Nuclear Medicine Imaging Techniques for Detection of Skeletal Metastases in Breast Cancer

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KEYWORDS

• Bone scintigraphy • SPECT • SPECT/CT • PET • PET/CT • ^{18}F-NaF • ^{18}F-FDG

KEY POINTS

- Bone is the most common site of metastases from advanced breast cancer.
- Whole-body bone scintigraphy (WBBS) has been most frequently used in the process of managing cancer patients; its advantage is that it provides rapid whole-body imaging for screening of osteoblastic or sclerotic/mixed bone metastases at reasonable cost.
- Recent advanced techniques, such as single photon emission computed tomography (SPECT)/CT, quantitative analysis, and bone scan index, contribute to better understanding of the disease state.
- More recent advances in machines and PET drugs improve the staging of the skeleton with higher sensitivity and specificity.

INTRODUCTION

In the United States, breast cancer is the most common nonskin cancer and the second leading cause of cancer-related death in women. Approximately 255,180 new cases of breast cancer and 41,070 total deaths from breast cancer are expected in 2017.[1] Breast cancer strikes women of all ages, races, ethnicities, socioeconomic strata, and geographic locales.[2]

The skeleton is the most common site of metastatic disease in advanced breast cancer. Approximately 30% to 85% of patients with metastatic breast cancer develop bone metastases, and 26% to 50% of patients with metastatic breast cancer have a bone lesion as the first site of metastasis.[3–9] The most common sites of solitary metastatic bone disease from breast cancer are the sternum (34%), pelvis (18%), thoracic spine (16%), lumbar spine (10%), ribs (7%), and pelvis, followed by skull and femur.[10,11] Over a long follow-up period, most patients presenting with a solitary bone metastasis develop metastases at other sites. Bone metastases cause skeleton-related events, including pain, fractures, hypercalcemia, and spinal cord compression; thus, the presence of bone metastases influences prognosis, quality of life, and local and systemic therapy.[12]

Imaging plays an important role in the care of patients with breast cancer. The early detection of skeletal involvement is crucial in the assessment of patients with breast cancer, because it influences clinical management.[13] This review presents data about the nuclear medicine techniques used for evaluation of the skeleton in breast cancer patients.

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BONE SCINTIGRAPHY

Whole-body bone scintigraphy (WBBS) is the most commonly used technique for detecting bone metastases.[14–17] It can identify the high osteoblastic activity and blood flow in the affected area.[16,18–20] Technetium Tc 99m (^{99m}Tc)– labeled bisphosphonates, such as methylene diphosphonate [^{99m}Tc-MDP], hydroxymethylene diphosphonate, or dicarboxypropane diphosphonate, are the most frequently used in the management of cancer patients, having the advantage of whole-body imaging at a reasonably low cost.

WBBS can accurately detect osteoblastic lesions, sclerotic/mixed bone lesions, and the reparative bone formed by osteolytic lesions; however, it is less sensitive in detecting purely osteolytic lesions, slow bone turnover, and avascular areas.[21,22] Despite the high sensitivity, the accumulation of radiotracer in sclerotic areas is not specific and reflects production of new bone in response to invasion by tumor cells.[23] WBBS identifies the metabolic reaction of bone that occurs not only in cancer but also in trauma, inflammation, and degenerative processes.[24–28]

WBBS has higher sensitivity than radiography (44% to 50%) for detecting early bone metastases[20,24,29]; for example, 30% to 75% of the normal bone mineral content has to be lost before radiographs can show the lesions in the lumbar vertebrae.[30] Limited contrast in the trabecular areas on radiographs results in difficulty identifying lesions in trabecular bone compared to cortical bone.[20] Radiographs can complement bone scintigraphy (BS), however, for the assessment of nonspecific or atypical findings or in patients with bone pain.[9]

Equivocal findings on WBBS can be further evaluated with single-photon emission CT (SPECT) and SPECT/CT, which allow 3-D imaging and can provide axial, sagittal, or coronal images.[31] Modern SPECT/CT scanners include multislice CT that provides detailed anatomic information. SPECT/CT improves both the sensitivity and the specificity for detecting bone metastases due to identification of the structural characteristics of lesions and a higher lesion to background contrast.[32] SPECT/CT improves the receiver operating characteristics (ROCs) and inter-reporter agreement for diagnosis of bone metastases compared with SPECT alone and SPECT and CT with side-by-side reading.[33] The more accurate diagnosis achieved with SPECT/CT leads to reduction in unnecessary additional studies.[34,35] Sharma and colleagues[36] reported that SPECT/CT is superior to SPECT alone for characterizing equivocal findings in patients with breast cancer. Recent developments in SPECT/CT make possible semiquantitative measurements[37] that may play a role in characterization of a lesion as benign versus malignant as well as in assessment of response to treatment.

The detection rate of bone metastases with WBBS is 0.82% for patients with stage I disease, 2.55% for stage II disease, 16.75% for stage III, and 40.52% for those with stage IV breast cancer.[9,27,38–41] Initial detection of an abnormality or asymptomatic bone metastasis by WBBS resulted in a 14% improvement in the overall survival rate at 4 years and a 10% improvement at 5 years.[42,43] According to a large randomized study of patients with breast cancer shortly after initial treatment, semiannual screening with WBBS detected more bone metastases than clinical follow-up alone, but it did not improve 5-year survival.[44] Another randomized controlled trial showed no difference in survival between patients followed-up with physical examinations, radiographs, and BS and those followed-up with physical examinations alone.[44,45] Another study suggested that early detection of asymptomatic breast cancer recurrence at any site, including bone lesions, did not lead to improvement of overall survival.[46,47]

The American Society of Clinical Oncology guidelines do not recommend using WBBS for post-treatment surveillance of asymptomatic disease[48]; most abnormal findings are caused by benign conditions, such as trauma and inflammation. Routine WBBS screening is not recommended for patients with early (stage I or II) breast cancer.

One use of WBBS is evaluation of the response to treatment of bone lesions; WBBS can measure the associated osteoblastic response rather than tumor response. The uptake in the bone lesions is decreased when there is response to therapy, whereas increased uptake or appearance of new lesions indicates progressive disease.[9] A retrospective study of breast cancer patients with bone metastasis showed that changes in the uptake of bone lesions between baseline and post-therapy scans was related to patient survival (mean survival 5.0 $\pm$ 2.7 years compared with 3.7 $\pm$ 1.9 years for stable disease and 2.2 $\pm$ 1.3 years for progressive disease).[32,49]

One of the pitfalls of WBBS is underestimating the therapeutic response due to the so-called flare phenomenon, which makes lesions appear more intense than on previous scans due to a transient rise in osteocalcin and alkaline phosphatase bone isoenzyme.[32] The flare response occurs 3.2 months $\pm$ 1.4 months after initiation of hormone treatment or chemotherapy, and its appearance stabilizes within 6.2 months $\pm$ 3.0 months.[50]