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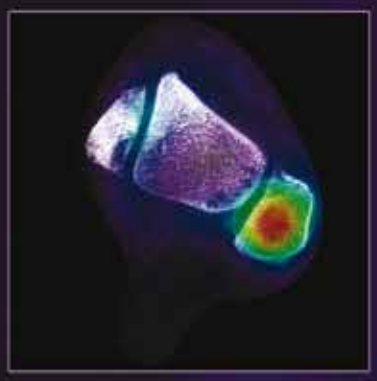
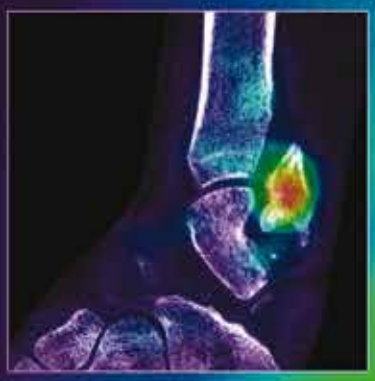
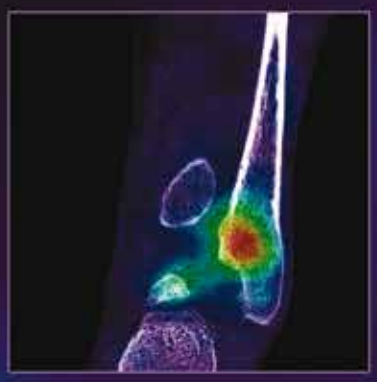
TIJDSCHRIFT VOOR NUCLEAIRE GENEESKUNDE







Special issue on orthopaedics

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1) Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours, J.K. Ramage et al, UKNET work for neuroendocrine tumours, GUT 2005, 54 (Suppl IV):iv1-iv16

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From the editors

Since several decades, radionuclide bone scanning has been used to characterise various types of bone pathology; especially bone metastases are detected well before radiographic modalities show structural abnormalities. For a long period of time, in many nuclear medicine practices the use of bone scanning in orthopaedics was limited. This was due to several factors such as the evolvement of radiologic techniques over the past three decades especially of magnetic resonance imaging, lack of guidelines concerning imaging in musculoskeletal diseases, varying experience of orthopaedic surgeons with nuclear medicine techniques, and the dependence on local availability of modern hybrid devices as SPECT/CT. The increased availability of SPECT/CT, which allowed us to detect subtle, nonspecific abnormalities on bone scans and interpret them as specific focal areas of pathology, has brought about important changes in this field. In recent years, bone scintigraphy combined with SPECT/CT has proven its value in the diagnostic workup of articular and non-articular arthropathy (especially in the hip-spine dilemma and chronic ankle and foot pain), occult fractures, stress injuries and many other musculoskeletal pathologies: enough reason to dedicate a special issue of our Journal to this subject, we believe.

As with any disease entity, a close collaboration between nuclear medicine specialists, radiologists and clinicians is mandatory to be able to achieve an optimal diagnostic workup in orthopaedics. We are pleased that this issue contains contributions from nuclear medicine specialists as well as from clinicians and radiologists. The first contribution is from drs. Navas, radiologist at the Leiden University Medical Center; she discusses the role and limitations of CT in the evaluation of the most common injuries around the ankle and foot. Subsequently, dr. van Dijk and dr. Lavalaye, orthopaedic surgeon and nuclear medicine physician at the St. Antonius Hospital in Nieuwegein, underline the importance of the synergistic information obtained with SPECT/CT and its impact on orthopaedic decision making, especially in complex bony structures as the ankle and foot.

Since many years nuclear medicine has played an important role in the diagnostic workup of bone infection. A variety of tracers and techniques have been developed for evaluation of osteomyelitis, spondylodiscitis and prosthetic joint infection; each with its own benefits and limitations. Drs. Glaudemans (nuclear medicine physician at the University Medical Center Groningen) provides us an overview of available nuclear imaging techniques in the field of infection and inflammation, with a special focus on spondylodiscitis and diabetic foot infections. This is followed by a contribution of drs. Jansen, orthopaedic surgeon at the Rijnland Hospital in Leiderdorp, in conjunction with drs. Smit and dr. Pereira Arias–Bouda, nuclear medicine physicians at the same hospital, focusing on the role of nuclear medicine techniques including ^{18}F-FDG PET/CT in diagnosis of prosthetic joint loosening and the ability of these techniques to differentiate between aseptic loosening and infection: a huge diagnostic challenge! The interesting results we (dr. Kartachova and dr. Pereira Arias–Bouda) obtained from our survey among 26 Dutch hospitals on the use of radionuclide techniques for this purpose underline the fact that there is no true consensus on the gold standard technique. Dr. Termaat, trauma surgeon at the Leiden University Medical Center and coworkers, who describe three interesting cases that highlight the diagnostic

value of ^{18}F-FDG PET/CT in patients with suspected osteomyelitis after osteosynthesis, close the subject on bone infections.

Last but not least, dr. Kartachova and coworkers describe an interesting observation from the field concerning the relation between findings on ^{99m}Tc-sestamibi scintigraphy and perfusion disorders of lumbar spine muscles after lumbar spine fusion surgery.

As guest-editors we hope this special issue of the Journal will give you support in dealing with the common diagnostic dilemmas in orthopaedics in daily practice. Enjoy reading!

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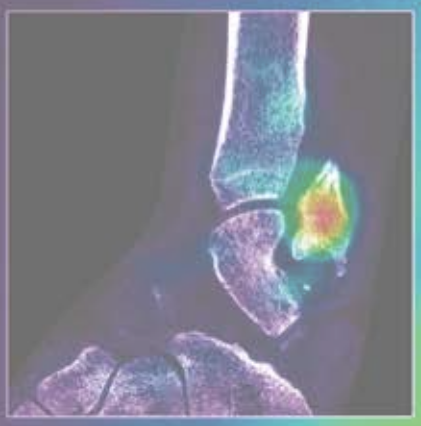

Front page
Example of a ^{99m}Tc-HDP SPECT/CT of the left ankle with transversal, sagittal and coronal fusion images. Provided by Peter Kaldeway, St. Antonius Hospital Nieuwegein.

Role of computed tomography in chronic ankle and foot pain

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Abstract

Navas A. Role of computed tomography in chronic ankle and foot pain. Chronic pain of the ankle and foot with or without previous injury is a common condition. In the evaluation process, the workup should be focused on whether the patient's chief chronic complaint is pain or instability. If the primary problem is instability, MR is the most useful exam to identify and confirm the problem. Nevertheless, if the primary problem is chronic pain, an effort should be made to rule out occult fractures, osteochondral defects, bony ankle impingement, degenerative changes, tarsal coalition and other conditions that are exquisitely studied with CT. The aim of this article is to analyse these particular conditions and to evaluate the role and limitations of computed tomography in the evaluation of the most common injuries around the ankle and foot.

Tijdschr Nucl Geneesk 2012; 34(4):961-967

Introduction

Numerous conditions can cause chronic foot and ankle pain. This can signal a serious medical condition, especially if the pain is caused by a traumatic injury or a chronic condition like diabetes. Chronic foot and ankle pain can also be caused by structural abnormalities or defects in the foot. Obscure and chronic pain around the foot and ankle can be notoriously difficult to localise, clinically and also radiologically. Radiographs should be the first imaging study obtained for the radiological evaluation of this pathology. Most of the time, computed tomography (CT) and magnetic resonance (MR) are used as the next step. In order to study correctly the pathology in the chronic painful ankle and foot, some basic knowledge of the anatomy is necessary.

The ankle is formed by the tibia, the fibula and the talus, creating a hinge joint. The tibial articular margin is called the tibial plafond (ceiling). The medial and lateral articular margins of the ankle joint are formed by the talus and medial malleolus, and by the talus and the lateral malleolus. The talar dome has a complex shape, semicircular when viewed from the side but subtly saddle-shaped when viewed anteriorly. The talus has sixty percent of its surface covered by articular cartilage. The stability of the ankle is supported by a complex array of ligaments and tendons around it.

The foot is divided into the hind foot (calcaneus and talus), mid foot (cuboid, navicular and cuneiforms), and forefoot (metatarsals and phalanges). The articulation between the hind foot and mid foot is termed Chopart's joint. The articulation between the mid foot and forefoot is termed Lisfranc's joint. Also in the case of the foot, the stability is supported by ligaments and tendons. Lisfranc's ligament is a particular one, connecting the lateral-distal margin of the medial cuneiform with the adjacent medial-proximal margin of the second metatarsal bone, injured in the Lisfranc's fracture-dislocation.

Due to this complex anatomy around the ankle and foot formed by bones, ligaments and tendons, it is not difficult to understand why conventional radiographic techniques and CT have an important but in some cases limited role in the evaluation of the chronic injured foot and ankle because in many cases chronic ankle and foot pain is caused by problems in the soft tissues that are not properly evaluated with CT. Nevertheless some particular conditions are exquisitely studied with CT, giving MR a secondary role. The aim of this article is to analyse these particular conditions and to evaluate the role and limitations of CT in the evaluation of the most common injuries around the ankle and foot.

1. Evaluating chronic ankle symptoms

Chronic pain of the ankle with or without previous traumatic injury is a common condition. In the evaluation process, the workup should centre on whether the patient's chief chronic ankle complaint is pain or instability. If the primary problem is instability, MR is the most useful exam to identify and confirm the problem. Nevertheless, if the primary problem is chronic pain, a concentrated effort should be made to rule out occult fractures, a talar dome osteochondral defect, bony ankle impingement or degenerative changes of the joint. These conditions are exquisitely studied with CT. If the CT examination doesn't show the cause of the pain, MR should be performed in order to evaluate other injuries as cause of the chronic ankle pain.

A. Osteochondral lesion of the ankle

Osteochondral lesions of the ankle occur more frequently in the talus than in the tibial plafond. Disparity in frequency results from the biomechanical topography of the human ankle cartilage, since tibial cartilage is stiffer than talar cartilage (1). The usual sites of osteochondral lesions of

the talar dome are the posteromedial aspect (56%) and the anterolateral aspect of the talus (44%). Occasionally, mirror-image osteochondral defects of the talus and distal tibia occur, suggesting trauma as a potential cause of both lesions (2). Osteochondral lesions of the talus can occur spontaneously or most commonly in association with ankle sprains being in these cases commonly overlooked. These occur when there is a compressive component to the inversion injury, especially when landing from a jump. Usually these lesions are not detected initially and the patient presents some time later complaining of an unremitting ache in the ankle, despite appropriate treatment for the ankle sprain. CT is the most efficient way of evaluating the osseous anatomy of these lesions but is not suitable to assess properly the integrity of the articular cartilage (figure 1). There are different classification systems of these lesions based on imaging modality. Years ago Ferkel and Sgaglione developed a classification system based on CT that is still in use (3):

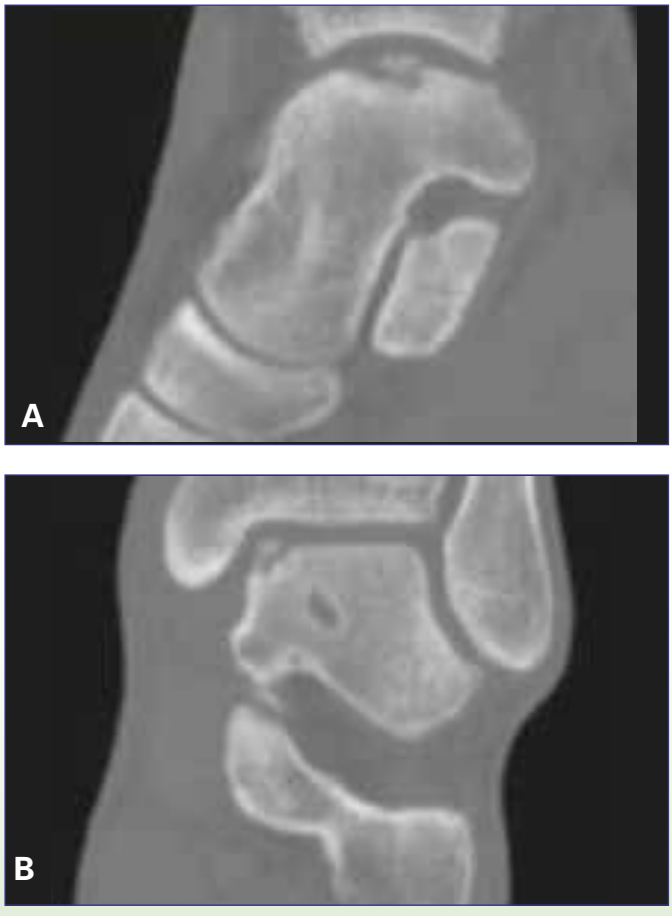

Figure 1. CT scan of the ankle with sagittal (A) and coronal (B) reconstructions demonstrates a non-displaced fragment with a lucency underneath without associated loose bodies in the medial talar dome consistent with an unstable osteochondral defect (stage III). Kindly provided by Eva Llopis.

- stage I: intact roof/cartilage with cystic lesion beneath (early stage)
- stage IIA: cystic lesion with communication to the surface (stable)
- stage IIB: open surface lesion with overlying fragment (unstable)
- stage III: non-displaced fragment with lucency underneath (unstable)
- stage IV: displaced fragment with formation of loose bodies (terminal)

Stage II, III and IV will be evident on CT, but stage I lesions are usually missed with CT. In these cases the MR plays an important role in the identification of radiographically or CT occult lesions and determining stability and viability.
The treatment of osteochondral lesions of the talus remains a challenge for the surgeon. Arthroscopic debridement and drilling will often provide satisfactory results. However, larger lesions and uncontained lesions are often associated with inferior functional outcomes and may require a more extensive initial procedure.

B. Anterior impingement syndrome of the ankle

Anterior impingement is a relatively common cause of chronic anterior ankle pain, especially in young athletes (soccer players) related to repeated stress in ankle dorsiflexion. It is usually the result of impingement with trapping of soft tissues between a 'beak-like' prominence typically formed at the anterior rim of the tibial plafond and the corresponding area over the apposing margin of the talus proximal to the talar neck ('kissing lesions'), well within the anterior ankle joint capsule (figure 2). These bony 'spurs' are the major component of anterior ankle impingement syndrome. The two major accepted hypotheses of the origin of these bony spurs are osteophyte formation due to repetitive micro trauma and enthesophyte development

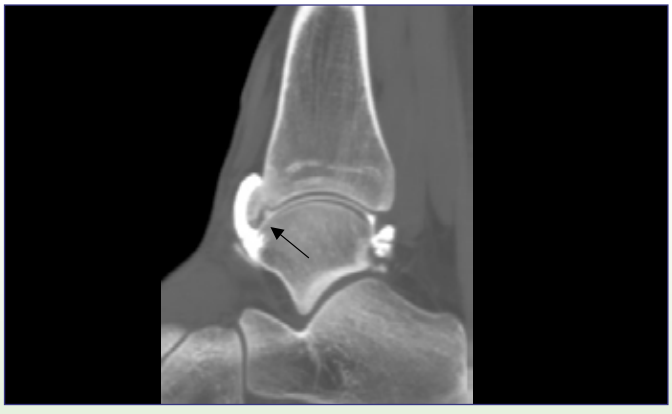

Figure 2. 34-year-old man with chronic anterior ankle pain with clinical suspicion of an osteochondral lesion of the talar dome in whom a CT arthrography was performed. The sagittal CT arthrography reconstruction doesn't show an osteochondral lesion of the talus but it does show bony 'spurs' formed at the anterior rim of the tibial plafond (arrow) and the corresponding area over the apposing margin of the talus proximal to the talar neck consistent with an osseous anterior impingement syndrome.

because of recurrent capsular or ligamentous traction (4). CT is the most efficient and reproducible means of evaluating the osseous anatomy of this condition. However, CT is less sensitive than MR for detecting associated joint effusion, chondral lesions, soft tissue abnormalities and bone marrow changes. Treatment should initially consist of conservative measures: rest, heel lifts, modification of activities and physical therapy. In patients with persistent pain despite conservative treatment, arthroscopic or open resection of both soft tissue overgrowths and osteophytes is an effective way of treating anterior ankle impingement.

C. Posterior impingement syndrome of the ankle

Posterior ankle impingement syndrome is a clinical disorder characterised by posterior ankle pain after acute trauma or much more frequently due to repetitive micro trauma/ stress in plantar flexion or push-off movements of the foot which produce compression (impingement) of the talus and the surrounding soft tissue between the tibia and the calcaneus, such as may occur during dancing, kicking or downhill running. Posterior impingement syndrome has been described under a variety of different names, including os trigonum syndrome and posterior tibiotalar compression syndrome. Some soft tissues are injured in the setting of posterior ankle impingement: posterior capsule of the joint, posterior talofibular, intermalleolar, tibiofibular ligaments and the flexor hallucis longus tendon. Nevertheless osseous pathology, of the os trigonum - posterior process of the talus, is the most common cause of this syndrome and due to this the osseous anatomy of the talus is the key factor in the occurrence of posterior ankle impingement syndrome. A secondary ossification centre posterolaterally from the talus forms between the age of 7 and 13 and unites with the rest of the talus within a year after its formation (5). After fusion it forms a posterior talar process, abnormally large posterior talar process is also known as Stieda process. If it fails to fuse, it forms os trigonum. The incidence of os trigonum is reported to be 7 to 14 percent, usually it articulates with the talus via a synchondrosis (5,6). Stieda process of the talus (figure 3) and os trigonum (figure 4) are extremely important in patients with posterior ankle pain. Compression of these structures between calcaneus and talus on extreme plantar flexion of the ankle could cause chronic pain and is also known as posterior impingement syndrome and os trigonum syndrome. CT is the most valuable method to define the osseous anatomy as a potential cause of impingement and also to detect some pathology of the posterior aspect of the ankle like degenerative changes, disruption at the os trigonum synchondrosis, identification of stress fracture of the Stieda process (7) or formation of loose bodies. Nevertheless CT usually fails to evaluate lesions of the soft tissues that accompany posterior ankle impingement like focal synovitis or tenosynovitis around the flexor hallucis longus tendon. Symptoms typically improve with nonsurgical management, but surgery may be required in refractory cases.

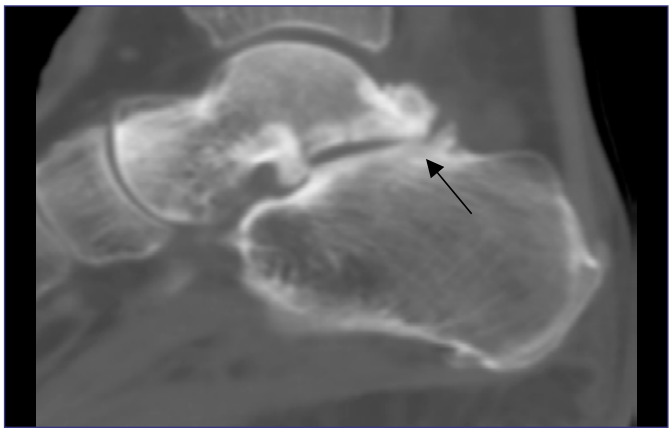

Figure 3. Clinically posterior impingement in a 37-year-old man. Sagittal CT reconstruction shows a prominent lateral posterior process of the talus (Stieda process) with secondary degenerative changes (arrow) between the posterior facet of the talus and the calcaneus consistent with a posterior impingement.

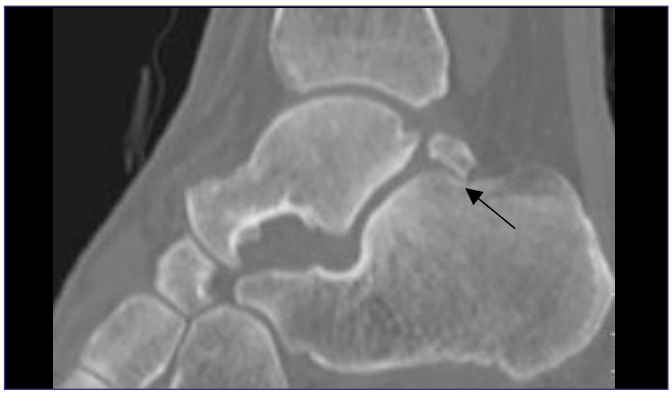

Figure 4. Clinically posterior impingement in a 40-year-old woman. Sagittal CT reconstruction shows a large os trigonum and a subtle inferior displacement of the os trigonum with bone-bone contact between the os trigonum and the calcaneus (arrow), suspicious of disruption of the synchondrosis as cause of the posterior impingement syndrome. CT fails to evaluate associated lesions of the soft tissues like focal synovitis or tenosynovitis around the flexor hallucis longus tendon.

D. Stress and insufficiency fractures around the ankle

Stress fractures have been classified as insufficiency or fatigue types. Insufficiency fractures occur when normal muscular activity or stresses are placed on abnormal bone or bone that has decreased elasticity. These are commonly seen in the postmenopausal population or patients with osteoporosis. Fatigue fractures occur when abnormal muscular stresses are applied to previously normal bones resulting in a fracture. These are commonly seen in athletes. Clinically, the patient typically describes gradually progressive onset of pain with activity. Initially, the pain occurs only with activity and resolves with rest. Later on, the activity is associated with progression of pain without any modification of activity, the pain may become constant and more chronic. Early clinical presentations can be subtle, so a high degree of

clinical suspicion and a systematic approach, coupled with an understanding of the diagnostic limitations present in early injury, is required. The early diagnosis is very important and it usually allows for simpler treatment and quick recovery. MR is the best diagnostic technique for the evaluation of patients in whom there is clinical suspicion for stress fracture and radiographs are negative. So CT has only a limited role in stress fracture detection, because of its inferior sensibility compared with that of bone scintigraphy and MR. CT may nevertheless help problem solving when there are equivocal findings on radiographs, MR or bone scintigrams or in cases of more advanced injuries or injuries in specific anatomic locations where the role of radiography is limited, like for example in suspected stress fracture of medial malleolus, talus or navicular bone (8). CT can also help in the differentiation of stress fractures from osteoid osteoma with reactive cortex thickening and bone sclerosis.

2. Evaluating chronic foot symptoms

Chronic foot pain is a common and often disabling clinical complaint that can interfere with patient's routine activities. Despite careful and detailed clinical history and physical examination, providing an accurate diagnosis is often difficult because chronic foot pain has a broad spectrum of potential causes. Therefore, imaging studies play a key role in diagnosis and management. Initial assessment is typically done by plain radiography, however, MR has superior soft-tissue contrast resolution and multi planar capability, which makes it important in the early diagnosis of ambiguous or clinically equivocal cases when initial radiographic findings are inconclusive. Nevertheless CT displays bony detail in arthritides, tarsal coalition and in some occasions in advanced cases of avascular necrosis. Other common causes of chronic foot pain such as Morton's neuroma, inter-metatarsal bursitis, plantar fasciitis and tarsal tunnel syndrome are not correctly evaluated with CT. In these particular cases, MR is necessary.

A. Tarsal coalitions

Tarsal coalition represents abnormal fusion between two or more bones. This condition may be either complete or incomplete, and may also be congenital or acquired secondary to trauma, infection (osteomyelitis) or articular disorders such as juvenile chronic arthritis and osteoarthritis. Coalitions can be bony (synostosis), cartilaginous (synchondrosis), or fibrous (syndesmosis). Symptoms from tarsal coalition generally appear in the second decade of life when the congenital coalition ossifies and becomes immobile. Patients describe pain and stiffness of the foot and reduced subtalar motion with local tenderness. Pes planus may be found on clinical examination. In the adolescent, symptoms from tarsal coalition are readily recognised, but the diagnosis is frequently delayed in older patients. This is possibly due to physicians' unawareness that coalition causes foot symptoms in older patients and to overlooking the coalition on plain film radiography. Therefore this diagnosis should be considered in all patients with chronic foot pain, subtalar stiffness with or without a pes planus deformity (9).

The classification of tarsal coalitions is based on the bones that are affected. The two most common types, calcaneonavicular and talocalcaneal, comprise the majority. Although calcaneocuboid, talonavicular, and cubonavicular tarsal fusion also occur, they are less common. Radiographs are important in screening for tarsal coalitions, especially with calcaneonavicular tarsal coalitions. Anteroposterior, lateral, and oblique views of the feet are the standard projections obtained (10). However, radiographs may not be sufficient for thorough evaluation of a complex subtarsal coalition and false-negative and false-positive findings with radiographs can also occur. Due to this, when clinical suspicion of coalition is high, CT remains a more cost-effective diagnostic modality than radiographs and MR. CT is advantageous also for evaluation of complicated cases of tarsal coalition for preoperative surgical planning. Proper assessment of tarsal coalitions on CT requires both axial and coronal reconstructions of the ankle and foot. Section thickness of three millimetres or less is optimal for evaluation. Nevertheless CT has also some limitations particularly in depicting non-osseous fibrous and cartilaginous coalitions (11,12,13,14). In these particular cases, MR is especially essential. The CT findings of the two most common types, calcaneonavicular and talocalcaneal, are as follows:

Calcaneonavicular coalition

- non-osseous coalition
  joint-space narrowing and reactive sclerosis between the calcaneus and the navicular bone (figure 5);
- osseous coalition

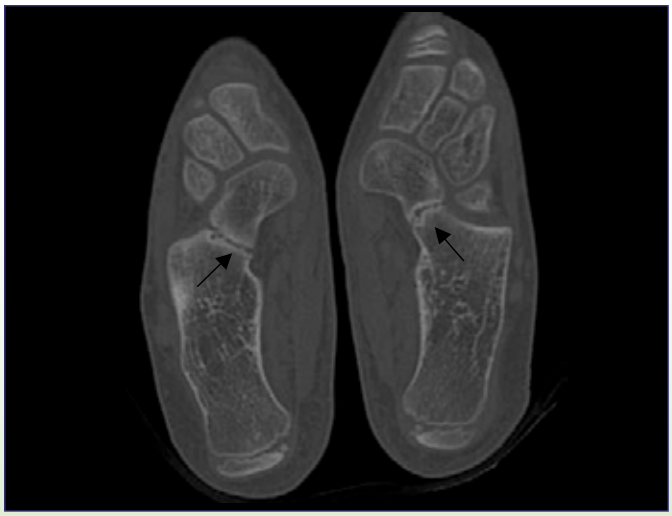

Figure 5. Calcaneonavicular coalition in an 11-year-old boy. Axial CT reconstruction shows bilateral apposition of the anterior dorsal calcaneus with the navicular, narrowing of the articular space and reactive sclerosis (arrow) consistent with a non-osseous calcaneonavicular coalition.

1. on axial views: medial broadening of the anterior and dorsal aspects of the calcaneus can occur at the navicular interface as it lies in apposition to the navicular;
2. on coronal views, lateral bridging with protrusion of an abnormal bony mass and rounding of the talus may be present.

Nevertheless the obliquity of the calcaneonavicular bridging, whether osseous or
non-osseous, makes it difficult to visualise the entire coalition on only one axial or coronal image (15) and multi planar reconstructions are in some cases required.

Talocalcaneal coalition (figure 6)

- coronal CT images are the most useful in the assessment of talocalcaneal coalitions; the middle facet of the talocalcaneal articulation is most frequently involved;
- occasionally, osseous bridging can be seen at the posterior and anterior facets; often, these findings are associated with more progressive cases;
- evaluating the sustentaculum tali carefully is important; the sustentaculum often extends in an upward medial direction; it may slant downward or laterally in talocalcaneal coalitions (15).

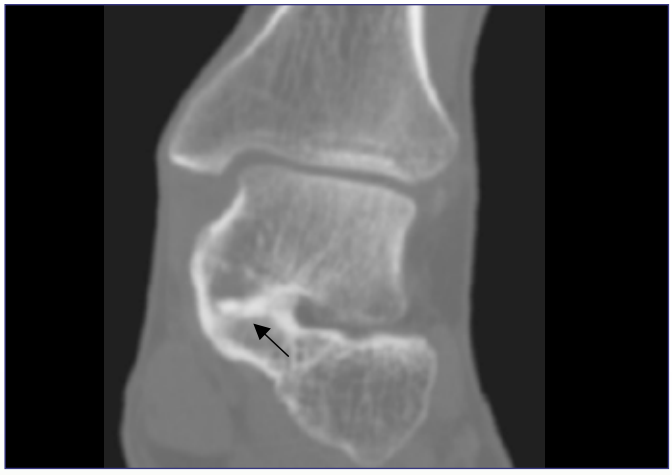

Figure 6. Osseous talocalcaneal coalition in a 35-year-old woman. Coronal CT reconstruction shows bone marrow contiguity across fused articulation between the talus and the calcaneus (arrow). Kindly provided by Eva Llopis.

As expected, findings on CT in non-osseous coalitions usually are subtler. Articular narrowing and reactive bony changes such as subchondral sclerosis and cystic changes can be seen. Nevertheless sometimes these changes are minimal or difficult to evaluate with CT and MR is required as the next step.
The treatment of tarsal coalition depends on the age and severity of the complaints. Depending on how uncomfortable or painful the foot is, treatment can be initiated with a cast, boot or a brace and then followed with orthotic arch supports. The boot or orthotic support will not ever be curative because the tarsal coalition and the abnormal bone connection are still present but it helps to live with less complaints. Conservative methods are frequently used to eliminate symptoms and improve the movement in the back of the foot, however in some cases surgery is required. The surgery is designed to remove the tarsal coalition and improve the inversion and eversion movement of the foot. There are times when removal of the tarsal coalition cannot completely correct the deformity. For these patients, especially for children, additional and more extensive surgery with, in some of the cases, tendon transposition may be necessary, particularly if the tarsal coalition is associated with a very flat foot. This is because simply removing of the tarsal coalition will not correct the arch of the foot itself.

B. Stress and insufficiency fractures around the foot

Stress fractures in the foot occur frequently in military and athletic populations and insufficiency fractures of the foot are commonly seen in the postmenopausal population or in patients with osteoporosis. As the clinical symptoms of this kind of fracture of the foot may mimic other less severe musculoskeletal injuries, the diagnosis of a fracture can often be delayed. It was explained before that MR is superior compared with CT in the early diagnosis of ambiguous or clinically equivocal cases when initial radiographic findings are inconclusive (16). So the role of CT in the diagnosis of stress/ insufficiency fractures of the foot is still limited and should be reserved only for specific indications because it also involves ionising radiation. Like in the ankle, CT may help problem solving when there are equivocal findings on radiographs or MR. CT scan can help, for example, in some cases in the differentiation of stress fractures from osteoid osteoma or reactive changes due to arthritides or osteomyelitis. Stress or insufficiency fractures are sometimes also incidentally seen in patients with vague foot complains in whom a CT scan is performed. Due to this, a general knowledge of the radiological manifestations of this kind of fractures on CT and the most common locations is required. CT findings include increased medullary cavity density, endosteal sclerosis, callus formation and soft tissue swelling (nonspecific findings). Only when actual failure lines are demonstrated by CT, a stress-related injury can be specifically suggested. Theoretically any of the bones of the foot can experience a stress of insufficiency fracture but the most common are the metatarsals, the calcaneus (figure 7), the navicular bone and the sesamoid bones under the toe (16,17).

C. Avascular necrosis of the ankle and foot

Avascular necrosis (AVN) or osteonecrosis is a disease caused by ischaemic death of the bony and marrow tissues due to interruption of the blood supply. The bone structures then collapse, resulting in bone destruction, pain, and loss of joint function. AVN is associated with numerous conditions and usually involves the epiphysis of long bones, such as the femoral and humeral heads and the femoral condyles, but the small bones of the ankle and foot can also be affected. Early

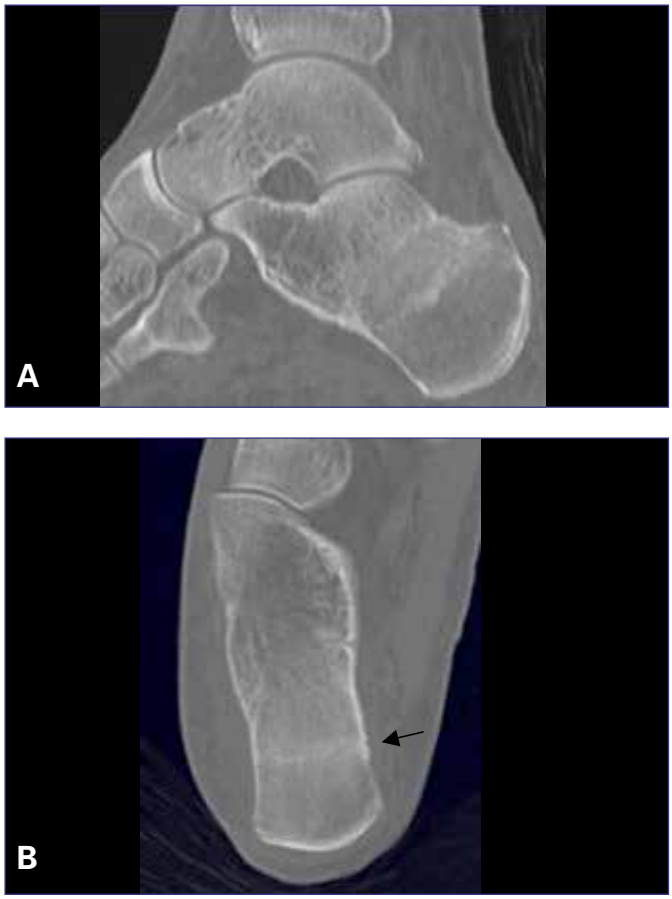

Figure 7. CT scan of the ankle with sagittal (A) and axial (B) reconstructions demonstrates an increased medullary cavity density of the calcaneus with focal disruption of the bony cortex medially (arrow) in a 45-year-old marathon runner consistent with a fatigue fracture.

diagnosis and appropriate intervention can delay the need for joint replacement. Without treatment, the process is almost always progressive, leading to joint destruction within five years. Patients taking corticosteroids and organ transplant recipients are particularly at risk of developing AVN. The value of CT in the detection of AVN is limited because CT scans do not demonstrate the early vascular and marrow abnormalities that result in osteonecrosis (18), so it doesn't play an important role in the early diagnosis of AVN. MR is the 'gold standard' for this early diagnosis and has largely replaced CT. Due to this, CT does not play a representative role in the proper or early diagnosis of AVN due to its low sensibility and specificity. Nevertheless CT can help in the evaluation of some complications of AVN like fragmentation of the bone, secondary degenerative changes with or without formation of loose bodies or in the evaluation of bone quality and morphology before surgery (arthrodesis or joint replacement). Some particular bones of the ankle and foot are particularly at risk of developing AVN like the talus, the navicular bone (Kohler's disease) (19) and the head of the metatarsal bones (Freiberg's disease) (20).

D. Charcot neuroarthropathy in diabetes mellitus

Charcot neuroarthropathy (CN) is a disease of bone and joints, characterised by painful or painless bone and joint destruction in limbs that have lost sensory innervations (21). Affected joints exhibit synovitis, instability, subluxation and destruction. Although not often recalled, trauma is thought to be an important initiating factor. The main cause of CN in the developed world is now diabetic polyneuropathy with the joints of foot being most commonly affected, specially the Lisfranc joint (21, 22). Neuropathic osteoarthropathy can be divided into an acute and a chronic form. The acute form presents clinically as a warm, swollen, erythematous foot that may simulate infection. Radiographs and CT have a limited diagnostic role in this stage because they may only reveal soft-tissue swelling and joint effusion. However, slight offset of the joints may be observed. For example, at the Lisfranc joint, the medial margin of the second metatarsal shaft should align precisely with the medial margin of the second cuneiform. Offset of this junction or widening of the distance between the first and second metatarsal bones should suggest early neuropathic disease in a diabetic patient. The bone density is generally preserved. MR of the foot is extremely sensitive in this stage, having a 100% detection of abnormalities and thus is the most sensitive modality at this point, but the differentiation between acute diabetic foot and infection can be a challenge. The chronic form is nevertheless easy to detect with CT, showing joint subluxation and dislocation as well as the destruction and fragmentation of the juxta-articular bone. In later stages of the disease, adjacent bones can become necrotic and collapse. The classic radiographic appearance of chronic neuropathic form has been characterised by words beginning with 'D', including destruction, dislocation, debris, disorganisation and preservation of bone density (figure 8) This chronic form of neuropathic disease in the Lisfranc joint typically results in superior and lateral subluxation of the metatarsals, leading to a 'rocker-bottom' type of deformity. Once Charcot's foot is identified, treatment generally involves immobilisation during the acute stage. When deformity develops, the orthopaedic foot and ankle surgeon must decide whether accommodative care with a combination of inlay depth shoes, accommodative foot orthoses, and ankle-foot orthoses is adequate. If a plantigrade weight-bearing surface cannot be achieved, surgical stabilisation or reconstruction requires rigid stabilisation in a normally poor biomechanical environment (23).

Conclusion

Chronic ankle and foot pain is a common and often disabling clinical complaint that can interfere with patient's routine activities. Despite careful and detailed clinical history and physical examination, providing an accurate diagnosis is often difficult because chronic ankle and foot pain has a broad spectrum of potential causes. Therefore, imaging studies play a key role in diagnosis and management. CT has an important but in some cases limited role in the evaluation of the chronic

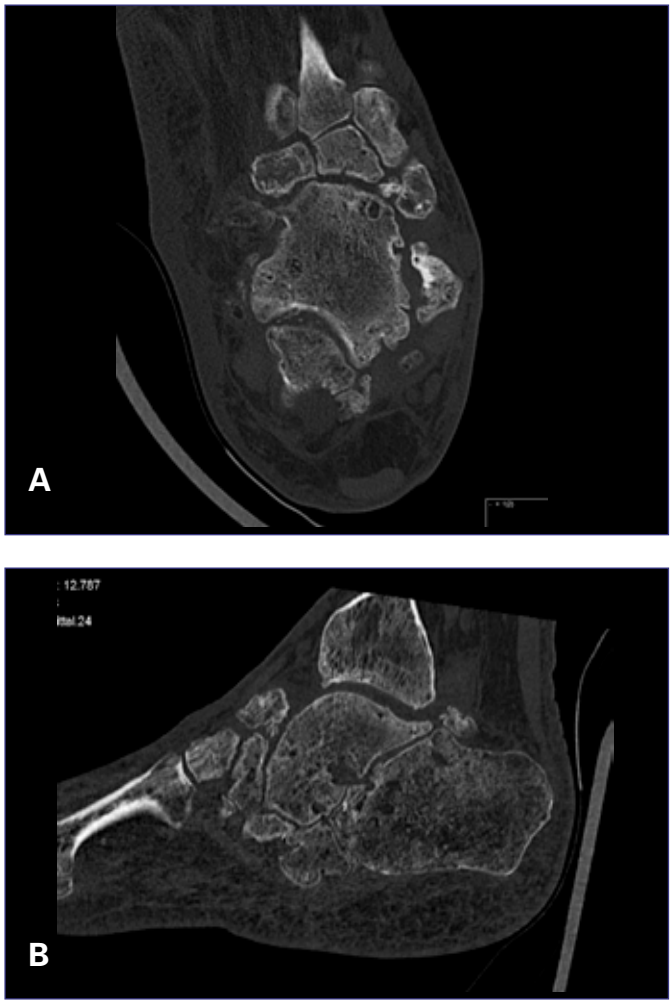

Figure 8. CT scan of the ankle with axial (A) and sagittal (B) reconstructions shows the classic radiographic appearance of chronic Charcot foot with destruction, dislocation and debris formation in the ankle and foot joint. Kindly provided by Herman Kroon.

injured foot and ankle because in many cases chronic ankle and foot pain is caused by a problem in the soft tissues that are not proper evaluated with CT. Nevertheless some particular conditions, as it was explained in this article, are exquisitely studied with CT, giving MR a secondary role.

References

1. Athanasiou KA, Niederauer GG, Schenck RC Jr. Biomechanical topography of human ankle cartilage. Ann Biomed Eng. 1995;23(5):697-704
2. Bauer M, Jonsson K, Linden B. Osteochondritis dissecans of the ankle. A 20-year follow-up study. J Bone Joint Surg [Br]. 1987;69(1):93-6
3. Berndt AL, Harty M. Transchondral fractures (osteochondritis dissecans) of the talus. J Bone Joint Surg Am. 1959;41:988-1020
4. Hayeri MR, Trudell DJ, Resnick D. Anterior ankle impingement and talar bony outgrowths:osteophyte or enthesophyte? Paleopathologic and cadaveric study with imaging correlation. AJR Am J Roentgenol. 2009;193(4):W334-8
5. Karasick D, Schweitzer ME. The os trigonum syndrome:imaging features. AJR Am J Roentgenol 1996;166:125–9
6. Robinson P, White LM. Soft-Tissue and Osseous Impingement Syndromes of theAnkle: Role of Imagingin Diagnosis and Management. RadioGraphics 2002; 22:1457–71
7. Maquirriain J. Posterior ankle impingement syndrome. J Am Acad Orthop Surg. 2005;13(6):365-71
8. Brockwell J, Yeung Y, Griffith JF. Stress fractures of the foot and ankle.Sports Med Arthrosc. 2009;17(3):149-59
9. Craig W. Carson, William W. Ginsburg et al. Tarsalcoalition: An unusual cause of foot pain—Clinical spectrum and treatment in 129 patients. Seminars in Arthritis and Rheumatism.1991;20(6):367-77
10. Crim JR, Kjeldsberg KM. Radiographic diagnosis of tarsal coalition. AJR Am J Roentgenol. 2004;182(2):323-8
11. Emery KH, Bisset GS 3rd, Johnson ND, Nunan PJ. Tarsal coalition: a blinded comparison of MRI and CT. Pediatr Radiol. 1998;28(8):612-6
12. Hochman M, Reed MH. Features of calcaneonavicular coalition on coronal computed tomography. Skeletal Radiol. 2000;29(7):409-12
13. Newman JS, Newberg AH. Congenital tarsal coalition: multimodality evaluation with emphasis on CT and MR imaging. Radiographics. 2000;20(2):321-32; quiz 526-7:532.
14. Wechsler RJ, Schweitzer ME, Deely DM et al. Tarsal coalition: depiction and characterization with CT and MR imaging. Radiology. 1994;193(2):447-52
15. Newman JS, MD, Newberg AH, MD. Congenital Tarsal Coalition: Multimodality Evaluation with Emphasis on CT and MR Imaging. RadioGraphics. 2000;20:321-32
16. Navas A, Kassarjian A. Bone marrow changes in stress injuries. Seminars in Musculoskeletal Radiology. 2011; 15(3):183-97
17. Shindle MK, Endo Y et al. Stress fractures about the tibia, foot, and ankle. J Am Acad Orthop Surg. 2012 Mar; July 2011;15(3):167-76
18. Sarikaya I, Sarikaya A, Holder LE. The role of single photon emission computed tomography in bone imaging. Semin Nucl Med. 2001;31(1):3-16
19. Borges JL, Guille JT, Bowen JR. Köhler's bone disease of the tarsal navicular. J Pediatr Orthop. 1995;15(5):596-8
20. Cerrato RA. Freiberg's disease. Foot Ankle Clin. 2011 Dec;16(4):647-58. Epub 2011 Oct 15.
21. Allman RM, Brower AC, Kotlyarov EB. Neuropathic bone and joint disease. Radiol Clin North Am. 1988;26:1373-81
22. Wilson M. Charcot foot osteoarthropathy in diabetes mellitus. Mil Med. 1991;156:563–9
23. Pinzur MS. Charcot's foot. Foot Ankle Clinc. 2000;5(4):897-912

Nuclear imaging in orthopaedic decision making with focus on ankle and foot

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Abstract

van Dijk M, Lavalaye J. Nuclear imaging in orthopaedic decision making with focus on ankle and foot. The complementary nature of combined functional and anatomical imaging in SPECT/CT is a rising modality in nuclear medicine in a number of indications which is increasingly recognised. The combination of SPECT and CT uses the high sensitivity of the bone scan and the high resolution of the CT and enables to improve difficult decision making in a wide range of orthopaedic indications, as in evaluation of hip and knee complaints, spinal disorders, oncology and infections, and foot and ankle disorders. In this article a selection will be briefly reported in the context of the orthopaedic practice with an emphasis on nuclear imaging with SPECT/CT of the ankle and foot.

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Introduction

Nuclear imaging continues to play a major role in the diagnosis and detection of skeletal and soft tissue disorders, since its introduction four decades ago, and despite advances in anatomical imaging, such as magnetic resonance imaging (MRI), multi-detector computerised tomography (MDCT), and high resolution ultrasound probes (1).

Skeletal scintigraphy has shown to be a diagnostic study, which is used to evaluate distribution of osteoblastic activity or active bone formation within the body. Due to the fact that no single imaging technique is ideal in all clinical conditions, selecting the appropriate imaging test depends on understanding the pathophysiology of the suspected condition and the limitations of every single technique (2).

In addition to the ability of bone scintigraphy to detect bone metastases from a variety of tumours well before other radiographic modalities show abnormalities, the superior sensitivity of bone scintigraphy is also used to detect arthrosis, occult fractures, non-accidental injuries, osteoid osteomas, and other pathologies of interest to orthopaedic surgeons (3). Therefore, patients with a wide variety of orthopaedic disorders can nowadays usefully be investigated by nuclear medicine techniques, and due to recent developments in imaging techniques, e.g. positron emission tomography (PET) and single photon emission computed tomography/computed tomography (SPECT/CT), the range of imaging, staging and treatment evaluation has been expanded.

The complementary nature of combined functional and anatomical imaging in SPECT/CT, to increase sensitivity and improve lesion localisation, has been a rising modality in nuclear medicine in a number of indications and increasingly recognised, particularly during the last decade. It is now routinely used for detection of sentinel nodes in breast oncology, localisation of the parathyroid gland in internal medicine and in neuroendocrine tumours, to name only a few of the possibilities.

However, a few years after the introduction, in our experience the largest number of SPECT/CT studies is carried out for orthopaedic indications. This can be partly explained by the large number of orthopaedic patients coming to a hospital compared to patients with carcinoid tumours. More important is the added value of a highly sensitive bone marker and a high resolution anatomical mapping.

For focal bone lesions in the axial skeleton it was shown that SPECT in combination with CT significantly increases certainty in diagnosis compared to planar imaging in benign and malignant lesions (4). Also in peripheral extremities, the added value of SPECT/CT has been shown by Linke et al (5).

Most imaging studies have focused on malignant lesions. In bone scintigraphy used for evaluating metastatic disease, it was even shown that SPECT/CT significantly outperforms SPECT alone for the interpretation of skeletal lesions in patients undergoing bone scanning for metastases (6). And a recent study reported the added value of multislice SPECT/CT in patients with equivocal bone metastases from carcinoma of the prostate (7).

Until very recent years there were minimal peer reviewed studies regarding SPECT/CT imaging for orthopaedic indications. Recently there are some studies making a set up for more scientific analysis of peripheral extremities using SPECT/CT (1,4,5).

Until now, there are sparse studies that compare different modalities, like the study of Leumann et al (8) comparing SPECT/CT and MRI in osteochondral lesions of the talus.

The publication dates give an indication of how fresh this

field of orthopaedic nuclear medicine is, and more comparing studies will certainly be published.

In general orthopaedic practice, plain radiography is mandatory, in addition to historical and physical examination, and has been found to be an accurate baseline technique for evaluation of widespread orthopaedic indications and skeletal disorders. However, in many orthopaedic patients supplementary imaging is necessary to localise and optimise diagnostic and treatment evaluation. Advances in nuclear imaging broadened the range of indications of imaging, as in evaluation of hip and knee complaints, spinal disorders, foot and ankle, orthopaedic oncology patients and infections. In this article a selection will be briefly reported in the context of the orthopaedic practice with an emphasis on nuclear imaging with SPECT/CT of the ankle and foot.

Methods

Orthopaedic SPECT/CT can actually be performed on any SPECT/CT scanner, and a variety of scanners is available, ranging from low-dose flat panel XCT to multislice CT with dedicated dose reduction schemes.
For routine imaging either ^{99m}Tc HDP or MDP can be used, in a dose range from 400 to 800 MBq. In our department we use 500 MBq ^{99m}Tc DPD, with the possibility of making a fast SPECT in less than fifteen minutes. For adolescents and young adults it can be considered to use a lower dose and use a longer scan time. A double headed gamma camera is mostly used, with acquisition times ranging from ten to twenty minutes in most used protocols. Acquisition times can be decreased to ten minutes for a SPECT with preservation of the image quality using resolution recovery software like Astonish. The image quality of the CT in extremities is mainly determined by the aim of the scan: purely anatomical matching for the SPECT findings or a high image quality for diagnostic purposes of the CT on its own. Flat panel CT technology provides excellent image quality, on a diagnostic level, with isotropic voxels of 0.33 mm. However, due to the configuration, only a limited field of view (about 14 cm) can be scanned in high resolution.

Radiation

Radiation is an important topic in orthopaedic imaging while most patients are relatively young and often scans are repeated over time. Nevertheless, radiation dose for the extremities is in a complete different range than for thorax or abdomen. A precise overview of radiation in radiological and nuclear medicine procedures does not even mention CT dose for the extremities (9). An interesting overview of radiation exposure from musculoskeletal CT scans was actually published in an orthopaedic journal (10). In this article a mean dose of twenty patients was calculated which resulted in a mean of 0.07 mSv for the ankle and foot. This is less than the effective dose of a conventional chest radiograph, which has been reported to be approximately 0.08 mSv. So, even standard CT adds only minimal radiation the SPECT/CT study, ranging from 0.1 to 0.5 mSv. Therefore, radiation safety is a minor issue in adding dose CT to the already delivered 2.3 mSv using a 500 MBq dose for scintigraphy (11).

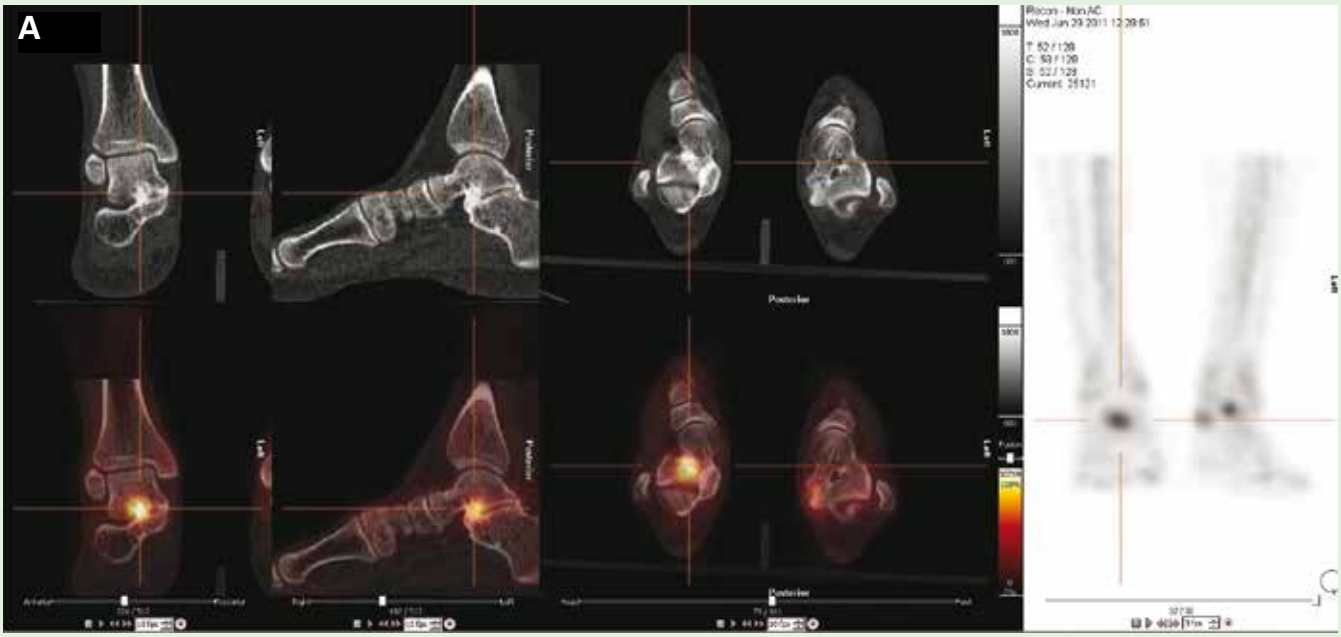
Practical

Important practical point in image acquisition is immobilisation of the feet. This can be done by taping the feet to a foot board, fixed in a 90 degree angle to the gantry bed. Software fusion of SPECT and CT is mostly done automatically, but when reporting, one has to keep in mind that only a small movement of the feet can make a fusion useless.
In our opinion a review session should start with an image quality check, by changing the threshold to check whether there is a complete match of SPECT and CT. All dedicated software makes it possible to manually adjust the image fusion.

Foot and ankle

The evaluation of the osseous ankle and foot pathology often poses a clinical and diagnostic challenge due to the complex anatomy and structural biomechanics of the region (12). The addition of SPECT/CT to routine planar bone scans has probably the largest effect in patients with foot and ankle disabilities, in which multiple joints may be affected by different pathologies, as also stated by Scharf (3).
SPECT/CT allows in detail to confirm radiographic abnormalities and localise symptoms and sources of pain in the foot and ankle. In line with this, it is of uppermost importance to determine the extent of degenerative chances in the ankle and foot before surgical planning. For example, in patients with an isolated arthrosis of the ankle joint and in which conservative treatment fails, an arthrodesis or arthroplasty of the ankle joint can be considered. However, in case of arthrosis of the ankle joint in combination with a talonavicular or talocalcanear arthrosis, a more extended arthrodesis, as a triple arthrodesis, is more appropriate to consider. Pagenstert et al (13) investigated the intra- and interobserver reliability of SPECT/CT compared to separate bone scanning and CT in degenerative joint disease of the foot and ankle. The mean intraobserver reliability for SPECT/CT was excellent (kappa= 0.86) and significantly higher than for CT and bone scanning together. Furthermore, SPECT/CT had significantly higher interobserver agreement, especially when evaluating the naviculocuneiform and tarsometatarsal joints (13). Kreztschmar et al (14) published a study on the feasibility and predictive value of SPECT/CT for image guided diagnostic infiltrations in patients with chronic foot pain. The patients underwent SPECT/CT imaging of both feet. The subsequent scintigraphically most active structures were subsequently infiltrated with local anaesthetics under CT-guidance. The pre- and postoperative pain intensity was measured using the visual analogue scale (VAS) and it was shown that SPECT/CT had a higher predictive value on the clinical outcome than the clinical assessment (14).

Case example 1.
A 30 year-old man sustained complaints of both feet for years, initially only with running, however, nowadays also in activities of daily living. The patient has sustained multiple ankle distortions in history. The pain was located anterolaterally, but on the right side also medially in the hind foot.
On physical examination a clear rigid plano valgus on the right side was observed and on the left side a plano valgus which is partially flexible. Furthermore, on the right side the subtalar joint was rigid, on the left a limited range of motion. The right posticus tendon shows limited strength. At last, the patient is hardly unable to stand on his toes.
Plain radiography showed a pes plano valgus, but furthermore no evident radiographic abnormalities. However, SPECT/CT imaging showed increased uptake in the subtalar joint, with a concomitant sign of an old tarsal coalition. At first conservative treatment was advised with the use of inlays; however, a subtalar arthrodesis will be planned if complaints are not reduced sufficiently.



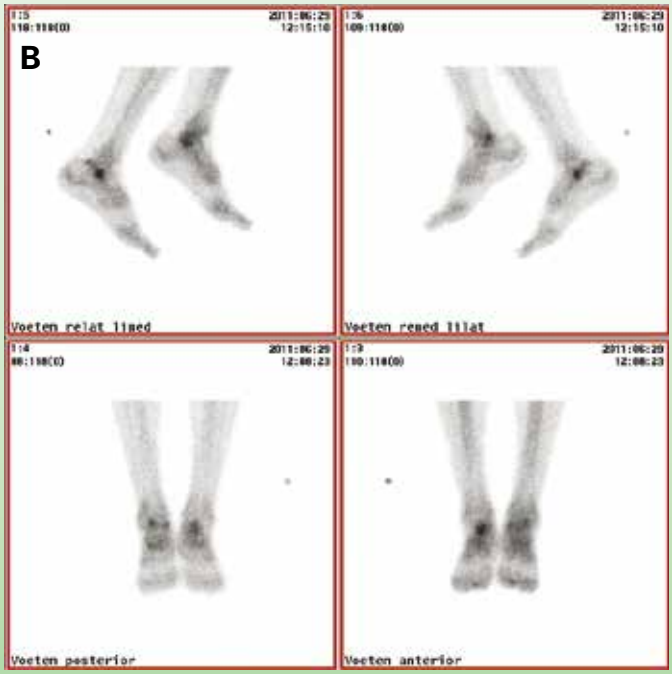


Figure 1. Bone scan with SPECT/CT(A) and planar images (B) of patient nr 1 showing uptake in the subtalar joint.

In addition, patients may have had previous (sports) injuries with anatomical abnormalities, from which the age is difficult to determine, which challenges evaluating these patients (3). Although the bone scan can be used to age fractures or stress injuries, it is only with SPECT/CT that details of complicated combinations of old and new injuries can be sorted out.

Furthermore, metatarsal stress fractures or sesamoiditis normally can be identified with a plantar image, however, in many patients the location of activity may not be obvious. In addition, an osteochondritis dissecans lesion, which can be seen after a repetitive stress injury, is frequently observed in the ankle joint. Because of the repetitive stress injury,

Case example 2.
A 31-year-old sustained posterolateral pain of his left ankle, while playing basketball without a real trauma. At physical examination, tenderness was found posteriorly at the ankle joint. Additional MRI imaging revealed bone bruise on the medial side of the talus with a concomitant osteochondritis dissecans lesion. Furthermore, an osteophyte of the distal tibia was observed together with an os trigonum at the posterior side of the ankle. A bone scintigraphy showed increased uptake at the distal fibula posteriorly, and barely increased uptake at the os trigonum, which was clearly detectable with additional SPECT/CT imaging. After conservative treatment failed, a posterior ankle arthroscopy was performed under the suspicion of a posterior impingement syndrome and nettoyage was performed at the posterolateral part of the fibula. Two months after surgery, the pre-operative posterior ankle complaints were disappeared and the patient returned to playing basketball.

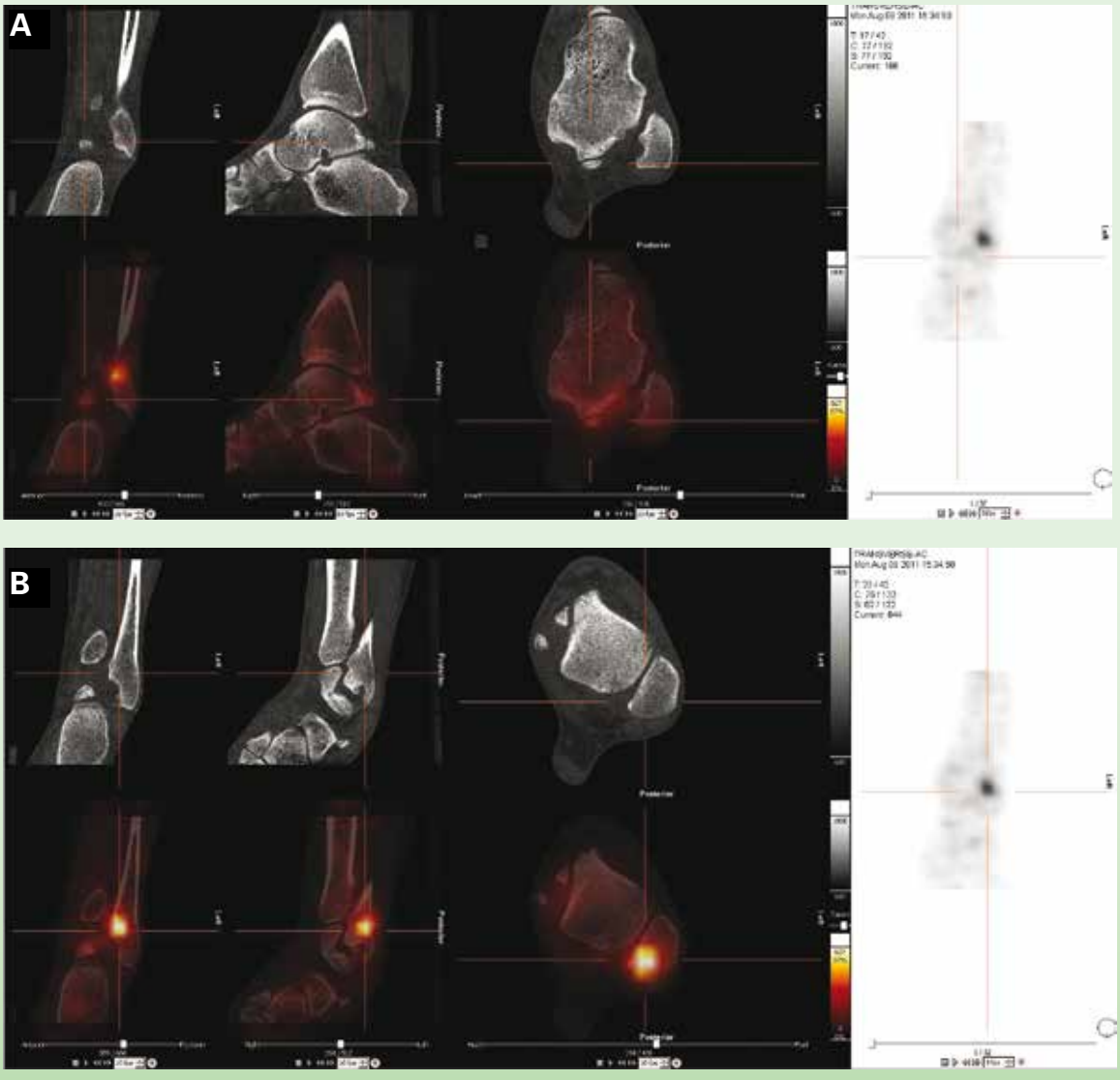


Figure 2. SPECT/CT of patient nr 2 showing increased uptake at the distal fibula posteriorly (B), and barely increased uptake at the os trigonum (A).

bone and cartilage fragments can separate, because of devitalisation of the subarticular region, and these fragments may cause severe pain in the joint.
Plain radiographs and MRI scanning are useful in diagnosing osteochondritis dissecans. However, SPECT/CT is helpful to determine if the lesion is symptomatic and likely the cause of the patients complaints, and to aid in surgical planning. Meftah et al (15) investigated the role of SPECT/CT in the management of ostechondral lesions of the talus. In 22 patients with an osteochondral lesion of the talus SPECT/CT and MRI scanning was performed. It was reported that SPECT/CT helped preoperative planning by identifying the exact location of the active lesion, especially in multifocal disease or revision surgeries while showing the depth of the active lesion, which is mandatory for the type of treatment. It was concluded that SPECT/CT provided additional diagnostic value by demonstrating concomitant abnormalities, the depth of the lesion and the precise location of the osteochondral lesion (15). In line with this, Leumann et al showed that SPECT/CT provides additional information and influences decision making of osteochondral lesion treatment, in a study comparing MRI and SPECT/CT in evaluating osteochondral lesions of the talus, as mentioned previously (8).

SPECT/CT plays nowadays an important role in the evaluation and treatment of patients with a tarsal coalition (3). Tarsal coalition is a condition in which there is congenital fusion of two or more tarsal bones with either a bony or fibrous bridge (16). These abnormal connections cause abnormal stress on the hind foot, with pain usually beginning in the early teenage years. Surgery is often required depending of age of presentation, in younger patients to separate the bones and in older patients a bony fusion of the tarsal bones may be considered in those patients who do not respond to conservative treatment.

Case example 3.
A 17-year-old man sustained a traffic accident at which he fell on his medial side of the right foot. Medical history revealed no abnormalities. The patient was presented at the hospital and a plaster cast was applied for six weeks. Hereafter, however, he complained of ongoing pain on the medial side of the right foot with a painful tenderness. Plain radiography showed an accessory bone of the navicular bone (os tibiale externum). Despite adequate conservative treatment the complaints did not diminish and a SPECT/CT of the right foot was performed, showing locally increased uptake at the level and interface of the accessory navicular and navicular bone. Because conservative treatment failed and due to the young age of the patient, it was decided to fixate the accessory to the navicular bone with screw fixation.

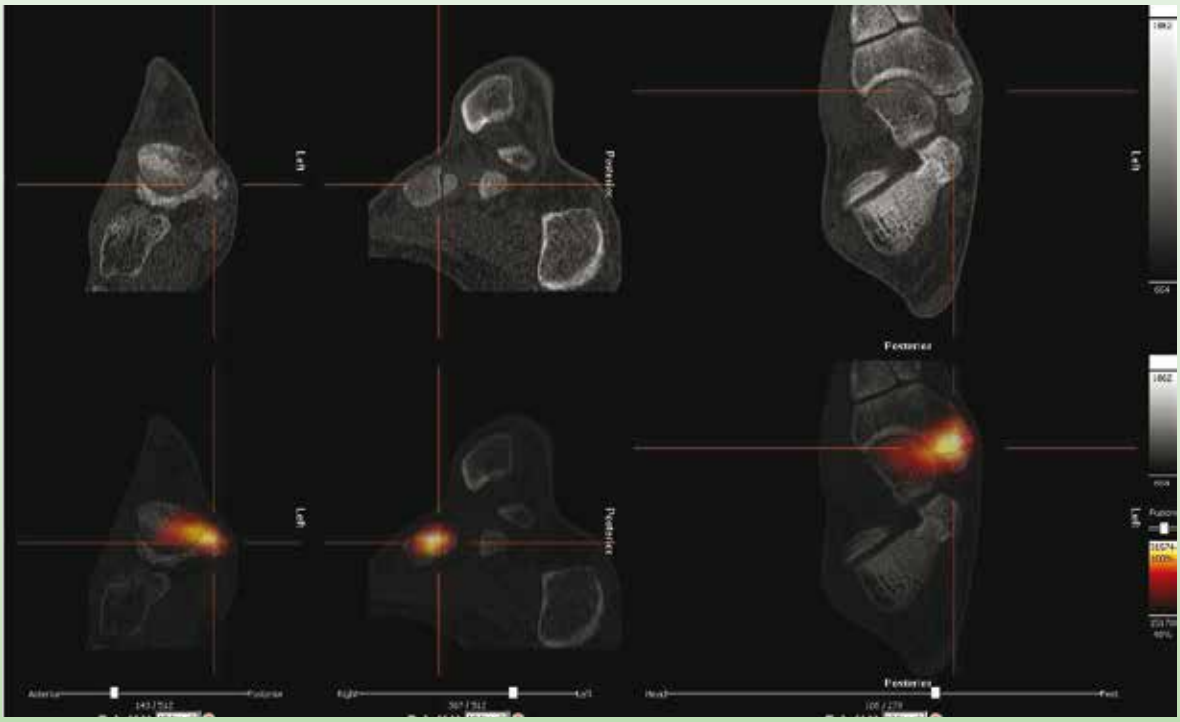


Figure 3. SPECT/CT of patient nr 3 showing locally increased uptake at the level and interface of the accessory navicular and navicular bone.

As clearly reported by Scharf (3) SPECT/CT also is an adjunctive and complementary imaging modality in patients with osteoid osteoma of the ankle or foot. Osteoid osteomas are benign tumours of bone often seen in teenagers (17). When conservative treatment is unsuccessful with rest and administration of salycates, surgical removal is frequently performed. Also radiofrequency ablation has also been reported to be successful. On the bone scan a focus of intense activity is almost always seen and a lucent nidus can usually be identified on CT scanning, but the findings can be difficult to interpret when they occur in the small bones of the mid foot. To optimise the decision making and surgical intervention SPECT/CT is valuable to localise and to identify the lesion.

Thus, the introduction of SPECT/CT in evaluation of patients with foot and ankle disorders enables to distinguish between a wide range of entities, among which are stress fractures of the mid foot, degenerative joint disease in the mid foot and hind foot, osteochondral lesions, tarsal coalition and osteoid osteoma, to improve treatment outcomes.

Hip and knee

In patients with hip and knee complaints plain radiography is the baseline imaging modality. However, in some patients plain radiographs are not conclusive and scintigraphy may be helpful to confirm degenerative changes in the hip and knee joint in order to plan e.g. total hip or knee arthroplasty accurately. In patients with a coxarthrosis and concomitant degenerative changes of the lumbar spine, bone scintigraphy attributes to predict possible persistent spinal complaints after total hip arthroplasty. In these cases, SPECT/CT and PET imaging have no additional value for treatment consideration. However, Gnanasegaran et al (1) reported that SPECT/CT can be useful in the evaluation of meniscal tears, and cruciate and collateral ligament injury (18-21). But it is difficult to characterise the abnormalities or localise the site without anatomical or structural correlation. Furthermore, MRI

Case example 4.
A 67-year-old woman sustained complaints of the right ankle without a recent trauma, but fifteen years ago she sustained a trimalleolar ankle fracture, which was treated operatively at the medial and lateral malleolus. At physical examination, there was tenderness at the ankle joint, however the subtalar joint was not painful. Plain radiographs revealed no abnormalities. Bone scan shows increased uptake in the distal tibia right at the malleolus tertius (which is the posterior aspect of the distal tibia en which was not fixated years before). In addition, SPECT/CT showed focal activity in the distal tibia posterolateral, apart from the tibiotalar joint. Low dose CT shows subchondral bone cysts. The patient was treated conservatively, but in the event of progressive posttraumatic degeneration of the ankle, an arthrodesis can be considered.
Conclusion: focal posttraumatic arthrosis of the tibiotalar joint, likely due to the former fracture.

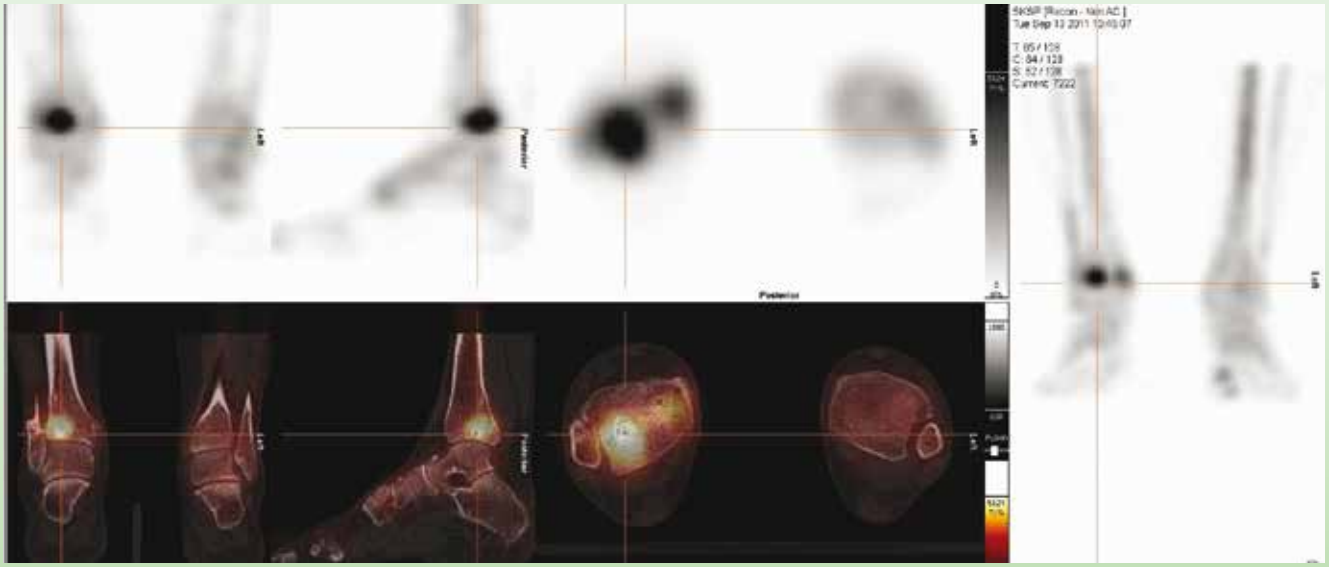


Figure 4. SPECT/CT of patient nr 4 showing increased uptake in the right distal tibia with subchondral bone cysts on low dose CT.

scanning of the knee, in addition to plain radiography, is the first choice of imaging to elucidate intra-articular pathology in detail. In our opinion, SPECT/CT is useful in localizing and characterizing of lesions around the hip and knee, as osteoid osteoma, loosening of a total knee or hip replacement, patella maltracking/subluxation, and symptomatic osteochondral defects of the knee or hip joint.

Spine

Back pain is a major cause of morbidity in our population with high costs due to workers compensation. More than in hip and knee evaluation, additive imaging besides plain radiography is performed, either to exclude or confirm spinal pathology or to localise more accurately the source of abnormality. In patients with suspected neurological impairment, MRI scanning of the spine is the first choice of imaging modality. However, bone scintigraphy and SPECT/CT scanning are very beneficial in patients with (osteoporotic) vertebral compression fractures with different times of onset, with or without concomitant degenerative changes. In addition, degenerative disc diseases and facet arthrosis can be localised with precision, and determine e.g. level of spinal fusion procedures. Furthermore, nuclear imaging may elucidate pseudarthrosis after spinal fusion procedures and SPECT/CT allows distinguishing between abnormalities that are caused by fractures of the pars interarticularis, facet joint arthritis, and Berlotti's syndrome, in which low back pain is caused by asymmetric fusion of the transverse processes of L5 with the sacrum. SPECT/CT also enables to localise the cause of residual or recurrent symptoms in patients after spinal fusion procedures with residual complaints (3).

Oncology

Encountering musculoskeletal neoplasia in the clinical practice of orthopaedic surgery is a rather uncommon event. Using a systematic approach to image these lesions includes evaluation with plain radiographs and other modalities such as bone scintigraphy, computed tomography, magnetic resonance imaging, and positron emission tomography (22). By applying specific imaging characteristics obtained from these different modalities, the radiologist and orthopaedic surgeon can jointly create an appropriate differential diagnosis (22).

It is well recognised that considerable bone destruction is required to detect bone metastases by plain radiography (1). Planar bone scanning is highly sensitive in the detection of bone metastases and has additional benefit of providing whole-body imaging. In addition, in patients with known or suspected cancer, the fusion of SPECT and CT data has been reported to improve the diagnostic evaluation when differentiating malignant from benign bone lesions. As reported by Gnanasegaran et al (1), current evidence suggests that the addition of localised SPECT/CT for the assessment of indeterminate foci both enables a definitive diagnosis in most cases and it improves diagnostic confidence, which may potentially lead to reduced use of additional imaging (1). Furthermore, imaging with nuclear medicine techniques plays an important role in diagnosis, staging, treatment planning, and follow-up (23). In line with this and due to the fact that clinical and histopathological response evaluations can be somewhat subjective, imaging tumour response quantitatively can provide clinically relevant objective information for treatment planning for these oncology patients.

Table 1. Advantages and limitations of SPECT/CT according to Gnanasegaran (1).

Advantages SPECT/CT
assessment of both anatomy and function
lesion localisation and characterisation
provides additional information
CT data can be used for attenuation and scatter correction
most tracers are technetium based
tracers are relatively less expensive and are easily available
no additional patient separation
half-life of SPECT tracers is relatively longer
principles of SPECT imaging is well established
incidental findings
the existing department needs minimal alteration
one stop imaging
greater comfort for the patient because transfer from one scanner to another is not necessary
Limitations
limited evidence
no definitive indications
no definitive protocols
additional radiation dose
multislice SPECT/CT is relatively expensive
histological confirmation of the lesions
training in cross-sectional imaging
few prospective studies

Infection

Patients with infection surrounding surgical hardware are challenging. Scarf (3) stated that the relatively poor specificity of gallium in comparison with labelled white blood cells was more than outweighed by its much greater sensitivity. Furthermore, it may be easier to deal with the occasional false-positive patient than to miss finding the chronic infections seen in some of these patients. SPECT/CT may be very helpful in detection of infection around surgical hardware after fracture treatment and localisation of possible osteomyelitis.

The accurate and early diagnosis of osteomyelitis remains

a diagnostic challenge, particularly in the diabetic foot or postoperative joint (1). Plain radiographs remain the base-line imaging modality; however, they are usually unremarkable in early stages of infection. A vast range of radionuclide tracers is available but the majority show high sensitivity and limited specificity. In general, MRI and dual or three-phase bone scintigraphy are the modalities of choice of osteomyelitis (24). The major limitation of radionuclide imaging includes anatomical localisation of the infection and non-specific tracer uptake. But these limitations may be overcome by complimentary use of CT in specific cases and has found to be beneficial in determining the precise anatomical location of infection in 50 to 85 percent (25). SPECT/CT images were found to provide accurate anatomical localisation and precise definition of the extent of infection.
Further large prospective studies are required, but generally SPECT/CT is not routinely performed or required for all patients with suspected infection/inflammation and is often indicated only if there are equivocal planar scintigraphic findings or accurate localisation is required (1).

Orthopaedic related benign uptake and artefacts

Artefacts are generated when differences are present between high-density metal objects and surrounding tissue. These possible artefacts mimic increased FDG uptake adjacent to the metal. The intensity of uptake caused by this kind of artefact depends on the size and shape of the metal hardware or prosthesis, the absorption properties of surrounding tissue, patient movement, and the image reconstruction method used (26,27). Because uptake is usually diffuse and located around the hardware or prosthesis, infection may falsely be diagnosed on interpretation of PET images.
Prolonged increased uptake after orthopaedic surgical interventions or concomitant with orthopaedic disorders can be observed, as reported by Liu (28). For instance, at the end of bone resection or amputation, focal increased uptake is often noted for months. Furthermore, heterotopic ossification (HO) refers to the formation of bone in non-osseous tissue. It is frequently noted following musculoskeletal trauma, spinal cord injuries or orthopaedic surgery related interventions, particularly amputations and total hip arthroplasty. HO may closely mimic the presentation of cellulitis, osteomyelitis, or thrombophlebitis in the early stage (29). Three-phase bone scintigraphy is the most sensitive imaging modality for early detection of heterotopic ossification.
Special postoperative complications secondary to orthopaedic surgical procedures occur, which may demonstrate abnormally increased or focal uptake on nuclear images, and cause a dilemma in interpretation. The distinction of normal from pathologic, benign from malignant uptake is very important to minimise the number of false positive results. SPECT/CT imaging will play an important role in the near future to assist in interpreting these difficult cases and to direct towards the appropriate treatment modality required.

Conclusion

The availability of hybrid devices that combine the latest single-photon emission computed tomography imaging technology with multislice computed tomography scanning has allowed us to detect subtle, non-specific abnormalities on bone scans and interpret them as specific focal areas of pathology, especially in the spine and foot and ankle. Nowadays, SPECT/CT imaging enables to localise pathology and to plan surgical intervention. In the future it will be expected that the range of indications for SPECT/CT imaging will expand and that collaboration between nuclear medicine clinicians and orthopaedic surgeons is mandatory for further optimisation in diagnosing and treatment evaluation of orthopaedic patients nowadays and in the future.

References

1. Gnanasegaran G, Barwick T, Adamson K et al. Multislice SPECT/CT in benign and malignant bone disease: when the ordinary turns into the extraordinary. Semin Nucl Med. 2009;39:431-42
2. Lee E, Worsley DF. Role of radionuclide imaging in the orthopaedic patient. Orthop Clin North Am. 2006;37:485-501
3. Scharf S. SPECT/CT imaging in general orthopaedic practice. Semin Nucl Med. 2009;39:293-307
4. Strobel K, Burger C, Seifert B et al. Characterisation of focal bone lesions in the axial skeleton: performance of planar bone scintigraphy compared with SPECT and SPECT fused with CT. Am J Roentgenol. 2007;188:467-74
5. Linke R, Kuwert T, Uder M et al. Skeletal SPECT/CT of the peripheral extremities. Am J Roentgenol. 2010;194:329-35
6. Ndlovu X, George R, Ellmann A et al. Should SPECT-CT replace SPECT for the evaluation of equivocal bone scan lesions in patients with underlying malignancies? Nucl Med Commun. 2010;31:659-65
7. Helyar V, Mohan HK, Barwick T et al. The added value of multislice SPECT/CT in patients with equivocal bony metastasis from carcinoma of the prostate. Eur J Nucl Med Mol Imaging. 2010;37:706-13
8. Leumann A, Valderrabano V, Plaass C et al. A novel imaging method for osteochondral lesions of the talus – comparison of SPECT-CT with MRI. 2011;39:1095-101
9. Mettler FA Jr, Huda W, Yoshizumi TT et al. Effective doses in radiology and diagnostic nuclear medicine: a catalog. Radiology. 2008;248:254-63
10. Biswas D, Bible JE, Bohan M et al. Radiation exposure from musculoskeletal computerized tomographic scans. J Bone Joint Surg Am. 2009;91:1882-9
11. Barneveld PC, van Urk P et al. Aanbevelingen NVNG. 2007. ISBN 978-90-78876-01-4
12. Nathan M, MohanH, Vijayanathan S et al. The role of 99mTc-diphosphonate bone SPECT/CT in the ankle and foot. Nucl Med Commun. 2012;Jun 10 (Epub ahead of print)
13. Pagenstert GI, Barg A, Leumann AG et al. SPECT-CT imaging in degenerative joint disease of the foot and ankle. J Bone Joint Surg Br. 2009;91:1191-6

14. Kretzschmar M, Wiewiorski M, Rasch H et al. 99mTc-DPD-SPECT/CT predicts the outcome of imaging-guided diagnostic anaesthetic injections: a prospective cohort study. Eur J Radiol. 2011;80:e410-5
15. Meftah M, Katchis SD, Scharf SC et al. SPECT/CT in the management of osteochondral lesions of the talus. Foot Ankle Int. 2011;32:233-8
16. Crim JR, Kjeldsberg KM. Radiographic diagnosis of tarsal coalition. Am J Roetgenol. 2004;182:323-8
17. Marcove RC, Heelan RT, Huvos AG et al. Osteoid osteoma. Diagnosis, localisation, and treatment. Clin Orthop Relat Res. 1991;267:197-201
18. Ryan PJ, Chauduri R, Bingham J et al. A comparison of MRI and bone SPET in the diagnosis of knee pathology. Nucl Med Commun. 1996;17:125-131
19. Ryan PJ, Reddy K, Fleetcroft. A prospective comparison of clinical examination, MRI, bone SPECT, and arthroscopy to detect meniscal tears. Clin Nucl Med. 1998;23:803-6
20. Cook GJ, Ryan PJ, Clarke SE et al. SPECT bone scintigraphy of anterior cruciate ligament injury. J Nucl Med. 1996;37:1353-6
21. Collier BD, Johnson RP, Carrera GF et al. Chronic knee pain assessed by SPECT: comparison with other modalities. Radiology. 1985;157:795-802
22. Parsons TW 3rd, Frink SJ, Campbell SE. Musculoskeletal neoplasia: helping the orthopaedic surgeon establish the diagnosis. Semin Musculoskelet radiol. 2007;11:3-15
23. Eary JF, Conrad EU, Imaging in sarcoma. J Nucl Med. 2011;52:1903-13
24. Pineda C, Vargas A, Rodriguez AV. Imaging of osteomyelitis: current concepts. Infect Dis Clin North Am. 2006;20:789-825
25. Bar-Shalom R, Yefremov N, Guralnik L et al. SPECT/CT using 67Ga and 111In-labeled leukocyte scintigraphy for diagnosis of infection. 2006;47:587-94
26. Schiesser M, Stumpe KD, Trentz O et al. Detection of metallic implant-associated infections with FDG PET in patients with trauma: correlation with microbiologic results. Radiology. 2003;226:391-8
27. Goerres GW, Ziegler SI, Burger C et al. Artifacts at PET and PET/CT caused by metallic hip prosthetic material. Radiology. 2003;226:577-84
28. Liu Y. Orthopedic surgery-related being uptake on FDG-PET: case examples and pitfalls. Ann Nucl Med. 2009;23:701-8
29. Jensen LL, Halar E, Little J et al. Neurogenic heterotopic ossification. Am J Phys Med Rehab. 1987;66:351-63

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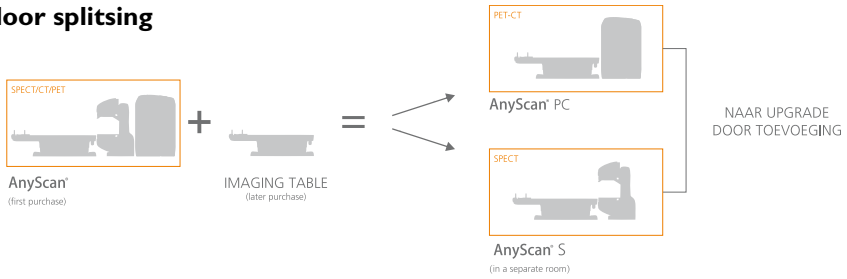

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Nuclear medicine techniques to image infections and inflammation with special attention to osteomyelitis/spondylodiscitis and the diabetic foot

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Abstract

Glaudemans AWJM. Nuclear medicine techniques to image infections and inflammation with special attention to osteomyelitis/ spondylodiscitis and the diabetic foot. This article tries to provide a short overview of available nuclear imaging techniques in the field of infection and inflammation. The differences between infection and inflammation (acute and chronic, primary and secondary) are described. Many radiopharmaceuticals are available to image various molecular targets in different time points of the infectious/inflammatory process. An overview is given of the nowadays most often used tracers (labelled white blood cells, labelled monoclonal antibodies, ^{18}F-FDG and labelled white blood cells with ^{18}F-FDG). Please keep in mind that there are many, many more already available. Since there is a huge variation within the Netherlands, but certainly worldwide, in the acquisition and interpretation of white blood cell scintigraphy, the method used in our hospital is described extensively. Finally, two musculoskeletal infectious diseases (osteomyelitis/ spondylodiscitis and diabetic foot infections) are described and the role of WBC scintigraphy and ^{18}F-FDG PET(/CT) is these diseases is discussed.

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Introduction

Inflammatory and infectious diseases are a heterogeneous class of diseases that can affect multiple organs (systemic) or can be localised to one specific organ. These diseases may be divided into infections, acute inflammation and chronic inflammation. Inflammatory diseases are diseases that often relapse, invalidate and may require lifelong treatment. Radiological imaging techniques – such as ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) – have high sensitivity but a lack in specificity. Nuclear medicine techniques allow the in vivo detection of physiologic and pathophysiologic phenomena and may offer non-invasive tools to detect early changes, before conventional radiological techniques may detect anatomical changes, and may sometimes even show changes before the onset of the disease.

Several procedural guidelines are available under approval of the Society of Nuclear Medicine (SNM) that also clarify the indications and practical aspects of the radionuclides used for imaging infection and inflammation (http://www.snm.org). A couple of years ago, guidelines for the labeling of leukocytes with indium-111 (^{111}In) oxine and technetium-99m exametazime (^{99m}Tc-HMPAO) were published by the Task Group of the European Association of Nuclear Medicine (EANM) which, besides the indications and practical aspects, also include quality control and safety procedures. These guidelines are written in accordance with the current European Union regulations and recommendations of the International Atomic Energy Agency (IAEA) (1,2).

For patients and clinicians, it is of invaluable importance to diagnose occult infections and inflammatory diseases as soon as possible. Clinicians often struggle with questions in patients dealing with presumed or established infective or inflammatory disorders. Nuclear medicine may offer a way to diagnose disease activity in an early stage, to distinguish the different phases of infections, to identify the cells involved in the process, to evaluate disease activity during and after therapy, and to monitor relapse of disease.

This article will try to provide an overview in some aspects of inflammatory and infectious diseases in which nuclear medicine may play an important role. First of all, the difference between infection and inflammation will be explained. Secondly, an overview will be provided of the most often used radiopharmaceuticals in these diseases and a description will be given of the acquisition protocol and interpretation of the white blood cell (WBC) scintigraphy. Finally, the role of nuclear medicine will be discussed in osteomyelitis and spondylodiscitis and in the diabetic foot.

Difference between infection and inflammation

First of all, infection is not synonymous with inflammation. An infection is caused by an exogenous pathogen, while inflammation is the response of the organism to the pathogen or tissue injury. Infection is often accompanied by an acute inflammation that may last for hours or days and is usually resolved without residual lesions; chronic inflammation can last from a few weeks to many years and usually causes late complications. Table 1 lists the diseases that are characterised by infection/acute inflammation and chronic inflammation.

Table 1. Diseases characterized by infection/acute inflammation and by chronic inflammation (39).

infection/acute inflammation	chronic inflammation
trauma and degenerative diseases	**organ specific autoimmune diseases**
	type 1 diabetes mellitus
bacterial infections	multiple sclerosis
	Crohn's disease
fungal infections	coeliac disease
	Sjögren syndrome
inflammatory bowel disease	rheumatoid arthritis
Crohn's disease	autoimmune thyroiditis
ulcerative colitis	autoimmune infertility
	granulomatosis
acute graft rejection	tuberculosis
kidney	sarcoidosis
lung	
liver	**infective diseases**
	fungal
atypical inflammatory diseases	viral
parasite infections	**graft rejection**
abscesses	kidney
spondylodiscitis	lung
endocarditis	liver
fever of unknown origin	
	atherosclerosis

Infection and acute inflammation

Colonisation of tissue or organs by pathogenic exogenous noxae (bacteria, viruses, fungi, etc.) leads to an infection. Tissues (or organs) react to the injuries caused by the noxae with a response (figure 1A), in a way that is independent of the possible cause. This phenomenon is called acute inflammation which activates various mechanisms, such as the release of histamine and serotonin, increase of vascular permeability, hyperexpression of adhesion molecules on endothelial cells and secretion of chemotactic factors. All these mechanisms together induce leukocyte rolling along the endothelium and migration of these leukocytes through

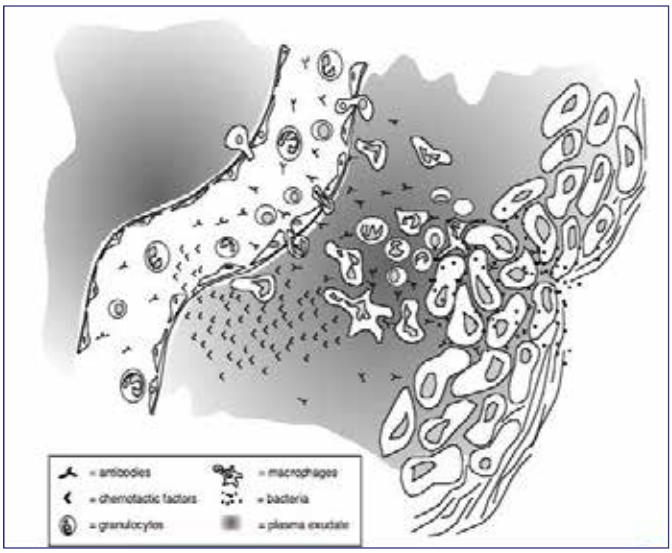

Figure 1A. Model of acute inflammation/infection. Cells are injured by pathogenic exogenous noxae (in this case bacteria), which leads to infection. The body is reacting with acute inflammation by the release of several chemotactic factors and antibodies, by the migration of granulocytes, by activation of endothelial cells and by an increase of vascular permeability leading to plasma exudates.

the capillary wall. As local response, there is continuous recruitment of cells from the peripheral blood, such as granulocytes, lymphocytes, monocytes, as well as several plasma proteins. The inflammation persists until elimination of the pathogenic noxae.
Nuclear medicine is able to image different targets involved in infection and acute inflammation: (1) the pathogens, (2) the activated endothelial cells, involved cytokines and mediators, (3) the macromolecules that accumulate in the inflamed tissue due to the increased vascular permeability, and (4) the polymorphonuclear cells (leukocytes, granulocytes).

Chronic inflammation

If the noxae exist, eventually chronic inflammation arises. Two main types of chronic inflammation exist: primary and secondary chronic inflammation. In primary chronic inflammation, a distinctive chronic reaction is observed from the onset with slightly increased vascularity and permeability and some neutrophilic infiltration. Usually this is observed in immune responses against cells of the body, after infection from intracellular micro-organisms or viruses, after generation of autoimmunity, and after cancer or transplantations.
These autoimmune diseases have different histological characteristics ranging from lymphocytic infiltration (as in thyroiditis) to a mixed cell population of T and B cells, plasma cells and neutrophils (as in rheumatoid arthritis).
In graft rejections, infiltration by cytotoxic lymphocytes is observed; tumors show infiltration by lymphomononuclear cells. Molecular imaging targets in this phase are T and B lymphocytes, monocytes/macrophages and apoptopic cells.

Secondary chronic inflammation is due to the persistence of the stimulus that caused the acute inflammation. In the chronic phase, the infiltration becomes predominantly mononuclear, consisting of lymphocytes, monocytes and macrophages (figure 1B). Further progression of this process is mainly via proliferation of these infiltrating cells. Clinical examples of this secondary chronic inflammation are chronic infections such as tuberculosis, leading to formation of chronic granulomas, sarcoidosis and contact dermatitis. The targets to image in this phase are T lymphocytes and monocytes/macrophages.

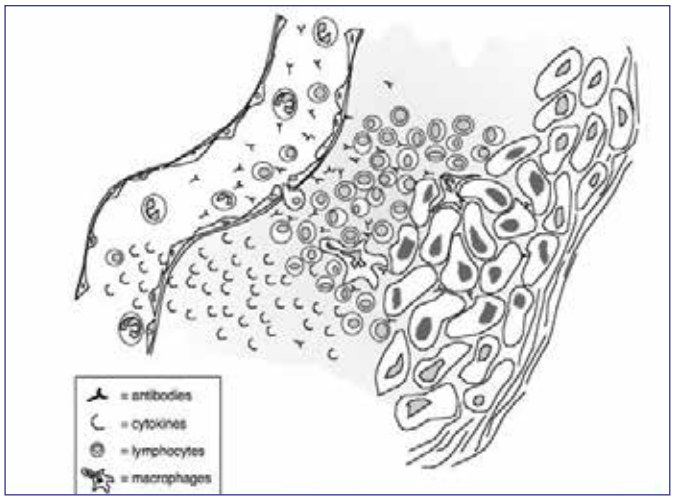

Figure 1B. Model of chronic inflammation. The vascular permeability is less than in the acute phase and the infiltration becomes predominantly mononuclear, consisting of lymphocytes and cells of the monocyte-macrophage series.

Table 2. Available radiopharmaceuticals for infection/acute inflammation and for chronic inflammation (39).

infection/acute inflammation	**chronic inflammation**
^{67}Ga-^{68}Ga-citrate	^{18}F-FDG
^{99m}Tc/^{99m}Tc-SnF$_2$/^{111}In/^{18}F-FDG/^{64}Cu-labelled WBC	^{99m}Tc-HIG
^{99m}Tc-labelled MoAb (LeuTech®, Leukoscan®, Scintimun®)	^{111}In-oxine/^{99m}Tc-HMPAO-lymphocytes
^{99m}Tc/^{111}In-HIG	^{111}In-macrophages
^{99m}Tc-nanocolloids	^{11}C-PK11195
^{18}F-FDG	^{99m}Tc-J001X
^{123}I-IL-1ra	^{111}In/^{99m}Tc-octreotide
^{99m}Tc-IL-8	^{123}I-IL-12p40
^{99m}Tc-P483H	^{99m}Tc-annexin V
^{99m}Tc-EP1-HNE2	^{125}I-Fas peptides
^{99m}Tc-a-E-selectin	^{123}I/^{111}In/^{99m}Tc/^{18}F-IL-2
^{99m}Tc-DMP444	^{99m}Tc-anti-TNF mAb
^{99m}Tc-chemotactic peptides	^{99m}Tc-anti-CD4 mAb
^{99m}Tc-PEG-liposomes	^{99m}Tc-anti-CD20 mAb
fungal infection	^{99m}Tc-anti-CD3 mAb
^{99m}Tc-fluconazole	
^{123}I-chitinase	
^{99m}Tc-CBP21	
^{99m}Tc-hLF 1-11	
bacterial infection	
^{99m}Tc/^{18}F-ubiquitidin 29-41	
^{99m}Tc-human neutrophil peptide 1-3	
^{99m}Tc-bacteriophage	
^{99m}Tc/^{111}In-biotin	
^{99m}Tc-PAMA4	
^{99m}Tc/^{18}F-labelled antibiotics	

Radiopharmaceuticals to image infection/inflammation

Table 2 provides an overview of the many tracers that are available to image the different phases of infection and inflammation. In this article however, only the most used tracers will be discussed.

White blood cells labelled ex vivo with ^{99m}Tc or ^{111}In

Imaging using ex vivo labelled autologous leukocytes (either with ^{99m}Tc-exametazine or ^{111}In-oxine) has already been developed in the 1970s and is still considered the gold standard imaging technique for infections. These autologous leukocytes are characterised by high specificity, since they only accumulate as a consequence of active migration into inflamed tissues (3). However, a degree of non-specific accumulation must be taken into account, depending on the degree of vascular permeability. After injection, radiolabelled WBCs show rapid clearance from the lungs and blood pool, with progressive migration into the spleen, liver, bone marrow and in sites of infections where a neutrophilic infiltrate predominates. The labelled WBCs adhere to the vascular endothelium and then migrate towards the infected area through the endothelium and basal membrane, thereby providing a specific indicator for leukocytic infiltration. ^{99m}Tc-labelled leukocytes have replaced ^{111}In-labelled leukocytes for most indications, since the radiation characteristics of ^{99m}Tc are favourable. However, for evaluation of abdominal organs, labelling with ^{111}In is preferable since a major advantage of ^{111}In-labelled WBC scintigraphy is that there is no major kidney, bladder or bowel excretion. Further on, ^{99m}Tc-exametazine is released from the leukocytes, which starts within a few minutes after administration and is excreted by kidneys up to seven percent of the label per hour and mainly by liver and gut, thus disturbing the imaging of the abdomen.
With regard to diagnostic accuracy, there is hardly no need for a better imaging agent. It has an established role in patients with orthopedic prostheses and for the detection of bone infections. However, the preparation of the labelled WBCs is laborious and must be performed in sterile conditions involving a complicated and time-consuming procedure, which takes a trained technician approximately three hours. In addition, the need to handle potentially contaminated blood may result in hazard to technicians and patients.

White blood cells labelled with ^{18}F-FDG

Recently, WBCs have been labelled in vitro with fluor-18 fluorodeoxyglucose (^{18}F-FDG), thereby attempting to develop a positron emitting tracer, leading to better imaging characteristics, better spatial resolution and better ways to quantify. Whole body and organ dosimetry are comparable with the results for conventional doses of ^{111}In-oxine-WBCs (4). The results of initial clinical investigations were encouraging. Intestinal foci of FDG-labelled WBCs were confirmed to represent inflamed bowel through histopathological or colonoscopic analysis, and the intensity of the foci measured in PET images correlated well with histopathological measures of degree of inflammation (5). ^{18}F-FDG-WBC gave better results as compared to ^{18}F-FDG alone in all sterile and septic inflammation rat models (6). Two patient studies reported diagnostic accuracies of 86 and 84 percent, respectively (7,8). However, no significant differences where found when comparing the FDG-labelled WBCs with ^{111}In-oxine labelled WBCs (8).

Several disadvantages have to be mentioned for this imaging technique. The labelling efficiency of FDG-labelled leukocytes is significantly less than that for ^{99m}Tc or ^{111}In and evidence is available that blood glucose levels affect the labelling efficiency of FDG (9). Moreover, the half-life of ^{18}F (110 minutes) means that it is technically not feasible to perform imaging later than four to five hours after injection. However, in many clinical situations, imaging at later time points is necessary due to the slow leukocyte accumulation in infected sites as compared to bone marrow.

Antigranulocyte monoclonal antibodies

Monoclonal antibodies (MoAbs) directed against granulocytes are easier to use compared to radiolabelled autologous WBCs and do not need the handling of potentially hazardous biological specimens. Moreover, by using antibodies directed against specific surface receptors, it is possible to study different cell populations. However, only a minor percentage of the injected antibody really binds to the cell populations. The majority will concentrate in the inflamed areas due to non-specific leakage as a result of increased permeability. Advantages of this technique are the possibility for whole body imaging and to detect infections in an early stage of disease. Disadvantages are the high molecular weight (resulting in slow diffusion into sites of inflammation), long plasma half-life and uptake in the liver due to clearance by the reticuloendothelial system. All this results in a high background, slowly decreasing in time. A long interval is therefore required between the administration of the labelled MoAbs and the acquisition of images to have a good target-to-background ratio. Some of the MoAbs are of heterologous origin and may induce production of human anti-murine antibodies (HAMA), with the possible development of allergic reactions, anti-idiotypic antibodies, altered pharmacokinetics and loss of molecular binding to the target.

The commercially available ^{99m}Tc-labelled antigranulocyte IgG1 murine antibody BW250/183 (Besilesomab, Scintimun®) recognizes the non-specific cross-reacting antigen 95 (NCA-95) expressed on human granulocytes. It has been used successfully in the study of septic loosening of hip (10) and knee prostheses (11) and in peripheral bone infections (12,13). However, in the latter case sensitivity decreased when the infection was located closer to the spine due to physiological bone marrow uptake. A large study that compared Scintimun® with ^{99m}Tc-labelled WBC in patients with suspected osteomyelitis of the peripheral skeleton showed comparable results (14).

Another commercially available 99mTc-labelled anti-stage specific embryonic antigen-1 (anti-SSEA-1) IgM murine MoAb (Fabolesomab, LeuTech®) binds to the CD15 antigen expressed on neutrophils and has been used in patients with osteomyelitis, diabetic foot ulcers and postsurgical infections (15-17). In some patients, a transient neutropenia has been noted; nevertheless, in most of these cases it did not represent a clinical problem and did not impair image quality. However, a major drawback of this MoAb was the incidence of serious and potentially fatal cardiopulmonary reactions associated with its use.

The use of antibody fragment (Fab') or humanisation of the antibodies should theoretically lead to lower immunogenicity, faster blood clearance and higher accumulation in infected areas. ^{99m}Tc-labelled sulesomab (LeukoScan®) is an antigranulocyte murine IgG1 antibody Fab' fragment binding to NCA-90 on granulocytes. Controversial results have been obtained using this MoAb. In bone and soft tissue infections, at first scintigraphy using LeukoScan® appeared to provide rapid localisation of infection (18,19). In other studies, however, it was found to be less specific for the diagnosis of musculoskeletal infections than labelled WBC scintigraphy (20,21).

^{18}F-FDG

As we all know, ^{18}F-FDG is a well-established diagnostic tool in oncology, but also accumulates in infections due to a high uptake in activated granulocytes. In fact, ^{18}F-FDG PET is now increasingly replacing conventional imaging methods since it has some intrinsic advantages over the conventional scintigraphy. With the exception of a few organs, physiological uptake of ^{18}F-FDG is low and clearance from non-target tissue is fast. High-contrast images of infectious and inflammatory lesions can be obtained early after tracer injection. Consequently, diagnosis can be completed with a single visit to the hospital. Of course, the characteristics of PET makes it also a preferable imaging technique over gamma camera imaging and SPECT.

The entrance of ^{18}F-FDG PET to the centre stage of infection and inflammation imaging has raised the question whether ^{18}F-FDG PET or WBC scintigraphy is the preferred imaging method (22,23). There is currently a lot of discussion about the method of choice, which is, however, not the topic of this article. The value of ^{18}F-FDG PET in many infectious

and inflammatory diseases is proven, however some disadvantages do exist. The costs of ^{18}F-FDG PET are much higher than those of labelled WBC scintigraphy. Further on, one should keep in mind that ^{18}F-FDG merely detects enhanced glucose metabolism and therefore is not able to discriminate between infection/inflammation and neoplastic disease. Consequently, the specificity is lower than that of labelled WBC. Furthermore, since ^{18}F-FDG is a non-specific tracer, it is not able to distinguish between the existing pathways in inflammation, nor is it able to distinguish between acute and chronic situation, which can be relevant in some clinical issues.

Acquisition modes and image interpretation criteria of radiolabelled WBC scintigraphy

Which tracer is used for which indication in infectious and inflammatory diseases differs between hospitals in the Netherlands. Moreover, when radiolabelled WBCs are used, various acquisition protocols and interpretation criteria exist, as is shown in another article of this Special Issue. Looking worldwide, even more differences can be detected. I will now describe the method that is used in the University Medical Center Groningen.

For image acquisition, a large-field-of-view gamma camera with a low-energy high-resolution collimator is preferred (140 keV using a 15-20 percent energy window). When ^{99m}Tc-exametazine is used as radionuclide, early imaging of the lungs for quality control is preferable, as well as imaging the abdomen and pelvis in children, because normal bowel activity is seen in twenty to thirty percent of children at 1 hour and two to six percent of adults at 3-4 hours after injection. Therefore, lung images are suggested at 30 minutes and images at 3-4 hours and 24 hours are compulsory. In case of abdominal infections and inflammatory bowel diseases, images can only be acquired 30 minutes and 3 hours after injection of ^{99m}Tc-exametazine-labelled WBCs, since ^{99m}Tc-exametazine is released by the WBCs with time, taken up by the liver and excreted via the bowel, thereby producing false-positive images at later time points.

Time-corrected images for isotope decay should be acquired (i.e., 200 seconds at 3 hours and 2000 seconds at 24 hours for ^{99m}Tc; 400 seconds at 3 hours and 500 seconds at 24 hours for ^{111}In) to reduce operator interference in final image interpretation, and to easily identify an objective increase in activity or size with time in infected sites. SPECT or SPECT/CT images are only mandatory in selected indications, e.g. endocarditis. Usually, SPECT scans at 3 hours are acquired with 15-20 seconds/step protocol with 64x64 matrix, and with a 30-40 seconds/step protocol at 24 hours.

The accumulation of labelled WBCs in infection sites is a dynamic process (figure 2). Accurate interpretation requires knowledge of the normal (blood and bone marrow) and abnormal variants of WBC localisations. The diagnosis of infection/inflammation is made by comparing early and delayed images. The images are classified negative if no

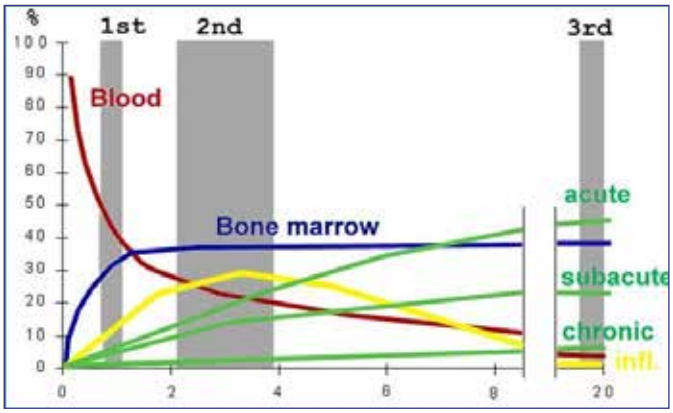

Figure 2. The accumulation of labelled WBCs in infection sites is a dynamic process (39).

uptake or a significant decrease in uptake from early to late images is present, positive when uptake is seen both in early and late images which increase with time, and equivocal when the uptake in early and late images is the same or slightly decreases. An example is shown in figure 3.

Figure 3. Patient with a non-healing fracture of the left fibula and upper jump joint after a surgical arthrodesis with osteosynthesis. (A) X-ray of the left ankle, (B) 99mTc-exametazine labelled WBC scintigraphy, early image after three hours, (C) late image after twenty-four hours. Increased uptake on the medial site of the left ankle, increasing in time, located at the distal part of the screw in the upper jump joint, suspect for an infection/inflammation.

When visual assessment is not sufficient or doubtful, semi-quantitative evaluation could help to differentiate. Regions of interest (ROIs) are drawn over the hottest region and copied to presumed normal reference tissue (e.g. anterior-superior iliac crest, unaffected contralateral bone, etc.). The mean pixel counts in these ROIs are recorded to calculate lesion-to-reference (L/R) ratios both in early and delayed images. Interpretation is as follows:

- when L/R ratio increases with time, the scan is considered positive for infection
- when L/R ratio is similar or slightly decreases with time, the scan is considered equivocal
- when L/R ratio decreases with time, the examination is classified negative for infection

Only in equivocal cases, bone marrow imaging could be performed for further differentiation.
If SPECT images are used, the delineation of the site of increased uptake may be calculated by a 50 percent isocontour on a single transaxial slice with the hottest activity and the reference tissue. The same criteria as for planar imaging may be used for quantification.

Osteomyelitis and spondylodiscitis

Osteomyelitis (OM) is defined as the infection and/or inflammation of the (trabecular) bone with extensive involvement of the bone marrow. It may extend to soft tissue (articular or extra-articular), by digestion of the cortical bone, or secondary to traumatic or surgical fractures. Beside these 'local' problems, a potential life-threatening danger is the development of bacteremia and haematogenous spread of the infection. There are acute and chronic forms and the disease can recur even after decades, or occur even years after surgery. In the developed countries 'spontaneous' OM tends to become less frequent, however the incidence of iatrogenic or secondary OM after surgery is rising. The quick identification and precise localisation is critical for early initiation of antimicrobial and/or surgical treatment and has a significant impact on patient outcome (24). Most frequent pyogenic bacteria are involved, e.g. Staphylococcus aureus and epidermidis, Pseudomonas, Salmonella, Haemophilus, E. coli, etc.
Conventional radiological imaging is often not suitable for OM. X-rays require thirty to fifty percent loss of bone density to become positive, CT and MRI are often normal at an early stage. The three-phase bone scan is highly sensitive, even in an early stage, however it lacks specificity, especially in the injured bone.
WBC imaging, combined if necessary with bone marrow imaging, is extensively studied in OM and found highly reliable with overall accuracy higher than ninety percent (25). ^{18}F-FDG PET(/CT) has been evaluated in patients with primary OM extensively, offering good sensitivities and specificities (26) and was found superior to MRI (27). However, for diagnosing acute OM limited information is available and it may have limited added value. In contrast, ^{18}F-FDG PET(/CT) may play an important role in patients with chronic OM, particularly in those patients with previously documented OM and suspected recurrence, or presenting with symptoms of OM for more than six weeks (chronic OM) (22).
^{18}F-FDG PET(/CT) can also be used to monitor response to antimicrobial treatment and to develop criteria for deciding when treatment can safely be stopped (28). In children with suspected OM, dissemination in multiple bones has to be kept in mind, for which ^{18}F-FDG PET(/CT) would be suitable. However, to avoid radiation exposure, pediatricians tend to perform MRI rather than ^{18}F-FDG PET(/CT) in these cases (29). Globally, ^{18}F-FDG PET(/CT) appears equivalent to or slightly less performing than labelled WBC scintigraphy. Advantages are the rapid imaging, no blood handling, low bone marrow uptake and an all-in-one technique with whole body imaging. However, also major limitations exist. The access is limited worldwide, there is the lack of specificity and the costs are higher. Moreover, there is the problem of the generation of artifacts in case of metallic implants, characterised by artificial FDG uptake adjacent to the implant, because of the inherent problem of partial volume mapping and overcorrection. Further on, non-specific ^{18}F-FDG uptake may be seen in healing tissues, up to six months after surgical intervention (30).
To conclude, at this moment, overall substitution of labelled WBC scintigraphy by ^{18}F-FDG PET(/CT) in OM cannot be recommended. The level of incidence remains low (2b at best), there is limited information about the use of ^{18}F-FDG PET(/CT) in acute OM, and performances may be different in selected groups. WBC imaging still remains the nuclear imaging technique of choice.

Spondylodiscitis (SD) is a combination of discitis (infection/inflammation of the intervertebral disc) and spondylitis (infection/inflammation of the adjacent vertebra(e)).
The performance of WBC imaging is poor in these cases: up to fifty percent of all patients with SD show photopenic lesions due to encapsulation of the infection, and therefore relatively hampered migration of leukocytes; as a result the specificity of this method is reduced (31). In these patients, ^{18}F-FDG PET(/CT) gave much better results: sensitivities ranging from 94 to 100 percent and specificities ranging from 87 to 100 percent (22). In a recent retrospective study, ^{18}F-FDG PET(/CT) had a strong impact on the clinical management (initiation or prolongation of antibiotic therapy) of 52 percent of patients with infectious SD (32). A recent review article highlights the clinical role of ^{18}F-FDG PET(/CT) in diagnosing spinal infections, especially in patients with contraindications to MRI, and in evaluating the postoperative spine (33).
In conclusion for SD, WBC imaging is not recommended. For ^{18}F-FDG PET(/CT) limited information in literature is available, however what is published shows good results. The evidence seems sufficient for the use of ^{18}F-FDG PET(/CT). An example of ^{18}F-FDG PET in SD is shown in figure 4.

The diabetic foot

Up to 15 percent of diabetic patients will develop foot ulcers, and about 15 to 25 percent of these patients require amputation. About 2.5 percent of diabetic patients have a Charcot joint, a progressive degenerative disease of the musculoskeletal system usually involving the tarsal and tarsometatarsal joints, resulting in destruction of bone

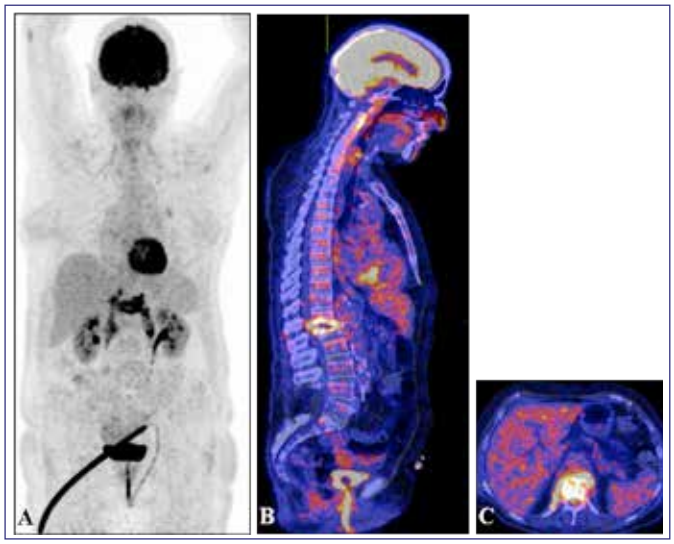

Figure 4. ^{18}F-FDG PET/CT of a patient with spondylodiscitis and involvement of the psoas muscles.

and soft tissue, causing significant damage to the bony architecture (34). Diabetic foot infection (DFI) is defined as an inframalleolar infection in a person with diabetes mellitus. These infections cause substantial morbidity, and are responsible for the largest number of diabetes related hospital bed days. The major predisposing factor is the foot ulcer. Once this cutaneous integument is breached, the wound may become actively infected, and by contiguous extension, infection can involve deeper tissues, including the bone, progressing to frank OM (35).
Diagnosing DFI is can be difficult. With clinical examination, it is difficult to differentiate between soft tissue infection and OM. Bone biopsy is not always performed since it is an invasive procedure that loses its reliability when the biopsy fragment is contaminated by cutaneous bacteria (36). Plain radiography and CT are used routinely but are not accurate enough. MRI is able to differentiate between OM and soft tissue infection, but the specificity is reduced if bony destruction, dislocation, marrow edema, synovial effusion, and loss of discernible/margins of bone and joint are present, conditions that characterise neuropathic joints as well as OM. Nuclear medicine techniques play an important role in the diagnosis of DFI. The sensitivity of three phase bone scintigraphy has been quite variable (< 75 percent), and specificity is even lower (34). The role of WBC imaging in DFI has been extensively investigated, and reported sensitivities ranged from 72 to 100 percent and specificities from 67 to 100 percent. Of course better results are achieved with SPECT/CT compared to planar imaging only.
For the use of ^{18}F-FDG PET/CT in DFI the results remain conflicting and heterogeneous. In a recent prospective study conducted in 110 patients with complicated diabetic foot, ^{18}F-FDG PET/CT was found to be a highly specific imaging modality for the diagnosis of OM and was deemed a useful complementary imaging modality for use with MRI (37).

Another prospective study in 63 patients including 22 patients with Charcot's foot observed a low degree of diffuse FDG uptake in the Charcot's joints, however with calculation of standardised uptake values (SUV) it was possible to discriminate Charcot's foot from the uncomplicated diabetic foot (38). However, another prospective study compared the results of ^{18}F-FDG PET/CT with WBC scintigraphy in 13 patients with suspected DFI and found, even with sequential imaging, a low overall diagnostic accuracy for ^{18}F-FDG PET/CT, lower than WBC scintigraphy (an example of one of the patients is shown in figure 5). Their findings suggested that ^{18}F-FDG PET/CT could not replace WBC imaging, particularly when WBC is acquired using SPECT/CT and bone marrow imaging is added for Charcot's foot (34).
In summary for DFI, published data are scarce, conflicting and heterogeneous. Patient selection is crucial, but may be very different. At this moment there is not a nuclear imaging modality of choice. The jury is still out.

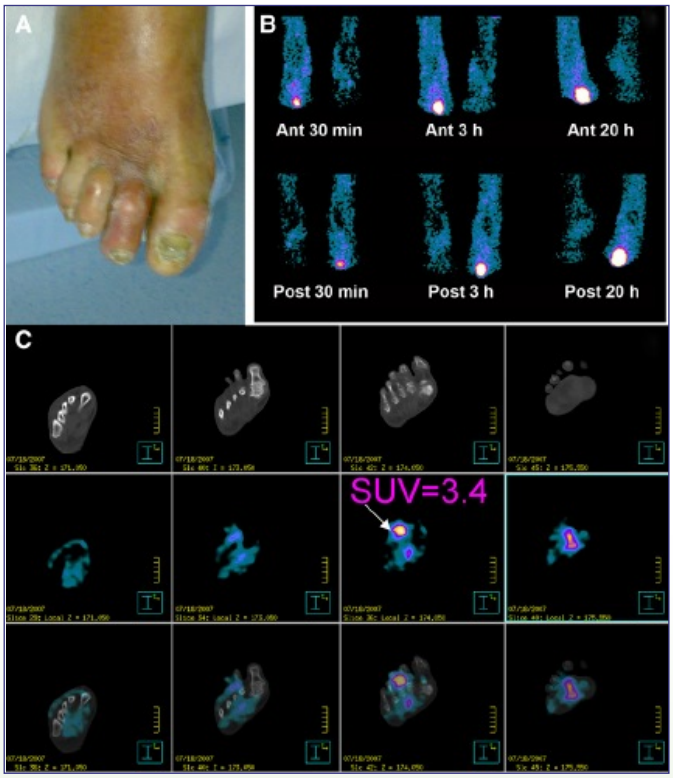

Figure 5. Positive scan results for diabetic foot infection: WBC scintigraphy (B) and ^{18}F-FDG PET/CT (C); with courtesy of Familiari et al (34).

In future

In this article an overview is given of only the most often used radiopharmaceuticals, and only two infectious and inflammatory diseases (osteomyelitis /spondylodiscitis and diabetic foot infections) are described, with only the role of labelled WBCs and 18F-FDG discussed in these diseases. Of course, nuclear medicine provides many more tracers and is able to provide information for the clinicians in many more

infectious and inflammatory diseases.
Clinicians often struggle with questions in patients dealing with presumed or established infective of inflammatory disorders. The main questions from clinicians to the field of nuclear medicine are: is there an infectious focus or inflammatory sign? What is the size and extent of the lesion? Can treatment be stopped, should be switched to another therapy, or should this therapy be prolonged?
Nuclear medicine is able to give answers to these questions. Nowadays, the goal is to distinguish the different phases of infection and also to identify the type, cells, and mediators of inflammation. Many tracers are already available that particularly focus on a special target in different phases as is shown in table 2. This is the aim for the future: to develop non-invasive tools for the in vivo detection of specific cells and targets involved in infection and inflammation, to evaluate the disease activity and to monitor the efficacy of therapy.

References

1. de Vries EF, Roca M, Jamar F, Israel O, Signore A. Guidelines for the labelling of leucocytes with (99m)Tc-HMPAO. Inflammation/Infection Taskgroup of the European Association of Nuclear Medicine. Eur J Nucl Med Mol Imaging. 2010;37(4):842-8
2. Roca M, de Vries EF, Jamar F, Israel O, Signore A. Guidelines for the labelling of leucocytes with (111)In-oxine. Inflammation/Infection Taskgroup of the European Association of Nuclear Medicine. Eur J Nucl Med Mol Imaging. 2010;37(4):835-41
3. Datz FL. Indium-111-labeled leukocytes for the detection of infection: current status. Semin Nucl Med. 1994;24(2):92-109
4. Forstrom LA, Dunn WL, Mullan BP et al. Biodistribution and dosimetry of [(18)F]fluorodeoxyglucose labelled leukocytes in normal human subjects. Nucl Med Commun. 2002;23(8):721-5
5. Pio BS, Byrne FR, Aranda R et al. Noninvasive quantification of bowel inflammation through positron emission tomography imaging of 2-deoxy-2-[18F]fluoro-D-glucose-labeled white blood cells. Mol Imaging Biol. 2003 ;5(4):271-7
6. Pellegrino D, Bonab AA, Dragotakes SC et al. Inflammation and infection: imaging properties of 18F-FDG-labeled white blood cells versus 18F-FDG. J Nucl Med. 2005;46(9):1522-30
7. Dumarey N, Egrise D, Blocklet D et al. Imaging infection with 18F-FDG-labeled leukocyte PET/CT: initial experience in 21 patients. J Nucl Med. 2006;47(4):625-32
8. Rini JN, Bhargava KK, Tronco GG et al. PET with FDG-labeled leukocytes versus scintigraphy with 111In-oxine-labeled leukocytes for detection of infection. Radiology. 2006;238(3):978-87
9. Palestro CJ, Love C, Miller TT. Diagnostic imaging tests and microbial infections. Cell Microbiol. 2007;9(10):2323-33
10. Boubaker A, Delaloye AB, Blanc CH et al. Immunoscintigraphy with antigranulocyte monoclonal antibodies for the diagnosis of septic loosening of hip prostheses. Eur J Nucl Med. 1995;22(2):139-47
11. Klett R, Kordelle J, Stahl U et al. Immunoscintigraphy of septic loosening of knee endoprosthesis: a retrospective evaluation of the antigranulocyte antibody BW 250/183. Eur J Nucl Med Mol Imaging. 2003;30(11):1463-6
12. Peltier P, Potel G, Lovat E, Baron D, Chatal JF. Detection of lung and bone infection with anti-granulocyte monoclonal antibody BW 250/183 radiolabelled with 99mTc. Nucl Med Commun. 1993;14(9):766-74
13. Scheidler J, Leinsinger G, Pfahler M, Kirsch CM. Diagnosis of osteomyelitis. Accuracy and limitations of antigranulocyte antibody imaging compared to three-phase bone scan. Clin Nucl Med. 1994;19(8):731-7
14. Richter WS, Ivancevic V, Meller J, Lang O et al. 99mTc-besilesomab (Scintimun) in peripheral osteomyelitis: comparison with 99mTc-labelled white blood cells. Eur J Nucl Med Mol Imaging. 2011;38(5):899-910
15. Gratz S, Behr T, Herrmann A et al. Intraindividual comparison of 99mTc-labelled anti-SSEA-1 antigranulocyte antibody and 99mTc-HMPAO labelled white blood cells for the imaging of infection. Eur J Nucl Med. 1998;25(4):386-93
16. Thakur ML, Marcus CS, Henneman P, Butler J et al. Imaging inflammatory diseases with neutrophil-specific technetium-99m-labeled monoclonal antibody anti-SSEA-1. J Nucl Med. 1996;37(11):1789-95
17. Thakur ML, Marcus CS, Kipper SL et al. Imaging infection with LeuTech. Nucl Med Commun. 2001;22(5):513-9
18. Becker W, Bair J, Behr T et al. Detection of soft-tissue infections and osteomyelitis using a technetium-99m-labeled anti-granulocyte monoclonal antibody fragment. J Nucl Med. 1994;35(9):1436-43
19. Becker W. Imaging osteomyelitis and the diabetic foot. Q J Nucl Med. 1999;43(1):9-20
20. Devillers A, Garin E, Polard JL et al. Comparison of Tc-99m-labelled antileukocyte fragment Fab' and Tc-99m-HMPAO leukocyte scintigraphy in the diagnosis of bone and joint infections: a prospective study. Nucl Med Commun. 2000;21(8):747-53
21. Gratz S, Schipper ML, Dorner J et al. LeukoScan for imaging infection in different clinical settings: a retrospective evaluation and extended review of the literature. Clin Nucl Med. 2003;28(4):267-76
22. Glaudemans AW, Signore A. FDG-PET/CT in infections: the imaging method of choice? Eur J Nucl Med Mol Imaging. 2010;37(10):1986-91
23. Signore A, Soroa VA, de Vries EF. Radiobelled white blood cells or FDG for imaging on inflammation and infection? Q J Nucl Med Mol Imaging. 2009;53(1):23-5
24. Concia E, Prandini N, Massari L et al. Osteomyelitis: clinical update for practical guidelines. Nucl Med Commun. 2006;27(8):645-60
25. Palestro CJ, Love C, Bhargava KK. Labeled leukocyte imaging: current status and future directions. Q J Nucl Med Mol Imaging. 2009;53(1):105-23
26. Wang GL, Zhao K, Liu ZF, Dong MJ, Yang SY. A meta-analysis of fluorodeoxyglucose-positron emission tomography versus scintigraphy in the evaluation of suspected osteomyelitis. Nucl Med Commun. 2011;32(12):1134-42
27. Gratz S, Dorner J, Fischer U et al. 18F-FDG hybrid PET in

patients with suspected spondylitis. Eur J Nucl Med Mol Imaging. 2002;29(4):516-24
28. Basu S, Chryssikos T, Moghadam-Kia S et al. Positron emission tomography as a diagnostic tool in infection: present role and future possibilities. Semin Nucl Med. 2009;39(1):36-51
29. Darge K, Jaramillo D, Siegel MJ. Whole-body MRI in children: current status and future applications. Eur J Radiol. 2008;68(2):289-98
30. Jones-Jackson L, Walker R, Purnell G et al. Early detection of bone infection and differentiation from post-surgical inflammation using 2-deoxy-2-[18F]-fluoro-D-glucose positron emission tomography (FDG-PET) in an animal model. J Orthop Res. 2005;23(6):1484-9
31. Van der Bruggen W, Bleeker-Rovers CP, Boerman OC, Gotthardt M, Oyen WJ. PET and SPECT in osteomyelitis and prosthetic bone and joint infections: a systematic review. Semin Nucl Med. 2010;40(1):3-15
32. Ito K, Kubota K, Morooka M et al. Clinical impact of (18) F-FDG PET/CT on the management and diagnosis of infectious spondylitis. Nucl Med Commun. 2010;31(8):691-8
33. Gemmel F, Rijk PC, Collins JM et al. Expanding role of 18F-fluoro-D-deoxyglucose PET and PET/CT in spinal infections. Eur Spine J. 2010;19(4):540-51
34. Familiari D, Glaudemans AW, Vitale V et al. Can sequential 18F-FDG PET/CT replace WBC imaging in the diabetic foot? J Nucl Med. 2011;52(7):1012-9
35. Palestro CJ. 18F-FDG and diabetic foot infections: the verdict is… J Nucl Med. 2011;52(7):1009-11
36. Wheat LJ, Allen SD, Henry M et al. Diabetic foot infections. Bacteriologic analysis. Arch Intern Med. 1986;146(10):1935-40
37. Nawaz A, Torigian DA, Siegelman ES et al. Diagnostic performance of FDG-PET, MRI, and plain film radiography (PFR) for the diagnosis of osteomyelitis in the diabetic foot. Mol Imaging Biol. 2010;12(3):335-42
38. Basu S, Chryssikos T, Houseni M et al. Potential role of FDG PET in the setting of diabetic neuro-osteoarthropathy: can it differentiate uncomplicated Charcot's neuroarthropathy from osteomyelitis and soft-tissue infection? Nucl Med Commun. 2007;28(6):465-72
39. Signore A, Glaudemans AW. The molecular imaging approach to image infections and inflammation by nuclear medicine techniques. Ann Nucl Med. 2011;25(10):681-700

The role of nuclear medicine techniques in differentiation between septic and aseptic loosening of total hip and knee arthroplasty

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Abstract

Jansen JA, Smit F, Pereira Arias-Bouda LM. The role of nuclear medicine techniques in differentiation between septic and aseptic loosening of total hip and knee arthroplasty. This article gives an overview of nuclear imaging techniques, which can be used to diagnose (a)septic loosening in joint replacements. The pathophysiology of loosening and the differences between septic and aseptic loosening with its therapeutical consequences are discussed. An overview is given of the advantages and limitations of frequently used techniques as triple-phase bone scanning and white blood cell scintigraphy. The additional value of SPECT/CT and the possible role of FDG PET/CT in the diagnosis of prosthetic joint infection is discussed.
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Introduction

A growing number of total hip and knee replacements are performed annually with a very good outcome in the majority of cases giving relief of arthritic pain and improved function. In some patients though complications occur of which loosening and infection are the most common (1-3).
The reason for approximately seventy percent of all re-operations in joint arthroplasty is loosening of the prosthesis. Symptoms of loosening are usually quite nonspecific with persistent pain at the arthroplasty site especially on weight bearing, and reduced mobility of the patient and the prosthesis (3,4). When prosthetic loosening is caused by infection it is classified as septic loosening, and in case of aseptic loosening it will be due to wear of the bearing surfaces (figure 1).
Infections occur in 2 to 3 percent of all primary joint replacements, and in 5 to 8 percent of revision joint replacement patients (5,6). About one third of the infections are directly post-operative, about one third are early infections within a year, and about one third are late infections more than one year after surgery (7). Infections are frequently caused by staphylococci from the skin, which can cause fulminant infections with purulent discharge from the operation wound in the early stage. Late onset and low grade infections usually have less specific infective signs though, but can also cause loosening on the long term as well. It can be very difficult to distinguish between septic and aseptic loosening, as both may be accompanied by similar symptoms (8).

Figure 1. Pictures of retrievals showing wear of the bearing surfaces of total hip (A) and total knee (B) prosthesis, causing wear and small particle disease that can lead to aseptic loosening.

Recent improvements in tribology of bearing surfaces and prosthetic coatings have influenced the incidence of aseptic prosthetic loosening. The highly cross-linking of polyethylene inserts in acetabular cups and knee liners has diminished wear and occurrence of small particle disease. The cross-linking process has improved wear resistance of polyethylene liners without impairment of other significant material properties (9). Also through hydroxyapetite coating or plasma-porous spraying of femoral and tibial prosthetic stems bony ingrowth and early stabilization of implants can be stimulated.
As an alternative to standard cobalt-chrome on polyethylene bearings also aluminium oxide ceramic bearings have been developed in order to improve performance and longevity. Alumina ceramic is entirely biostable and bioinert material with good mechanical properties. Through more precise manufacturing and contact surface geometry the fracture risk of the ceramic heads and liners has been reduced, but squeaking still remains a concern in ceramic-on-ceramic bearings (10). More recently metal-on-metal bearings have received a lot of media attention. Although these hard-on-hard bearings offer the potential use of large heads especially in resurfacing hips, recent studies have shown increased metal

wear especially in cases of high inclined cups with edge wear resulting in formation of pseudotumors and high metal ion serum levels (11). Because of the increased complication rate, lack of superiority, greater cost and potential for adverse medical effects, the Dutch Orthopaedic Society has recently given a negative advice for the use of metal-on-metal bearings especially given more recent publications (12,13).

Diagnosis of prosthetic loosening and prosthetic joint infection

Because septic and aseptic loosening require different treatments, clinical differentiation between these causes is very important. In septic loosening it is necessary to treat the infection before revision. In a first stage this will be done by removal of the prosthesis and replacement by an antibiotic loaded cement spacer and intravenous antibiotics. After discharge the antibiotics are continued orally for six weeks in total. The second procedure will be planned after antibiotic treatment is stopped and inflammatory markers are normalised. Usually a couple of months after the first procedure the definitive surgery will be performed, during which the cement spacer is removed and replaced by the revision prosthesis (6,14). Revision in case of aseptic loosening can be done in a single procedure with removal of the loosened prosthesis and replacement by the revision prosthesis in the same procedure. This allows quicker mobilisation, a shorter hospital admission, has fewer complications and less costs.

On plain radiographs prosthetic loosening can frequently be recognised by the occurrence of progressive radiolucency in the bone-prosthesis interface or by migration of the implant. In many cases, especially in early stages of loosening, the radiographs are indeterminate or even false negative. The important difference between prosthetic joint infection (PJI) and aseptic, mechanical loosening can also not be seen on radiographs (3).

A very useful test for diagnosis of infection is pre-operative joint aspiration followed by prolonged culture. Especially in low-grade infections pre-operative aspiration frequently renders a negative culture result though, so even with a negative bacteriology culture result the diagnosis of infection cannot be excluded (15). Although the specificity is very high (>90%), the value of aspiration and culture is limited due to the variable sensitivity, ranging from 28 to 92 percent (16,17). Other laboratory tests with inflammatory markers as erythrocyte sedimentation rate, C-reactive protein, and peripheral white blood cell count are more sensitive but not very specific for an infected prosthesis (18).

Additional imaging with cross-sectional imaging techniques as computed tomography (CT) and magnetic resonance imaging (MRI) is not very useful due to imaging artefacts by the metallic implants.

In contrast to these techniques nuclear medicine examinations are not impaired by the metallic implants. Unfortunately, there is no true consensus about the gold standard technique since each radionuclide modality has its drawbacks and limitations. The triple-phase bone scan (TPBS) still is a frequently used diagnostic procedure in case of a painful joint replacement. It is sensitive for identifying the failed joint replacement, but cannot differentiate between infection and aseptic loosening. Bone scintigraphy has been used in combination with gallium scintigraphy to increase accuracy. Augmentation with a gallium scan can detect infection with an accuracy of 65 to 80 percent (19). However, gallium uptake is mainly related to inflammation and not to infection specifically (6,20). In addition, the suboptimal imaging characteristics of gallium, the high radiation dose and the need for multiple imaging sessions over several days are disadvantages to the technique. White blood cell (WBC) imaging is also used for diagnosing complications of arthroplasty, and in combination with bone marrow scintigraphy its accuracy can be improved (6,14,16,20,21). More recently, positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG PET) is increasingly used in patients with suspected infection of joint replacements (22,23). The main limitation of functional imaging though is the lack of structural delineation of the pathology. The use of hybrid single-photon emission computed tomography/computed tomography (SPECT/CT) and PET/CT scans gives both functional and anatomical data. This combination registers the precise anatomical location of bone and joint lesions, and in this way the accuracy of the nuclear imaging can be improved (24). A better localisation of increased radiotracer uptake allows a more precise differentiation between soft tissue and bone infection, which can improve choice of treatment and outcome (25).

Triple-phase bone scan

Triple-phase bone scintigraphy (TPBS) using bone seeking tracers such as ^{99m}Tc-labelled diphosphonates MDP or HDP is the mainstay of nuclear medicine around the world in orthopaedic nuclear medicine. There is a large body of evidence for its usefulness in all kinds of orthopaedic problems (26-28). This includes the scanning of prosthetic problems like loosening, infection and inflammation. Uptake is related to blood flow and the rate of new bone formation. In case of a prosthesis enhanced uptake can be seen in areas of osteolysis induced by polyethylene wear debris. In fact, any cause of accelerated new bone formation, including postoperative physiological bone remodelling, as well as pathological conditions such as heterotopic ossification, aseptic loosening and infection may show increased periprosthetic activity. This explains the low specificity of this modality for detection of loosening. Although specificity can be improved significantly by adding SPECT/CT (29), the interpretation of the images remains difficult due to the variable periprosthetic uptake related to the physiological response in the first year after implantation. And this is exactly the period in which most prosthetic joint complications occur. Although a completely normal TPBS excludes loosening and

infection with high certainty, one should keep in mind that loosening still can be present under these circumstances. Our experience is that this can be due to loosening at the cement bed - prosthesis interphase, which not necessarily leads to bone reaction (unpublished data).
In addition to the limitations mentioned above, TPBS alone cannot differentiate between aseptic loosening and infection. Although the presence of infection almost always goes hand in hand with pathological findings in the arterial flow and soft tissue phase of the TPBS (figure 2), the specificity of these findings is low, meaning that also in uninfected cases pathological findings can be present in the early phases (30). In view of these findings, it appears that TPBS alone has only limited value in diagnosing joint replacement infections. Some investigators suggest that bone scintigraphy should be used as a screening test only, while others believe the diagnosis of infection should be based on the combined interpretation of findings from bone scintigraphy and other radionuclide techniques like WBC imaging or gallium scintigraphy.

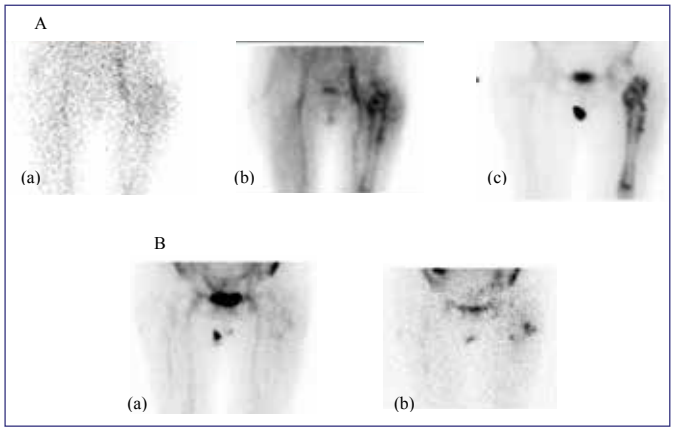

Figure 2. A patient with PJI of the left hip. (A) TPBS with anterior images of (a) arterial phase, (b) soft tissue phase and (c) static phase: the early phases show marked hyperaemia and soft tissue uptake around the femoral component of the hip prosthesis and diffuse patchy uptake around the femoral component in the static phase, suspicious of PJI. The WBC scan (B) with anterior images at 4 hours after injection (a) and 24 hours after injection (b) shows moderate pathological uptake around the proximal part of the stem, increasing in time and therefore suspicious of infection. Note the spatially non-congruent distribution compared to the bone scan.

White blood cell scintigraphy

White blood cell (WBC) scintigraphy or scintigraphy with anti-granulocyte antibodies like Scintimun® have shown in selected studies a high sensitivity in detecting bacterial infection of the bone, including the infected prosthesis (31,32). There is enough evidence that WBC scanning with ex vivo labelled autologous leucocytes, either with ^{111}In-oxine- or ^{99m}Tc-hexamethypropyleneamineoxime (HMPAO), can be a useful adjunct to the abnormal bone scan for differentiation between aseptic and septic loosening. The most challenging diagnostic situation however, is the patient with persistent pain after surgery. In these circumstances, the distinction between delayed (chronic) infection and failure related to prosthetic wear debris can be very difficult. Unfortunately, sensitivity of WBC in low grade, chronic infections is decreased, probably due to a less degree of neutrophil-influx under these circumstances. Other causes of decreased sensitivity are the formation of a protective membrane called glycocalyx or biofilm by bacteria in bone infection (33) and the negative influence of administered antibiotics (34). On the other hand, specificity is hampered by the presence of non-specific inflammation and interference of ectopic bone marrow induced by prosthetic surgery. As with bone scintigraphy, specificity of WBC scintigraphy increases when SPECT/CT is added. Fillippi and Schillaci showed both high sensitivity and specificity using ^{99m}Tc-WBC SPECT/CT in patients with suspected orthopaedic implant infection (35).

Improvement of the accuracy of radionuclide diagnosis of prosthetic joint infection

Combination of WBC imaging with bone scintigraphy

It has been suggested that radionuclide diagnosis of infection could be enhanced by combination of WBC imaging with bone scintigraphy. In this situation positive findings for infection are usually defined as the presence of non-congruent bone and leucocyte uptake, either in spatial distribution or in intensity (figure 2). However, this combined interpretation of both modalities doesn't seem to improve the accuracy for detecting PJI, as was shown by Teller et al (36). On the contrary, van Acker and co-workers managed to improve specificity from 53 to 93 percent when only lesions that were identified on a bone scan were taken into account, without affecting sensitivity (37).

Combination of WBC imaging with bone marrow scintigraphy

WBC imaging can be combined with bone marrow imaging to deal with the interference of ectopic bone marrow induced by prosthetic surgery, which can lead to false positive findings when interpreting the WBC scan alone. Both WBC imaging and bone marrow imaging with ^{99m}Tc-sulphur colloid reflect radiotracer accumulation in the reticuloendothelial system of the marrow. In patients without infection the images of WBC and bone marrow scans are congruent (figure 3), in contrast to patients with PJI in whom WBC and bone marrow scans are spatially incongruent due to the fact that infection stimulates uptake of leucocytes but suppresses uptake of sulphur colloid. The reported results using this combination of modalities consistently show a high accuracy, with sensitivity and specificity rates over ninety percent (38,39).

Multiphase WBC imaging

Since the accumulation of neutrophils at the site of infection is a dynamic process, interpretation of the scan may be

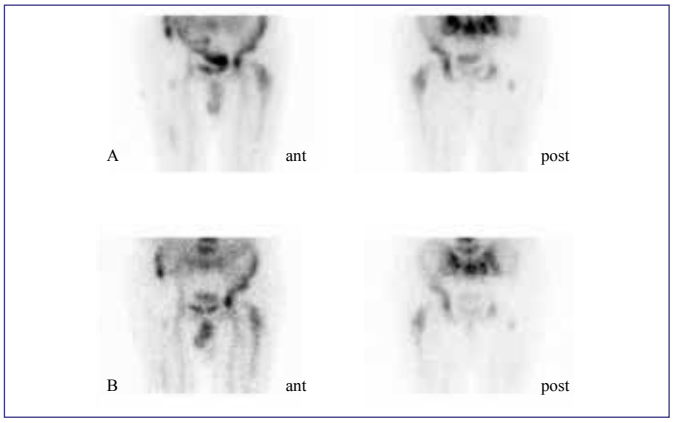

Figure 3. (A) WBC scintigraphy and (B) bone marrow scintigraphy of a patient with bilateral hip arthroplasty and persisting complaints of the left upper leg. The WBC images show diffuse uptake along the stem at the left side, and more discrete focal uptake at the right side. This is related to ectopic bone marrow rather than migration of leucocytes, as was confirmed by the bone marrow scan showing spatially congruent images.

improved by comparing early and delayed images (40). Findings are classified as positive for infection if an increase in uptake intensity is observed with time (figures 2 and 4). Dual- or multiphase imaging leads to an increase in both sensitivity and specificity, especially if semi-quantitative evaluation is added (30,41).

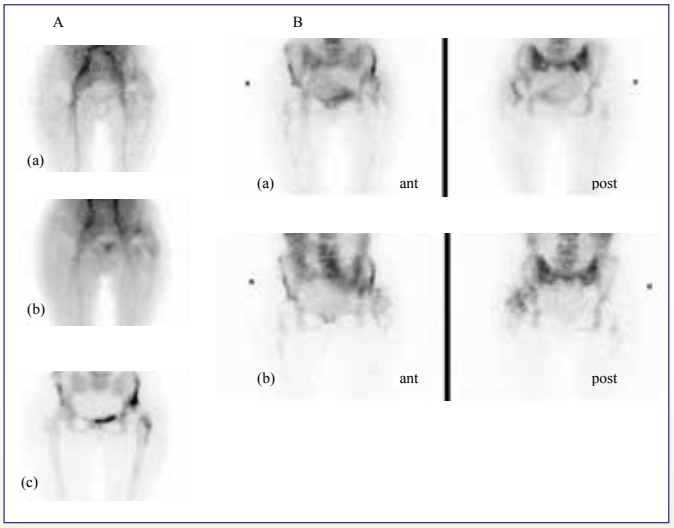

Figure 4. TPBS (A) and WBC scan (B) of a patient with persisting pain at the left hip after arthroplasty. The anterior images of the bone scan show only mild hyperaemia (a) and soft tissue uptake (b) at the left side of the hip and increased bone activity at the cranial acetabular part and mild activity around the (proximal) stem (c). The WBC images at four hours post-injection (a) show pathological uptake at the proximal part of the prosthesis, with increasing intensity with time (b, 24 hours post-injection). Per-operative cultures revealed Enterobacter cloacae colonies around the stem of the prosthesis.

Positron emission tomography with ^{18}F-fluorodeoxyglucose

^{18}F-FDG is a non-specific metabolic tracer, transported into cells by glucose transporters. FDG accumulates in cells with high glucose consumption, like tumour cells, but also in activated inflammatory cells such as lymphocytes, neutrophils and macrophages.

Investigators have reported inconsistent results on the performance of FDG PET/CT in diagnosis of prosthetic loosening and PJI (42-44). In our opinion this is mainly due to selection bias and non-uniform interpretation criteria. However, there are some consistent findings that are worthwhile to mention. In the first six months after arthroplasty surgery a non-specific periprosthetic uptake of FDG can be found due to post-operative remodelling, making the images difficult to interpret in the post-operative period. On the other hand, with a negative PET result PJI can be ruled out due to its high sensitivity. One should be aware of the possibility of false-negative results in pure mechanical loosening when the loosening occurs between the cement bed and the prosthesis. Since there are no cellular elements in this area, no enhanced periprosthetic glucose uptake is found (44). As mentioned before, we had the same experience using bone scintigraphy.

Differentiation between PJI and aseptic loosening and/or inflammation is difficult, since activated neutrophils and macrophages in inflamed tissue can show high glucose consumption, as high as in case of an infection. There is a high degree of overlap of intensity of the periprosthetic uptake in these conditions. This is particularly the case in patients with signs of polyethylene and metal-wear-induced chronic inflammation followed by periprosthetic osteolysis (42,44). In these patients often intense FDG accumulation is found in the joint capsule and around the prosthesis neck (44,45). The fact that FDG PET/CT has a high sensitivity for detecting small particle disease could be of high clinical value, since it could predict loosening in an early phase.

Since it is impossible to differentiate PJI from aseptic loosening by qualitative or quantitative assessment of the intensity of periprosthetic FDG uptake, investigators attempted to define uptake patterns to increase specificity. A well-known uptake pattern classification for hip prostheses was introduced by Reinartz (46) (table 1). Even so, using this uptake pattern classification Delanke and co-workers found a high degree of overlap between the patterns present in septic loosening and aseptic, abrasion-caused inflammation (pattern 4a-c and 5) (44). It has been proposed that combined reading of FDG PET/CT and the bone scan could be helpful in differentiating PJI from inflammation, defining only congruent pathological uptake positive for infection (37). Figure 5 shows an example of the patterns found on bone scan, PET/CT and WBC imaging in a patient with bilateral hip arthroplasty and persisting complaints at the right hip.

FDG PET/CT has a limited role in evaluating patients with persistent pain after total knee replacement; a diffuse uptake

Table 1. Patterns of FDG PET findings and their clinical correlates in patients with a total hip prosthesis. Reproduced with permission and copyright © of the British Editorial Society of Bone and Joint Surgery (46).

Pattern	Description	Clinical correlation
1	No increased uptake of FDG in the prosthesis-tissue interface	
2	Increased uptake of FDG in the area of the femoral neck	
3a	Increased uptake of FDG in the area of the femoral neck and in parts of the prosthesis-bone interface of the acetabular cup without covering the whole cup	No loosening
3b	Increased uptake of FDG in the area of the femoral neck and in parts of the proximal stem	
3c	Pattern 3a and 3b	
4a	Increased uptake of FDG in the area of the femoral neck and in the whole prosthesis-bone interface of the acetabular cup	
4b	Increased uptake of FDG in the area of the femoral neck and in wide parts of the prosthesis-bone interface of the stem	Loosening
4c	Pattern 4a and 4b	
5	Uptake of FDG in the periprosthetic soft tissue	Infection

in the synovia is often encountered even without infection. Several investigators reported a worse performance of FDG PET/CT in total knee replacement compared to total hip replacement (43,44).

Conclusions

An increasing number of hip and knee replacements is performed annually with an excellent outcome in the majority of cases. If complications do occur though, infections and loosening are most common and the cause of more than 70 percent of all re-operations. Symptoms of septic and aseptic loosening can be very non-specific with pain on weight bearing and reduced mobility. Because both require a different treatment, it is very important to differentiate between the two causes of loosening.

Although radionuclide imaging plays an important role in the diagnostic work-up, there is no true consensus about the gold standard technique since each radionuclide modality has its drawbacks and limitations. At this moment dual phase WBC scintigraphy and WBC SPECT/CT combined with bone marrow scintigraphy seems to be the imaging modality of choice, showing the highest accuracy. The exact role of FDG PET/CT is not yet fully established. A normal scan rules out PJI with high certainty. Differentiation between PJI and loosening or inflammation is difficult however, even when using specific uptake pattern classifications. This is particularly the case in patients with signs of polyethylene and metal-wear-induced chronic inflammation. On the other hand, the high sensitivity of FDG PET/CT for small particle disease could be of high clinical value as an early predictor of loosening. Combined reading of FDG PET/CT and the bone scan could be helpful to differentiate PJI from abrasion-caused inflammation. The role of FDG PET/CT in patients with persistent pain after total knee replacement seems to be limited.

References

1. Herberts P, Malchau H. Long-term registration has improved the quality of hip replacement: a review of the Swedish THR register comparing 160,000 cases. Acta Orthop Scand. 2000;71:111-21
2. Garellick G, Malchau H, Herberts P. Survival of hip replacements: a comparison of a randomized trial and a registry. Clin Orthop. 2002;402:157-63
3. Keogh CF, Munck PL, Gee R, Lai PC, Marchinkow LO. Imaging of the painful hip arthroplasty. Am J Roentgenol. 2003;180:115-20
4. Mahomed NN, Barrett JA, Katz JN et al. Rates and outcomes of primary and revision total hip replacement in the United States Medicare population. J Bone Joint Surg [Br]. 2003;85-A:27-32
5. Della Valle CJ, Bogner E, Desai P et al. Analysis of frozen sections of intraoperative specimens obtained at the time of reoperation after hip or knee resection arthroplasty for the treatment of infection. J Bone Joint Surg [Am]. 1999;81:684-9
6. Palestro CJ. Nuclear medicine, the painful prosthetic joint, and orthopedic infection. J Nucl Med. 2003;44:927-9
7. sukayama DT, Estrada R, Gustilo RB. Infection after total hip

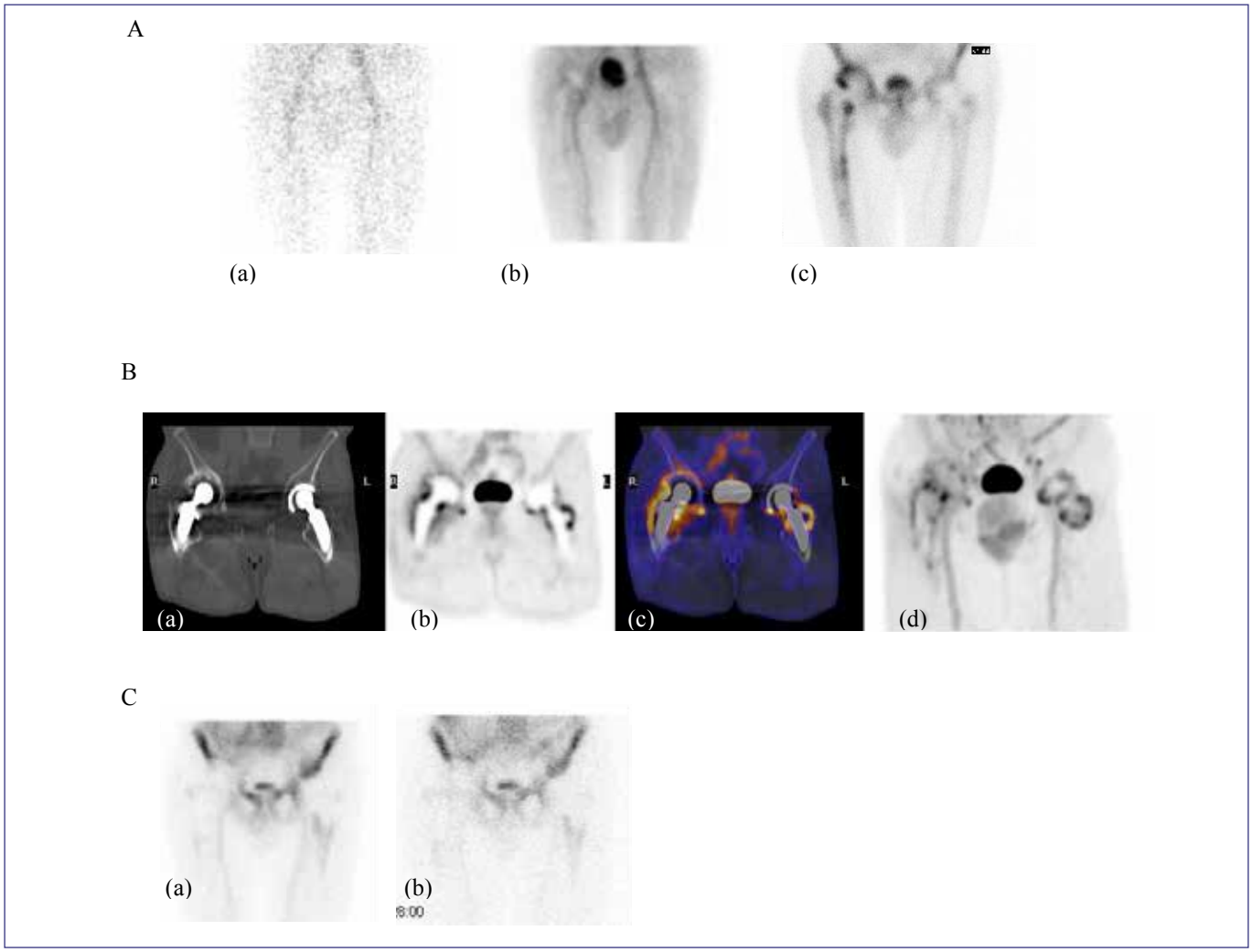

Figure 5. A patient with bilateral hip prostheses and persisting complaints at the right side. TPBS (A) shows no hyperaemia (a) and only subtle soft tissue uptake (b) around the cup and stem of the prosthesis at the right side and patchy uptake in these regions in the static phase (c). Normal findings at the left side. PET/CT images (B) with (a) coronal CT (b) coronal PET, (c) fused coronal images and (d) maximum intensity projection revealed high glucose consumption at wide parts of the bone – prosthesis interface of the stem and in the whole bone-prosthesis interface of the acetabular cup at the right side and FDG accumulation in the joint capsule and around the prosthesis neck at the left side, corresponding to Reinartz classification 4c and 3a, respectively. It was concluded that there was loosening of the acetabular cup and stem at the right side and small particle disease without loosening at the left side. However, infection at the right side could not be ruled out because of the presence of periprosthetic soft tissue uptake (b). A WBC scan (C) was performed with consent of the patient, showing no signs of infection.

arthroplasty. A study of the treatment of one hundred and six infections. J Bone Joint Surg [Am]. 1996;78:512-23
8. Roder C, Eggli S, Aebi M et al. The validity of clinical examination in the diagnosis of loosening of components in total hip arthroplasty. J Bone Joint Surg [Br]. 2003;85-B:37-44
9. Santavirta S, Bohler M, Harris WH et al. Alternative materials to improve hip replacement tribology. Acta Orthop Scand. 2003;74:380-8
10. Hannouche D, Zaoui A, Zadegan F, Sedel L, Nizard R. Thirty years of experience with alumina-on-alumina bearings in total hip arthroplasty. Int Orthop. 2011;35:207-13
11. Zywiel MG, Sayeed SA, Johnson AJ, Schmalzried TP, Mont MA. State of the art in hard-on-hard bearings: how did we get here and what have we achieved? Expert Rev Med Devices. 2011;8:187-207
12. Voleti PB, Baldwin KD, Lee GC. Metal-on-metal vs conventional total hip arthroplasty: a systematic review and meta-analysis of randomized controlled trials. J Arthroplasty. 2012 July [Epub ahead of print]
13. Qu X, Huang X, Dai K. Metal-on-metal or metal-on-polyethylene for total hip arthroplasty: a meta-analysis of prospective randomized studies. Arch Orthop Trauma Surg. 2011;8:187-207
14. Love C, Thomas MB, Marwin SE et al. Role of nuclear medicine in diagnosis of the infected joint replacement. Radiographics. 2001;21:1229-38

15. Fehring TK, Cohen B. Aspiration as a guide to sepsis in revision total hip arthroplasty. J Arthroplasty. 1996;11:543-7
16. Johnson JA, Christie MJ, Sandler MP et al. Detection of occult infection following total joint arthroplasty using sequential technetium-99m HDP bone scintigraphy and indium-111 WBC imaging. J Nucl Med. 1988;29:1347-53
17. Barrack RL, Harris WH. The value of aspiration of the hip joint before revision total hip arthroplasty. J Bone Joint Surg [Am]. 1993;75:66-76
18. Spangehl MJ, Masri BA, O'Connell JX et al. Prospective analysis of preoperative and intraoperative investigations for the diagnosis of infection at the sites of two hundred and two revision total hip arthroplasties. J Bone Joint Surg [Am]. 1999;81:672-83
19. Palestro CJ and Love C. Radionuclide imaging of musculoskeletal infection: Conventional agents. Semin Musculoskelet Radiol. 2007;11:335-52
20. El-Maghraby TA, Moustafa HM, Pauwels EK. Nuclear medicine methods for evaluation of skeletal infection among other diagnostic modalities. Q J Nucl Med Mol Imaging. 2006;50:167-92
21. Palermo F, Boccaletto F, Paolin A et al. Comparison of technetium-99m-MDP, technetium-99m-WBC and technetium-99m-HIG in musculoskeletal inflammation. J Nucl Med. 1998;39:516-21
22. Reinartz P. FDG-PET in patients with painful hip and knee arthroplasty: technical breakthrough or just more of the same. Q J Nucl Med Mol Imaging. 2009;53:41-50
23. Zoccali C, Teori G, Salducca N. The role of FDG-PET in distinguishing between septic and aspetic loosening in hip prosthesis: a review of literature. Int Orthop. 2009;33:1-5
24. van der Bruggen W, Bleeker-Rovers CP, Boerman OC, Gotthardt M, Oyen WJ. PET and SPECT in osteomyelitis and prosthetic bone and joint infections: a systematic review. Semin Nucl Med. 2010;40:3-15
25. Schillaci O. Hybrid imaging systems in the diagnosis of osteomyelitis and prosthetic joint infection. Q J Nucl Med Mol Imaging. 2009;53:95-104
26. Collier BD Jr, Fogelman I, Brown ML. Bone scintigraphy: Part 2. Orthopedic bone scanning. J Nucl Med. 1993;34:2241-6
27. Lee E and Worsley DF. Role of radionuclide imaging in the orthopedic patient. Orthop Clin North Am. 2006 Jul;37:485-501
28. Hsu W and Hearty TM. Radionuclide Imaging in the Diagnosis and Management of Orthopaedic Disease. J Am Acad Orthop Surg. 2012;20:151-9
29. Horger M, Eschmann SM, Pfannenberg C et al. Added value of SPECT/CT in patients suspected of having bone infection: preliminary results. Arch Orthop Trauma Surg. 2007;127:211-21
30. Larikka MJ, Ahonen AK, Junila JA et al. Extended combined 99mTc-white blood cell and bone imaging improves the diagnostic accuracy in the detection of hip replacement infections. Eur J Nucl Med. 2001;28:288–93
31. Palestro CJ, Love C, Bhargava KK. Labeled leukocyte imaging: current status and future directions. Q J Nucl Med Mol Imaging 2009;53:105-23
32. Richter WS, Ivancevic V, Meller J et al. 99mTc-besilesomab (Scintimun) in peripheral osteomyelitis: comparison with 99mTc-labelled white blood cells. Eur J Nucl Med Mol Imaging. 2011;38:899-910
33. Evans RP, Nelson CL, Bowen WR, Kleve MG, Hickmon SG. Visualization of bacterial glycocalyx with a scanning electron microscope. Clin Orthop. 1998;347:243–9
34. Datz FL and Thorne DA. Effect of antibiotic therapy on the sensitivity of indium-111-labeled leukocyte scans. J Nucl Med. 1986;27:1849–53
35. Filippi L and Schillaci O. Usefulness of hybrid SPECT/CT in 99mTc-HMPAO-labeled leukocyte scintigraphy for bone and joint infections. J Nucl Med. 2006;47:1908-13
36. Teller RE, Christie MJ, Martin W, Nance EP, Haas DW. Sequential indium-labeled leukocyte and bone scans to diagnose prosthetic joint infection. Clin Orthop Relat Res. 2000;373:241-7
37. Van Acker F, Nuyts J, Maes A et al. FDG-PET, 99mtc-HMPAO white blood cell SPET and bone scintigraphy in the evaluation of painful total knee arthroplasties. Eur J Nucl Med Mol Imaging. 2001;28:1496-1504
38. Palestro CJ, Kim CK, Swyer AJ et al. Total-hip arthroplasty: periprosthetic indium-111-labeled leukocyte activity and complementary technetium-99msulfur colloid imaging in suspected infection. J Nucl Med. 1990;31:1950–5
39. Fuster D, Duch J, Soriano A et al. Potential use of bone marrow scintigraphy in suspected prosthetic hip infection evaluated with 99mTc-HMPAO-leukocytes. Rev Esp Med Nucl. 2008;27:430–5
40. Signore A and Glaudemans AW. The molecular imaging approach to image infections and inflammation by nuclear medicine techniques. Ann Nucl Med. 2011;25:681-700
41. Pelosi E, Baiocco C, Pennone M et al. 99mTc-HMPAO-leukocyte scintigraphy in patients with symptomatic total hip or knee arthroplasty: improved diagnostic accuracy by means of semiquantitative evaluation. J Nucl Med. 2004;45:438-44
42. Mumme T, Reinartz P, Alfer J et al. Diagnostic values of positron emission tomography versus triple-phase bone scan in hip arthroplasty loosening. Arch Orthop Trauma Surg. 2005;125:322-9
43. Stumpe KD, Romero J, Ziegler O et al. The value of FDG-PET in patients with painful total knee arthroplasty. Eur J Nucl Med Mol Imaging. 2006;33:1218-25
44. Delank KS, Schmidt M, Michael JW et al. The implications of 18F-FDG PET for the diagnosis of endoprosthetic loosening and infection in hip and knee arthroplasty: results from a prospective, blinded study. BMC Musculoskelet Disord. 2006;7:20-8
45. Kisielinski K, Cremerius U, Reinartz P et al. Fluordeoxyglucose positron emission tomography detection of inflammatory reactions due to polyethylene wear in total hip arthroplasty. J Arthroplasty. 2003;18:528-32
46. Reinartz P, Mumme T, Hermanns B et al. Radionuclide imaging of the painful hip arthroplasty: positron-emission tomography versus triple-phase bone scanning. J Bone Joint Surg [Br]. 2005;87-B:465-70

Nuclear medicine techniques and protocols used for diagnosis of (a)septic loosening of total joint replacements; a survey performed among the members of the Dutch Society of Nuclear Medicine

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Abstract

Kartachova MS, Pereira Arias-Bouda LM. Nuclear medicine techniques and protocols used for diagnosis of (a)septic loosening of total joint replacements; a survey performed among the members of the Dutch Society of Nuclear Medicine. Aim: A short survey was designed to assess the use of nuclear medicine techniques for the diagnosis of (a)septic loosening of total joint prostheses under the members of the Dutch Society of Nuclear Medicine.
Methods: A questionnaire was sent to all members of the Dutch Society of Nuclear Medicine, except clinical physicists and pharmacologists.
Results: 37 responses were received from 26 hospitals. Data were analysed to assess the frequency of different nuclear medicine procedures used in nuclear medicine departments in the Netherlands when (a)septic loosening of the prosthesis was suspected.
Conclusion: Results of this survey indicate that a wide range of techniques is currently used to assess patients with suspected infection of total joint replacement in the Netherlands. This variation in techniques reflects the fact that there is no true consensus on the gold standard technique for the diagnosis of septic or aseptic loosening. In addition, limited availability of blood cell labelling facilities restricts the use of leukocyte scintigraphy. Due to a growing availability of hybrid imaging systems, the use of PET/CT and SPECT/CT is increasing.
Tijdschr Nucl Geneesk 2012; 34(4):994-997

Introduction

Patients with suspected (a)septic loosening of a total joint prosthesis are frequently referred to the nuclear medicine department. A wide scale of nuclear medicine techniques is currently available for detection of (a)septic loosening of the total joint prosthesis. Due to its high sensitivity and high negative predictive value, three phase bone scintigraphy is a valuable adjunct modality when loosening is suspected (1, 2). However, differentiation between septic (infectious) and aseptic (mechanical) loosening remains a challenge, as there is no consensus on the gold standard technique, due to the fact that all currently available modalities have their limitations and impediments (2).
The purpose of this survey was to assess the frequency of different nuclear medicine procedures used in nuclear medicine departments in the Netherlands, if septic or aseptic loosening of the prosthesis is suspected.

Methods

The survey was conducted by submitting a 17-question survey to all members of the Dutch Society of Nuclear Medicine, except clinical physicists and pharmacologists. The survey contained both questions concerning the facilities available at the department, as well as questions about equipment and procedures used when (a)septic loosening of a total joint prosthesis is suspected. The respondents were asked to fill in the questionnaire electronically and were assured that all information would be treated confidentially.

Results

We received 37 responses from 26 hospitals, of whom 6 were university hospitals, 19 non-university and 1 categorical hospital. All participating hospitals are listed in table 1.
The total number of studies performed in the departments per year varied from 2700 to 20000. The total number of bone scans varied from 400 to 3000. The percentage of bone scans performed for orthopaedic indications varied from 5 to 85%. Regarding orthopaedic indications, 2 to 75% were performed to evaluate suspected prosthetic joint loosening.

Table 1.

Participating Hospitals

Academisch Medisch Centrum, Amsterdam
Admiraal De Ruyter Ziekenhuis, Vlissingen
Antoni van Leeuwenhoek Ziekenhuis, Amsterdam
Atrium Medisch Centrum, Heerlen
Verbeeten Institute, Tilburg
Catharina Ziekenhuis, Eindhoven
Deventer Ziekenhuis, Deventer
Ziekenhuis Gelderse Vallei, Ede
Ziekenhuis Rijnstate, Arnhem
Isala Klinieken, Zwolle
Jeroen Bosch Ziekenhuis, 's-Hertogenbosch
Maxima Medisch Centrum, Veldhoven
Medical Center Alkmaar, Alkmaar
Medisch Centrum Haaglanden, Den Haag
Orbis Concern, Sittard-Geleen
Streekziekenhuis Koningin Beatrix, Winterswijk
Reinier de Graaf Ziekenhuis, Delft
Rijnland Ziekenhuis, Leiderdorp
Slingeland Ziekenhuis, Doetinchem
St. Antonuis Ziekenhuis, Nieuwegein
Universitair Medisch Centrum Groningen
Universitair Medisch Centrum Maastricht
Universitair Medisch Centrum Utrecht
VieCuri Ziekenhuis, Venlo
Vlietland Ziekenhuis, Schiedam
VU Medisch Centrum, Amsterdam

The majority of the respondents (67%) worked in a department equipped with radionuclide laboratories, but one third of respondents indicated that there is no laboratory available on site. Blood cell labelling could be performed in 45% of the laboratories, 42% of the responding departments do not have this possibility and in 13% of the hospitals blood cell labelling was outsourced to external (pharmaceutical) companies or neighbouring hospitals.
83% of the respondents reported to have SPECT/CT at their disposal. 92% of the respondents reported to have a PET/CT scanner at their disposal, from whom 8% in a collaborating hospital. The remaining 8% had no possibilities to perform PET/CT.

Aseptic loosening

In patients with suspected aseptic loosening of a prosthetic joint, three-phase bone scintigraphy (TPBS) was the examination of choice. TPBS was performed in all cases according to 33/36 respondents (92%), 3/36 respondents (8%) reported to perform TPBS only if the prosthesis was placed more than one year ago. A combination of TPBS with SPECT/CT was performed on indication by half of the respondents, in a few hospitals it was performed in all patients. SPECT/CT was not considered as a method of choice by 14 respondents (39%).

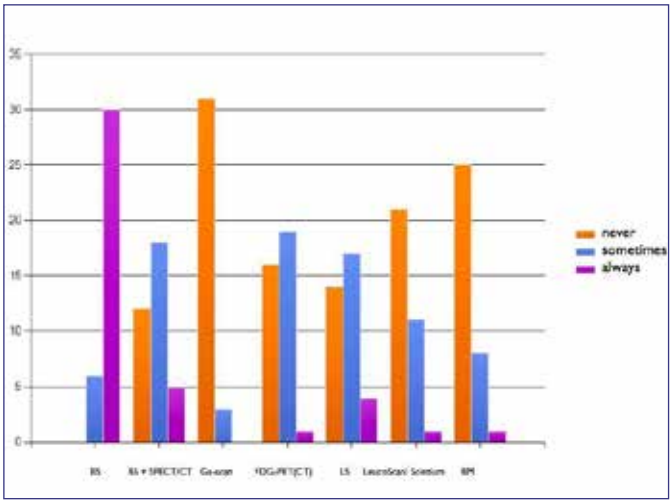


Figure 1. Examinations reported to be performed if septic loosening is suspected (numbers of respondents)
BS - bone scan; BS+SPECT/CT - bone scintigraphy with SPECT/CT; FDG-PET(CT) -^{18}F-FDG PET or PET/CT; LS - leukocyte scintigraphy; BM- bone marrow scintigraphy

Septic loosening

The radionuclide imaging techniques that are performed when septic loosening is suspected are shown in figure 1.
TPBS was reported to be used as a screening technique by almost all respondents. Equivocal results on TPBS were mentioned to be the most frequent indication for further evaluation. Again, TPBS with SPECT/CT was used by half of the respondents. As an additional test, leukocyte scintigraphy (LS) was reported to be performed in all cases by 11% of the respondents and only when TPBS was abnormal by 49% of the respondents; 40% of the responders never performed LS. LS was combined with bone marrow scintigraphy on indication by 26% of the respondents. Twelve respondents said to perform the LeucoScan as additional test, predominantly in centres without blood cell labelling facilities on site. Gallium scintigraphy was still used in one of the participating hospitals. PET/CT is reported to be a method of choice as an additional modality by 56% of the respondents in cases of positive or equivocal TPBS, suspected involvement of the surrounding soft tissues and/or suspected disseminated infection. 44% of the respondents said never to use PET/CT as an additional test. Several respondents highlighted that PET/CT is used in their hospital only if septic loosening of a total hip prosthesis was suspected.

Protocols and evaluation of leukocyte and PET/CT

Protocols used for LS and LeucoScan are summarised in

figure 2. Static images obtained 4 and 24 hours after injection are the most frequently used sequences. 84 and 79% of the respondents uses them, respectively. LS was combined with SPECT/CT by 23% of the respondents. Most frequently mentioned indications for additional SPECT/CT are doubt about the exact location of pathological uptake and equivocal scan results. Evaluation of LS was reported to be based on

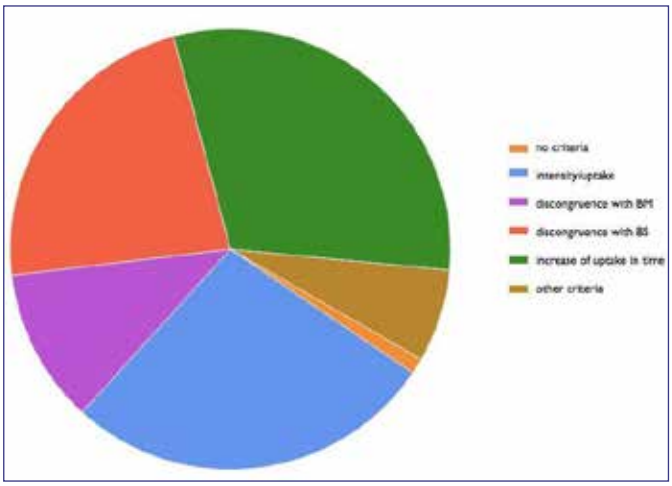


Figure 2. Criteria used for evaluation of leukocyte scintigraphy and LeucoScan BS- bone scintigraphy; BM- bone marrow scintigraphy

visual analysis by 88% of the respondents, 78% reported to consider (an increase of) intensity and uptake patterns as key elements during evaluation. Criteria used for evaluation of LS are summarised in figure 3.
When PET/CT was used for evaluation of suspected prosthetic joint infection, both partial scans of a diseased

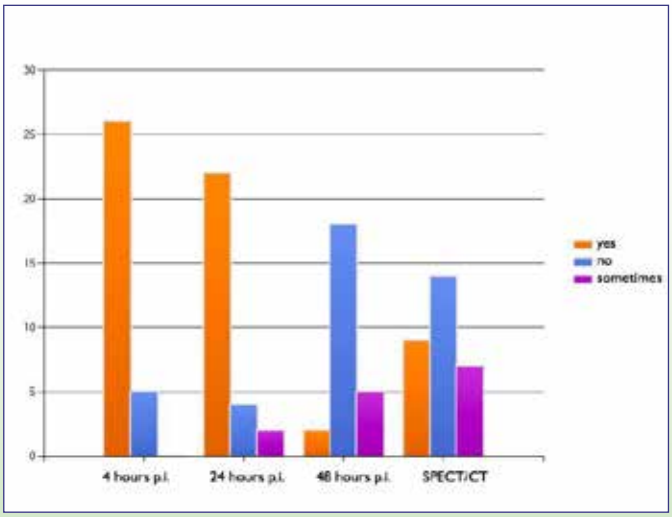


Figure 3. Protocols used for leukocyte scintigraphy and LeucoScan (numbers of respondents)

prosthesis as well as whole body scans were performed. PET/CT scans were evaluated based on intensity of the tracer uptake by 22 respondents (79%). Nineteen respondents (70%) used uptake pattern criteria to analyse the images (figure 4).

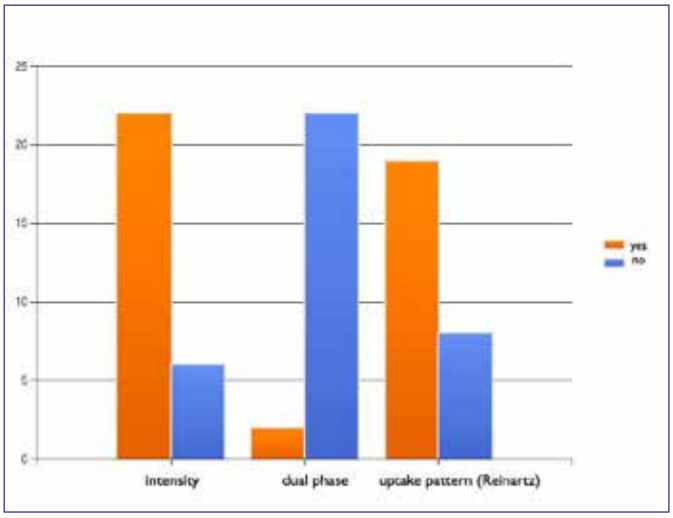


Figure 4. Criteria used for evaluation of ^{18}F-FDG PET/CT (numbers of respondents)

Discussion

Despite the limited number of respondents in this survey (approximately 25% of all Dutch nuclear medicine physicians), we do believe the results are illustrative, since both representatives from university medical centres as well as non-university hospitals have participated.
The data show that, as expected, TPBS is the method of choice in patients with suspected aseptic loosening, in 50% of the hospitals combined (on indication) with SPECT/CT.
With regard to septic prosthetic loosening, the survey results and protocols confront us with a diversity of nuclear imaging modalities that are currently utilised for this indication in the Netherlands. Negative TPBS is generally believed to exclude prosthetic loosening. Combinations of modalities used for diagnosis of septic loosening vary from TPBS with gallium scintigraphy, TPBS with LS or LeucoScan sometimes followed by bone marrow scintigraphy, all the way to TPBS followed by PET/CT.
The results of this survey underline the diversity of methods currently used for diagnosis of orthopaedic problems in general and prosthetic loosening in particular in the Netherlands.

Conclusion

With the help of this survey we illustrate the variety of techniques and protocols currently used in the Netherlands for the diagnosis of (a)septic prosthetic loosening. The survey revealed that the use of nuclear imaging techniques for orthopaedic indications varies strongly per hospital. As

we expected, TPBS is the method of choice when aseptic loosening is suspected. On the other hand, the wide variety of techniques and protocols that are used for diagnosis of septic loosening reflects the current lack of consensus on state-of-the-art imaging concerning the prosthetic joint infection on national and international level (2). Moreover, the use of leukocyte scintigraphy is restrained by limited availability of on-site labelling facilities. The use of SPECT/CT both with TPBS and LS varies strongly, which is only partly due to limited availability. It is interesting to see that a substantial part of the respondents use ^{18}F-FDG PET/CT, even though the exact role of FDG PET/CT is not yet fully established for this indication.

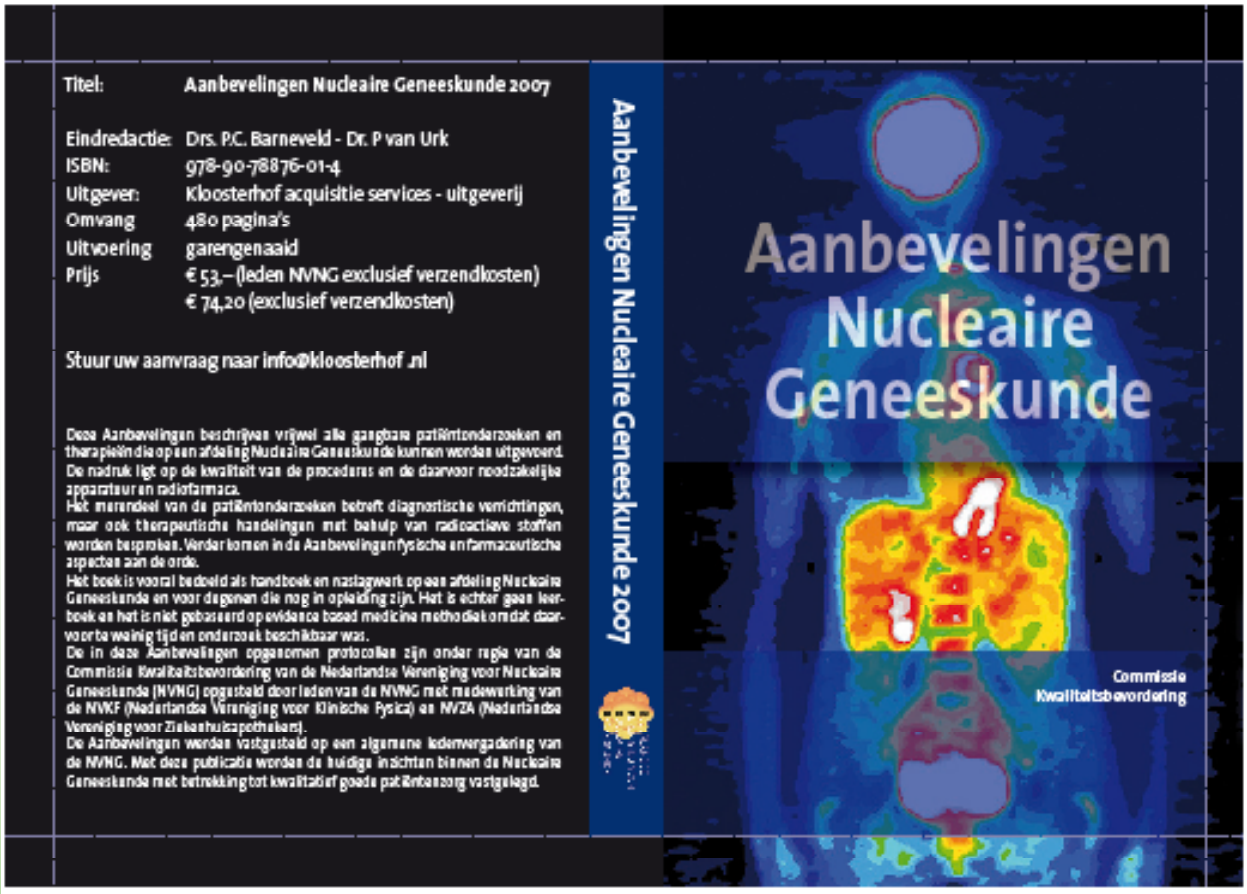
In conclusion, the results of this survey underline that there is no true consensus about the gold standard technique for diagnosis of septic prosthetic loosening in the Netherlands.

Acknowledgments

The authors gratefully acknowledge all respondents for participating in this survey.

References

1. Temmerman OP, Raijmakers PG, Berkhof J et al. Accuracy of diagnostic imaging techniques in the diagnosis of aseptic loosening of the femoral component of a hip prosthesis: a meta-analysis. J Bone Joint Surg Br. 2005;87:781-5
2. Gemmel F, Van den Wyngaert H, Love C et al. Prosthetic joint infections: radionuclide state-of-the-art imaging. Eur J Nucl Med Mol Imaging. 2012;39:892–909



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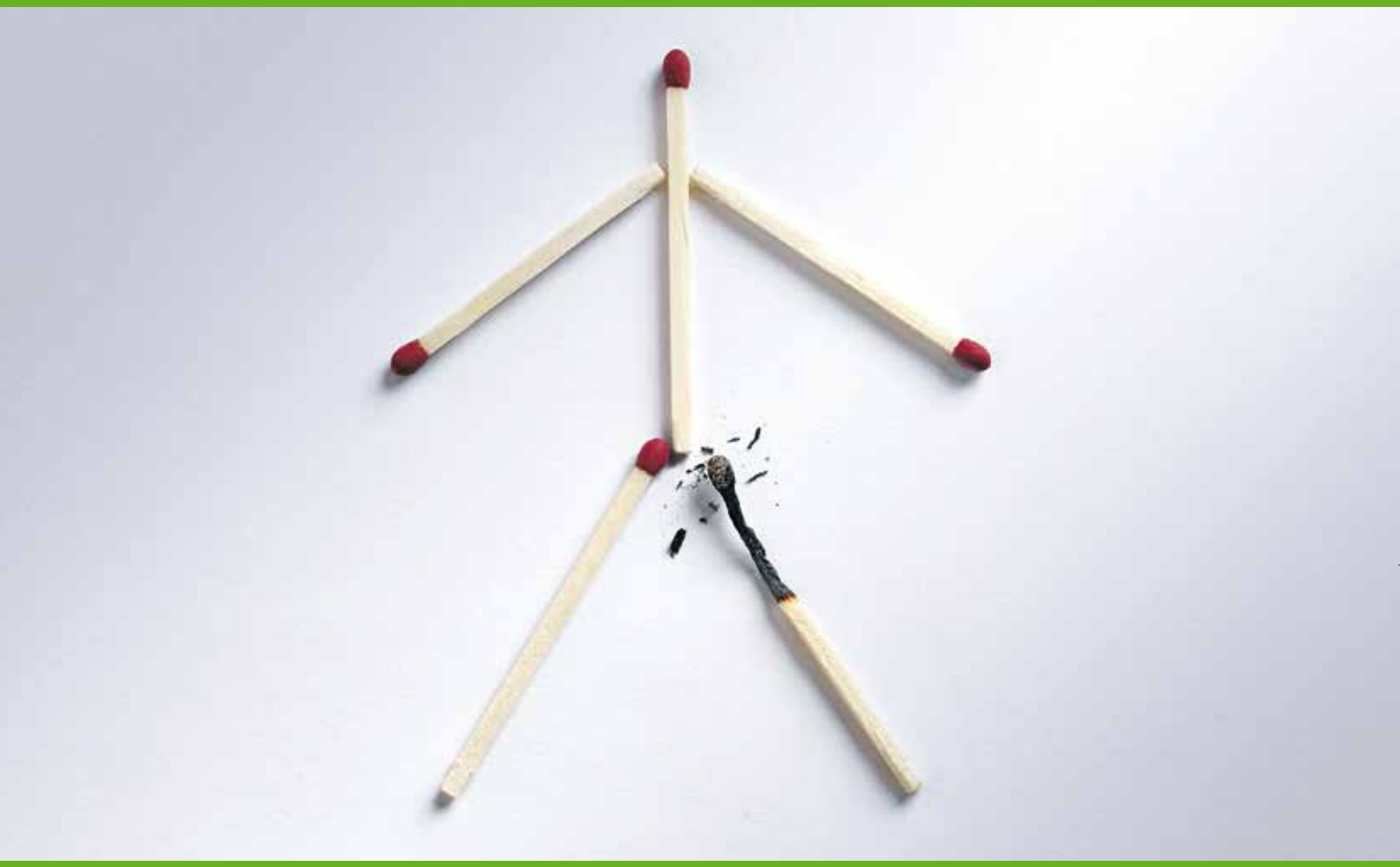

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Only limited data is available about binding of technetium (^{99m}Tc) besilesomab to CarcinoEmbryonic Antigen (CEA) expressing tumours in vivo. In vitro, besilesomab cross-reacts with CEA. False positive findings in patients with CEA expressing tumours cannot be excluded. False results may be obtained in patients with diseases involving neutrophil defects and to patients with haematological malignancies including myeloma. Scintimun contains sorbitol therefore patients with rare hereditary problems of fructose intolerance should not be administered this product. Human Anti-Mouse Antibodies (HAMA): Administration of murine monoclonal antibodies can lead to the development of Human Anti-Mouse Antibodies (HAMA). Patients who are HAMA positive may have a greater risk for hypersensitivity reactions. 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^{18}F-FDG PET/CT, not only diagnostic tool in post-traumatic chronic osteomyelitis but also guidance for operative treatment

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Introduction

Infections of bone after trauma are rare but severe complications. Acute osteomyelitis is usually diagnosed readily on clinical grounds and localised signs of infection of the involved bone, whereas the diagnosis of chronic osteomyelitis is much more difficult. Post-traumatic chronic infections in bone are characterised by a low-grade presentation, with lymphocytic and plasma cell infiltration which eventually leads to necrosis and osteosclerosis (1). Several classification systems for chronic osteomyelitis have been published. Schauwecker and coworkers published a manageable definition; osteomyelitis requiring more than one episode of treatment and/or a persistent infection lasting for more than six weeks should be considered chronic (2).
The early diagnosis of (chronic) osteomyelitis is of vital importance in the management of this condition as early surgical debridement and antibiotic therapy are essential in order to eradicate the infection. Though, establishing the diagnosis is difficult as recent trauma to bone and previously performed operative treatment alter the normal anatomy and physiology of bone. In these patients additional imaging is required to establish or rule out an active bone infection (3). Recent studies have indicated that ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) has the best diagnostic accuracy among a variety of diagnostic modalities, including radiolabelled white blood cell (WBC) scintigraphy, bone scintigraphy, and magnetic resonance imaging (MRI) (4). FDG accumulates at sites of infection as activated inflammatory cells metabolise glucose as source of energy, thus ^{18}F-FDG PET provides a physiological/metabolic imaging modality (5). The images produced by PET (without attenuation correction) are largely unaffected by metallic implants which favours the interpretation of such scans in trauma patients with osteosynthesis (6). Moreover, hybrid imaging using both PET and computed tomography (CT) combines the detailed anatomical information of CT with the physiological/metabolic information of ^{18}F-FDG PET (5,7) which further optimises the interpretation of the scans. In this case series, we describe three patients with suspected osteomyelitis after osteosynthesis in whom ^{18}F-FDG PET/CT demonstrates its (early) diagnostic value, provides a clear anatomical localisation of the bone infection, and provides additional information for operative planning.
The patients were informed that data concerning the case would be submitted for publication, to which they consented.

Discussion

The diagnosis of chronic osteomyelitis in trauma patients remains challenging and failure to diagnose a deep infection will lead to a delay in treatment and may require more extensive surgery once it is recognised.
A variety of radiological techniques (including radiography, CT and MRI) are available and often used for evaluation of suspected deep bone infection although their diagnostic accuracy is very limited. ^{18}F-FDG PET has demonstrated the highest accuracy of all currently available imaging techniques (4). Although yet to be published, there is no doubt that the combination of ^{18}F-FDG PET with CT imaging substantially increases the accuracy by providing anatomical details.
In case one and three, the presence and the distribution of the intra-osseous infection could be visualised or excluded in the presence of osteosynthesis. Subsequently, the extra-osseous findings of the soft tissue infection was demonstrated. Noteworthy is the finding of the sub-clinical sinus tract of a fistula in case one. Case two demonstrated that PET/CT has additional value for surgical management as a deep infection could be excluded by PET/CT at 5 months after the trauma and conservative therapy could be continued.
The efficacy of ^{18}F-FDG PET in patients with mentioned non-specific symptoms has been demonstrated but these symptoms may occur after many months/years due to ongoing infection. Until now, no early diagnostic test has been available for the diagnosis of a low grade infection which may progress to clinical chronic osteomyelitis in time. The development of an early diagnostic tool, such as ^{18}F-FDG PET/CT, is of great importance to improve surgical treatment in the relatively young trauma patient, to reduce patient morbidity, and to reduce costs in health care. Case two demonstrates that early detection of ongoing osteomyelitis is possible before clinical symptoms occur.

Further clinical studies have to demonstrate the implications of PET/CT findings in patients with chronic osteomyelitis for definitive surgical management. For example, there is no literature on positive ^{18}F-FDG PET findings in bone and the relation and time course to recent surgery. A very interesting feature of ^{18}F-FDG PET is the potential to monitor treatment efficiency of surgical and antibiotic management; this has already been described for spinal infections (8).
^{18}F-FDG PET has demonstrated the highest accuracy for detection of chronic osteomyelitis as compared to other imaging modalities. The presented case reports demonstrate the major advantage and the potential therapeutic guidance of combining this technique with CT for trauma patients with osteosynthesis in whom a deep infection is suspected.

Case Reports

Case 1. A 36-year-old man was presented to our emergency department after severe trauma which resulted in a complex left acetabulum fracture and left metaphyseal femoral fracture, and a number of other injuries. The femoral fracture was primarily stabilised by external fixation and femoral traction was initiated for the acetabulum.
After two weeks, the acetabulum fracture was treated by plate osteosynthesis, and the external fixation was converted to antegrade reamed intramedullary nailing. During outpatient control at six months after discharge, a small persistent skin defect at the previous proximal pin site was noted. At nine months, the patient was evaluated in the emergency department for pain and local signs of infection at the distal pin sites. Laboratory examination showed leukocyte count of 12.4 x 10^9/L (normal 4.0 to 12.0 x 10^9/L) and C-reactive protein level of 150 mg/L (normal 0 to 0.8 mg/L).
A soft-tissue abscess was drained; however, cultures showed no bacterial growth. Conventional radiographs of the femur showed consolidation of at least one of the cortices and no signs of osteolysis or infection (figure 1). The presence of a deep infection was suspected and PET/CT scan was obtained (figure 2).

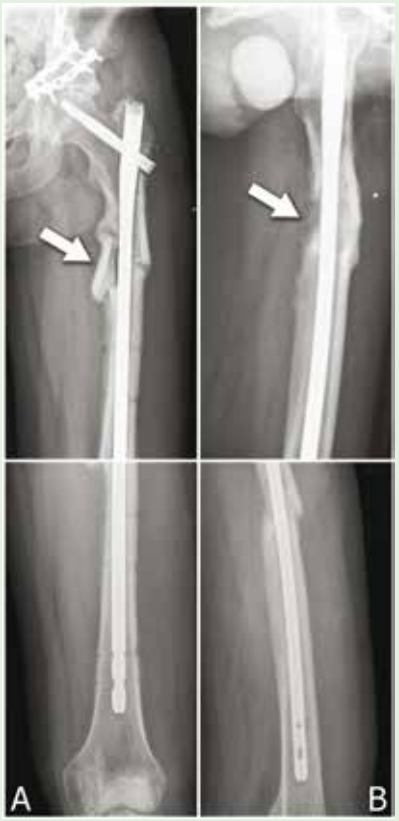

Figure 1. Anteroposterior (A) and lateral (B) conventional radiographs of left femur at nine months after secondary osteosynthesis demonstrated delayed union with no clear signs of osteomyelitis (large arrows).

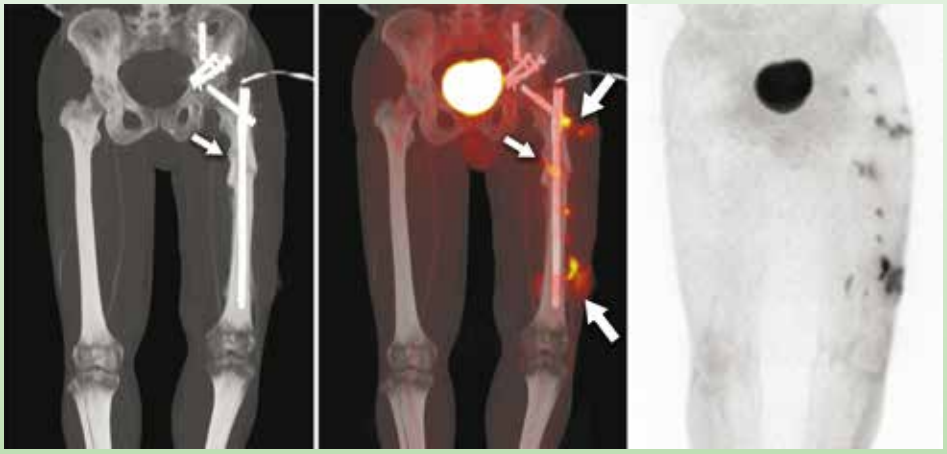

Figure 2. ^{18}F-FDG PET showed diffuse FDG uptake of the intramedullary canal. Focal uptake at the pseudarthrosis site was also noted (small arrows). A soft tissue sinus tract was found corresponding with the skin defect proximally (large arrow). FDG uptake was clearly noted at the drained distal infection site of the femur (large arrow).

Case 2. A 22-year-old man was presented with severe multi-trauma with amongst others open fractures of the left tibia and shaft fractures of both femurs. The fractures were primarily fixated externally and secondarily stabilised by intramedullary nailing for the femurs and plate fixation for the left tibia. Due to major soft tissue injury a vascularised free flap was placed at the distal left fibula. After five months, an osteomyelitis was suspected and PET/CT was performed (figure 3A, B). No laboratory examination was performed at this time point. After seven months, the patient reported increasing pain of his right leg during weight bearing. Laboratory examination showed leukocyte count of 11.3 x 10^9/L and C-reactive protein level of 52.2 mg/L. Because of the previously noticed uptake of FDG at the fracture of his right leg, PET/CT was repeated (figure 3C). A starting union of the femur fracture was seen on PET/CT with (osteo-)myelitis of the femur shaft. Antibiotic therapy was started and surgical procedure was planned with removal of the proximal screws in order to start dynamic compression of the fracture to stimulate bone healing. Deep cultures during this operation revealed Enterobacter cloacae.

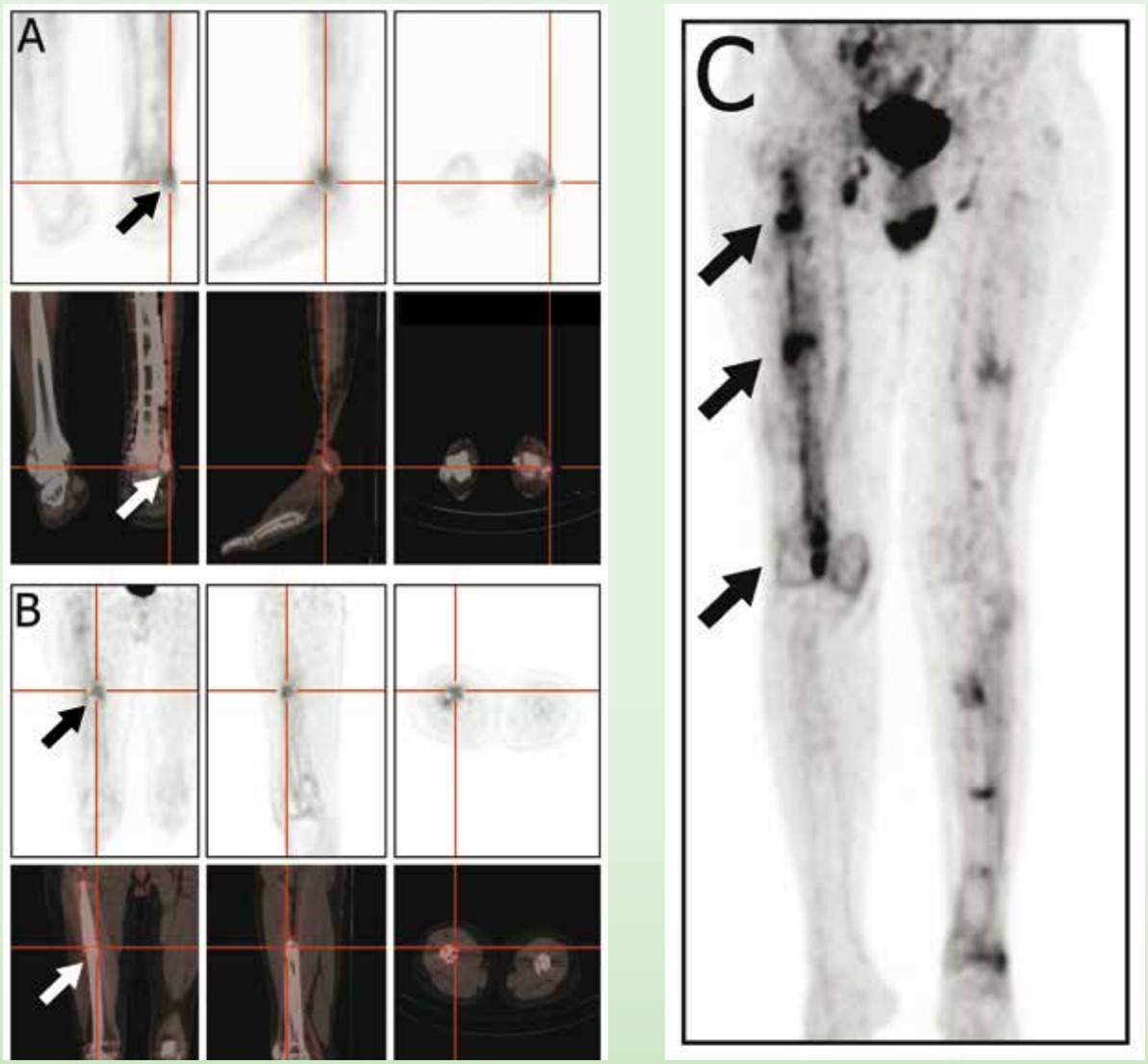

Figure 3A: Five months after the trauma, the ^{18}F-FDG PET of the left tibia showed no deep infection. Uptake of FDG was seen in the soft-tissue / vascularised flap but no osseous FDG uptake was demonstrated (panel A, arrow). 3B: The PET/CT of the right femur shows uptake of FDG at the fracture site and intramedullary at the proximal femur (arrow). At this point of time, the patient had no complaints about his right leg which was fully weight bearing. Due to the fact that it was unclear whether FDG uptake at this stage of the fracture healing was physiological or due to ongoing chronic osteomyelitis, no surgical interventions took place. 3C: After seven months, the PET/CT showed increased FDG-uptake at the fracture site but also extension to the proximal and distal intramedullary canal (arrows), indicating an ongoing osteomyelitis. A maximum intensity projection (MIP) is displayed. In this case, ^{18}F-FDG PET/CT demonstrated its potential role in early diagnostics for osteomyelitis.

Case 3. A 72-year-old woman with morbid obesity was treated for a right subtrochanteric femoral fracture with a dynamic hip screw (DHS).
Fourteen days postoperatively, persisting leakage of the wound was present, thus a wash-out of the surgical site was performed. Cultures demonstrated a Proteus mirabilis infection. After three months, the patient was presented at the emergency department with local signs of infection and abscess formation at the operation site. The abscess was drained operatively and during the procedure the deep fascia appeared intact and therefore no deeper exploration was performed. Postoperatively, a persistent cellulitis was observed clinically after starting antibiotic therapy. Laboratory examination showed leukocyte count of 13.1 x 10^9/L and C-reactive protein level of 204 mg/L. The presence of deep infection was suspected and a PET/CT scan was obtained (figure 4 and 5). The PET/CT excluded a deep infection, antibiotic therapy was continued and the cellulitis resolved in time.

Figure 4. Anteroposterior conventional radiographs of the right femur at four months after osteosynthesis. Ongoing consolidation was seen without signs of infection.

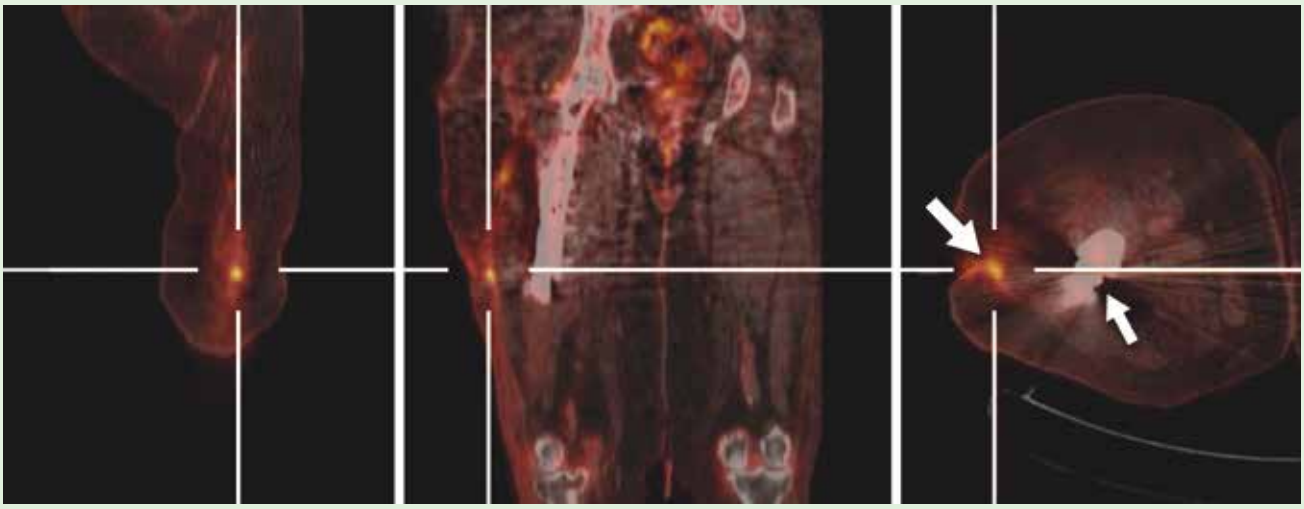

Figure 5. ^{18}F-FDG PET/CT of the right femur showed uptake of FDG in the soft tissue at the site of the superficial infection (large arrow). A deep or subfascial infection/osteomyelitis could be excluded. Scattering of the plate of the dynamic hip screw below the local infection site was present on the CT but no uptake of FDG was shown on the PET images (small arrow).

References

1. Tiemann AH, Krenn V, Krukemeyer MG et al. Infectious bone diseases. Pathologe. 2011;32(3):200-9
2. Schauwecker DS. Osteomyelitis: diagnosis with In-111-labeled leukocytes. Radiology. 1989;171:141-6
3. Kaim AH, Gross T, von Schulthess GK. Imaging of chronic posttraumatic osteomyelitis. Eur Radiol. 2002;12:1193-202
4. Termaat MF, Raijmakers PGHM, Scholten HJ et al. The accuracy of diagnostic imaging for the assessment of chronic osteomyelitis: a systematic review and meta-analysis. J Bone Joint Surg AM. 2005;87:2464-71
5. Basu S, Chryssikos T, Moghadam-Kia S et al. Positron emission tomography as a diagnostic tool in infection: present role and future possibilities. Semin Nucl Med. 2009;39:36-51
6. Schiesser M, Stumpe KD, Trentz O, Kossmann T, Von Schulthess GK. Detection of metallic implant-associated infections with FDG PET in patients with trauma: correlation with microbiologic results. Radiology. 2003;226:391-8
7. Hartmann A, Eid K, Dora C et al. Diagnostic value of 18F-FDG PET/CT in trauma patients with suspected chronic osteomyelitis. Eur J Nucl Med Mol Imaging. 2007;34:704-14
8. Kim SJ, Kim IJ, Suh KT, Kim YK, Lee JS. Prediction of residual disease of spine infection using F-18 FDG PET/CT. Spine. 2009;34:2424-30

^{99m}Tc-sestamibi scintigraphy in perfusion disorders of lumbar spine muscles after lumbar spine fusion surgery

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Results of the first 50 scans (rest and post-stress) in 25 consecutive patients with recurrent LBP after lumbar fusion surgery were retrospectively analysed. Scans were evaluated and scored as abnormal in 14 patients (56%) and as normal in 11 patients (44%). Decreased or absent ^{99m}Tc-sestamibi uptake was observed in both left and right lumbar spine muscles in 4/14 (29%) patients, in the right-sided lumbar spine muscles in 6/14 (42%) patients and in left-sided lumbar spine muscles in 4/14 (29%) patients. No differences in tracer distribution in lumbar spine muscles were found in patients scanned after exercise as compared to rest scans. Decreased uptake in paraspinal muscles correlated with muscle hypoperfusion as detected during fasciotomy, performed in 8 of 14 patients with decreased lumbar muscle uptake.
Based on these data we concluded that it is feasible to evaluate lumbar muscle perfusion after lumbar fusion surgery by ^{99m}Tc-sestamibi scintigraphy. Furthermore we decided to perform only post-stress scan in this group of patients.

Nuclear medicine departments offer a large diversity of diagnostic and therapeutic procedures, which often play a central role in patient management. Besides standardised procedures, new tracers and alternative applications of already existing tracers are continuously introduced.
In this context we would like to share our experience at the nuclear medicine department of the Medical Center Alkmaar with an alternative application of ^{99m}Tc-sestamibi scintigraphy for visualisation of perfusion of lumbar spine muscles after lumbar spine fusion surgery.

Low back pain (LBP) is one of the most commonly encountered complaints in adults. Dysfunction of the lumbar spine muscles is considered as one of the causes of chronic LBP (1).
Although lumbar spine fusion surgery is known to be less effective in patients with chronic LBP, it has been attested to be an effective intervention in spondylolisthesis and degenerative disc disease (2). However, some patients undergoing lumbar fusion therapy show no improvement. In a number of cases, dysfunction of the lumbar spine muscles is suggested to be an explanation. This results in pain and neuromuscular dysfunction, due to increased pressure in muscles with secondary blood flow reduction and, hence, chronic ischemia. Intramuscular pressure measurements (IMP) usually detect elevated muscle pressure as a sign of compartment syndrome (3) but show large interindividual variability and is frequently inconsistent with the clinical symptoms (4). In this context the question was raised if nuclear medicine can offer an imaging technique which may be suitable to detect reduced muscular blood flow.
In daily nuclear medicine practice, ^{99m}Tc-sestamibi is used for myocardial perfusion imaging but imaging of skeletal muscle perfusion has also proven to be feasible. For instance, the radiotracer was used successfully for imaging muscle perfusion in lower extremity peripheral disease (5) as well as reduced muscle perfusion in patients with compartment syndromes of the legs (6). In 2004 the following protocol was developed in our department to evaluate spine muscle perfusion using ^{99m}Tc-sestamibi scintigraphy:

^{99m}Tc-sestamibi scintigraphy

Patients perform an exercise test consisting of 40 shoulder/back lifts in prone position (figure 1). After 30 lifts, 750 MBq ^{99m}Tc-sestamibi (Bristol-Myers Squibb, Sermoneto, Italy) is administrated intravenously.
A single-photon emission computed tomography/computed tomography (SPECT/CT) is acquired fifteen minutes after injection of the radiotracer using a GE Millennium VG5 Hawkeye system (GE Healthcare, Little Chalfont, Buckinghamshire, United Kingdom). For SPECT acquisition an energy window of 140 KeV ± 15%, a matrix of 128 x 128 and 60 (angle 6 °) frames of 45 sec are used. For the mapping CT, acquisition parameters include a matrix of 256 x 256 at 140 kV, 2.5 mA, with 10 mm slice thickness, 10 mm slice step and 2.6 rotations per minute.
The scans are visually evaluated. The muscle perfusion

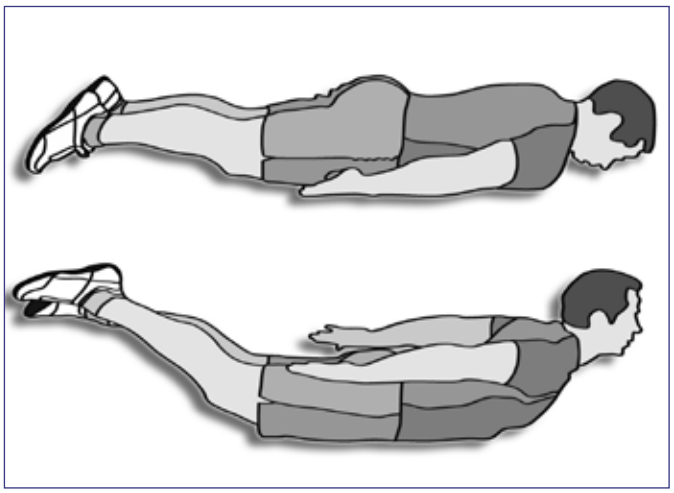

Figure 1. Shoulder/back lift in prone position.

is considered normal if there is symmetric homogeneous distribution of ^{99m}Tc-sestamibi in lumbar spine muscles. It is considered abnormal if there is asymmetrically decreased or absent ^{99m}Tc-sestamibi uptake in lumbar spine muscles (figure 2).

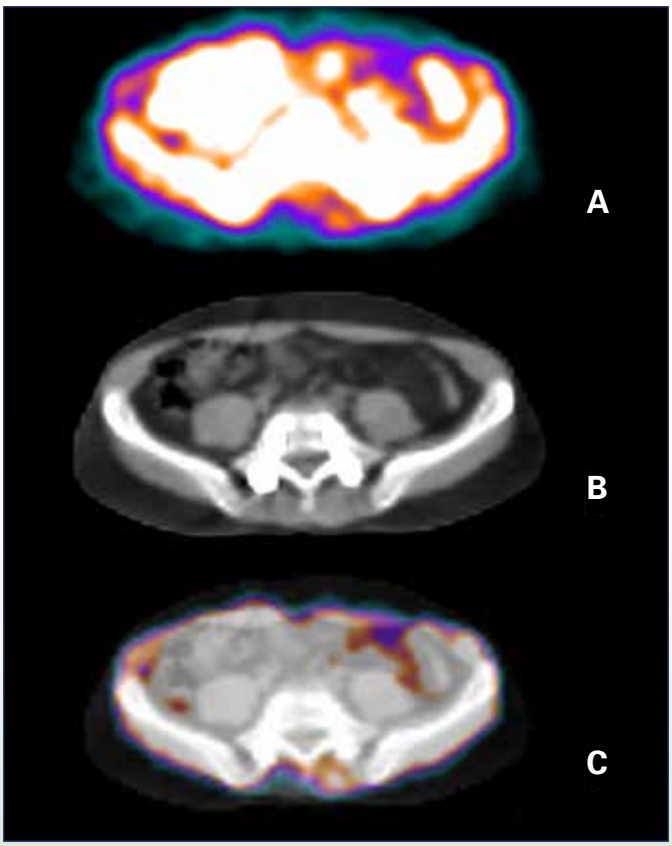

Figure 2. An example of decreased ^{99m}Tc-sestamibi uptake in paraspinal muscles; transaxial SPECT (A), CT (B) and fusion SPECT/CT (C) images obtained after standard exercises show decreased uptake in paraspinal muscles on the right side.

Discussion

Lumbar back pain is a frequently encountered and challenging problem. In a selected group of patients, lumbar spine fusion surgery can relieve symptoms. However, in some patients the complaints do not disappear after spine fusion surgery, or they may recur. Besides infection or malfunction of the fusion material, dysfunction of the paraspinal muscles could be a cause of persistent back pain.
^{99m}Tc-sestamibi scintigraphy is a reliable technique to detect disturbances in myocardial perfusion but could also be used for imaging perfusion of skeletal muscles. In our hospital we use this tracer to evaluate perfusion disturbances of paraspinal muscles after lumbar spine fusion surgery.

Conclusion

We believe that it is feasible to detect hypoperfusion of lumbar spine muscles after lumbar spine fusion surgery using ^{99m}Tc-sestamibi scintigraphy, and thus see it as an alternative application of a well established technique.

References

1. Andersson G. The function of the trunk muscles in health and with low back pain. Semin Spine Surg.1993;5:3-9
2. Carreon LY, Glassman SD, Howard J. Fusion and nonsurgical treatment for symptomatic lumbar degenerative disease: a systematic review of Oswestry Disability Index and MOS Short Form-36 outcomes. Spine J.2008;8:747-55
3. Styf J, Lysell E. Chronic compartment syndrome in the erector spinae muscle. Spine.1987;12:680-2
4. Kramer M, Völker H, Weikert E. Simultaneous measurements of intramuscular pressure and surface electromygraphy of the multifidus muscle. Eur Spine J.2004;13:530-6
5. Sayman HB, Urgancioglu I. Muscle perfusion with technetium-MIBI in lower extremity peripheral arterial diseases. J Nucl Med.1991;32:1700-3
6. Edwards PD, Miles KA, Owens SJ, Kemp PM, Jenner JR. A new non-invasive test for the detection of compartment syndromes. Nucl Med Commun.1999;20:215-8

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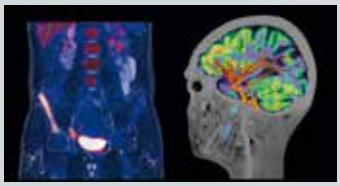

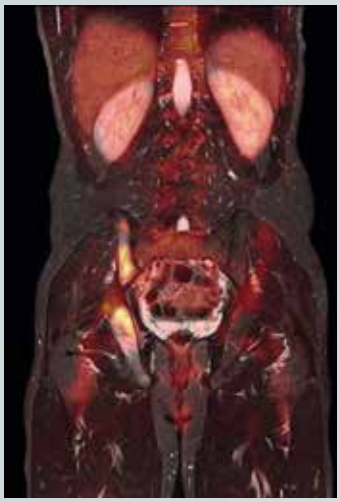

PET en MR geïntegreerd in één systeem

De Biograph mMR, 's werelds eerste en enige whole-body moleculaire MR

De Biograph mMR brengt een revolutie in diagnostische beeldvorming tot leven. Voor het eerst zijn state-of-the-art 3T MRI en cutting-edge moleculaire beeldvorming volledig geïntegreerd in één systeem. Alleen Siemens maakt het mogelijk om gelijktijdig beelden te genereren van de morfologie, functie en het metabolisme van het hele lichaam. Whole-body PET en MR volledig geïntegreerd.

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Biograph mMR – PET en MR zijn vanaf nu één.

www.siemens.nl/healthcare

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Cursus- en Congresagenda

TOPIM 2013 - the 7th ESMI Winter Conference
20 – 25 January, 2013. Les Houches, France. www.e-smi.eu

NKRV Workshop
25 January, 2013. Nijmegen, The Netherlands. www.nkrv.nl

2nd European Conference on Clinical Neuroimaging
11 – 12 February, 2013. Lille, France. www.eanm.org

IDKD Musculoskeletal Diseases
2 – 6 April, 2013. Davos, Switzerland. www.idkd.org

2nd Tübingen PET/MR Workshop 2013
8 – 12 April, 2013. Tübingen, Germany. www.eanm.org

NuklearMedizin 2013
17 – 20 April, 2013. Bremen, Germany. www.eanm.org

ICNC 11, Nuclear Cardiology and Cardiac CT
5 – 8 May, 2013. Berlin, Germany. www.escardio.org

20th International Symposium on Radiopharmaceutical Sciences (ISRS)
12 – 17 May, 2013. Jeju, Korea. www.isrs2013.org

EMIM 2013 - 8th European Molecular Imaging Meeting
26 – 28 May, 2013. Torino, Italy. www.e.smi.eu

BELNUC 16th Biennial Congress
24 - 26 May, 2013. Ostend, Belgium. www.belnuc.be

JIOC (Joint International Oncology Congress)
27 - 29 May, 2013. San Francisco, U.S.A.

SNM 2013 – 60th Society of Nuclear Medicine Annual Meeting
8 – 12 June, 2013. Vancouver, Canada. www.snm.org

Adreswijzigingen

Regelmatig komt het voor dat wijziging in het bezorgadres voor het Tijdschrift voor Nucleaire Geneeskunde op de verkeerde plaats worden doorgegeven. Adreswijzigingen moeten altijd aan de betreffende verenigingssecretariaten worden doorgegeven. Dus voor de medisch nucleair werkers bij de NVMBR, en voor de leden van de NVNG en het Belgisch Genootschap voor Nucleaire Geneeskunde aan hun respectievelijke secretariaten.
De verenigingssecretariaten zorgen voor het doorgeven van de wijzigingen aan de Tijdschrift adresadministratie.
Alleen adreswijzigingen van betaalde abonnementen moeten met ingang van 1 januari 2011 rechtstreeks aan de abonnementenadministratie van Kloosterhof Neer B.V. worden doorgegeven: Kloosterhof Neer B.V., t.a.v. administratie TvNG, Napoleonsweg 128a | 6086 AJ Neer of per E-mail: nucleaire@kloosterhof.nl

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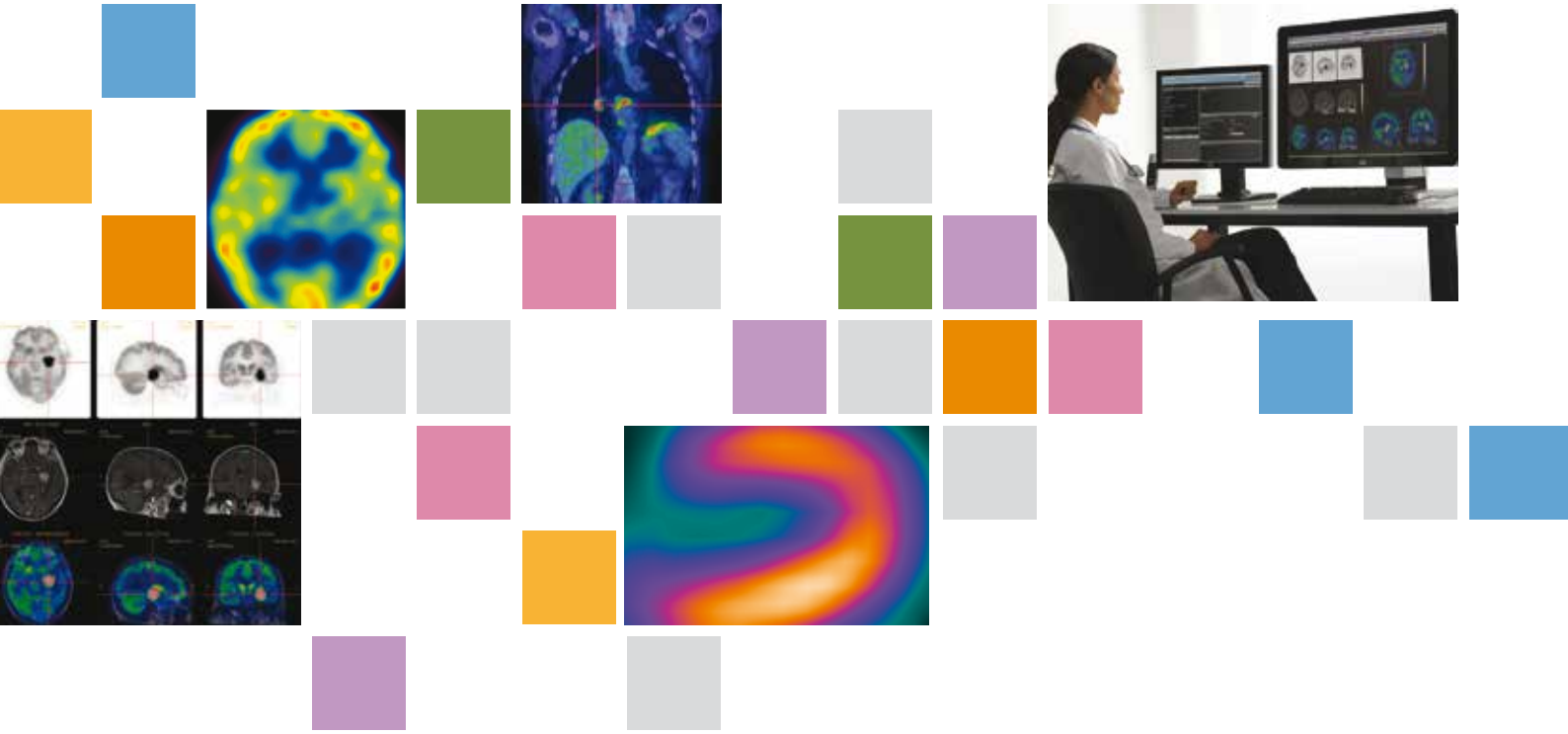

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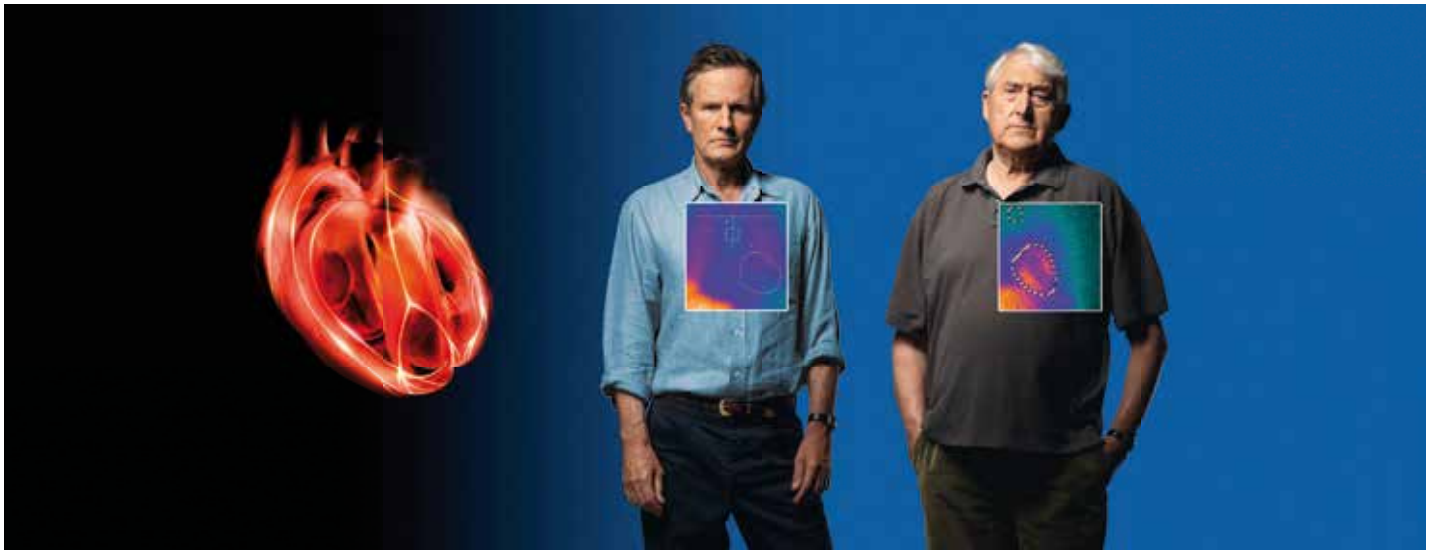

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PRESENTATION Vials containing 74 MBq/ml [^{123}I]Iobenguane at calibration date and hour. Available pack size: 37 to 740 MBq. **DIAGNOSTIC INDICATIONS** • Assessment of sympathetic innervation of the myocardium as a prognostic indicator of risk for progression of symptomatic heart failure, potentially fatal arrhythmic events, or cardiac death in patients with NYHA class II or class III heart failure and LV dysfunction. • Diagnostic scintigraphic localisation of tumours originating in tissue that embryologically stems from the neural crest. These are pheochromocytomas, paragangliomas, chemodectomas and ganglioneuromas. • Detection, staging and follow-up on therapy of neuroblastomas. • Evaluation of the uptake of iobenguane. The sensitivity to diagnostic visualisation is different for the listed pathological entities. The sensitivity is approximately 90% for the detection of pheochromocytoma and neuroblastoma, 70% in case of carcinoid and only 35% in case of medullary thyroid carcinoma (MTC). • Functional studies of the adrenal medulla (hyperplasia). **DOSAGE AND METHOD OF ADMINISTRATION** Cardiology: For adults the recommended dosage is 370MBq. Children under 6 months: 4 MBq per kg body weight (max. 40 MBq), the product must not be given to premature babies or neonates. Children between 6 months and 2 years: 4 MBq per kg body weight (min. 40 MBq). Children over 2 years: a fraction of the adult dosage should be chosen, dependent on body weight (see SPC for scheme). No special dosage scheme required for elderly patients. Oncology: For adults the recommended dosage is 80-200 MBq, higher activities may be justifiable. For children see cardiology. No special dosage scheme required for elderly patients. Administer dose by slow intravenous injection or infusion over several minutes. **CONTRAINDICATIONS** Hypersensitivity to the active substance or to any of the excipients. The product contains benzyl alcohol 10.4 mg/ml and must not be given to premature babies or neonates **WARNINGS AND PRECAUTIONS** Drugs known or expected to reduce the iobenguane(123-I) uptake should be stopped before administration of AdreView (usually 4 biological half-lives). At least 1 hour before the AdreView dose administer a thyroid blockading agent (Potassium Iodide Oral Solution or Lugol's Solution equivalent to 100 mg iodine or potassium perchlorate 400 mg). Ensure emergency cardiac and anti-hypertensive treatments are readily available. In theory, iobenguane uptake in the chromaffin granules may induce a hypertensive crisis due to noradrenaline secretion; the likelihood of such an occurrence is believed to be extremely low. Consider assessing pulse and blood pressure before and shortly after AdreView administration and initiate appropriate anti-hypertensive treatment if needed. This medicinal product contains benzyl alcohol. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old. **INTERACTIONS** Nifedipine (a Ca-channel blocker) is reported to prolong retention of iobenguane. Decreased uptake was observed under therapeutic regimens involving the administration of antihypertensives that deplete norepinephrine stores or reuptake (reserpine, labetalol), calcium-channel blockers (diltiazem, nifedipine, verapamil), tricyclic antidepressives that inhibit norepinephrine transporter function (amitryptiline and derivatives, imipramine and derivatives), sympathomimetic agents (present in nasal decongestants, such as phenylephrine, ephedrine, pseudoephedrine or phenylpropanolamine), cocaine and phenothiazine. These drugs should be stopped before administration of [123I]iobenguane (usually for four biological half-lives to allow complete washout). **PREGNANCY AND LACTATION** Only imperative investigation should be carried out during pregnancy when likely benefit exceeds the risk to mother and foetus. Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If uncertain, radiation exposure should be kept to the minimum needed for clinical information. Consider alternative techniques. If administration to a breast feeding woman is necessary, breast-feeding should be interrupted for three days and the expressed feeds discarded. Breast-feeding can be restarted when the level in the milk will not result in a radiation dose to a child greater than 1 mSv. **UNDESIRABLE EFFECTS** In rare cases the following undesirable effects have occurred: blushes, urticaria, nausea, cold chills and other symptoms of anaphylactoid reactions. When the drug is administered too fast palpitations, dyspnoea, heat sensations, transient hypertension and abdominal cramps may occur during or immediately after administration. Within one hour these symptoms disappear. Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations the current evidence suggests that these adverse effects will occur with low frequency because of the low radiation doses incurred. **DOSIMETRY** The effective dose equivalent resulting from an administered activity amount of 200 MBq is 2.6 mSv in adults. The effective dose equivalent resulting from an administered activity amount of 370 MBq is 4.8 mSv in adults. **OVERDOSE** The effect of an overdose of iobenguane is due to the release of adrenaline. This effect is of short duration and requires supportive measures aimed at lowering the blood pressure. Prompt injection of phentolamine followed by propanolol is needed. Maintain a high urine flow to reduce the influence of radiation. **CLASSIFICATION FOR SUPPLY** Subject to medical prescription (POM).**MARKETING AUTHORISATION HOLDERS.** DE: GE Healthcare Buchler GmbH & Co. KG, 18974.00.00. DK: GE Healtcare B.V., DK R. 1013. FR: GE Healthcare SA, NL 18599. NL: GE Healthcare B.V., RVG 57689. NO: GE Healthcare B.V., MTnr. 94-191. **DATE OF REVISION OF TEXT** 9 August 2010 .

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References: 1. Jacobson AF *et al*. Myocardial Iodine-123 *Meta*-Iodobenzylguanidine Imaging and Cardiac Events in Heart Failure. Results of the Prospective ADMIRE-HF (AdreView Myocardial Imaging for Risk Evaluation in Heart Failure) Study. J Am Coll Cardiol 2010;55.

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