

SPECT/CT in infection and inflammation

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Abstract Nuclear medicine procedures are part of the evaluation armamentarium used in patients with suspected or confirmed infection. The strength of functional imaging modalities rests on their being non-invasive tests that provide pathophysiological information early in the course of disease. Their limitations, related to a somewhat low specificity of radiotracers and image resolution, have largely been overcome over the last 15 years following the introduction of the hybrid SPECT/CT technology. SPECT/CT is redefining the diagnostic workup of patients with suspected or known infectious and inflammatory processes involving the musculoskeletal system as well as those with infectious and inflammatory disease located in various soft-tissue sites. Furthermore, it has been shown that in addition to improving diagnostic accuracy (by adding specificity to the inherent high sensitivity of single-photon emission tomography), SPECT/CT leads to changes in the subsequent clinical management of patients. The main indications for SPECT/CT in infection, as well as updated literature data on this topic, are presented in the following review.

Keywords SPECT/CT · Infection · Musculoskeletal system · Soft tissues

Introduction and general considerations

The development of hybrid imaging devices has been an important advance in nuclear medicine. SPECT/CT has increased the diagnostic value of procedures performed with many single-photon emitting radiopharmaceuticals, some of which were on the verge of being withdrawn from the market but have now been given a new lease of life by hybrid imaging [1]. Before the introduction of dedicated SPECT/CT cameras, various software algorithms had been developed to allow image fusion of anatomical (CT or MRI) and functional imaging studies (SPECT) [2]. Hasegawa et al. [3] demonstrated for the first time that CT data can be used for attenuation correction, allowing superior quantification of radiotracer uptake. This technology translated into the first commercial SPECT/CT system, Hawkeye™ (GE Healthcare) [4], which was followed by next-generation SPECT/CT hybrid systems, nowadays available from all major manufacturers.

Scintigraphy of infectious and inflammatory processes is performed following the administration of a variety of radiopharmaceuticals including ^{99m}Tc -diphosphonates for three-phase bone scintigraphy, polyclonal human immunoglobulins labeled with ^{99m}Tc , as well as more specific agents such as ^{67}Ga citrate, leucocytes (WBCs), either autologous labeled in vitro with ^{111}In -oxine or ^{99m}Tc -HMPAO, or anti-granulocyte antibodies labeled in vivo with ^{99m}Tc [5]. Table 1 presents the standard acquisition protocols, including the physiological targeting mechanisms, for each of the commercially available radiopharmaceuticals.

Color figures online at <http://link.springer.com/article/10.1007/s40336-014-0092-9>.

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Table 1 Targeting mechanism of the commercially available radiopharmaceuticals for imaging infection and inflammation diseases

Radiopharmaceutical/ preparation	Targeting mechanism	Pathophysiological process	Administered dose (MBq)	Effective dose (70 kg pt, mSv)
^{99m}Tc -diphosphonates	Adsorption on hydroxyapatite crystal	Enhanced vascular permeability increased osteoblastic activity	740	4.4
^{99m}Tc -polyclonal human immunoglobulins	Extravasation from bloodstream	Local hyperemia, enhanced vascular permeability	555	4.4
^{67}Ga -citrate	Transferrin and lactoferrin receptor binding, siderophores bacteria	Enhanced vascular permeability,	185	20.4
^{99m}Tc -HMPAO/ ^{111}In -oxine WBCs	Cell migration for chemotaxis	Enhanced vascular permeability, chemotaxis, cell recruitment, immune response	200/18.5	2.2/10.4
^{99m}Tc -anti-NCA-95 IgG, BW 250/183, besilesomab (Scintimun [®])		Enhanced vascular permeability, cell	700–900	5.8–7.7
^{99m}Tc -anti SSEA-1 IgM, falonesomab (Leu-Tech [®]), NeutroSpec [®])	Antigen binding	targeting, immune response	370–740	6.7–13.3
^{99m}Tc -anti-NCA-90 Fab', sulesomab (Leukoscan [®])			750	7.7

SPECT/CT studies as an add-on to scintigraphy have been extensively applied to evaluate infectious diseases in various clinical scenarios. These include circumstances that require anatomical landmarks, e.g., when soft-tissue infection has to be differentiated from osseous involvement, in cases in which it is necessary to define all sites of disease and the whole extent of the infectious process in regions with a complex anatomy, as well as when infection is suspected in regions or organs with underlying structural alterations following surgery or implantation of medical devices [5–10]. The superiority of SPECT/CT (performed with ^{111}In -labeled WBCs) over side-by-side reading of SPECT and CT images has been demonstrated in a recent study [11]. The data obtained from the CT component also make it possible to obtain attenuation-corrected scintigraphic data, thus improving on the quality of the SPECT image [12]. SPECT/CT, when compared to stand-alone SPECT, has impacted on the overall accuracy of nuclear medicine procedures [13, 14], allowing definite diagnoses to be made in the majority of patients with indeterminate scintigraphic findings in non-oncologic settings [15].

It should be recognized that adding CT to SPECT increases the radiation dose to the patient. The CT component of SPECT/CT, usually requiring a lower dose (50 mAs and 130 kV) compared with other diagnostic CT procedures, results in additional radiation exposure across the body, ranging from below 0.1 mSv for the extremities to a few mSv for the torso. However, the potential benefits to be derived from the addition of CT exceed the risks associated with the increased radiation exposure. The use of SPECT/CT in childhood requires special consideration

due to the higher risk associated with radiation exposure at a young age [16]. SPECT/CT examinations in children should be tailored to the individual patient to ensure adherence to the ALARA (“as low as reasonably achievable”) principle for radiation protection, which also means ensuring delivery of a low dose with or without the use of intravenous contrast.

In this review, we discuss the role of SPECT/CT in the field of infection and inflammation imaging performed using commercially available radiopharmaceuticals and the main referral indications based on the published literature evidence. Original papers on SPECT/CT in infectious disease were identified in the PubMed database in May 2014. The following combination of keywords was used: “SPECT”, “SPECT/CT”, “nuclear medicine” and “infection”, “sepsis”, “osteomyelitis”, “spondylodiscitis”, “endocarditis”, “pyogenic”, “fever”, “prosthesis”, “abscess”, “cholecystitis”. We excluded all papers with fewer than 10 patients and all case reports. Twenty-eight papers were selected (Table 2).

SPECT/CT in bone infection and inflammatory diseases

Osteomyelitis (hematogenous, secondary to a contiguous focus of infection, or associated with vascular insufficiency) is most commonly caused by pyogenic bacteria and mycobacteria. The clinical manifestations are heterogeneous, depending on the age of the patient, the specific causative microorganism, the anatomical area involved and/or the segment of bone affected, the route of

Table 2 Summary of the main manuscripts on the use of SPECT/CT in infection and inflammation

References	Year of publication	Patients, <i>n</i>	Study type	Radiopharmaceutical (s)	Endpoint (s)
Mixed infections					
Bar-Shalom et al. [6]	2006	82	R	¹¹¹ In-oxine-WBC ⁶⁷ Ga-citrate	Added value of SPECT/CT
Roach et al. [126]	2006	18	R	⁶⁷ Gallium citrate	Diagnostic accuracy of SPECT/CT
Ingui et al. [11]	2007	16	R	¹¹¹ In-oxine-WBC ⁶⁷ Gallium citrate	Added value of SPECT/CT
Erba et al. [20]	2013	235	R	^{99m} Tc-HMPAO-WBC	Added value of SPECT/CT
Horger et al. [19]	2007	31	P	^{99m} Tc-DPD	Added value of SPECT/CT
Osteomyelitis, skull and jaw					
Chakraborty et al. [32]	2013	20	R	^{99m} Tc-MDP	Diagnostic accuracy of SPECT/CT
Sharma et al. [33]	2013	13	R	^{99m} Tc-MDP	Added value of SPECT/CT
Bolouri et al. [34]	2013	42	R	^{99m} Tc-DPD	Diagnostic accuracy of SPECT/CT
Osteomyelitis, diabetic foot infection					
Filippi et al. [7]	2009	18	P	^{99m} Tc-HMPAO-WBC	Diagnostic accuracy of SPECT/CT
Heiba et al. [60]	2010	213	P	^{99m} Tc-MDP & ¹¹¹ In-oxine-WBC	Diagnostic accuracy of SPECT/CT
Erdman et al. [62]	2012	77	R	^{99m} Tc-HMPAO-WBC	Novel standardized hybrid image-based scoring system to diagnose diabetic foot infection
Aslangul et al. [58]	2013	55	P	⁶⁷ Ga citrate	Diagnostic accuracy of SPECT/CT
Heiba et al. [59]	2013	227	R	^{99m} Tc-MDP & ¹¹¹ In-oxine-WBC	Diagnostic accuracy of SPECT/CT
Vouillarmet et al. [61]	2014	29	R	^{99m} Tc-HMPAO-WBC	Diagnostic accuracy of SPECT/CT after antimicrobial treatment
Spondylodiscitis					
Fuster et al. [76]	2012	34	P	⁶⁷ Ga citrate & [¹⁸ F]FDG	Comparison between SPECT/CT and PET/CT
Lehman et al. [128]	2013	212*	R	^{99m} Tc-MDP	Identification of causes of spine/sacrum pain
Lazzeri et al. [82]	2010	72	P	¹¹¹ In-oxine biotin	Added value of SPECT/CT
Prosthetic joint Infections					
Kaisidis et al. [94]	2005	21	R	Leukoscan	Diagnostic accuracy of SPECT/CT
Filippi L et al. [30]	2006	28	P	^{99m} Tc-HMPAO-WBC	Added value of SPECT/CT
Graute et al. [31]	2010	31	R	^{99m} Tc-BW 250/183 antibodies	Added value of SPECT/CT
Kim et al. [92]	2014	164	R	^{99m} Tc-HMPAO-WBC	Added value of SPECT/CT
Infectious endocarditis					
Erba et al. [8]	2012	131	P	^{99m} Tc-HMPAO-WBC	Diagnostic performance WBC scintigraphy
Hyafil et al. [102]	2013	42	P	^{99m} Tc-HMPAO-WBC	Diagnostic performance of WBC scintigraphy
Cardiac implantable electronic device					
Litzler et al. [101]	2010	13	P	^{99m} Tc-HMPAO-WBC	Diagnostic accuracy of SPECT/CT and treatment response
Erba et al. [9]	2013	63	P	^{99m} Tc-HMPAO-WBC	Diagnostic performance of WBC scintigraphy
Vascular prosthesis infection					
Lou et al. [117]	2010	11	R	^{99m} Tc-HMPAO-WBC	Diagnostic accuracy of SPECT/CT
Erba et al. [10]	2014	55	P	^{99m} Tc-HMPAO-WBC	Diagnostic performance of WBC scintigraphy
Abdominal infections					
Arabi et al. [127]	2013	53	R	^{99m} Tc iminodiacetic acid	Added value of SPECT/CT

contamination, systemic and local host factors, as well as the presence of underlying comorbidities. Laboratory parameters are generally elevated in acute disease. X-rays are used to exclude other diseases (e.g., fractures, tumors) that can mimic osteomyelitis; however, it should be noted that X-rays show bone changes around 10–21 days later; this explains the low and variable sensitivity (43–75 %) and specificity (75–83 %) of X-ray evaluations [17]. MRI is highly sensitive for detecting osteomyelitis from the very early phase of the disease (as early as 3–5 days), with a sensitivity of 82–100 % and specificity of 75–96 %. When the symptoms are not localized or if there is a clinical suspicion of multifocal osteomyelitis, bone scintigraphy is performed [18]. Bone scanning has a high sensitivity and specificity (over 90 %) for diagnosing osteomyelitis in normal bone. The specificity decreases to 35 % in the case of post-traumatic or post-surgical osteomyelitis. In these clinical scenarios, SPECT/CT increases the specificity of bone scintigraphy by decreasing the number of false-positive and equivocal findings [19]. In cases in which bone scanning does not provide the expected answer to the clinical question, WBC scintigraphy should be considered as the next diagnostic step. The acquisition protocol for WBC scintigraphy in patients with suspected osteomyelitis of a complicated bone should include at least two acquisitions after the injection of the tracer: delayed (3–4 h) and late (20–24 h). Early imaging, at between 30 min and 1 h after tracer injection, can be used optionally as a surrogate for bone marrow uptake [20]. WBC scintigraphy has a diagnostic accuracy of up to 89 % and sensitivity and specificity values ranging from 83 to 89 % and from 84 to 90 %, respectively [21–24]. In the event of doubtful images with suspected bone marrow expansion, imaging with ^{99m}Tc -colloids can be added to reduce the false-positive rate [25]. The presence of abnormal WBC uptake, characterized by time-dependent increases in intensity or extent between the delayed and late planar images, is the criterion for defining a study positive for skeletal infection on visual analysis. By contrast, uptake that is stable over time or that decreases slightly over time in intensity and extent is considered to represent inflammation [26]. The use of a time- and decay-corrected acquisition protocol is recommended to reduce operator interference and bias [20]. Semi-quantitative analysis, performed by drawing regions of interest and calculating target-to-back-ground ratios, may also be helpful when visual interpretation is equivocal. Using these parameters a diagnostic accuracy of WBC scintigraphy of 94.5 % has been reported [27]. Anti-granulocyte scintigraphy with monoclonal antibodies also shows good performance indices, with a sensitivity of 81 % and specificity of 84 % for diagnosis of infection, and higher values for lesions in the appendicular as compared with the axial skeleton [28].

The addition of SPECT/CT has been shown to allow optimized diagnosis and localization of infectious sites using both ^{67}Ga and WBCs (labeled with either ^{111}In or ^{99m}Tc -HMPAO) in up to 55 % of patients with newly diagnosed osteomyelitis [6, 29] or relapsing infection in bone with post-traumatic structural abnormalities [30, 31]. The value of SPECT/CT lies in its ability to provide precise anatomical localization and delineation of the extent of the infectious process already identified on planar images (Figs. 1, 2).

Skull and jaw

Infection of the skull, both primary and post-surgical, is diagnosed in general by neurological examination, laboratory tests and imaging (CT and MRI). In specific cases additional evaluation is required. The use of hybrid imaging has improved diagnosis of osteomyelitis of the skull [32, 33]. Radiolabeled diphosphonates and 2-deoxy-2- ^{18}F fluoro-D-glucose (^{18}F -FDG) are the most commonly used radiopharmaceuticals. The addition of SPECT/CT to three-phase bone scintigraphy was found to help in localizing abnormal tracer uptake, with CT providing additional information, such as the presence of destructive changes in some patients [32]. SPECT/CT using a flat-panel device has been performed in patients with suspicion of osteomyelitis of the jaw and its performance was compared with those of conventional orthopantomography, planar bone scintigraphy and stand-alone CT. SPECT/CT improved the specificity and accuracy of planar bone scintigraphy (86 vs 71 % and 98 vs 95 %, respectively) and also showed a higher sensitivity than stand-alone CT (79 %) and conventional orthopantomography (66 %) in assessing the presence of osteomyelitis of the jaw [34].

Appendicular skeleton

Hand and wrist

Disorders of the hand and wrist, a region with a multitude of articulating joint surfaces and joint spaces, are difficult to assess both clinically and radiologically. SPECT/CT bone scintigraphy shows good sensitivity and specificity for the assessment of painful conditions of the wrist [29, 35–38]. In particular, bone SPECT/CT can detect pathological processes that are not demonstrated by other imaging modalities, such as post-traumatic bone remodeling and occult fractures at the metacarpal interface, and can precisely localize hot spots seen on planar bone scans. Although, on scintigraphy, these hot spots may appear similar in extent, intensity and location, they may be due to different underlying pathologies and it is essential to establish the correct diagnosis to plan further treatment.

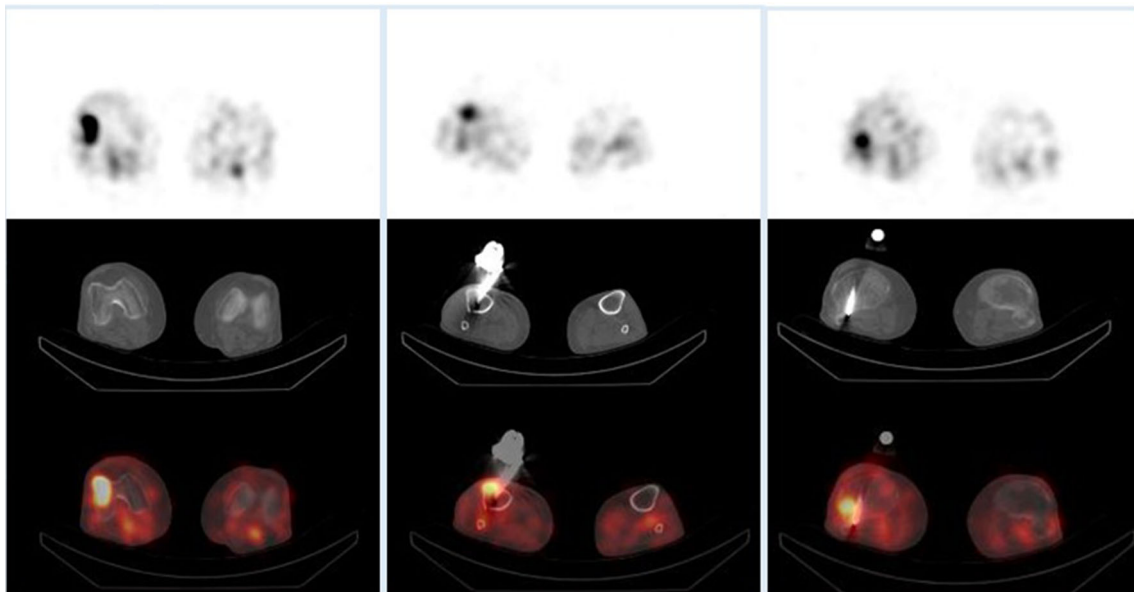


Fig. 1 Example of SPECT/CT images (transaxial view at different levels) in a patient with post-traumatic osteomyelitis of the right tibia. Focal sites of increased ^{99m}Tc -HMPAO WBC uptake are evident at the proximal part of the anterolateral aspect of the right leg, resulting at the tibial plateau and at the proximal tibia on SPECT/CT images,

along the length of the fixator screws resulting at the tibial plateau and at the proximal tibia on SPECT/CT images, along the length of the fixator screws (*upper panel* emission images, *middle panel* CT images, *lower panel* superimposed SPECT/CT images) (color figure online)

Simultaneous SPECT/CT imaging of both hands may be beneficial in the assessment of inflammatory disorders such as rheumatoid or psoriatic arthritis. The combination of CT arthrography and SPECT/CT in a single investigation, called SPECT/CT arthrography, enables visualization of critical structures such as the scapholunate and lunotriquetral ligaments, the triangular fibrocartilage complex and the articular cartilage [39]. Patients with contraindications to MR or with metal implants may be the main beneficiaries from the addition of SPECT/CT.

Shoulder and elbow

Many degenerative, inflammatory, neoplastic or traumatic conditions lead to pain and/or functional impairment of the shoulder. Limited data have described the use of ^{99m}Tc -DPD SPECT/CT of the shoulder. SPECT/CT is used mainly as a problem-solving tool in individual patients if and when other imaging methods are inconclusive. Initial efforts to define loosening of the humeral or glenoid component or to identify causes of sustained pain, such as acromioclavicular joint osteoarthritis or subacromial impingement, have been promising [40].

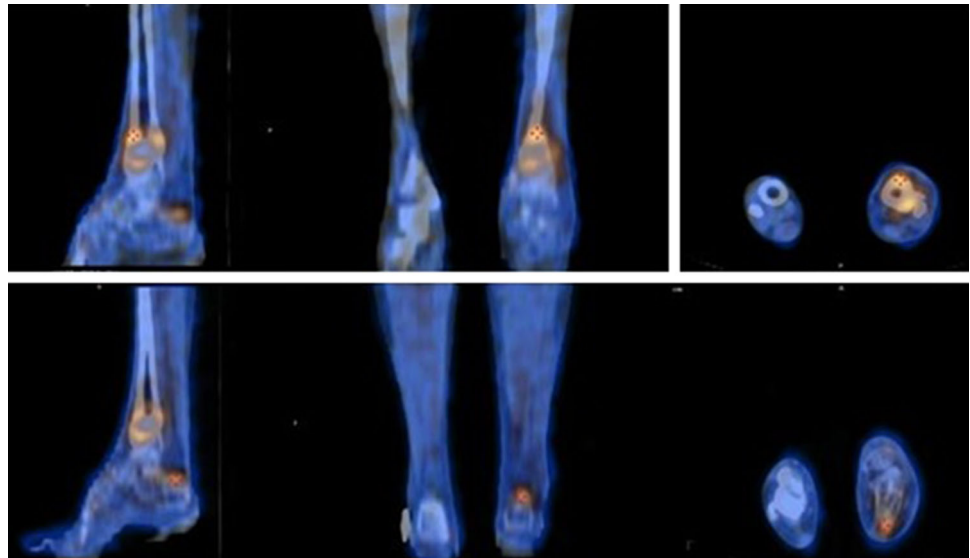
Foot

Due to the close proximity of multiple small bones and complex joints, clinical evaluation of the painful foot is also often challenging. In clinical practice it is often

necessary to evaluate the extent of osteoarthritis in the foot and this can be done accurately using SPECT/CT, thus facilitating therapy planning (corticosteroid injection or arthrodesis). Bone SPECT/CT has been shown to allow excellent localization of osteoarthritic changes in the foot, performing significantly better than CT or planar bone scintigraphy [41], and prompting a modification of the treatment plan in up to 78 % of patients [42]. Bone SPECT/CT can be used for the post-arthrodesis evaluation of the foot, to assess non-union or the development of osteoarthritis in adjacent joints due to mechanical overload, as well as to evaluate bone healing in calcaneal fractures after osteosynthesis and the development of subtalar joint osteoarthritis [43].

One of the most commonly encountered complications in diabetic patients is osteomyelitis of the foot. Early diagnosis of diabetic foot infection is important to define further patient management. Three-phase bone scintigraphy shows high sensitivity even in the absence of signs and symptoms (69–100 %). Nevertheless, fractures, neuropathic joints, and even pedal ulcers can all yield positive three-phase bone scans, making the specificity of this method relatively low: 30–59 %, with an even lower value (10 %) reported in one series [44–52]. The sensitivity of ^{111}In -oxine-labeled WBCs for the diagnosis of diabetic foot infection ranges from 75 to 100 % and the specificity from 69 to 89 % [44, 47, 48, 53–55], while in the case of ^{99m}Tc -HMPAO labeling these performance indices range from 86 to 93 % and 80 to 98 %, respectively [51, 56, 57].

Fig. 2 SPECT/CT images (*left panel* sagittal, *middle panel* coronal and *right panel* transaxial images at two different levels) in a patient with post-traumatic osteomyelitis of the left tibia. A focal site of increased ^{99m}Tc -HMPAO WBC uptake is evident at the distal tibia; a smaller additional focus of ^{99m}Tc -HMPAO WBC uptake is also evident at the tibial–calcaneal joint (color figure online)



In diabetic foot infection, WBC SPECT/CT can increase the specificity of the test. Adding the CT component has been suggested as a substitute for performing ^{99m}Tc -MDP bone scanning. SPECT/CT can discriminate bone involvement from soft-tissue localization of the infectious process resulting in a change in study interpretation in up to 53 % of cases both with ^{67}Ga -labeled and radiolabeled WBCs [6, 7]. Coupling ^{67}Ga SPECT/CT with bone puncture reduced the need for antibiotic treatment in 55 % of suspected cases [58]. WBC SPECT/CT increased the number of patients undergoing more selective bone resection instead of major amputations and shortened the duration of hospitalization [59, 60]. In addition, negative WBC SPECT/CT was demonstrated to represent a good marker for diagnosis of diabetic foot osteomyelitis remission and could therefore be very useful in guiding antibiotic therapy [61]. The integration of WBC SPECT/CT findings into a recently proposed new Composite Severity Index was found to be of prognostic value in a preliminary study [62]. WBC SPECT/CT acquisition improves diagnostic accuracy, at least for the mid and hind foot, whereas its role in evaluation of the forefoot is still a matter of debate. In evaluation of the metatarsal bones and toes, their relatively small size might make it difficult to discriminate bone from soft-tissue infection even with SPECT/low-dose CT [63]. It remains to be seen whether the use of new-generation SPECT/multislice CT equipment will make it possible to overcome these challenging obstacles.

Axial skeleton

Persistent back pain is present in about 10–20 % of patients after lumbar fusion surgery (LFS). This may be related to loosening of the metallic implants or to a failure of the

graft to immobilize the fused segments. However, infection also needs to be ruled out. Planar radiography can identify lytic zones around metallic implants as well as their malpositioning and demonstrate the presence of degenerative spine disease, but not the degree of the disease activity [64]. Despite the development of more advanced software, CT images are often degraded by streak artifacts caused by the metal implants [65]. Depending on the material, orthopedic implants can affect the image quality of MRI scans [66, 67]. Bone SPECT/CT has been reported to detect instability of the spondylodesis [68], leading to a change in the diagnostic category in approximately half of patients with lower back pain after LFS [69].

Vertebral osteomyelitis accounts for up to 10 % of all cases of osteomyelitis and commonly affects the elderly. MRI, showing a diagnostic accuracy of 90 %, is currently the modality of choice when spinal infection is suspected, particularly primary spinal infection [70]. However, post-surgical structural changes may hamper correct interpretation of MRI, both in the diagnostic phase and during follow-up and disease monitoring [71–73]. CT-guided biopsy has a specificity of 100 % but because of its variable sensitivity, ranging between 58 and 91 % [74], and its invasiveness, this procedure is not routinely employed. At present, ^{18}F -FDG PET/CT is the first-choice functional test for diagnosis in patients with a high suspicion of spinal infection and potentially for the follow-up of patients after antibiotic treatment. It has an extremely high sensitivity, about 99.9 %, but a lower specificity, 87.9 % [75, 76]. Three-phase bone scintigraphy is of limited value in the spinal region due to the presence of major vessels and also due to its overall high sensitivity but lower specificity. Complementary ^{67}Ga scintigraphy is often used to enhance the specificity of the study. However, this dual-tracer

approach is time consuming [77]. SPECT/CT improves the specificity of bone scintigraphy, particularly when osteomyelitis is located in the lower vertebral column; it may spare the need to combine data deriving from scintigraphy with ^{67}Ga and bone scintigraphy, and it increases the sensitivity for diagnosis of soft-tissue infection [15, 78]. Radiolabeled WBC imaging can give false-negative results, with the site of infection often appearing as a “cold spot” [79]. The sensitivity and specificity values of WBC scintigraphy for diagnosis of vertebral osteomyelitis range from 63.4 to 83.8 % and from 54.9 to 100 %, respectively. SPECT/CT improves the specificity of stand-alone SPECT by distinguishing, on the basis of pattern of uptake, between different spinal diseases [64]. In spinal infections, the primary site is the intervertebral disc or the endplates with secondary destruction of the vertebral bodies. As seen with ^{18}F -FDG PET/CT, diagnosis in patients with suspected spondylodiscitis is improved by taking into account the pattern of uptake in the image interpretation; this pattern separates them from patients with spondylitis or unspecific findings [80].

Due to the relatively low performance of conventional SPECT radiopharmaceuticals for the diagnosis of spinal osteomyelitis, new agents have been investigated for this specific clinical question. $^{99\text{m}}\text{Tc}$ -ciprofloxacin was found to show a sensitivity of 100 % but a specificity of up to 74 %, even with SPECT. The false-positive rate is high, particularly in the early post-operative setting [81]. ^{111}In -biotin SPECT/CT demonstrated an accuracy of 93 % for the diagnosis of spinal infection [82], but this radiopharmaceutical is still obtained only as an in-house preparation and is not yet commercially available.

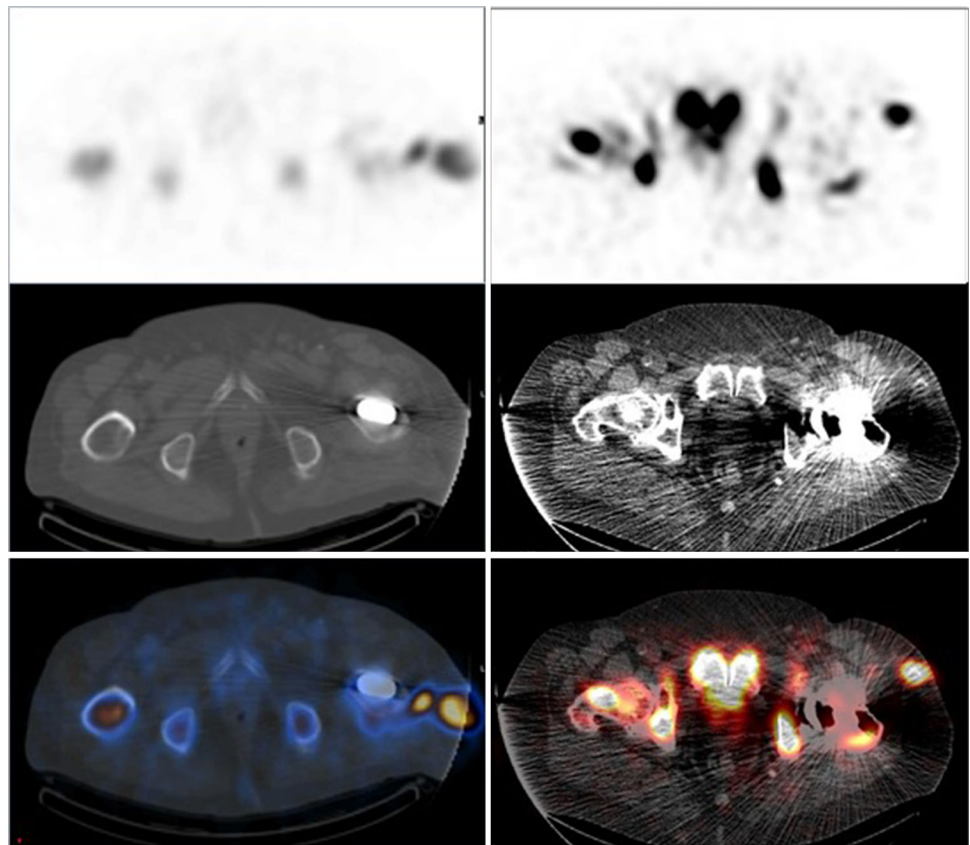
SPECT/CT in orthopedic prosthetic infection

While radiographic techniques can easily diagnose prosthetic failure caused by heterotopic ossification, fracture and dislocation, the differential diagnosis between aseptic loosening, which occurs in over 25 % of all prostheses, and infection, which occurs with 1–2 % of primary implants and with 3–5 % of revisions, is challenging. Joint aspiration with Gram stain and culture (considered the gold standard) has variable sensitivity, ranging from 28 to 92 %, but high specificity, ranging from 92 to 100 %. Plain radiographs are neither sensitive nor specific and CT and MRI may be limited by hardware-induced artifacts (this limitation may also apply to the CT component of SPECT/CT procedures and warrants careful consideration in this setting too). Functional imaging modalities are the test of choice for this differential diagnosis. The inherent limitation due to poor anatomical landmarks has been overcome with the availability of hybrid imaging (SPECT/CT and

PET/CT) thus improving the diagnostic accuracy of scintigraphy. $^{99\text{m}}\text{Tc}$ -HDP bone SPECT/CT has recently been shown to be a good tool for assessing painful knee prostheses, confirming mechanical loosening and ruling out other pathologies such as infections or patellofemoral osteoarthritis [83]. By assessing the uptake in the three knee joint compartments (patellofemoral, medial tibiofemoral, lateral tibiofemoral) and combining this with morphological and metabolic data, SPECT/CT provides important information for therapy planning, e.g., for choosing between partial and total joint arthroplasty. Bone SPECT/CT of the knee prosthesis indicates the position of the prosthesis as well as the presence of joint effusion, osteolysis and fractures. Hirschmann et al. implemented a standardized approach for the evaluation of radiolabeled diphosphonate uptake in painful knee implants; they reported high inter- and intraobserver agreement and provided evidence for the diagnostic impact of bone SPECT/CT in 83 % of 23 consecutive patients. Patellofemoral osteoarthritis (11 patients), loosening of the tibial component (3 patients) and of the femoral component (2 patients) were the main diagnoses made with SPECT/CT [84–86]. A novel four-dimensional SPECT/CT approach has been shown to correlate tracer uptake and joint replacement component positioning in patients after total knee arthroplasty, with excellent inter- and intraobserver agreement. It may become the evaluation standard of the future [87, 88]. Recently, SPECT/CT arthrography of the knee was introduced to increase the value of SPECT/CT alone. This technique allows visualization of cartilage, menisci, synovial structures and loose bodies after intra-articular administration of contrast medium [89].

Bone SPECT/CT is frequently used for the routine clinical evaluation of hip prostheses, including situations in which there is a suspicion of infection. However, there is only limited literature available to support this application; in particular, there is a lack of prospective targeted studies [90]. The main radiopharmaceuticals used for the diagnosis of prosthetic infection are autologous radiolabeled WBCs (either with $^{99\text{m}}\text{Tc}$ -HMPAO or ^{111}In -oxine), implemented as a stand-alone procedure or in combination with bone marrow scintigraphy. This test has a diagnostic accuracy of about 89 %, a sensitivity of 83–89 % and a specificity of 84–94 % [23]. SPECT/CT further increases the diagnostic accuracy, providing better anatomical localization, defining whether the infection extends to the bone and joint, and discriminating between involvement of the prosthesis and/or soft tissue [30, 91–93]. The use of $^{99\text{m}}\text{Tc}$ -anti-granulocyte antibody SPECT/CT significantly improves the performance of this test for diagnosis and localization of suspected low-grade prosthetic joint infection, giving sensitivity, specificity, positive, and negative predictive values of 89, 73, 57, and 94 %, respectively [31, 94]. Moreover, in

Fig. 3 SPECT/CT images in two patients with infection of the prosthetic hip. SPECT/CT images (*upper panel* emission images, *middle panel* CT images, *lower panel* superimposed SPECT/CT images) clearly localize the sites of increased ^{99m}Tc -HMPAO WBC uptake, showing them to be limited to peri-prosthetic soft tissue (*left panel*) or to involve both soft tissue and the posterior aspect of the hip prosthesis (*right panel*) (color figure online)



patients with suspected post-traumatic chronic osteomyelitis SPECT/CT makes it possible to differentiate between soft-tissue and bone infection and to precisely localize cortical, corticomedullary and subperiosteal foci, i.e., with a sensitivity of 100 % and specificity of 89 % [93] (Fig. 3). SPECT/CT also increases the level of interobserver agreement, thus suggesting that this method of imaging offers greater reliability.

SPECT/CT in soft-tissue infection

All tissues with a density different from that of bone are defined as soft tissues and they include the skin, muscles and abdominal and thoracic organs. Soft-tissue infection (STI) can occur either by hematogenous spread of microorganisms or by local contamination, including surgical infection, or diffusion from adjacent areas. In general, STIs are classified according to their location, clinical and pathogenic features. They frequently present with non-specific signs and symptoms and therefore require invasive procedures such as histology sampling or biopsy for microorganism isolation. STIs, in particular those caused by *S. aureus*, are a growing cause of morbidity [95] and hospitalizations [96]. One special category is that of post-operative STIs, particularly those occurring in elderly

patients. Ultrasound is widely used for the assessment of suspected STIs. It is readily available, can be performed quickly even in an emergency setting, and allows guided biopsies. Conventional X-rays and CT scans are ancillary investigations, but they may be of value in thoracic infections. MRI is the best option, particularly in the presence of associated musculoskeletal infections.

Due to the variety of possible sources of infection in patients presenting with symptoms and signs of STIs, especially ones involving deep soft tissues, the optimal imaging modality should be capable of exploring the whole body and of providing high-resolution images. For example, ^{18}F -FDG PET/CT is a good option in cases of fever of unknown origin [97, 98], while ^{99m}Tc -WBC SPECT/CT should be preferred when the patient presents with septic fever and a high pre-test probability of bacterial infections.

SPECT/CT in cardiovascular infection

Diagnosis of infectious endocarditis (IE) is essentially clinical. Microbiological tests for germ characterization and echocardiography (either transthoracic or transesophageal) for visualization of vegetations and local complications are needed to formulate the diagnosis according to the modified Duke criteria [99], while additional imaging techniques are necessary for the detection of emboli [100]

which occur with higher frequency in the presence of vegetation greater than >10 mm in size, with irregular profile and localized at the anterior leaflet of the mitral valve (size and site probability criteria). The Duke classification has a sensitivity of 80 %, being associated with an at least 20 % rate of doubtful cases. Nuclear medicine techniques may be of value in cases of undetermined echocardiographic findings (i.e., marantic vegetations, artifacts deriving from a mechanical prosthesis or the device catheter) as well as for the detection of emboli. Furthermore, treatment discontinuation is determined empirically (the standard duration is 6 weeks of treatment) since fever, WBC count, erythrocyte sedimentation rate and C-reactive protein may normalize within a few days of starting antibiotic therapy. The real breakthrough for the use of nuclear medicine procedures in IE was made following the introduction of SPECT/CT and PET/CT. An in-depth assessment of the region of the heart is impossible without the possibility of acquiring 3D images of the thorax. ^{99m}Tc -HMPAO WBC SPECT/CT has been shown to have the ability to accurately diagnose cardiac and additional unsuspected extra-cardiac sites of infection in up to 41 % of patients with IE [8, 101–103]. SPECT/CT is, therefore, mandatory when WBC scintigraphy is performed in cases of suspected IE (Fig. 4).

The rate of infection of cardiac implantable electronic devices (CIEDs) ranges from 1 to 7 % and is associated with significant morbidity and mortality [104]. Staphylococci are the main etiological agents, present in 60–80 % of cases, while Gram-negative bacilli are found in 5–10 %. In the remaining cases, cultures are most often negative. The majority of infections begin in the surgical pocket. When the infection persists, it may progress through the catheter leads and produce a systemic infection involving the bloodstream and/or endocardium. In other cases, systemic involvement is caused by colonization of the leads by bacteremia that originated in other foci, as can be seen in healthcare-related procedures; vascular catheter-related bacteremia is an example of this scenario [105]. The extent of the process may be underestimated in patients presenting with localized pocket infections. In fact, when local manifestations are present at the site of the device implantation, associated infection of the intravascular part of the leads can often occur (in up to 79 % of patients) [106]. Imaging modalities that can define the extent of the infectious process should always be considered. In addition, since these infections almost invariably imply bacteremia, metastatic sites of disease including septic arthritis, osteomyelitis, and/or endophthalmitis are frequent. CIED infections rarely respond to conservative management with antibiotics [107] and usually require complete removal of all hardware [108]. Some years after the initial implantation, device replacement may become necessary due to battery

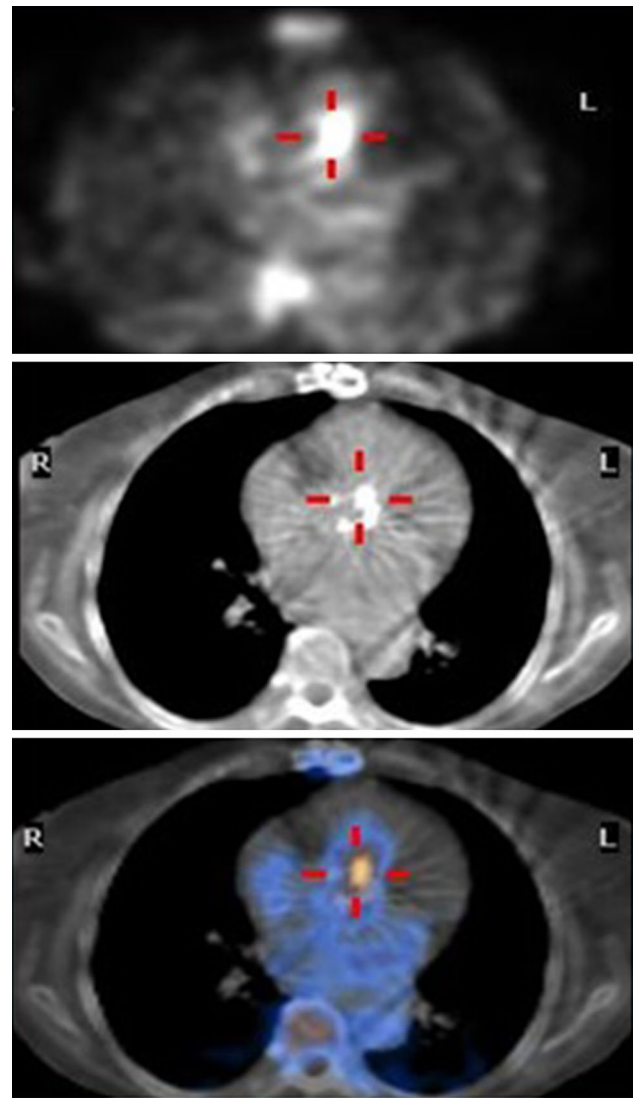


Fig. 4 Radiolabeled WBC scintigraphy in a patient with suspected infectious endocarditis of the mechanical aortic valve. SPECT/CT images (*upper panel* emission images, *middle panel* CT images, *lower panel* superimposed SPECT/CT images) clearly depict and localize the focus of increased ^{99m}Tc -HMPAO WBC uptake at the prosthetic valve (color figure online)

depletion or for upgrades. Infection rates are higher with replacement CIEDs than with initial implants [109].

The diagnosis of CIED infection is generally based on microbiological assessment of cultures of the blood and of exudates from the pocket, and transesophageal echocardiography, which can also be used to define the likelihood of disease according to the Duke criteria [99, 110]. Caution is warranted and the Duke criteria, originally developed for diagnosing IE, should not be applied in cases of suspected CIED infections without implementing appropriate measures, such as clinical assessment of the surgical pocket (although a diagnostic gold standard is still lacking) and evaluation of echocardiographic findings. However, even

when implementing these measures, the extent of CIED infection can still be underestimated. While several nuclear medicine techniques have been used to evaluate patients with suspected or ascertained CIED infection, it is the introduction of hybrid imaging that has revealed the real usefulness of these procedures. ^{99m}Tc -HMPAO-WBC SPECT/CT has been shown to be of value in defining the presence of CIED and left ventricular assist device infection and in evaluating its extent [9, 111–113], leading to improved patient management [101, 113]. ^{99m}Tc -HMPAO-WBC SPECT/CT showed a sensitivity of 94 % for CIED infection, with no false-positive results. False-negative ^{99m}Tc -HMPAO-WBC SPECT/CT cases were most likely related to infections caused by low leukocyte recruiting microorganisms [114] such as *Candida* spp. and *Enterococcus* spp. and therefore, when infections sustained by such microorganisms are suspected discontinuation of antimicrobial treatment should be considered to enhance the diagnostic performance of the test. SPECT/CT images were of value not only in diagnosing infection, but also in defining the infection burden; in particular, they helped in distinguishing patients with infection limited to either the pocket or the lead(s) from patients with more severe infection involving both the pocket and the lead(s) and/or other sites of infection (Figs. 5, 6). ^{99m}Tc -HMPAO WBC SPECT/CT has also been shown to allow the detection of additional unsuspected extra-cardiac sites of infection in up to 23 % of patients with device-related sepsis [101], although with some limitations in the case of spine and small CNS emboli. ^{99m}Tc -HMPAO-WBC SPECT/CT has a higher specificity and a higher overall accuracy (96.8 %) as compared to planar scans (68.3 %) and stand-alone SPECT (84.1 %). SPECT/CT precisely defines the disease burden, thus allowing patient risk stratification and facilitating therapeutic decision making. Similarly to what is observed with ^{18}F -FDG PET/CT results, negative scans have consistently been associated with a favorable clinical outcome when antimicrobial therapy alone is initiated. A negative ^{99m}Tc -HMPAO-WBC SPECT/CT can be used as a guide for choosing the most suitable therapeutic strategy, conservative antimicrobial treatment alone or removal of the generator, versus full hardware extraction. In view of the frequent underestimation of infection burden when this is based on clinical signs alone, an additional important feature of ^{99m}Tc -HMPAO-WBC SPECT/CT is its ability, shared only by PET/CT, to detect all sites of infection in a single examination [115].

SPECT/CT in suspected vascular graft infection

Vascular prosthesis infection (VPI) occurs in 0.5–5 % of implants. VPI is associated with significant morbidity, including major amputation and death [116]. The success

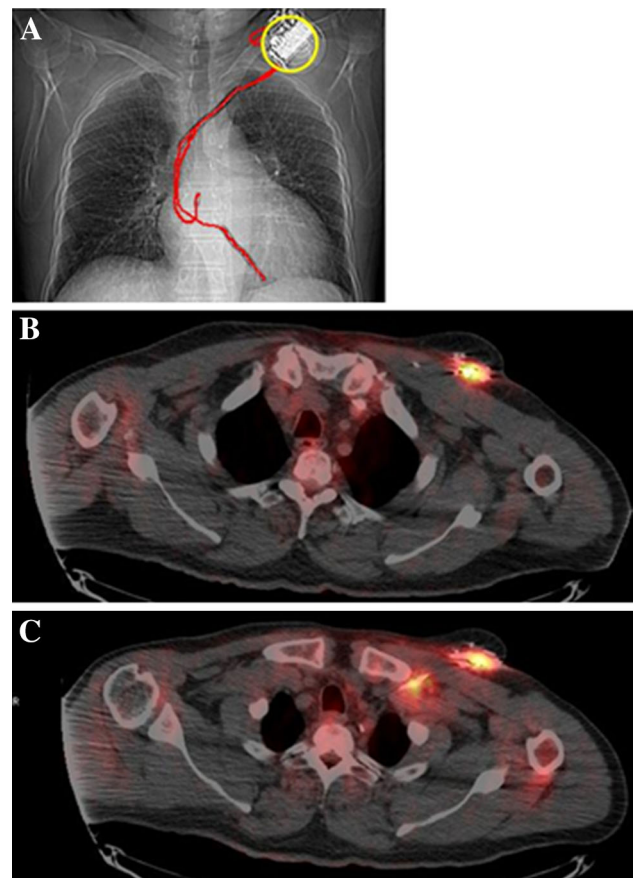


Fig. 5 Radiolabeled WBC scintigraphy in a patient with fever and suspected CIED infection. **a** Plain X-ray with a schematic representation of the different components of the CIED: in the yellow circle the pocket where generator is located, in red the course of the leads of the device. Superimposed SPECT/CT transaxial images show increased ^{99m}Tc -HMPAO WBC uptake at the site of the pocket in a case of isolated pocket infection (**b**) and at both the pocket and the intravascular portion of the lead (**c**) (color figure online)

rate of surgical interventions is closely dependent on an early diagnosis. CT angiography is considered as the technique of choice both for confirming graft infection as well as for detecting additional complications, with a sensitivity ranging from 85 to 100 %. Nuclear medicine techniques and MRI are used in equivocal situations when the sensitivity of CT decreases, as in cases of low-grade infection and in patients with suspected VPI early after surgery. WBC scintigraphy, with cells labeled either with ^{99m}Tc or ^{111}In , is the most frequently used test, but ^{67}Ga -citrate, radiolabeled human immunoglobulins and anti-granulocyte antibodies have been also evaluated. When a graft located in the abdominal region has to be evaluated and ^{99m}Tc -HMPAO WBC is used, an optimized imaging protocol with adequate image acquisition time must be used to decrease the rate of false-positive findings. SPECT/CT increases both the sensitivity and specificity of ^{99m}Tc -HMPAO WBC by decreasing the rate of false-positive

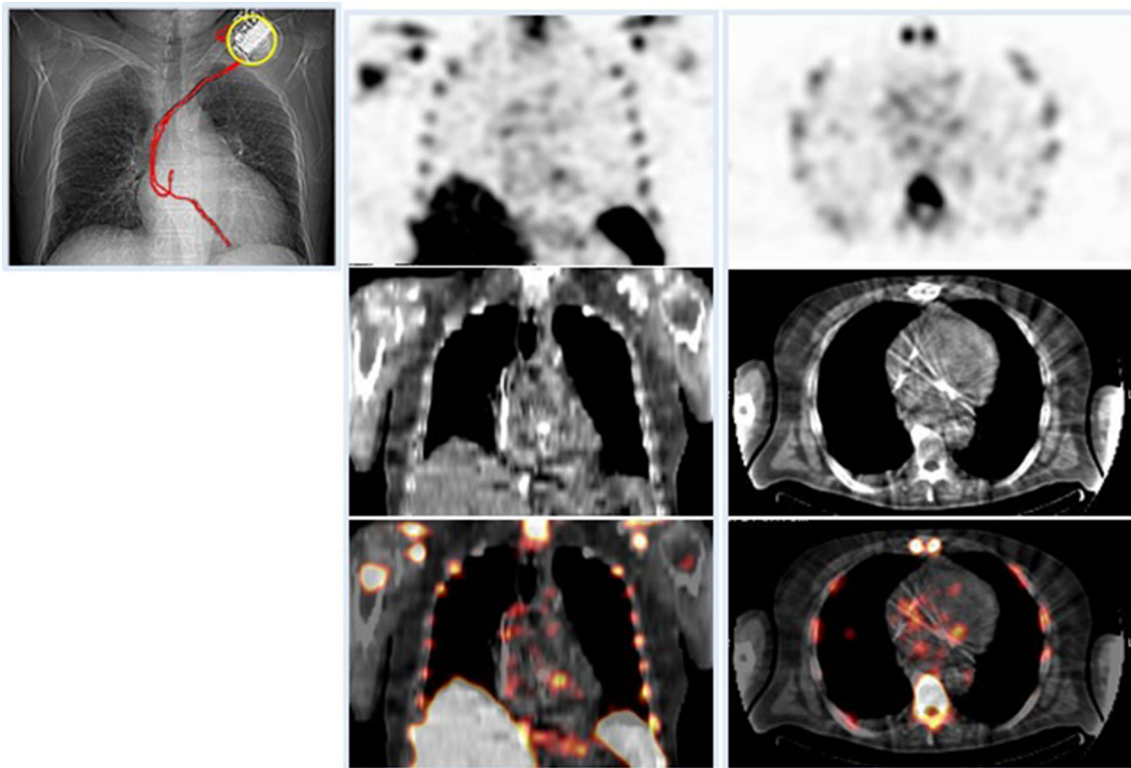


Fig. 6 SPECT/CT images (*middle column* coronal view, *left column* transaxial view, *upper panel* emission images, *middle panel* CT images, *lower panel* superimposed SPECT/CT images) show increased ^{99m}Tc -HMPAO WBC uptake at the tip of the intracardiac portion of the lead in a patient with suspected CIED infection. In the

left column, plain X-ray with a schematic representation of the different components of the CIED: the *yellow circle* shows the pocket where generator is located, while the course of the leads of the device is shown in *red* (color figure online)

results such as those due to abdominal non-specific accumulation, and by accurately localizing and determining the extent of increased radiotracer uptake. Graft involvement in the infectious process can thus be confirmed or excluded even in the presence of post-surgical distortions and in complex anatomical sites [6, 10, 91, 117].

SPECT/CT provided more accurate data than did planar imaging and SPECT for the diagnosis and localization of VPI using both ^{67}Ga -citrate and ^{111}In -oxine-labeled WBCs. In 67 % of patients with suspected VPI, SPECT/CT improved the interpretation in 36 % of ^{67}Ga -citrate studies and 63 % of ^{111}In -oxine-labeled WBC studies [6]. SPECT/CT, by defining uptake as physiological in the vascular pool or as non-specific abdominal accumulation and providing accurate characterization of the localization and extent of abnormal foci, produced a significant decrease in false-positive findings in 37 % of patients as compared to stand-alone SPECT. This was an important advantage [10] (Fig. 7). The high specificity of SPECT/CT has been demonstrated even in studies performed during the first month after surgery [10, 118]. ^{99m}Tc -HMPAO-WBC SPECT/CT has a major impact on patient management in late, low-grade VPI, partly thanks to its ability to reliably

monitor treatment response by distinguishing patients who respond favorably to antibiotics from those who require intensified administration or alternative treatment options [10].

SPECT/CT in abdominal infection and inflammatory disease

Inflammatory bowel disease (IBD)

Crohn's disease and ulcerative colitis are the two main subtypes of IBD. Although ulcerative colitis only affects the colon, Crohn's disease can affect any part of the gastrointestinal tract, with involvement of the terminal ileum found in 90 % of cases. Ileocolonoscopy has gained wide acceptance as the reference standard for diagnosing colonic or ileal involvement. For small bowel disease, barium examinations using an enteroclysis technique are still considered the standard of Ref. [119], with the exception of pediatric patients [120]. Disease activity is measured by clinical scores. WBC imaging (preferably with ^{99m}Tc for better image quality, but with acquisition within 2 h of re-injection) has been extensively used for diagnosis of IBD

and for correct detection of the bowel segment involved, and shown high sensitivity and specificity, ranging from 80 to 90 % in adults and children [121–123]. WBC scintigraphy can also help to diagnose treatment resistance within days of the start of therapy [124]. A meta-analysis of prospective studies on imaging of IBD has demonstrated that ultrasonography, MRI and WBC scanning perform similarly, with sensitivities ranging from 84 to 93 % and specificities ranging from 84 to 95 % [125]. Software fusion of SPECT with CT was shown to be superior to traditional side-by-side assessment of SPECT and CT for ^{111}In -labeled WBC or ^{67}Ga scans, with greater diagnostic confidence achieved in 71 % of cases. Fused images altered image interpretation in almost half of the studies [11]. In a comparison of SPECT/CT vs stand-alone SPECT, Roach et al. [126] found that final reports were significantly different in 26 % of patients following the interpretation of hybrid images. Figure 8 shows an example of SPECT/CT in a patient with active Crohn's disease.

Recently, the added value of SPECT/CT as part of routine hepatobiliary $^{99\text{m}}\text{Tc}$ -iminodiacetic acid studies was evaluated in patients with acute cholecystitis. SPECT/CT resulted in a change in interpretation in 41–43 % of studies,

either from normal to abnormal scan findings (13–28 %) or from a positive to a negative examination (13–30 %) [127].

Conclusions

In spite of the common belief that, following advent of new and powerful antibiotics and other modern treatments, infection is a thing of the past, recent decades have seen a resurgence of increasingly aggressive diseases. In addition, diabetes, the epidemic of the 21st century, is frequently associated with infectious processes. Accurate assessment is hugely important to ensure appropriate care of patients with suspected infectious processes. Early diagnosis and precise localization of infection can change patient management and outcome. Nuclear medicine procedures, specifically ones using single-photon emitting radiotracers, are very sensitive for the early detection of infectious processes. Radiological imaging modalities such as ultrasound, MRI, and specifically CT, provide precise details of tissue and organ alterations in the presence of infection. Combining these two imaging modalities in an integrated SPECT/CT device enables single-session imaging of

Fig. 7 SPECT/CT images (from left to right coronal, sagittal and transaxial view, upper panel emission images, middle panel CT images, lower panel superimposed SPECT/CT images) demonstrate infection in a patients with aortobisiliac vascular prosthesis. Increased $^{99\text{m}}\text{Tc}$ -HMPAO WBC uptake is located at the level of the vascular graft just before the aortobisiliac bifurcation and extends to the surrounding soft tissue (color figure online)

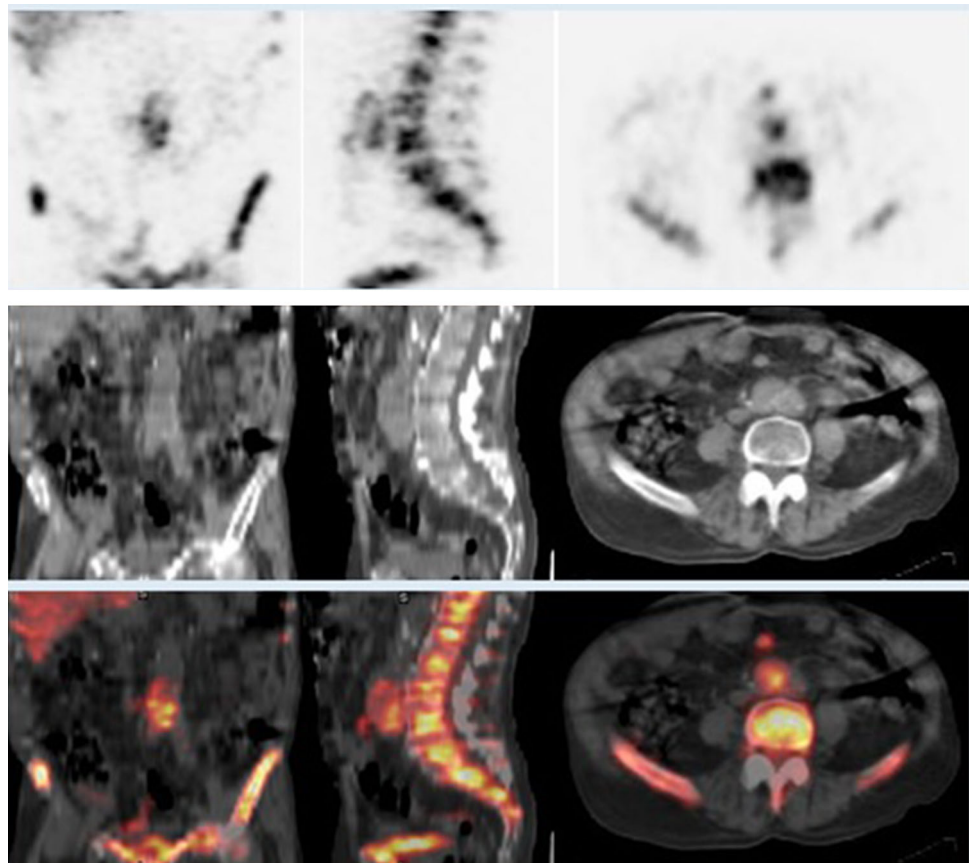
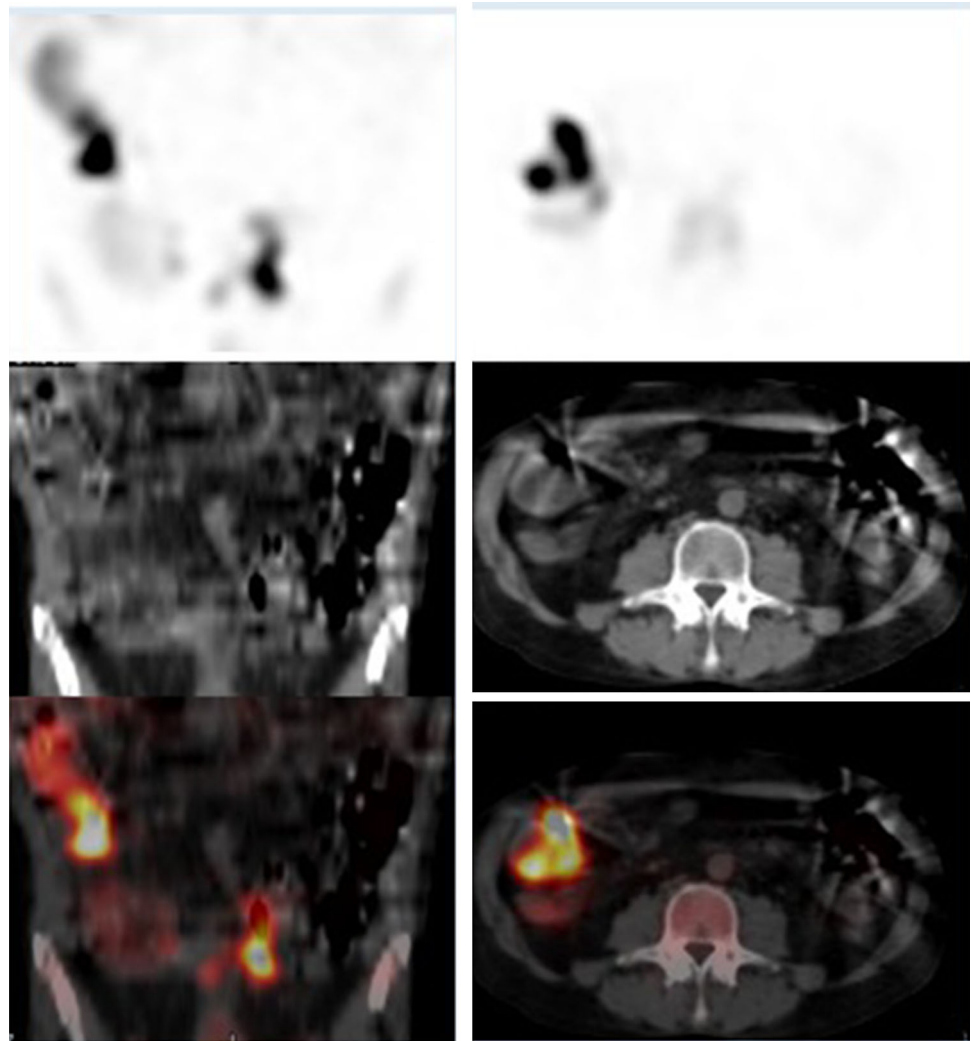


Fig. 8 Example of SPECT/CT images (*left column* coronal view, *left column* transaxial view, *left column* emission images, *upper panel* emission images, *middle panel* CT images, *lower panel* superimposed SPECT/CT images) in a patient with suspected activation of Crohn's disease. ^{99}Tc -HMPAO-WBC SPECT/CT images are acquired 2 h after the radiopharmaceutical injection and clearly show intense uptake at the distal ileum–proximal ascending colon, confirming the presence of active disease (color figure online)



infectious and inflammatory processes that adds high specificity to the inherent high sensitivity of the functional test. Emerging literature data, although still mainly from single-center studies with relatively small patient populations, demonstrate that SPECT/CT is extremely important in the clinical care of patients with suspected infection.

Conflict of interest The authors declare that they have no conflict of interest.

Compliance with ethical guidelines This article does not contain any studies with human or animal subjects performed by any of the authors.

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