Diagnostic accuracy of ^{99m}Tc-antigranulocyte SPECT/CT in patients with osteomyelitis and orthopaedic device-related infections: A retrospective analysis

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Abstract: OBJECTIVES Conventional imaging techniques are routinely used in the diagnostic work-up of patients with suspected osteomyelitis or orthopaedic implant-associated infections. Hybrid nuclear medicine imaging techniques are a suitable alternative to routine imaging modalities as they provide anatomical and functional information within one procedure. Our study investigated the performance of anti-granulocyte SPECT/CT using ^{99m}Tc-labelled monoclonal antibodies in the diagnosis of osteomyelitis and orthopaedic implant-associated infections. METHODS In this retrospective analysis, we included all patients with ^{99m}Tc-antigranulocyte SPECT/CT acquired in the context of a suspected bone and joint infection. All patients underwent routine diagnostics and/or had a clinical follow-up of at least 12 months. RESULTS 26 episodes were included. Fifteen exams were performed for suspected osteomyelitis, and 11 for suspected orthopaedic implant-associated infection. SPECT/CT was ordered most often if standard diagnostic tests or conventional imaging modalities remained inconclusive. The overall sensitivity and specificity for the diagnosis of an infection was 77.8% and 94.1%, respectively. The positive predictive value was 87.5% and the negative predictive value 88.9%. Diagnostic accuracy was 88.5%. CONCLUSIONS ^{99m}Tc-antigranulocyte SPECT/CT imaging has a high accuracy in the diagnosis of osteomyelitis and orthopaedic implant-associated infections and is a suitable non-invasive diagnostic tool if standard diagnostic examinations are inconclusive or not applicable.

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Diagnostic accuracy of ^{99m}Tc-antigranulocyte SPECT/CT in patients with osteomyelitis and orthopaedic device-related infections: A retrospective analysis

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ABSTRACT

Objectives: Conventional imaging techniques are routinely used in the diagnostic work-up of patients with suspected osteomyelitis or orthopaedic implant-associated infections. Hybrid nuclear medicine imaging techniques are a suitable alternative to routine imaging modalities as they provide anatomical and functional information within one procedure. Our study investigated the performance of anti-granulocyte SPECT/CT using ^{99m}Tc-labelled monoclonal antibodies in the diagnosis of osteomyelitis and orthopaedic implant-associated infections.

Methods: In this retrospective analysis, we included patients with ^{99m}Tc-antigranulocyte SPECT/CT acquired in the context of a suspected bone and joint infection. All patients underwent routine diagnostics and/or had a clinical follow-up of at least 12 months.

Results: 26 episodes were included. Fifteen exams were performed for suspected osteomyelitis, and 11 for suspected orthopaedic implant-associated infection. SPECT/CT was ordered most often if standard diagnostic tests or conventional imaging modalities remained inconclusive. The overall sensitivity and specificity for the diagnosis of an infection were 77.8% and 94.1%, respectively. The positive predictive value was 87.5% and the negative predictive value 88.9%. Diagnostic accuracy was 88.5%.

Conclusions: ^{99m}Tc-antigranulocyte SPECT/CT imaging has a high accuracy in the diagnosis of osteomyelitis and orthopaedic implant-associated infections and is a suitable non-invasive diagnostic tool if standard diagnostic examinations are inconclusive or not applicable.

Introduction

Bone and joint infections are challenging to diagnose and treat. This is particularly true for osteomyelitis (OM) and orthopaedic implant-associated infections, such as osteosynthesis-associated infections (OAI), or periprosthetic joint infections (PJI). A definitive diagnosis of bone and joint infections can be safely made if two tissue samples exhibit growth of the same pathogen. Although clinical and laboratory parameters (Metsemakers et al., 2018; Osmon et al., 2013; Parvizi et al., 2013; Parvizi and Gehrke, 2014) may help in establishing a suspicion for an infection, a confirmative diagnosis is not achieved in many cases. There is no non-invasive diagnostic biomarker that definitely allows diagnosing or excluding an infection. Joint aspiration with analysis of the synovial cell count with differentiation might be helpful in suspected infections with joint involvement (Parvizi et al., 2013; Parvizi and Gehrke, 2014), but not in other bone infections and OAI. In these cases or in cases with dry aspiration of the joint, diagnostic imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) are often used as additional diagnostic tools. However, these cross-sectional imaging modalities have limited sensitivity and specificity in the presence of metal implants, which might exhibit artifacts (Verberne et al., 2016). Several studies report the use of nuclear imaging techniques in the diagnosis of bone and joint infection (Graute et al., 2010; Love and Palestro, 2016; Navalkissoor et al., 2013; Verberne et al., 2016; Verberne et al., 2017). Two meta-analyses revealed high sensitivity and specificity of leucocyte scintigraphy (up to 88%, and 92%, respectively) and of fluorodeoxyglucose-positron emission tomography scintigraphy (FDG-PET)

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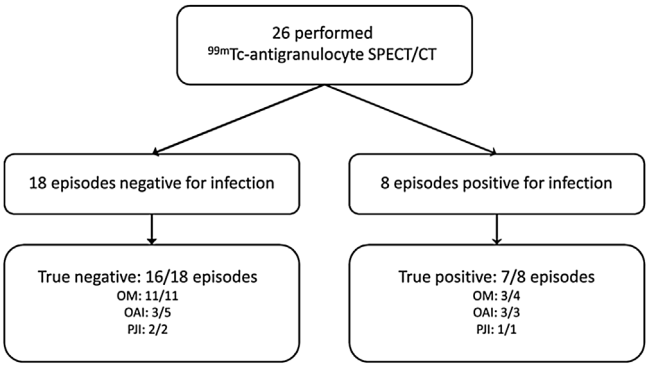

Figure 1. Diagnostic flowchart of 26 performed ^{99m}Tc-antigranulocyte SPECT/CT in 24 patients.
OAI: osteosynthesis associated infection; OM: osteomyelitis; PJI: periprosthetic joint infection.

(up to 86%, and 93%, respectively) for the diagnosis of hip and knee PJI (Verberne et al., 2016; Verberne et al., 2017). Lower sensitivity has been published for studies on FDG-PET for the diagnosis of septic loosening of hip prostheses, partly owing to exceptional criteria applied for positivity (Stumpe et al., 2004; Verberne et al., 2017). Newer hybrid imaging techniques such as leucocyte SPECT/CT and FDG-PET/CT have a reported sensitivity of up to 90% (Love and Palestro, 2016).

^{99m}Tc-antigranulocyte scintigraphy uses radioactively labeled monoclonal antibodies that target surface antigens of leucocytes in inflamed tissues (Graute et al., 2010; Navalkissoor et al., 2013). In 2019, antigranulocyte scintigraphy is for the first time recommended as part of the diagnostic work-up of PJI (Signore et al., 2019) and of peripheral bone infections (Glaudemans et al., 2019), although studies are still limited. These recent guidelines recommend antigranulocyte scintigraphy as part of the diagnostic workflow only in patients with late infections to confirm positive findings of a previous 3-phase bone scan or FDG-PET/CT. Particularly in the preoperative setting, where clinical diagnostic opportunities are basically limited to laboratory tests and joint fluid aspiration, additional imaging modalities may improve the diagnostic accuracy.

In our study, we retrospectively investigated the diagnostic value of ^{99m}Tc-antigranulocyte single photon emission computed tomography (SPECT)/CT for the diagnosis of bone and joint infections.

Methods

In this retrospective analysis covering the period between 2012 and 2018, we evaluated the diagnostic accuracy of ^{99m}Tc-antigranulocyte SPECT/CT for infections in the presence of an arthroplasty, a fracture-related osteosynthesis, or in native bones/joints in patients treated at the University Hospital Zurich, Zurich, Switzerland or at the Orthopaedic University Hospital Balgrist, Zurich, Switzerland. All patients with a diagnostic ^{99m}Tc-antigranulocyte SPECT/CT documented in the database of the department of nuclear medicine of our institution were reviewed for inclusion. We only included patients with a suspected bone and joint infection and available preoperative and/or intraoperative diagnostic test (at least two of the following: cross-sectional imaging (CT/MR), joint aspiration with cell count and/or microbiological analysis, intraoperative histological, or microbiological analysis) or a clinical follow-up of at least 12 months. We excluded patients with diabetic feet infections, patients with incomplete medical records, subjects without consent to scientific analysis of health-related data, or a follow-up of less than 12 months. The treating physician decided about indication and time point of the SPECT/CT.

The revised MSIS criteria published in 2013 served as reference standard for the diagnosis of PJI (Parvizi et al., 2013; Parvizi and Gehrke, 2014). The reference standard for the diagnosis of OM and OAI was proof of the same pathogen in two intraoperatively obtained specimen and/or clear evidence of OM in histopathology (Depypere et al., 2019). Histology was positive if signs of acute inflammation with dominance of neutrophils in at least one tissue sample were present.

Nuclear medicine imaging

^{99m}Tc-antigranulocyte SPECT/CT used a routine clinical protocol. After preparation of the kit, patients were injected with a standardized dose of 800 MBq of a ^{99m}Tc-labelled mouse monoclonal antibody against granulocytes (besilesomab, Scintimun®, b.e.imaging AG, Schwyz, Switzerland). The first image acquisition (planar images, SPECT) was done five hours after injection. The second image acquisition (planar images, SPECT/CT) was done 24 h after injection. Persistence or increase of focal radiotracer uptake from 5 h to 24 h in the target area indicated prevalence of an infection. The CT scan was acquired both for attenuation correction and for diagnostic purposes. No iodinated contrast medium was used.

Statistical analysis

The results of the ^{99m}Tc-antigranulocyte SPECT/CT test were reported as either positive or negative. The sensitivity, specificity, and positive and negative predictive values of ^{99m}Tc-antigranulocyte SPECT/CT were calculated based on the standards of reference mentioned above.

Ethics

The local ethics committee of Zurich, Switzerland approved the study protocol (Kantonale Ethikkommission, BASEC Number 2017-00973), and all included patients signed an informed consent to contribute their health-related data to science.

Results

Study population

Retrospective analysis of clinical medical charts revealed 41 subjects with a ^{99m}Tc-antigranulocyte SPECT/CT and signed informed consent. However, due to missing diagnostics for comparison (n = 11) or missing follow-up (n = 6), only 24 patients fulfilled our inclusion criteria. Two patients had a ^{99m}Tc-antigranulocyte SPECT/CT for more than one diagnostic question (i.e., affection of different bones), hence we analyzed a total of 26 episodes.

Fourteen out of 24 (58%) subjects were male, with a median age of 59 years (range 19–80). ^{99m}Tc-antigranulocyte SPECT/CT was performed in suspected PJI (n = 3), in suspected OAI (n = 8), in suspected OM (n = 9), and in cases with the need of an implant with the history of a previous bone infection (n = 6). No patient suffered from allergic side effects against xenoproteins of the tracer, as the monoclonal antibody was derived from mouse.

According to the standard of reference, three patients were categorized to have an OM, five to have an OAI, and one to have a PJI.

Diagnostic value of ^{99m}Tc-antigranulocyte SPECT/CT in 26 episodes

^{99m}Tc-antigranulocyte SPECT/CT was negative in 18 episodes (69.2%) (OM [n = 11], OAI [n = 5], and PJI [n = 2]), and positive in

Table 1
Episodes with negative 99mTc-antigranulocyte SPECT/CT (n = 18, thereof 2 infections, 16 no infections).

Patient	Age	Sex	Anatomic site	Clinical background	CT/MRI	AGS	Time between AGS and surgery (months)	Clinical Impact of MOAB	Outcome (Follow up, months)	AGS performance
A: Total joint arthroplasty planned after previous bone infection										
1	66	m	Knee (r)	Exclusion of infection before TJA after PJI with *Pseudomonas aeruginosa* and *Staphylococcus epidermidis.*	Large seroma-hematoma, inconclusive if infection (MRI). Patella osteolysis (CT).	No infection, large joint effusion.	<1	TJA implantation.	Good (12). Intraoperative biopsies negative.	TN
2	65	m	Knee (r)	Posttraumatic osteoarthritis, osteosynthesis tibia and fibular.	No infection, but difficult to interpret due to tibia implants (CT).	No infection.	4	TJA implantation.	Good (12)	TN
3	54	m	Knee (l)	Posttraumatic osteoarthritis with multiple metal splinters after war injury.	Metal in tibia and os naviculare, no osteomyelitis (CT).	No infection.	3	TJA implantation.	Good (26)	TN
4	62	m	Knee (r)	Osteoarthritis. Previous septic arthritis and crystal deposition disease. Punctio sicca.	n.d.	Reactive synovitis. No infection.	1	TJA implantation.	Good (14)	TN
5	50	f	Knee (l)	Posttraumatic osteoarthritis and previous OAI.	Bone edema, multiple bone pieces after trauma. Inconclusive regarding infection (MRI).	No infection.	9	TJA implantation.	Good (21)	TN
6 – 2	47	f	Knee (l)	Previous septic arthritis.	Suspected osteomyelitis Tibia (MRI) (5 months before OP).	No infection.	4	TJA implantation.	Good (21)	TN
B: Suspected osteomyelitis										
7	63	m	Foot (l)	Chronic ulcer.	n.d.	No infection.	4	Direct skin closure with flap reconstruction without previous septic debridement.	Good (16)	TN
8	62	f	Lower leg (r)	Chronic ulcer. History of necrotizing myositis 5 years ago.	No infection (CT). MRI contraindicated (neurostimulator).	No infection.	n.a.	No operation. Conservative management.	Good (15)	TN
9	46	m	Lower leg (l)	History of tibia fracture. Fistula after UTN removal. Peroneus paresis.	n.d.	No infection.	3	Tendon transfer, no septic surgery.	Good (13)	TN
10–1	80	m	Lower leg (l)	Chronic ulcer lower leg and suspected knee PJI.	n.d. MRI contraindicated (pacemakter).	No infection in the tibia underlying an ulcer, but clear PJI.	n.a.	No operation. Conservative management.	Good (26)	TN
11	57	m	Lower leg (r)	History of OSM removal in tibia. Pain.	Suspicious for a stress fracture (MRI) but no explanation for severe pain.	Stress fracture, but no signs for infection.	n.a.	No operation or further diagnostics.	Good (14)	TN
C: Suspected PJI										
12	51	m	Knee (l)	Painful TJA.	Articular effusion, synovitis (MRI).	No infection.	n.a.	No operation. Conservative management of a peripheral neurinoma.	Good (28)	TN
13	62	m	Knee (r)	Painful TJA. Knee joint aspiration with negative culture, cell count not available.	Joint effusion (CT).	No infection.	n.a.	No operation. Conservative management.	Good (6)	TN
D: Suspected OAI										
14	46	f	Malleolus lateralis (l)	Chronic wound healing disorder after osteosynthesis-related infection with *S. aureus.*	No infection (CT). Subcutaneous inflammation (MRI).	No osteomyelitis. Suspected wound infection.	2	Operative revision and flap reconstruction.	Good (14)	TN
15	19	f	Lower leg (l)	Non-union after osteosynthesis of an open tibia and fibula fracture.	No infection (CT).	No infection.	5	Re-osteosynthesis with retention of part of the implant. No septic debridement.	Good (9)	TN
16	52	f	Ulna (l)		n.d.		<1		Good (3)	TN

Table 1 (*Continued*)

Patient	Age	Sex	Anatomic site	Clinical background	CT/MRI	AGS	Time between AGS and surgery (months)	Clinical Impact of MOAB	Outcome (Follow up, months)	AGS performance
				Non-union after osteosynthesis of an ulna fracture.		Soft tissue infection. No obvious OAI.		Revision with implant removal (two-stage procedure) diagnostic sampling.		
17	49	f	Lower leg (r)	History of tibia non-union. Wound dehiscence.	n.d.	No infection.	<1	Revision and osteosynthesis removal.	Good (3)	FN *S. aureus* in several bone specimen.
18	61	f	UAJ (l)	Fracture of malleolar osteosynthesis.	n.d.	Soft tissue infection.	1	Re-osteosynthesis (one stage).	Good (5)	FN Intra operative positive histology (Talus).

AGS: antigranulocyte scintigraphy; CT: computed tomography; f: female; FN: false negative; l: left; m: male; MRI: magnetic resonance imaging; n.a.: not applicable; n.d.: not done; OAI: osteosynthesis associated infection; OM: osteomyelitis; OSM: osteosynthesis material; PJI: periprosthetic joint infection; r: right; TJA: total joint arthroplasty; TN: true negative; UAJ: upper ankle joint; UTN: unreamed tibia nail.

Table 2
Episodes with positive ^{99m}Tc-antigranulocyte SPECT/CT (n = 8, thereof 7 infections).

Patient	Age	Sex	Anatomic site	Clinical background	CT/MRI	AGS	Time between AGS and surgery (months)	Clinical impact of AGS	Pathogen if infection	AGS performance
A: Suspected OAI										
19	65	m	UAJ (l)	History of UAJ arthrodesis. Septic shock originating from an erysipelas at the UAJ.	No signs of osteomyelitis, abscess or fasciitis (MRI).	Infection Talus, and periimplant infection around the screw in tibia.	<1	Osteosynthesis removal	*S. aureus*	TP
20	70	m	Tibia (r)	Painful tibia osteosynthesis.	No signs of infection (CT).	Suspected infection of tibia intramedullary nail.	4	Osteosynthesis removal	SCN	TP
21	27	f	Lower leg (r)	Broken osteosynthesis.	Broken osteosynthesis, no osteomyelitis, metal artifacts (MRI).	OAI with osteomyelitis Tibia.	<1	Osteosynthesis removal	*E. cloacae*	TP
B: Suspected PJI										
10 - 2	80	m	Knee (l)	Chronic tibia ulcer near knee prosthesis, and suspected knee PJI.	n.d. MRI contraindicated (pacemaker).	No infection below the ulcer in tibia but clear PJI.	1	TJA removal	SCN	TP
C: Suspected OM										
22	79	m	Foot (l)	Increasing pain after soft tissue infection with pseudomonas.	Bone destruction, suspicious for OM (MRI).	Osteomyelitis of tuber calcanei and os metatarsale IV.	n.a.	OM treatment	*P. aeruginosa*	TP
6–1	47	f	Knee (r)	History of septic arthritis.	n.d.	Suspicion of persistent infection in the knee with OM at posterior tibia plateau.	<1	Diagnostic arthroscopy	n.a.	FP No proof of infection intraoperatively
23	77	f	Heel (r)	Chronic ulcer.	OM (MRI).	Focal OM in tuber calcanei.	<1	Extensive debridement	Mixed infection[a]	TP
24	51	m	Lower leg (l)	Chronic stump ulcer.	No OM (CT). Suspicion of OM (MRI).	Focal OM in tibia stump.	<1	Stump revision	*S. aureus*	TP

AGS: Antigranulocyte scintigraphy; CT: computed tomography; *E. cloacae: Enterobacter cloacae;* f: female; FP: false positive; l: left; m: male; MRI: magnetic resonance imaging; n.a.: not applicable; n.d.: not done; OAI: osteosynthesis-associated infection; OM: osteomyelitis; *P. aeruginosa*: *Pseudomonas aeruginosa*; r: right; *S. aureus*: *Staphylococcus aureus*; *SCN: Staphylococcus coagulase negative*; PJI: periprosthetic joint infection; TP: true positive; UAJ: upper ankle joint.

[a] Mixed infection with *S. aureus, Enterobacter cloacae, Enterococcus faecalis, Klebsiella pneumonia,* and *Escherichia coli.*

Table 3
Diagnostic performance of ^{99m}Tc-antigranulocyte SPECT/CT.

	Suspected OM (n = 15)	Suspected OAI or PJI (n = 11)	Total (n = 26)
AGS TP	3	4	7
AGS FP	1	0	1
AGS TN	11	5	16
AGS FN	0	2	2
Sensitivity (95%CI)	100 (29.24–100)	66.67 (22.28–95.67)	77.78 (39.99–97.19)
Specificity (95%CI)	91.67 (61.52–99.79)	100 (47.82–100)	94.12 (71.31–99.85)
PPV (95%CI)	75 (31.48–95.14)	100	87.50 (50.32–97.98)
NPV (95%CI)	100	71.43 (44.64–88.57)	88.89 (70.09–96.47)
Accuracy (95%CI)	93.33 (68.05–99.83)	81.82 (48.22–97.72)	88.46 (69.85–97.55)

AGS: Antigranulocyte scintigraphy; CI: confidence interval; FN: false negative; FP: false positive; n: number of performed tests; NPV: negative predictive value; OAI: Osteosynthesis-associated infection; OM: Osteomyelitis; PJI: Periprosthetic joint infection; PPV: positive predictive value; TP: true positive; TN: true negative.

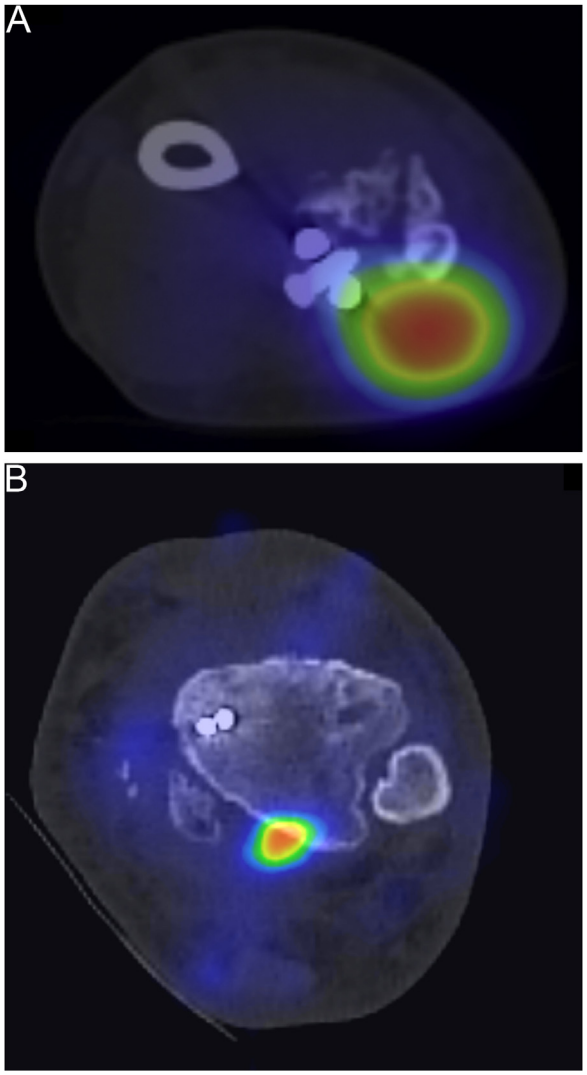

Figure 2. Discrimination between soft tissue and bone infection with ^{99m}Tc-antigranulocyte SPECT/CT in two patients with suspected osteomyelitis.
Panel part A shows a 24 h ^{99m}Tc-antigranulocyte SPECT/CT image of the forearm in a 52 year old woman (patient 16 in Table 1). ^{99m}Tc-antigranulocyte SPECT/CT was positive for soft tissue infection, but negative for osteomyelitis. Intraoperative microbiological sampling confirmed absence of bone infection. Panel part B shows a representative ^{99m}Tc-antigranulocyte SPECT/CT image of the ankle in a 61 year old woman (patient 18 in Table 1), which was positive for a soft tissue infection, but showed no clear sign of bone marrow involvement. However, intraoperative histological specimen (obtained 41 days later) were positive for acute osteomyelitis with dominance of neutrophils.

eight episodes (OM [n = 4], OAI [n = 3], and PJI [n = 1]). (Figure 1, Tables 1 and 2). Diagnostic performance of ^{99m}Tc-antigranulocyte SPECT/CT in each diagnosis group is shown in Table 3. Due to the low numbers in the PJI group, we calculated a combined diagnostic accuracy for subjects with implanted osteosynthesis or arthroplasties.

Osteomyelitis (OM) (infections: n = 3 out of 15)

In the group of potential OM, the ^{99m}Tc-antigranulocyte SPECT/CT was true negative in 11 episodes, as confirmed by intraoperative diagnostics or unremarkable follow-up without any surgical intervention. In three out of 15 episodes, ^{99m}Tc-antigranulocyte SPECT/CT was true positive and in one episode false positive (Table 2, episode number 6–1). The patient with a false positive test had a history of traumatic injury of both lower legs with bilateral haematogenous *Staphylococcus aureus* (*S. aureus*) osteoarthritis of the knee. One month after the end of antibiotic therapy, the patient suffered from pain in the knee. Systemic infection parameters were normal, but a joint aspiration showed 1,000 cells/μl (50% neutrophils) without bacterial growth, and ^{99m}Tc-antigranulocyte SPECT/CT was positive. A diagnostic arthroscopy revealed no bacterial growth in several tissue and bone samples, which virtually excludes a persistent infection.

Osteosynthesis-associated infections (OAI) (infections: n = 5 out of 8)

In the setting of potential OAI, ^{99m}Tc-antigranulocyte SPECT/CT was true negative in three episodes. Thereof in two episodes, a superficial soft tissue infection was correctly identified by SPECT/CT, correctly ruling out a suspected peri-implant infection (Figure 2A). SPECT/CT was true positive in three episodes, and false negative in two episodes (episode number 17 and 18). Episode number 17 had a history of tibia osteosynthesis and presented with a wound dehiscence and non-union of bone fragments. Here, ^{99m}Tc-antigranulocyte SPECT/CT showed no sign of infection. In contrast, several intraoperative bone biopsies were positive for *S. aureus*. Episode number 18 suffered from pain elicited by a broken malleolar osteosynthesis. While ^{99m}Tc-antigranulocyte SPECT/CT was negative for an implant-associated infection or osteomyelitis (Figure 2B), histological specimen showed a focal osteomyelitis with dominance of neutrophils. Unfortunately, the patient received broad-spectrum antibiotic therapy at the time of revision, and intraoperative biopsies remained negative.

Periprosthetic joint infections (PJI) (infections: n = 1 out of 3)

In the context of three painful joint arthroplasties, the ^{99m}Tc-antigranulocyte SPECT/CT correctly excluded a PJI in two episodes and correctly diagnosed one PJI.

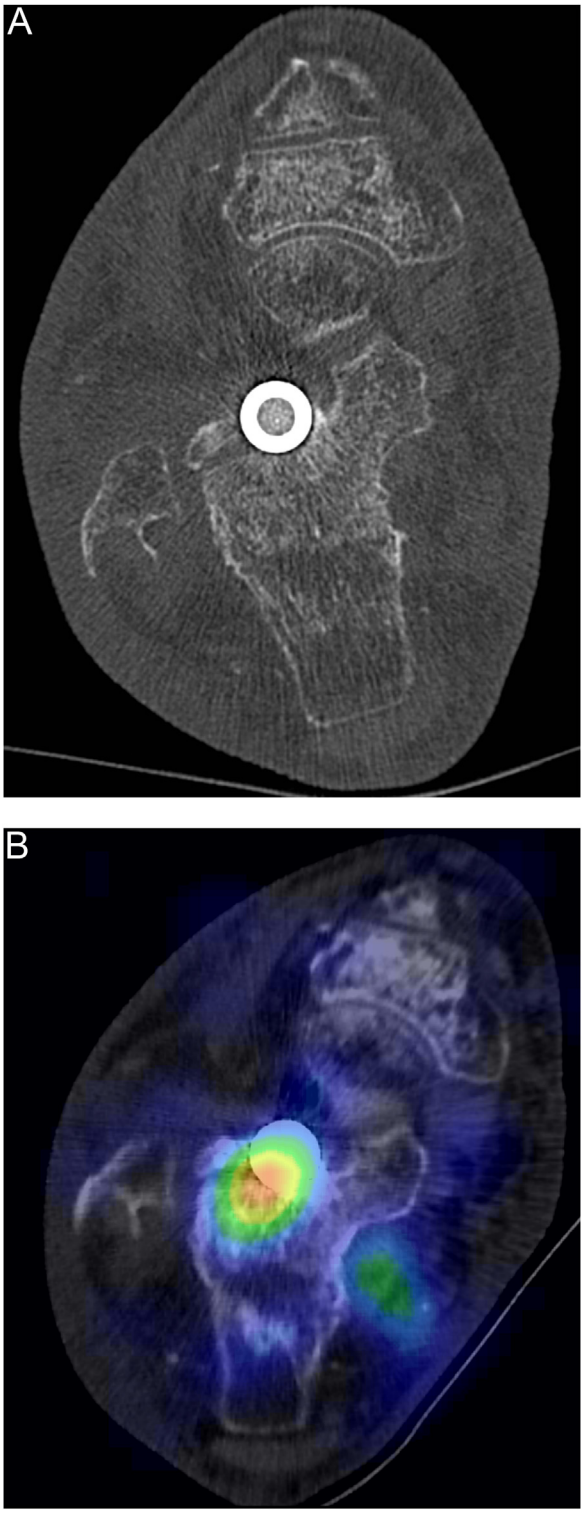

Figure 3. Correct identification of an osteosynthesis-associated infection with ^{99m}Tc-antigranulocyte SPECT/CT.
Panel part A shows a CT scan of the ankle in a 70-year-old man with a painful tibia osteosynthesis (patient 20, Table 2). The CT scan was interpreted as negative for infection. Panel part B shows the corresponding 24 h ^{99m}Tc-antigranulocyte SPECT/CT image displaying intense focal radiotracer uptake in the calcaneus immediately posterior to the osteosynthetic metal. This uptake is highly suggestive for an implant-related infection. Intraoperatively, a low-grade infection with *coagulase negative staphylococci* was confirmed.

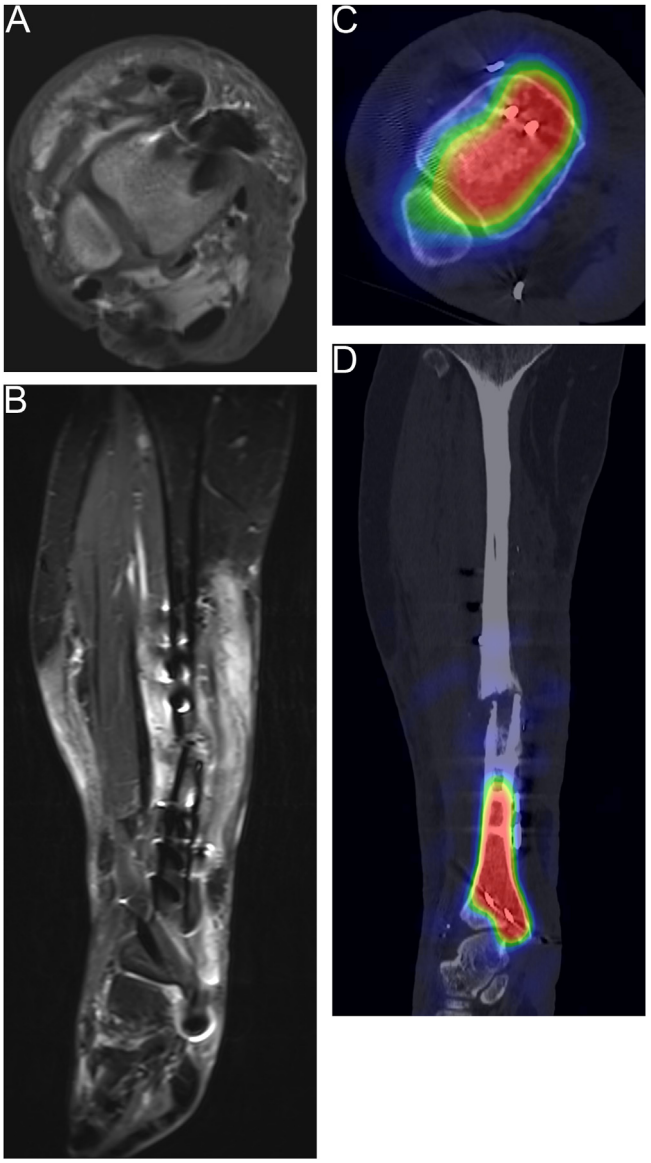

Figure 4. Superiority of ^{99m}Tc-antigranulocyte SPECT/CT compared to MRI in a patient with osteosynthesis-related infection.
Panel parts A and B show the ankle (axial; T1-weighted) and lower leg (coronal, turbo-inversion recovery-magnitude weighting) in a 27 year old woman (patient 21 in Table 2) with a broken osteosynthesis and non-union of the tibia. MRI showed no sign of infection (hypointensity of bone marrow on T1-weighted images, hyperintensity of bone marrow on T2-weighted fat-suppressed images, pathologic contrast enhancement and/or soft-tissue alterations adjacent to bone), but diagnosis was reported to be limited by metal artifacts. Panel parts C and D show corresponding 24 h ^{99m}Tc-antigranulocyte SPECT/CT images with intense uptake throughout the whole distal tibia, highly suggestive for an osteosynthesis-associated infection. Intraoperatively, an infection with *Enterobacter cloacae* was confirmed.

Discussion

In this analysis, we report the diagnostic value of ^{99m}Tc-antigranulocyte SPECT/CT in a cohort of 24 patients with 26 episodes of suspected bone and joint infection. We found a comparably high diagnostic accuracy of ^{99m}Tc-antigranulocyte SPECT/CT of 88.5% that advocates its use as an alternative diagnostic tool in cases where standard diagnostic methods are inconclusive or not applicable.

Nuclear medicine imaging such as ^{99m}Tc-antigranulocyte SPECT/CT combines the advantages of functional and morphological imaging. In case of a bone infection, it allows detecting the infection by pathological radiotracer uptake and morphological alterations to bone. In addition to standard diagnostic imaging and microbiological diagnostics, ^{99m}Tc-antigranulocyte SPECT/CT is recommended by current guidelines (Glaudemans et al., 2019) as an alternative to classic radiological techniques such as MRI in the diagnosis of an OM. Current literature reports good sensitivity and specificity (Govaert et al., 2017; Pakos et al., 2007). ^{99m}Tc-antigranulocyte SPECT/CT might serve as an alternative diagnostic tool if the patient cannot undergo MRI (e.g., due to MRI-incompatible devices). Besides suspected OM in peripheral bones, ^{99m}Tc-antigranulocyte SPECT/CT was used in our cohort to exclude a low-grade OM in native joints before TJA. The test was performed in patients with inconclusive preoperative diagnostics and/or a personal history, which increased the individual risk for a low-grade OM (previous bone infection, trauma or a history of battlefield injury), since ^{99m}Tc-antigranulocyte SPECT/CT seems to have a high diagnostic accuracy in trauma-related and combat-related infections as well (Loessel et al., 2019). As various factors were identified to be associated with an increased risk of infection after TJA (Solarino et al., 2015), a screening for an uncontrolled local inflammatory process is done in most centers before TJA. However, standard clinical evaluation may be inconclusive: Serum infectious parameters (CRP or ESR) may be slightly elevated without an identifiable cause, and joint aspiration may be dry or inconclusive. There is a lack of larger studies that evaluate the diagnostic accuracy of ^{99m}Tc-antigranulocyte SPECT/CT in a native joint or as part of the preoperative evaluation before TJA. In our cohort, TJA was implanted in all cases after the negative ^{99m}Tc-antigranulocyte SPECT/CT and there was no implant failure so far.

In 11 episodes, the ^{99m}Tc-antigranulocyte SPECT/CT was performed in the context of implant-associated infections, namely PJI or fracture-related osteosynthesis with a sensitivity and specificity of 66.7%, and 100%, respectively. Diagnosis of these infections is often challenging with current standard diagnostic tools (Metsemakers et al., 2018; Osmon et al., 2013; Parvizi et al., 2013; Parvizi and Gehrke, 2014). In cases of low-grade PJIs, dry joint aspirations or inconclusive results due to lack of synovial leucocyte count, a preoperative differentiation between an aseptic and septic cause is not always possible. Since surgical revisions (e.g., for mechanic reasons) are not inevitably necessary in every patient and repeated punctures per se harbor the risk of an iatrogenic infection, non invasive ^{99m}Tc-antigranulocyte SPECT/CT may serve as an additional diagnostic tool in these patients. In 2013, Xing et al. reported in a meta-analysis a pooled sensitivity of 83% and a specificity of 79% for anti-granulocyte scintigraphy for the diagnosis of PJI, irrespective of the affected joint (Xing et al., 2013). A more recent meta-analysis reported high sensitivity and specificity for knee TJA (90% and 95%) (Verberne et al., 2017) and slightly inferior accuracy for hip TJA (sensitivity 84% and specificity 75%) (Verberne et al., 2016). In our cohort, a knee PJI was correctly diagnosed in one case and was excluded correctly in two cases with SPECT/CT. However, ^{99m}Tc-antigranulocyte SPECT/CT provided additional information because joint aspiration remained inconclusive. Instead of repeated invasive diagnostics (re-puncture or open biopsy), ^{99m}Tc-antigranulocyte SPECT/CT excluded an infection. The clinicians decided consequently to refrain from further invasive diagnostics.

In the setting of fracture-related osteosynthesis, the infection rate is reported to be between 2% and 52%, depending on the class and severity of the fracture (Fang et al., 2017). Compared to PJI, the preoperative diagnostics are even more limited, as classic aspiration cannot be performed. Despite the use of metal artifact reduction technologies, the diagnostic accuracy of classic cross-sectional imaging techniques is often limited and antigranulocyte scintigraphy has superior diagnostic accuracy in patients with posttraumatic or combat-related infections (Govaert et al., 2017; Loessel et al., 2019). Such was also the case in three patients of our cohort (19–21), where cross-sectional imaging with CT and/or MRI showed no sign of infection, but ^{99m}Tc-antigranulocyte SPECT/CT did (Figures 3 and 4) confirmed by intraoperative diagnostics. However, both in PJI and OAI, MRI remains the cross-sectional method of choice, owing to its widespread availability, same-day results and lower costs compared to nuclear medicine imaging using anti-granulocyte antibodies.

^{99m}Tc-antigranulocyte SPECT/CT is recommended in OM or PJI as addition or alternative to FDG-PET/CT by recent guidelines (Glaudemans et al., 2019; Signore et al., 2019). FDG-PET/CT imaging is less time-consuming compared to ^{99m}Tc-antigranulocyte SPECT/CT. However, despite the high sensitivity of FDG-PET/CT in the diagnosis of bone and joint infections reported in the literature, it is hampered by low specificity. Hence, there is an obvious discrepancy in the reported overall diagnostic accuracy across different studies and comparative studies between FDG-PET/FDG-PET/CT and leucocyte labeling imaging methods such as ^{99m}Tc-antigranulocyte SPECT/CT show partly contradicting results (Aksoy et al., 2014; Gemmel et al., 2012; Palestro, 2016; Stumpe et al., 2004). Also, different levels of sensitivity and specificity have been published for FDG-based methods in the literature, partly owing to the use of different imaging tools (PET only, hybrid PET/CT) and different criteria applied for positivity (Aksoy et al., 2014; Gemmel et al., 2012; Palestro, 2016; Stumpe et al., 2004; Verberne et al., 2016). One important drawback of ^{99m}Tc-antigranulocyte SPECT/CT needs to be acknowledged: Owing to the high physiologic population of granulocytes and granulocyte precursors in hematopoietic bone marrow, ^{99m}Tc-antigranulocyte SPECT/CT is of limited value in these regions. Hence, infections of the spine, shoulder and hip joints should be examined with other methods.

This study has some limitations. First, we report data of a selective patient group in which nuclear imaging was performed with inconclusive previous standard diagnostic assessment at the discretion of the responsible clinician. Thus, the indication for performing a SPECT/CT was not standardized, nor were the patients recruited in a consecutive manner. However, despite this selection bias, accuracy in our cohort is comparable to the overall accuracy reported in the literature. Second, we describe a heterogeneous cohort consisting of patients with OM and orthopaedic implant-associated infections. Thus, the overall number of subjects in each subgroup is comparatively small and subgroup analyses have to be interpreted with caution.

In conclusion, even in the setting of equivocal or conflicting previous tests, ^{99m}Tc-antigranulocyte SPECT/CT yields a high diagnostic accuracy for bone and joint infections. It is therefore a useful clinical tool in complicated cases. However, due to resource requirements, availability and radiation exposure, ^{99m}Tc-antigranulocyte SPECT/CT should be reserved to situations in which standard diagnostic approaches remain inconclusive or are not possible due to technical reasons or patient-specific contra-indications.

Declarations of interest

None.

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