Monitoring bone marrow metastases: Nuclear medicine versus MRI

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Metastatic bone disease is a common manifestation of advanced cancers with autopsy studies indicating a high prevalence in breast, prostate and lung cancers. Osteolytic metastases in particular cause bone and compressive nerve pain, impairs mobility, results in pathological fractures and causes spinal cord compression. Other consequences of bone metastases include anemia and symptoms related to hypercalcemia. Once bony metastases have occurred, cancer cure becomes impossible and therapy is instituted with a palliative intent. Bone metastases therapies are a priority for development with many recent introductions into the clinic of active treatments for a variety of tumor types. Systemic therapies aimed at the bone matrix and tumor cells are administered for disseminated disease. Local treatments are used to control pain and to treat/prevent local complications.

SKELETAL THERAPY ASSESSMENT TOOLS

Accurate response evaluations of patients with bone metastases are notoriously difficult to do because measureable bony soft tissue disease occurs infrequently. Symptom assessments and development of skeletal-related events are preferred markers of therapeutic efficacy in clinical trials. More objectively, response can be gauged by a combination of imaging and clinical findings often used in combination with serum and urine biochemical markers of tumor burden and bone turnover. Serum tumor markers of response are not available or are ineffective for the vast majority of tumors that metastasize to bone.

Regardless of the method(s) used, current response biomarkers focus on assessing disease progression rather than positively addressing therapy benefit. The clinical consequences of using progression criteria include “prolonged exposure to potentially ineffective medications” and “all patients potentially getting all drugs – often too late”. Thus, currently available assessment methods can have negative impacts on oncologists’ thinking regarding therapy choices for patients with metastatic bone disease

99mTc-MDP **bone scans** are the commonest imaging method for the follow-up of bone metastases. Unfortunately, bone scintigraphy and its higher spatial resolution PET counterpart using 18F-sodium fluoride (**NaF-PET**) reflect only on the osseous component of bone. Drug trials utilizing bone scans have criteria for progression (two categories only: no new lesions/new lesions) but not for response. To mitigate against healing flare reactions, apparent progression needs to be confirmed by follow-up bone scans when new focal “hot spots” have to be documented. Patients with diffuse metastatic bony disease and bone superscans cannot be followed for progression. Furthermore, the need to defer the decision of progression raises the issue of timeliness of the bone scan readouts for guiding clinical decision making.

A number of PET tracers have been evaluated for their ability to monitor bony therapy response including non-tumor type specific tracers (18F-flurodeoxyglucose (**FDG**) and 11C/18F-choline (**FCH**)). Most studies have focused on FDG-PET with the PERCIST criteria gaining widespread acceptance. Tumor size measurements remains important under PERCIST with

changes in size of lesions without metabolic changes requiring clarification by follow-up scans. Importantly, FDG-PET response criteria do allow the positive identification of therapy benefit.

A number of MRI sequences can evaluate bone for metastasis response assessments. Morphologic response criteria have been described for morphologic sequences [1]. However, a number of problems have also been noted including (1) arrested resolution of abnormalities despite effective therapy, (2) evaluating disease activity on scarred background is problematic (progression can only be documented on previously uninvolved marrow, (3) T1 - pseudoprogression due to bone edema, (4) the sclerotic progression phenomenon and, (5) mixed response patterns.

Therapy assessments on WB-DWI are made by observing changes in the volume and symmetry of signal intensity abnormalities on high b-value images together with changes in ADC values [2]. Cross correlating DW imaging findings with morphological appearances on T1W, fat-saturated T2W/STIR and Dixon images is important. Several distinct patterns being recognized in the therapy assessment setting:

1. Increases in the volume of previously documented abnormal signal intensity, new areas of abnormal signal intensity, or increases in the intensity of abnormalities on high b-value DW images can indicate disease progression. Modest increases, unchanged or slight decreases in ADC values compared to pretherapy values can occur in the setting of progression.
2. T2-shine through - occasionally unchanged high signal intensity on high b-value images associated with marked rises in ADC values is observed. This pattern indicates that there has been a successful response to therapy.
3. Decreases in bone marrow disease signal intensity on high b-value images are generally observed with successful treatments. The extent of ADC increases seems to depend on the type of treatment given. It has been noted that ADC increases are greater for cytotoxic chemotherapy and radiation. When patients are treated successfully with hormonal therapies or antiangiogenics, ADC value increases seem to be less marked.
4. Occasionally high b-value signal intensity decreases are associated no ADC increases. Generally this pattern generally occurs in clinical responders although very occasionally we have noted it in non-responders (so called sclerotic progression). These appearances as thus indeterminate and currently we use morphologic and clinical assessments to assign the final response category.
5. Stable disease is characterized by unchanging appearances on high b-value images. ADC changes can be variable, often remaining stable but are sometimes slight decreased presumably because of increases in cell density within lesions that are unchanging in their extent.

[1] Lecouvet FE, et al. MRI for response assessment in metastatic bone disease. Eur Radiol. 2013; 23(7):1986-97. [2] Padhani AR, et al. Therapy monitoring of skeletal metastases with whole body diffusion MRI. J Magn Reson Imaging 2014 [ahead of print]