Monitoring Bone Marrow Metastases Treatment with Whole-Body Diffusion 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 perform because measureable bony soft tissue disease occurs infrequently. Symptom assessments and the 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. 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 informs only on the osseous/osteoblastic component of bone (not on the bone marrow). 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 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 whole-body diffusion-weighted MR imaging (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 is important. Distinct patterns of response can be recognized in the therapy assessment setting:

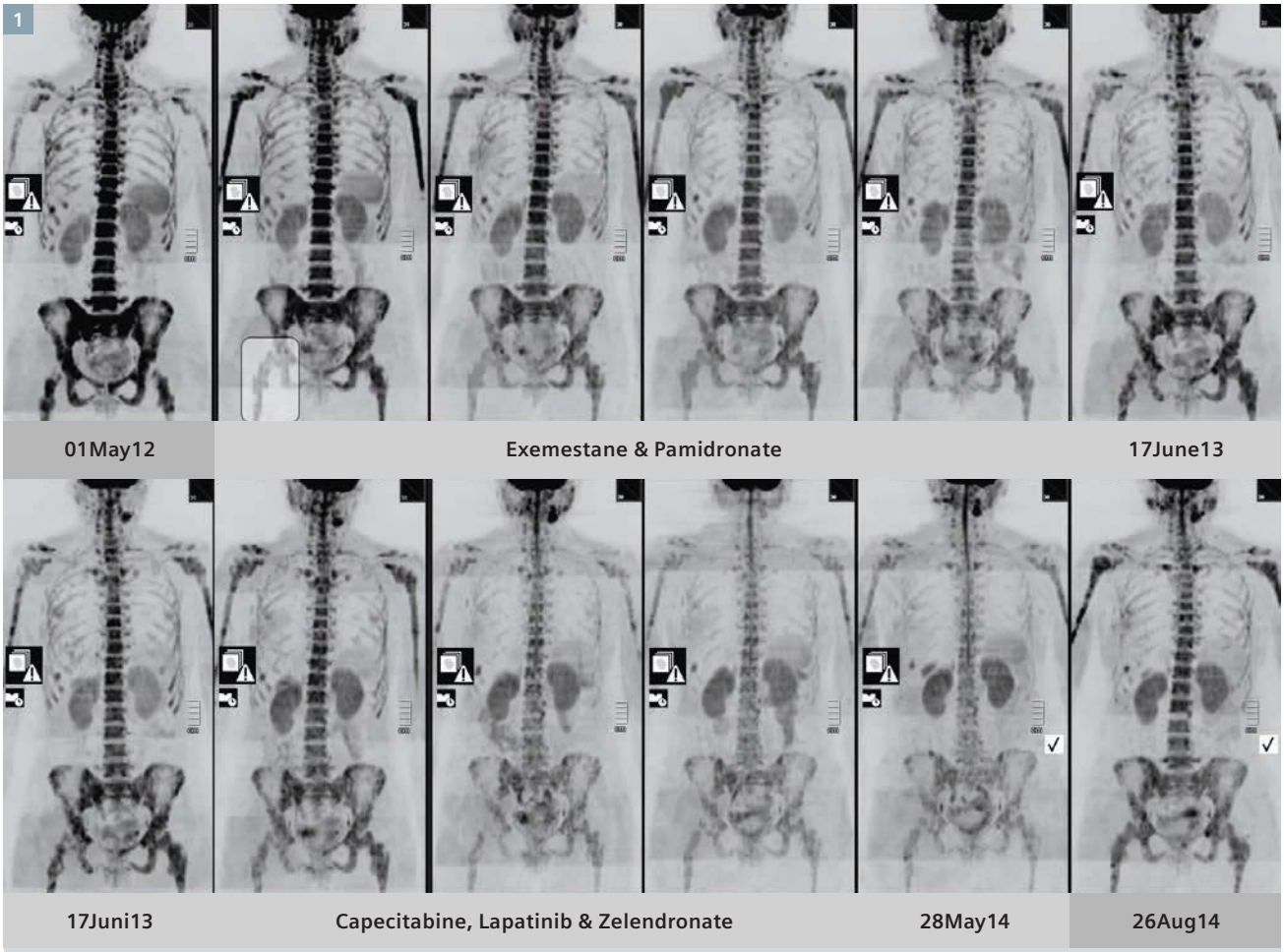
1. Increases in the volume of previously documented abnormal signal intensity lesions, new areas of abnormal signal intensity, or increases in the intensity of abnormalities on high b-value DW images can indicate disease progression. Modest increases, unchanged or slight decreases in ADC values compared to pretherapy values can occur in the setting of progression.
2. T2-shine through pattern: Occasionally unchanged high signal intensity on high b-value images is associated with marked rises in ADC values is observed. This pattern indicates 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 (see case study below). It has been noted that ADC increases are greater for cytotoxic chemotherapy and radiation. When patients are treated successfully with hormonal therapies, the ADC value increases seem to be less pronounced.
4. Occasionally high b-value signal intensity decreases are associated

with no ADC increases. Generally this pattern generally occurs in clinical responders (sclerotic response) although very occasionally we have noted it in non-responders (so called sclerotic progression). These appearances as thus considered indeterminate and currently we use morphologic and clinical assessments to assign the final response category.

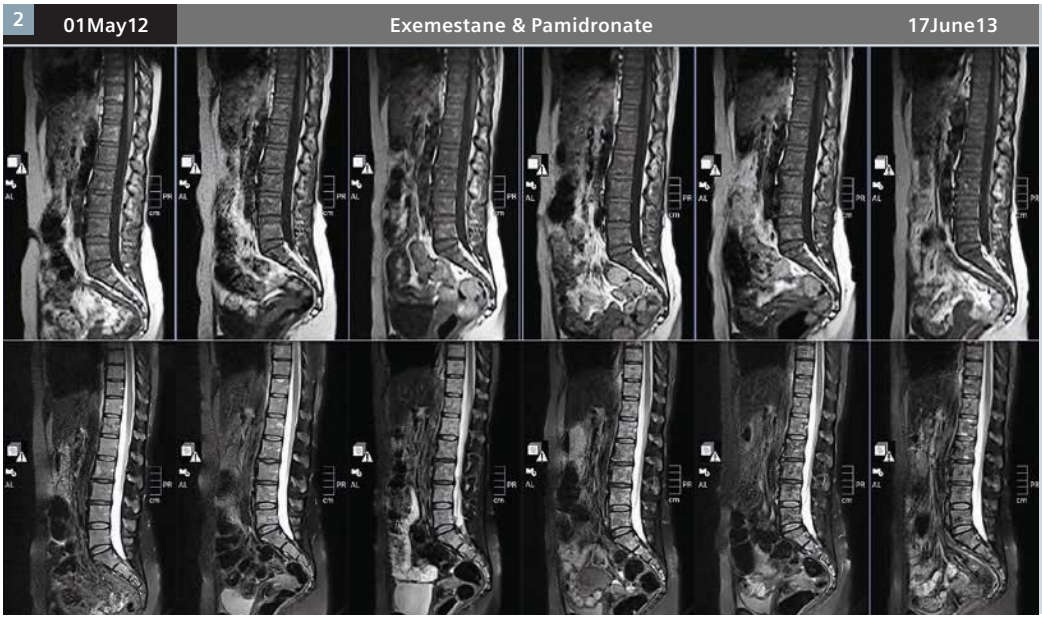
5. Stable disease is characterized by unchanging appearances on high b-value images. ADC changes can be variable, often remaining stable but are sometimes slight decreased presumably because of increases in cell density within lesions that are unchanging in their extent within the confines of a fixed marrow space.

Case study

58-year-old woman with metastatic invasive breast cancer, ER and HER-2 neu positive disease initially treated with hormone therapy (Exemestane) and bisphosphonates (Pamidronate) and then with chemotherapy (Capecitabine), HER-2 neu blockage (Lapatinib) and bisphosphonates (Zoledronic acid). She remained moderately symptomatic with bone pain through the course of treatments, receiving a single fraction of radiotherapy to the right hip in May 2012. Chemotherapy was terminated in June 2014 because of toxicity. Serial examinations with whole-body diffusion MRI using b-values of b50 and 900 s/mm^2 together with spinal T1w and T2w (spectral fat suppression) were undertaken to monitor response to treatment. Eleven examinations were performed at 2–4 monthly intervals.



1 b900 3D MIP (inverted scale). The bone marrow is diffusely infiltrated in the axial skeleton with relative sparing of the humeri. Single fraction radiotherapy was administered to the right proximal femur to palliate bone pain. Decreases in the signal intensity of bone marrow with hormone therapy can be seen to occur slowly but there are focal areas of persistent hyperintensity indicating the presence of active disease (top row). By June 2013, the b900 signal intensity has increased indicating repopulation by cancer cells of the bone marrow and therapy failure. One year of therapy benefit with hormones is in line with the expected duration of patient benefit. The patient was switched to Capecitabine chemotherapy, augmented by HER-2 neu blockage with Lapatinib. The bisphosphonate was changed to Zoledronic acid. An impressive response to treatment is observed with marked reductions of signal intensity to levels lower than those achieved by hormone therapy alone (bottom row). However, when chemotherapy is stopped due to toxicity, rebound tumor growth can be seen between May and August 2014.



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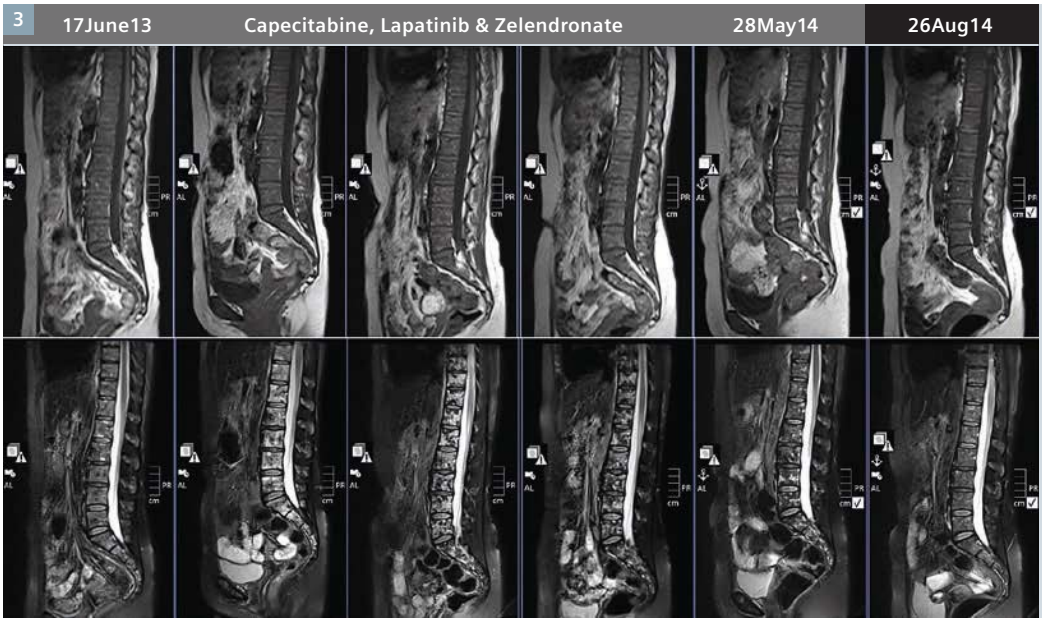
Whole-spine T1-weighted (top row) and T2-weighted images with spectral fat suppression (bottom row) show diffuse bone marrow infiltration with no discernable changes over time, during the period of hormonal therapy. The lack of change of T2-weighted signal intensity despite apparent therapeutic efficacy demonstrated on the diffusion-weighted b900 images (Fig. 1) is consistent with the mechanism of action of hormone therapy which acts via the induction of tumor cell apoptosis. Apoptosis is not accompanied by an inflammatory response so ADC increases are modest (see Figs. 4, 5).



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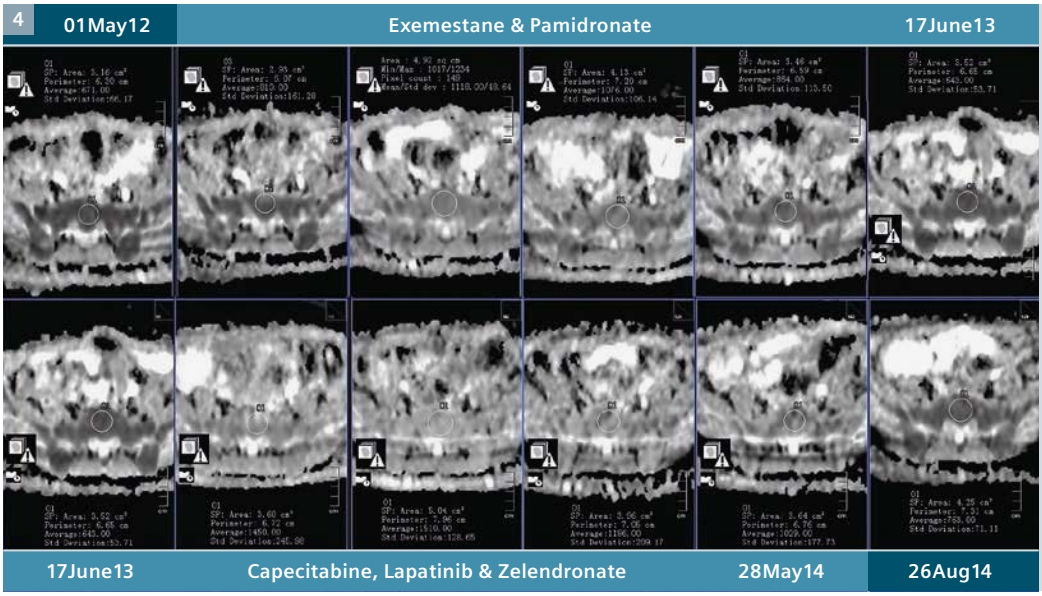
Whole-spine T1-weighted images (top row) show no discernable changes over time during the period of chemotherapy. However, the T2-weighted images with spectral fat suppression (bottom row) show marked initial increases in signal (bottom row examinations 2 and 3) consistent with bone marrow edema which decreases by May 2014. The increase in bone marrow water that accompanies chemotherapy is indicative of effective tumor cell kill; inflammatory edema is known to occur during the process of chemotherapy induced tumor cell necrosis which results in marked ADC increases (see Figs. 4, 5).



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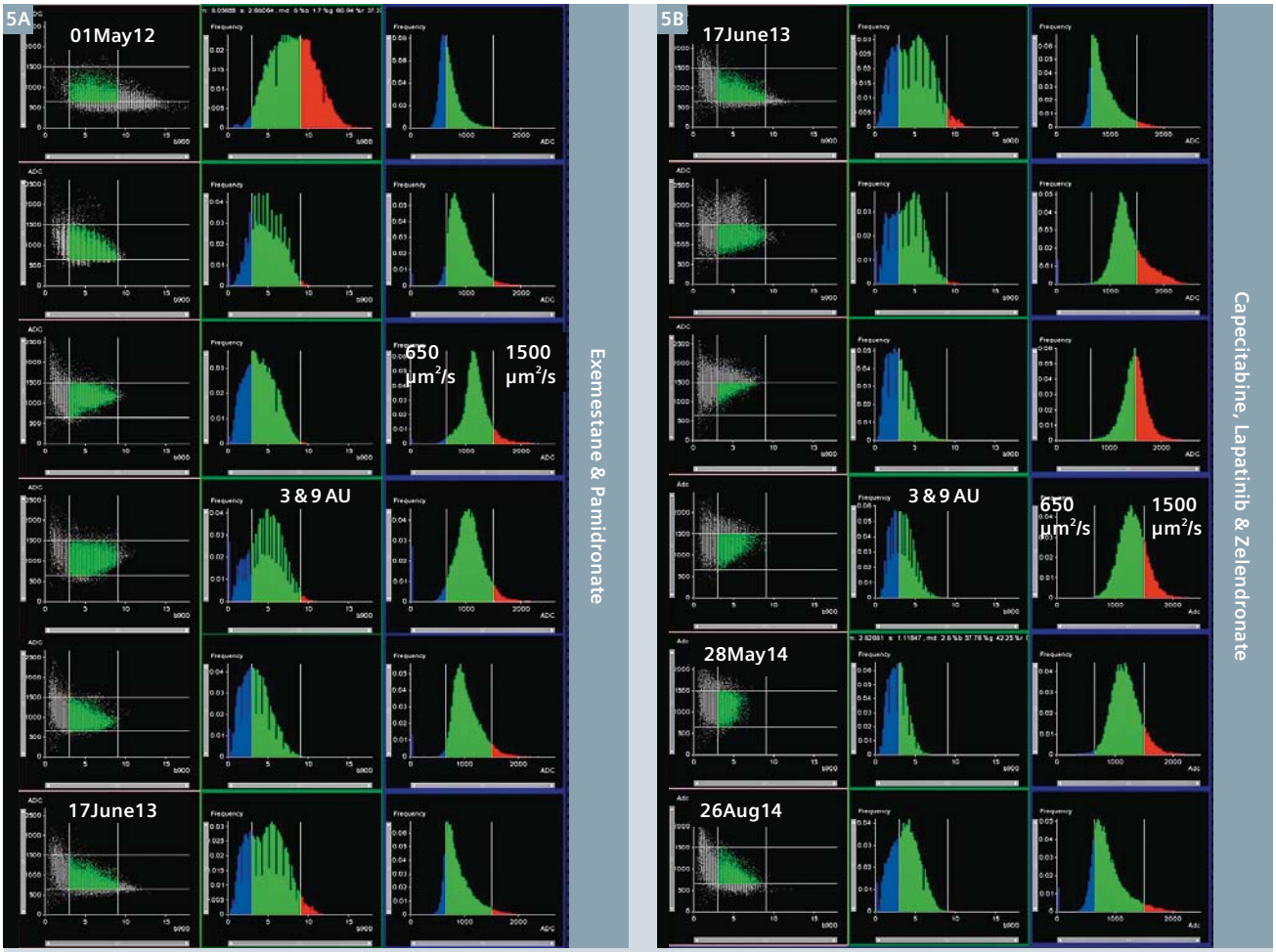
Serial changes on ADC maps with region-of-interest measurements placed on the sacrum. ADC increases with hormone therapy are modest (pre-treatment ADC 671 $\mu m^2/s$; maximum ADC increase 1118 $\mu m^2/s$). Larger changes in ADC are seen with chemotherapy (pre-treatment ADC 643 $\mu m^2/s$; maximum ADC increase 1510 $\mu m^2/s$). At disease relapse following chemotherapy termination, the ADC value has returned to low values; 763 $\mu m^2/s$.



5 Histogram analysis of b900 signal intensity and of ADC values.
A whole pelvis volume-of-interest defined on examination 1 (using b900 images) and applied to all examinations after robust, elastic image registration. Left column: pixel scatter plots of muscle normalized b900 signal intensity (x-axis) and ADC values (y-axis). Middle and right columns: Relative frequency, muscle normalized b900 and ADC histograms showing serial changes over time (superior to inferior) for both treatments. The control lines on the histograms and scatter plots are placed on 3 and 9 for normalized b900 signal intensity and 650 and 1500 µm²/s for ADC. A unimodal, non-normal ADC histogram with a positive skewness and kurtosis is observed at baseline and each time the patient relapses. Hormone therapy results in a shift of the ADC histogram towards higher values (fewer blue pixels) but mean ADC increases are not large. With chemotherapy, the mean ADC values increase markedly with a negative skewness consistent with decreasing cellularity due to chemotherapy. ADC values decrease over time with chemotherapy but without high kurtosis developing consistent with bone marrow repair utilizing mechanisms including the removal of dead tumor cells, loss of tissue water, bone sclerosis, fat deposition and reduced perfusion (see Fig. 3 above for T2-weighted imaging correlate). However, once chemotherapy is stopped, positive skewness and increasing kurtosis of ADC histograms re-emerges consistent with disease relapse. Note how the scatter plot moves to the left each time the patient responds (decreases in normalized b900 signal intensity). All analyses were done using OncoCare* software (Siemens Healthcare, Erlangen, Germany).

References

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; 39(5):1049-78.

*Works-in-progress the product is currently under development and is not for sale in the US and other countries. Its future availability cannot be ensured.

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