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Diffusion Weighted Magnetic Resonance Imaging of Metastatic Bone Disease: a biomarker for treatment response monitoring

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Abstract

Diffusion Weighted Magnetic Resonance Imaging (DW-MRI) combined with conventional MRI can provide a whole body assessment of metastatic bone disease, improved lesion detection compared to other imaging techniques and a direct quantitative assessment of treatment response. In bone marrow, the presence of fat and bone trabeculae and their changing contributions with disease progression and response to treatment present unique challenges for data acquisition and image interpretation. This article discusses these challenges and reviews the potential of DW-MRI to provide a biomarker of response in metastatic bone disease.

Introduction

Advances in targeted cancer therapies with growing investment in drug development are driving the need for quantitative imaging of metastatic bone disease. Currently, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), $^{99m}$Tc-MDP (Technetium 99m methylene diphosphonate) bone scintigraphy and sometimes $^{18}$F-fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)/CT are used to compliment one another in the assessment of the bony skeleton. However used conventionally, none of them combines a sensitive and specific quantitative assessment of treatment response with good anatomical resolution. As a result, updated Response Evaluation Criteria in Solid Tumours (RECIST)
guidelines still classify osteoblastic metastases as non measureable, with imaging being used merely to “confirm the presence or disappearance of bone lesions” [10].

With MRI, hardware and software advances have meant that Diffusion Weighted techniques (DW-MRI), initially successfully implemented in neurological applications, are now used for body imaging [7]. In bone, DW-MRI has potential to provide new and previously unobtainable quantitative measures of response of metastatic lesions. Further, it allows fusion of functional data from whole body acquisitions with the corresponding anatomical data whilst avoiding radiation exposure and intravenous contrast agents (Figure 1). However, imaging the bony skeleton in this way presents unique challenges in order to achieve robust and meaningful results. This article reviews basic principles and techniques for implementing DW-MRI in bone and discusses the unique histology of bone marrow and its implications for DW-MRI interpretation, addressing its clinical strengths and limitations.

**Basic concepts of Diffusion Weighted MRI**

To achieve diffusion weighting in MRI, two complimentary motion sensitising gradients are incorporated into the imaging sequence. For stationary molecules, the effects of these gradients are reciprocal and there is no signal change. For water molecules that are moving, loss in MR signal intensity with the application of diffusion sensitising gradients provides a measure of water diffusion. The loss in MR signal intensity in relation to the applied gradient may be quantified and expressed as an apparent diffusion coefficient (ADC). Thus DW-MRI can quantify image contrast based on diffusion properties of water within tissues at a cellular level. In a highly cellular tissue, extracellular water would not be able to diffuse far during the MR observation period without being blocked by structural interfaces such as cell membranes; this would lead to a short diffusional path and a reduced ADC. Soft tissue tumours which
consist of tightly packed cells therefore appear as areas of restricted diffusion relative to normal soft tissues [19].

The motion sensitizing gradients used to provide diffusion weighting can be varied in terms of their amplitude, duration and spacing to provide different degrees of diffusion weighting. The variation of these gradient parameters is represented by a “b” value which is measured in s/mm². Use of multiple b values enables a plot of signal intensity against b value: the slope of this log plot provides a pixel by pixel quantitation of the ADC which is measured in mm²/s (Figure 2). Depending on choice of b values the slope of the curve may be exponential but particularly over a wide range of b values it may be bi or even multi-exponential. Low b values (range 0-100 s/mm²) interrogate large diffusion distances and are therefore sensitive to flow in blood vessels. Large b values (>100-1000 s/mm²) detect small diffusion distances postulated to be related to extracellular space distances and therefore thought to be directly related to cell packing/cellularity. The inverse correlation between cell density and ADC (using b values up to 1000 s/mm²) has been extensively described [15;33;57;59]. This is further supported by indirect evidence that choline, a marker of cell turnover is inversely correlated with ADC in glioma[16]. However cellularity is not the sole factor influencing ADC and the relationship between cellularity and ADC has not been so impressive in other cell types [15] particularly renal tumours[56]. Other factors may influence ADC, for example cellular architecture, cell size, viscosity of cytoplasm, bulk flow in capillaries and active transport have been variously implicated in small studies, but their effect remains to be proven. Theoretically, with very large b values (>4000 s/mm²) it is possible to interrogate the movement of intracellular water protons, but at a practical level signals obtained with these large b values are very low and long TEs are required resulting in low signal-to-noise ratios so that with current imaging methods the measurement is not robust. This can to some extent be overcome but at the expense of
resolution or increased imaging time due to the use of multiple averages [65]. Volume fractions of slow-diffusing and fast-diffusing water populations extracted from simple biexponential analysis have been shown in some cases to deviate significantly from known ratios of intracellular and extracellular water. This may well be due to differing T2 relaxation times of compartments. Alternative explanations are the presence of more than two compartments, exchange between compartments, anisotropy and varying restriction of intracellular water by cell membranes [50]. However evidence from preclinical brain studies indicates that compartmentalisation is not an essential feature of biexponential decay as it persists despite presence of disintegrated cell membranes on electron-microscopy [54]. ADC may therefore be used clinically as a measure of cellularity but its value in separating intra or extracellular water is not yet clinically viable.

In response to treatment, the increased free water within a tumour manifests as an increase in ADC [8]. This has been exploited in several tumour types including brain, breast, prostate and liver metastases [7;8;48;61], where it has been used to predict treatment response ahead of conventional imaging and serum markers [22;37]. Some studies have gone further and used DW-MRI to detect the emergence of drug resistance during the course of therapy [29]. In comparison, measurement of tumour volume which does not change or may even increase where there is cellular swelling, extracellular oedema and accumulation of dead cells [22;49] under-estimates tumour response. In bone, tumour volume changes are usually unreliable as tumour often lies within a bony defect.

Studies of DW-MRI as a marker of treatment response have traditionally compared a mean tumour ADC encompassing the whole volume of tumour before and after treatment. However, to take into account heterogeneity within human tumours, Moffat et al [37] investigated the
functional diffusion map (fDM). This allows spatial, voxel by voxel tracking of changes in water diffusion values within tumours using digital registration techniques. Work on patients with gliomas revealed that the fDM could be used to stratify patients as responsive or nonresponsive at 3 weeks and the fDM was proposed as a potential predictive tumour imaging biomarker for early stratification of tumour response. Preclinical models which correlate fDM changes with survival and cell kill also support this [36;37]. The exact mechanisms by which a response to therapy causes an increase in ADC are poorly understood and are likely to be tumour type, mode of therapeutic action and timing dependant. Apoptosis leads to cell shrinkage and increased mobility of extracellular water. Necrosis also has been shown to cause a rise in ADC in the absence of apoptosis. The current wisdom is that cell shrinkage in apoptosis, and breakdown of plasma membranes in necrosis [38] are the main factors that result in an increased ADC tumours responding to treatment.

Unfortunately these patterns of ADC change are not directly applicable to metastatic bone disease.

**Diffusion Weighted MRI in bone**

i. Technical Considerations

The key factors to successful imaging of the bony skeleton with MRI are speed and coverage. Although bone is less prone to bulk motion, short scan times with high signal-to-noise ratios and resolution with minimal geometric distortion are highly desirable. DW-MRI is very prone to artefacts from eddy currents and magnetic susceptibility effects at soft-tissue/bone or air interfaces. However considerable advances and growing understanding of the technique mean that image quality is now of a very high standard [26]. Speed can be achieved by using echo-planar (EPI) sequences (rapid gradient switching to acquire all phase and frequency data in a
single cycle) which have become the mainstay of DW-MRI as well as parallel imaging (simultaneous signal acquisition from multiple regions within the imaged volume with multiple receiver coil elements). Techniques such as steady state free precession have resulted in inaccuracies in calculated ADCs [26;45] while stimulated echo techniques suffer from limited SNR [55]. Traditionally, respiratory motion artefacts in the upper abdomen and thorax on MRI have been addressed by use of breath holding techniques. However the inherently reduced signal-to-noise ratio of these fast imaging methods can be improved by adopting a “free-breathing” approach over several minutes and increasing the number of signal averages acquired. Thin partitions of 4-5mm improve spatial resolution and allow multiplanar reformats. Line scan diffusion imaging was developed to overcome motion artefacts but produces low spatial resolution perpendicular to the readout and has low signal-to-noise ratio [34]. With diffusion-weighted sequences, it is reported that motion artefact is not a problem with a free breathing technique due to the speed of the diffusion sensitising gradients which results in effects of such bulk motion being averaged out [58]. Currently non breath hold spin echo EPI combined with fat suppression is a useful all purpose sequence.

Susceptibility differences between neighbouring tissues produce inhomogeneities in the magnetic field and subsequent image distortion. This can be minimised by manual shimming [66]. Reducing the echo time (TE) with parallel imaging is also beneficial as it allows less time for dephasing [24]. The susceptibility artefacts tend to be more severe with increasing b value and any image distortion will cause errors in ADC calculations. Geometric distortions can be reduced by using high receiver bandwidth, large field of view, acquiring thick slices and using a radiofrequency coil of cylindrical geometry such as a body coil.
Eddy currents are induced when diffusion gradient pulses are switched rapidly. These result in magnetic gradients that combine with the imaging gradient pulses to produce geometric distortions proportional to the gradient pulses that therefore vary between different b values. Also, mismatch between the applied and effective gradients cause variations in voxel size. Variability in distortion and voxel size on individual diffusion sensitized images used for generating ADC maps this leads to inaccuracies in calculated ADCs. Eddy current artefacts may be reduced by refocusing the signal twice with the use of four diffusion sensitising gradients [46] or by slightly increasing the upward and downward slopes of the gradient pulses to compensate or by using postprocessing software [26]. On EPI chemical shift artefact is most pronounced in the phase encode direction where bandwidth is small and all phase encode lines are acquired quickly. This artefact can be up to 8 pixels wide [11] and can be reduced with fat suppression techniques [6;23;46].

To encompass the skeleton, whole body coverage needs to be achieved in a realistic time frame. This involves imaging sections of the body at a number of “stations” usually in five to seven 30 cm blocks. More recently a continuously moving table set up at a speed of 10 mm/s with interleaved slice readout allows a more seamless technique mimicking spiral CT. Employing such techniques over a number of body sections can achieve a whole body DW-MRI scan in 20 minutes. Although data is commonly acquired in the axial plane it can be processed and reformatted to be viewed in any plane or as a 3 dimensional volume. Whole body acquisitions can be used to provide bone tumour load based on ADC values of lesions and with background body signal suppression (DWIBS technique, Diffusion Weighted Whole Body Imaging with Background Body Signal Suppression [58]. This technique has a potential
role as a screening tool for bone metastases because the ADC values of metastases are significantly different from those of normal marrow with very little overlap.

ii Tissue Structure Considerations
The unique structure of cortical bone and bone marrow presents particular challenges both in data acquisition and in image interpretation. Cortical bone consists of a calcified matrix with very little free water for diffusion. Bone marrow has a high fat content where paucity of free water protons causes profound diffusion restriction. The water fraction of vertebral marrow in an adult male can be as low as 48% and is affected by factors such as age which influences the proportion of hematopoietic to fatty marrow [20]. In order to achieve optimal image contrast for bony lesions therefore, judicious choice of parameters for diffusion weighting is essential. ADC values of normal and metastatic bone marrow indicate that maximal contrast between them is achieved with a b value of 1400 s/mm². Lower b values diminish contrast while higher b values can lead to image distortion due to eddy current effects as well as being low on signal-to-noise ratio. On a conventional imaging system multiple averages and techniques to minimise eddy current distortions [46] make imaging at b values of 1400 s/mm² feasible without significant image degradation (Figure 2).

Soft tissue tumour classically appears as a focus of restricted diffusion relative to surrounding normal tissues. In contrast, metastatic bone disease is recognisable as an area of increased diffusivity relative to the restricted diffusion of normal fatty marrow [41] (Figure 2). DW-MRI not only matches conventional fat suppressed imaging techniques for lesion detection but compliments them by increasing sensitivity and specificity further [32;40;63]. In contrast to soft tissue tumours, there is positive correlation between ADC values and cellularity for bone tumour. Whenever there is an increase or decrease in the number of haematopoietic cells in
marrow there is a corresponding decrease/increase in the number of fat cells. Thus haematopoietically active marrow has more intracellular water and adjacent free water than less active marrow. This seems to make room for more molecular diffusion in cellular than less cellular marrow [41]. In keeping with this T2 relaxation was consistently elevated in bone marrow of 7 hypercellular patients with leukaemia relative to the bone marrow of normal volunteers [1]. However it is likely that there is a point at which increased cellularity begins to restrict diffusion. This is described in a patient following granulocyte colony stimulating factor (G-CSF)[2]. Differentiation of diffuse pathological marrow from normal hypercellular marrow in young adults or patients with hypercellular marrow related to treatment can be more challenging as mean ADC values of normal hypercellular marrow have been shown to be very similar to those of lymphoma [41]. At b values <100 s/mm² perfusion effects may also be influential, as more blood supply is likely when hematopoietic cells are abundant or when malignant cells have infiltrated marrow. In these cases changes in ADC from baseline values will be of most use.

Measured ADCs are also strongly influenced by the balance of osteoblast and osteoclast activity. Predominantly osteolytic activity in metastases, e.g. from renal cell carcinoma, will elevate ADC within the marrow because of the displacement of fat by tumour cells and their associated extracellular matrix. A dominant sclerotic component such as in prostate carcinoma results in a smaller ADC rise because bony matrix restricts water diffusion. However, despite ADC values of sclerotic metastases being lower than lytic metastases, they remain higher than those of normal fatty marrow [35]. DW-MRI also has been extensively applied in the differentiation of benign and pathological vertebral compression fractures. Several groups have recorded greater restriction of diffusion in malignant vertebral compression fractures; this may be due to packed tumour cells whereas in benign fractures oedema predominates [3;4].
Measuring Treatment Response

Unlike soft tissue tumours, ADC changes in bone following treatment are difficult to interpret because the effects of cell death may be masked by other changes in tissue content (Figure 3). In progressing bone metastases increased replacement of normal fatty marrow (with its restricted diffusion) by tumour cells can cause an ADC rise. An osteolytic component will cause the ADC to rise further (Figure 4). Conversely, increased cellularity and/or sclerosis in proliferating metastases will restrict diffusion and lead to an ADC fall. In all responding bone metastases cell death results in a rise in ADC (Figure 5). In sclerotic metastases, a decrease in osteoblastic activity may also contribute to this. Conversely, ADC also may fall in responding lesions due to a return of normal fatty marrow and this is an important confounding factor. Sclerosis as part of the osteoblastic healing process also has potential to cause a fall in ADC.

These conflicting processes necessitate special consideration when interpreting ADC changes following treatment. At the outset quantifying changes in the fraction of fat within lesions is critically important. This can be done using subtraction of sequences which image fat and water in and out of phase to give fat only images. Alternatively, histograms of ADC values within a lesion can be generated and changes in the number of pixels representing normal fatty marrow (ADC values for normal marrow have already been established [41] can be measured (Figure 6). Segmentation of ADC maps to characterise tissue populations has been used in the brain [21] but has not been explored for bony lesions.

Identifying and quantifying the component contributing to the osteoblastic healing process is essential in osteoblastic metastases but is not necessary in all tumour types e.g. myeloma. Isolating and measuring the osteoblastic process by MR alone is challenging because the
relaxation time of sclerotic lesions is very short and these lesions return very little signal on conventional imaging. Newer techniques such as ultra short TE (UTE) sequences which enable measurement of signal from cortical bone [47] will address this issue in future, but are currently difficult to implement routinely in clinical MR protocols. Currently, a more pragmatic approach is to use corresponding CT Hounsfield units as a measure of density of the lesion before and after treatment. Correlation of these density changes with ADC changes may give some indication of the contribution of osteoblastic activity to ADC.

Because of the variety of tissue responses to treatment in bone efforts to use DW-MRI to quantify these changes have been limited. Subjective falls in marrow signal on DWI-MRI [2;5] and increased ADC following successful treatment have been reported however [1]. An fDM approach has been successfully applied to preclinical models of prostate carcinoma bone metastases demonstrating treatment response with an ADC rise preceding tumour volume changes at 7 days post treatment [30;51]. The fDM approach does however require registration of pre and post therapy ADC maps which generates errors if lesions change in morphology or size. Despite this the fDM has been used in the clinic in a feasibility study of a single patient with bone metastases from carcinoma of the prostate to demonstrate that ADC rises with treatment response were more sensitive than mean ADC used alone or tumour volume [28].

**Comparison of DW-MRI with other imaging for evaluating metastatic bone disease**

Over the last several decades ⁹⁹mTc-MDP bone scintigraphy has been used as a robust albeit non quantitative indicator of response assessment of bone metastases to treatment. However, false positives frequently secondary to degenerative/inflammatory change occur. Increased uptake at 3 months can also be due to osteoblastic response mimicking progressive disease (the flare response) with follow up ⁹⁹mTc-MDP bone scintigraphy at 6 months being required to
resolve disease status [31;44]. In acknowledgement of the flare response the Prostate Cancer Clinical Trials Working Group recommend confirmatory $^{99m}$Tc-MDP bone scintigraphy 6 weeks later if new lesions are found on the first assessment [52].

In standard clinical practice, conventional T1W and T2W MRI with fat suppression are routinely used in assessing focal bone lesions because MRI delivers exquisite soft tissue contrast between normal and pathological bone marrow. Sensitivities and specificities for lesion detection are 100% and 88% respectively (compared to a sensitivity of 46% and specificity of 32% on $^{99m}$Tc-MDP bone scintigraphy) but do not provide quantitative data [27;60]. Attempts to apply RECIST criteria to T1W imaging of bone [62] have not been widely adopted due to lack of lesion definition and lesion heterogeneity. MRI can also assess purely lytic marrow pathologies which are not visualised on $^{99m}$Tc-MDP bone scintigraphy. Further MRI also provides detailed and critically important anatomical assessment of the spinal cord and nerve roots. However, coverage to include the whole skeleton has only recently been implemented. MRI remains expensive and resource limitations mean that whole body $^{99m}$Tc-MDP bone scintigraphy continues to be a very useful workhorse for the diagnosis of metastatic bone disease.

To achieve quantitative data, new techniques such as PET have been explored. PET/CT offers the advantage of superior resolution and fusion of structural and functional data. A variety of tracers are showing promise but none have been fully validated for use in response assessment of bone metastases. $^{18}$FDG reflects glucose metabolism of tissues and is used most commonly but is not specific to bone. Sclerotic metastases show little $^{18}$FDG uptake compared with lytic lesions [9;13;39;64] and limit utility of the technique. Another non-specific bone PET tracer, $^{18}$F-fluoride, whose uptake by bone metastases is related to their osteoblastic
activity, can detect bone metastases earlier than $^{99m}$Tc-MDP bone scintigraphy [12;53]. Specificity problems with $^{18}$F-Fluoride PET are similar to those encountered with traditional MDP bone scintigraphy, although the improved spatial resolution achieved secondary to almost 100% first pass extraction into bone and the combination with CT helps differentiate between benign and malignant processes in equivocal cases by clarifying anatomical location [12;25]. Interest in choline tracers also has grown from evidence that malignant cells have elevated levels of choline and upregulation of choline kinase activity as a result of increased cell turnover [18;42]. $^{18}$F-choline PET/CT therefore has shown potential both to upstage and downstage bone disease in prostate cancer compared to $^{99m}$Tc-MDP bone scintigraphy. It has a longer half life (110 minutes) than $^{11}$C choline (half life of 20 minutes) which limits its use to sites with cyclotrons [17;25].

DW-MRI of bone offers several advantages over isotope techniques. It is quantifiable. It avoids the use of ionising radiation. It is much simpler to implement on conventional MR scanners and cheaper than PET/CT. It also allows simultaneous assessment of spinal cord and nerve roots. Thus, DW-MRI fused with anatomical MR images has potential to reduce the cascade of imaging (plain film, CT, bone scan, MRI, PET/CT) that can occur in assessing metastatic bone disease.

**Future utility in clinical trials**

With time to progression and progression free survival frequently used as intermediate endpoints for overall survival in clinical trials it is critical that the methodology for defining progressive disease in imaging assessment of bone metastases is clear. Variation in assessment can have a significant impact on progression free survival endpoints [14]. Conventional CT and $^{99m}$Tc-MDP bone scintigraphy at 3 months post treatment can be
misleading because of the flare response. Even within the first 6 months of treatment these modalities are unreliable as intermediate endpoints. This is of particular importance in trials of castrate resistant prostate cancer where, in our experience, bone metastases are present in 80% of patients with bone as the only site of visible disease in a third of cases.

The use of DW-MRI in the clinical trial setting for assessing treatment response of bone metastases is in its infancy. Case studies of patients with prostatic bone metastases, marrow disorders and leukaemia treated with docetaxol using a whole body DW-MRI have shown possible treatment related changes in keeping with clinical and haematological/marrow response respectively [2;28]. In our experience these changes are not always reliably demonstrated, but further technical refinements are likely to improve this.

**Conclusion**

As experience of DW-MRI of metastatic and myeloma bone disease grows it is apparent that detailed attention to technique and data interpretation is required. The need for optimal imaging parameters whilst minimising artefacts pushes current system hardware to its limits. In contrast to soft tissue tumours, bone metastases are conspicuous as foci of increased diffusivity relative to normal fatty marrow. ADC changes must be interpreted in light of the shifting relationship between fat, cellularity and bony trabecular matrix as tumours respond to/ progress on treatment. Of course, these relationships are also dependant on tumour type, timing and therapy. DW-MRI can be applied as a whole body technique and the combination of functional and anatomical data is highly informative.

The utility of DW-MRI in metastatic and myeloma bone disease needs to be developed further within a framework of biomarker development. Preclinical studies are of paramount importance
for histopathological validation as in clinical studies bone biopsy is rarely feasible and validation relies on indirect markers of disease activity. Protocols and methods of analysis appropriate to bone require consensus agreement. Reproducibility and repeatability specific to imaging bone need to be established. Also, the degree of heterogeneity between and within tumours needs documenting as it is will affect powering of future studies and impacts on the potential use/success of any biomarker [43]. Only when this groundwork is done can we progress to clinical trials with a robust biomarker of response assessment in bone. DW-MRI is becoming established as a powerful tool in oncology and its potential in imaging malignant bone disease should be exploited. Success relies on rigorous and systematic development within consensus groups.

Search strategy and selection criteria

Relevant information for this review was identified by searches of PubMed and references from relevant articles using the search terms: “Diffusion Weighted Magnetic Resonance Imaging”, “Bone Marrow”, “Bone Metastases”, “Bone Magnetic Resonance Imaging”, “Bone Metastases Imaging”. No date restrictions were used. Only papers in English were included.

Contributors

Authors contributed equally to literature search, figures, and writing.

Conflicts of interest

The authors declared no conflict of interest.
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**Figures**

Figure 1. 64 year old male with lymphoma involving the spine (arrows). Coronal whole body MRI (a) and sagittal reformat (b) of fused anatomical (water only image, 3 point dixon technique) and diffusion-weighted data (free breathing technique, b 1400s/mm² in orange) acquired in 3 stations. Total scan duration 20 minutes.

Figure 2. DW MRI of normal and pathological bone marrow. DWI-MRI with b values of b0 – b1400s/mm² demonstrating lymphoma involving the pelvic bones (arrows). The ADC map generated from these shows normal marrow to be restricted (dark, *) relative to disease (arrows).
Figure 3. Diagrams demonstrating water diffusion barriers in normal bone marrow and tumour. In normal bone marrow (a) water diffusion (arrows) is restricted predominantly by fat cells but also by haematopoietic cells and bone trabeculae. Tumour cells (brown) (b) with their increased water content destroy bone trabeculae and replace fat, elevating ADC. Osteolytic progression (c) causes further destruction of trabeculae and replacement of fatty marrow. Conversely, if the density of tumour cells increases this may reduce intercellular distances and restrict water diffusion within the tumour. Trabecular thickening in osteoblastic progression (d) restricts water movement but increased diffusivity usually predominates due to replacement of fat. In response to treatment (e) a return of fat cells sometimes with new trabeculae/trabecular thickening causes restriction of water diffusion. Areas of necrosis however may cause an increase in diffusion distances. The process which has the predominant effect on measured ADC is partly affected by the MR protocol which determines the diffusion distance being measured.

Figure 4. Progressive metastatic bone disease. MRI in a patient with breast carcinoma: T1W MRI and corresponding ADC map at baseline (a,b) and 12 week follow-up (c,d). T1W images show an increase in disease at follow-up compared to baseline. This can be quantified by DW-MRI as marrow fat with restricted diffusion (dark) at baseline increases in ADC when it is replaced by tumour at follow-up (arrows).

Figure 5. Responding metastatic bone disease. ADC maps at baseline (a) and after 12 weeks follow-up (b) with regions of interest (red) drawn around the prostate metastasis in the right iliac bone. Prostate specific antigen response (357ng/ml at baseline and 31.5ng/ml at follow up) was mirrored by a rise in ADC of the lesion from 879 x 10^-6mm^2/s to 1496 x 10^-6mm^2/s.
Figure 6. Progressive metastatic bone disease. ADC histogram of a progressing bone metastasis at baseline (blue) and after 12 weeks follow-up (pink). At follow-up the histogram has shifted (arrow) to the right i.e., the number of pixels with low ADCs (restricted diffusion) have reduced. This reflects the replacement of marrow fat by tumour cells and their associated extracellular matrix.