Bony Metastases - Assessing Response to Therapy

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Background

Metastatic bone disease is a common manifestation of advanced cancers with autopsy studies indicating a prevalence of 30-40% in thyroid, lung and renal cancers [1]. There is a greater prevalence of bony metastases in breast and prostate cancers (more than 70%) [1-3]. Bone metastases cause much of the morbidity and disability in patients suffering from tumors. Osteolytic disease in particular causes pain, impairs mobility, and makes hypercalcemia effects happen. Osteolytic disease results in pathological fractures & spinal cord compression.

Once bony metastases have occurred, cancer cure becomes impossible and therapy is instituted with a palliative intent. Therapy goals are to delay progression, palliate symptoms, improve quality of life and achieve a modest survival benefit if possible. In general, systemic therapies (including chemotherapy, endocrine therapy and bisphosphonates) are given for disseminated disease and local treatments (for example radiotherapy, surgery and spine cement augmentation) to control pain and treat complications.

Clinical need for bone marrow therapy assessment tools

There are overwhelming clinical needs to develop and validate non-invasive response biomarkers for bone metastases [4-6]. There are however, no universally accepted methods for assessing tumour response in skeletal sites with disease; response being estimated by a combination of imaging tests, serum and urine biochemical markers, and clinical evaluations [7, 8]. Symptom assessments (including analgesic requirements) and development of skeletal related events are frequently used markers of therapeutic efficacy in clinical trials [7]. Serum markers of response are not available for the vast majority of tumours that metastasize to bone. Circulating tumour cells are emerging as powerful response biomarkers for breast, colorectal and prostate cancers [9].

Bone scintigraphy (99mTc-MDP bone scans) with plain radiographs or cross-sectional imaging, such as computed tomography (CT) or magnetic resonance imaging (MRI), remain the commonest imaging methods for the follow-up of bone marrow metastases. A positive bone scan occurs due to an osteoblastic response occurring secondary to an underlying bone abnormality and is thus an indirect indicator of metastatic bone marrow activity. Bone scintigraphy maybe unsuitable for the therapy assessment of predominantly lytic disease without an associated osteoblastic response such as typically seen in myeloma, renal or thyroid cancers (that is, cold spots on bone scans cannot be followed for progression). Similarly patients with metastatic superscans on bone scans cannot be followed for progression. As a result, drug trials utilizing bone scans have criteria for progression but not for response; apparent progression needing to be confirmed by follow-up bone scans after more than 6 weeks, when new focal “hot spots” have to be documented [7]. Scintigraphic/healing flare occurs in 30% of patients usually within 3 months in patients responding to treatment [10, 11] confounding early therapy assessments.

MRI assessments of bony disease

There are a number of MRI methods that can evaluate the bones for metastasis detection and response assessments [12, 13]. Sequences relevant to the evaluation of bony metastases include T1-weighted spin-echo, T2-weighted (with fat suppression) & short tau inversion recovery (STIR) sequences which are sensitive to the cellular, fat and water content of the bone marrow [14]. Gradient-echo T1 sequences (including in- and opposed phase imaging) can be used to evaluate the relative fat: water content of bone marrow. Susceptibility weighted (T2*) sequences can be made sensitive to susceptibility induced dephasing induced
by trabecular bone [14]. Recently, ultrashort TE (UTE) sequences have been utilized to image trabecular bone structure in healthy and metastatic disease [15]. A number of studies have evaluated bone marrow vascularisation using dynamic contrast enhanced MRI techniques [16].

In the context of bone marrow assessment by metastatic disease, diffusion weight (DW) MRI is increasingly being used because it is sensitive to bone marrow cell density, the relative proportions of fat and marrow cells, water content and bone marrow perfusion [16]. Whole body DW imaging (WB-DWI) has emerged as an accurate bone marrow assessment tool for detection and therapy monitoring of bone metastases [13, 17]. Major advantages of WB-DWI include the fact that no ionizing radiation is administered and no injection of isotopes or any contrast medium is necessary. Importantly, whole body examinations are possible in reasonably short data acquisition times. The information obtained can be quantified and displayed as parametric maps, thus enabling spatial heterogeneity of tissues/tumours to be analyzed, before and in response to treatment. DW-MRI-derived parameters, such as the apparent diffusion coefficient (ADC), are theoretically independent of magnetic field strength and the relative simplicity of data acquisition facilitates multicenter and longitudinal studies [18]. In this talk we focus on the imaging observations and mechanisms underlying the assessment of bony metastatic response to therapy with DW-MRI [19].

**DW-MRI correlations with bone marrow cellularity**

Unlike the inverse correlations between ADC and cell density seen in many soft tissue tumours [20-27], ADC alterations in bone marrow as a consequence of metastatic disease are not-inverse but the explanation for this observation is incompletely understood [28-31]. Yellow fatty marrow has lower cell density with an abundance of fat cells compared to red bone marrow or metastatic disease. Yellow bone marrow has low signal intensity and low ADC values [28, 32] probably because of the reduced proton density, the hydrophobic nature of fat and lower bone marrow perfusion (compared to red bone marrow) [33]. With increasing bone marrow cellularity (which displaces fat cells and increases the vascularity of the bone marrow), the signal intensity on high b-value images increases, and appears to paradoxically return higher ADC values compared to yellow bone marrow [30-32, 34-36]. However once all bone marrow fat cells are displaced, increasing bone marrow cell density within the confines of a fixed marrow space may cause ADC reductions (as in non-bone marrow tissues) but this latter effect has not been comprehensively documented.

**Diffusion MRI for bone marrow therapy monitoring – mechanisms & patterns of change**

Therapy assessments are made by observing changes in the extent, symmetry and intensity of signal on high-b-value images, corresponding alterations in ADC values, seeking correlations on morphological sequences. Four general patterns of treatment-induced change can be recognized on WB-DWI (table) [19].

<table>
<thead>
<tr>
<th>Proposed DW-MRI response criteria for bone marrow lesions EARLY after starting cytotoxic chemotherapy [19]*</th>
<th>ADC changes in relation to tumour specific cut-off values</th>
<th>Possible biological explanation &amp; interpretation</th>
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</thead>
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<tr>
<td>Signal intensity/extent on high b-value images</td>
<td>ADC changes in relation to tumour specific cut-off values</td>
<td>Possible biological explanation &amp; interpretation</td>
</tr>
<tr>
<td>↑</td>
<td>ADC values decrease, remain unchanged or increase but remain &lt;cut-off</td>
<td>Persistent hypercellularity → no evidence of response</td>
</tr>
<tr>
<td>↑</td>
<td>ADC values increase with most pixels &gt;cut-off</td>
<td>Necrosis, hypocellularity, T2-shine through → evidence of response</td>
</tr>
<tr>
<td>↓</td>
<td>ADC values increase with most pixels &gt;cut-off</td>
<td>Hypocellularity → evidence of response</td>
</tr>
</tbody>
</table>

ADC values decrease or remain unchanged with most pixels <cut-off → Possible sclerotic or fibrotic reaction → indeterminate for response

*Criteria may not apply to non-cytotoxic therapies
*The timelines for the applicability of these criteria are undefined

ADC change needs to be judged in relation to cut-off values defined from untreated patients. Cut-off values are likely to be tumour type and imaging protocol dependent.

1. Disease progression can be determined by observing an increased extent of previously documented disease, as new areas of abnormal signal intensity, or by increases in the intensity of abnormalities on high b-value images. Importantly, bony metastases that progress can have variable changes in ADC values. Messiou et al. has noted slight increases, unchanged or even slight decreases in ADC values compared to pretherapy values [36]. In the setting of disease progression, stability or reductions in ADC values have rational biophysical mechanisms (more tumour of the same type increasing in geographic extent, and increasing tumour cell density (greater number of tumour cells per high power field, limited within a fixed bone marrow space).

The causes for slight increases in ADC values have been discussed above (see histologic correlates). Briefly, increasing bone marrow tumour infiltration displaces fat cells and increases vascularity, thus returning higher ADC values compared to yellow or mixed bone marrow [30-32, 34, 35]. The important point to note is that increases in ADC values with progression tend to be of small magnitude provided that the metastatic lesions remain non-necrotic. This is in contrast to bony metastases that respond to treatment, which have much larger increases in ADC values [36]. A practical way of dealing with the variable change in ADC values in order to distinguish responders from non-responders is to define an upper limit cut-off value of untreated lesions. Readers should note that such cut-off values are likely to be dependent on b-value choice and probably on the tumour type dependent.

2. When bone marrow disease is treated successfully, then tumour cell death results in initial increased water diffusivity manifested as higher ADC values [36, 37]. As already mentioned, the magnitude of ADC increases are usually greater than the smaller increases in ADC change seen in disease progression. The extent of ADC increases may be related to the mechanism of tumor cell death induced by the treatment given. It would be expected that ADC increases would be greater for therapies that result in tumour cell kill acting via necrosis mechanisms rather than via apoptosis, although this has not been definitively shown. This is because necrotic cell death is associated with an inflammatory response which is generally not found in tumor cell apoptosis [38]. Regardless of the mechanism of tumor cell death, in the majority of lesions responding to therapy, signal intensity decreases are noted on high b-value images.

3. Occasionally when there has been a successful response to therapy, marked rise in ADC values are seen but no signal intensity reductions are observed. In this situation, bony lesions are of high signal intensity and have high ADC values (termed T2-shine through). This pattern has been noted particularly in patients with multiple myeloma, lymphoma and occasionally in other solid metastatic neoplasms. The development of T2-shine through in bony lesions should indicate successful therapy response, re-emphasizing the need to always interpret high b-values images with corresponding ADC maps, correlating with other imaging findings as necessary.

4. The rarest pattern observed is the finding of signal intensity decreases on high b-value images with unchanging or slight decreases in ADC values. We have observed this pattern in patients who are clinical responders and occasionally in non-responding patients also. The biophysical mechanisms and therapy implications for these changes early after instituting therapy are unclear with an absent guidance literature. By observing changes in morphologic sequences and on CT scans we have noted that increasing calcification...
of metastases does lead to this appearance. Since this pattern can be seen in responders and non-responders, these appearances should be considered as indeterminate and currently we resort to morphologic and clinical assessments to categorise response.

As already pointed out, the patterns described above are seen soon after instituting therapy. The long term changes observed on WB-DWI are not well described. At this point it is important to recall that bone marrow disease responding successfully to therapy ultimately results in long term reductions of signal intensity on high b-value images accompanied by reductions in ADC values. This occurs via a number of mechanisms including removal of dead tumour cells, the development of bone sclerosis, re-emergence of yellow marrow, loss of tissue water, secondary myelofibrosis and decreased tissue perfusion [13]. These water diffusivity changes occur slowly becoming visible many months after starting therapy [39, 40], depending on the tumour type and type of therapy administered. Of course, if tumour relapses within the bone marrow then signal intensity on high b-value images has corresponding appearances as described above (pattern 1).

References