Nuclear Medicine Imaging of Knee Injuries

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Michael T. Hirschmann, Flavio Forrer, Enrique Testa, and Helmut Rasch

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M.T. Hirschmann, MD (✉)
Department of Orthopaedic Surgery and Traumatology, Kantonsspital Baselland (Bruderholz, Liestal, Laufen), Bruderholz CH-4101, Switzerland
e-mail: michael.hirschmann@ksbl.ch, michael.hirschmann@unibas.ch

E. Testa, MD
Department of Orthopaedic Surgery and Traumatology, Kantonsspital Baselland Bruderholz, Bruderholz CH-4101, Switzerland

F. Forrer, MD • H. Rasch, MD
Institute for Radiology and Nuclear Medicine, Kantonsspital Baselland Bruderholz, Bruderholz CH-4101, Switzerland

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Abstract

This chapter deals with the clinical value of nuclear medicine, in particular SPECT/CT, in patients with knee injuries. A thorough overview of nuclear medicine imaging protocols, diagnostic algorithms and the clinical value for different knee pathologies is given. These knee pathologies or variants include patients with anterior knee pain; jumper's knee; runner's knee; patellar dislocation; patellar maltracking; patellar fractures; meniscal lesions; ligament tears such as anterior cruciate ligament, posterior cruciate ligament or collaterals; Stieda-Pellegrini lesion; cartilage lesions; osteochondral lesions; overloading of a knee compartment; osteoarthritis and fractures. The clinical value is further illustrated by images and typical instructional case descriptions.

Abbreviations

CT	Computerized tomography
SPECT	Single-photon emission computerized tomography
MRI	Magnetic resonance imaging
PPV	Positive predictive value

30.1 Introduction

In the last decades, nuclear medicine imaging has undergone a significant technical evolution (Bybel et al. 2008; Collier et al. 1985; Cook and Fogelman 1996; Delbeke et al. 2009; Dorchak et al. 1993; Dye and Chew 1993; Dye and Boll 1986; Franc et al. 2012; Gnanasegaran et al. 2009; Gregory et al. 2004; Hart et al. 2008; Hogervorst et al. 2000a, b; Jeer et al. 2006; Kim et al. 2008; Lorberboym et al. 2003; Madsen 2007; Murray et al. 1990; Naslund et al. 2005; O'Connor and Kemp 2006; Petersson et al. 1998; Scharf 2009). First, there was a clear diagnostic shift from conventional planar scintigraphic imaging (bone scans), which only offered 2D images of a 3D pathology, to 3D scintigraphic imaging and single-photon emission computerized tomography (SPECT) (Dorchak et al. 1993; Dye and Chew 1993; Dye and Boll 1986; Hart et al. 2008; Hogervorst et al. 2002; Hogervorst et al. 2000a, b; Jeer et al. 2006; Kim et al. 2008; Lorberboym et al. 2003; Murray et al. 1990; Petersson et al. 1998; Van Den Eeckhaut et al. 2003; Vellala et al. 2004; Yildirim et al. 2004). Then, hybrid single-photon emission tomography (SPECT/CT) systems, which combine conventional computerized tomography (CT) with SPECT, were introduced and are now available for clinical routine use in an increasing number of institutions worldwide (Bybel et al. 2008; Delbeke et al. 2009). In the last 3 years, SPECT/CT has been increasingly recognized by the orthopaedic and sports medicine fraternity as a clinically helpful diagnostic imaging modality in patients after knee injuries or before/after surgical procedures (Hirschmann et al. 2010a, b; 2011a, b, c, d; 2012c; Horger et al. 2007; Konala et al. 2010; Scharf 2009; Strobel et al. 2012).

The introduction of multimodality hybrid imaging, mainly SPECT/CT, into clinical routine has multiplied the clinical value of nuclear medicine imaging in orthopaedics (Amarasekera et al. 2011; Biersack et al. 2012; Breunung et al. 2008; Gnanasegaran et al. 2009; Graute et al. 2010; Hirschmann et al. 2010a, b; 2011a, b, c, d; 2012b, c; Horger et al. 2007; Konala et al. 2010; Lee et al. 2008; Madsen 2008; Mohan et al. 2010; Pagenstert et al. 2009; Scharf 2009; Strobel et al. 2012). It is not only the sensitivity but also the specificity and along with these the diagnostic confidence in detecting and interpreting bone and joint pathologies that has been significantly increased (Amarasekera et al. 2011; Biersack et al. 2012; Breunung et al. 2008; Gnanasegaran et al. 2009; Graute et al. 2010; Hirschmann et al. 2010a, b; 2011a, b, c, d; 2012b, c; Horger et al. 2007; Konala et al. 2010; Lee et al. 2008; Madsen 2008; Mohan et al. 2010; Pagenstert et al. 2009; Scharf 2009; Strobel et al. 2012).

Major advantage of SPECT/CT is the combined evaluation of precise anatomical and mechanical information (CT) and of data on bone metabolism (SPECT). SPECT/CT often demonstrates disease prior to abnormalities being detected on conventional radiographs, CT or even magnetic resonance imaging (MRI) (Hirschmann et al. 2012b).

SPECT/CT visualizes the loading history of the different knee compartments (patellofemoral, medial and lateral tibiofemoral) (Hirschmann et al. 2012b). In our own work, we have further demonstrated that the intensity and distribution of SPECT/CT tracer uptake correlated with mechanical and anatomical axes (Hirschmann et al. 2012b). In patients with a mechanical varus axis, increased tracer uptake in the medial tibiofemoral knee compartment and, in patients with a mechanical valgus axis, increased tracer uptake in the lateral tibiofemoral knee compartment were observed (Hirschmann et al. 2012b). The degree of osteoarthritis according to Kellgren and Lawrence also correlated with the intensity and location of SPECT/CT tracer uptake (Hirschmann et al. 2012b). In an unpublished work, we could also demonstrate that patellar position and tilt significantly influence SPECT/CT tracer uptake intensity and distribution. Buck et al. found that increased tracer uptake in bone scintigraphy was more sensitive for medial knee pain than bone marrow oedema on MRI (Buck et al. 2009).

We strongly believe that due to its limitations and inferior diagnostic confidence, a planar scintigraphy and single SPECT should only be the exception and not the standard imaging modality anymore. In most of the patients with knee injuries, a SPECT/CT is recommended. There has been tremendous effort to establish diagnostic standards and guidelines for the use of SPECT/CT in orthopaedics and sports medicine (Hirschmann et al. 2010b; 2012c). An increasing number of clinical indications and scenarios have been identified, in which SPECT/CT holds the promise of establishing a better more specific diagnosis (Hirschmann et al. 2010a, b; 2011a, b, c, d; 2012b; Konala et al. 2010). However, further clinical studies need to explicitly determine the good and the bad indications for the use of SPECT/CT in terms of diagnostic quality, cost-efficacy, benefits to the orthopaedic surgeon and impact on further treatment.

PET/CT or PET/MRI is still experimental and has not yet reached the clinical practice but might in future enrich the diagnostic armamentarium in patients with knee injuries. Hence, we will concentrate in this chapter on SPECT/CT imaging. With this chapter, we describe the basic principles of SPECT/CT imaging and protocols in patients with knee injuries and review the current evidence for different pathologies and potential clinical applications.

30.2 SPECT/CT Imaging

SPECT/CT is a combination of 3D scintigraphy (SPECT) and a single or preferably multislice conventional computerized tomography (CT). Generally, for bone imaging, patients are injected intravenously with 10–20 mCi (340–740 MBq) of technetium-labelled diphosphonates, which reflect the osteoblastic activity in the delayed phase. Within the first minute after tracer injection, planar two-plane perfusion images and, 2–5 min after tracer injection, planar two-plane blood pool images are obtained. Finally, SPECT is performed at 3–5 h after tracer injection (delayed phase), followed immediately by a CT with the patient in the same table position. For musculoskeletal imaging, low-dose protocols, which reduce the radiation exposure to the patient, have been reported. Using our published protocol for SPECT/CT knee imaging, which includes for the CT 3 mm slices of the femoral head, 0.7 mm slices of the knee and 3 mm slices of the ankle joint, the radiation dose is approximately 3 mSv. Using this protocol, not only structural and metabolical data (pattern and intensity distribution) but additional information on anatomical and mechanical alignment of the knee joint are available.

30.3 Pathologies of the Knee

30.3.1 Patellofemoral Problems (Patellar Dislocation, Patellar Maltracking, Patellar Fractures)

Pain within the patellofemoral joint is one of the most frequent problems in orthopaedics and sports medicine (Hirschmann et al. 2011a, b). The establishment of the correct diagnosis and cause of the problem is often difficult. The history, the clinical examination and radiological investigations such as conventional radiographs, computerized tomography (CT), magnetic resonance imaging (MRI) or SPECT very often do not unambiguously guide towards the right diagnosis (Hirschmann et al. 2011a, b). Often all fail to identify the origin of the patient's pain (Hirschmann et al. 2011a, b). Conventional radiographs are the primary imaging in patients with patellofemoral problems, but in these only gross malposition, malalignment and clear osteoarthritis can be identified (Hirschmann et al. 2011a, b). CT and MRI clearly offer more anatomical detail but as static investigation do not elucidate the pathology of patellar maltracking. However, the correlation between radiographic, CT and MRI abnormalities and patellofemoral pain is poor.

Lorberboym et al. compared the findings in ^{99m}Tc-MDP-SPECT with arthroscopy in 27 patients with anterior knee pain (Lorberboym et al. 2003). They found that when compared to arthroscopy, SPECT had a sensitivity of 100 % and a specificity of 64 % for patellofemoral abnormalities (Lorberboym et al. 2003). In the patellofemoral joint, SPECT often lacks precise anatomical detail and is limited due to poor localization ability.

SPECT/CT combining the advantages of SPECT and CT provides a view into the loading and remodelling of the bone, helps to identify patellar maltracking and evaluates the efficacy of realignment procedures in offloading the patellofemoral joint (Fig. 30.1) (Hirschmann et al. 2011a, b).

30.3.2 Cartilage and Osteochondral Lesions

The importance of the integrity of the subchondral bone plate has not only recently gained increasing interest. Generally, MRI is the standard imaging procedure in patients with suspected cartilage lesions (Hayashi et al. 2012). It is able to accurately characterize the size and depth of the cartilage lesions (Hayashi et al. 2012). In addition, it has been shown that the bone oedema present in MRI is a predictive factor for outcome of these cartilage lesions. However, it is very unspecific and it remains unclear what pathophysiology the bone oedema reflects (Buck et al. 2009). The major advantage of SPECT/CT in patients before and after cartilage surgery lies in its strength to evaluate the integrity of the subchondral bone plate (Hirschmann et al. 2012b). We believe that in contrast to MRI, SPECT/CT helps to differentiate between pure chondral and osteochondral pathologies. Hence, we use SPECT/CT preoperatively to establish the optimal indication for chondral or osteochondral surgery and postoperatively to follow up patients after osteochondral repair procedures (Fig. 30.2).

Etchebehere et al. noted that bone scans precede radiographic changes in osteonecrosis of the knee (Etchebehere et al. 1998). Another established indication of SPECT/

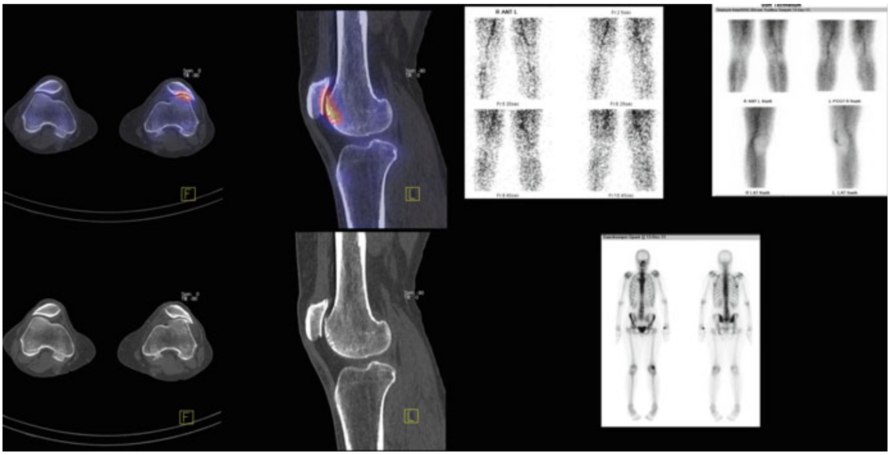

Fig. 30.1 A 55-year-old female patient presenting with symptomatic patellofemoral osteoarthritis due to patellar maltracking and increased lateral patellar tilt – SPECT/CT images show an increased ^{99m}Tc-HDP tracer uptake within the lateral part of the patellofemoral joint

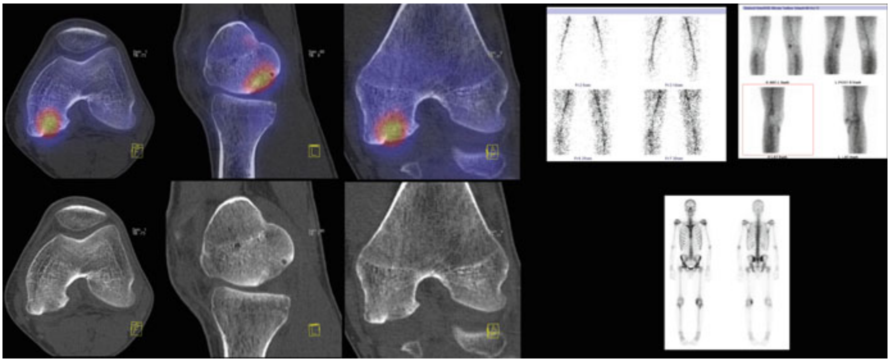

Fig. 30.2 An asymptomatic 19-year-old patient 1 year after osteochondral grafting (MaioRegen, Finceramica, Italy) due to osteochondritis of the medial femoral condyle

CT is the assessment of osteochondritis dissecans (OCD) (Konala et al. 2010). Konala et al. described that SPECT/CT was helpful in patients with pain after refixation of OCD (Konala et al. 2010). In particular in cases of delayed healing and suspected non-union, SPECT/CT proved beneficial to judge the healing and integration of the osteochondral fragment and guide further treatment (Konala et al. 2010). In our experience, SPECT/CT arthrography further improves the assessment of stability of the OCD fragment and subsequent decision-making pre- and postoperatively (Fig. 30.3).

30.3.3 Meniscal Lesions

Clearly, MRI is considered to be the gold standard in the diagnosis of meniscal lesions. Most studies looking into bone scans or SPECT for diagnosing meniscal lesions were performed before the introduction of MRI (Collier et al. 1985; Dorchak et al. 1993; Murray et al. 1990).

However, there are still some indications for nuclear medicine modalities as second-line diagnostics, for example, when a patient has metal implants around the knee joint causing extensive metal artefacts or an implanted pacemaker.

Grevitt et al. investigated 60 patients using SPECT, which then underwent an arthroscopy of the knee due to a suspected meniscal lesion (Grevitt et al. 1993). They reported a sensitivity of 90 %, specificity of 81 % and accuracy of 84 % in diagnosing meniscal lesions (Grevitt et al. 1993). Typically a crescent-shaped pattern of tracer uptake was found (Grevitt et al. 1993). Collier et al. found similar results in terms of sensitivity and specificity (Collier et al. 1985). The biggest problem with these studies is that in most of these studies, chondral and osteochondral lesions as well as the type of meniscal lesion were not taken into account. It is further unclear what the tracer uptake pattern really reflects. Some believe that the uptake is within the vascular zone of the meniscus, others believe that the traction on the coronary ligaments occurring at the time of meniscal trauma and subsequent bony lesions on the attachment site or subchondral bone are responsible for the development of this uptake pattern (Collier et al. 1985; Grevitt et al. 1993). Changes

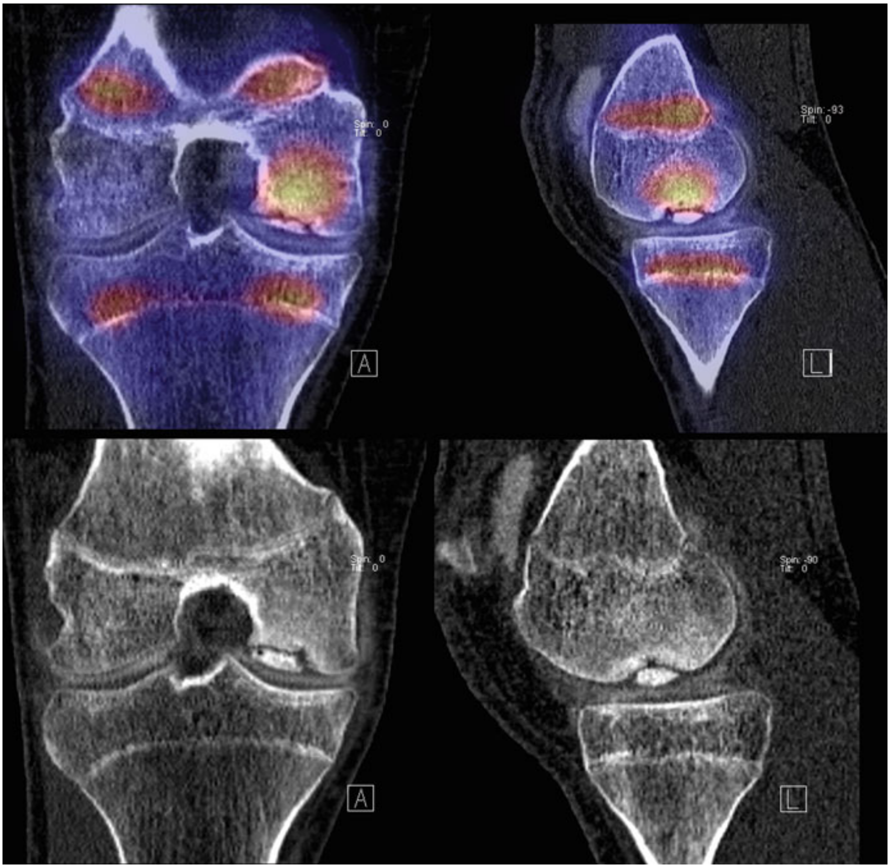

Fig. 30.3 ^{99m}Tc-HDP arthro-SPECT/CT (*upper images*) and CT (*lower images*) of a 16-year-old patient with an osteochondritis dissecans (OCD) of the right medial femoral condyle. The arthro-SPECT/CT shows an intact surface of the OCD and physiologically increased bone tracer uptake at the growth plates

within the adjacent femoral condyles are also taken into consideration for posterior horn lesions (Collier et al. 1985; Grevitt et al. 1993).

In our experience, SPECT/CT is helpful to visualize and identify mechanical overloading of the different knee compartments, which could be regularly seen in patients after total or subtotal meniscectomy (Fig. 30.4). If SPECT/CT is not available, SPECT could also be used considering its limitations. SPECT/CT is also beneficial before and after meniscal substitution surgery, e.g. using polyurethane or collagen meniscus implants. One could evaluate if the preoperatively existing SPECT/CT tracer uptake within the overloaded knee compartment disappears or is at least reduced due to the performed surgery. Using SPECT/CT, the orthopaedic surgeon, sports physician and patient have a direct view into the joint homeostasis and biological state of the knee joint (Hirschmann et al. 2010a; 2011a, b; 2012b). In a currently unpublished date, Hirschmann et al. have shown that in comparison to MRI, the overloading of the knee

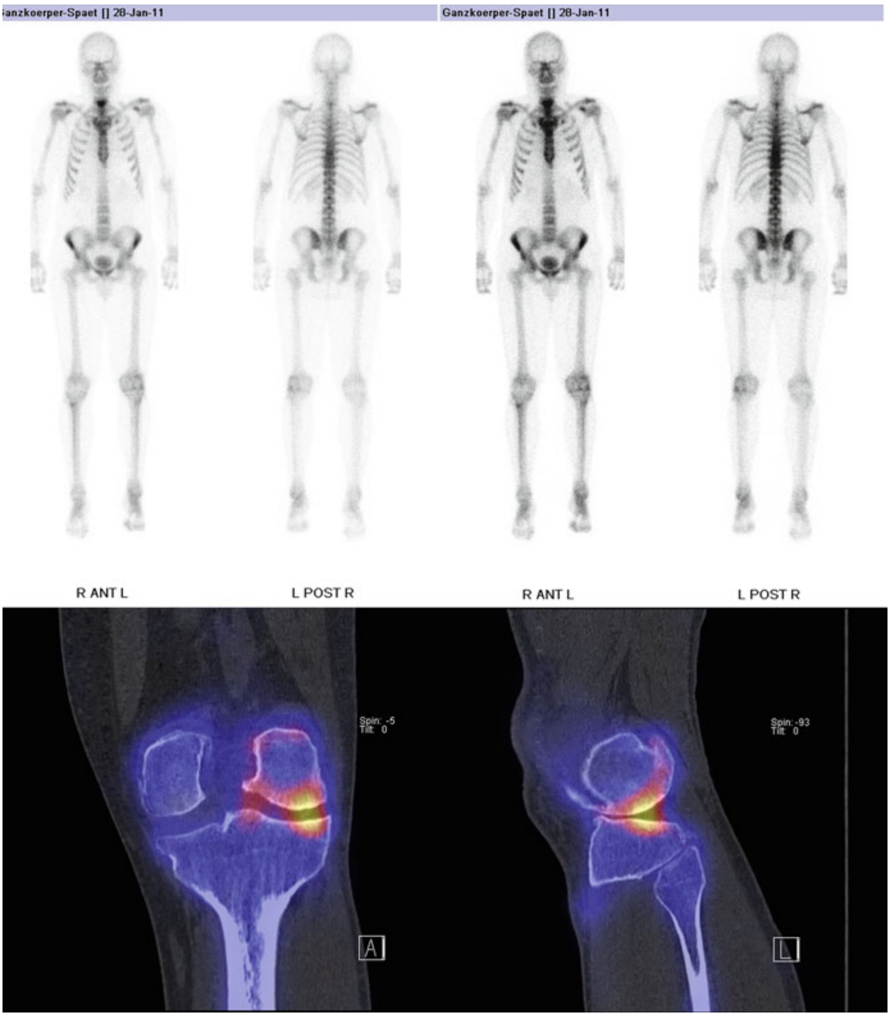

Fig. 30.4 ^{99m}Tc-HDP SPECT/CT of a 55-year-old female patient 10 years after lateral subtotal meniscectomy indicating an overloading of the lateral knee compartment

compartment can be visualized. It was found that bone marrow oedema does not reflect overloading, but bone tracer uptake does. It then guides the optimal treatment (e.g. meniscal substitution, high tibial osteotomy, cartilage or osteochondral repair).

30.3.4 Mechanical Overloading of Knee Compartments

Mechanical overloading of the knee joint is characterized by a disbalance of knee protective factors and mechanical loading of the different knee compartments. It is well understood that one of the most important factors leading to mechanical overloading of the medial tibiofemoral knee is a proximal tibial varus deformity, in which the mechanical axis passes medially from the knee centre. Mechanical overloading inevitably leads to an increased risk of osteoarthritis. A variety of nonsurgical such as deloader braces or insoles and surgical therapeutic options (e.g. distal femoral or proximal tibial osteotomies, patellofemoral realignment procedures) aim to reduce the loading in the corresponding medial, lateral or patellofemoral knee compartment.

Conventional radiographs in anterior-posterior, lateral and patella skyline views and long leg radiographs to assess the mechanical leg axis are considered to be the primary imaging in patients under suspicion of a mechanical overloading. In the last decades, bone scans and SPECT have been mainly used as second-line imaging in patients not doing well after correction osteotomy. However, in the last 5 years, the clinical value of SPECT/CT in these patients has been increasingly recognized (Hirschmann et al. 2012b). SPECT/CT offers the combined assessment of structure, mechanical and anatomical alignment and functional information. Only recently Hirschmann et al. reported that the anatomical and mechanical alignment of the knee correlated significantly with the distribution pattern and intensity values of SPECT/CT tracer uptake (Hirschmann et al. 2012b). Mechanical varus alignment showed increased tracer uptake on the medial compartment and a valgus alignment on the lateral side (Hirschmann et al. 2012b). To our knowledge, this is the first study showing a clear relationship between knee alignment and compartment-specific tracer uptake in SPECT/CT.

Based on these findings, SPECT/CT was proposed to be used in clinical practice for twofold: firstly, it should be used as preoperative imaging modality to characterize the pattern of overloading aiming for a better targeted treatment such as nonsurgical therapy, osteotomies and partial or total knee replacements. Secondly, it should also be considered for postoperative follow-up of patients after osteotomies. SPECT/CT could differentiate between optimal, over- or undercorrection (Fig. 30.5) (Hirschmann et al. 2012b).

30.3.5 Ligament Lesions

The radiological diagnostics of ligament lesions such as anterior cruciate ligament tears clearly is the domain of MRI. However, in particular in patients with a retear after ligament reconstruction, MRI could be disturbed by metal artefact splatter. In addition, the evaluation of the tunnel position as well as the assessment of tunnel widening is preferably performed on CT. Numerous authors have emphasized the benefits of 3D-CT for the assessment of tunnel position after ACL reconstruction (Basdekis et al. 2009; Hirschmann et al. 2012a; Purnell et al. 2008).

To date, bone scans or SPECT did not play an important role in the diagnostics of patients with a ligament lesion. However, Even-Sapir et al. correlated the findings of 94 SPECT/CTs of the knee with arthroscopy ($n=74$) and MRI ($n=37$) or both (Even-Sapir et al. 2002). The patients were suspected to have an ACL lesion or a meniscal tear (Even-Sapir et al. 2002). In 38 patients, an ACL injury was present (Even-Sapir et al. 2002). In these SPECT identified the indirect signs of increased

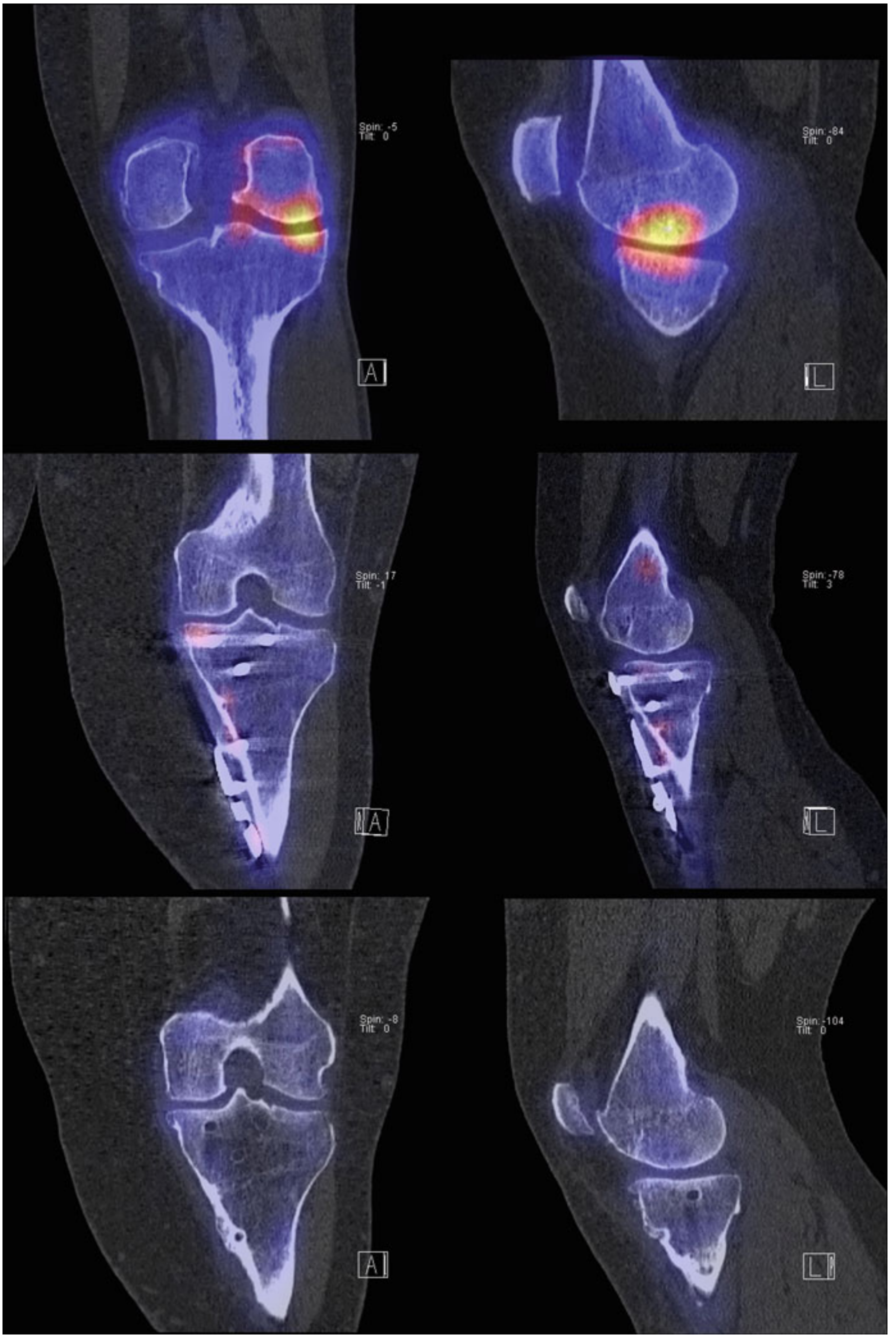

Fig. 30.5 Images of a 42-year-old female patient before and 1 year and 2 years after high tibial osteotomy for correction of varus-deformed knee. ^{99m}Tc-HDP preoperative SPECT/CT (*upper images*) showed increase tracer uptake within the medial femoral knee compartment indicating a mechanical overloading. The 2- and 2-year-follow-up SPECT/CT images showed no tracer uptake anymore indicating an adequate correction of the varus deformity

tracer uptake in the posterior lateral tibial plateau (positive predictive value 93 %, negative predictive value 97 % (Even-Sapir et al. 2002). Only in 55 % of these patients, increased tracer uptake was also seen in the lateral femoral condyle (Even-Sapir et al. 2002). On MRI bone bruise was present in 64 %, while all patients had increased tracer uptake in the posterior lateral tibial plateau (Even-Sapir et al. 2002).

In contrast, So et al. reported that an increased SPECT tracer uptake at the ACL attachment site is a primary sign of an anterior cruciate ligament lesion (So et al. 2000). The positive predictive value (PPV) of this primary sign was 94 %, while the PPV of the secondary sign of increased SPECT tracer activity in the tibia or femur was only 81 % (So et al. 2000).

Hogervorst et al. investigated the tibial bone tunnels of 68 patients 2 years after ACL reconstruction using bone scans (Hogervorst et al. 2000b). They found that increased scintigraphic uptake was associated with tibial tunnel enlargement of more than 35 % and a graft length in the tibial tunnel over 14 mm (Hogervorst et al. 2000b). The tracer uptake was also significantly correlated with tunnel enlargement, and tunnel enlargement was significantly correlated with the graft length inside the tibial tunnel (Hogervorst et al. 2000b). They further concluded that return to normal osseous tracer uptake at the tibial tunnel can take more than 2 years when fixation is more than 14 mm below the joint (Hogervorst et al. 2000b).

Just recently the clinical value of SPECT/CT was highlighted for patients after ACL reconstruction (Hirschmann et al. 2012a). We have reported a specific algorithm to analyse and report the position of the tunnels and SPECT/CT tracer uptake in patients after ACL reconstruction (Hirschmann et al. 2012a). High inter- and intraobserver reliability were reported (Hirschmann et al. 2012a). Major advantage is the combined assessment of mechanical alignment, tunnel position and loading of the joint (Fig. 30.6) (Hirschmann et al. 2012a). Its clinical value has to be seen in complex revision cases, in which all these aspects have to be taken into consideration for optimal planning of the subsequent surgical treatment.

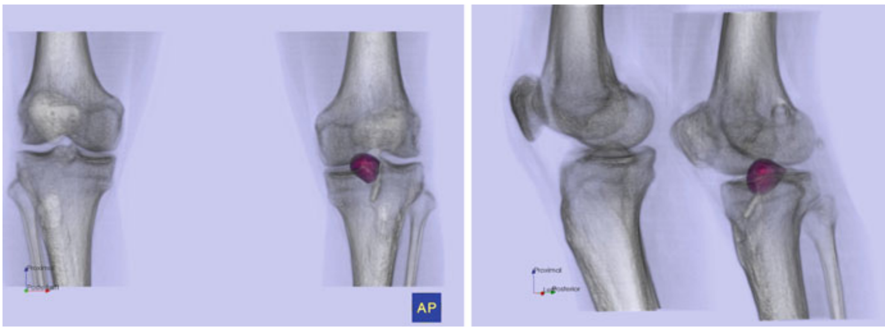

Fig. 30.6 3D reconstructed transparent SPECT/CT images of a 40-year-old patient with a cyclops lesion 1 year after ACL reconstruction (OrthoExpert©)

30.3.6 Osteoarthritis

Bone scintigraphy and SPECT and recently SPECT/CT have proven to be very sensitive for diagnosing osteoarthritis (OA) in early stages, which is the major advantage of nuclear medicine imaging over radiographs, CT or MRI (Hirschmann et al. 2012b). In conventional radiographs as well as CT and even MRI, osteoarthritis can only be diagnosed when the disease already has caused structural damage. SPECT and SPECT/CT open up new vistas into the aspect of biological joint homeostasis. In our experience, SPECT/CT enables the surgeon to precisely characterize the extent and grade of osteoarthritis. This more accurate evaluation of the grade and type of osteoarthritis of the knee could lead to a more targeted and less invasive treatment. Hart et al. found that SPECT helps the surgeon to identify if a patient is instead of total knee arthroplasty suitable for a less invasive procedure such as a high tibial osteotomy or medial unicondylar knee arthroplasty (Hart et al. 2008).

If OA and overloading of the knee joint are identified early, even before any symptoms occur, treatment could be specifically tailored to a more preventive approach. As overloading and overuse injuries are common in sports, SPECT/CT could be used to improve and develop training and prevention programmes, which consider the biological and functional state of the knee joint.

30.3.7 Shin Splint Syndrome, Fractures, Pseudoarthrosis and Osteonecrosis

Bone scans, SPECT and SPECT/CT are very sensitive and specific diagnostic tools for the diagnosis of shin splint syndromes, stress fractures, occult fractures, delayed healing of fractures and pseudoarthrosis (Marks et al. 1992; Ryan and Fogelman 1994).

Yildirim et al. evaluated the knees of 42 active asymptomatic soccer players using bone SPECT to identify stress fractures (Yildirim et al. 2004). In 66 % of patients, increased SPECT tracer uptake indicated a stress fracture (tibia 62 %, femur 5 %).

Etchebehere et al. highlighted that in case of delayed healing of fractures, bone scans are able to differentiate between avascular and hypervascular non-unions and delayed unions (Etchebehere et al. 1998). They further noted that SPECT accurately detects decreased metabolism associated with posttraumatic closure of the physeal plate, which could then lead to growth arrest and leg deformities.

30.3.8 Insertion Tendinopathies (Enthesopathy) and Friction-Related Peritendinous Disease

Insertion tendinopathies are typical overuse injuries, which at the beginning only are symptomatic during and shortly after activity (Adams 2004; Molnar and Fox 1993; Taunton et al. 1987). The iliotibial band friction syndrome is common in runners, that is why it is called runner's knee (De Geeter et al. 1995; Van Den Eeckhaut et al. 2003). It is caused by friction of the iliotibial tract on the lateral femoral epicondyle (De Geeter et al. 1995; Van Den Eeckhaut et al. 2003). Other common insertion tendinopathies of the knee are the jumper's and reversed jumper's knee (Fig. 30.7) (Adams 2004; Molnar and Fox 1993; Taunton et al. 1987).

In SPECT and SPECT/CT, all these pathologies typically show increased SPECT tracer uptake at the site of mechanical irritation or insertion (De Geeter et al. 1995; Van Den Eeckhaut et al. 2003). In contrast to planar bone scans, SPECT and SPECT/CT are able to clearly identify these lesions, which is due to its accurate localization ability.

30.3.9 Accessory Bones

The most common accessory bones of the knee are the fabella and bi- or multipartite patella (Hirschmann et al. 2011b). In our own work, we have demonstrated that SPECT/CT is able to detect symptomatic bipartite patella in patients with knee problems (Hirschmann et al. 2011b). In the case presented here, the patient, who is a world-class downhill skier, suffered from osteoarthritis of the fabellar bone in his knee, which was unambiguously identified. Using SPECT/CT, the orthopaedic surgeon or sports medicine physician is enabled to accurately localize the pain generator (Fig. 30.8). In particular clear differentiation of OA of the fabellar or lateral femoral joint is possible.

30.4 Summary and Future Perspectives

There is growing clinical evidence indicating good clinical value of SPECT/CT in patients with musculoskeletal knee problems. Although there are yet no clear diagnostic guidelines for patients with knee injuries, the use of SPECT/CT has proven

Fig. 30.7 ^{99m}Tc-HDP SPECT/CT with increased tracer uptake of the insertion of the quadriceps tendon indicating an insertion site tendinopathy of the quadriceps tendon

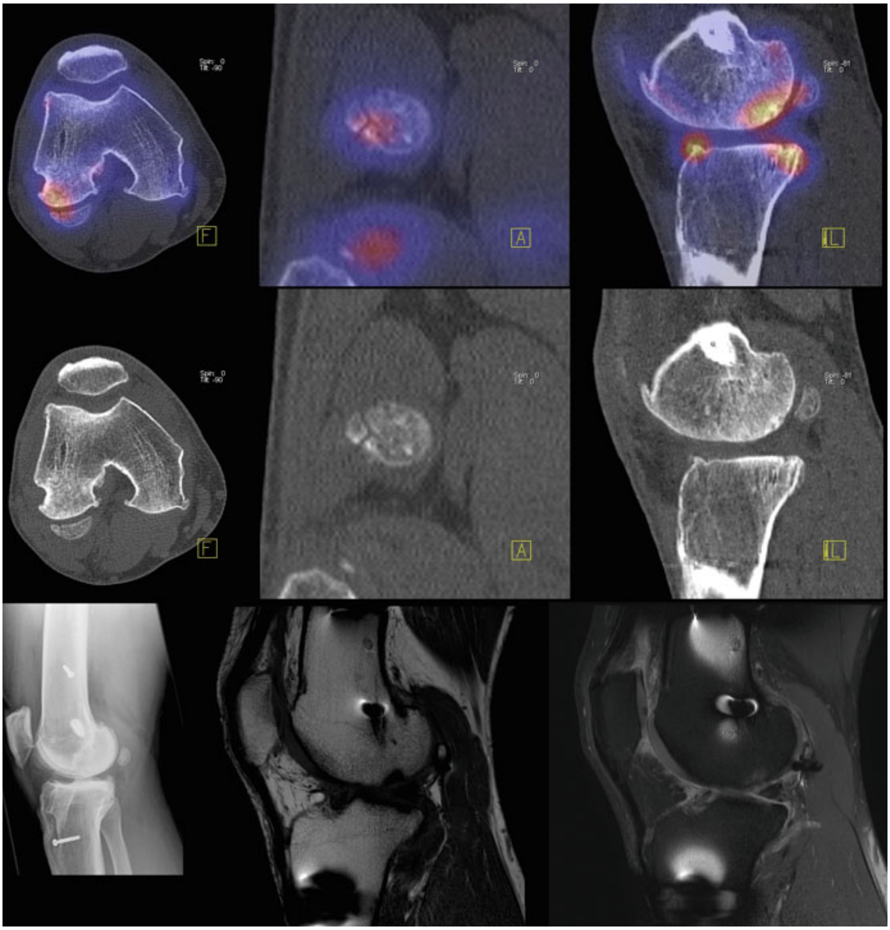

Fig. 30.8 ^{99m}Tc-HDP SPECT/CT images of a 33-year-old professional skier complaining about posterior activity-related knee pain. In contrast to radiographs, MRI or CT, SPECT/CT was able to identify the overloading of the fabellar bone

beneficial in diagnosing a variety of different knee pathologies. In comparison to bone scans or SPECT, the introduction of SPECT/CT significantly raised the diagnostic confidence, sensitivity and specificity.

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