Evolution of the Malignant Bone Marrow with Successful Therapy – Quantitative Analysis with Whole-body Diffusion-weighted MRI

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Introduction

Bone disease is a common occurrence in metastatic breast cancer (MBC), but accurate evaluation of treatment benefit is notoriously difficult to do. There is a critical clinical need to develop non-invasive biomarkers to assess therapeutic effects of bone involvement in MBC. This is because the detection of primary non-responders and secondary therapy failure when disease burden is lowest, can help guide therapy decisions [1]. Currently, imaging assessments can only determine bone disease progression, because of which many patients with bone predominant disease receive ineffective medications for prolonged periods, and as a result do not change treatments until disease burdens become large, thus potentially hindering the effectiveness of follow-on treatments. It has been suggested, that aggressive disease detection methods and response monitoring could promote precision oncology in patients with bone involvement in MBC [2].

Guidelines from the American Society of Clinical Oncology and the European School of Oncology have recognized these limitations, advocating the use of serum tumor markers in addition to clinical assessments and imaging for monitoring MBC response [3, 4]. There is however, confusion regarding what constitutes suitable imaging for bone disease monitoring. All guidelines advocate the use of computed tomography (CT) and bone scans (BS), thus side stepping the limitations of CT/BS for assessing response in women with bone predominant metastatic disease.

Figure 1: Serial changes on morphological whole-spine sagittal T1-weighted images.

Diffuse metastatic infiltration throughout the spine, however note the small amount of fat on examination 6 (Ex6). The re-emergence of fat signal intensity is best appreciated on the last study (Ex9). The nature of the darker background signals on Ex9 is uncertain, but bone marrow (BM) scarring and/or residual active disease must be considered.
There is accumulating evidence showing the added value of PET/CT and whole-body MR imaging (WB-MRI) for decision making in metastatic breast cancer [5, 6]. WB-MRI with morphological and diffusion-weighted sequences has emerged as a powerful tool for detecting and assessing the response of MBC with good efficacy in the assessment of bone metastases [7]. The key advantage of WB-MRI is that the success of therapies can be positively assessed (CT/BS scans use the ‘no evidence of progression’ category as meaning therapy success). As a result, WB-MRI has the potential to alter clinical diagnostic thinking when assessing bone disease response [6]. Uniquely, quantitative apparent diffusion coefficient values (ADC; unit µm²/s) can bring objectivity to therapy response assessments.
Semi-automated threshold-based, quantitative ADC mapping and histogram analysis has been introduced as a viable and efficient tool for whole-body ADC mapping [8].

This case report applies the methodology of the companion article by Dalili et al. on the ability of the syngo.via Frontier MR Total Tumor Load software\(^1\) to distinguish ADC changes ascribable to tumor response and bone marrow recovery [9]. We discuss how ADC changes can be explained by the mechanism of tumor cell death and introduce a biologic model that explains imaging observations during the repair phase after effective therapy [10].

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\(^1\) syngo.via Frontier is for research only, not a medical device.

\(^\) syngo.via Frontier MR Total Tumor Load is a released research prototype.

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### Case study

A 49-year-old peri-menopausal woman presented with bone only metastatic lobular carcinoma (ER-positive, HER2-neu negative) in 2013. Bilateral mastectomy (left breast for risk reduction), axillary node clearance and breast reconstructions were performed with completion radiotherapy to the right supraclavicular fossa and chest wall. She underwent initial systemic anticancer therapy with Tamoxifen and Zoledronic acid infusions. During treatment, she developed bone pain but CT scans were unhelpful regarding the status of her bone disease. Subsequently she was referred for a whole-body MRI scan to assess her disease status (volume and tumor viability). Nine WB-MRI studies were then performed every 3–4 months over the next 3.5 years for therapy response assessments.
Histograms were created using the methodology of the accompanying article [9] at each time point. Fixed ADC thresholds were chosen (650 and 1500 µm²/s) because examination 1 was an ‘on treatment’ (Tamoxifen and Zoledronic acid) study (that is, no true pre-therapy baseline study was available). These default thresholds are based on literature values [12, 13]. Therefore, voxels in the red range are likely to represent untreated disease or those that have no-detected response. Green colored voxels have ADC values ≥ 1500 µm²/s (representing voxels that are ‘likely’ to be responding). Yellow voxels lie below 650 µm²/s and represent regions ‘likely’ to represent normal bone marrow.

**Ex1 Ex2:**
At baseline (Ex1), the histogram is negatively skewed (tail to the left) consistent with the therapy effects of Tamoxifen, although 86% of segmented voxels are in the active range (between 650–1500 µm²/s). With the change of treatment to Anastrozole and Goserelin (Ex2), a positive therapy change effect can be detected with a small right sided shift of the histogram. The bulk of the voxels on Ex2 (75%), remain in the red-voxel range (650–1500 µm²/s). The emergence of a new peak below 650 µm²/s is noteworthy and these yellow voxels seem confined to the limb bones (Fig. 4 – bottom row).

**Ex3 Ex4:**
With the change of treatment to Everolimus and Exemestane (Ex3), a more dramatic histogram change becomes visible with 2 well separated peaks (below 650 µm²/s and above 1500 µm²/s). The peak above 1500 µm²/s indicates large cell kill and highly likely response and these green voxels can be located to the axial skeleton (Fig. 4 – top row). The enlarging peak below 650 µm²/s is consistent with further return of the mixed bone marrow depicted as yellow areas in the limb bones (Fig. 4 – lower row). This twin peak histogram pattern does not change much in the 6 month period between Ex4–Ex6.

**Ex6 Ex9:**
A change of the histogram becomes visible 12 months later, on Ex9. At this point, the higher peak of the ADC histogram has begun to shift towards the red region, visible as increasing red regions on the MIP-ADC low projection images in Fig. 4. However, these emerging red voxels are unlikely to represent tumor regrowth because the b900 signal intensity has remained low (Fig. 3) and fat has remerged in the marrow spaces (Fig. 1). So, it’s most likely that the emerging red regions on Ex9 are likely to represent bone marrow scarring/bone sclerosis according to the model in Fig. 6. This remains to be confirmed.

After the first WB-MRI examination (examination 1), therapy was changed to Anastrozole and Goserelin with Zoledronic acid infusions. She remained symptomatic and a follow-up WB-MRI (examination 2) did not demonstrate appreciable cell kill to the therapy change. Subsequently she was switched to Exemestane and Everolimus (mTOR inhibitor) with good symptomatic relief of bone pain. Symptomatic relief of bone pain was accompanied by a good therapy effect on whole-body MRI scans (examinations 3 and 4). However, her blood hemoglobin levels remained below the normal range at 90 g/L between examinations 1 and 4. Eventually she returned to work and currently, she suffers only from minor drug toxicity related side effects. Her hemoglobin recovered to the normal range by examination 6 (120 g/L) at 18 months, and improved further to 130 g/L by examination 9 at 30 months, thus confirming an overall good systemic response.

In this report, we illustrate six WB-MRI examinations, with the initial four studies performed consecutively at 3–4 month intervals (Ex1–Ex4) and the latter two (Ex6 and Ex9) at 18 months and 30 months respectively. All studies were undertaken using the same 1.5T MAGNETOM Avanto scanner, utilizing a published protocol [11]. The diffusion-
weighted images of examinations were analysed using threshold-based segmentation with syngo.via Frontier MR Total Tumor Load prototype software\(^1\) [8]. Response to treatment was displayed using the methodology described in the accompanying article [9].

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**Discussion**

The premise for the use of ADC as a parameter of tissue characterization in the setting of treatment response, is that therapy-induced cell death precedes macroscopic lesion size changes. As a result of cellular necrosis, which results in loss of cell membrane integrity and increases in extracellular space water, ADC values typically increase.
During the following weeks to months, tumors may show shrinkage, with a resorption of the free extracellular fluid and fibrotic conversion leading to decreases in ADC values, although tumor recurrence can also result in reduced ADC values.

The degree of increase in ADC with successful therapy is highly dependent on the mode of cellular death with necrotic cell death resulting in higher ADC values due to associated inflammation and increased tissue water. Thus, chemotherapy typically results in greater degrees of tumor cell death and greater increases in ADC values [10]. With hormonal therapy, the mode of cell death is typically apoptotic and ADC value increases are smaller [12] as shown by the small ADC histogram shift between examinations 1 and 2 (Anastrozole and Goserelin therapy). When combination treatments are used, a synergistic, additive therapy effect can be observed clinically. This explains the greater ADC change in this case where Everolimus and Exemestane (mTOR inhibitor and hormonal therapy) were used together (examinations 3–6) resulting in two distinct peaks in the ADC histogram.

The phenomenon of 'T2-shine through' indicates a successful therapeutic effect with bone marrow edema. 'T2-shine through' can take a long time for high b-value signal intensity and ADC to decrease to normal levels [10]. The emergence of bone sclerosis, bone marrow fibrosis and/or return of bone marrow fat are part of repair processes, reducing high b-value signal intensity and lowering ADC values visible on the Ex9 images [10]. This latter phenomenon of decreasing ADC values with tissue repair highlights the need to evacuate all the acquired images (multiparametric assessments) for the correct interpretation of likely tissue disease status. So relying on ADC histograms alone may be misleading in the setting of tissue repair and recovery, making it necessary to take into account morphological appearances and quantitative parameters such as fat fraction and high b-value signal intensity to distinguish between healing processes from recurrent/residual cancer.

References