quantitative bone SPECT/CT applications for cartilaginous bone neoplasms

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## Abstract

**Objectives:** To evaluate the ability of quantitative values obtained with bone single photon emission computed tomography/computed tomography (SPECT/CT) to differentiate benign from malignant cartilaginous bone neoplasms. **Subjects and Methods:** Bone SPECT/CT scans of 10 patients with 8 benign cartilaginous bone neoplasms (4 enchondromas, 1 periosteal chondroma, 1 osteochondroma, 1 bizarre parosteal osteochondromatous proliferation, 1 chondroblastoma) and 2 malignant cartilaginous bone neoplasms (1 periosteal chondrosarcoma, 1 chondrosarcoma) were retrospectively analyzed with maximum standardized uptake value (SUVmax), mean SUV (SUVmean), metabolic bone volume (MBV), and total bone uptake (TBU) of primary lesions. **Results:** Mean SUVmax of 8 benign and 2 malignant cartilaginous bone neoplasms were  $1.93 \pm 1.02$  (range 0.59-3.41) and  $6.07 \pm 0.86$  (5.46-6.67), respectively with no overlap ( $P=0.028$ ). Mean SUVmean of those were  $1.24 \pm 0.71$  (range 0.36-2.36) and  $4.05 \pm 0.30$  (3.84-4.26), respectively with no overlap ( $P=0.00036$ ). Mean MBV of those were  $7.17 \pm 4.19$  (range 3.17-13.77) and  $10.29 \pm 10.05$  (3.19-17.4), respectively with no significant difference ( $P=0.74$ ). Mean TBU of those were  $9.22 \pm 8.31$  (range 1.15-23.61) and  $43.19 \pm 43.7$  (12.26-74.13), respectively with no significant difference ( $P=0.47$ ). **Conclusion:** Standardized uptake value obtained with bone SPECT/CT may be useful to differentiate benign from malignant cartilaginous bone neoplasms, thus helping the orthopedic surgeon towards the most appropriate treatment procedure.

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## Introduction

Cartilaginous tumors, which are primarily composed of cartilage, represent a wide variety of neoplasm ranging from benign to extremely aggressive malignant lesions. Enchondroma is a benign tumor, characterized by the formation of well-circumscribed nodules of mature hyaline cartilage or rarely fibro-cartilaginous tissue, while chondrosarcoma is a malignant cartilaginous tumor showing the production of atypical cartilage matrix and infiltrative growth pattern encasing pre-existing trabecular bone [1]. The differential diagnosis of cartilaginous bone lesions is based on histology which has to be interpreted considering clinical and imaging findings; nevertheless biopsy sample is not always representative of the whole lesion, which is often highly heterogeneous. Accurate imaging diagnosis is essential in guiding management decisions about whether a lesion can be observed, or whether biopsy or surgery is needed.

Although bone scintigraphy with technetium-99m (<sup>99m</sup>Tc) examinations are widely used to evaluate osteoblastic activity, it is technically difficult to quantify local tracer uptake using conventional bone scintigraphy, even with images acquired using single photon emission computed tomography (SPECT) [2, 3]. On the other hand, recent advances including integration of computed tomography (CT) for attenuation correction together with sophisticated reconstruction techniques have enabled quantitative measurements with SPECT/CT suitable for derivation of standardized uptake value (SUV) [4-6]. It is considered that quantitative SPECT/CT may soon have an enormous clinical effect in the practice of modern nuclear medicine by making imaging biomarkers available. Several recently published studies have demonstrated the clinical application of quantitative bone SPECT/CT for diagnosing bone metastasis [7, 8]. However, to the best of our knowledge, no original studies of quantitative bone SPECT/CT for primary musculoskeletal neoplasm have been presented, and the clinical utility of quantitative bone SPECT/CT for diagnosing cartilaginous bone neoplasm has yet to be clarified. The purpose of this study was to evaluate the ability of quantitative values obtained from bone SPECT/CT to differentiate benign from malignant cartilaginous bone neoplasms.

## Subjects and Methods

### Patients

Our institutional review board granted approval for this retrospective review of clinical and imaging data, and waived the need for obtaining informed consent from the patients. From June 2018 to March 2020, 10 patients (4 males, 6 females; mean age  $44.4 \pm 24.3$  years; range 15-87 years) with cartilaginous bone neoplasms, as determined by pathological findings (n=6) by the surgery or the biopsy and findings of clinical and other radiological imaging modalities (n=4) such as X-ray, CT, or magnetic resonance imaging (MRI), underwent bone SPECT/CT scanning. Patient and tumor characteristics are shown in Table 1. Four of the patients had enchondroma of the radius (n=1), femur (n=1), finger bone (n=1), or toe bone (n=1). One patient each had periosteal chondroma of the finger bone, osteochondroma of the femur, bizarre parosteal osteochondromatous proliferation in the finger bone, and chondroblastoma of the tibia. Whereas, one patient had low grade periosteal chondrosarcoma of the tibia and one had low grade chondrosarcoma of the femur.

### Bone scintigraphy

Planar bone scintigraphy was performed 3-4 hours after intravenous administration of  $^{99m}\text{Tc}$ -hydroxymethylene diphosphonate ( $^{99m}\text{Tc}$ -HMDP) with 555MBq dose (or effective doses

proposed by EANM [9] in paediatric patients), using a SPECT/CT scanner (NM/CT670; GE Healthcare, Pittsburgh, Pa) equipped with a low-energy high-resolution collimator. Quantitative SPECT/CT images were acquired by using a hybrid system. Computed tomography images were first obtained by using the following parameters: tube voltage of 120kV, tube current of 40-80mA with "autoMa" function and 35 noise level, X-ray collimation of 20mm (16x1.25mm), table speed of 5mm/sec, table feed per rotation of 27.5mm per rotation, tube rotation time of 0.5 seconds, pitch of 1.375:1, and matrix of 512x512. The CT images were reconstructed by using adaptive statistical iterative reconstruction algorithm (ASiR; GE Healthcare) into 3.75mm-thick sections. Then, SPECT images were acquired by using the following parameters: energy peak of 140.5KeV with 7.5% window (130-151KeV), step-and-shot mode acquisition (15 seconds per step and 60 steps per detector) with 6° angular increment, and body contour scanning option. Extra window for scatter correction was set at 120KeV with 5% window (114-126KeV). Single photon emission tomography images were reconstructed by using an iterative ordered subset expectation maximization algorithm (10 iterations and 10 subsets) with CT-based attenuation correction, scatter correction, and resolution recovery in the vendor-supplied software (Volumetric MI; GE Healthcare). Post-reconstruction filter (Gauss filter with frequency of 0.48 and order of 10) was applied. Reconstructed images were set at a matrix of 128x128 with section thickness of 4.42mm and zoom factor of 1.0.

**Table 1.** Patient and tumor characteristics.

	Sex	Age	Site	Diagnosis	SUVmax	SUVmean	MBV	TBU
1	Male	15	Distal phalanges of ring finger	Periosteal chondroma	0.59	0.36	3.17	1.15
2	Female	53	Tibia	Chondroblastoma	1.13	0.71	10.62	7.54
3	Female	17	Metacarpal bone of fourth toe	Enchondroma	1.24	0.76	5.62	4.27
4	Female	47	Metacarpal bone of little finger	Enchondroma	1.29	0.76	5.49	4.15
5	Male	58	Radius	Enchondroma	2.15	1.36	5.19	7.07
6	Female	39	Femur	Enchondroma	2.54	1.52	13.77	20.89
7	Female	87	Proximal phalanges of index finger	Bizarre parosteal osteochondromatous proliferation	3.10	2.36	2.14	5.05
8	Male	71	Femur	Osteochondroma	3.41	2.08	11.35	23.61
9	Female	42	Tibia	Periosteal chondrosarcoma	5.46	3.84	3.19	12.26
10	Male	15	Femur	Chondrosarcoma	6.67	4.26	17.4	74.13

SUVmax: maximum standardized uptake value, SUVmean: mean standardized uptake value, MBV: metabolic bone volume, TBU: total bone uptake

matrix of 128×128 with section thickness of 4.42mm and zoom factor of 1.0.

### Image analysis

The delineation of the volumes of interest (VOI) was retrospectively re-performed by a board-certified nuclear medicine physician with 14 years' experience in adult patient's SPECT and 4 years' experience in pediatric SPECT and blinded to patient information including clinical history and results of bone marrow biopsy for this paper using a commercially available software GI-BONE (AZE Co., Ltd., Tokyo Japan), which reports the statistics for the various SUV, such as max (SUV<sub>max</sub>) and mean (SUV<sub>mean</sub>), metabolic bone volume (MBV), and total bone uptake (TBU) [10]. Maximum SUV was defined as the maximum concentration in the target lesion (maximum radioactivity/voxel volume)/(injected radioactivity/body weight). Mean SUV was defined as (total radioactivity/VOI volume)/(injected radioactivity/body weight). Metabolic bone volume (mL) was the calculated volume obtained by the accumulation of radiopharmaceutical. Total bone uptake (g) was expressed by the product of MBV and SUV<sub>mean</sub>. The VOI was calculated as follows. First, a histogram of image counts was created. Then, it decreased value of 95% from the maximum is the base value. The threshold value is obtained by adding 0.5 standard deviation (SD) to the base value.

### Statistical analysis

The patients were divided into 2 groups, benign and malignant cartilaginous bone neoplasms, and the mean value and SD for SUV<sub>max</sub>, SUV<sub>mean</sub>, MBV, and TBU were determined, with statistical differences assessed with t-test. All analyses were performed using the SAS software package, version 9.3 (SAS Institute, Cary, NC), and P values less than 0.05 were considered to indicate statistical significance.

## Results

Maximum SUV, SUV<sub>mean</sub>, MBV, and TBU for all 10 cartilaginous bone neoplasms with 8 benign and 2 malignant tumors are shown in Table 1. Two representative cases are shown in Figures 1, 2.

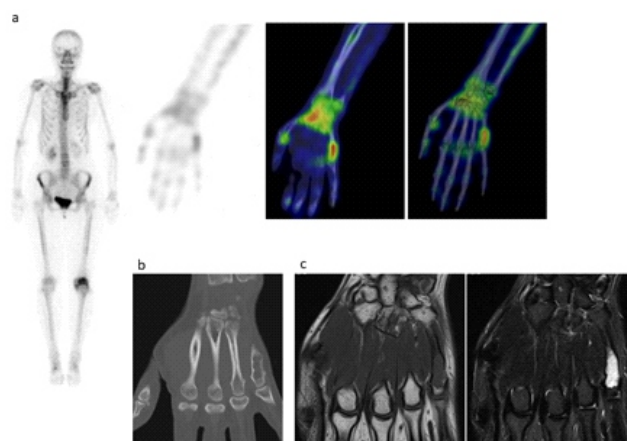
Maximum SUV of periosteal chondroma, chondroblastoma, enchondroma, Bizarre parosteal osteochondromatous proliferation, and osteochondroma were 0.59, 1.13, 1.24-2.54, 3.10, and 3.42, respectively. Whereas, SUV<sub>max</sub> of periosteal chondrosarcoma and chondrosarcoma were 5.46 and 6.67. Mean SUV<sub>max</sub> of 8 benign and 2 malignant cartilaginous bone neoplasms were  $1.93 \pm 1.02$  (range 0.59-3.41) and  $6.07 \pm 0.86$  (5.46-6.67), respectively with no overlap. The SUV<sub>max</sub> of malignant cartilaginous bone neoplasms were significantly higher than that of benign cartilaginous bone neoplasms ( $P=0.028$ ).

Mean SUV of periosteal chondroma, chondroblastoma, enchondroma, Bizarre parosteal osteochondromatous proli-

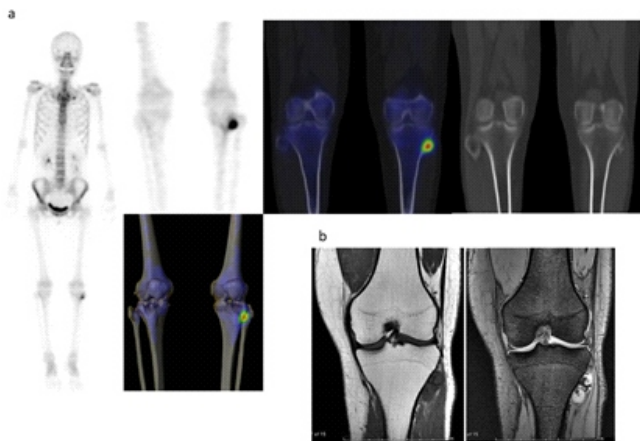
feration, and osteochondroma were 0.36, 0.71, 0.76-1.52, 2.36, and 2.08, respectively. Whereas, SUV<sub>mean</sub> of periosteal chondrosarcoma and chondrosarcoma were 3.84 and 4.26. Mean SUV of 8 benign and 2 malignant cartilaginous bone neoplasms were  $1.24 \pm 0.71$  (range 0.36-2.36) and  $4.05 \pm 0.30$  (3.84-4.26), respectively with no overlap. The SUV<sub>mean</sub> of malignant cartilaginous bone neoplasms were significantly higher than that of benign cartilaginous bone neoplasms ( $P=0.00036$ ).

Metabolic bone volume of periosteal chondroma, chondroblastoma, enchondroma, Bizarre parosteal osteochondromatous proliferation, and osteochondroma were 3.17, 10.62, 5.19-13.77, 2.14, and 11.35, respectively. Whereas, MBV of periosteal chondrosarcoma and chondrosarcoma were 3.19 and 17.4. Mean MBV of 8 benign and 2 malignant cartilaginous bone neoplasms were  $7.17 \pm 4.19$  (range 3.17-13.77) and  $10.29 \pm 10.05$  (3.19-17.4), respectively. Metabolic bone volume of malignant cartilaginous bone neoplasms were little higher than that of benign cartilaginous bone neoplasms with no significant difference ( $P=0.74$ ).

Total bone uptake of periosteal chondroma, chondroblastoma, enchondroma, Bizarre parosteal osteochondromatous proliferation, and osteochondroma were 1.15, 7.54, 4.15-20.89, 5.05, and 23.61, respectively. Whereas, TBU of periosteal chondrosarcoma and chondrosarcoma were 12.26 and 74.13. Mean TBU of 8 benign and 2 malignant cartilaginous bone neoplasms were  $9.22 \pm 8.31$  (range 1.15-23.61) and  $43.19 \pm 43.7$  (12.26-74.13), respectively. Total bone uptake of malignant cartilaginous bone neoplasms were higher than that of benign cartilaginous bone neoplasms with no significant difference ( $P=0.47$ ).



**Figure 1.** A 47-year-old female with chondroma (Case 4) of the metacarpal bone of left little finger underwent preoperative quantitative bone SPECT/CT scanning. Histological diagnosis of the surgical specimen was enchondroma. a. Bone scintigraphy image and single photon emission computed tomography/computed tomography (SPECT/CT) showing faint radiotracer uptake at the metacarpal bone of left little finger with maximum standardized uptake value (SUV<sub>max</sub>), SUV<sub>mean</sub>, metabolic bone volume (MBV) and total bone uptake (TBU) values of 1.29, 0.76, 5.49 mL, and 4.15 g, respectively. B. Coronal CT (bone image) showing osteolytic change and endosteal scalloping of the metacarpal bone of left little finger. c. Coronal T1-weighted MR image showing hypointense mass and fat-suppressed T2-weighted MR image showing intense hyperintense mass at the metacarpal bone of left little finger.



**Figure 2.** A 42-year-old female with periosteal chondrosarcoma (Case 9) of the left tibia underwent preoperative quantitative bone SPECT/CT scanning. Histological diagnosis of the surgical specimen was low grade periosteal chondrosarcoma. a. Bone scintigraphy image and SPECT/CT showing focal moderate radiotracer uptake at the left tibia with SUVmax, SUVmean, MBV and TBU values of 5.46, 3.84, 3.19mL, and 12.26g, respectively. b. Coronal T1-weighted MR image showing multilobular mass projecting outwardly from left tibia as area of hypointensity and proton density-weighted MR image showing multilobular and hyperintense mass with hypointense septa and region, likely reflecting calcification.

## Discussion

This is the first original paper to present findings showing effective clinical application of quantitative bone SPECT/CT for differentiating benign from malignant cartilaginous bone neoplasms. We found SUVmax and SUVmean were useful to differentiating benign from malignant cartilaginous bone neoplasms with no overlap. Thus, our findings suggest that an improved management algorithm could incorporate a strategy of active surveillance when SUV is very low and biopsy when SUV is high. By identifying the region of greatest SUV for percutaneous biopsy, quantitative bone SPECT/CT could reduce the rate of false-negative biopsies.

Single photon emission computed tomography/CT is a state-of-the-art modality that produces objective quantitative data and known to be a powerful investigative tool in clinical practice. Using results of robust algorithms for CT-based attenuation correction, scatter correction, and resolution recovery, SPECT/CT generates imaging voxels, denoted as units of radioactivity per volume [i.e., kilobecquerels (kBq)/mL]. This is a fundamental difference as compared to traditional nuclear imaging methods, such as planar scintigraphy, SPECT, and nonquantitative SPECT/CT, with which counts per second are used to produce imaging units. With quantitative SPECT/CT, lesion radioactivity can be normalized for determination of injected radioactivity, resulting in quantitative parameter values, such as percent injected dose and SUV [4–6]. Zeintl et al. (2010) [4] found that advanced SPECT/CT technology can facilitate quantitative  $^{99m}\text{Tc}$  SPECT imaging with excellent accuracy in both phantom (error <3.6%) and patient (error <1.1%) studies. Furthermore, in a phantom study, Gnesin et al. (2016) [6] reported that both absolute and

concentration of activity results determined with quantitative  $^{99m}\text{Tc}$  SPECT/CT were within 10% of the expected values.

Several other recently published studies have also demonstrated clinical application of quantitative bone SPECT/CT for diagnosing bone metastasis in patients with prostate cancer [7, 8]. Kuji et al. (2017) [7] investigated 170 patients with prostate cancer who underwent skeletal quantitative SPECT/CT using  $^{99m}\text{Tc}$ -methylene diphosphonate ( $^{99m}\text{Tc}$ -MDP) and reported mean SUVmax values of  $40.9 \pm 33.5$  for bone metastasis ( $n=126$ ),  $7.6 \pm 2.4$  for normal thoracic vertebra bodies ( $n=100$ ),  $8.1 \pm 12.2$  for normal lumbar vertebra bodies ( $n=140$ ), and  $16.7 \pm 6.7$  for degenerative changes ( $n=114$ ), and concluded that those values for cases with bone metastasis were significantly higher as compared to cases with normal vertebra bodies or degenerative change. Furthermore, Tabotta et al. (2019) [8] examined results related to 264 bone metastatic lesions in 26 prostate cancer patients, as well as 24 spinal and pelvic osteoarthritic lesions in 13 patients with no malignancy obtained with skeletal quantitative SPECT/CT using  $^{99m}\text{Tc}$ -2,3-dicarboxy propane 1,1-diphosphate ( $^{99m}\text{Tc}$ -DPD). They reported that mean SUVmax was  $34.6 \pm 24.6$  for spinal and pelvic bone metastasis cases, and  $14.2 \pm 3.8$  for osteoarthritic lesion cases. Moreover using an optimum SUVmax cut-off of 19.5 for discriminating spinal and pelvic bone metastasis from osteoarthritic lesions, sensitivity and specificity were 87% and 92%, respectively.

All four patients with enchondroma who did not have severe pain or fracture showed relatively low SUVs in our series. Kim et al. (2003) [11] demonstrated that typically, benign enchondroma shows normal or only slightly increased uptake of a bone-seeking agent on delayed bone scintigraphy and markedly increased activity of enchondroma with pain is most often associated with pathologic fracture or malignant degeneration.

Several groups have reported the usefulness of fluorine-18-fluorodeoxyglucose ( $^{18}\text{F}$ -FDG)-positron emission tomography/computed tomography (PET/CT) for differentiating benign from malignant cartilaginous bone neoplasms [12–14]. In a systemic review analysis, Subhawong et al. (2017) [12] reported that SUV of 101 malignant cartilaginous bone neoplasms and 65 benign cartilaginous bone neoplasms were  $4.4 \pm 2.5$  and  $1.6 \pm 0.7$ , respectively with significant difference ( $P < 0.0001$ , t-test). In a study of 17 chondromas and 19 chondrosarcomas, Jesus-Garcia et al. (2016) [13] reported that the ability of  $^{18}\text{F}$ -FDG PET/CT for differentiating chondroma from chondrosarcoma showed good performance (sensitivity/specificity/accuracy = 94.7%/94.1%/94.4%) using a SUV cut-off of 2.2. However, low-grade chondrosarcomas (grade 1) show low SUV, therefore  $^{18}\text{F}$ -FDG PET/CT scan is not a reliable tool to differentiate enchondroma from low-grade chondrosarcomas, due to a high overlap of metabolic activity between these two entities [12, 14]. This limitation of  $^{18}\text{F}$ -FDG PET/CT may apply to bone SPECT/CT. Bone scintigraphy showed considerable overlap between enchondroma and low-grade chondrosarcoma [15], with 65% of low-grade chondrosarcomas exhibiting low radiotracer uptake and 21% of enchondromas exhibiting increased radiotracer up-

take [16]. If larger number of patients with cartilaginous bone neoplasms will be included in the future, we will encounter overlap of SUV between benign and malignant cartilaginous bone neoplasms.

Computed tomography has a limitation of soft tissue characterization. It has been increasingly discussed whether MRI might be an appropriate alternative for CT in a hybrid imaging system (morphological and functional imaging procedures) for several reasons: 1) MRI offers a superior soft tissue contrast in contrast to CT, 2) MRI can provide functional information such as T2-weighted imaging, MR spectroscopy, diffusion weighted imaging, contrast-enhanced imaging, and perfusion imaging complementary to PET, unlike to CT, and 3) MRI does not cause a radiation exposure that may be a concern in young patients and in case of repetitive examinations or follow-up studies [17]. Also the use of specific PET tracers according to tumor types instead of  $^{18}\text{F}$ -FDG should be actively developed for more effective and exact results in the future.

The main limitations of this study are the small subject population, and lack of histological confirmation for all benign disease. However, it would have been unethical to investigate all affected patients using invasive procedures. We consider that diagnosis of primary benign cartilaginous tumor based on radiological imaging and follow-up results is clinically valid. Especially the number of chondrosarcoma was limited in our series. Therefore, the grade (e.g., low-grade (G1), intermediate-grade (G2), high-grade (G3)) or histological subtype (e.g., conventional, myxoid, clear cell) of chondrosarcoma cannot be evaluated. Nevertheless, the usefulness of quantitative values obtained with bone SPET/CT in patients with primary cartilaginous tumor should be tested with a larger cohort.

*In conclusion*, SUV obtained with bone SPECT/CT may be useful to differentiate benign from malignant cartilaginous bone neoplasms, thus helping the orthopedic surgeon towards the most appropriate treatment procedure. Furthermore, objective quantitative bone SPECT/CT has potential to improve management of patients affected by primary skeletal disease.

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*The authors declare that they have no conflicts of interest.*

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