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FULL PAPER

Value of SPECT/CT in the assessment of necrotic bone fragments in patients with delayed bone healing or non-union after traumatic fractures

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Objective: To evaluate the value of single-photon emission computed tomography / computed tomography (SPECT/CT) compared with planar bone scintigraphy (BS) in the assessment of necrotic bone fragments in patients with delayed bone healing or non-union after traumatic fractures.

Methods: Retrospective evaluation of patients with traumatic fractures and suspected delayed healing or non-union and/or persistent pain or suspected infection who had undergone planar late phase BS and SPECT/CT between 2011 and 2018. On the BS and SPECT/CT images, a necrotic fragment was considered if there was an area of absent radiotracer uptake (photopenia) related to bone at the fracture site. Histology served as a reference standard (presence or absence of necrotic bone fragments). If histology was not available, intra-operative findings and combined clinical and imaging follow-up served as reference standards.

Results: In 37 consecutive patients with traumatic fractures (femur ($n = 18$), tibia (11), humerus (6), radius (1),

jaw (1)), necrotic bone fragments were suspected in 11 fractures (29.7%) on BS and in 16 fractures (43.2%) on SPECT/CT. 35 fractures (94.6%) had metallic implants. Histology showed necrotic fragments in 10/11 (90.9%) patients. For the detection of necrotic bone fragments, SPECT/CT showed sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 100%, 95%, 94%, 100%, and 97%, respectively, and BS 67%, 95%, 91%, 81%, and 83%, respectively. SPECT/CT significantly outperformed BS with better area under curve (AUC) for SPECT/CT (0.9773) compared to planar imaging (0.8106) (p -value < 0.01).

Conclusions: SPECT/CT is an accurate tool in the assessment of necrotic bone fragments in patients with delayed bone healing or non-union after traumatic bone fractures and is superior to conventional planar BS.

Advances in knowledge: SPECT/CT is accurate and superior to planar BS in identification of necrotic bone fragments, responsible for delayed bone healing/non-union after fractures.

INTRODUCTION

Approximately 5.6 million fractures occur annually in the USA and up to 10% of these fractures result in delayed healing or non-union.¹ Risk factors for delayed healing or non-union are either patient-dependent or patient-independent. The patient-dependent risk factors include sex, old age, history of smoking, various medical comorbidities like diabetes, hypertension, genetic disorders, prolonged use of NSAIDs, nutritional deficiencies, and metabolic disorders.² Patient-independent risk factors responsible for delayed healing or non-union include pattern of fracture (such as transverse, linear, oblique, spiral, comminuted, etc), its location and extent of displacement, degree of bone loss, severity of soft tissue injury (minor or severe),

presence or absence of infection, and quality of surgical treatment (clean and skilled surgery versus post operative complications).³ Correct assessment of fracture healing is essential for patients because it determines whether they will tolerate weight-bearing, whether they can return to work and routine activities with restored quality of life, or whether any additional surgery is required for further improvement. Non-unions are not only challenging from the treatment side but also have socio-economic implications with loss of job, wages, coupled with mounting treatment cost leading to debt trap and subsequent social fall outs.⁴ Diagnostic tests for assessment of fracture healing include plain radiography, CT, MRI, bone scintigraphy (BS), and several laboratory tests, which are important for

the evaluation and detection of infection as well as metabolic and endocrine abnormalities. The imaging hallmarks which point to delayed healing or non-union include absence of bony bridging between the fracture ends, persistent fracture lines with visualized gap, absence of improvement or evidence of healing on serial radiographs, problems with the surgical metal implants (loosened or broken), and persistent or progressive deformity.⁴

The diagnosis of sequestrum or necrotic bone fragment in patients with non-union after traumatic fractures has important impact on the surgical approach. Necrotic bone fragments prevent bone healing, thus have to be removed and augmentation with bone grafts might be necessary.⁵ CT is a very accurate modality for the assessment of fracture healing but limited regarding the detection of necrotic fragments.⁶ MRI may be limited by artifacts caused by metal hardware used for fracture fixation.

BS with Tc-99m (^{99m}Tc)-labeled diphosphonates has been used for decades for the assessment of bone disorders. The two important factors responsible for the degree and intensity of radiotracer accumulation at a particular site in bone are its blood supply and the rate of new bone formation.⁷ BS can detect most of the fractures within 24 h of the occurrence. On an average, the minimum time for normalization of radiotracer activity is around 6 months post-development of fracture, and by around 2 years of the event, most of the fractures would have shown normalization of the radiotracer activity.⁸ However, in non-aligned fractures, the process of bone remodeling is going on continuously, and hence, these fractures may not exhibit regression of the radiotracer activity with normal scintigraphic appearance. One of the causes for delayed healing or non-union of the fracture is presence of a necrotic fragment at the fracture site.

In this study, we assessed the value of single-photon emission computed tomography/computed tomography (SPECT/CT) for the detection of necrotic fragments in patients with delayed bone healing or non-union and/or persistent pain or suspected infection after traumatic fractures and compared the performance of SPECT/CT with planar BS.

METHODS AND MATERIALS

Retrospective analysis of consecutive patients with traumatic fracture and suspected delayed healing or non-union and/or persistent pain between 2011 and 2018 who had undergone both BS and SPECT/CT was performed. 10 out of 54 patients without available follow-up were excluded. This study was approved by the ethics committee, and the need for written informed consent was waived (EKNZ 2019-00594).

The study includes consecutive patients from a single institution. The inclusion criteria were: (a) patients who underwent BS with SPECT/CT from 2011 to 2018; (b) clinical indication being delayed bone healing/non-union of traumatic fracture with suspicion of necrotic bone fragment; (c) in house surgery and further clinical management; and (d) histology or follow-up (clinical/radiological) available. Most of these patients had only X-ray as a prior imaging due to the presence of metal implant MRI was not feasible and not performed.

SPECT/CT PROTOCOL

All patients underwent BS with Tc-99m-DPD (Tc-99m-3,3-diphosphono-1,2-propanedicarboxylic acid; Teceos, Behringwerke AG, Marburg, Germany). The radiotracer was injected intravenously (average tracer activity 657.92 MBq (17.78 mCi); range: 580 to 704 MBq (15.7 to 19 mCi)) and early-phase planar scintigraphy images were obtained 5 min post-injection (matrix size: 256×256 mm, field of view: 40 cm) under the hybrid SPECT/CT scanner with a built-in flat-panel CT component (BrightView XCT; Philips Healthcare, Best, The Netherlands). Planar late-phase scintigraphy images were acquired 3 h post-radiotracer injection (matrix size: 256×256, field of view: 40 cm), followed by the acquisition of SPECT/CT images of the region of interest (fracture site). SPECT was performed in step-and-shoot mode with 64 projections, at the speed of 20 s per projection (SPECT frame matrix size: 128×128). SPECT images were reconstructed with an iterative 3D ordered subsets expectation maximization (OSEM) algorithm (Astonish, Philips, Netherlands). CT images were acquired in high-resolution mode with an isotropic CT voxel size of 0.33×0.33×0.33 mm³ (CT slice thickness 0.33 mm, matrix size of 512×512 mm) and reconstructed with iterative filters. SPECT and CT images were automatically fused with dedicated software (Extended Brilliance Workspace; Philips Healthcare, Netherlands), reformatted in coronal and sagittal planes.

IMAGE INTERPRETATION

Planar (early and late phase) and SPECT/CT images were reviewed by an experienced nuclear medicine physician and a double board-certified radiologist and nuclear medicine physician with specialized training in musculoskeletal (MSK) imaging. The final image interpretation was done with consensus of these two reviewing physicians.

- (1) The state of fracture healing was assessed using the CT images from the SPECT/CT [non-union (no bony bridging), partial union (partial bridging), complete union (complete bridging)].
- (2) The early and late planar phases of every BS were assessed for the presence or absence of abnormal radiotracer accumulations.
- (3) The radiotracer uptake at the fracture site on the planar image of the BS was visually graded as absent (grade 0), mild (Grade 1), moderate (Grade 2), and high (Grade 3) in relationship to normal bone uptake on the contralateral side.
- (4) On the planar late-phase images and SPECT/CT images, necrotic fragment was considered present if there was an area of absent radiotracer uptake (photopenia) related to bone at the fracture site. The two physicians reviewing the images were blinded to the detailed clinical information except for the main purpose of the study: assessment of delayed bone healing/non-union with suspicion of necrotic bone fragment.
- (5) The size of the necrotic bone fragment was measured (largest diameter in any plane).
- (6) Statistics: Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were assessed and the performance of SPECT/CT and BS was compared with ROC analysis.

- (7) Reference standard: In operated patients, intraoperative finding and histology served as reference standard. In histology, osteocytes with missing nucleoli and fat necrosis were signs of necrotic bone. In those patients in which no histology was obtained, imaging and clinical follow-up served as reference standards. If complete fracture healing was visible on follow-up imaging (X-ray and/or CT) without demarcation of a bony fragment, this case was diagnosed as “no necrotic fragment”. Clinically absence of pain, overall improvement in general condition with improved quality of life, as well as improved mobility of the bone/joint in question, and no more suspicion of infection were taken as improvement and negative for necrotic fragment. The average follow-up period was 25 months [range: 3 to 91 months].

RESULTS

44 patients were identified. Seven patients who were not available for follow-up were excluded. Therefore, 37 patients [23 male, 14 female; average age 51.6 years (range: 22 to 84 years)] were assessed with following fractures: femur ($n = 18$), tibia (11), humerus (6), radius (1) and jaw (1). The average time from fracture to BS was 30 months (range: 2 to 312 months). 35 fractures (94.6%) had metal implants in the form of metal plates, screws, rods, intramedullary nails, external fixators, or wires. 19 fractures showed non-union, 11 partial union and seven complete union in SPECT/CT based on the bridging of fracture line as seen on the CT part of the SPET/CT. Out of 37 patients, 13 had SPECT/CT within 6 months of the fracture, whereas 24 patients had it more than 6 months after the fracture. (Table 1)

11 patients had suspicion of infection and the early phase of bone scan showed hyperemia in 10 patients, of which six had necrotic bone fragments.

The late phase of BS and SPECT/CT showed increased activity at the fracture site in all patients. There was suspicion of necrotic

bone fragment (presence of focal photopenia) on late phase of planar BS in 11 fractures out of 37 (29.7%) and in 16 fractures out of 37 (43.2%) on SPECT/CT. Out of 16 fracture sites with necrotic fragments, three fracture sites had two necrotic fragments, while the rest had one necrotic fragment only.

Out of the 37 fracture sites, seven had mild degree of uptake (of which two showed no bridging on CT, four showed partial bridging, and one showed complete bridging), 22 had moderate uptake (of which 11 showed no bridging, six partial bridging, and five complete bridging) and remaining eight had high uptake (of which six showed no bridging, one partial bridging, and one complete bridging). This translates as 17 patients with moderate-to-high radiotracer uptake had no bridging on the CT images, and 16 patients with mild-to-moderate uptake had partial-to-complete bridging on the CT images (Table 2, Figure 1).

The sizes of the necrotic fragments ranged from 1 to 10 cm (average size: 3.7 cm).

Out of these 37 patients, 25 underwent surgery. Necrotic fragments were resected in 11 patients of which 10 had positive histology for necrotic fragment and one was negative (Figures 2–4). The remaining patients had conservative management and routine follow-up. According to the defined reference standards, SPECT/CT showed sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 100%, 95%, 94%, 100%, and 97%, respectively, for detection of necrotic bone fragments and delayed healing/non-union. Corresponding values for planar imaging for prediction of necrotic fragment and non-union were 67%, 95%, 91%, 81%, and 83% respectively (Tables 3–5). The ROC analysis showed improved performance with SPECT/CT with better area under the curve (AUC) for SPECT/CT (0.9773) compared to planar imaging (0.8106) (p -value < 0.01) (Figure 5).

DISCUSSION

In the present study, SPECT/CT was an accurate tool for the assessment of necrotic bone fragments in non-unions after traumatic fractures. SPECT/CT was superior to planar BS. Detection of a necrotic bone fragment with SPECT/CT helps in deciding subsequent revision surgery. Critical factors for the viability of bone in a traumatic fracture are sufficient blood and oxygen supply and adequate balance between different local osteoblastic and osteoclastic factors. Functional imaging with BS and SPECT/CT has been successfully used for the detection of avascular necrosis and osteonecrosis.⁹ The main biochemical mechanism underlying the uptake of radiotracer in BS during the process of bone remodeling and new bone formation is the high affinity of Tc-99m-labelled bisphosphonates to newly formed hydroxyapatite crystals by the process of chemisorption.¹⁰ This process of chemisorption, in turn, depends upon maintained regional vascular supply of the bone and preserved osteoblastic activity. According to the pathological definition, a bony sequestrum or necrotic fragment is defined as a piece of devitalized bone which has separated from the surrounding bone during the process of necrosis.¹¹ The imaging appearance of a sequestrum on radiographic and CT images is in the form of a piece of calcified bone,

Table 1. Patient characteristics

N (Total Number)	37 patients
Male : Female	23 : 14
Age	Average 52 years (range: 22–84)
Bones involved	18 (Femur), 11 (Tibia), 6 (Humerus), 1 (Radius), 1 (Jaw)
Metal Implant	Present: 35; Absent: 2
Average time from fracture to BS	30 months (range: 2–312)
BS within 6 months of fracture	13
BS more than 6 months after fracture	24
Histology available	11
Average follow-up period	25 months (range: 3–91)
Surgery	25
Conservative management	12

Table 2. Grade of radiotracer uptake at the fracture site versus grade of osseous bridging in CT images

Grade of osseous bridging in CT images	Grade of radiotracer uptake at the fracture site			
	No uptake	Mild	Moderate	High
No bridging	0	2	11	6
Partial bridging	0	4	6	1
Complete bridging	0	1	5	1
Total (n = 37):	0	7	22	8

sometimes within a lucent lesion.¹¹ CT with multiplanar reformations is a better modality compared to conventional X-rays for the evaluation and detection of a sequestrum. However, differentiating between necrotic bone, residual viable bone, or foci of matrix calcification or ossification on the imaging is not always possible with radiography or CT. MRI has the potential to differentiate sequestrum from vascularized normal bone but in traumatic fractures presence of metal hardware restricts the use of MRI because of artifacts. SPECT/CT is less vulnerable for metal artifacts. In our study, 35 (94.6%) patients had metal implants at the fracture site.

Fracture healing is an ongoing dynamic and complex process, which includes biological as well as mechanical components. Unfortunately, assessment of fracture healing is still limited.⁴ In current practice, fractures not healing for more than 6 months without cortical bridging and persistent fracture lines on conventional radiographs might be labeled as delayed union and more than 9 months as non-union.¹² CT scans add important additional cross-sectional morphological information.

Pseudarthrosis, literally translated means a false joint, refers to a failure of fusion of fractured ends of a bone, leading to an abnormal union with fibrous tissue between the fragments, and is a long-term outcome of non-union.^{12,13} It may take months to years to develop and not all patients with pseudarthrosis are symptomatic. There are two main types of non-unions according to the viability of the ends of fractured bone fragments, hypervascular or hypertrophic and avascular or atrophic non-unions.¹² The hypervascular non-unions have presence of blood supply in the ends of the fractured bone fragments and

are capable of biological reaction and there is variable amount of callus formation. In avascular non-unions, the bony fragments have a poor blood supply and are incapable of biological reaction, and there is lack of callus formation, eventually leading to formation of necrotic bone fragments or dead bone within. In such situation, debridement of dead bone with bridging of viable bone ends with bone grafts is needed for good recovery. The typical scintigraphic appearance of the lesions reveals increased radiotracer uptake during the chronic reparative process, which is usually peripheral with central photopenia (area of reduced activity). Published literature regarding the performance of SPECT/CT for the evaluation of necrotic bone or pseudarthrosis is very sparse. SPECT has proven to be valuable for the diagnosis of femoral head osteonecrosis and was more sensitive than MRI (100% vs 66%) in a study by Ryu et al.¹⁴ In our study, SPECT/

Figure 2. 26-year-old male with osteosynthesis of left distal femur fracture 6 months ago. He was being evaluated in view on delayed union. Early-phase [images A (anterior), B (posterior)] and late-phase [images C (anterior), D (posterior)] images of planar bone scintigraphy show moderate radiotracer accumulation in the area of left distal femur fracture site. Plain radiography (E) shows incomplete consolidation of the fracture. SPECT/CT (Coronal SPECT/CT: F and Coronal CT: G) images show increased uptake at some parts of the former fracture as signs of bone remodeling. Additionally, there is a loose unconsolidated bone fragment of 6.0×1.3 cm size, dorsolaterally at the fracture site with complete absence of radiotracer uptake (photopenia), suggestive of necrotic bone fragment. The patient underwent revision surgery with removal of necrotic bone fragment. Follow-up CT (post 15 months) images (CT coronal: H, 3D VRT: I, J) and X-ray (post 21 months) images (K, L) show union at the fracture site.

Figure 1. Osseous bridging on CT versus grade of radiotracer activity at the fracture sites.

Figure 3. Hematoxylin and Eosin staining of the resected bone fragment of the same patient as in figure 2. Images show missing osteocyte nuclei and fat necrosis indicating necrotic bone fragments (images courtesy Dr. Zenklusen, Institute of pathology, Cantonal Hospital Lucerne, Switzerland).

Figure 4. 54-year-old female with osteosynthesis of left distal femur fracture after car accident 6 months ago. Osteosynthesis was removed because of infection and external fixator was installed. Early phase of bone scintigraphy (BS) [images A (anterior), B (posterior)] shows mild-to-moderate amount of radiotracer accumulation in the left distal femur, knee joint, as well as in the region of left ankle. The late phase images [C (anterior), D (posterior)] of planar BS show persistent increasing accumulation of radiotracer in above areas along with a photopenic area in the left distal femur. SPECT/CT images (E: coronal CT, F: coronal SPECT, G: coronal SPECT/CT fusion, H: sagittal CT, I: sagittal SPECT, J: sagittal SPECT/CT fusion) show absence of radiotracer accumulation in the two bone fragments in the left distal femur in and around the fracture site. The patient underwent revision surgery with removal of necrotic bone fragments. A vitality was proven histologically. Follow-up X-ray (image K) post 6 months shows improvement with good healing and union of the fracture site.

Table 3. Frequency table for bone scintigraphy

		Bone Scintigraphy	
Reference Standard	Positive	Negative	Total
Positive	10	5	15
Negative	1	21	22
Total	11	26	37

CT could detect necrotic bone fragments in 16 out of 37 fracture sites (43.2%) compared to only 11 (29.7%) detected on planar BS.

The absence of activity on bone SPECT/CT in persistent fractures is a highly specific marker for non-union.¹⁵ Lioudakis et al retrospectively evaluated the role of SPECT/CT in 10 patients, involving fractures of upper and lower extremity, in diagnosing and planning the treatment of avascular/atrophic non-unions with surgical exploration as the reference standard.¹⁵ SPECT/CT identified all the four vital pseudarthroses and three of the six non-vital pseudarthroses. The sensitivity of SPECT/CT in diagnosing non-vital atrophic non-unions was 50%, and the specificity was 100%. We obtained improved sensitivity for SPECT/CT detection of necrotic bone fragments leading to delayed healing/non-union with sensitivity of 100% and specificity of 95%. Diedrichs and colleagues compared the diagnostic performance of bone SPECT/CT and MRI for the evaluation of bone viability in patients after girdlestone arthroplasty (two-stage revision technique).¹⁶ In their study, the prostheses were removed after the diagnosis of periprosthetic joint infection, and it was followed by 6 to 8 weeks of antibiotic therapy. Revision total hip arthroplasty was performed after successful treatment of infection; and 24h prior to this revision surgery, SPECT/CT and MRI were performed. So, their patients did not have metal hardware *in situ*, and hence they could perform MRI. They found high sensitivity and specificity for SPECT/CT as well as for MRI for differentiation between viable and non-viable bone tissue, although SPECT/CT had slightly better sensitivity (90%) and specificity (94%) compared to MRI. They found statistically significantly higher uptake values for vital bone compared to non-vital bone. Although the metal prosthesis was removed before imaging, some metal particles remaining behind in tissues close to the bone gave rise to imaging artifacts on MRI contributing to some false-positive results.

Niikura et al¹⁷ evaluated 48 patients with uninfected fracture non-unions, in a retrospective study, and compared radiographs with Tc-99m BS and tried to study the detailed pattern and features of radiotracer uptake. They observed positive radiotracer uptake

Table 4. Frequency table for SPECT/CT

		SPECT/CT	
Reference Standard	Positive	Negative	Total
Positive	15	0	15
Negative	1	21	22
Total	16	21	37

Table 5. Comparative values of sensitivity, specificity, PPV, NPV, and accuracy in SPECT/CT and bone scintigraphy for the detection of necrotic bone fragments in traumatic fractures with suspected delayed healing or non-union

	SPECT/CT	BS
Sensitivity (%)	100	67
Specificity (%)	95	95
Positive Predictive Value (PPV) (%)	94	91
Negative Predictive Value (NPV) (%)	100	81
Accuracy (%)	97	83

in all cases and classified the uptake patterns into four types. They proposed a treatment algorithm of uninfected non-unions which incorporated BS. They recommended BS in the evaluation of non-hypertrophic non-unions, whereas hypertrophic non-unions can do without BS and secured fixation will lead to bony union. If BS reveals a photon-deficient area, then an autologous bone graft can be implanted for better and faster healing. On the other hand, if BS does not reveal any photopenic area, then secured fixation is good enough to achieve bony union and appropriate healing.

Song Q et al¹⁸ evaluated 144 patients with known/suspected chronic-infected fracture non-union osteomyelitis in lower

Figure 5. Receiver operative curve (ROC) analysis of SPECT/CT versus planar scintigraphy (BS).

limb using SPECT/CT and found it better than standalone BS and CT imaging with improved diagnosis of non-union with precise localization of osteomyelitis which is critical for surgical management. Their group looked at osteomyelitis and soft tissue infection and their focus was on increased radiotracer activity suggesting infection. Our group, on the other hand, assessed the presence of necrotic bone fragments which might be responsible for delayed bone healing and non-union and is characterized by absence of radiotracer activity.

We did not intend to compare SPECT with SPECT/CT as in our opinion SPECT/CT has completely replaced SPECT alone in bone and joint imaging as demonstrated in many studies. The CT part of the study is so important for anatomic correlation and bone healing assessment in this situation of fractures that referring surgeons would not want to waive this important information.

Limitations of our study include: a) possible selection bias, as we targeted traumatic bone fractures with delayed bone healing specifically; b) retrospective design of the study; c) the reference standard histology was available in only 11 patients (out of 37); d) quantitation of the radiotracer uptake using SUV max could not be performed due to technical issues and should be evaluated in subsequent studies.

CONCLUSION

SPECT/CT is an accurate tool in the assessment of necrotic bone fragments in patients with delayed bone healing or non-union after traumatic fractures and is superior to conventional planar BS.

AUTHORS' CONTRIBUTIONS

All authors contributed in a significant way to the content and revision of the manuscript. All authors read and approved the final manuscript.

COMPLIANCE WITH ETHICAL STANDARDS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics committee approval was obtained for the study (Ethikkommission Nordwest- und Zentralschweiz EKNZ 2019-00594). Informed consent was waived by the ethics committee due to the retrospective design.

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