PET Imaging of Skeletal Metastases and Its Role in Personalizing Further Management

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KEYWORDS

• Neoplasms/Carcinoma • Bone • Skeletal metastasis • Tumor biology • Functional imaging • Radionuclide imaging • Translational medicine • Evidence based medicine

KEY POINTS

- It is crucial to accurately detect, quantify, and evaluate treatment response in skeletal metastatic disease so that the patient is appropriately staged and optimally managed.
- Multimodal PET/computed tomography imaging is not only accurate but superior for the assessment of skeletal metastatic disease.
- Multiparametric hybrid PET/MR imaging is emerging as an innovative and potential multimodality imaging tool for detecting and delineating metastatic skeletal disease.
- PET-based bone-specific and tumor-specific methods for noninvasively imaging bone metastases have the ability to contribute to individual patient management decisions at all stages of diagnosis and treatment.

INTRODUCTION

The skeleton is one of the most common sites for metastatic disease and the related complications pose a major management challenge, significantly affecting the quality of life of these patients.[1] These complications have been described as skeletal-related events (SREs) and include a range of clinical presentations, including bone pain, pathologic fractures, hypercalcemia, nerve root compression, myelosuppression, and cord compression.[2–4] Bone is the most frequent and may be the first and only involved metastatic site in patients with solid tumors. Therapeutic options have improved. For example, in prostate cancer, skeletal metastases are associated with overall survival (OS) ranging from 12 to 53 months.[5] Other solid tumors that are frequently associated with skeletal metastases are breast, lung, thyroid, kidney, and urinary bladder and the incidence of bone metastases at the time of diagnosis in such patients is as high as 40%.[6,7] The overall survival of patients with cancer has significantly improved over the past 2 decades, and this has led to increase in the incidence of metastatic disease. It has been found that approximately 70% of the patients with advanced breast or prostate cancer

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have bone metastases.[7,8] Thus, it is crucial to accurately detect, quantify, and evaluate treatment response in skeletal metastatic disease so that the patient is appropriately staged and optimally managed.[9,10] A wide range of imaging modalities are available for diagnosing bone metastases.[11] The main recommended anatomic modalities are computed tomography (CT) and magnetic resonance (MR) imaging, and the main functional modalities widely accepted and recommended for diagnosing bone metastases are bone scintigraphy and PET imaging with tumor-specific or bone-specific tracers.[12,13] In this review, we summarize the current state of PET imaging of the skeleton as an established tool for diagnosing bone metastases and monitoring response to treatment.

PATHOPHYSIOLOGY OF SKELETAL METASTASES

Breast and prostate cancers have a high predisposition for skeletal metastases and are also known as osteotropic malignancies, whereas other cancers, including cervix, endometrium, and gastrointestinal tract, have a very low incidence of skeletal metastases.[14] The "seed and soil" hypothesis of the tumor biology first described by Stephen Paget explains the selective affinity of circulating malignant cells for deposition and further proliferation of some cancer cells in the bone environment.[15] Metastatic spread to bones can occur by direct extension but more commonly by hematogenous dissemination.[7] Adhesion molecules play an important role in homing of the circulating tumor cells, where chemotactic and growth factors secreted by the normal bone remodeling process provide the required nutritive support for their growth.[16] Some tumors release factors, such as parathyroid hormone–related protein, tumor necrosis factor α or β, and interleukin (IL)-1 and IL-6, that upregulate osteoclastic activity leading to osteolysis. There are certain tumors in which factors such as insulinlike growth factors, epidermal growth factors and transforming growth factors α and β cause upregulation of osteoblastic activity leading to predominant osteosclerosis.[17] These form the basis of bone forming, that is, osteoblastic (eg, prostate cancer) or bone destructive, that is, osteolytic metastases (eg, kidney, thyroid, and lung). However, many tumors present with a spectrum of blastic and lytic bone lesions with abnormal osteoblast and osteoclast activity whatever the dominant morphology. Compared with osteoblastic metastases, osteolytic metastases generally have a more aggressive course with early clinical presentation and progression.[18] Also noteworthy is that bone marrow involvement usually predates bone destruction, and metastases at this stage may be more easily detected with tumor-specific rather than bone-specific imaging techniques, a process that may contribute to false negatives on conventional nuclear bone scintigraphic imaging.[19]

IMAGING OF SKELETAL METASTASES: AN OVERVIEW

In the emerging era of "personalized medicine" in oncology, imaging acts as both a predictive and prognostic biomarker that in turn permits clinicians to individualize treatment for patients by identifying those who may or may not benefit from a particular treatment plan.[20]

With skeletal metastases, the main questions that will affect an individual patient's management include the following:

1. Are there any bone metastases? If skeletal metastases are diagnosed, then treatment for the patient will generally become palliative rather than curative and so a sensitive diagnostic test is required to ensure correct prognostication and treatment strategy.
2. Is there a single, multiple, or (oligo) metastasis, and are metastases confined to the skeleton? Patients with a solitary bone metastasis or metastases confined to the skeleton generally have a better prognosis than those with multiple skeletal metastases or a combination of skeletal and visceral disease. A solitary metastasis may be eligible for attempted curative therapy, for example, stereotactic radiotherapy or surgery.[21,22] As well as a sensitive and specific test, this management will require an imaging method that can also detect or exclude nodal and visceral disease with high accuracy.
3. Are there any metastases that may lead to an SRE, for example, spinal cord compression? For this complication there is generally a requirement for good morphologic characterization of a bone lesion to assess the amount of bone destruction and risk of fracture, as well as the relation to adjacent structures at risk, such as the spinal cord. Systemic treatments, as well as being palliative can reduce future SREs and local radiotherapy or kyphoplasty may be required for symptomatic lesions or where there is risk of an SRE.
4. Should treatment be systemic, local, or both? Systemic treatment is generally palliative but may reduce SREs and prolong progression-free survival (PFS) and OS. As well as cytotoxic chemotherapy, for example, docetaxel in

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