Advances in whole body MRI for musculoskeletal imaging: Diffusion-weighted imaging

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ABSTRACT

Recent advances in imaging technology have enabled the acquisition of anatomical and functional imaging from head to toe in a reasonably short scan time. Accordingly, whole body magnetic resonance imaging (WB-MRI) and diffusion-weighted imaging (WB-DWI) have gained recent attention for the management of musculoskeletal problems such as bone tumors and rheumatologic diseases. WB-MRI is especially useful in diagnosing systemic or widespread disease requiring whole body evaluation, such as bone metastases, multiple myeloma, lymphoma, neurofibromatosis, and spondyloarthropathies. Among WB-MRI sequences, the WB-DWI technique greatly increases the value of WB-MRI in the evaluation of disease extent and characterization as well as treatment monitoring. In support of the utilization of WB-MRI and WB-DWI in orthopedic clinics for various musculoskeletal diseases, we provide an overview of the technical aspects of WB-MRI and WB-DWI and their clinical applications in musculoskeletal tumors and rheumatic diseases.

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1. Introduction

In orthopedic clinical practice, imaging is an essential part of disease diagnosis, treatment planning, and response assessment. Recently, advances in magnetic resonance imaging (MRI) techniques have greatly contributed to improvements in the management of musculoskeletal disease. Thus far, the majority of MRI performed for musculoskeletal disease is in a localized region such as the knee, shoulder, or spine. However, in cases of multiple sites of or systemic disease, localized MRI scans are less helpful. Whole body MRI (WB-MRI) techniques have been developed and greatly advanced over the last decade to overcome these drawbacks and broaden MRI applications.¹

WB-MRI provides significant advantages in the evaluation of bone tumors, including bone metastases and multiple myeloma as well as systemic syndromes such as rheumatic disease. Compared to compounding multiple localized MRI or other imaging tools, the

WB-MRI can evaluate such diseases in a single scan, potentially rendering it more cost effective and time saving for whole body evaluations.^{2–4}

WB-MRI can be used for whole body evaluation and treatment response monitoring. In particular, diffusion-weighted imaging (DWI) is now available for whole body scanning by incorporating it into one of the main sequences of WB-MRI. Whole-body DWI MRI (hereafter referred to as WB-DWI) provides unique benefits such as excellent lesion contrast and no need for contrast agents, leading to increased use thereof in orthopedic patients.³

This article offers an overview of WB-MRI techniques including WB-DWI. We also discuss the clinical applications of WB-MRI for musculoskeletal issues including tumors and rheumatic diseases, to provide specific information for orthopedics healthcare providers.

2. WB-MRI technique

WB-MRI is an emergent technique for head to toe evaluation (Fig. 1). The coronal plane is the preferred imaging plane for whole body scanning, including extremities, and is the most efficient way to cover the entire patient in the least amount of scan time.⁵ However, the sagittal plane is preferred for whole spine imaging, and in many centers, a WB-MRI includes sagittal imaging

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Fig. 1. Common sequences and planes for whole-body MRI. A 63-year-old male with multiple myeloma underwent a whole-body MRI scan for staging, including T2- and T1-weighted coronal images of the whole body (a, b); T2- and T1-weighted sagittal images of the spine (c, d); diffusion-weighted coronal and sagittal images of the torso (e, f); and contrast-enhanced axial images of the torso (g).

sequences specifically for the cervical, thoracic, and lumbar spine. Axial (transverse) plane imaging might be required only for the neck, chest, abdomen, and pelvis in oncological settings to evaluate organs and lymph nodes as well as bones.² Imaging planes should be optimized depending on WB-MRI purpose and disease characteristics.

A WB-MRI is divided into anatomical and functional sequences (Table 1). In anatomical sequences, the T1-weighted image (T1-WI) or T2-weighted image (T2-WI) are primary and provide anatomical information on basic physiochemical properties of tissues and disease. Water-containing lesions show T2 hyper-intensity and T1 hypo-intensity, while fat shows hyper-intensity in both.⁴ In certain clinical situations, contrast-enhanced MRI is necessary via intravenous administration of contrast agents.⁶ In patients with tumors, contrast-enhanced MRI improves disease detection and characterization, identification of lesion extent, and treatment response monitoring. For patients with rheumatic disease, contrast-

enhanced MRI allows a clearer evaluation of the distribution of joint inflammation simultaneously in the axial and peripheral joints.⁷ However, caution is advised due to the risk of nephrogenic systemic fibrosis or acute renal dysfunction.

Recently, the WB-MRI technique has added functional sequences such as short tau inversion recovery (STIR), chemical shifting imaging such as the Dixon technique, and WB-DWI.^{8,9} The STIR sequence is a highly fluid-sensitive imaging technique with fat suppression that provides information on the water content of tissues, even in fatty tissue, and is used to evaluate bone marrow composition abnormalities such as bone marrow edema or tumor infiltration as well as inflammation such as enthesitis or myositis.^{2,10} The Dixon technique is used in the acquisition of T1-WI and provides information on the fat component of tissue, especially in the bone marrow.¹⁰ The WB-DWI sequence was developed in accordance with an increasing need for the objective quantification of functional properties, as described in further detail below. No

Table 1
Common whole-body MRI sequences.

Anatomical sequences	Applications
T2-weighted images	<ul style="list-style-type: none"> Basic anatomical information on whole body Identification of skeletal lesions (e.g., tumors and inflammation)
Non-enhanced T1-weighted imaging	<ul style="list-style-type: none"> Basic anatomical information on whole body Bone marrow fat composition evaluation
Contrast-enhanced T1-weighted imaging	<ul style="list-style-type: none"> Detailed anatomical information of lesions Detection and characterization of and treatment response in lesions
Functional sequences	Applications
Fluid-sensitive sequences (e.g., STIR)	<ul style="list-style-type: none"> Information on water content (e.g., bone marrow edema, soft tissue fluid)
Chemical shift Imaging (e.g., Dixon)	<ul style="list-style-type: none"> Bone marrow fat composition evaluation (e.g., marrow edema vs. Red marrow from tumor)
Diffusion weighted imaging	<ul style="list-style-type: none"> Detection of lesions Characterization of lesions (e.g., differentiation between malignant and benign lesions) Quantitative treatment response assessment based on ADC values

single pulse sequence is sufficient to provide all necessary information for musculoskeletal evaluation; each has its own distinctive advantage, whether it is for lesion characterization, assessment of tumor infiltration extent, or treatment response evaluation.⁶

3. WB-DWI technique

The DWI is a functional MRI technique that visualizes water molecule movement known as Brownian motion. Water molecules are in constant motion, but movement in the tissue microenvironment is related to tissue cellularity and diffusion and can vary based on the underlying pathologic state.¹¹ Malignant tissues are generally more cellular than benign tissues, and extra-cellular water molecule diffusion is lower in the former than in the latter.¹² Accordingly, visualization of water movement therein aids in the evaluation of the characteristics and biological aggressiveness of tissue damage through non-invasive imaging.¹³

DWI can quantify pathological states using the apparent diffusion coefficient (ADC). This value represents the diffusion characteristics of tissues analyzed by measuring the movement of water molecules¹⁴ and reflects the interaction between water molecules and their environment (Fig. 2). ADC values can be utilized for differentiation between malignant and benign tumors and treatment response assessment.

Applications of DWI in the musculoskeletal imaging field are in the detection of pathologic diseases, differentiation between benign lesions and malignant lesions, and treatment response

monitoring.¹⁵ WB-DWI provides excellent tissue contrast on maximum intensity projection images of the whole body for bone lesion detection.¹³ Skeletal tumors show higher ADC values than normal marrow; normal yellow marrow demonstrates restricted water movement compared to tumors, because of low water content, confined extracellular matrix, and large adipocytes. This contrast between normal marrow and tumors enables relatively easy detection of bone tumors.¹³

In terms of treatment response assessment, DWI and ADC values can objectively quantify responses to treatment¹⁶; in general, ADC values increase in tumors responding to treatment (Fig. 3), and the interval of increase in ADC helps to quantify treatment responses.¹⁴

Nevertheless, DWI interpretation should be performed with caution. Lesions containing large amounts of fluid can cause a “T2 shine through” effect due to long T2 tissue relaxation times, resulting in a lesion appearing bright on DWI despite not being diffusion-restricted. Detection of malignant lymph nodes can be particularly challenging because of the high cellularity of lymphoid tissue. On DWI, benign and malignant lymph nodes may appear equally bright.¹ Another drawback of DWI is that it is highly sensitive to motion and respiratory and heart movement can easily degrade image quality and cause artifacts.¹¹ Caution is also recommended in DWI evaluation of sclerotic lesions. Sclerotic bone lesions have a low water content that may mask vertebral metastases, decreasing DWI diagnostic accuracy.¹⁴ ADC values can also be affected by different types of MRI machines and sequence parameters. When analyzing a lesion with DWI, it is thus important to

		ADC	DWI
Normal cells	Free diffusion → High ADC
Tumor cells	Hindered diffusion → Low ADC
T2 shine through	Vasogenic edema. Gallbladder, endometrium

Fig. 2. Diagram of the associations between cellularity, diffusion of water molecules, and signal intensities of ADC and DWI. Low cellularity in normal cells results in high ADC values, while high cellularity in tumor cells restricts diffusion resulting in low ADC values.

Fig. 3. 53-year-old patient with multiple myeloma treated with chemotherapy.

(a) Before treatment, a large mass in the sternum and chest wall (thick arrows) showed contrast enhancement on CE (upper), high signal intensity on DWI (middle), and low ADC values on ADC map (lower). (b) Two months after initiation of chemotherapy, mass (thin arrows) shows decreased contrast enhancement (upper), decreased signal intensity on DWI (middle), and increased ADC value on ADC map (lower).

consider its appearance and combine findings with anatomical information gleaned from conventional MRI sequences such as T1-WI and T2-WI.¹² Several studies have suggested that combining image information from DWI with T1-WI/T2-WI diminished interpretation errors when compared to DWI alone.¹³

4. Applications for musculoskeletal tumors

Primary tumors in the musculoskeletal system originate in the bone, cartilage, soft tissues such as fat or muscle, and hematologic system. Of these, common applications of WB-MRI are for the evaluation of tumors that originate from the hematologic system and are more likely to cause systemic disease, such as multiple myeloma and lymphoma.¹⁷ WB-MRI also has been increasingly used in patients with myxoid liposarcoma (Fig. 4) and neurofibromatosis.^{18,19}

For multiple or widespread bone metastases, WB-MRI and WB-DWI are very helpful in evaluating disease extent and monitoring treatment response. The use of WB-MRI and WB-DWI has also increased significantly in prostate and breast cancers.^{1,20,21} In this section, we discuss how to apply WB-MRI and WB-DWI in different representative clinical settings.

4.1. Multiple myeloma

Multiple myeloma is a cancer of the plasma cells characterized by an accumulation of proliferating clonal bone marrow plasma cells resulting in end-organ damage. Bone disease is a common sign of disease in multiple myeloma and presents as lytic bone lesions and bone fractures significantly related to morbidity and mortality in these patients.²² WB-MRI has been accepted as a valuable method for the diagnosis of bone involvement in multiple myeloma. Several studies have shown that MRI is superior to whole-body x-ray in the detection of bone involvement therein.²²

In 2015, the International Myeloma Working Group (IWMM) updated management guidelines for active multiple myeloma and approved WB-MRI for initial disease detection and prognosis evaluation. Active multiple myeloma is defined by the presence of more than one focal lesion at least 5 mm size and requires

treatment.¹⁷ WB-MRI can detect bone marrow invasion, allowing for early diagnosis of bone involvement by malignant cells before the consequent bone remodeling. Since multiple myeloma bone lesions have low fat content, high cellularity, and a high water component due to trabecular bone destruction, they are generally hypo-intense on T1-WI and hyper-intense on fat-suppressed T2-WI. On WB-MRI, patterns of lytic bone lesion are classified into five categories: normal, focal, diffuse, combined focal and diffuse and salt and pepper.²³ Diffuse infiltration, in particular, has been shown to have an adverse prognosis compared to other patterns.²⁴ Currently, IMWG guidelines do not include the diffuse infiltration pattern as a diagnostic criterion for multiple myeloma because imaging interpretation thereof is difficult and a consensus has not yet been reached. WB-DWI can, however, provide an additional advantage in the detection of diffuse marrow infiltration, focal lesions, and extra-osseous disease.²⁵ A previous study reported that diffuse disease was detected in 37% of patients with DWI, compared to 7% with PET-CT.²²

Another potential advantage of WB-DWI in multiple myeloma patients is in quantitative treatment response assessment.²⁶ Conventional MRI sequences may not accurately assess treatment responses since bone defects can remain even after tumor cells have been altered or eradicated. WB-DWI reflects the cellularity of the tissue and is useful in monitoring treatment-induced changes in tumor cells.²⁴ Elevation in ADC values is noted in patients with good treatment response even early in the treatment period (Fig. 3), and evaluation of early treatment responses could be beneficial for patients that might require adjustments to their treatment plans. In one study, ADC values in focal lesions were notably increased in those responding to treatment, whereas no notable ADC differences were observed in diffuse and salt and pepper patterns.²⁷ Use of WB-DWI for treatment response assessment in multiple myeloma patients, however, will necessitate the establishment of standardized methods for acquiring and quantitatively analyzing the DWI.²⁸

4.2. Bone metastases

Bone is a common site of metastasis for malignancies, and metastatic bone tumors are more common than primary bone

Fig. 4. A 39-year-old male with large thigh mass diagnosed as myxoid liposarcoma. Whole-body coronal T2-WI and T1-WI images (a, b) showing a large mass containing fat and myxoid components suggestive of myxoid liposarcoma. Additional thigh MRI provides detailed anatomical information of tumor (c, d).

tumors.^{1,20,21} Primary tumors of the prostate, breast, and lung are responsible for 80% of bone metastases. Whole body bone imaging is frequently required in cancer management for these patients, and the use of WB-MRI and WB-DWI therein continues to increase.²⁹

MRI is generally superior to other imaging modalities for the detection of bone metastases. Indeed, a meta-analysis by Yang et al. revealed that WB-MRI had a higher sensitivity for bone metastasis detection than FDG-PET or bone scans, at 97%, 91%, and 79%, respectively.²¹ In addition, the study evaluating treatment responses in breast cancer patients reported that about 30% of progressive disease was only visible in WB-MRI and was not diagnosed by CT examination.²¹ Guidelines developed by the European Association of Urology also suggest that MRI is more sensitive than choline PET-CT or bone scans for detecting bone metastasis in prostate cancer patients, at 97%, 91%, and 78%, respectively.³⁰ Several studies on the application of WB-DWI for the detection of bone metastases and primary tumors from prostate and breast cancers have reported high sensitivities ranging from 82% to 96%,¹ and evidence favoring the use of WB-MRI and WB-DWI for cancer patients continues to accumulate.³¹

WB-DWI can provide an overview of bone metastases in the whole body with maximum intensity projection images. WB-MRI and WB-DWI can also evaluate extraosseous disease and bone tumors in a single examination which allows quantification of tumor burden and assessment of treatment response.^{1,29}

However, certain caveats should be discussed in using DWI for

bone metastases evaluation. As mentioned before, tumor cell necrosis after treatment may be observed as persistent hyperintensity on DWI due to the T2-shine through effect despite increased ADC values. In addition, sclerotic or calcified metastatic lesions may appear falsely negative on DWI. As such, DWI results should be correlated with conventional MRI data.³²

4.3. Malignant fracture

During the management of patients with malignant bone tumors, distinguishing between benign and malignant fractures is a common clinical challenge. Compression fractures in the spine are especially problematic; spine metastases occur in up to 10% of patients with primary tumors, while up to one-third of vertebral compression fractures in patients with known malignancies are due to benign causes.^{33,34} Contributing factors to the difficulty include the fact that both benign and malignant fractures tend to occur in elderly patients, as well as that certain cancer chemotherapy regimens, may accelerate bone mineral loss resulting in secondary osteoporotic compression fractures.³² Conventional imaging techniques may not be specific enough to differentiate between benign or malignant compression fractures.³⁵

The application of WB-MRI and WB-DWI has shown promise in differentiating between benign and malignant fractures.¹⁴ On DWI, osteoporotic compression fractures tend to present as hypo-intense compared to normal vertebrae because of additional extracellular fluid. In contrast, pathological fractures tend to be hyper-intense

compared to normal vertebrae because of higher cellularity and extracellular fluid content. Although ADC values can significantly overlap between benign and malignant fractures, they are generally higher in osteoporotic compression fractures than in malignant fractures.³² Nevertheless, no definite cutoff ADC value has been suggested, and standardization for the analysis and interpretation of ADC values requires further research.^{12,34–36}

5. Applications for rheumatic disease

One of the main applications of WB-MRI is in rheumatic disease, mainly in spondyloarthropathies such as ankylosing spondylarthritis and psoriatic arthritis, multifocal bone disorders such as synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO), and chronic recurrent multifocal osteomyelitis (CRMO). WB-MRI can also be used for the management of patients with degenerative arthritis, rheumatoid arthritis, systemic sclerosis, polymyalgia rheumatica, and idiopathic inflammatory myopathies.³⁷

WB-MRI provides a variety of benefits to patients with these diseases, such as early diagnosis, evaluation of disease extent and activity, treatment choice, and evaluation of treatment response. X-ray radiography, a basic evaluation modality, only detects disease in cases of structural changes or deformities to the bones and joints. WB-MRI can detect lesions in pre-structural inflammatory stages and can evaluate the extent and severity of inflammation in soft tissue such as enthesitis and synovitis.³⁷ Functional sequences such as WB-DWI and STIR are also helpful in differentiating between active inflammation and chronic lesions, information useful in determining which patients need active treatment.

Since the patients responding well to treatment show significant decrease in ADC values, WB-DWI helps monitor treatment response.¹² Since new therapeutic agents such as TNF-alpha blockers are increasingly used in rheumatic diseases, WB-DWI could be especially meaningful as a treatment evaluation tool therein.

Ankylosing spondylitis is a seronegative spondyloarthropathy that mainly involves the axial joints, including the sacroiliac joints and spine, and less frequently involves peripheral joints such as hips, knees, hands, or the thoracic wall.³⁸ In ankylosing spondylitis,

long term inflammation of the bone and soft tissue in the spine and joints results in erosion, new bone formation, and eventually fusion (ankylosis). WB-MRI can evaluate and quantify synovitis, enthesitis, and juxtaarticular bone destruction (Fig. 5).²

DWI has proven useful in distinguishing degenerative disease from infection because ADC values are higher in patients with bone marrow infection. ADC values show negative correlations with intervertebral disc degeneration, suggesting promising potential for objectively quantifying degrees of individual lumbar disc degeneration.¹²

6. Pitfalls of WB-MRI and WB-DWI

Major obstacles to the use of WB-MRI in clinical practice are low image resolution and contrast, long scan times, lack of availability of MRI machines with whole body coil, and a lack of functional imaging.^{2–4} Localized regional MRIs such as knee or shoulder MRI are still of higher quality than WB-MRI, favoring the former in presurgical planning for local disease. WB-DWI, in addition to the limitations of WB-MRI, is prone to image artifacts which may lead to false-positive and false-negative findings.

In addition, WB-DWI requires extra caution when interpreting the image. For example, nonmalignant lesions such as inflammatory lesions can have low ADC values mimicking malignant lesions. Normal structures such as the lymph nodes, spleen, spinal cord, ovaries, testes and more can show wide range of impeded water diffusion degree at DWI which may lead to false-negative findings. Because medical implants prostheses may cause imaging artifacts, it may also lead to false-negative findings. Therefore the clinical history, clinical presentation and symptoms should always be taken into consideration.³⁹

7. Conclusion

The WB-MRI is a non-invasive and radiation-free imaging modality for head to toe evaluation of bone and soft tissue. The incorporation of DWI sequence information with WB-MRI has greatly improved disease detection accuracy and the assessment of tumor burden and treatment responses. Use of WB-MRI is growing

Fig. 5. A 55-year-old male with hepatocellular carcinoma and back pain. T2-weighted coronal (a), sagittal (b), and axial (c) whole-body MRI show multifocal lesions with bone marrow signal alteration (thin arrows) at the costovertebral junctions and corners of vertebral bodies. T2-weighted axial image at sacroiliac joint level (d) shows bony ankyloses at bilateral sacroiliac joints (thick arrows) suggesting ankylosing spondylitis.

in clinical practice, supporting the utilization of WB-MRI and WB-DWI in orthopedic clinics for various musculoskeletal diseases, including tumors and rheumatic disease. Understanding the techniques and current musculoskeletal applications of WB-MRI and WB-DWI will be helpful for orthopedics healthcare providers in managing patients and improving the clinical decision-making process.

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Conflicts of interest

Nothing to disclose.

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