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The Role of Single-Photon Emission Computed Tomography/Computed Tomography in Benign and Malignant Bone Disease

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Radiological (plain radiographs, computed tomography [CT], magnetic resonance imaging [MRI]) and nuclear medicine methods (bone scan, leukocyte scan) both provide unique information about the status of the skeleton. Both have typical strengths and weaknesses, which often lead to the sequential use of different procedures in daily routine. This use causes the unnecessary loss of time and sometimes money, if redundant information is obtained without establishing a final diagnosis. Recently, new devices for hybrid imaging (single-photon emission computed tomography/computed tomography [SPECT/CT], positron emission tomography/computed tomography [PET/CT]) were introduced, which allow for direct fusion of morphological (CT) and functional (SPECT, PET) data sets. With regard to skeletal abnormalities, this approach appears to be extremely useful because it combines the advantages of both techniques (high-resolution imaging of bone morphology and high sensitivity imaging of bone metabolism). By the accurate correlation of both, a new quality of bone imaging has now become accessible. Although researchers undertaking the initial studies exclusively used low-dose CT equipment, a new generation of SPECT/CT devices has emerged recently. By integrating high-resolution spiral CT, quality of bone imaging may improve once more. Ongoing prospective studies will have to show whether completely new diagnostic algorithms will come up for classification of bone disease as a consequence of this development. Besides, the role of ultrasonography and MRI for bone and soft-tissue imaging also will have to be re-evaluated. Looking at the final aim of all imaging techniques—to achieve correct diagnosis in a fast, noninvasive, comprehensive, and inexpensive way—we are now on the edge of a new era of multimodality imaging that will probably change the paths and structure of medicine in many ways. Presently, hybrid imaging using SPECT/CT has been proven to increase sensitivity and specificity of bone scintigraphy. This was mainly achieved by identifying benign bone conditions with increased bone turnover. Therefore, SPECT/CT should be applied whenever equivocal findings of planar bone imaging occur. It also helps to improve accuracy of leukocyte scanning to detect/exclude osteomyelitis and to define sites of inflammation. We therefore regard SPECT/CT as a valuable tool to optimize bone imaging, which might become even more important if new radiopharmaceuticals become available to image specific cell functions.

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For more than 30 years, bone scintigraphy has been known as one of the most sensitive noninvasive methods to detect focal bone pathology. However, new imaging procedures, such as magnetic resonance imaging (MRI), ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), or ^{18}F-fluoride PET, have emerged that are now in competition with bone scanning in this diagnostic field. Because of its widespread availability, moderate costs, and extensive clinical experience, bone scintigraphy is still firmly established in the diagnostic algorithms to detect or characterize bone lesions of all kinds. It is known that the visualization of exact anatomical localization and morphology of underlying bone pathology may improve the specificity of bone scans considerably. In the majority of nuclear medicine institutions, bone scans are currently obtained in whole-body technique using double-head gamma camera systems equipped with high- or even ultra-high resolution collimators allowing for high-image quality. In case of focal abnormalities, additional spot views or single-photon emission com-

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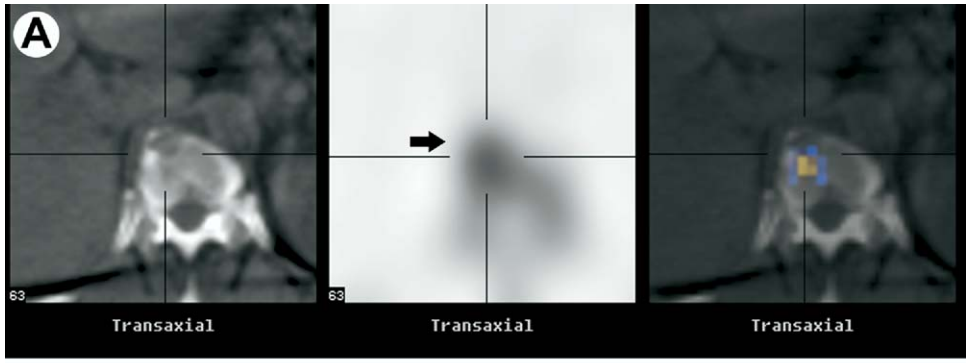

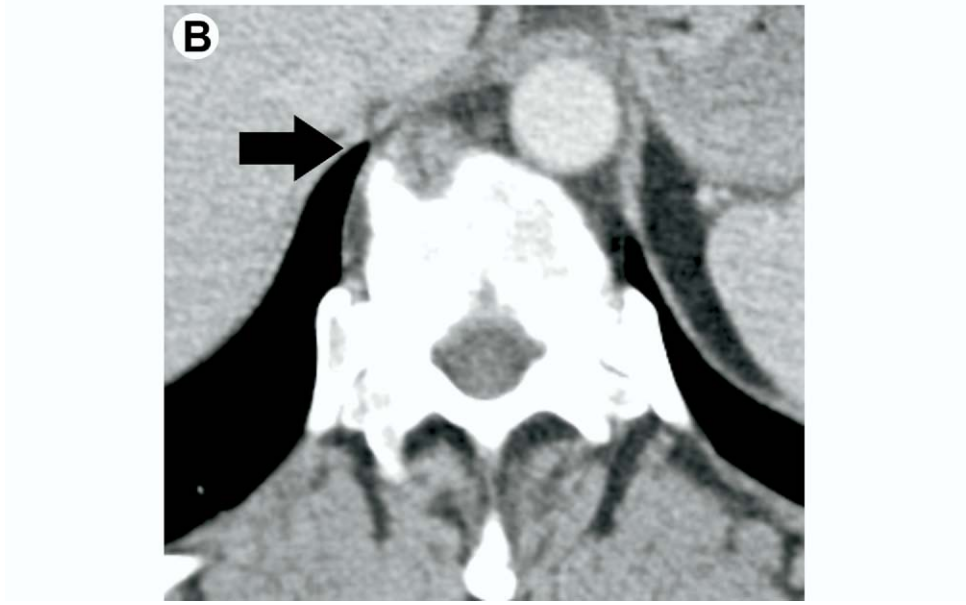

Figure 1 (A and B) A 57-year-old man with lung carcinoma is shown. Bone SPECT reveals focal uptake at the anterior rim of 11th thoracic vertebral body (arrow in A) supposed to be caused by coexisting spondylosis. However, bone erosion and accompanying soft-tissue tumor was seen on SPECT/low dose CT, later on high-end CT (arrow in B), and finally confirmed by biopsy.

puted tomography (SPECT) is performed. This technique enables the accurate localization of tracer accumulations, especially in anatomical regions that are otherwise difficult to interpret because of complex architecture of skeletal structures such as the spine, pelvis, or skull. Because tracer uptake on planar scans may be similar in different malignant as well as benign conditions, SPECT has the potential to improve diagnostic specificity on the basis of correct anatomical lesion localization. However, even so, in many instances, especially in tumor patients with solitary lesions in the axial skeleton or in patients suspected to have a primary bone tumor or infection, correlation with high-quality anatomic images is mandatory for final diagnosis. Therefore, the usual way to establish the correct diagnosis often begins with separate anatomical (planar radiograph, CT, MRI), and functional imaging (planar bone scanning, SPECT) and ends with the combined evaluation of all procedures using various systems for image analysis.

In some situations, even this difficult and time-consuming process will prove unsatisfactory, in particular if patients present with coexisting pathology (eg, degenerative bone disease, inflammation, metabolic disease). Therefore, several attempts have been made to fuse images using either external or internal landmarks, or a combination of both.[1] Obtaining functional and anatomical data on different devices, however, necessarily leads to errors in realignment because of motion, respiration, or other effects. Furthermore, until now, it was time consuming, thus preventing its routine application.[2-4] As a possible solution of this dilemma, an imaging device combining a dual-head gamma camera with a low-

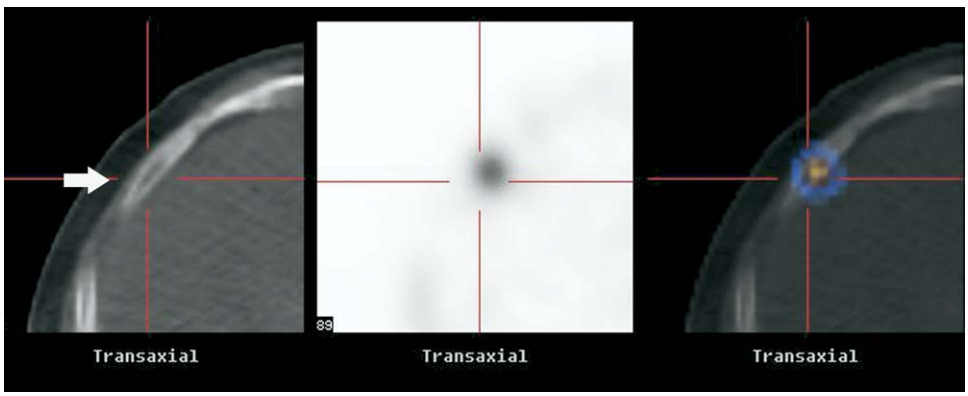

Figure 2 A 56-year-old man with newly diagnosed lung carcinoma is shown. Bone scintigraphy shows a suspicious lesion in the 10th right rib. On SPECT/low-dose CT no anatomical abnormality can be identified, especially no fracture, indicating presence of a medullary metastasis.

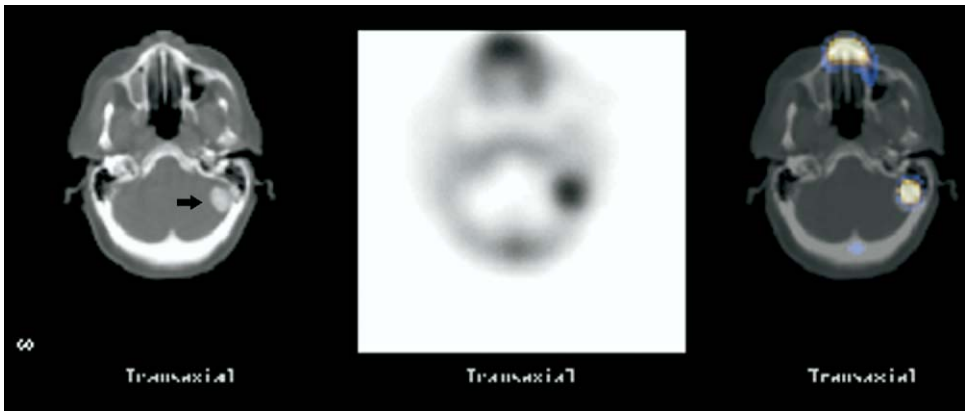

Figure 3 A 73-year-old woman with breast carcinoma is shown. On planar scintigraphy and SPECT, an intense focal accumulation is found along the inner edge of temporal bone left sides, suggesting a bone metastasis. SPECT/CT shows a densely calcified intracranial, extra-axial mass (arrow) with dural tail suggestive for meningioma.

dose radiograph tube has been recently introduced for combined SPECT/low-dose CT. This radiograph tube-based CT system, however, has limited diagnostic performance because of low-resolution anatomic images (approximately 4 mm), which are sometimes not sufficient for image interpretation. Currently, hybrid SPECT/CT installations consisting of a high-end multislice CT scanner allowing for isotropic images by thin-collimation (0.5 mm) and a dual-head gamma camera have become available, enabling high diagnostic accuracy.

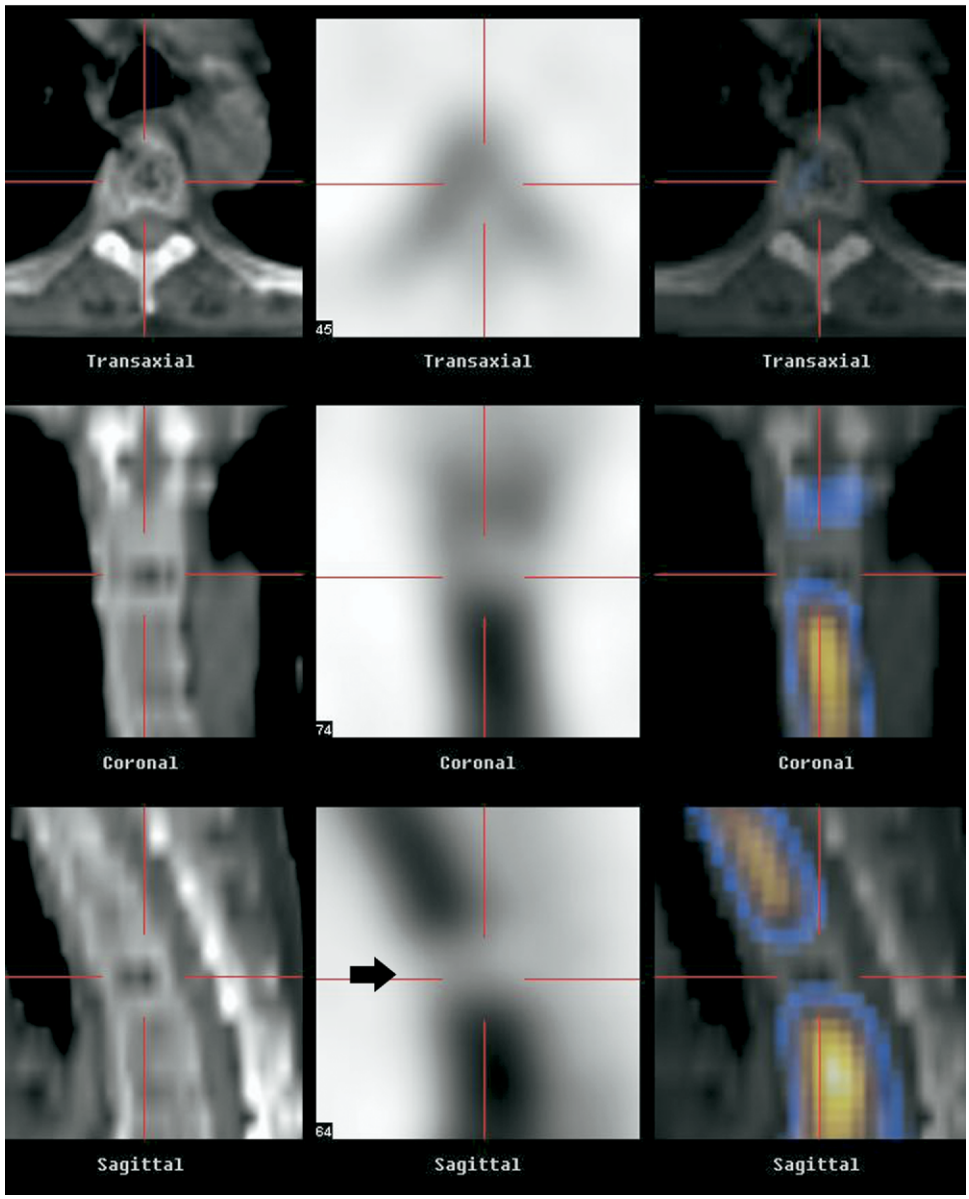

Figure 4 A 71-year-old man with squamous cell head and neck carcinoma is shown. On planar bone scintigraphy and SPECT, a cold lesion (arrow) is visible covering the entire 5th thoracic vertebral body being suspicious for a metastasis. SPECT/CT demonstrates typical coarsening of trabecular bone with lowered central density due to fat by vertebral hemangioma.

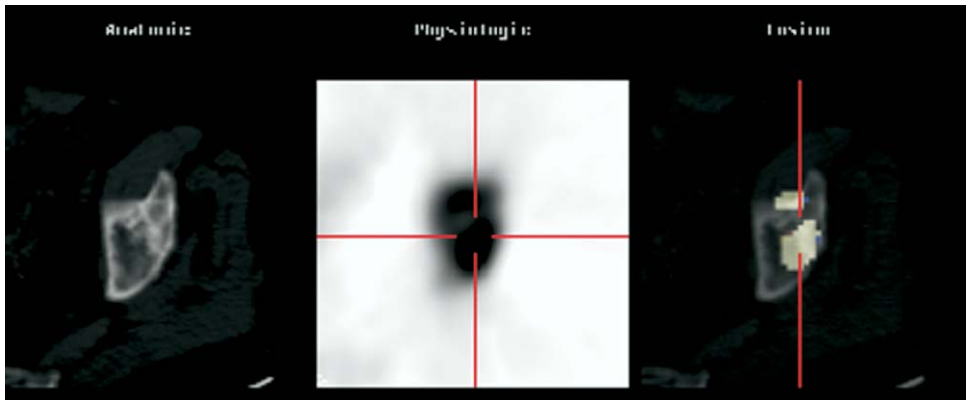

Figure 5 A 67-year-old man with pain in his left hip, supposedly caused by recent minor trauma, is shown. Planar bone scintigraphy and SPECT reveal intense tracer uptake in the acetabular region, which can be identified as mixed lytic-sclerotic metastasis by SPECT/CT (primary tumor: lung carcinoma, diagnosed later).

The radiopharmaceutical most often used in bone scintigraphy is ^{99m}Tc-methylene diphosphonate. This compound binds to bone by chemiadsorption to the hydroxiapatite crystal. Two to six hours after intravenous injection, approximately 50% of the injected dose is accumulated in the skeletal system. Enhanced uptake (focally or diffusely) reflects increased bone turnover caused by changes of bone vascularization and/or osteoblastic activity. In some instances, bone scintigraphy will reveal an abnormality long before a morphological alteration is visible or may indicate which skeletal area should undergo further radiological examinations.

Bone scanning with ^{99m}Tc-methylene diphosphonate detects abnormalities of bone metabolism as early as 24 to 48 hours after the onset of pathology and is nearly always positive by 8 days. Thus, fractures and other manifestations of bone stress can be diagnosed very sensitively by bone scintigraphy. On the other hand, bone scintigraphy can be used successfully in ruling out bone infection. If triple-phase bone scintigraphy is negative and vascular problems can be excluded, osteomyelitis is highly unlikely. By applying quantitative analysis of bone uptake, the sensitivity for the detection of osteomyelitis can be further increased.[5] Nonetheless, leukocyte scanning using ^{111}In- or ^{99m}Tc-labeled leukocytes or granulocytes is still the gold standard to diagnose bone infection. It is known to be highly sensitive as well as specific,[6,7] although scan analysis is often difficult. Although the presence of inflammation can be substantiated or ruled out by analysis of sequential images, exact anatomical definition of infectious foci is very demanding, in particular if they are located in distant parts of the extremities. The combined use of SPECT and image fusion might solve this problem.

Finally, combined SPECT/CT imaging might also be useful when using other radiopharmaceuticals that specifically localize bone metastases of certain tumors (eg, ^{131}I in skeletal metastases of thyroid carcinoma, ^{123}I-mIBG/^{111}In-octreotide in skeletal metastases of neuroendocrine tumors or neuroblastoma).

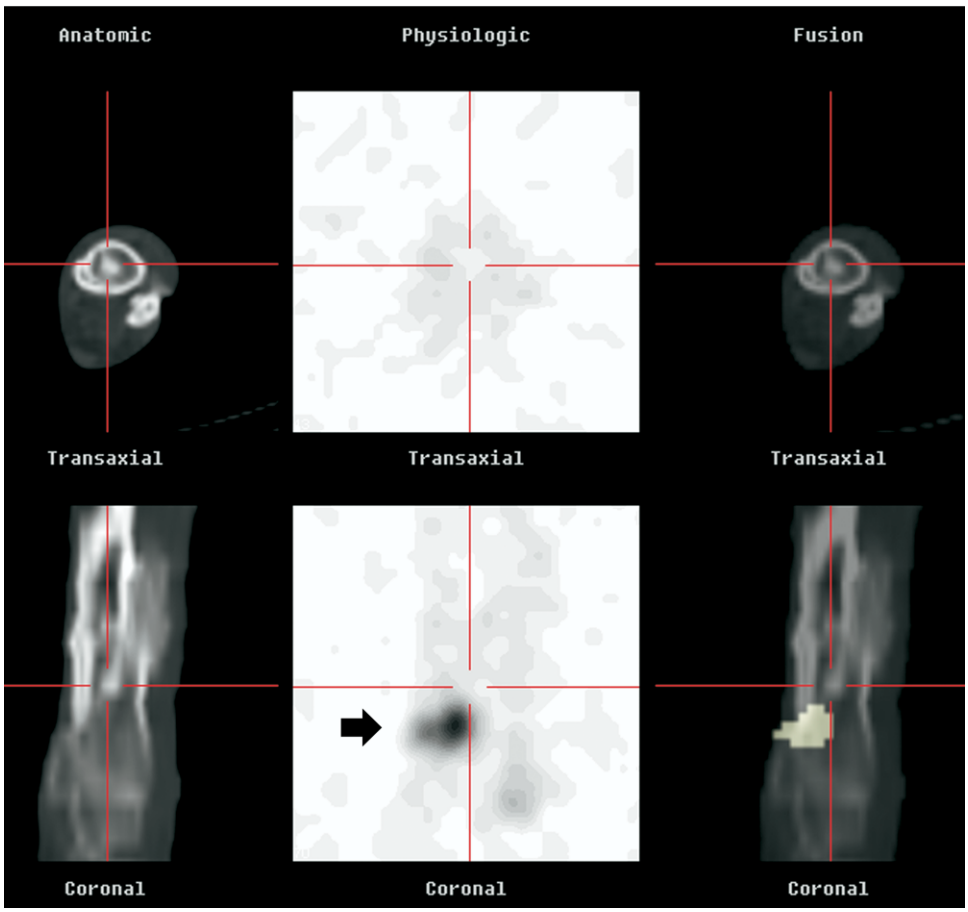

Figure 6 A 59-year-old man with known chronic tibial osteomyelitis and a history of several surgical intervention who presented with signs of reactivation is shown. Leukocyte scan after injection of ^{99m}Tc-labeled antigranulocyte antibodies demonstrates focal uptake (arrow), which was considered to correspond to a supposed sequester shown on plain radiographs. SPECT/CT demonstrates the real location of infection inside the tibial bony canal, distal from the intramedullar bone remodelling, thus, directly influencing planning for surgery.

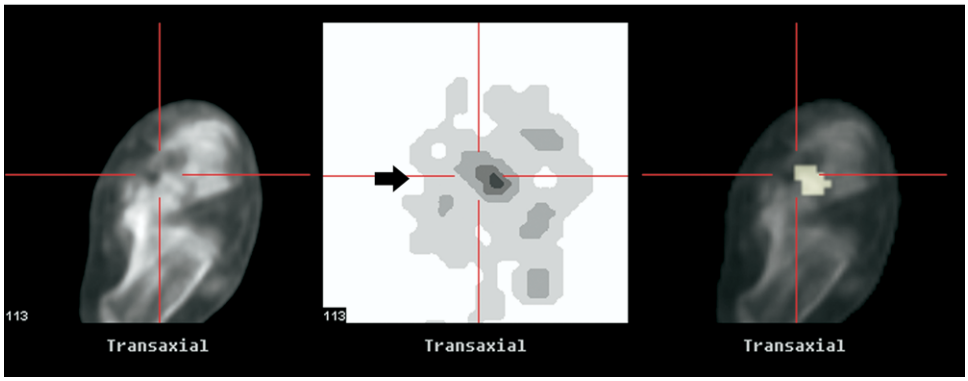

Figure 7 A 54-year-old man with chronic osteomyelitis after open fracture of the heel is shown. Leukocyte scan after injection of ^{99m}Tc-labeled antigranulocyte antibodies shows increased uptake in this area (arrow). Because of destroyed bone architecture, infected sequester was difficult to depict on plane radiographs and even on low-dose CT, alone. The use of SPECT/CT, however, enabled the correct identification of the infectious focus after burst fracture.

Indications for Bone Scintigraphy, SPECT and SPECT/CT

Physiological Tracer Uptake

In general, whole-body scans are used for bone scintigraphy, which permit the assessment of the overall distribution of the radiopharmaceutical. Both anterior and posterior studies are reviewed in parallel comparing any alteration, and noting eventual asymmetries on both sides of the midline. The evaluation of symmetry is of great importance implying optimal positioning of the patient before starting the study. Some sources of error do exist that have to be considered, such as increased uptake due to normal muscle stress, or intense uptake of the metaphyseal–epiphyseal area in children. Normal tracer distribution makes the use of SPECT/CT unnecessary.

Primary and Secondary Malignant Bone Diseases

In oncology, whole-body bone scintigraphy is the standard procedure in the following clinical situations: the pretherapeutic staging of disease (detection of metastases or local invasion), the prediction of pathologic fractures, the check-up of laboratory findings indicating bone involvement, the differential diagnosis of new musculoskeletal symptoms, and the evaluation of treatment response.[8] Additional spot views are obtained if a specific clinical problem that needs to be further clarified is detected on whole-body imaging. In case of a negative scan, no further imaging is needed. Under certain conditions, however (eg, local symptoms suggestive for metastases, high pretest likelihood for metastases), additional SPECT scans of the body area in question should be considered to increase diagnostic sensitivity. Because the diagnosis of bone metastases indicates short or limited survival and the need for additional or intensified treatment, the accurate differentiation between benign and malignant lesions is of paramount importance.[9-12]

Careful analysis of uptake pattern and intensity as well as the use of SPECT allow for a correct diagnosis in many cases. However, in some instances SPECT/CT is necessary to make the correct diagnosis. As indicated earlier, in patients with a high risk of bone metastases, additional anatomical information is often necessary. Particularly, bone lesions located in the spine and thoracic cage cannot be sufficiently assessed by conventional radiograph examinations and instead require the additional use of CT or MRI. Multiplanar SPECT/low-dose CT imaging is superior to plain radiograph techniques and has proven to be extremely useful in identifying benign skeletal abnormalities, such as osteochondrosis, spondylopathy, or degenerative spondylarthrosis, as the reason for abnormal tracer uptake (Fig. 1). As a consequence, further imaging procedures will not be necessary. Sometimes, however, malignant bone lesions do not reveal any morphological abnormality and can therefore not be confirmed by low-dose CT. Nonetheless, exclusion of evident benign causes for focal tracer uptake makes metastatic involvement more likely (Fig. 2). Conversely, incidental benign lesions in patients with known malignancy can pose serious differential diagnostic problems in case of focal tracer accumulation, especially when there is only a solitary lesion (Fig. 3).

As with myeloma-induced lytic bone lesions, metastases become first visible on radiographs or even CT scans, once the have destroyed 50% to 75% of trabecular bone. Thus, the lack of anatomical findings to explain increased tracer uptake suggests medullary metastases, if bone trauma or infection can be ruled out clinically. In these cases, SPECT/low-dose CT usually provides a correct diagnosis, illustrating the benefit of combined SPECT/CT imaging fusion in tumor patients as a one-step procedure.

Besides the typical appearance of bone metastases as “hot spots” from

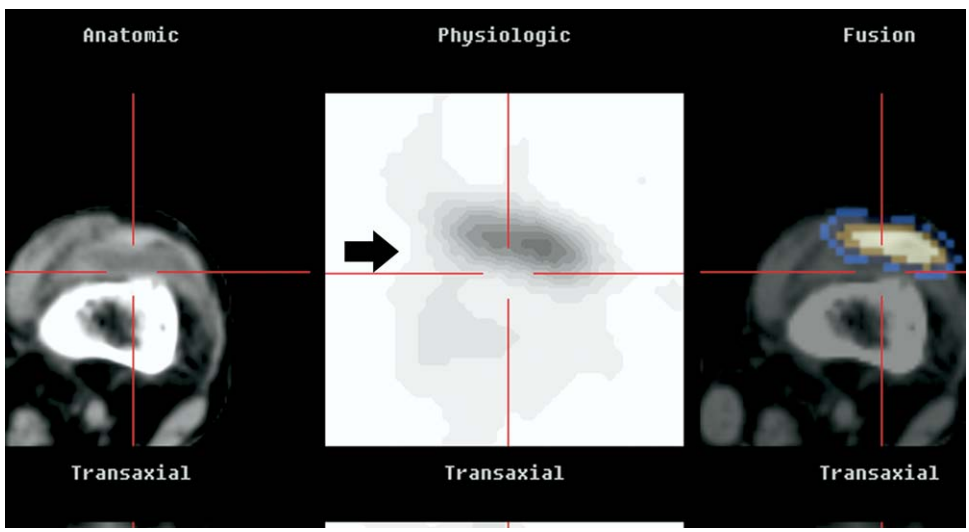

Figure 8 A 53-year-old man with knee joint empyema is shown. Leukocyte scan using antigranulocyte antibodies was interpreted as suggestive for osteomyelitis. SPECT/CT correctly diagnosed infection of the joint space. Note optimal matching between anatomic and physiological data.

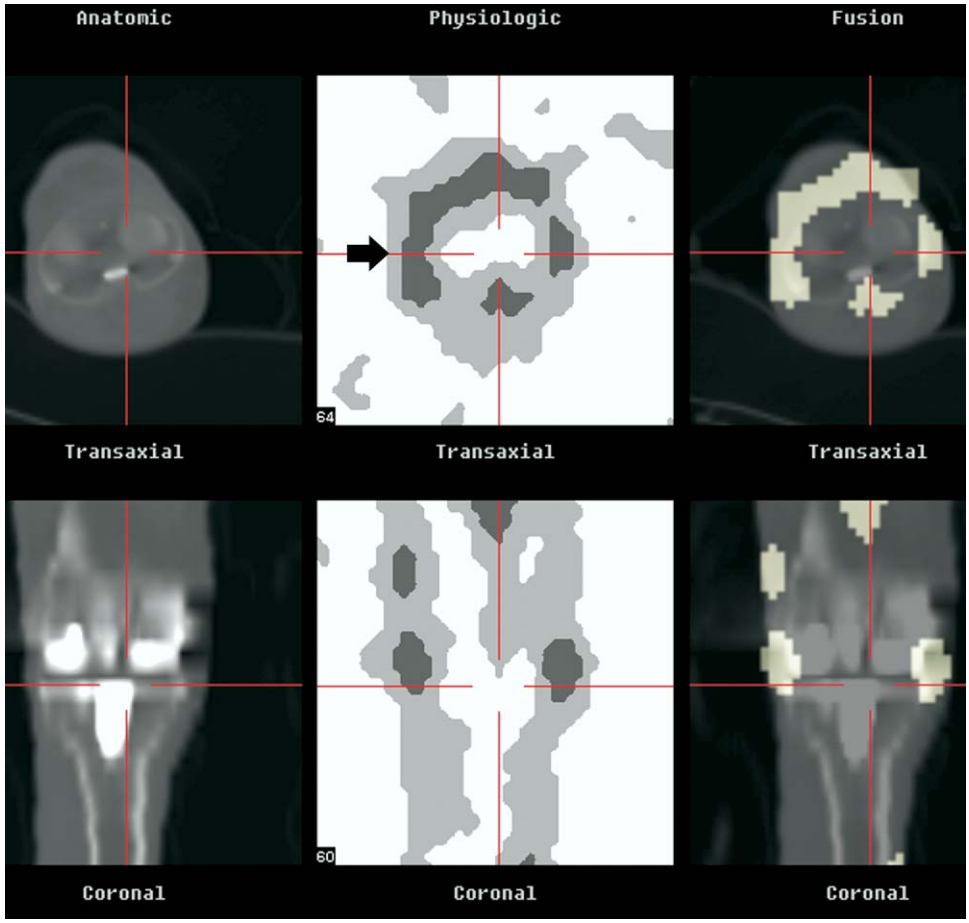

Figure 9 A 55-year-old man with a history of prosthetic knee surgery is shown. Leukocyte scanning (planar and SPECT) was not able to differentiate between septic prosthetic loosening and joint empyema (arrow) reliably. SPECT/CT clearly shows that uptake was restricted to the joint space, thus excluding infection of the prosthesis.

increased bone turnover in the neighborhood of tumor, bone metastases may sometimes appear as "cold" or photopenic areas as a consequence of very rapid tumor growth. Because benign conditions such as hemangioma or others may also present as photopenic spots, the accurate differentiation from malignant disease is extremely important.[13] It often can be achieved by analyzing anatomical details provided by low-dose CT (Fig. 4). Minor trauma in patients with undiagnosed malignant tumors can also be a source of confusion, sometimes delaying the correct diagnosis of tumor (Fig. 5). Another benefit of SPECT/CT is the definition of suspicious bone lesions to guide subsequent biopsy.

Bone Infection

Osteomyelitis is not a single disease entity but instead encompasses a spectrum of conditions that can be defined according to the immunologic status of the host, preexisting bone disease, or the nature of the infecting organism. Interactions between these factors determine the site of involvement and dictate the results of any diagnostic imaging. There are chronic infectious as well as noninfectious diseases that show features that allow clear and rapid diagnosis—or may lead to diagnostic confusion. Because clinical and biochemical parameters often are too unspecific to establish a correct diagnosis, modern imaging modalities are of great importance in the assessment of disease activity and extent.[14] Rapid technical changes have dramatically influenced current algorithms to image bone pathology. Radiolabeled autologous white cells are still considered as gold standard for any scintigraphic procedure to localize infection. As this technique requires time-consuming ex vivo separation of blood cells with special equipment and trained personnel, an alternative approach using ^{99m}Tc-labeled monoclonal antigranulocyte antibodies directed against surface antigens of human granulocytes has

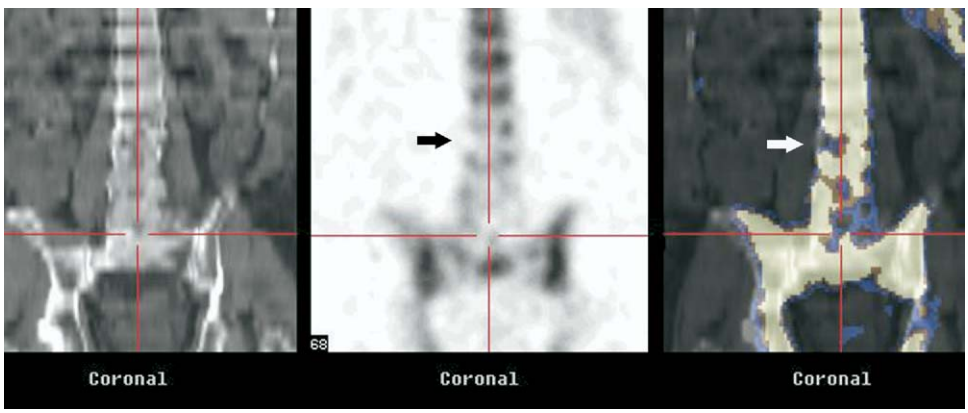

Figure 10 A 65-year-old man with known osteoarthrosis of the spine now suffering from increasing pain in the lower back is shown. Because conventional x-ray could not confirm spondylodiscitis, leukocyte scanning was performed. Cold lesions in the lumbar spine (arrow), especially on the left, were interpreted as highly suspicious for infection, which was confirmed by biopsy.

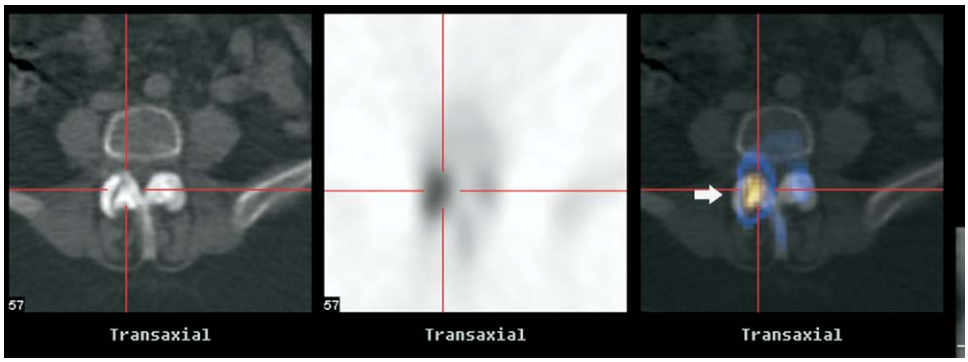

Figure 11 A 79-year-old woman with gastric carcinoma and lumbar pain is shown. Bone scintigraphy, including SPECT, reveals a solitary hot spot at the right apophyseal joint of the 4th lumbar vertebra (arrow) and interpreted compatible with spondylarthrosis. This was confirmed by low-dose CT of SPECT/CT demonstrating the typical changes associated with joint degeneration.

been developed, which has been shown to be highly sensitive as well as specific to detect infectious foci in the appendicular skeleton.[15-19] An even higher specificity for infection has been reported for ^{99m}Tc-labeled ciprofloxacin, which accumulates in high concentrations in living bacteria. However, the sensitivity of this technique is limited because of microorganisms, with a cell membrane that is impermeable for ciprofloxacin.

Another diagnostic option that is commonly available is 3-phase bone scanning using ^{99m}Tc-labeled diphosphonates.[20] It is known to have a high sensitivity, whereas specificity is limited as the result of many other possible reasons for increased bone turnover, such as fracture, pseudarthrosis, or increased bone mass (remodeling). Positive findings during the early phases (arterial blood flow and blood pool) reflect increased regional vascularization and alterations in the bone extracellular fluid resulting from changes in capillary permeability encountered not only with infectious but also in different inflammatory or neoplastic diseases.[21] Therefore, only the combination of local hyperperfusion, increased bone turnover, and a matching clinical and biochemical context should lead to the diagnosis of infection. Interpretation of 3-phase bone scans therefore requires not only images of high quality with appropriate supplementary views, but also additional clinical information, and in particular visualization of underlying anatomy.

Typical findings such as cortical bone erosion, periosteal elevation, osteolysis, as well as sequestration or formation of involucra are, together with increased tracer uptake, highly suggestive for bone infection. Particularly in chronic active osteomyelitis, the accurate differentiation between increased uptake caused by relapsing infection or remodeling is essential for patient management (Fig. 6). Untreated bone infection leads to destruction and necrosis and is frequently the reason for recurrent bone or soft tissue fistulae.[22,23] Furthermore, it reduces life quality and may cause disability.

Adding SPECT/CT to the procedures mentioned previously has the potential to further improve diagnostic sensitivity and specificity for inflammation. CT is able to detect small areas of cortical destruction, foci of gas, foreign bodies, sequestration, involucra, or cloacae.[24] Furthermore, CT can identify surrounding soft-tissue abscesses, the replacement of the normal bone marrow by pus, or joint empyema (Fig. 7). By means of image fusion, morphological CT data can be correlated to the accumulation of granulocytes, or increased bone turnover, thus confirming or excluding infection in or around altered bone structures. Fused images may guide the surgeon to the most suitable place for windowing the diaphyseal cortex and avoiding vital structures. Furthermore, they may help to adapt the width of the window and the extent of debridement of the inner bone surface, which in turn may reduce postoperative instability (Fig. 8). Recognition of sequestra or involucra in patients with posttraumatic osteomyelitis often is difficult, leading to unnecessary operations such as opening the intramedullary canal in patients with soft-tissue infection without bone involvement.[25]

It is obvious that combined anatomical and functional information makes interpretation of SPECT as well as CT images easier and more reliable. The reason for the poor specificity of SPECT alone is the fact that many patients with suspected osteomyelitis have a history of fracture and one or more episodes of bone surgery, leading to long-lasting increases in bone turnover and making differentiation from low-grade infection difficult. Additional information from CT concerning bone infection is highly dependent on the underlying structural changes, being different from case to case.

Although infectious foci in the appendicular skeleton can be diagnosed reliably by bone scintigraphy with SPECT/CT, lesions located in the axial skeleton are sometimes more difficult to identify. After the insertion of orthopedic devices sensitivity and specificity of bone scintigraphy is as low as 67% or 50%, respectively. Differentiation between septic prosthetic loosening and joint empyema can be difficult on planar scintigraphy or SPECT as well because tracer uptake follows the bony contours, which means that it is localized either between bone and the prosthetic device, or around the prosthesis. Therefore, anatomical details are of utmost importance for correct image interpretation (Fig. 9).

When using labeled white cells for the diagnosis of spine infection, attention must be paid to photopenic areas that may arise at the site of infection as the result of bone marrow edema with subsequent low tracer uptake (Fig. 10). In such cases, combined SPECT/CT imaging can ease diagnosis by visualizing bone changes suggestive for spondylodiscitis correlated with cold areas along the involved parts of the spinal column.

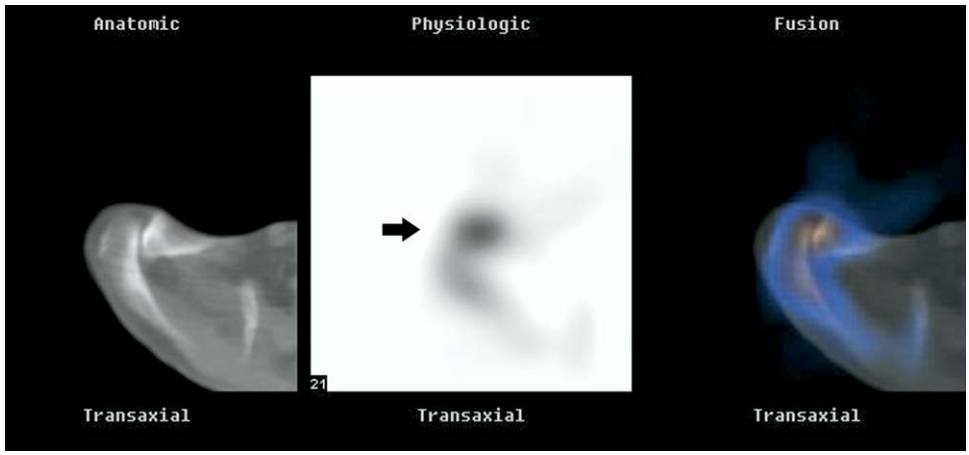

Figure 12 Example of bone scintigraphy in patients with known malignant disease and focal lesions caused by osteoarthrosis. Shown is increased acromioclavicular uptake caused by arthritis (arrow).

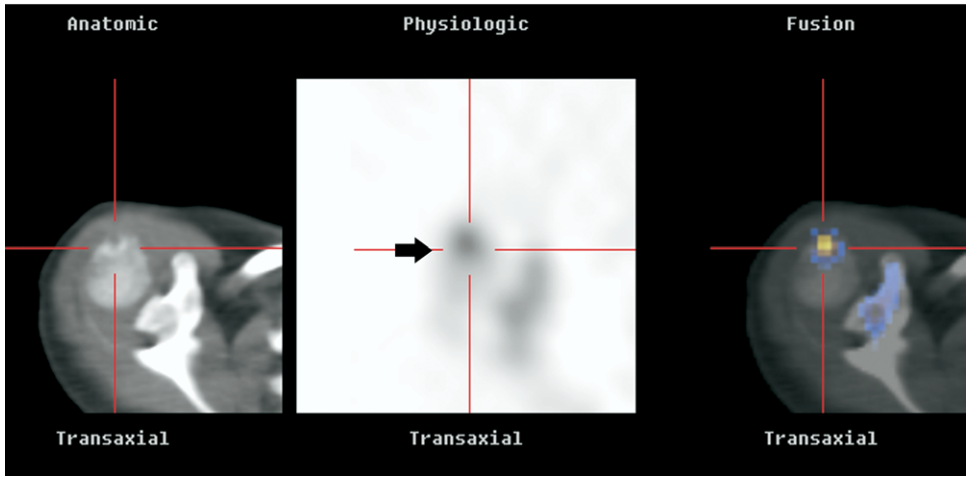

Figure 13 Examples of bone scintigraphy in patients with known malignant disease and focal lesions caused by osteoarthrosis. Shown is reactive osteitis along the bicipital groove caused by active tendosynovitis (arrow).

Degenerative Bone Changes

Osteoarthrosis of spine or peripheral joints is the most frequent articular affliction. It is caused by a variety of different processes and predominantly affects elderly people. In the vertebral column, the major types of degenerative disease include the cartilaginous joints (eg, intervertebral osteochondrosis and spondylosis deformans), the uncovertebral joints, synovial joints (apophyseal joint osteoarthritis and costovertebral osteoarthritis; Fig. 11), and the fibrous joints and entheses (diffuse idiopathic skeletal hyperostosis, ossification of the posterior longitudinal ligament, degenerative changes of the supraspinous and interspinous ligaments). Each of these is characterized by morphological abnormalities that allow for their differentiation from other types of disease (eg, tumor, inflammation, etc). Disc space narrowing, vacuum phenomena, well-defined sclerotic vertebral margins, osteophytosis, eburneation, and perivertebral calcifications all represent radiographic signs of spine degeneration.

The spectrum of extraspinal degenerative diseases is even more widespread, including synovial and cartilaginous joints, as well as syndesmoses and entheses, usually involving more than one joint. Because patients presenting with degenerative diseases (in addition to oncological patients and those suspected of having bone infection) are very frequent, reliable differentiation of these entities is of great importance.

In bone scintigraphy, areas of abnormal uptake indicate sites of increased bone turnover. Such findings are typical for intervertebral osteochondrosis and osteoarthritis but are found less often in spondylosis deformans. Occasionally, extreme spinal osteophytosis may be found on radiographs whereas the bone scan is completely normal. It is well known that abnormal radionuclide uptake in the spine is most often related to degenerative disease; however, it is difficult to differentiate from other skeletal abnormalities, in particular metastases. Therefore, additional morphological information is needed that can conveniently be obtained by SPECT/CT. In this situation, image fusion has a dramatic impact and should be used routinely. In contrast, periarticular uptake in extraspinal locations is highly predictive for degenerative diseases and correlates well with radiographic signs (eg, osteophytosis, bone sclerosis) posing no serious problems for differential diagnosis (Figs. 12 and 13).

Trauma and Postsurgery Status

Increased bone turnover induced by fractures can be visualized within 1 to 7 days after trauma depending on the injured site. Diagnosis of traumatic fracture is usually made by means of x-ray. However, stress fracture, insufficiency fractures, as well as pathological fractures can sometimes be missed by plain radiographs. Therefore, evidence of increased bone turnover demonstrated by bone scan and correlation of physiological and anatomical data by SPECT/CT can be helpful in case of equivocal radiological findings, particularly in tumor patients who often suffer from bone pain (Fig. 14). Sometimes, pain can be a confusing symptom, if different causes for pain are possible (eg, after trauma or surgery). Especially in such patients, combined imaging methods can be very beneficial (Fig. 15).

Incidental Findings

There are a lot of unexpected findings in patients with cancer who are undergoing bone scintigraphy for staging. Besides the already-mentioned degenerative, traumatic, or inflammatory disorders that are responsible for increased focal, there are far more differential diagnoses, such as benign bone tumors, that cannot be correctly diagnosed without corresponding

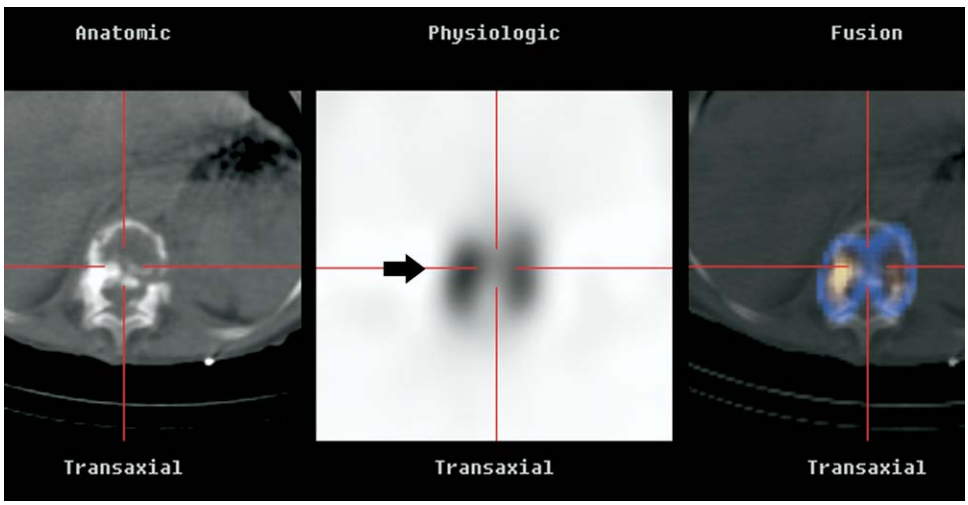

Figure 14 A 66-year-old woman with metastatic breast carcinoma and long-lasting bone pain is shown. Bone scintigraphy (planar and SPECT) showed many skeletal foci interpreted as metastases. SPECT/CT additionally demonstrated a pathologic fracture (arrow) as reason for increasing back pain.

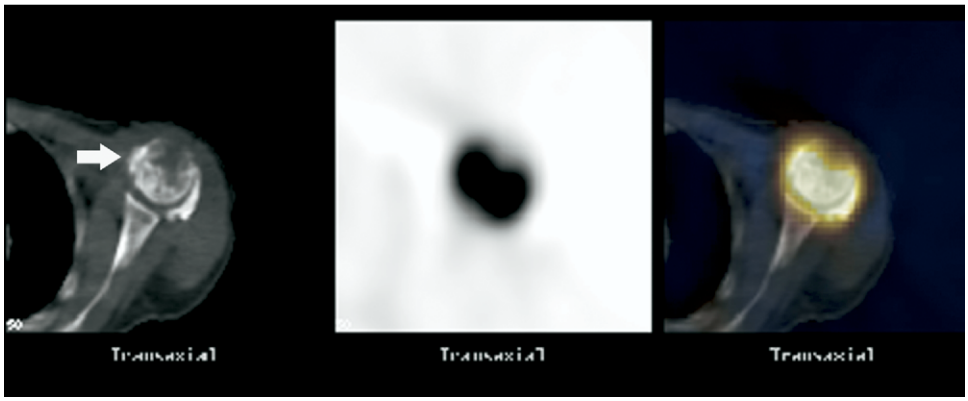

Figure 15 A 40-year-old man with a history of subcapital humeral fracture is shown. After removal of osteosynthesis material, pain in the left shoulder did not improve. Bone scan revealed increased bone turnover; however, it was SPECT/CT that demonstrated a permeative bone lesion with destruction of the trabecular structure of the humeral head (arrow) suggestive for osteomyelitis, confirmed later by surgery.

anatomical images. Extraosseous uptake associated with calcification might also be found in some instances. Considering patients with soft-tissue infection accompanying chronic osteomyelitis, this information might even gain therapeutic relevance in selected situations. Extraosseous uptake has also been described in amyloidosis, rhabdomyolysis, infarction of heart, spleen, and also in long-standing congestive heart failure.[26] To differentiate this great variety of possible causes, again, morphological information is needed, which can easily be obtained by SPECT/CT.

References

1. Wahl RL, Quint LE, Cieslk RD, et al: "Anatometabolic" tumor imaging. Fusion of FDG-PET with CT or MRI to localize foci of increased activity. J Nucl Med 34:1190-1197, 1993
2. Shreve PD: Adding structure to function. (invited commentary). J Nucl Med 41:1380-1382, 2000
3. Eubank WB, Markoff DA, Schmiedl UT, et al: Imaging of oncologic patients: benefit of combined CT and FDG-PET in the diagnosis of malignancy. AJR Am J Roentgenol 1103-1110, 1998
4. Even-Sapir E, Keidar Z, Sachs J, et al: The new technology of combined transmission and emission tomography in evaluation of endocrine neoplasms. J Nucl Med 2001;42:998-1004
5. Front D, Israel O, Jerushalmi J, et al: Quantitative bone scintigraphy using SPECT. J Nucl Med 30:240-245, 1989
6. Georgi P, Kaps HP, Sinn HJ: Leukozytenszintigraphie bei entzündlichen Prozessen der Wirbelsäule. Radiologe 25:324-328, 1985
7. Palestro C, Kipper S, Weiland F, et al: Osteomyelitis: Diagnosis with 99mTc-labelled antigranulocyte antibodies compared with diagnosis with 111In-labelled leukocytes-Initial experience. Radiology 223:758-764, 2002
8. Clain A: Secondary malignant disease of bone. Br J Cancer 19:15-29, 1965
9. Pomeranz SJ, Pretorius HT, Ramsingh PS: Bone scintigraphy and multimodality imaging in bone neoplasia: strategies for imaging in the new health climate. Semin Nucl Med 24:188-207, 1994
10. Krishnamurthy GT, Tubis M, Hiss J, et al: Distribution pattern of metastatic bone disease. A need for total body skeletal image. JAMA 237: 2504-2506, 1977
11. McNeil BJ: Value of bone scanning in neoplastic disease. Semin Nucl Med 14:277-286, 1984
12. Abrams HL, Spiro R, Goldstein N: Metastases in carcinoma. Analysis of 1000 autopsied cases. Cancer 2:74-85, 1950
13. Han BK, Ryu J, Moon DH, et al: Bone SPECT imaging of vertebral hemangioma. Correlation with MR imaging and symptoms. Cli Nucl Med 20:916-921, 1995
14. Bamberger DM: Diagnosis and treatment of osteomyelitis. Comp Ther 16:48-53, 1990
15. Becker W, Goldenberg DM, Wolf F: The use of monoclonal antibodies and antibody fragments in the imaging of infectious lesions. Semin Nucl Med 24:142-153, 1994
16. Reuland P, Winkler KH, Heuchert T, et al: Detection of infection in postoperative patients with technetium-99m-labelled monoclonal antibodies against granulocytes. J Nucl Med 32:2209-2214, 1991
17. Kaim A, Maurer T, Ochsner P, et al: Chronic complicated osteomyelitis of the appendicular skeleton: diagnosis with technetium-99m labelled monoclonal antigranulocyte antibody-immunoscintigraphy. Eur J Nucl Med 24:732-738, 1997
18. Palestro CJ, Chun CK, Swyer AJ, et al: Radionuclide diagnosis of vertebral osteomyelitis: indium-111 leucocyte and technetium-99m methylene diphosphonate bone scintigraphy. J Nucl Med 31:413-416, 1990
19. Palestro CJ, Kipper S, Weiland F, et al: Osteomyelitis: Diagnosis with ^{99m}-Tc-labelled antigranulocyte antibodies compared with diagnosis with ^{111} In-labelled leukocytes-Initial experience. Radiology 223:758-764, 2002
20. Maurer AH, Chen DCP, Camargo EE, et al: Utility of three-phase scintigraphy in suspected osteomyelitis. J Nucl Med 22:941-949, 1981
21. Israel O, Gips S, Jerushalmi J, et al: Osteomyelitis and soft tissue infection: differential diagnosis with 24 hour/4hour ratio of Tc99m MDP uptake. Radiology 163:725-726, 1987
22. Wing VW, Jeffrey RB, Federle MP, et al: Chronic osteomyelitis examined by CT. Radiology 154:171-174, 1985
23. Seltzer SE: Value of computed tomography in planning medical and surgical treatment of chronic osteomyelitis. J Comput Assist Tomogr 8:482-487, 1984
24. Tumeh SS, Aliabadi P, Weissman BN, et al: Disease activity in osteomyelitis: role of radiography. Radiology 165:781-784, 1987
25. Crim JR, Seeger LL: Imaging evaluation of osteomyelitis. Crit Rev Diagn Imaging 35:201-256, 1994
26. Love C, Din AS, Tomas MB, et al: Radionuclide bone imaging: an illustrative review. Radiographics 23:341-358, 2003