Evaluation of Osseous Metastasis in Bone Scintigraphy

Diego Davila, MD, Alexander Antoniou, MD, and Muhammad A. Chaudhry, MD

Bone scintigraphy (BS) is an imaging tool commonly used for screening patients with cancer, especially those with high prevalence of osseous metastases including the breast, prostate, lung, thyroid, and kidney, which account for 80% of osseous metastasis. BS has been shown to be of value in the initial and subsequent treatment strategy of various malignancies. The purpose of this article is to evaluate the technical and imaging aspects of BS and to examine the present research into improved detection of osseous metastasis.

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Introduction

An estimated 1.6 million new cancer cases were diagnosed in 2013. Approximately 50% of these tumors can metastasize to the bone.2 Bone is the third most common site for metastatic disease (after lung and liver) and is more commonly found in adult patients (>40 years of age).

Primary cancers can spread to nearly all tissues of the body, but certain cancers such as breast, prostate, lung, thyroid, and kidney cancers are more likely to spread to bone. According to the American Cancer Society, more than 67% of breast and prostate cancers and approximately 33% of lung, thyroid, and kidney cancers that spread to other parts of the body spread to the bones.3 More specifically, at postmortem examination, the reported incidence of bone metastases was 73% for breast cancer, 68% for prostate cancer, 42% for thyroid, 35% for kidney, 36% for lung, and 5% for gastrointestinal tract.4

Among people with the similar malignancies, bulky tumors that have already spread to lymph nodes are generally more likely to spread to bone. In a variety of malignancies, high-grade and specific genetic mutations favor spread to bones. Additionally, having a cancer that is found after it has spread to other organs raises your risk of bone metastases.

Common sites for bone metastases include the spine (typically can result in a vertebral compression fractures), pelvis (hip), upper leg bone (femur), upper arm bone (humerus), ribs, and skull.5

The most common symptom of bone involvement is pain. Other symptoms vary, depending on the location and size of the cancer. Surgery is often the main treatment for bone cancer. Other treatments may include amputation, chemotherapy, and radiation therapy. Because bone cancer recurs after treatment, regular follow-up visits are important.1,3

In general, once bone metastases are present, patient survival is dramatically reduced. Most patients with metastatic bone disease survive for 6-48 months following diagnosis. Among patients with prostate and breast cancer, the median survival from time of diagnosis of bone metastasis is estimated in years. In contrast, patients with lung cancer had a median survival of only a few months.3,4

Technical Aspects of Bone Scintigraphy

Radiopharmaceuticals

The typical radiopharmaceuticals are 99mTc-labeled phosphonates (more commonly used) or phosphates. The phosphonates include a class of molecules known as bisphosphonates or biphosphonates, such as medronate (MDP) or oxidronate that consist of 2 phosphate groups (PO3) linked to carbon in what is commonly referred to a P–C–P linkage. They mimic endogenous pyrophosphate (P–O–P), which accumulates in bone for the formation of hydroxylapatite (Ca10(PO4)(OH)2).5,6 Osteoclasts, which are increased in osteoporosis, ingest the hydroxylapatite. Drugs

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aimed at the treatment of osteoporosis are bisphosphonates with an alteration of the long R2 side chain that defines its chemical properties. They are commonly grouped into nitrogen-containing and non–nitrogen-containing bisphosphonates whose main mechanism of action is apoptosis of osteoclast cells either via generation of a toxic analogue of adenosine triphosphate or inhibition of the farnesyl diphosphate synthase.5,6 The basic principle of bone scintigraphy (BS) is thus accumulation of radiotracer in areas of increased hydroxylapatite deposition or bone formation.

**Dosage.** The recommended administered activity for adult patients is 20-30 mCi (740-1110 MBq), with a weight-dependent activity level for obese patients (250-300 μCi/kg up to 40 mCi) and pediatric patients (250-300 μCi/kg with a minimum of 1 mCi). Careful quality control is necessary as introduction of oxygen into the 99mTc-labeled phosphonates can lead to oxidation and subsequent imaging artifact from free pertechnetate.7,8

**18F-Sodium Fluoride**

18F-sodium fluoride (18F-NaF) is a highly sensitive bone-seeking PET tracer used for the detection of skeletal abnormalities. The uptake mechanism of 18F-fluoride resembles that of 99mTc-MDP with better pharmacokinetic characteristics including faster blood clearance and 2-fold higher uptake in bone. Uptake of 18F-NaF reflects blood flow and bone remodeling.

**Dosage.** 18F-NaF is injected intravenously by direct venipuncture or intravenous catheter. The adult activity is 185-370 MBq (5-10 mCi). A higher activity (370 MBq and 10 mCi) may be used in obese patients. Pediatric activity should be weight based (2.22 MBq/kg and 0.06 μCi/kg), using a minimum and maximum activity of 18.5-185 MBq (0.5-5 mCi).9

**Localization**

Cancers spread to bone hematogenously, where they first localize in the bone marrow. That is why more than 90% of bone metastases can be found in the red marrow (axial skeleton) of adults. As the lesion grows, it produces a cortical response whether lytic (if rapidly growing) or sclerotic (if slow growing). Bladder, kidney, thyroid, and multiple myeloma malignant processes more commonly result in lytic lesions. Thus, bone scans are typically more suited for sclerotic predominant cancers such as of the breast, prostate, and lung.10

To radiographically detect bone metastasis, considerable destruction of bone needs to occur. The literature cites 30%-70% demineralization requirement before a metastatic lesion can be seen on plain film radiographs. Thus, bone scans can detect early metastasis 2-18 months before they are seen on plain film radiographs. Once bone destruction has occurred, the sensitivity of computed radiography ranges from 71%-100%. The value of radiography is in confirming the sensitive but nonspecific findings seen on bone scans. Conversely, MRI is very useful in detecting early metastasis to bone marrow that happens to replace fat as it grows and produces longer T1 and T2 sequences with subsequent enhancement when contrast is used.10 MRI is limited to regional evaluation after a bone scan and CT have been compared. However, there may be a future potential for whole-body (WB) MRI for evaluation of early metastasis seen on bone scan but not yet demonstrated on CT.

**Planar**

Traditionally, delayed anterior and posterior WB images are obtained between 2 and 5 hours in a 256 × 1024 × 16 matrix or greater with at least 1 million counts and additional 128 × 128 × 16 matrix or greater spot views with a minimum of 500-1000k counts.7,8 Common spot views of the chest and pelvis are obtained, but additional spot views may be required such as the spine, ribs, femora, and humerus.

**Table 1** Sensitivity, Specificity, Positive and Negative Predictive Values of Planar, SPECT and SPECT/CT Among Common Malignancies of Breast, Lung, Prostate and Thyroid Gland. SPECT provides improved sensitivity and specificity that is further improved utilizing hybrid spect/CT imaging.

<table>
<thead>
<tr>
<th></th>
<th>Planar</th>
<th>SPECT</th>
<th>SPECT/CT</th>
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<tbody>
<tr>
<td><strong>Breast</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sensitivity</td>
<td>91.2%</td>
<td>87%-92%</td>
<td>12</td>
</tr>
<tr>
<td>Specificity</td>
<td>63.2%</td>
<td>91%-93%</td>
<td>12</td>
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<tr>
<td>PPV</td>
<td>68.9%</td>
<td>96%</td>
<td>13</td>
</tr>
<tr>
<td>NPV</td>
<td>88.9%</td>
<td>96%</td>
<td>13</td>
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<tr>
<td><strong>Lung</strong></td>
<td></td>
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<tr>
<td>Sensitivity</td>
<td>86%</td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td>Specificity</td>
<td>88%</td>
<td></td>
<td>82%</td>
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<tr>
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<tr>
<td>NPV</td>
<td>100%</td>
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<td>86%</td>
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<tr>
<td><strong>Prostate</strong></td>
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<tr>
<td>Sensitivity</td>
<td>70%</td>
<td>92%</td>
<td>16</td>
</tr>
<tr>
<td>Specificity</td>
<td>96.9%</td>
<td>96%</td>
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<tr>
<td>PPV</td>
<td>64%</td>
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<td>NPV</td>
<td>75.6%</td>
<td>72%</td>
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<tr>
<td><strong>Thyroid</strong></td>
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<tr>
<td>Sensitivity</td>
<td>78%</td>
<td>93%</td>
<td>19</td>
</tr>
<tr>
<td>Specificity</td>
<td>91.4%</td>
<td>97%</td>
<td>19</td>
</tr>
<tr>
<td>PPV</td>
<td>85%</td>
<td>98%</td>
<td>19</td>
</tr>
<tr>
<td>NPV</td>
<td>78%</td>
<td>92%</td>
<td>19</td>
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as anterior oblique views to differentiate uptake in the sternum from the thoracic spine or a caudal (squat or tail on detector) view of the pelvis to differentiate uptake in the pelvis from activity in the bladder.

Planar BS has very high sensitivity but is known for its lower specificity (Table 1). SPECT can increase specificity by up to 30%-50% and can be used to characterize the extent, location, and presence (when planar imaging is negative). Reported sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for SPECT are 91%, 93%, 73%, and 98%, respectively.

SPECT/CT
Hybrid SPECT/CT can further improve accuracy by improving anatomical localization and providing attenuation correction. Recommended SPECT acquisition parameters are 60-120 stops (120 projections for single-head gamma camera and 60 for dual-head cameras), 64 × 64 × 16 or greater matrix and 10-40 seconds per stop, and with regards to SPECT of the pelvis, rapid acquisitions of 5-10 minutes are recommended to avoid bladder-filling artifacts.

PET/CT
In a patient with normal body mass index, good images of the axial skeleton may be obtained with an acquisition time of 3 minutes per bed position starting 45 minutes after injection of 185 MBq (5 mCi) of $^{18}$F-NaF. Good WB images may be obtained with an acquisition time of 3 minutes per bed position starting 2 hours after injection of 370 MBq (10 mCi) of $^{18}$F-NaF.

Common Applications of BS
Bone Scintigraphy
Osteolytic lesions are well visualized on plain film radiography but only after 30%-70% or of the lesion has demineralized. CT can detect cortical involvement but is limited in evaluation of marrow involvement, which is where the initial metastatic...
Figure 2 A 70-year-old man with newly diagnosed prostate adenocarcinoma, Gleason score of 9, with baseline (A) bone scintigraphy showing extensive osseous involvement in the pelvis with foci of radiotracer accumulation noted in the axial skeleton (predominantly lumbar spine) and a few ribs. Baseline laboratory studies showed raised alkaline phosphatase and PSA levels. Follow-up bone scintigraphy (B) 3 months after initiation of treatment showed progression of radiotracer accumulation at various sites in the axial skeleton despite the patient being asymptomatic with normal levels of alkaline phosphatase. Subsequent clinical follow-up did not reveal any progression.
lesion begins. By contrast, BS can detect bone formation with as little as 5%-10% changes. 

Breast

Osseous metastases are only found in 1%-2% of patients at diagnosis but in up to one-third of patients presenting with recurrence. Breast cancer has a high proportion of lytic and sclerotic lytic bone metastasis 11 (Fig. 1). The vertebral column is the most common site of spread followed by the ribs. The sternum, more so in breast cancer, can demonstrate metastasis from direct extension of the tumor via the internal mammary chain. 10 In 72 patients, 18F-NaF-PET/CT showed the highest sensitivity and NPV, followed by 99mTc-MDP, and then FDG-PET/CT. However, the reverse is true for specificity and PPV with the highest values in FDG-PET/CT. 11

BS is not recommend for early-stage breast cancer as the risk of metastasis to bone ranges between 0.8% and 2.6% for stages I and II, in comparison with 16.8%-40.3% for stages III and IV. 10

Prostate

Patients with prostate cancer are the most commonly referred patients for BS owing to the fact that most bone lesions tend to be osteoblastic rather than lytic, yielding a high sensitivity for positive results on scans. 10

The Prostate Cancer Working Group 2 has established guidelines to standardize the interpretation of bone scans as they relate to prostate cancer metastases in their clinical trials. These include simplified formats summarizing the outcomes as improved, stable, or worse. These account for the “flare” phenomenon in recently treated patients by discouraging the use of recent posttreatment scans to assess whether to change patient treatment. These criteria have been abbreviated by a

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Figure 3 A 67-year-old-man with history of prostate cancer presenting with rising PSA level following radical prostatectomy (2009). Whole-body bone scintigraphy ((A) anterior and (B) posterior view) demonstrates an intense focus of increased radiotracer activity within the right side of pelvis (more prominent anteriorly, black arrow). Axial fused ((C) SPECT/CT) images show intense focal uptake localizing to the anterior right acetabulum, with axial CT images (black arrow in (D)) showing underlying sclerotic changes.
“2 + 2” criteria, referring to the presence of 2 new lesions on second subsequent scans.

Incidence of bone metastasis with prostate-specific antigen (PSA) level <20 ng/mL is low and ranges from 0.03%-11.1% (Fig. 2).

The guidelines regarding selective referral for bone scan based on PSA level vary, with the American Urological Association discouraging bone scans in asymptomatic patients with PSA level <20 ng/mL, whereas the American College of Radiology discourages bone scans in patients with a PSA level <10 ng/mL.22

Alternatively, the National Comprehensive Cancer Network recommends bone scans in symptomatic patients with a life expectancy >5 years, PSA level ≥20 ng/mL, and Gleason score (GS) ≥8.

In a study of pretreatment staging of asymptomatic treatment-naive patients with prostate cancer, the sensitivity and specificity for positive scans for PSA level (>33 ng/mL) of 83.6% and 69.6%, for alkaline phosphatase (>286 IU/L) of 72.7% and 91.9%, and for GS (≥6) of 80% and 51.4%.23 In a multivariate analysis of the same study, GS was not an independent predictor of osseous metastasis whether...
measured quantitatively ($P = 0.25$) or dichotomously with GS $= 8$ as the cutoff ($P = 0.22$). The authors observed improved sensitivity of 98% for a positive scan when either PSA level $> 20$ ng/mL or increased alkaline phosphatase was used in deciding to order a bone scan but at the cost of decreased specificity to 48.6%.\(^2\)\(^3\) (Fig. 3).

A large meta-analysis demonstrated positive bone scans in 2.3%-5.3% of patients with PSA level $< 20$ ng/mL and 5.6% of patients with GS $\leq 7$ (compared with 30% for GS $> 8$).\(^1\)\(^0\)

In a study of 49 patients with prostate cancer, $^{18}$F-fluoride-PET/CT showed the highest sensitivity and NPV, followed by $^{99}$mTc-MDP, and then $^{18}$F-FDG-PET/CT. However, the reverse was true for specificity and PPV, with the highest values seen with FDG-PET/CT.\(^1\)\(^1\)

Various patterns of radiotracer accumulation are noted in cancer, extending from focal uptake to diffuse osseous involvement, where virtually all of the radiotracer is concentrated in the skeleton, with little or no activity seen in the soft tissues or urinary tract. This pattern is sometimes referred to as superscan (Fig. 4).

**Lung**

Osseous metastases are present in 20%-30% of patients at diagnosis and in 35%-66% at autopsy. Non–small cell lung cancer has a high proportion of lytic and sclerotic lytic bone metastasis.\(^1\)\(^1\) In a study of 30 patients with lung cancer, Damle et al.\(^1\)\(^1\) demonstrated better sensitivity and NPV with $^{99}$mTc-MDP and $^{18}$F-NaF-PET/CT compared with FDG-PET/CT, but they found a higher specificity and PPV with $^{18}$F-FDG-PET in comparison with the others. However, the accuracy of all 3 modalities was not significantly different (Fig. 5).

**Osteolytic Metastases (Including Renal Cell Carcinoma, Hepatocellular Carcinoma, Thyroid, and Myeloma)**

Bone scan is not an effective method to follow up lytic metastases. However, recognizing how these can manifest remains important owing to the ubiquity of the study’s availability and how pathologic fractures can often become the initial presentation of these malignancies (Fig. 6). As should always be the case, correlation with the known clinical history helps guide the interpretation of the study.

In general, BS reveals areas of bone remodeling at the margin of lesions as region of irregular activity of variable intensity. If the lesions are aggressive enough, they may overcome the osteoblastic response and appear altogether photopenic. The
sensitivity decreases significantly with cancers with larger proportion of lytic lesions.

In a study by Damle et al., $^{18}$F-fluoride-PET/CT detected the largest number of sclerotic lesions, followed by $^{99m}$Tc-MDP, whereas $^{18}$F-FDG-PET/CT detected the largest number of lytic lesions followed by $^{18}$F-fluoride. Figure 7 shows a newly diagnosed multiple myeloma undergoing planar BS with minimal areas of radiotracer accumulation.

Figure 6 A 65-year-old woman presenting with newly diagnosed high-grade breast cancer in the left breast with metastatic ipsilateral axillary lymph nodes underwent whole-body scintigraphy for staging. Foci of radiotracer accumulation noted in calvarium, scapula, left iliac bone, and femora. Whole body scintigrams and spot images (A). Axial CT images through the pelvis (B), lytic lesions involving bilateral femoral head with adjacent sclerotic margins. On the right side, lytic lesion is extending into the femoral neck (black arrow), posing an increased risk of pathologic fracture.
Nonmalignant Variants
Although BS is extensively used in a wide variety of malignancies with a significant effect on management, BS using a nonspecific radiotracer shows accumulation in both malignant and a variety of benign conditions (Figs. 8 and 9).

PET/CT
18F-Sodium Fluoride
In a recent update from National Oncologic PET Registry (NOPR) NaF Registry on more than 3500 data sets, it has been shown that, in the absence of bone imaging, the referring physician would not have changed the management in approximately half of the patients. After performing 18F-NaF-PET, the plan was revised to treatment in 77%, 52%, and 71% patients for initial staging, first osseous metastasis, and suspected progression of osseous metastases, respectively. When intended management was classified as either treatment or nontreatment, the overall change in intended management ranged from 44%-52% and from 12%-16% if no effect was assumed for those cases with pre-PET plans for other imaging. The interpreting physician recorded the definite findings of bone metastasis in 14%, 29%, and 76% for initial staging, first osseous metastasis, and suspicion of progressions of osseous metastasis, respectively24 (Table 2).

18F-FDG
As has been demonstrated in lung and breast cancers, 18F-FDG-PET has taken a central role in the successful staging and therapeutic response assessment of these tumors in settings that include the skeletal and visceral systems. However, even for osteoblastic prostatic metastases, 18F-FDG-PET has demonstrated sensitivities comparable to bone scan as well as greater specificity. Moreover, standardized uptake value quantitation for metastatic lesions is proving to be effective in the prognostic assessment to treatment response as a reliable and accessible biomarker.27 A recently published meta-analysis28 reported sensitivity and specificity of PET/CT as 0.93 (95% CI: 0.82-0.98) and 0.99 (95% CI: 0.95-1.00) and of BS as 0.81 (95% CI: 0.58-0.93) and 0.96 (95% CI: 0.76-1.00), respectively. Area under the curve values of PET/CT and BS were 0.98 (95% CI: 0.98-1.00) and 0.94 (95% CI: 0.92-0.96), respectively (Fig. 10).

Current Research or Future Directions
National Oncologic PET Registry
The NOPR (http://www.cancerpetregistry.org/) was developed and began collecting data in 2006 and was revised in 2009. The NOPR was created in response to the Centers for Medicare and Medicaid Services (CMS) proposal to expand coverage for PET with 18F-(NaF-PET) to identify bony metastasis of cancer. CMS subsequently released its Decision Memo on February 26, 2010 (CAG-00065R) and concluded that the evidence was not sufficient to determine that the results of NaF-PET to identify bone metastases improved health.

Figure 7 Minimal radiotracer accumulation is noted within osseous structures in a newly diagnosed multiple myeloma. Anatomical imaging showed (not shown here) widespread involvement of axial and proximal appendicular skeleton.
outcomes. The decision memo also concluded that the available evidence was sufficient to allow for NaF-PET coverage under coverage with evidence development.

In response to this decision memo and in consultation with CMS, the NOPR investigators have initiated a new (second) registry within NOPR that builds on current experience, infrastructure, and staffing for the ongoing FDG-PET evaluations to begin prospective data collection, evaluation, and reporting of NaF-PET. The overall design and concept of the new registry (hereafter called NOPR

Figure 8 A 67-year-old man, with a history of radical nephrectomy performed in 2007 for renal cell carcinoma, presented with low back pain. Anterior whole body images (A) and posterior whole body images (B). Subsequent plain film radiographs showed indeterminate results. Whole-body bone scintigraphy showed foci of uptake at L3 and L4 level. Corresponding 3-views SPECT/CT images ((C-E) crosshair) confirms uptake to localize to end plates, consistent with degenerative changes.
[NaF-PET]) are similar to those of the FDG-PET register. The NOPR (NaF-PET) registry again only uses the data set from consented patients and physicians (both referring and interpreting physicians). Changes in intended patient management as a result of upstaging or downstaging and changes to more appropriate palliative or curative care are of specific interest.27 As of 2013, 979 sites have been enrolled with submission of more than 25,000 patient data.

**Technical Innovations**

**Whole-Body 99mTc-MDP-SPECT**

As technology changes, newer and more efficient techniques might be expected and encouraged. Promising alternatives in the immediate future include 18F-NaF PET/CT and WB MRI. Further, advances in MRI by means of PET and MRI fusion or PET/MRI coacquisition and direct molecular imaging of bone turnover through 19F-MR spectroscopy provide exciting avenues for future research.

In the more immediate setting, the addition of field-of-view SPECT or SPECT/CT has proven excellent supplantations to the standard planar bone scan protocol in regions of questionable abnormalities. Even-Sapir et al16 were able to demonstrate significant improvements in the sensitivity and specificity of BS by 3-4 field-of-view acquisitions focusing on the axial skeleton.

Another strategy that keeps in mind patient comfort, limitation of dose exposure, and comparable throughput may be to entirely replace the current planar acquisition technique with WB 99mTc-MDP-SPECT. Current technology allows for the generation of 4-5 stop tomographic images in

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**Table 2** Comparative Analysis of 18F-NaF and 18F-FDG-PET/CT Across a Variety of Malignancies. FDG-PET/CT Provides Higher Specificity Whereas NaF PET-CT Provides Higher Sensitivity

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>18F-NaF</th>
<th>18F-FDG</th>
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</thead>
<tbody>
<tr>
<td>Lung (Kruger et al)</td>
<td>Sensitivity: 94% (76.9-100) 55.6% (35.5-55.6) Specificity: 80% (61.5-80) 100% (79.9-100)</td>
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**Figure 9** A 32-year-old man presenting with pain. Immediate anterior (left) and right (right) (A, top). Delayed anterior (left) and right (right) (A, bottom). Bone scintigraphy on immediate and delayed imaging showed a faint local area of radiotracer accumulation within the right supraclavicular or clavicular region, which is more prominent on posterior delayed images (arrow). Subsequent SPECT/CT images (B) show local radiotracer accumulation in the right distal clavicle with cortical thickening noted on CT imaging; typical findings of an osteoid osteoma.
Time spans that are similar to those of WB planar bone scan plus spot views—which often require physician evaluation of extra views or the addition or repetition of spots views. Generating WB SPECT images with rotating maximum intensity projections also obviates the need for patient voiding and repositioning for specialized pelvic views, thereby improving patient comfort and throughput. This has the added benefit of obtaining images that can be more accurately
assessed and correlated with existing CTs or directly fused by software or direct correlative imaging experience.

Conclusions

BS with planar imaging has evolved over time to SPECT imaging and now to hybrid imaging techniques, including SPECT/CT and PET/CT. It is an invaluable tool in assessing disease involvement of osseous structures at various stages of disease management. With the increasing use of hybrid imaging, overall sensitivity and specificity has increased to signify the utility of combined anatomical and molecular imaging evaluation. Newer techniques and methods are being used to decrease radiation exposure and imaging time in line with patient comfort. This will enable us to individualize disease assessment leading to effective treatments.

Acknowledgment

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