De Novo Assessment of Pediatric Musculoskeletal Soft Tissue Tumors: Beyond Anatomic Imaging

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Abstract

MRI plays a central role in the assessment of pediatric musculoskeletal soft tissue tumors. Although these neoplasms may initially be evaluated on other modalities, such as sonography, MRI is essential for accurately determining the extent of disease. Traditionally, MRI has been performed with sequences that provide excellent anatomic detail, with T1-weighted, fluid-sensitive, and static postcontrast T1-weighted sequences. However, with the introduction of noncontrast sequences such as diffusion-weighted imaging and magnetic resonance spectroscopy to the arsenal of available MRI techniques, functional and metabolic features of a neoplasm can now be examined noninvasively. These more recent MRI methods offer information for lesion characterization, the assessment of treatment response, and the distinction of postoperative scar from recurrence. Dynamic contrast-enhanced perfusion imaging is another useful functional technique that can be acquired before conventional static postcontrast imaging, without requiring additional contrast material. This review presents recent advances in MRI methodology that enable a comprehensive clinical assessment of musculoskeletal tumors in the pediatric population. The roles and challenges of combining anatomic, functional, and metabolic MRI sequences will be discussed as they relate to newly discovered soft tissue tumors in children.

A principal role for MRI in the evaluation of pediatric musculoskeletal tumors is the determination of extent of disease for appropriate preoperative planning. Diffusion-weighted imaging (DWI), dynamic contrast-enhanced perfusion imaging (DCE-MRI), and magnetic resonance spectroscopy (MRS) have expanded the role of MRI to include lesion characterization, treatment response, and the detection of postsurgical recurrence. In this review, conventional (anatomic sequences) and advanced (functional and metabolic sequences) imaging will be discussed, with an emphasis on how these sequences are used in the clinical setting of newly discovered (de novo) pediatric soft tissue tumors. The assessment of treatment response and postsurgical recurrence is beyond the scope of this article.

Challenges in the Pediatric Patient

Pediatric imaging presents unique challenges that are not encountered in the adult setting. The need for sedation in young children requires that a comprehensive protocol also be succinct. A complete tumor protocol that includes anatomic, functional, and metabolic sequences has been previously described.1 The examination requires 60 minutes, with 15 minutes of this time allotted to MRS if desired (see Table 1).

Additional challenges encountered in pediatric patients include their small size with resultant decreased signal and inherently low scan resolution.
Therefore, choosing a coil that closely matches the field of view being imaged is critical to extracting the maximum signal from pediatric patients. Three-dimensional volumetric imaging with isotropic resolution allows for high spatial resolution without gap imaging and reconstruction in other planes from only 1 acquisition; as such, an accurate lesion size can be obtained.

Understanding the advantages and disadvantages of each sequence in the tumor protocol (discussed below) allows the radiologist to choose specific sequences to best optimize the protocol in an effort to conserve time and tailor an examination to a particular clinical indication (Table 2).

**TUMOR PROTOCOL: ANATOMIC IMAGING**

**T1-Weighted Sequences**

Pure spin-echo T1-weighted imaging is performed to take advantage of the differences in T1 relaxation properties between a tumor and the surrounding tissues. In fact, a nonenhanced spin-echo T1-weighted image has been established as the most important sequence for the assessment of marrow replacement or intraosseous extension of a neoplasm.2

**Fluid-Sensitive Sequences**

Although both short tau inversion recovery (STIR) and chemical fat suppression of T2-weighted sequences can produce fluid-sensitive images, STIR reportedly offers greater contrast resolution between fluid and the surrounding tissues.3,4 Recent developments in producing fluid-sensitive imaging include three-dimensional sequences of isotropic resolution, such as the steady state gradient echo sequences; however, as yet, these sequences have not been specifically studied to determine if they provide optimal contrast between a tumor and other musculoskeletal structures.

**Static Postcontrast T1-Weighted Sequences**

The application of fat suppression to a T1-weighted postcontrast sequence provides improved contrast resolution for identifying areas that exhibit contrast enhancement. In addition, static postcontrast parameters may be combined with high spatial resolution (isotropic resolution) with the use of three-dimensional gradient-echo sequences; the latter may be acquired in a single plane ~3 to 5 minutes after contrast injection, then subsequently reformatted into multiple other planes. Subtraction images are also valuable and can be constructed by subtracting the unenhanced images from the contrast-enhanced images to further exploit the difference in contrast between an enhancing tumor and surrounding normal musculoskeletal tissues.

**TUMOR PROTOCOL: FUNCTIONAL IMAGING**

**DWI**

Unlike anatomic sequences, DWI is a method of functional imaging.5-13 DWI measures the Brownian motion of water at a microscopic level within the intra- and extracellular spaces.5,6 Water flows relatively freely in the extracellular space and demonstrates restricted diffusion in the intracellular space.5 Therefore, cellular regions, such as tumors, show restricted diffusion and DWI can be used to gauge the degree of cellularity or cellular integrity.

Any sequence may be altered to be diffusion sensitive, although in clinical practice, T2-weighted sequences are most commonly used

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**TABLE 1 MRI Sequences in a Comprehensive Protocol for Imaging Tumors at 3T**

<table>
<thead>
<tr>
<th>Technique</th>
<th>Pulse Sequence</th>
<th>Time Allotted, min</th>
<th>Relevant Parameters</th>
<th>Application to Soft Tissue Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomic</td>
<td>T1-weighted (in 2 planes)</td>
<td>6</td>
<td>TR/TE=700/15, 5-mm slice thickness</td>
<td>Determination of extent</td>
</tr>
<tr>
<td></td>
<td>Fat-suppressed T2-weighted or STIR (in 2 planes)</td>
<td>9</td>
<td>TR/TE=3600/70 or 4000/19, 5-mm slice thickness</td>
<td>Detection</td>
</tr>
<tr>
<td></td>
<td>Unenhanced three-dimensional fat-suppressed T1-weighted (isotropic volumetric sequence)</td>
<td>3</td>
<td>TR/TE=4.6/1.4, 1-mm slice thickness Flip angle 9.5°</td>
<td>Characterization</td>
</tr>
<tr>
<td></td>
<td>Delayed contrast-enhanced three-dimensional fat-suppressed T1-weighted volumetric sequence</td>
<td>3</td>
<td>TR/TE=4.6/1.4, 1-mm slice thickness Flip angle 9.5°</td>
<td>Determination of extent</td>
</tr>
<tr>
<td>Functional</td>
<td>Subtraction images</td>
<td>0</td>
<td>Subtraction</td>
<td>Characterization</td>
</tr>
<tr>
<td></td>
<td>DWI with ADC maps</td>
<td>3</td>
<td>TR/TE=760/80, b=5000 s/mm2</td>
<td>Characterization</td>
</tr>
<tr>
<td></td>
<td>Time resolved MR perfusion</td>
<td>3</td>
<td>TR/TE=2.5/0.9, Flip angle 20° Temporal resolution~10 s for total 5 min</td>
<td>Characterization</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Proton MRS</td>
<td>15</td>
<td>PRESS 2000/135 Single voxel</td>
<td>Characterization</td>
</tr>
</tbody>
</table>
for this purpose. The magnitude of the sensitivity of the sequence to Brownian motion is described by the b-value and at least 2 (preferably >2) different b-values are used. The choice of exact b-value is likely not critical as long as a mixture of low and high b-values are used. In our practice, b-values of 50, 400, and 1000 s/mm² are used but values of 0 and 1000 s/mm² have also been discussed.

DWI analysis can be qualitative or quantitative. For a qualitative analysis, the images are assessed visually for approximate loss of signal as diffusion weighting successively increases. For quantitative analysis, a region of interest (ROI) is drawn and the minimum, average, and maximum apparent diffusion coefficient (ADC) values may be recorded. Viable malignant tissue shows little loss of signal intensity on diffusion-weighted images obtained with successively heavier diffusion weighting, whereas benign tissues or malignant tissues that have undergone necrosis lose their signal intensity with progressively heavier diffusion weighting. There is no standard procedure for the size or placement of the ROI used to determine ADC values, a potential cause for interreader variability among studies. In our practice, an elliptical ROI is placed to encompass most of the lesion on multiple images, where the tumor appears to have the lowest signal on the ADC map.

Although DWI has many advantages, there are pitfalls as well: DWI has inherent low signal-to-noise and resolution (making it unreliable in small subcentimeter lesions) and is prone to susceptibility artifacts (producing false-positive regions of apparent restricted diffusion in areas containing or adjacent to blood products and air). As such, DWI is always interpreted in conjunction with anatomic sequences. It may, however, be particularly useful when intravenous contrast cannot be administered, which is an additional advantage in the pediatric population.

**Perfusion/DCE-MRI**

DCE-MRI is typically performed with rapid, volumetric, gradient-echo sequences that cover a volume of interest repeatedly after the intravenous administration of a contrast agent. Contrast material is usually injected intravenously at a rate of 2 to 5 mL/second, and imaging takes place with a temporal resolution of 3 to 10 seconds carried out for as short as 2 minutes or as long as 5 to 7 minutes. The temporal resolution chosen for this pulse sequence depends on the need for spatial resolution and field-of-view coverage. In our practice, we perform a highly time-resolved magnetic resonance (MR) angiographic sequence, which uses a spiral trajectory that acquires k space from the center to the periphery, relying on partial k-space undersampling and increased sampling of the center of k-space.
compared with its periphery. This method of undersampling enhances image contrast rather than fine detail, an advantage when trying to detect regions of hyperenhancement relative to nonenhancement.\(^{15}\)

Similar to DWI, DCE-MRI can also be analyzed qualitatively or quantitatively. A qualitative analysis consists of visually inspecting the pattern of enhancement within a lesion over time to establish whether rapid arterial enhancement is present, a characteristic of malignant tissue, although some benign lesions may show a similar pattern of enhancement.\(^{16}\)

Semiquantitative methods of postprocessing exist, with the creation of time-intensity curves from an ROI. Distinguishing patterns of enhancement have been described for benign and malignant musculoskeletal lesions,\(^{17-22}\) primarily by assessing the first-pass kinetics. More absolute quantitative approaches with pharmacokinetic modeling also exist to quantify tumor blood flow, tumor microvasculature, and capillary permeability, although these have been investigated to a very limited degree in osteosarcomas\(^{23,24}\) but have not been reported in soft tissue tumors and are not used clinically.

**TUMOR PROTOCOL: METABOLIC IMAGING**

**MRS**

MRS is a means of molecular characterization of tumors with MR, and like DWI, requires no intravenous contrast medium, making it a noninvasive technique. Proton MRS is a technique that is more easily integrated into a clinical MRI protocol, although phosphorous MRS has been studied in osteosarcomas.\(^{25}\)

Phosphorous MRS, a form of heteronuclear MRS, requires specialized equipment and is not practical in a clinical tumor protocol. Its feasibility in the pediatric musculoskeletal system has been demonstrated in a multicenter study of proton MRS concentrated on Duchene muscular dystrophy.\(^{26}\) MRS detects signals from water, lipid, and other metabolites from a specific ROI to identify the underlying metabolic makeup of a lesion. Results from previous studies have suggested that trimethylamine, which participates in the phospholipid metabolism of cell membranes and is affected by cell turnover, is elevated in malignant neoplasms.\(^{27-30}\) This technique is currently under investigation and is not widely used in pediatric musculoskeletal tumor imaging, but it has been shown to play an important role in lesion characterization by offering high negative predictive value.\(^{31}\)

**APPLICATIONS OF MRI FOR NEWLY DISCOVERED SOFT TISSUE MASSES**

Soft tissue tumors are rare in childhood and adolescence. The most common benign mass is vascular (a hemangioma of infancy or a vascular malformation in later ages), whereas the most common malignancy is rhabdomyosarcoma.\(^{32}\) The non-rhabdomyosarcoma soft tissue sarcomas include synovial sarcoma, malignant fibrous histiocytoma, fibrosarcoma, and malignant peripheral nerve sheath tumors (especially in neurofibromatosis type 1).\(^{32}\) The role of various MR sequences for the detection, characterization, and determination of tumor extent in soft tissue masses will be discussed below.

![Diagram](http://pediatrics.aappublications.org/)

**FIGURE 1**

Diagnostic workup for a pediatric patient presenting with a palpable soft tissue mass.
Detection

The initial detection of pediatric soft tissue masses is usually on a clinical basis, with the patient having a palpable mass that is discovered by the parent or physician. Uncommonly, soft tissue masses in the deep tissues are detected by cross-sectional imaging. Ultrasound is typically performed for the assessment of superficial lesions, but for the deep tissues computed tomography or MRI is more useful. For the purpose of detection, noncontrast anatomic MRI techniques (T1 and fluid-sensitive sequences) are sufficient for detecting a soft tissue mass. Intravenous contrast and functional and metabolic techniques are not typically required for the sole purpose of detection.

Characterization

Most soft tissue tumors in children are benign, with hemangiomas, vascular malformations, neurofibromas (in neurofibromatosis syndromes), and aggressive and juvenile fibromatosis being most common. Not all soft tissue tumors require imaging for characterization, because an experienced pediatrician or pediatric surgeon can recognize benign hemangiomas on the basis of clinical features. The term “hemangioma” encompasses a group of benign endothelial neoplasms including infantile hemangioma, congenital hemangioma, and kaposiform hemangioendothelioma. In comparison, vascular malformations arise from dysplastic vascular channels and demonstrate normal endothelial turnover, growing with the child without involution. Infantile hemangiomas are not visible at birth but manifest during the first few weeks of life. On the contrary, congenital hemangiomas are mature at birth and categorized by their clinical course with rapid involution or proportional growth.

MRI features of infantile hemangiomas differ according to their biological phase. In the proliferating phase, they appear as well-defined, lobulated, T2-hyperintense masses with flow voids due to high-flow feeding arteries and draining veins as well as intense, uniform contrast enhancement that can be characterized by DCE-MRI. During the involuting phase, appearances are more varied and heterogeneous, with increasing fatty replacement of tumor and less avid enhancement. Hemangiomas characteristically lack perilesional edema and arteriovenous shunting. Hence, when perilesional edema is identified, other neoplastic lesions should be excluded. For masses that do not meet strict clinical criteria for benignity by the pediatrician or surgeon, the first-line study in children is typically an ultrasound, and cysts, hemangiomas, and fibrous pseudotumors (eg, fibromatosis coli) can often be characterized with ultrasound alone (Fig 1).

Otherwise, primary soft tissue masses are a heterogeneous group with variable T1 and T2 relaxation properties and enhancement patterns (Fig 2). The T1 and T2 signal characteristics represent variations within the tumor microenvironment related to hemorrhage, necrosis, mineralization, and myxoid content and generally do not indicate...

**Figure 2**

Nine-year-old girl with right calf myxofibroma. A, Axial T1-weighted image (TR/TE 450/16) shows a right posterior calf subcutaneous mass (arrow) that is isointense and indistinguishable from adjacent skeletal muscle. B and C, Fluid-sensitive STIR (TR/TE 3600/35/180) (B) and static post-contrast fat-suppressed images (TR/TE 17.5/9.52) (C) are essential in lesion detection and characterization, identifying the posterior knee soft tissue mass (arrow) as a solid lesion rather than a cyst. D, The ADC map also shows the hypointense mass (arrow) with a minimum ADC value of 0.934 $\times 10^{-3}$ mm$^2$ per second and an average ADC value of 1.22 $\times 10^{-3}$ mm$^2$ per second.
a specific histology. However, a few lesions have characteristic features on conventional sequences and include cysts or ganglions, abscesses, hemangiomas, vascular malformations, and lipomatous masses (lipoblastomas).

For diagnosing a soft tissue cyst, ultrasound has been the traditional method used for diagnosis. Some periarticular cysts, such as Baker’s cysts, can be characterized by the presence of fluid in a characteristic location (between the tendons of the semimembranous and medial gastrocnemius). Otherwise, with MRI, intravenous contrast is typically needed, and a thin rim-enhancing soft tissue mass by MRI without internal enhancement is the criterion used to rule out a tumor and diagnose a cystic lesion; the latter may represent a simple cyst, an abscess, or a lymphatic malformation, depending on the clinical context. A cystic lesion with clinical features of infection is consistent with an abscess. A mass containing predominantly fluid signal with only septal enhancement can be characterized with a high degree of confidence as a macrocystic lymphatic malformation. Recently, quantitative DWI was described as a noncontrast alternative MRI technique for distinguishing cysts and solid tumors with high negative predictive value for ruling out a tumor and diagnosing a cyst. Lesions containing macroscopic fat (lipomatous masses) are characterized by their high T1 signal that is suppressed on fat-suppressed sequences. A lipoblastoma in an older child can be diagnosed due to its intrinsic macroscopic fatty composition and resultant high T1 signal; however, lipoblastomas in younger children may contain more myxoid elements, confounding the diagnosis. The more important dilemma for characterizing lipomatous masses is deciding whether they are benign or malignant. Usually, lipoblastomas cannot be confidently distinguished from liposarcomas by imaging alone, although liposarcomas are extremely rare in children, comprising 3% of non-rhabdomyosarcoma sarcomas.

Intravenous contrast may be helpful in identifying enhancing nodular nonlipomatous regions in a tumor to identify malignancy. There is little information on the use of functional techniques in the assessment of lipomatous masses and a report of

**FIGURE 3**
Thirteen-year-old girl with desmoid of the chest. A, Coronal T2-weighted image (TR/TE 6292/56) shows a large right hemithoracic hyperintense mass (arrow). It is indistinguishable from a malignant lesion on anatomic imaging alone. B, Coronal image from a dynamic contrast-enhanced study (TR/TE 2.66/0.98) shows lack of early arterial enhancement (arrow) (a feature of benignity). C, Subtraction postcontrast T1-weighted image (TR/TE 4.24/1.74) shows minimal homogeneous enhancement (arrow), consistent with, but not specific for, benign disease (because malignant lesions are more commonly heterogeneous).

**FIGURE 4**
Seven-year-old girl with right calf alveolar rhabdomyosarcoma. A, There is a right calf anterior compartment mass that is minimally hyperintense to skeletal muscle on T1-weighted image (TR/TE 688/16). B and C, The fluid-sensitive images (TR/TE 6292/56) (B) and static postcontrast images (TR/TE 4.24/1.74) (C) aid in the assessment of tumor extent. However, there is considerable overlap in the anatomic imaging features of this malignant lesion compared with the benign myxofibroma in Fig 1. D, The ADC map (TR/TE 7000/73) shows restricted diffusion centrally with a minimal ADC value of $0.52 \times 10^{-3} \text{mm}^2/\text{sec}$ and an average ADC value of $0.688 \times 10^{-3} \text{mm}^2/\text{sec}$. E, In addition the maximum intensity projection from a dynamic contrast-enhanced study (TR/TE 2.66/0.98) demonstrates diffuse early arterial enhancement, a pattern that favors malignancy.
MRS showed its potential utility in confirming a benign etiology within a complex lipomatous mass.\textsuperscript{37}

Once cystic, lipomatous, and vascular lesions have been ruled out, it is estimated that the ability of MRI to accurately characterize lesions is low, often <50%\textsuperscript{38–41}. Patterns of contrast enhancement in benign and malignant lesions overlap,\textsuperscript{38} and with DCE-MRI malignant lesions typically demonstrate rapid early arterial enhancement and higher slopes of enhancement compared with benign lesions,\textsuperscript{15,17–19} but this pattern is not entirely specific (Fig 3).

DWI has been used for the purpose of characterization, although some overlap in the ADC values of benign and malignant entities have been reported.\textsuperscript{9–12,42} Humphries et al\textsuperscript{43} prospectively correlated the ADC and the histopathologic cell count to characterize soft tissue masses as benign or malignant in 19 children. A comparison of median ADC values with the median cell count for a specimen on high-power microscopy revealed an inverse relationship between ADC and cell count. Although there was no significant difference in the ADC values between benign and malignant lesions, all highly cellular (>150 cells per high-power field) lesions had an ADC value $<1.5 \times 10^{-3} \text{ mm}^2 \text{ per second}$. In general, the lower the ADC in a lesion, the higher the likelihood of malignancy (Figs 4 and 5).

Finally, MRS is an emerging technique that has recently been applied to the characterization of musculoskeletal tumors. At this time, the utility of MRS lies with its high negative predictive value.\textsuperscript{1} If no appreciable choline-containing compounds are detectable in a tumor, it is likely to be benign (Fig 6). And, as various quantitative methods are validated,
MRS may prove to yield additional specificity for lesion characterization.37

Determination of Extent

For soft tissue tumors, contrast material is routinely administered, although primarily for characterization purposes (to help distinguish cystic from solid soft tissue masses) rather than for defining the extent. T1-weighted and fluid-sensitive sequences provide adequate anatomic detail for defining the borders of the tumor, but perilesional enhancement after contrast administration is important in identifying tumor extension beyond the direct boundaries of a sarcoma.

Conclusions

Conventional anatomic MRI sequences remain essential in the initial workup of a pediatric musculoskeletal tumor, especially for the determination of tumor extent. However, for soft tissue mass characterization, conventional sequences are often deficient. Functional and metabolic techniques provide information for characterizing lesions for malignancy. Importantly, many of the nonconventional techniques described here require no intravenous contrast and add only little time to an MRI protocol, making these sequences particularly worthwhile in the pediatric population.

Abbreviations

ADC: apparent diffusion coefficient
DCE-MRI: dynamic contrast-enhanced perfusion imaging
DWI: diffusion-weighted imaging
MR: magnetic resonance
MRS: magnetic resonance spectroscopy
STIR: short tau inversion recovery
ROI: region of interest

References

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