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Early-Phase SPECT/CT for Diagnosing Osteomyelitis: A Retrospective Pilot Study

Soo Jin Lee, MD, PhD[1], Kyoung Sook Won, MD, PhD[2], Hyung Jin Choi, MD[1], Yun Young Choi, MD, PhD[1]

[1]Department of Nuclear Medicine, Hanyang University Medical Center, Seoul, Korea; [2]Department of Nuclear Medicine, Keimyung University Dongsan Hospital, Daegu, Korea

Objective: The aim of this pilot study was to investigate the potential of early-phase single-photon emission computed tomography (SPECT)/computed tomography (CT) using technetium-99m methyl diphosphonate (^{99m}Tc-MDP) for diagnosing osteomyelitis (OM).
Materials and Methods: Twenty-one patients with suspected OM were enrolled retrospectively. Three-phase bone scan (TPBS), early-phase SPECT/CT (immediately after blood pool planar imaging), and delayed-phase SPECT/CT (immediately after delayed planar imaging) were performed. The final diagnoses were established through surgery or clinical follow-up for over 6 months. We compared three diagnostic criteria based on (I) TPBS alone, (II) combined TPBS and delayed-phase SPECT/CT, and (III) early-phase SPECT/CT alone.
Results: OM was diagnosed in 11 of 21 patients (nine surgically and two clinically). Of the 11 OM patients, criterion-I, criterion-II, and criterion-III were positive in six, seven, and 10 patients, respectively. Of the 10 non-OM patients, criterion-I, criterion-II, and criterion-III were negative in five, five, and seven patients, respectively. The sensitivity/specificity/accuracy of criterion-I, criterion-II, and criterion-III for diagnosing OM were 54.5%/50.0%/55.0%, 63.6%/50.0%/57.1%, and 90.9%/70.0%/87.5%, respectively.
Conclusion: This pilot study demonstrated the potential of using the early-phase SPECT/CT to diagnose OM. Based on the results, prospective studies with a larger sample size should be conducted to confirm the efficacy of early-phase SPECT/CT.
Keywords: *Bone and bones; Radionuclide imaging; Single photon emission computed tomography computed tomography*

INTRODUCTION

The three-phase bone scan (TPBS) consisting of blood flow, blood pool, and delayed bone phase is considered a sensitive technique for diagnosing osteomyelitis (OM); however, its specificity is poor, especially when the bone has been compromised. In a recent systematic review on the accuracy of diagnostic imaging modalities for peripheral post-traumatic OM, TPBS had a high sensitivity, ranging from 89% to 100%, but low specificity (0% to 10%) (1).

Single-photon emission computed tomography (SPECT)/ computed tomography (CT) provides a precise anatomical correlation of tracer uptake; for example, distinguishing between bone and soft tissue uptake (2). It has been reported that the addition of delayed-phase SPECT/CT improves the diagnostic performance of TPBS for OM by avoiding false-positive or equivocal results, which increases the specificity (3, 4). However, the specificity still appears to be suboptimal, especially for diagnosing OM involving compromised bones, for example, post-traumatic OM, despite the addition of delayed-phase SPECT/CT (5).

The criteria for a positive TPBS include increased flow and blood pool activity in the bone affected by OM. However, it is not always easy to determine the degree of flow and blood pool activity within the area of suspected OM on planar images, especially when they have increased blood pool activity in the surrounding soft tissue. As OM is often accompanied by soft-tissue swelling or cellulitis, the increased flow and blood pool activity in the compromised

bone can be ambiguous due to those in the soft tissues. Since SPECT/CT provides a more precise anatomical localization of tracer activity than planar images, we thought that early-phase SPECT/CT would provide more accurate information about blood pool activity within the area of suspected OM. A recent case report demonstrated that early-phase SPECT/CT conducted 15 minutes after a single intravenous injection of technetium-99m methyl diphosphonate (^{99m}Tc-MDP) was useful for delineating the tracer activities of synovitis and an osteoarthritic joint (6).

The aim of this study was to evaluate and compare the diagnostic potential of early-phase SPECT/CT in patients with suspected OM with those of TPBS and delayed-phase SPECT/CT.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Hanyang University Medical Center (IRB No. 2017-05-020), and the need for written informed consent was waived.

Patients

This study retrospectively enrolled 21 patients (9 males and 12 females; mean age, 56.4 ± 15.9 years) with suspected OM who underwent all the three modalities of bone scan, which were conventional TPBS, early-phase SPECT/CT, and delayed-phase SPECT/CT, between August 2015 and May 2017. OM was suspected if there were pain and at least one other clinical symptom, such as swelling, redness, or fever, as well as an elevated level of C-reactive protein or erythrocyte sedimentation rate.

Seven patients had a history of fracture; six of them had a surgical repair, and one did not. Two had underlying rheumatoid arthritis, and two had diabetic foot ulcers. A patient had an epidural abscess. The remaining nine patients had no other remarkable history.

TPBS and Early- and Delayed-Phase SPECT/CT

All the patients underwent TPBS as well as early- and delayed-phase SPECT/CT. The flow and blood pool planar images, early-phase SPECT/CT images, and delayed-phase SPECT/CT images were obtained using a dual-head SPECT/CT gamma camera (Symbia T16, Siemens Medical System). Delayed planar images were obtained using the same Symbia T16 system or another dual-head gamma camera (ECAM, Siemens Healthineers). Both systems were equipped with a low-energy high-resolution collimator. Symbia T16

was equipped with a 16-slice CT scanner.

Patients were encouraged to be well-hydrated before imaging. After an intravenous injection of ^{99m}Tc-MDP ranging from 740 MBq to 925 MBq, dynamic flow images of the area of interest were obtained for 60 seconds (one second/frame), immediately followed by blood pool images from 1 minute to 2 minutes. An early-phase SPECT/CT scan was performed immediately after the blood pool scan (from 2 minutes to 11 minutes after injection). Increased activity on early-phase SPECT/CT was expected because of the increased blood pool activity and the early bone uptake in the affected bone; SPECT/CT was not completed within 10 minutes after the injection. Delayed regional and whole-body planar bone images were obtained 4 hours after the injection. Patients emptied their urinary bladder just before delayed imaging. Delayed-phase SPECT/CT was performed immediately after the delayed planar imaging.

During SPECT/CT imaging, gentle physical restraints were used to immobilize the upper and lower extremities to prevent misalignment from a patient's unintended movements. Each detector acquired sixty-four step-and-shoot images with 3-degree intervals for 8 seconds per step. The energy window was centered at 140 keV ± 7.5%. SPECT images were reconstructed into 256 x 256 matrices using an iterative algorithm with 8 iterations and 8 subsets. After SPECT acquisition, a helical CT scan was performed with acquisition settings of 110 kVp, 100 mAs, and a pitch of 0.938. The images were reconstructed into 1.25-mm slices.

Image Interpretation

Two experienced nuclear medicine physicians who were blinded to the clinical, surgical, and pathologic results (two physicians with 6 and 25 years of experience in nuclear imaging, respectively) reviewed and analyzed the images independently, and a consensus was reached. Each reader reviewed three image sets (TPBS alone, TPBS and delayed-phase SPECT/CT combined, and early-phase SPECT/CT alone) separately at one-week intervals in a random order using the following interpretation criteria.

- Criterion-I using TPBS alone (more than 4 hours after tracer injection)
: increased uptake within the suspected bone in both blood pool and delayed images.
- Criterion-II using blood pool images of TPBS and

delayed-phase SPECT/CT (more than 4 hours after tracer injection)

: when blood pool activity within the suspected bone lesion in TPBS is consistent with that of delayed-phase SPECT/CT.

- Criterion-III using early-phase SPECT/CT alone (within 11 minutes after tracer injection)

: increased tracer activity in the suspected bone lesion of early-phase SPECT/CT.

Criterion-I (TPBS Only)

TPBS was considered positive for OM if the tracer uptake had increased within the bone with suspected OM on the delayed bone images and it corresponded with increased tracer activity on blood pool images. Findings on blood flow images were not taken into consideration. If the presence of increased activity on blood pool or delayed images within the bone or in the soft tissue was equivocal, TPBS was classified as negative for OM.

Criterion-II (TPBS and Delayed-Phase SPECT/CT)

It was considered positive if delayed-phase SPECT/CT

images showed increased tracer uptake within the boundary of the bone associated with increased tracer activity on planar blood pool images, regardless of the increased tracer activity within the bone with suspected OM on delayed bone images of TPBS. It was considered negative if SPECT/CT showed no significantly increased uptake in the bone, regardless of the presence or absence of increased tracer uptake in the surrounding soft tissue. Findings on delayed planar images were not taken into consideration for criterion-II.

Criterion-III (Early-Phase SPECT/CT Only)

It was considered positive for OM if early-phase SPECT showed increased activity in the bone with suspected OM and negative if there was no increased activity in the bone. Any other findings on TPBS or delayed-phase SPECT/CT were not taken into consideration.

Images were obtained more quickly with early-phase SPECT/CT (in 11 minutes after the injection) than with the other methods (more than 4 hours in criterion-I and -II) used in this study.

Table 1. Patient Data and Results of Three Interpretation Criteria

Patients No.	Location	Symptom Duration	Underlying Conditions	Three-Phase Bone Scan			Criteria			Final Diagnosis	Diagnostic Method
				Flow	Pool	Bone	I	II	III		
1*	Skull	1 mo	Epidural abscess	+	+	+	OM	OM	-	-	Surgery
2	Knee	20 d	-	+	+	+/-	-	-	-	-	Surgery
3*	Tibia	2 mo	Fracture + surgery	+	+	+	OM	OM	-	-	Surgery
4	Tibia	1.5 mo	Fracture + surgery	+	+	+	OM	OM	OM	-	Clinical FU
5	Ankle	10 d	Fracture	-	+	+/-	-	-	-	-	Clinical FU
6	Ankle	5 mo	-	-	+/-	-	-	-	-	-	Surgery
7	Foot	1 mo	-	-	-	-	-	-	-	-	Clinical FU
8	Foot	2 mo	Fracture + surgery	-	+	+	OM	OM	OM	-	Surgery
9	Wrist	3 mo	-	-	-	+/-	-	-	-	-	Clinical FU
10	Knee	1 mo	-	+	+	+	OM	OM	OM	-	Clinical FU
11*	Sternum	12 d	-	-	-	+/-	-	-	OM	OM	Surgery
12	Spine	2.6 mo	-	+	+	+	OM	OM	OM	OM	Surgery
13	Spine	10 d	-	-	+	+	OM	OM	OM	OM	Clinical FU
14	Tibia	3 mo	-	+	+	+	OM	OM	OM	OM	Surgery
15	Tibia	1.4 mo	Fracture + surgery	-	+	+	OM	OM	OM	OM	Surgery
16*	Tibia	12 mo	Fracture + surgery	-	+	-	-	OM	OM	OM	Surgery
17*	Tibia	1.1 mo	Fracture + surgery	+	+/-	+	-	-	OM	OM	Surgery
18	Foot	4 mo	Arthritis	-	+	+	OM	OM	OM	OM	Surgery
19	Foot	4 mo	Arthritis	+	+	+	OM	OM	OM	OM	Surgery
20	Foot	1 mo	Diabetic foot ulcer	-	-	+	-	-	-	OM	Surgery
21*	Foot	15 d	Diabetic foot ulcer	+	+	-	-	-	OM	OM	Clinical FU

*Denotes the six patients in whom criterion-III was correct while criterion-I and/or criterion–II was incorrect. d = days, FU = follow-up, mo = months, OM = osteomyelitis, + = positive finding, - = negative finding, +/- = equivocal finding

### Pathological and Clinical Diagnosis

The gold standard for the diagnosis of OM was pathology results from surgical specimens or the confirmation of clinical progression during 6 months of follow-up.

Statistical Analyses

We calculated and compared the sensitivities, specificities, and accuracies of each of the three criteria. The McNemar chi-squared test was used to compare the diagnostic accuracies.

RESULTS

All the patients were clinically suspected of having OM. Results of the locations of suspected OM, underlying conditions, imaging diagnoses based on each of the three interpretation criteria, and the final diagnoses in the 21 patients are detailed in Table 1. OM was finally diagnosed in 11 patients (52.4%) (by surgery in nine and by clinical follow-up in two) and excluded in 10 patients (by surgery in five and by clinical follow-up in five).
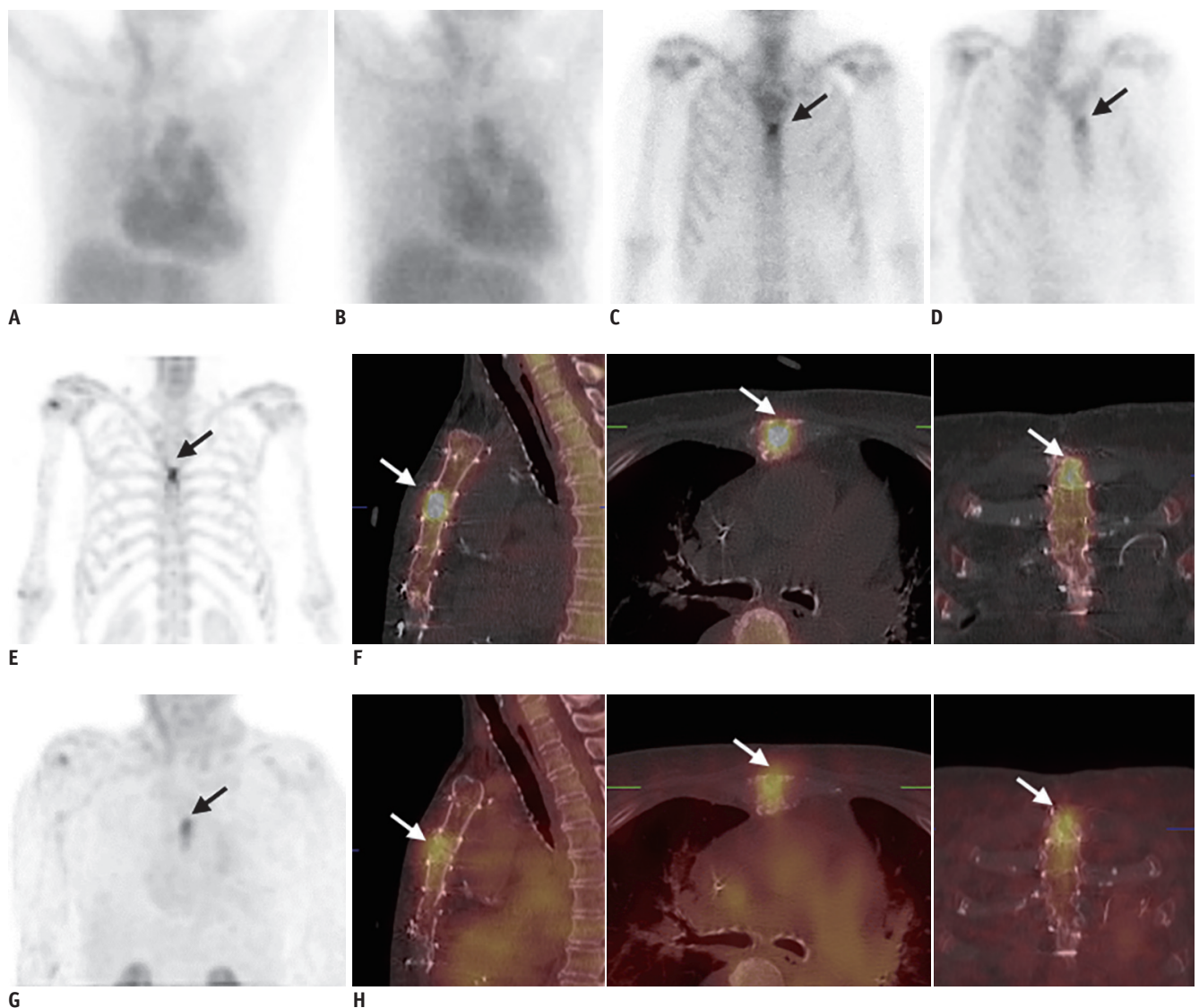
Fig. 1. A 72-year-old female patient with sternal OM (patient no. 11 in Table 1).
Anterior and right oblique blood pool images did not show a significant abnormal tracer localization **(A, B)**, while anterior and right oblique delayed planar images **(C, D)**, a MIP image **(E)** and selected sagittal, transverse, and coronal delayed-phase SPECT/CT images **(F)** showed increased tracer uptake in the upper sternum (arrows). A MIP image **(G)** and sagittal, transverse, and coronal early-phase SPECT/CT **(H)** showed tracer localization in the upper sternum (arrows), but no other bone uptake was observed. Surgery confirmed sternal OM. This positive finding of early-phase bone SPECT/CT may be due to the increased blood pool activity as well as the early bone uptake in the infected sternum. MIP = maximum intensity projection, OM = osteomyelitis, SPECT/CT = single-photon emission computed tomograph/computed tomography
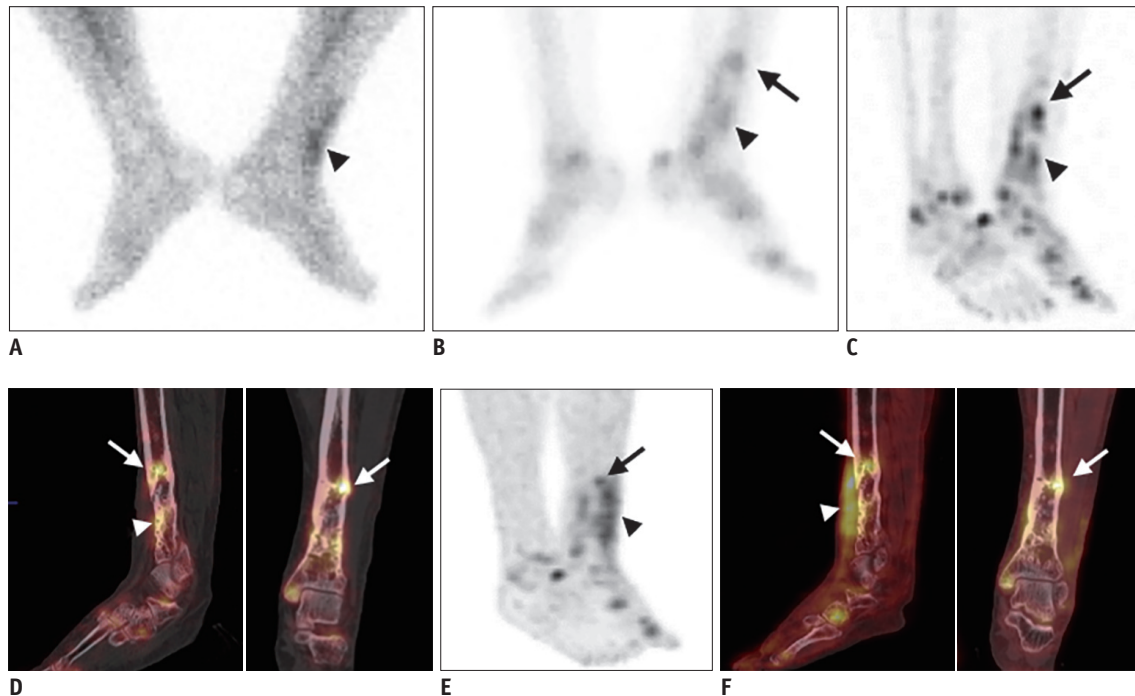
Fig. 2. A 58-year-old male patient with tibia OM (patient no. 17 in Table 1).
He had undergone surgery for a tibia fracture 5 years before bone scan and removal of an implant 4 months earlier. After that, serous drainage from the wound continued. A medial blood pool image **(A)** showed diffuse linear tracer localization along the soft tissue anterior to the distal left tibia (arrowhead); it was ambiguous to evaluate the tibia involvement (equivocal). The medial delayed planar image **(B)** showed two foci of increased uptake at the left distal tibia (arrow, arrowhead); the upper focal lesion matched the fracture site, and the lower focal lesion was observed in the cortical bone on bone SPECT/CT (arrows, arrowheads, **C, D**). The finding of blood pool planar images was equivocal and consequently evaluated as not OM (negative by criterion-I and -II). Early-phase MIP, sagittal fused SPECT/CT, and coronal SPECT/CT images (criterion-III) showed focally increased activity at the upper fracture site of the tibia (arrows, **E, F**); this focal activity in the tibia was not observed (or at best equivocal) on the planar blood pool image **(A)**. The diffuse linear activity in the blood pool **(A)** was more observed in the soft tissue on early-phase SPECT/CT, especially on sagittal SPECT/CT (arrowhead, **F**). Surgery had confirmed the OM at the upper fracture site of the left tibia.

Table 2. Diagnostic Values of Three Criteria

	Criterion-I	Criterion-II	Criterion-III
Sensitivity (%)	54.5	63.6	90.9
Specificity (%)	50.0	50.0	70.0
PPV (%)	54.5	58.3	81.0
NPV (%)	54.5	55.6	76.9
Accuracy (%)	55.0	57.1	87.5

NPV = negative predictive value, PPV = positive predictive value

Performance of the Three Interpretation Criteria

The backgrounds of the 11 patients with OM are as follows: six were positive by criterion-I; seven were positive by criterion-II, including the six patients who were positive by criterion-I and one with post-traumatic OM; ten were positive by criterion-III, including all of the seven patients who were positive by criterion-II and three more patients (one with no underlying disease, one with fracture and surgical history, and one with diabetic foot ulcer). Figures 1 and 2 illustrate two cases of OM (sternal OM in Patient

No. 11 and tibial OM in patient no. 17) that were true-positives by criterion-III (increased activity in bone on early-phase SPECT/CT); they were not by criterion-I or -II (no significantly increased activity or equivocal activity on the planar blood pool images).

Of the ten patients without OM, five were false positives for OM by criterion-I and criterion-II (three with fractures and surgery [patient nos. 3, 4, and 8], one with epidural abscess [patient no. 1], and one with no underlying disease [patient no. 10]). Of these five patients, two (patient nos. 1 and 3) were true negatives by criterion-III, while the remaining three were false positives by criterion-III. No case was false-positive by criterion-III among the cases with true-negative by citerion-I or criterion-II.

The sensitivities, specificities, and accuracies are detailed in Table 2. Briefly, criterion-III had the highest sensitivity (90.9%), specificity (70.0%), and accuracy (87.5%). Criterion-I and criterion-II had considerably lower sensitivities, specificities, and accuracies, all of which
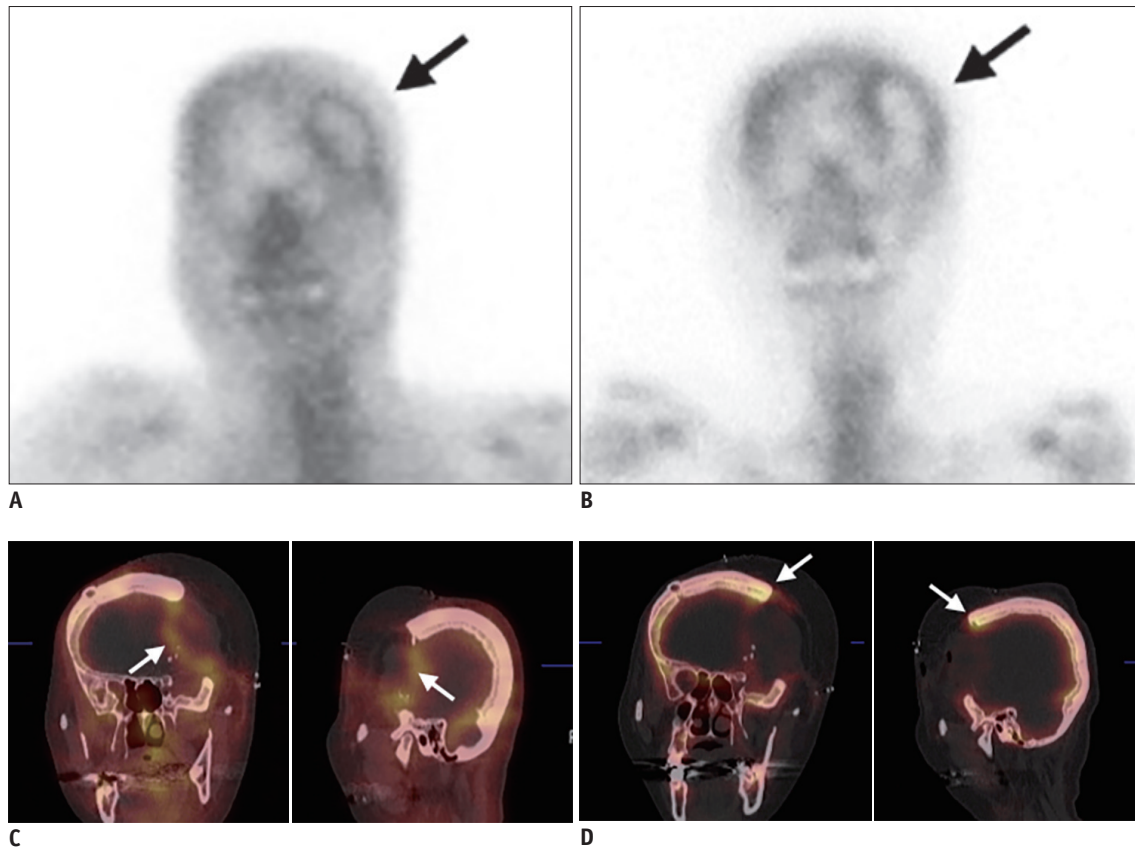
Fig. 3. A 46-year-old female patient with frontal epidural abscess (patient no. 1 in Table 1).
She had undergone a craniectomy due to brain hemorrhage 10 years earlier. Anterior planar blood pool image **(A)** and delayed image **(B)** showed curvilinear tracer localization at the left calvarium (arrows), which was considered positive for OM. On the other hand, coronal and sagittal early-phase SPECT/CT **(C)** showed tracer accumulation primarily in the soft tissue along the peripheral soft tissue of abscess (arrows) but not in the bone, which was negative for OM by criterion-II. Delayed-phase coronal and sagittal SPECT/CT **(D)** showed increased uptake in the bone at the craniectomy site (arrows), which was most likely due to surgery that had been performed one month before the bone scan, given that no OM was found.

ranged from 50% to 64%. The sensitivities of criterion-II and criterion-III were not significantly different ($p >$ 0.05, McNemar test). Criterion-III and criterion-II had comparable sensitivities, but OM diagnosis with criterion-III was quicker.

DISCUSSION

In this pilot study, we compared three diagnostic criteria: (I) TPBS alone, (II) combined TPBS and delayed-phase SPECT/CT, and (III) early-phase SPECT/CT alone. As we expected, Criterion-III based on the early-phase SPECT/CT alone showed good potential for diagnosing OM.

Patients with suspected OM often have substantial cellulitis. In an animal model of OM and cellulitis, blood flow in OM lesions assessed by O–15 labeled H_2O PET imaging was elevated by a factor 1.5; blood flow in an inflamed soft tissue was significantly more elevated (by a

factor 6) (7). Although this study did not involve humans, it still showed why it could be difficult to visually assess blood flow and blood pool activity in bones with suspected OM surrounded by inflamed soft tissue using conventional TPBS, which is a 2-dimensional imaging technique. Therefore, we thought that early-phase SPECT/CT would facilitate a more precise assessment of blood pool activity in bones affected by OM.

In our study, the early-phase SPECT/CT (i.e., criterion-III) was useful for reclassifying two of the five false-positive cases and three of the four false-negative cases by criterion-I and criterion-II into true-negatives and true-positives, respectively. On the other hand, none of the three false-positive cases and the false-negative case by criterion-III was true-negative or true-positive by criterion-I or criterion-II. As shown in Figures 1 and 2 (false-negative cases of criterion-I and -II), although the increased blood pool activities of OM were difficult to distinguish on blood

pool planar images due to the blood pool activities of each mediastinum and overlying soft tissue inflammation of the tibia (each negative and equivocal), the early-phase SPECT/CT showed increased activities (partly from blood pool activities and partly from early bone uptakes) with accurate anatomical localization. Similarly, in Figure 3 (false positive case by criterion-I and -II), early-phase SPECT/CT confirmed curvilinear tracer localization at the left calvarium on blood pool planar images, which was in the soft tissue along the peripheral soft tissue of the abscess but not in the bone. Identifying blood pool activity and finding its precise anatomical correlation using early-phase SPECT/CT improved the sensitivity and specificity.

Previous studies reported 78% sensitivity and 50% specificity for OM diagnosis using TPBS, including SPEC/CT (3). In our study, the sensitivity and specificity of TPBS, including SPECT/CT (criterion-II), were 63.6% and 50%. The relatively lower sensitivities observed in our study may have been due to the underlying conditions of the enrolled patients. In our study, the patients had various underlying diseases; six had fractures with surgical repairs, one had a fracture, two had rheumatoid arthritis, two had diabetic foot ulcers, and one had an epidural abscess. Of the 11 patients diagnosed with OM, combined TPBS and delayed SPECT/CT had four false-negative cases (1 without underlying disease, 1 with a fracture with surgical repair, and 2 with diabetic foot ulcers). In the sternal OM without an underlying disease in Figure 1, the sternal blood pool activity in TPBS was difficult to detect because it was obscured by the background activity of the mediastinal great vessels. The other false-negative cases of blood pool activity in TPBS obtained from the two cases of diabetic foot ulcers and 1 case of a fracture with surgical repair may be attributed to the difficulty in distinguishing the superimposed infections resulting from diabetic neuroarthropathy and increased osteoblastic activity due to recent fractures with surgical repair. On visual assessment, these may be misinterpreted in 2-dimensional images of TPBS.

The sample size was small because the current retrospective pilot study had to include patients with suspected OM who underwent all the three modalities of bone scan: TPBS, early-phase SPECT/CT, and delayed-phase SPECT/CT. Although this was a small study, the sensitivities of combined TPBS and delayed-phase SPECT/CT and early-phase SPECT/CT alone were not significantly different, and the results are meaningful.

In our study, TPBS and early- and delayed-phase SPECT/

CT after a single 99mTc-MDP injection were performed consecutively in a day, and early-phase SEPCT/CT was not completed within 10 minutes after injection. Further studies need to assess the diagnostic potential of earlier-phase SPECT/CT (blood pool SPECT/CT) in a large population of patients immediately after a 99mTc-MDP injection to ensure only blood pool activity and prevent early bone uptake in the infected bone.

In conclusion, this pilot study demonstrated the potential of using early-phase SPECT/CT to diagnose OM. The results are encouraging, and prospective studies with a larger sample size should be conducted to confirm the efficacy of early-phase SPECT/CT.

Conflicts of Interest
The authors have no potential conflicts of interest to disclose.

ORCID iDs
Soo Jin Lee
  https://orcid.org/0000-0002-5600-1315
Kyoung Sook Won
  https://orcid.org/0000-0001-7185-911X
Hyung Jin Choi
  https://orcid.org/0000-0003-2003-813X
Yun Young Choi
  https://orcid.org/0000-0002-7535-4343

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