Nuclear Imaging in Orthopaedic Practice

A Critical Analysis Review

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Abstract

» Nuclear imaging techniques, including bone scintigraphy, labeled leukocyte scintigraphy, positron emission tomography (PET), and single-photon emission computed tomography (SPECT) combined with computed tomography (CT), have wide applications in orthopaedics for evaluating trauma, painful total joint arthroplasty, musculoskeletal infection, and orthopaedic oncology.

» Three-phase bone scintigraphy is a first-line, highly sensitive nuclear medicine study for evaluating orthopaedic pathology when initial studies are inconclusive. However, its specificity is limited, and findings may be falsely positive for up to 2 years after total joint arthroplasty because of physiologic bone remodeling.

» Labeled leukocyte scintigraphy or gallium scintigraphy can improve diagnostic accuracy in patients with a positive bone scan and suspected musculoskeletal or periprosthetic joint infection.

» 18-Fluorodeoxyglucose PET/CT demonstrates high sensitivity and specificity for diagnosing bone neoplasms, infections, and metabolic disorders. Emerging PET/magnetic resonance imaging technology offers reduced radiation exposure and greater soft-tissue detail but presents technical and cost challenges.

» SPECT/CT provides valuable functional and anatomic detail for characterizing the extent and location of bone pathology, serving as an important adjunct to other imaging modalities.

» Ultimately, the choice of nuclear imaging modality should consider the specific clinical context, diagnostic accuracy, impact on management, and cost-effectiveness on a case-by-case basis.

Nuclear imaging is an invaluable tool in the diagnosis and management of various orthopaedic conditions, providing real-time functional and metabolic information that complements traditional anatomic imaging modalities[1-5]. By detecting pathophysiologic changes at the molecular level, nuclear imaging techniques offer unique insights into disease processes and treatment responses, often before structural abnormalities become apparent on conventional radiographs, computed tomography (CT), or magnetic resonance imaging (MRI)[6].

In recent years, advancements in nuclear medicine technology have expanded the applications of these modalities in orthopaedic practice. Bone scintigraphy, a long-established technique, remains a highly sensitive first-line tool for detecting fractures, infections, and malignancies[7-10].

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Labeled leukocyte scintigraphy has emerged as a valuable adjunct for diagnosing musculoskeletal infections, particularly in the setting of periprosthetic joint implants[7,11,12]. Positron emission tomography (PET), especially when combined with CT or MRI, provides exceptional diagnostic accuracy for evaluating bone tumors, metastatic disease, and periprosthetic joint infections[13-16]. Furthermore, single-photon emission computed tomography (SPECT) and SPECT/CT have shown promise in identifying pain generators and guiding targeted treatments for complex orthopaedic conditions[6,7,17,18].

However, despite the diagnostic advantages of nuclear imaging, its utilization in orthopaedic practice remains variable[1,19]. This may be attributed to factors such as limited accessibility, higher costs compared with conventional imaging, and a lack of familiarity among orthopaedic surgeons regarding the indications, techniques, and interpretation of these studies. Moreover, the optimal diagnostic algorithms incorporating nuclear imaging alongside other modalities have not been well-defined for many orthopaedic conditions[18].

In this comprehensive review, we aim to bridge this knowledge gap by providing an up-to-date analysis of the current state of nuclear medicine in orthopaedics. We will discuss the principles, indications, and performance characteristics of various nuclear imaging techniques relevant to orthopaedic practice. By critically examining the available evidence, we seek to guide judicious utilization of these powerful diagnostic tools and identify areas for future research to further refine their role in patient care. An electronic search was performed in MEDLINE through PubMed. All possible combinations of the following keywords were used for the search: "bone scintigraphy," "bone scan," "labeled leukocyte scintigraphy," "white blood cell scan," "leukocyte scintigraphy," "Gallium-67 citrate (Ga-67) scintigraphy," "gallium scintigraphy," "Ga-67 scintigraphy," "positron emission tomography (PET) scan," "PET," "positron emission tomography," "PET-CT," "Positron Emission Tomography-Computed Tomography," "PET/MR," "PET-MRI," "Positron Emission Tomography-Magnetic Resonance Imaging," "SPECT," "Single Photon Emission Computed Tomography," "total joint arthroplasty," "TJA," "Total hip arthroplasty," "THA," "Total Knee Arthroplasty," "TKA," "Periprosthetic Joint Infection," "PJI," "trauma," "fracture," "fragility fracture," "open reduction internal fixation," "ORIF," "avascular necrosis," "AVN," "infection," "osteomyelitis," "oncology," "metastasis," "tumor," and "cancer." Furthermore, the references of the included articles were manually checked for potential inclusion and further potential information.

Modalities

Bone Scintigraphy

Bone scintigraphy, commonly referred to as bone scan, is commonly used in orthopaedic surgery because of its high sensitivity, low cost, and accessibility[8]. It can be a useful tool in the diagnosis and management of varied pathology including insufficiency and occult fractures, metastatic lesions, staging and surveillance of sarcoma, musculoskeletal infection, and nonaccidental trauma (Table I). It also plays an important role in the workup of painful total joint arthroplasty (TJA).

In bone scintigraphy, a radiotracer such as technetium-99m (99mTc), technetium-99m hydroxymethylene diphosphonate (99mTc-HMDP), or technetium pyrophosphate (99mTc-PYP) is injected intravenously, and a 3-phase bone scan using a gamma camera is used to create planar images that map the tracer[21]. Specifically, these 3 phases are the flow or angiographic phase, the blood pool phase, and the delayed phase[22]. The flow phase is a set of images that are obtained at 2 to 5 seconds per frame for 60 seconds and can be used for the determination of perfusion and blood flow to specific areas[22]. The blood pool phase is an image obtained in the same field of view that is usually obtained at 5 minutes after injection, which makes it useful for determining inflammation using capillary dilation and flow rates[23]. The delayed phase is generally taken at 2 to 4 hours after injection, which makes it especially useful for determining uptake of radiotracer because of bone response of the scan. A specific application for the 3-phase bone scan is to determine whether a patient has complex regional pain syndrome (CRPS)[24-28]. Although CRPS is generally diagnosed clinically using the Budapest criteria, the 3-phase bone scan is commonly ordered by clinicians for confirmation of the diagnosis. However, the sensitivity and specificity of the 3-phase bone scan for CRPS have a massive range, and the use of the 3-phase bone scan for CRPS diagnosis remains controversial[24,26,28-30]. Bone-seeking radiotracers accumulate on the surface of bone mineral matrix at areas of high metabolic activity seen with bone remodeling and inflammatory reactions (Fig. 1).

Total Joint Arthroplasty

Bone scintigraphy has been extensively investigated in the assessment of pain after TJA[8,31,32]. In the postoperative period, increased metabolic activity is expected and represents physiologic bone remodeling. Studies in asymptomatic patients have shown uptake around cemented total knee arthroplasties (TKAs) in 20% of patients at 1 year postoperatively and 10% at 2 years[33], as well as 10% to 30% in cemented total hip arthroplasties (THAs), typically around the acetabulum, trochanters, and tip of the stem. In cementless THA, uptake ratios were seen to stabilize after 3 months[21,34,35].

However, after the immediate postoperative period, increased uptake is generally a manifestation of an inflammatory reaction caused by loosening, polyethylene debris, or periprosthetic joint infection (PJI). The abnormal uptake pattern will be related to the type

TABLE I Graded Recommendations for the Application of Nuclear Imaging within Orthopaedic Surgery

Technique	Recommendation	Grade of Recommendation*
Bone scintigraphy	Useful screening test, accompanied by other techniques	C
Labeled leukocyte scintigraphy	Used to differentiate infection from aseptic loosening	B
Gallium scintigraphy	Limited data supporting use. Existing data suboptimal	B
Positron emission tomography	Used for determining metastatic lesions and response to treatment. Promising data for infectious etiologies	I
Single-photon emission computed tomography/computed tomography	Limited data supporting use. Existing data is promising	I

*According to Wright[20], grade A indicates good evidence (Level I studies with consistent findings) for or against recommending intervention; grade B, fair evidence (Level II or III studies with consistent findings) for or against recommending intervention; grade C, poor-quality evidence (Level IV or V studies with consistent findings) for or against recommending intervention; and grade I, insufficient or conflicting evidence not allowing a recommendation for or against intervention.

of implant, motion across the prosthesis-cement-bone interface, and the use of cement vs. a porous-coated cementless implant. In the evaluation of painful arthroplasty, a key issue is to distinguish between infection and aseptic loosening. Nagoya et al.[36] evaluated the use of 3-phase bone scintigraphy in patients suspected of THA PJI and proposed that uptake during the blood-pooled phase without uptake in the late phase is suggestive of aseptic loosening, whereas PJI was more likely to show uptake in all 3 phases and reported high sensitivity and specificity. However, the overall literature regarding diagnostic efficiency of bone scintigraphy shows considerable variability. In meta-analyses by Verberne et al., bone scintigraphy had a pooled sensitivity and specificity of 93% and 56%, respectively, for PJI after TKA[37] and 80% and 69% for PJI after THA[38]. Studies have shown bone scintigraphy to have higher sensitivity and lower specificity compared with fluorodeoxyglucose (FDG) PET, while being more cost-effective and available as a tool to differentiate infection and aseptic loosening[8,39-41].

Trauma

Bone scintigraphy is useful in the trauma setting because it can detect and discriminate between different phases of fracture healing. Specifically, there is a different scintigraphic appearance of

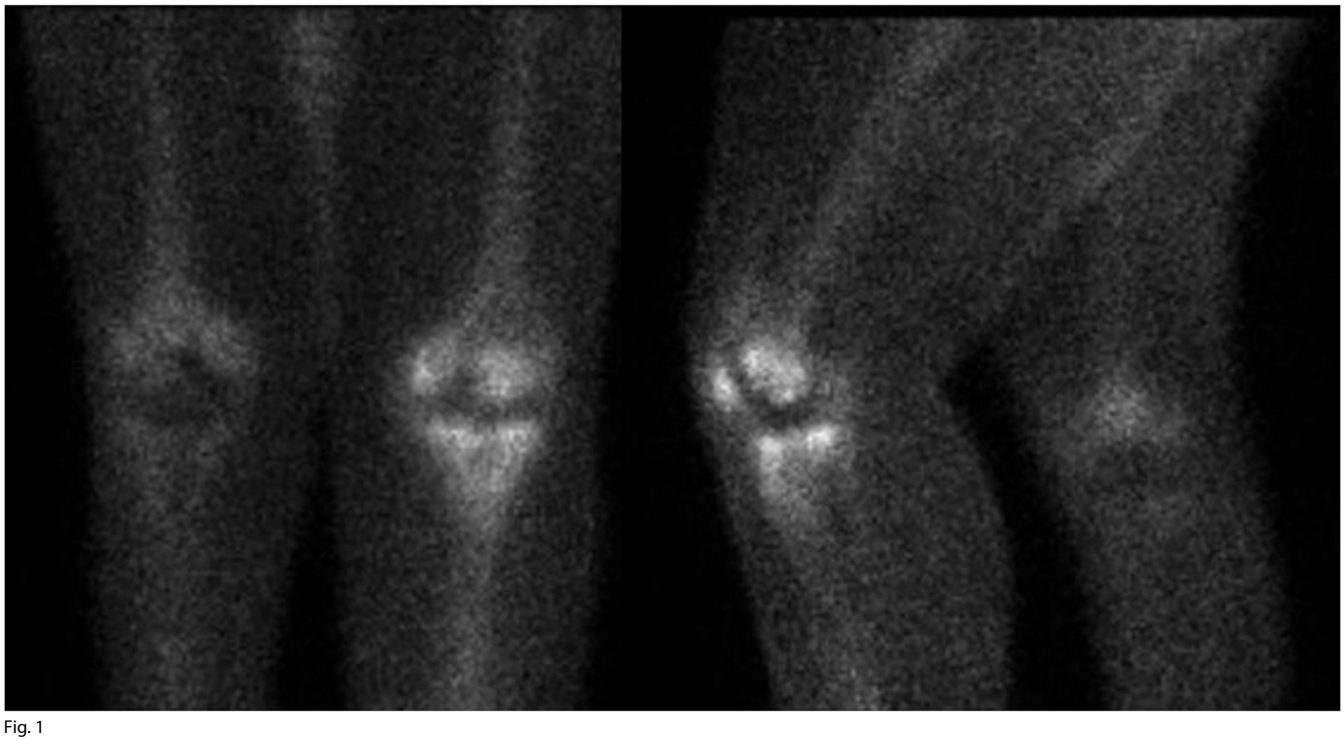

Fig. 1

Single-photon emission computed tomography—indium-111–labeled white blood cell.

fracture in the acute phase (up to 4 weeks), subacute phase (2-3 months), and progressive healing phase (>3 months)[9]. Uptake normalizes in 6 months to 2 years, but will persist in cases of nonunion or infection[9,42]. This is particularly useful in the detection of occult fractures.

In an extensive literature review, Hsu et al. reported >95% sensitivity and >99% specificity in detecting occult fractures in areas such as the carpal bones, proximal femur, ribs, talar dome, pelvis, and spine[7]. In the setting of scaphoid fractures, studies agree it is statistically the best diagnostic modality to establish a definitive diagnosis[17,43,44]. In occult hip fractures, bone scintigraphy is useful, but inferior to MRI (sensitivity 97.8% and 100%, respectively; specificity 94% and 100%, respectively)[7,8,45,46]. Similar results are seen in the diagnosis of sacral insufficiency fractures, with bone scintigraphy showing lower accuracy than MRI and CT[47]. In spinal fragility fractures, however, bone scintigraphy can help determine the presence and acuity of the fracture[48].

Avascular Necrosis

Bone scintigraphy is also useful in monitoring the development of avascular necrosis (AVN) in the femoral head, hand, and foot[49]. For instance, after nondisplaced femoral neck fractures after surgery, bone scintigraphy can be used to monitor healing and development of AVN in the femoral head, as uptake changes in real time[8]. In idiopathic AVN of the hip in pediatric patients, decreased tracer uptake can be observed early in the disease, which can be useful if bone scintigraphy is pursued early in the disease[50]. In early Kienbock disease (osteonecrosis of the lunate) and Freiberg disease (osteonecrosis of the lesser toes), bone scintigraphy can identify early signs of osteonecrosis when plain radiographs are normal[51-53].

Musculoskeletal Infection

Triple-phase bone scan is a highly sensitive, inexpensive, accessible whole-body imaging modality that allows for examination of bones and soft tissue without interference from orthopaedic implants, a benefit over CT and MRI. It is highly sensitive to bone and soft-tissue infection and can be valuable as a screening tool. However, its specificity is relatively low, particularly in the acute phase. It is often difficult to distinguish infection from fracture, a neuropathic joint, postoperative changes, or aseptic loosening of a prosthesis on a bone scan. Thus, in complicated cases, other nuclear studies may be preferred[6-8,49,54].

The pattern of uptake during bone scintigraphy will aid in diagnosis. Although osteomyelitis will manifest as increased uptake in all 3 phases, soft-tissue infection will generally only be positive in the first two[4]. It can also be used to detect multiple sites of primary and hematogenous osteomyelitis, which is useful in the pediatric population. This has been suggested as an appropriate first test before MRI in cases of suspected hematogenous osteomyelitis with negative radiographs[7,55]. In spinal infections, MRI is the preferred diagnostic tool at symptom onset, showing the highest sensitivity and specificity. However, the accuracy of MRI decreases in the postoperative period because of a combination of hardware artifacts and unpredictable imaging characteristics after surgical or medical management[4,54]. In this setting, bone scintigraphy has shown greater accuracy in detecting primary and postoperative spinal infections (88.5%), albeit with low specificity (35.8%)[7,54].

Musculoskeletal Oncology

In musculoskeletal oncology, bone scintigraphy is a useful, widely available modality that can evaluate the entire body to identify early bone involvement, determine extent of skeletal disease, and monitor lesion progression and response to therapy over time[8,56]. Neoplasia tends to show increased uptake, given its increased metabolism, which can be detected by bone scintigraphy with a sensitivity of up to 95%[3].

In patients with a primary bone lesion, bone scintigraphy has a role in evaluating osseous and soft-tissue involvement, presence of skip lesions, metastasis, and response to therapy. For instance, it has shown higher sensitivity than FDG-PET in detection of osseous metastases from osteosarcoma and inferior but acceptable performance in Ewing sarcoma[8,57-61].

Labeled Leukocyte Scintigraphy

Labeled leukocyte scintigraphy (or white blood cell [WBC] scan) remains the nuclear medicine study of choice to evaluate orthopaedic infections in the immunocompetent population. They are useful in diagnosing infection around metallic implants and can help differentiate between osteomyelitis and a neuropathic joint, among other applications[42,49,62] (Fig. 2; Table II). It is typically the nuclear medicine test performed to increase specificity after a positive bone scan.

In labeled leukocyte scintigraphy, autologous WBCs are labeled with a radioactive nuclide (indium-111 oxyquinoline or Tc-99m hexamethylpropylene amine oxime) and reintroduced in the circulation (Fig. 3). Radiolabeled inflammatory cells, mostly neutrophils, then migrate to sites of neutrophil-mediated inflammation such as bacterial infection[11,62].

Total Joint Arthroplasty

Labeled leukocyte scintigraphy is the nuclear study of choice to diagnose PJI, and it is typically performed after a positive bone scan. Labeled WBCs (mostly neutrophils) migrate and show increased uptake in zones of infection, but do not accumulate at sites of increased bone turnover or remodeling in the absence of infection[62,63]. Thus, this modality is able to distinguish between an infected prosthesis and the inflamed, aseptically loosened prosthesis in which neutrophils are absent. This improves accuracy in identifying PJI[11,63].

TABLE II Summary of Imaging Techniques*

Technique	Radiotracer	Test Parameters	Positive Study	Negative Study	Advantages	Disadvantages	Applications
Bone scintigraphy	^{99m}TC diphosphonate ^{99m}TC-hydroxymethelene diphosphonate ^{99m}TC pyrophosphate	IV injection of radiotracer Flow perfusion scan after injection Bone scan 2-4 hours after initial injection	Uptake of tracer that is greater than the ipsilateral extremity	Uptake of tracer equal or less than the ipsilateral extremity	High sensitivity Availability	Variable specificity Invasive Limited use in early postoperative period	Trauma Pain after total joint arthroplasty
Labeled leukocyte scintigraphy	Indium-111 oxyquinoline or ^{99m}TC hexamethylpropylene amine oxime	Delayed images at 4-6 hours Late images at 0-24 hours	Increased tracer uptake at location positive bone scintigraphy finding	No increased tracer uptake at site of interest in bone scintigraphy	High sensitivity High specificity	Additional radiation Patient discomfort Blood product exposure Laborious	Osteomyelitis PJI
Gallium scintigraphy	Ga-67 citrate	IV injection of radiotracer Flow perfusion scan after injection Bone scan 2-4 hours after initial injection	Uptake of tracer that is greater than the ipsilateral extremity	Uptake of tracer equal or less than the ipsilateral extremity	Greater specificity than bone scintigraphy Can be used in neutropenic patients	Higher radiation exposure Greater risk of cardiopulmonary adverse events Not commonly performed	Spine infections PJI
Positron emission tomography	^{99m}Tc-labeled phosphates 18F-FDG 18-F sodium fluoride	Patient achieves blood glucose <200 mg/dL through 4-hour fast IV injection of radiotracer The patient rests for 1 hour, and imaging was performed 1-2 hours after initial injection	Contingent on uptake pattern: increased uptake in neck, whole cup, and shaft consistent with loosening; uptake along entire implant-bone interface consistent with infection	Contingent on uptake pattern: no increased uptake, uptake around the prosthetic neck, or uptake along the neck and part of cup or proximal shaft	Sensitive for inflammation Excellent spatial resolution Fast	Limited infection specificity, should not be used within 1 year after surgery Attenuation artifacts Low accuracy for TKA Expensive Limited availability Uncertain role in prosthetic joint imaging	Bone neoplasms Osteomyelitis Bone metabolic disorders
SPECT/CT	99mTC Iodine-123 Thallium-201	IV injection of radiotracer Rotating gamma camera detector and tomographic imaging obtained 2-4 hours after initial injection	>2 mm of latency Early phase tracer accumulation	Radiotracer uptake not uniform, contingent on cement use and implant type	Excellent spatial resolution Can potentially distinguish soft tissue from bone infection	Attenuation artifacts Should not be used within 1 year of surgery Uncertain role in prosthetic joint imaging	Aseptic pain after total joint arthroplasty Complex traumatic injuries PJI Osteomyelitis localization Bone metastases

*CT = computed tomography, IV = intravenous, PJI = periprosthetic joint infection, SPECT = single-photon emission computed tomography, and TKA = total knee arthroplasty.

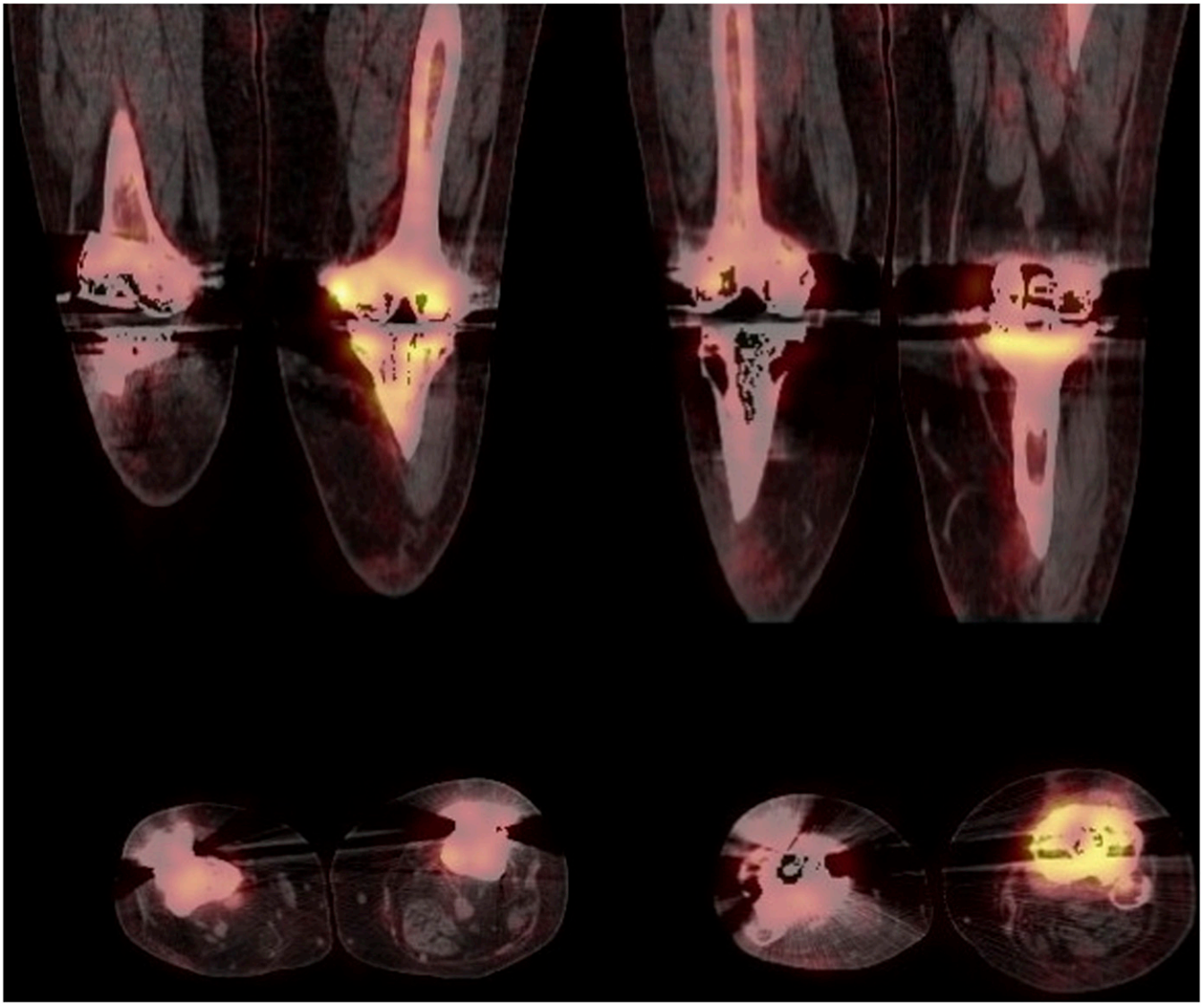

Fig. 2

Single-photon emission computed tomography—indium-111–labeled white blood cell.

The results of labeled leukocyte scintigraphy are variable. Some investigators report that the technique is highly sensitive but not specific, whereas others report high specificity but low sensitivity[32,63]. Notably, in their systematic review and meta-analysis, Verbene et al.[37,38] reported a pooled sensitivity and specificity of 88% and 92% for PJI in THA and 84% and 77% for PJI in TKA. The high variability in reported sensitivities and specificities has limited the role of isolated leukocyte scintigraphy in arthroplasty. However, their use in combination with other modalities can overcome many of these limitations[32,37,38,63].

Musculoskeletal Infection

The diagnosis of musculoskeletal infection can be clinically challenging, and labeled leukocyte scintigraphy has a meaningful role in the process. In the setting of intact bone, bone scintigraphy is usually sufficient. However, in cases of complicating osteomyelitis, in which infection is superimposed on processes that increase bone remodeling, labeled leukocyte scintigraphy is the nuclear medicine study of choice, usually in combination with bone marrow imaging to increase accuracy[11,54]. Although WBCs do not usually accumulate in areas of increased bone turnover, they do accumulate in the bone marrow to different degrees and migrate to areas of infection[7,62,64].

Fracture-related osteomyelitis, also referred to as post-traumatic osteomyelitis, is another area in which labeled leukocyte scintigraphy can play a meaningful role. After orthopaedic trauma, diagnosis of infection can be difficult because of a number of factors. First, bone remodeling and inflammation are expected as part of the fracture healing process. Moreover, uptake on bone scan may be abnormal for up to 2 years after injury, and metal implants can influence imaging outcomes[5]. Labeled leukocyte scans can

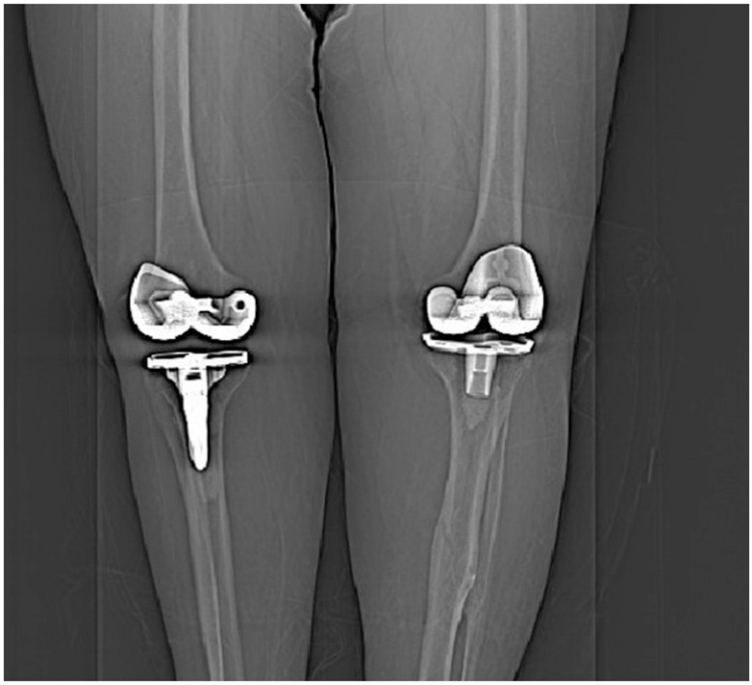

Fig. 3

Single-photon emission computed tomography (SPECT)—indium-111–labeled white blood cell—corresponding technetium-99m sulfur colloid matching uptake.

overcome these factors, targeting increased leukocyte uptake at sites of infection. However, this study presents a number of disadvantages: They require significant preparatory work, and they involve re-injecting cells into a suspected infected patient and require scans at both 3 to 4 hours and 24 hours after injection, which can be costly and time-consuming[5].

Gallium Scintigraphy

Gallium-67 citrate (Ga-67) scintigraphy has been used for decades as a diagnostic tool to localize musculoskeletal infection. Gallium-67 binds to transferrin in plasma and uses its receptors to enter the cell. Increased blood flow and vascular membrane permeability result in increased delivery and accumulation of transferring-bound gallium at inflammatory foci. (Direct bacterial uptake of gallium has also been reported[62].)

Total Joint Arthroplasty

In arthroplasty, gallium scintigraphy has been used to aid the diagnosis of PJI since the 1970s[62,65]. However, this modality is not accurate enough to diagnose PJI alone because gallium not only accumulates in PJI but also in postoperative joints, aseptic loosening, fractures, and reactions to bone cement. Although it can be used in combination with bone scintigraphy to increase accuracy, it has not shown significant improvement over bone scintigraphy alone, whereas introducing drawbacks relates to the use of gallium-67 citrate such as allergic reactions and increased radiation dose when compared with other tracers[32,63,66-69].

Spinal Pathology

In the spine, gallium scans have been found to be the most sensitive in detecting primary and postoperative infections, albeit with low specificity[7,54]. In osteomyelitis, gallium scintigraphy can be useful in distinguishing cellulitis from osteomyelitis, for precise localization of a focus of infection, and for separating acute from chronic osteomyelitis[67]. Finally, gallium scintigraphy is able to detect infection in patients with few or no circulating white cells and thus is very useful in the immunocompromised population[62].

PET Scan

PET scans produce 3-dimensional images through the detection of positron elimination events indirectly emanating from a positron imaging radioactive tracer that is typically introduced intravenously at/before imaging, depending on the desired sequence[7,49,70]. Injectable tracers visualize blood flow, capillary bed permeability, as well as soft-tissue and bone cellular metabolic activity, the latter being the predominant implementation in orthopaedic surgery. PET scans leverage 3 primary tracers to evaluate for orthopaedic derangements: traditional 99mTc-labeled phosphates, fluorine 18F-FDG, relatively less commonly used fluorine-18 sodium fluoride (18F) ion[12,13,31,70-72]. 18F-FDG is a veritable cellular metabolism marker because its uptake depends on crossing the cellular membrane through open glucose transporters. Conversely, the 18F isotope is reliably taken up by osseous tissue and deposits on surfaces corresponding with high bone remodeling/turnover. The above isotopes demonstrate superior capillary permeability to that of TC-99 mm phosphonate as well as a better target-to-background ratio, which translates into improved contrast/localization images[7].

As such, PET scans are widely used to diagnose and monitor primary/metastatic bone neoplasms, infections,

and bone metabolic disorders, including bone healing vs. nonunion, stress fractures, and graft incorporation/fusion[7,13,14,54,70,73-75]. More recently, PET scans have been increasingly used in conjunction with CT (PET-CT) and MRI (PET-MRI), thereby affording a combined functional-structural imaging modality for improved anatomic localization[15,76-79].

Musculoskeletal Oncology

Overall, PET scan is not the gold standard first-line modality used for initial detection of primary/secondary metastatic bone lesions owing, in part, to the difficulty in differentiating between inflammatory and neoplastic lesions on PET scan[7,13,70,80,81]. However, PET scans can provide in vivo semiquantitative estimates of tissue metabolic rates using glucose intake as a surrogate. Consequently, PET scans are leveraged to gauge differential metabolic rates between highly active malignant lesions and benign tumors of lower metabolic footprint once infectious etiology is not in question. PET scans can provide a venue for evaluating neoadjuvant/radiation therapeutic effect to estimate tissue viability. Combination of PET scan with CT/MRI further enhances its utility and determining lesion size/location. Furthermore, sensitivity can be modified based on tracer type; F-FDG PET demonstrates superior sensitivity in detecting bone marrow, lytic metastasis, and soft-tissue lesions, whereas 18F tracers are more capable of evaluating osteoblastic and osteolytic lesions with high sensitivity.

Musculoskeletal Infections: Prosthetic Joint Septic/Aseptic Loosening

Activated leukocytes demonstrate increased metabolic activity with subsequent increase in glucose consumption[32]. Although said increased energy consumption acts as the scientific basis for FDG-PET ability to detect infectious foci, the exact mechanism of leukocyte FDG uptake is regulated by the ratio of phosphatase and hexokinase which remains poorly understood[12,31,72,82]. As such, F-FDG PET has demonstrated utility in diagnosing bone and soft-tissue infections with sensitivity/specificity of up to 100%/83% for bone and 96%/70% for soft-tissue infections respectively[7,39,83]. These values are slightly higher or comparable with those demonstrated by contrasted MRI studies, which have reported sensitivities of 88% and specificity of 93% and diagnosis of chronic musculoskeletal infections[84-86]. The aforementioned equivalence does not qualify PET scans as the gold standard diagnostic modality for musculoskeletal infections, given the associated radiation exposure compared with MRI without added diagnostic utility in common infections among MRI-eligible patients. However, FDG-PET scan's role in infection diagnosis accentuates the setting of concomitant orthopaedic implants, which would otherwise limit MRI utility even with use of metal artifact suppression protocols. Similarly, FDG-PET scan affords infectious diagnostic utility among MRI-ineligible patients because of retained metallic fragments or non–MRI-compatible devices. When evaluating for PJI, adding CT (FDG-PET/CT) enhances anatomic localization and metal artifact attenuation correction. Indeed, FDG-PET/CT has reported sensitivity of 94.1% and specificity of 87.3% in detecting peripheral osteomyelitis in the presence of orthopaedic implants vs. 88.2% and 84.7% for MRI, respectively[54,87].

Although the evidence for FDG-PET in diagnosis of PJI remains less widespread than bone scintigraphy, literature to date is promising[7] (Table III). FDG-PET/CT use is not recommended until at least 1 year after primary TJA, given that the initial surgical inflammatory response can effectuate increased local tissue metabolic activity and spurious positive results. It is critical to note that PET scan is not considered a standalone criterion for diagnosis of PJI or loosening; however, its use is gaining traction to identify underlying causes of chronic persistent prosthetic joint pain in the absence of gross radiographic loosening or reliable indicators of infection as reflected by Musculoskeletal Infection Society criteria[12,72,115,131].

Obtained images are interpreted qualitatively and semiquantitative based on amount and pattern of tissue uptake. Specifically, 5 different patterns of FDG-PET distribution have been demonstrated in the literature, over which the initial 3 do not indicate concern for loosening or infection: (1) absence of increased uptake; (2) localized uptake around the prosthetic neck; and (3) localized uptake around the prosthetic neck in addition to part of the top and/or proximal femoral shaft[7,132]. Conversely, PJI/aseptic loosening is characterized by diffuse uptake throughout all prosthetic-bone interfaces and periprosthetic soft tissue[16,132,133]. Uptake around the femoral head and neck has been suggested to be associated with synovitis vs. infection. Still, it requires further interpretation in the context of associated laboratory values and other advanced imaging modalities.

Emerging Developments: PET/MRI

Technological advances over the past decade allow for the development of PET/MR, consisting of a whole-body MRI combined with a PET scan similar to CT scans in the context of PET/CT[76,77,79]. PET MRI might provide several advantages over the traditional PET/CT, especially in the pediatric population given reduction to exposure to ionizing radiation. Similarly, young adults who may require repeat follow-up imaging for an extended period might benefit from such a protective effect. Furthermore, PET MRI affords greater soft-tissue delineation compared with its CT counterpart, which is critical to identifying ligamentous/tendinous and muscular derangements[134]. In addition, because MRI is generally a part of oncologic evaluation of suspected lesions, using PET MRI can serve as a "one-stop shop" for patient workup or diagnostic MRI of the pertinent

TABLE III Potential Future Approaches to Imaging Modalities*

Modality	Studies	Directions for Development/Future Research
Bone scintigraphy		
Total joint arthroplasty	88-91	Unilateral knee arthroplasty aseptic and septic loosening
		Disease activity in rheumatoid arthritis
Trauma	92,93	Supplementing negative skeletal surveys for pediatric fractures
Avascular necrosis	94-96	Avascular necrosis of the jaw
Musculoskeletal infection	97,98	Microorganism specific imaging
Musculoskeletal oncology	99-102	Improved efficiency and lowered cost secondary to AI assistance
Labeled leukocyte scintigraphy		
Total joint arthroplasty/musculoskeletal infection	103,104	Chronic PJI
Gallium scintigraphy		
Musculoskeletal infection/spine	105,106	Osteotomy determination
		Ga-68-citrate imaging
PJI	107-109	Chronic PJI vs. aseptic loosening determination
PET scan		
Musculoskeletal oncology	110-114	Whole-body PET systems
Musculoskeletal infection/prosthetic joint septic/aseptic loosening	115-117	Simultaneous PET/MRI for PJI infection foci
		Aseptic loosening vs. infection determination
SPECT/CT		
Total joint arthroplasty	118-122	Painful noninfected knees
		Aseptic loosening
Trauma	123	Necrotic bone fragment assessment
Spinal pathology	124,125	Evaluating recurrent or persistent pain
		Chronic infection determination
Musculoskeletal infection	126-128	Further determination after inconclusive testing
		Outcome prediction
Musculoskeletal oncology	129,130	AI-supported detection and diagnosis

*AI = artificial intelligence, CT = computed tomography, MRI = magnetic resonance imaging, PET = positron emission tomography, PJI = periprosthetic joint infection, and SPECT = single-photon emission computed tomography.

anatomic location can be concurrently performed[134]. Although investigations into the utility of PET MRI vs. PET CT and musculoskeletal applications are to be performed, there are anticipated downsides to PET MRI utilization. For example, PET CT has improved attenuation correction in comparison with PET MRI, a critical benefit in the setting of orthopaedic medical hardware/implants. Furthermore, the availability and low cost of PET/CT limits the use of the significantly more expensive and time-consuming PET/MRI. PET/CT is also often indicated as a substitute among patients who have contraindications to MRI use, such as implantable devices that would preclude the use of PET MRI. Finally, technical challenges associated with this field's novelty/continual advancement include persistent artifact distortion with more extensive fields of view and limited experience with interpretation.

SPECT and SPECT/CT

SPECT is used to provide clinicians with highly detailed information on the physiology of tissues throughout the body. Similar to bone scintigraphy, SPECT most often relies on a combination of technetium-99m and a tissue-specific, biologically active ligand (Fig. 4). With a relatively short half-life, Tc minimizes radiation exposure to the patient while providing more clear images at higher dosages[135]. However, SPECT is notably limited in its ability to provide sufficient anatomical detail for disease characterization. Clinicians can effectively address this deficiency by adding CT imaging. In doing so, they can obtain functional data from SPECT while also gathering more detailed anatomical information from CT, thereby improving diagnostic accuracy[136].

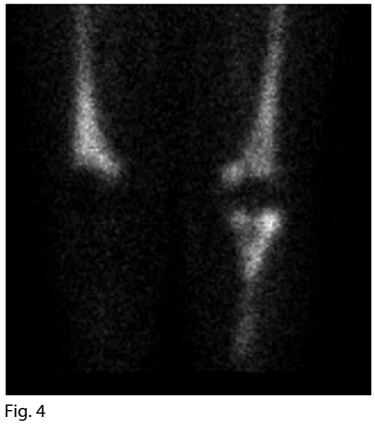

Fig. 4
Three-phase bone scan.

Total Joint Arthroplasty

Workup for joint pain after TJA can be particularly problematic, as pain can be secondary to several causes. Anzola et al.[118] performed a systematic review on the diagnostic accuracy of SPECT/CT among noninfected TKA patients experiencing pain postoperatively, demonstrating notably high sensitivity and specificity in cases of loosening, patellofemoral disorders, and malalignment. Bao et al.[119] validated these findings, demonstrating a high diagnostic accuracy (97%) in cases of postoperative loosening among both THA and TKA patients with persistent pain using SPECT/CT.

Trauma

Although most orthopaedic pathology involving trauma can be diagnosed using CT or MRI, SPECT/CT can be used when anatomically complex regions including the pelvis and spine are involved, as discussed by Scheyerer et al.[137] Specifically, imaging detection of occult fractures along with identification of inflammatory bone/joint disease, chronic diseases, and postoperative complications including instability warrant further workup through nuclear imaging[137].

Spinal Pathology

Scharf highlighted the clinical utility of SPECT/CT in differentiating spinal abnormalities secondary to pars fractures and other conditions, which appear similar on MRI, including facet joint arthritis and transitional lumbosacral vertebral pain (Bertolotti syndrome)[138]. Kato et al.[139] addressed challenges in diagnosing low back pain in the setting of degenerative spine disease among 5 cases of elderly patients. Using SPECT/CT, they were able to accurately diagnose and treat conditions including degenerative discopathy and insufficiency fracture, drastically improving patient symptoms and avoiding unnecessary surgery.

Musculoskeletal Infection

Although not conventionally used, SPECT/CT can be of use in performing periprosthetic joint infection (PJI) assessment. Specifically, SPECT/CT offers a far more accurate depiction of bone infection localization, allowing for a more detailed characterization of the extent of infection spread. Therefore, it can be implemented after the presence of infection is indicated through bone scintigraphy, as described by Valero-Martínez et al.[140] Tian et al.[120] retrospectively analyzed 74 prosthetic joints with suspicion for loosening or infection, including both knees and hips, finding SPECT/CT to be highly viable in differentiating infection from loosening, particularly among hip prostheses. Similarly, Yama et al.[141] found SPECT/CT to be useful in differentiating cases of infection from noninfection at the hip.

Musculoskeletal Oncology

Bone scintigraphy is best used for the detection of musculoskeletal lesions. However, its ability to differentiate benign pathologies from malignant is highly limited, with markedly low anatomical specificity. Addressing this deficiency, SPECT/CT has shown tremendous potential in characterizing the extent of bone metastases. Numerous studies have demonstrated notably higher definitive diagnoses using SPECT/CT when compared with SPECT alone, as reviewed by Kopula et al.[142-146] Of note, lesions can go undetected when low-dose CT is performed under the CT portion, and separate CT and SPECT studies have yet to be compared with SPECT/CT when performed concurrently[147-150].

Conclusion

Nuclear imaging plays a vital role in the diagnosis and management of orthopaedic conditions, providing valuable functional and metabolic information that complements traditional anatomic imaging modalities. By understanding the strengths and limitations of each technique and collaborating closely with nuclear medicine specialists, orthopaedic surgeons can harness the full potential of these powerful diagnostic tools to improve patient outcomes. As the field of nuclear medicine continues to evolve, it is essential for the orthopaedic community to engage in ongoing education, research, and multidisciplinary collaboration to optimize the utilization of these modalities in musculoskeletal imaging and patient care.

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