Diffusion-weighted MR Imaging for Characterizing Musculoskeletal Lesions¹

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Abbreviations: ADC = apparent diffusion coefficient, DW = diffusion-weighted, ROI = region of interest, SNR = signal-to-noise ratio, TE = echo time, TR = repetition time

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TEACHING POINTS

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Diffusion-weighted (DW) imaging is a functional magnetic resonance (MR) imaging technique that can readily be incorporated into a routine non-contrast material-enhanced MR imaging protocol with little additional scanning time. DW imaging is based on changes in the Brownian motion of water molecules caused by tissue microstructure. The apparent diffusion coefficient (ADC) is a quantitative measure of Brownian movement: Low ADC values typically reflect highly cellular microenvironments in which diffusion is restricted by the presence of cell membranes, whereas acellular regions allow free diffusion and result in elevated ADC values. Thus, with ADC mapping, one may derive useful quantitative information regarding the cellularity of a musculoskeletal lesion using a nonenhanced technique. The role of localized DW imaging in differentiating malignant from benign osseous and soft-tissue lesions is still evolving; when carefully applied, however, this modality has proved helpful in a subset of tumor types, such as nonmyxoid soft-tissue tumors. Studies of the use of DW imaging in assessing the treatment response of both osseous and soft-tissue tumors have shown that higher ADC values correlate with better response to cytotoxic therapy. Successful application of DW imaging in the evaluation of musculoskeletal lesions requires familiarity with potential diagnostic pitfalls that stem from technical artifacts and confounding factors unrelated to lesion cellularity. Further investigation is needed to evaluate the impact of DW imaging–ADC mapping on management and outcome in patients with musculoskeletal lesions.

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Introduction

Magnetic resonance (MR) imaging plays a vital role in the characterization of musculoskeletal lesions, particularly in defining their composition, extent, compartmental involvement, and relationship to the adjacent viscera and neurovasculature (1). Conventional MR imaging relies primarily on a qualitative interpretation of variations in the T1 and T2 relaxation properties of normal and pathologic tissue. However, there is considerable overlap in the signal characteristics of neoplasms (both benign and malignant) and nonneoplastic reactive or inflammatory lesions. Furthermore, it is often

difficult to distinguish hyperintense tumor from reactive peritumoral edema with fluid-sensitive sequences (2). Consequently, contrast material enhancement characteristics are a key component of the conventional MR imaging assessment of masses in terms of differentiating solid tumors from cysts, delineating mass margins, and defining the amount of tumor necrosis (3). However, contrast material administration requires intravenous access, is relatively contraindicated in pregnant patients, and may be prohibited by an allergy to contrast material or by poor or deteriorating renal function due to the risk of nephrogenic system fibrosis (4).

Diffusion-weighted (DW) imaging is a non-enhanced functional MR imaging technique that reflects differences in the Brownian motion of water caused by variations in tissue microstructure. The apparent diffusion coefficient (ADC) is a quantitative measure of Brownian motion: Low ADC values reflect highly cellular microenvironments in which diffusion is limited by an abundance of cell membranes, whereas high ADC values are observed in acellular regions that allow free diffusion of water molecules (5). Thus, DW imaging offers quantitative functional assessment of cellularity at the molecular level, with the potential to help differentiate between benign and malignant lesions as well as improve the MR imaging evaluation of treatment response. Specific benefits of DW imaging include short scanning time and the lack of need for intravenous contrast material; hence, the ease with which it may be incorporated into a routine imaging protocol. DW imaging has been used for the diagnosis of primary osseous and soft-tissue neoplasms, the detection of bone metastases, and the assessment of treatment response for both osseous and soft-tissue tumors (6–8). In this article, we review the technical aspects of quantitative DW imaging with ADC mapping and discuss how DW imaging–ADC mapping can complement and augment conventional MR imaging in the oncologic evaluation of musculoskeletal lesions during initial characterization and in the posttreatment setting.

DW Imaging Technique

DW imaging makes use of two symmetric motion-probing gradient pulses (“crushers”) about a 180° refocusing pulse. Moving protons are not refocused, resulting in an exponential signal loss at increasingly high gradient strengths. **This signal loss from free diffusion is quantified as the ADC; protons in a more restricted, densely cellular environment exhibit less signal loss than do freely mobile protons and, therefore, have comparatively lower ADC values** (9). The word

apparent is used because this in vivo quantification encompasses other factors besides diffusion that contribute to signal loss, including restriction in closed spaces, tortuosity around obstacles (eg, organelles, cells, and fibers) in biologic tissues, and flow within vessels. Molecules flowing through tissue capillaries follow no specific dimensional orientation, so that this perfusion can be seen as a sort of “pseudodiffusion” or “fast diffusion” component; this effect is accentuated at lower gradient strengths (b values) (5,10). Thus, the use of lower b values results in an “ADC_{fast}” calculation, whereas higher b values weight the ADC calculation toward diffusion of extracellular molecules in the range of 1–10 mm (“ADC_{slow}”) (11).

The ADC value for a specific region of interest (ROI) is calculated by plotting the change in signal of the region as it varies with different diffusion gradient strengths (b values). In its simplest form, using a monoexponential fit, the ADC value is defined mathematically as the slope of the line representing the logarithmic decrease in signal intensity between two or more b values (Fig 1). ADC values are generated on a pixel-by-pixel basis, and minimum, maximum, and mean ADC values can be measured for a particular ROI, usually expressed in units of $10^{-3} \times$ square millimeters per second:

$$ADC = \sum_{i=1}^n \frac{-\ln\left(\frac{S_i}{S_0}\right)}{b_i}, \quad (1)$$

where b_i = diffusion gradient value, S_0 = signal intensity of the first image, and S_i = signal intensity of the i th image.

b Values

The b value is a parameter used for DW imaging that incorporates multiple gradient terms that describe how signal is affected by diffusion, as shown in the following equation:

$$b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3), \quad (2)$$

where γ = gyromagnetic ratio, G = gradient strength, δ = diffusion gradient duration, and Δ = time between diffusion gradient pulses.

The b value reflects the acquisition parameters and is expressed in seconds per square millimeter. Images obtained at lower b values preserve the signal-to-noise ratio (SNR) (due to T2 weighting) but are more strongly affected by perfusion effects, whereas those obtained at higher b values accentuate differences in the diffusion properties of the tissue but suffer from lower signal. In weighing these tradeoffs, the number and spread of b values

Figure 1. Graph illustrates how the ADC value is calculated by plotting the natural logarithm of the signal intensities in the ROI on the DW images obtained with different b values and fitting a linear regression line (assuming a monoexponential fit). The ADC value is the negative of the slope of that line. In this case (that of a 24-year-old man), a benign neurofibroma exhibits a higher ADC value (mean, $2.3 \times 10^{-3} \text{ mm}^2/\text{sec}$) than does a malignant peripheral nerve sheath tumor in the pelvis (mean, $1.2 \times 10^{-3} \text{ mm}^2/\text{sec}$), reflecting the fact that the ADC value is generally higher for benign than for malignant disease.

Sample DW Imaging Protocol at 3.0 T

Parameter	Description
Timing of sequence	Before intravenous contrast material injection
Plane of acquisition	Axial (local MR imaging) Coronal or axial (whole-body MR imaging)
Sequence	Single-shot multiecho echoplanar (EPI factor = 88)
TR/TE (msec)	1500/80
Number of signals acquired	2
Gradient strength (mT/m)	50
Field of view (mm²)	180–250
Matrix size (pixels)	256 × 256
b values (sec/mm²)	50, 400, and 800
Scanning time (min:sec)	2:32

Note.—EPI = echoplanar imaging, TE = echo time, TR = repetition time.

selected for DW imaging are controversial. It has been recommended that at least three b values be used for DW imaging with ADC quantification (6). Given these considerations, our approach is to use b values of 50, 400, and 800 sec/mm²; a b value of 50 sec/mm² rather than 0 sec/mm² is used to reduce the contribution of blood perfusion to the ADC measurement.

MR Imaging Protocol

A sample DW imaging protocol at 3.0 T is shown in the Table. DW imaging is a nonenhanced

sequence, and when it is performed as part of a comprehensive imaging protocol with T1-weighted, fluid-sensitive, and contrast material-enhanced sequences, it must be performed prior to the intravenous administration of contrast material. The scanning time required for DW imaging is minimal (well under 3 minutes), and all MR product manufacturers offer a DW sequence that can easily be incorporated into a clinical scan. The single-shot echoplanar spin-echo sequence predominates in current clinical use due to its fast acquisition of data and high SNR.

Analysis of DW Imaging

Analysis of DW imaging can be performed both visually and quantitatively after drawing an ROI. DW images demonstrate decreases in signal intensity on successively higher b -value images; the magnitude of this decline is higher for free water than for solid tissue. Regions with high free water content will exhibit higher signal intensity on ADC maps relative to muscle, whereas in areas of restricted diffusion the ADC map will show relative iso- or hypointensity. There is no standard method for constructing an ROI on an ADC map. Mean ADC value is conceptually straightforward; if measured in a largely necrotic tumor, however, it could lead to underestimation of tumor cellularity in residual viable tissue. Hence, some authors suggest using the minimum ADC value (12) because it theoretically reflects the area of highest tumor cellularity. Methodologies also vary in terms of whether the ROI should include the entire tumor or only the areas with the lowest values. Limiting the ROI to arbitrarily small portions of a lesion could lead to image-selection bias and poorer inter- and intraobserver agreement. In light of these considerations, we position circular or elliptic ROIs to encompass the largest area of tumor possible (excluding adjacent bone or soft tissues). This is usually performed on images on which the tumor appears to have the lowest ADC (and presumably the most cellular tissue). Both minimum and mean ADC values are measured (Fig 2).

Applications for DW Imaging

Lesion Characterization

Soft-Tissue Tumors.—Because free water demonstrates high ADC values, soft-tissue masses composed primarily of fluid (eg, ganglia or paralabral cysts) exhibit high ADC values (Fig 3), and these masses are often diagnosed based on the absence of contrast enhancement and/or their being in a characteristic location (eg, Baker cyst). However, reliably characterizing musculoskeletal soft-tissue neoplasms as benign or malignant on the basis of imaging features alone is challenging, since malignant soft-tissue sarcomas may, like benign neoplasms, be well circumscribed and enhance homogeneously. The hypothesis that malignant tumors should exhibit lower ADC values has been explored in multiple studies, with mixed results. Maeda et al (13) found no significant difference between the ADC values of malignant and benign soft-tissue tumors. Einarsdóttir et al (14) demonstrated substantial overlap in the ADC values of 16 benign soft-tissue lesions and 13 soft-tissue sarcomas (mean ADC = 1.8×10^{-3} mm²/sec and 1.7×10^{-3} mm²/sec, respectively).

Figure 2. ADC map of the pelvis (same patient as in Fig 1). Various ROI techniques have been used by different investigators, since there is no consensus in the literature as to how the ADC value for lesions should be measured. Here, a small ROI (circle) has been positioned in the malignant peripheral nerve sheath tumor, within an area that was visually judged to be the most hypointense and therefore suspected of having the highest lesion cellularity, yielding a minimum ADC of 0.61×10^{-3} mm²/sec and a mean ADC of 0.93×10^{-3} mm²/sec. Alternatively, a larger ROI (oval) encompassing most of the malignant peripheral nerve sheath tumor yielded a minimum ADC of 0.41×10^{-3} mm²/sec and a mean ADC of 1.2×10^{-3} mm²/sec. The lower minimum but higher mean ADC for the larger ROI highlight the potential for technical factors to skew results and complicate the interpretation of results achieved with various methodologies.

They noted that one of the highest ADC values for a sarcoma was seen in a myxoid liposarcoma. This fact reflects the need to consider myxoid and nonmyxoid tumors separately, since a myxoid matrix will result in increased ADC values (13). Nagata et al (15) found that, although there was no significant difference between the mean ADC of benign (2.1×10^{-3} mm²/sec) and malignant (2.05×10^{-3} mm²/sec) myxoid tumors, nonmyxoid malignant tumors did exhibit a lower mean ADC (0.94×10^{-3} mm²/sec) than did nonmyxoid benign tumors (1.31×10^{-3} mm²/sec).

Other studies have shown a difference between the ADC values of benign and malignant lesions. In a recent study involving aggressive fibromatosis and desmoid tumors, the mean ADC value of desmoid tumors ($n = 8$) (Fig 4) was higher ($1.36 \pm 0.48 \times 10^{-3}$ mm²/sec) than that of malignant soft-tissue tumors ($0.88 \pm 0.20 \times 10^{-3}$ mm²/sec) (16). In a study involving a wider range of disease, Razek et al (17) reported that malignant tumors tend to exhibit a lower mean ADC value than benign soft-tissue tumors and proposed using a

a.

b.

c.

Figure 3. Right hip ganglion in a 61-year-old man. **(a)** Sagittal short inversion time inversion-recovery SPACE (sampling perfection with application-optimized contrast using different flip-angle evolutions) image (TR/TE = 2290/171, flip angle = 120°) shows a T2-hyperintense mass with heterogeneously hypointense internal signal intensity anterior to the right hip. **(b)** Axial ADC map reveals a region of elevated ADC values (mean, 2.6×10^{-3} mm²/sec; minimum, 1.8×10^{-3} mm²/sec) in the area corresponding to the mass (arrow). **(c)** Postcontrast volume-interpolated breath-hold examination image (TR/TE = 6.35/1.48) helps confirm that the nonenhancing mass is a periarticular ganglion.

threshold mean ADC value of 1.34×10^{-3} mm²/sec to help distinguish benignity from malignancy. Use of this threshold value yielded a sensitivity of 94%, a specificity of 88%, and an overall accuracy of 91% (17). Furthermore, higher-grade sarcomas exhibited lower mean ADC values than did well-differentiated sarcomas (Figs 5, 6) (17).

The discrepancies in the literature likely stem from the fact that many factors besides lesion cellularity influence ADC values, such as the composition of the tumor matrix, the presence of spontaneous necrosis, and differing imaging protocols for DW imaging-ADC mapping. Recent studies have corroborated that lower ADC values are as-

sociated with malignancy and suggest that ADC values are particularly useful in discriminating between cysts and solid lesions when intravenous contrast material cannot be administered. Using a DW imaging protocol with three *b* values, Subhawong et al (18) found that a threshold mean ADC value of 2.5×10^{-3} mm²/sec yielded a sensitivity of 80% and a specificity of 100% for classifying a soft-tissue mass as a cyst, indicating that no soft-tissue neoplasms were missed with DW imaging-ADC mapping. Nevertheless, other studies have revealed ADC values of over 2.5×10^{-3} mm²/sec in soft-tissue myxomas when DW imaging-ADC mapping was performed with a different protocol

Figure 4. Desmoid tumor (initially thought to represent a sarcoma) in a 25-year-old man. (a, b) Axial T2-weighted MR image (TR/TE = 3600/73) (a) and contrast-enhanced fat-suppressed T1-weighted volume-interpolated breath-hold examination image (TR/TE = 3.54/1.24) (b) show a large, mildly heterogeneous, avidly enhancing mass in the anterior abdominal wall (arrowheads in b). (c) Axial ADC map shows intermediate signal intensity in the mass (arrowheads), with minimum and mean ADC values of $1.1 \times 10^{-3} \text{ mm}^2/\text{sec}$ and $1.8 \times 10^{-3} \text{ mm}^2/\text{sec}$, respectively, higher than expected for a nonmyxoid sarcoma. Biopsy and surgical resection revealed the mass to be fibromatosis (desmoid tumor). Ghosting artifact (arrows) can be seen with motion during DW imaging, although here, assessment of most of the mass is not affected.

(14). Because of the frequency with which cystic-appearing soft-tissue lesions are encountered, the potential utility of DW imaging as a nonenhanced alternative or adjunct technique in determining whether a soft-tissue mass is a true cyst warrants further investigation.

Teaching Point

Hematomas.—Generalizations about solid soft-tissue masses exhibiting lower ADC values than fluid collections must be tempered by the observation that hematomas may demonstrate low ADC values at DW imaging (Fig 7). Although Oka et al (19) showed that the mean ADC value of chronic expanding hematomas ($1.55 \pm 0.12 \times 10^{-3} \text{ mm}^2/\text{sec}$) was higher than that of malignant soft-tissue tumors ($0.92 \pm 0.14 \times 10^{-3} \text{ mm}^2/\text{sec}$) ($P < .01$), there were only six chronic expanding hematomas in their series. Anecdotal evidence from our institutions has shown that hematomas can indeed exhibit low ADC values, a fact that has also been alluded to by other authors investigating pitfalls in the interpretation of whole-body DW imaging (20). Interestingly, signal at DW imaging shows significant variation throughout the evolution of intracranial hematomas, which correlates with changes seen at T2-weighted imaging. On the other hand, ADC values have been found to be

consistently low throughout hematoma evolution (21). The underlying biophysical mechanism for this observation has not been well elucidated, but theories include (a) clot retraction with shrinkage of extracellular space, (b) alterations in the shape of extravasated erythrocytes, (c) formation of the fibrin network associated with clot, and (d) structural changes in intracellular hemoglobin (22). Similar studies are needed to better elucidate how ADC values differ at varying stages in the evolu-

Figures 5, 6. (5) Sciatic nerve schwannoma in a 79-year-old woman. (a) Axial fat-suppressed fast spin-echo T2-weighted MR image (TR/TE = 4060/71) shows a round, hyperintense mass associated with the sciatic nerve and having a “target sign” appearance. (b) Corresponding ADC map shows the target sign appearance of the mass (arrow), created by a central area with greater cellularity (lower ADC values and hence lower signal intensity) than the lesion periphery. The tumor had a mean ADC of $1.8 \times 10^{-3} \text{ mm}^2/\text{sec}$ and a minimum ADC of $1.5 \times 10^{-3} \text{ mm}^2/\text{sec}$. (6) High-grade sarcoma in a 56-year-old woman. (a) Axial fat-suppressed fast spin-echo T2-weighted MR image (TR/TE = 3300/71) shows a large, partially cystic mass in the left thigh. (b) Corresponding axial ADC map shows high signal intensity in the areas of necrosis and low signal intensity in the medial peripheral cellular portions of the mass (overall minimum and average ADC values of $0.3 \times 10^{-3} \text{ mm}^2/\text{sec}$ and $1.9 \times 10^{-3} \text{ mm}^2/\text{sec}$, respectively). Unlike the ADC map in Figure 4 (periarticular cyst), which showed no low-signal-intensity cellular region in the mass, this ADC map shows a sarcoma with a highly cellular peripheral component (arrows) and a necrotic center (*).

5a.

5b.

6a.

6b.

tion of soft-tissue hematomas, since the imaging characteristics of hemorrhage in the musculoskeletal system (unlike in the brain) generally do not follow a predictable pattern of evolution.

Abscesses.—Soft-tissue abscesses may present a diagnostic dilemma in that they occasionally mimic soft-tissue neoplasms (23) when thick or nodular rim enhancement is present following contrast ma-

terial administration. Although the clinical setting usually provides enough information to discriminate between these two types of lesions, it is important to be aware that there is substantial overlap in the DW imaging characteristics of abscesses and tumors. Because the high-viscosity pus within abscesses contains inflammatory cells, cellular debris, bacteria, and proteins, water diffusion may be restricted (Fig 8). In their review of eight cases

Figure 7. Trauma-related hematoma in a 33-year-old man. **(a)** Axial fat-suppressed fast spin-echo T2-weighted MR image (TR/TE = 4060/71) shows a well-circumscribed, heterogeneous, T2-hyperintense mass in the posteromedial soft tissues of the calf. Foci of low signal intensity along the lateral and posterior margins of the mass represent blood products. **(b)** Corresponding ADC map reveals low average and minimum ADC values in the lesion ($0.52 \times 10^{-3} \text{ mm}^2/\text{sec}$ and $0.16 \times 10^{-3} \text{ mm}^2/\text{sec}$, respectively) (arrows), findings that falsely suggest a solid neoplasm. **(c)** Postcontrast image reveals no internal enhancement within the mass, with a nonenhancing clot in the dependent portion. The mass was clinically confirmed to be a hematoma.

a.

b.

c.

a.

b.

Figure 8. Abscess in a 22-year-old woman. **(a)** Axial fat-suppressed T2-weighted MR image (TR/TE = 6130/54) shows a hyperintense mass with perilesional edema in the posterior compartment of the right thigh. Because the patient was pregnant, she did not receive intravenous contrast material for characterization of the mass. **(b)** Corresponding axial ADC map shows low signal intensity in the mass (arrows), with minimum and average ADC values of $0.3 \times 10^{-3} \text{ mm}^2/\text{sec}$ and $0.6 \times 10^{-3} \text{ mm}^2/\text{sec}$, respectively, findings that are suspicious for malignancy. However, purulent discharge at needle biopsy and subsequent culture of *Staphylococcus aureus* confirmed the final diagnosis of an abscess.

of soft-tissue abscess, Harish et al (24) found that DW imaging better depicted abscess formation than did conventional contrast-enhanced imaging in two cases; in a third case, intravenous contrast material could not be administered due to renal failure, highlighting the utility of DW imaging as a nonenhanced technique. In a larger review of 50 patients with apparent soft-tissue cystic lesions by Unal et al (25), DW imaging was shown to have 92% sensitivity and 80% specificity for diagnosing an abscess (using aspiration as the standard of reference). Interestingly, in the latter series, two cases were prospectively interpreted as an abscess but proved to be superinfected neoplasms at histologic analysis. However, ADC values were not obtained, raising questions as to what role quantitative DW imaging could play in distinguishing truly cystic entities from solid tumors. Ultimately, the overlap in DW imaging characteristics underscores the need for comprehensive multiparametric MR sequence selection and the importance of clinical information in assessing soft-tissue masses. Intravenous contrast material administration (unless contraindicated) is still advised for the optimal assessment of soft-tissue masses, particularly when there is a high pretest probability of soft-tissue infection.

Teaching Point

Bone Marrow.—The interpretation of DW imaging in bone lesions differs from that in soft tissues in that ADC values in hypercellular and malignant lesions are higher than those in normal fatty marrow (26,27). A possible explanation is that yellow marrow has reduced water content with little extracellular matrix, and that the larger lipid-laden cells in yellow marrow may restrict water movement to a greater degree than the smaller hematopoietic cells of red marrow (7). Fat itself, being hydrophobic, may act as more than just a physical barrier to diffusion and function as a repellent. Furthermore, the greater intramedullary blood flow in hematopoietic marrow increases the perfusion-weighted component of the ADC derived from lower b values (27). These principles are important to bear in mind when evaluating pediatric patients, since normal skeletal maturation will result in a decrease in the ADC values of bone marrow as it undergoes fatty replacement (eg, in the epiphysis) (28). This also means that, unlike with soft-tissue lesions, the ADC values of suspicious bone lesions will be higher than the proposed cutoff values for differentiating tumor from normal marrow. Recently, Padhani et al (29) showed that the 95th percentile for ADC values in bone metastases was $1.21 \times 10^{-3} \text{ mm}^2/\text{sec}$, and that using a cutoff value of $0.77 \times 10^{-3} \text{ mm}^2/\text{sec}$ resulted in a sensitivity of 85% and a specificity of 90% in differentiating neoplastic marrow infiltration from normal marrow.

In the spine, a common clinical challenge is the characterization of a vertebral body fracture as benign or pathologic. Baur et al (30) first reported using DW imaging to discriminate between pathologic and benign compression fractures. They proposed that water mobility would be more restricted in the presence of accumulated tumor cells and less restricted in cases of benign fracture due to trabecular disruption, attendant edema, and an increase in the interstitial space (30). Although these authors used a DW steady-state free precession sequence that precluded calculation of ADC values, in a recent meta-analysis of 265 cases from eight studies, higher mean ADC values correlated well with benign vertebral body fractures (31). Although there is some controversy in the literature regarding the role of DW imaging in assessing vertebral body lesions (32), Dietrich et al (33) summarized the literature on DW imaging in vertebrae by saying that ADC values in normal vertebral marrow typically range between 0.2 and $0.5 \times 10^{-3} \text{ mm}^2/\text{sec}$, whereas marrow-infiltrating lesions demonstrate values in the range of 0.7 to $1.0 \times 10^{-3} \text{ mm}^2/\text{sec}$. Benign traumatic or osteoporotic fractures exhibit yet higher values, generally between 1.0 and $2.0 \times 10^{-3} \text{ mm}^2/\text{sec}$ (33). In our experience, similar values are seen for lesions in the appendicular skeleton (Fig 9).

Primary Bone Tumors.—In clinical practice, malignant primary bone tumors are rare compared with bone metastases, and lesions that do indeed represent primary tumors are traditionally best assessed with conventional radiography and MR imaging for the purpose of characterization and determining the need for biopsy. There is little information on the role of DW imaging in characterizing untreated primary bone tumors, although whole-body DW imaging has been used for detecting metastatic bone lesions. Hayashida et al (34) found that for a small sample ($n = 20$) of T2-hyperintense bone lesions (bone cysts, fibrous dysplasia, and chondrosarcoma), ADC maps were not helpful in differentiating malignant from benign lesions, since the mean ADC for chondrosarcomas ($2.29 \times 10^{-3} \text{ mm}^2/\text{sec}$) was intermediate between that of simple bone cysts ($2.57 \times 10^{-3} \text{ mm}^2/\text{sec}$) and that of fibrous dysplasia ($2 \times 10^{-3} \text{ mm}^2/\text{sec}$).

In another series, Yakushiji et al (35) showed that minimum ADC values allowed good discrimination between chondroblastic osteosarcoma and chondrosarcoma, despite their having similar chondroid-type matrix enhancement patterns. The authors found that the minimum ADC values of chondroblastic osteosarcoma ($1.24 \pm 0.10 \times 10^{-3} \text{ mm}^2/\text{sec}$) were higher than those of other types of

Figure 9. Stress fracture in a 15-year-old girl with lower leg pain. The patient was referred from an outside institution for what was thought (based on marrow signal abnormalities) to be Ewing sarcoma. **(a)** Coronal T1-weighted MR image (TR/TE 730/9.2) shows an area of low signal intensity in the tibial diaphysis. **(b)** Axial fat-suppressed fast spin-echo T2-weighted MR image (TR/TE = 4060/71) shows intramedullary and periosteal edema. **(c)** ADC map shows a mean ADC of $1.6 \times 10^{-3} \text{ mm}^2/\text{sec}$ and a minimum ADC of $1.4 \times 10^{-3} \text{ mm}^2/\text{sec}$ in the region of bone marrow edema (arrow), findings that are consistent with a non-marrow-replacing stress fracture. The resolution of symptoms at clinical follow-up confirmed the diagnosis.

a.

b.

c.

osteosarcoma ($0.84 \pm 0.15 \times 10^{-3} \text{ mm}^2/\text{sec}$) and lower than those of conventional chondrosarcoma ($1.64 \pm 0.20 \times 10^{-3} \text{ mm}^2/\text{sec}$) (35). However, the literature says little about the ability of DW imaging to ameliorate the ongoing diagnostic dilemma of distinguishing low-grade chondrosarcomas from enchondromas, since it is generally not helpful in characterizing bone lesions as malignant. Figure 10 illustrates the assessment of a pelvic osteosarcoma with DW imaging and the significant difference in ADC values between the tumor and normal bone marrow. This difference highlights

the utility of DW imaging as a technique for tumor detection against a background of normal marrow, although the role of DW imaging in tumor characterization remains unclear.

Assessment of Treatment Response

Soft-Tissue Sarcomas.—Early knowledge of response to therapy can provide important prognostic information and potentially shorten the duration of undesired side effects from the prolonged administration of ineffectual agents. Histologic

Figure 10. Right pelvic osteosarcoma in a 14-year-old girl who had undergone chemotherapy. **(a)** Axial 3.0-T T1-weighted MR image (TR/TE = 576/9.4) shows a marrow-replacing tumor in the right acetabulum and an associated soft-tissue mass. Normal marrow is seen in the left acetabulum. **(b)** On an axial ADC map, the treated osteosarcoma demonstrates high signal intensity (minimum ADC, $1.7 \times 10^{-3} \text{ mm}^2/\text{sec}$; average ADC, $2.1 \times 10^{-3} \text{ mm}^2/\text{sec}$). In contrast, the normal marrow in the left acetabulum has a minimum ADC of $0.3 \times 10^{-3} \text{ mm}^2/\text{sec}$ and an average ADC of $0.6 \times 10^{-3} \text{ mm}^2/\text{sec}$. Unlike in the soft tissues, the ADC values of tumors are greater than those of normal bone marrow, making DW imaging a useful technique for bone tumor detection.

tumor necrosis is the hallmark of tumor response to anticancer therapy, but it can be assessed only after surgical resection. Preoperative imaging allows evaluation of changes in tumor size and contrast enhancement pattern, thereby informing an estimate of treatment response. However, ADC maps can also provide quantitative information regarding therapy response by delineating regions of increased diffusivity reflecting successful cytotoxic treatment (Fig 11). Because cellular changes are expected to precede morphologic changes in tumor volume, it has been suggested that DW imaging may help detect good treatment response earlier than conventional imaging (36), and DW imaging findings have shown good correlation with changes in tumor perfusion at dynamic contrast-enhanced MR imaging in animal models (37). Schnapauuff et al (38) provided additional empiric evidence that minimum ADC values correlate inversely with tumor cellularity as assessed histologically, regardless of whether the imaging is performed before the initiation of treatment or in a neoadjuvant setting. Furthermore, there are several morphologic changes that occur within a sarcoma following treatment due to the development of hyaline fibrosis and granulation tissue, in addition to necrosis (39). Compared with conventional static contrast-enhanced studies, **DW imaging is expected to more readily help differentiate areas of granulation tissue and scarring from viable cellular tumor, given that both features of a treated soft-tissue sarcoma enhance following contrast material administration.**

Primary Bone Tumors.—Although DW imaging-ADC mapping often fails to provide much insight beyond that already afforded by radiography and conventional MR imaging in the diagnosis of pri-

mary bone tumors, early results regarding the use of DW imaging in monitoring treatment are more promising. A study by Hayashida et al (40) of 18 patients with osteosarcoma and Ewing sarcoma revealed that the change in mean ADC values—but not that in tumor volume or contrast-to-noise ratio—after the administration of gadolinium-based contrast material showed a statistically significant difference between good and poor response to neoadjuvant chemotherapy. ADC values increased by approximately 95% in tumors that showed greater than 90% necrosis (indicative of good response), whereas changes in tumor volume and contrast-to-noise ratio were not significant on T2-weighted or contrast-enhanced images. These results were corroborated in a subsequent study by Oka et al (12) of 22 patients with osteosarcoma. The authors showed that ADC values increased in tumors after chemotherapy and stressed the importance of minimum ADC values, which were significantly higher in patients with a good therapeutic response to chemotherapy (defined as >90% tumor necrosis at resection) ($1.01 \pm 0.22 \times 10^{-3} \text{ mm}^2/\text{sec}$) than in patients with a poor response ($0.55 \pm 0.29 \times 10^{-3} \text{ mm}^2/\text{sec}$) (Fig 12) (12).

Pitfalls in DW Imaging Technique and Interpretation

In general, 3.0-T MR imagers provide increased SNR compared with lower-field-strength magnets and are thus desirable for musculoskeletal tumor imaging, given the inherently lower spatial resolution of functional (relative to conventional) sequences. However, this increase in SNR comes at the expense of more severe susceptibility artifacts of all types due to higher B_0 . In addition,

Figure 11. Rhabdomyosarcoma in an 81-year-old woman. (a, b) Coronal 3.0-T short inversion time inversion-recovery (TR/TE = 3500/23) (a) and axial T2-weighted (TR/TE = 2330/64) (b) MR images obtained prior to chemotherapy show a mass with perilesional edema. (c) Corresponding axial ADC map ($b = 50, 400, \text{ and } 800 \text{ sec/mm}^2$) shows an area of low signal intensity that corresponds to a cellular tumor (arrow), with minimum and average ADC values of $0.4 \times 10^{-3} \text{ mm}^2/\text{sec}$ and $1.1 \times 10^{-3} \text{ mm}^2/\text{sec}$, respectively. (d) Axial 3.0-T T2-weighted MR image obtained following chemotherapy shows a slight decrease in tumor size and a slight increase in signal heterogeneity. (e) Corresponding ADC map shows the tumor with increased signal intensity (arrow) and minimum and average ADC values of $1.1 \times 10^{-3} \text{ mm}^2/\text{sec}$ and $2.0 \times 10^{-3} \text{ mm}^2/\text{sec}$, respectively, findings that are consistent with good treatment response and the final histologic results (90% treatment-related sclerosis, 5% necrosis, and only 5% viable tumor).

a.

b.

c.

d.

e.

Figure 12. Primary bone lymphoma in a 23-year-old man. **(a, b)** Sagittal T1-weighted (735/9.5) **(a)** and axial T2-weighted (3600/71) **(b)** 3-T MR images before chemotherapy show a marrow-replacing tumor in the distal femur. Arrows in **b** = extraosseous soft-tissue mass medial and posterior to the tumor. **(c)** Corresponding axial ADC map shows diffuse low signal intensity in the tumor, with minimum and average ADC values of $0.3 \times 10^{-3} \text{ mm}^2/\text{sec}$ and $1.1 \times 10^{-3} \text{ mm}^2/\text{sec}$, respectively. **(d)** Axial 3-T T2-weighted MR image after chemotherapy shows decrease in size of the soft-tissue mass. **(e)** Corresponding ADC map shows interval increase in the signal intensity of the tumor, with minimum and average ADC values of $1.7 \times 10^{-3} \text{ mm}^2/\text{sec}$ and $2.1 \times 10^{-3} \text{ mm}^2/\text{sec}$, respectively, findings consistent with excellent treatment response (confirmed at follow-up).

although imaging of the central nervous system relies heavily on echoplanar sequences, these sequences are particularly sensitive to susceptibility artifacts induced at tissue boundaries (eg, at the fat-water interfaces ubiquitous in the mus-

culoskeletal system) in both bone marrow and soft tissues. A variety of other sequences that are less vulnerable to such limitations in the musculoskeletal system include spin-echo, stimulated-echo, single-shot multiple spin-echo, half-Fourier

acquired single-shot turbo spin-echo or single-shot fast spin-echo diffusion, turbo spin-echo, multishot (segmented) echoplanar, and line scan diffusion sequences (41).

One of the best-known pitfalls in DW imaging is the limitation of analysis to a qualitative assessment of images obtained at a single b value due to areas of hyperintensity from T2 shine-through (42). This error can be eliminated by careful correlation with corresponding ADC maps. Another potential pitfall in DW imaging is its lowered sensitivity for sclerotic lesions in the evaluation of bone lesions (43), which can result in false-negative hypointense vertebral metastases due to low water content (44). Such a problem may account for some of the controversy in the literature regarding the value of DW imaging in assessing vertebral body lesions (33). As suggested earlier, the presence of blood products can potentially result in a false-positive low-ADC lesion that is actually nonneoplastic; similarly, infection or abscess formation with decreased ADC values can be mistaken for a soft-tissue sarcoma.

Like most MR sequences, most DW sequences are sensitive to patient motion, resulting in large phase shifts between views and possibly affecting the phase-encoding process. The net result of motion is a ghosting artifact on DW images (Fig 4), an artifact that can be mitigated by the adoption of single-shot echoplanar imaging and motion correction (navigation); however, motion between views generally mandates rescanning (45). Single-shot echoplanar DW imaging does require fat saturation, and images and ADC values obtained with this type of sequence may be unreliable when fat suppression fails or is inhomogeneous. Furthermore, because normal bone marrow has a large fatty component and fat has a diffusion coefficient approximately two orders of magnitude below that of water, lipid contamination in the ROI will artifactually lower the measured ADC (46).

Conclusion

DW imaging is a nonenhanced functional MR imaging technique that is easily incorporated into a routine MR imaging protocol with little additional scanning time and that offers useful information regarding the cellularity of a musculoskeletal lesion. The use of whole-body DW imaging for the purpose of tumor detection has been studied, and localized DW imaging is a promising technique for characterizing lesions and assessing treatment response. Further investigation is still needed to identify the influence of DW imaging–ADC mapping on management and outcome in patients with musculoskeletal lesions.

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Diffusion-weighted MR Imaging for Characterizing Musculoskeletal Lesions

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This signal loss from free diffusion is quantified as the ADC; protons in a more restricted, densely cellular environment exhibit less signal loss than do freely mobile protons and, therefore, have comparatively lower ADC values.

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Einarsdóttir et al demonstrated substantial overlap in the ADC values of 16 benign soft-tissue lesions and 13 soft-tissue sarcomas (mean ADC = 1.8×10^{-3} mm²/sec and 1.7×10^{-3} mm²/sec, respectively). They noted that one of the highest ADC values for a sarcoma was seen in a myxoid liposarcoma. This fact reflects the need to consider myxoid and nonmyxoid tumors separately, since a myxoid matrix will result in increased ADC values.

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Generalizations about solid soft-tissue masses exhibiting lower ADC values than fluid collections must be tempered by the observation that hematomas may demonstrate low ADC values at DW imaging.

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The interpretation of DW imaging in bone lesions differs from that in soft tissues in that ADC values in hypercellular and malignant lesions are higher than those in normal fatty marrow.

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DW imaging is expected to more readily help differentiate areas of granulation tissue and scarring from viable cellular tumor, given that both features of a treated soft-tissue sarcoma enhance following contrast material administration.