INTRODUCTION

Imaging of brain tumors has significantly improved with the use of advanced magnetic resonance (MR) techniques, such as MR spectroscopy (MRS), perfusion-weighted imaging, diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), susceptibility-weighted imaging (SWI), and functional MR (fMR) imaging.1–10 Conventional MR imaging techniques provide anatomic/structural information about the brain. Unlike conventional imaging, advanced MR techniques also provide physiologic and functional information concerning metabolism; hemodynamics; and, with diffusion-weighted technique, information on brain tumor cellularity. Recently, the introduction of DNA methylation profiling for molecular classification has been proposed, which outperforms the current histopathologic classification and thus might serve as a basis for the next World Health Organization classification scheme for central nervous system (CNS) tumors. In the future, this may have a great impact on the correlation between advanced imaging assessment and the newly proposed molecular classification. This overview is based on the literature between the currently used histopathologic classifications of pediatric brain tumors and their characteristics on advanced MR imaging techniques. In the near future it will be mandatory to scan with advanced imaging protocols in all pediatric brain tumors, classified by their molecular phenotype to reevaluate their diagnostic value.
The most useful clinical applications of these advanced MR techniques in pediatric brain tumors, stratified by the current classification, are discussed here.

1. DWI approaches (DWI, DTI, diffusion kurtosis imaging [DKI])
2. MRS (single-voxel [SV] imaging, and chemical shift imaging [CSI])
3. Perfusion-weighted techniques (dynamic susceptibility contrast [DSC] technique; dynamic contrast-enhanced [DCE]; and arterial spin labeling [ASL], a noncontrast technique)
4. Other advanced MR imaging sequences, useful for diagnosis and presurgical planning in children suspected to have a brain tumor (SWI and fMR imaging)

Diffusion-Weighted Imaging Technique

(Diffusion-Weighted Imaging, Diffusion Tensor Imaging, Diffusion Kurtosis Imaging)

DWI is commonly used by (pediatric) neuroradiologists in everyday clinical practice. Although it is no longer a novel imaging technique, it provides information that is not obtainable using conventional MR sequences and is therefore discussed in this article.

The additional information is obtained by measuring the mobility of water molecules, assuming a process of random, unrestricted, but potentially hindered diffusion. The diffusion probability distribution function, the chance of a particular proton diffusing from one location to another in a given time, is thus considered a gaussian distribution, with the standard deviation relating to the apparent diffusion coefficient (ADC). The ADC value depends on the complexity of the cytoarchitecture, determined by, for example, cell membranes, intracellular organelles, and the rapid exchange of protons between different compartments (Fig. 1). The cytoarchitecture of the tumor can inhibit random brownian motion and thus causes water diffusion to deviate from strict gaussian behavior. This restricted diffusion appears hyperintense on the diffusion trace map and dark on the ADC map (Fig. 2). In clinical practice and research, ADC maps and ADC values have been used to assess tumor cellularity and tumor grade (Fig. 3). Recently, Poretti and colleagues\(^4\) showed that tumor grade as estimated by ADC values could be better assessed only from the solid, contrast-enhancing part of the tumor rather than the entire tumor. Further, ADC values can also be used to assay treatment response and detect tumor recurrence and even to differentiate tumor recurrence from pseudoprogression.\(^5\)

Although mainly used in the treatment scheme of high-grade gliomas in adults, antiangiogenic drugs may also be a treatment option in pediatric patients with brain tumors. DWI based on ADC analyses is less affected by vascular permeability changes caused by antiangiogenic treatment than contrast-enhanced T1-weighted imaging and is therefore a good imaging marker of treatment outcomes. However, clinicians should beware of areas of restricted diffusion that may appear after antiangiogenic treatment, which were stable on follow-up MR imaging studies, and therefore are more consistent with necrosis than tumor recurrence/progression.\(^6\)

There are studies focusing on treatment-induced changes in ADC values by comparing pretreatment and early posttreatment measures.\(^7\) Some reports even advocate the use of functional diffusion map methods by voxel-wise subtraction of the pretreatment and posttreatment ADC maps for accurate assessment of changes in ADC values at all tumor locations.\(^8\) Also ADC value changes over time, suggesting that serial MR (DWI) imaging may be useful to investigate possible changes in volume of low-ADC regions within the tumor.

Although the results from DWI and quantitative ADC look promising and DWI imaging is easy and quick to perform, clinicians should keep in mind that variations in equipment (even from the same brand) and acquisition parameters can result in significant differences in calculated ADC values. Even using ratios by comparing with normal-appearing brain tissue as a reference may produce inconsistent results. This possibility is especially important in follow-up scanning, making it sometimes more difficult to differentiate between tumor growth and necrosis. Second, brain tumors may become more heterogeneous after treatment, which may influence ADC values and result in inaccurate diagnosis of tumor progression. Some investigators suggest histogram-based methods but this is a time-consuming approach.\(^9\)

Diffusion tensor imaging

The diffusion-weighted technique not only uses the magnitude of the diffusion but can also provide the direction of diffusion and is therefore sensitive to directional movements of water molecules using DTI. DTI has been used extensively for the identification of functional white matter tracts in vivo. In neuro-oncology, DTI has the potential to establish spatial relationships between normal-appearing white matter and tumor borders and provide clinically valuable information on
possible progression of tumor into the surrounding white matter tracts and visualization of displacement or loss of white matter tracts as a result of tumor behavior and postoperative status.

In gray matter, it is usually sufficient to characterize diffusion properties with a single ADC, because measured water diffusivity is largely independent of the orientation of the tissue. However, in anisotropic areas, such as white matter, where diffusivity is known to depend on the orientation of the tissue, a single ADC is not able to describe the orientation-dependent water mobility in the

Fig. 1. A 5-year-old girl presents with headache and vomiting. There is a midline solid tumor, with cystic components compromising the cerebellar vermis. On the T2 (A) and T1 without (B) and with contrast (C) it is difficult to suggest the correct diagnosis. Looking at the ADC map (D) no restriction is seen, which is most consistent with a pilocytic astrocytoma.
tissue. Brain tumors not only invade gray matter but also white matter and may severely displace white matter tracts (Fig. 4). To avoid accidental resection or transection of important white matter tracts, accurate localization of these tracts may be obtained using DTI.

If the decision is surgery, DTI can address issues such as the best surgical approach to avoid damage to major white matter tracts, minimizing adverse neurologic outcomes.

Diffusion kurtosis imaging
Recently, van Cauter and colleagues\textsuperscript{10} showed that DKI is better at distinguishing between low-grade and high-grade gliomas in adults than DTI or the most simple approach, DWI. The investigators stated that, using DKI, additional information on microstructure and microdynamics in gliomas could be obtained by exploring non-Gaussian diffusion properties. This ability is helpful in differentiating between low-grade and high-grade gliomas. DKI uses a similar pulse sequence to those used in DWI and DTI. However, the important difference is the use of higher and at least 2 nonzero b-values. The advantage of DKI is that, besides kurtosis parameters (axial, radial, and mean kurtosis), it also generates all conventional DTI parameters (fractional anisotropy, radial
diffusivity, axial diffusivity, and mean diffusivity) and therefore allows comparison with published DTI data on brain tumor grading. Another advantage of using higher b-values is that the diffusion signal decay is no longer monoexponential, and may result in greater imaging contrast between different tissue types, and may improve brain tumor characterization.11 A disadvantage is the longer scanning time. To date there is only evidence that DKI can help to differentiate between groups of patients with low-grade and high-grade gliomas but not on an individual level. Larger prospective studies need to be performed, not only in adults but also in children with brain

Fig. 3. A 3-year-old girl has symptoms of vomiting and nausea. The tumor is asymmetrically located in the pons, well demarcated. The tumor is hyperintense on T2 (A), hypointense on T1 (B), with nearly no enhancement (C; axial T1 with contrast). The ADC map (D) shows no diffusion restriction, but on histology it was a high-grade tumor, grade III astrocytoma.
tumors, to validate the power of DKI as a new noninvasive biomarker in grading gliomas or other types of brain tumors.

**Magnetic Resonance Spectroscopy (Magnetic Resonance Spectroscopy, Single-Voxel Imaging, and Chemical Shift Imaging)**

MRS provides radiologists with the opportunity to gain information on biochemical and cellular metabolite analyses of brain tissue. Proton MRS is the most commonly used MRS technique.\(^3\) There are multiple metabolite peak assessments possible, depending on the echo time (TE) used. Five predominant metabolite peaks can be identified:

1. Choline (Cho)-containing compounds, which reflect membrane turnover and cellularity.
2. Creatine (Cr), which represents energy synthesis and serves as an internal control for determining metabolite ratios given its relative stability, except in instances of energy failure (tumor necrosis).
3. \(N\)-acetyl aspartate (NAA), which is found mostly in neurons but may also be found in glial cells.

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**Fig. 4.** A 1-year-old boy presents with cranial nerve palsy and vomiting. The conventional MR sequences ([A], T2 image, [B], T1 image, and [C], T1 image with contrast) show extension of the tumor to the left cerebellar-pontine angle, suggesting an ependymoma. Also the ADC map (D) shows no severe diffusion restriction. The structural map (colored direction map) (E) shows invasion of the left middle cerebellar peduncle, favoring the diagnosis of ependymoma.
and serves mostly as a marker of neuronal cells.

4. Lactate, which results from anaerobic metabolism and is seen not only in necrotic tumors but also in low-grade tumors, like pilocytic astrocytomas. A lactate peak can be seen in hypoxic or infarcted tissue and also in brains of children with metabolic diseases.

5. Lipids can appear when there are increased cellular and myelin breakdown products or nonviable necrotic tissue. Lipids may also be shown in cystic lesions such as pilocytic astrocytomas.

Many other metabolites can be detected, especially with short TE (35 milliseconds) and when using higher field strengths (3 T or higher). In the literature, multiple articles focus on MRS and its use in children with a suspected brain tumor. On a 1.5-T MR system, the most commonly used proton MRS technique in children suspected to have a brain tumor is short TE (<35 milliseconds). This short TE allows additional metabolite peaks such as myo-inositol (ml, a glial cell marker), glycine, glutamine/glutamate (Glx), taurine (Tau), alanine (Ala), and citrate (Cit) to be identified. These metabolites can be useful in suggesting histology and its biological behavior or malignancy grade of a brain tumor. The observable MR metabolites provide powerful information, but many notable metabolites are not detectable in brain MR spectra; for example, DNA, RNA, most proteins, enzymes, and phospholipids are missing. Some key neurotransmitters, such as acetylcholine, dopamine, and serotonin, are also absent with either their concentrations being too low, or the molecules being invisible to MRS.

Proton MRS can be used for diagnosing and differentiating brain tumor types, as well as predicting tumor grade and pretherapy/biopsy planning. Also, posttherapy assessment, including differentiating radiation necrosis from tumor recurrence, is possible because normal brain metabolite levels after treatment favor edema and postsurgical changes. Tzika and colleagues showed that the metabolic profile of a brain tumor obtained with MRS gives additional information that is not provided by other tumor imaging parameters, such as enhancement, diffusion, and relative cerebral blood volume. The MR spectroscopic hallmark of brain tumors relative to normal brain tissue is increased choline and decreased NAA levels.

In general, the grading of the tumor increases when NAA and creatine levels are decreased, and choline, lactate, and lipid levels are increased. Very malignant tumors have high metabolic activity and deplete their energy storages, resulting in reduced creatine levels. Very high cellular tumors with rapid growth have high choline levels. Lipids are found in necrotic portions of tumors, and lactate appears when tumors outgrow their blood supply and start using anaerobic glycolysis.

However, pilocytic astrocytoma, a grade I low-grade tumor, usually shows very low levels of NAA and Cr, and high choline, lipid, and lactate levels in the spectra, mimicking aggressive lesions.

For an accurate assessment of the tumor biology, the spectroscopic voxel should preferably be placed over the enhancing part of the tumor, avoiding areas of necrosis, hemorrhage, calcification, cysts, or cerebrospinal fluid.

As mentioned earlier, MRS can also play an important role in assessing therapeutic response. For example, early detection of treatment failure is important because an ineffective treatment can be modified before a significant progression of disease.

MRS data can be obtained in SV or multivoxel mode.

**Single-voxel technique**

In SV mode, the most commonly used methods for volume selection/excitation are stimulated echo acquisition mode (STEAM) and point-resolved spectroscopy sequence (PRESS). In general, shorter TEs are better achieved with STEAM; however, it is more sensitive to motion. In theory, for the same total TE, the signal of PRESS is twice as great as that of STEAM; PRESS is also less sensitive to motion. To date, PRESS seems to be the most commonly used method of volume selection in clinical neuro-oncology practice. The major advantage of SV 1H-MRS is its short acquisition time (approximately 3 minutes compared with about 7–9 minutes for multivoxel).

With a short TE of 35 milliseconds or less, metabolites with both short and long T2 relaxation times can be detected. With a long TE of 288 milliseconds, only metabolites with a long T2 are seen, producing a spectrum containing primarily NAA, creatine, and choline. One other helpful TE is 144 milliseconds because it inverts lactate below baseline at 1.3 ppm and therefore makes it easily distinguishable from lipids and macromolecules, which resonate at the same concentration (Fig. 5).

As a general rule, SV, short-TE MRS is used to make the initial diagnosis, because the signal/noise ratio is high and all metabolites, which can be used for further characterizing the brain tumor, are represented. Its major flaw is that it...
lacks spatial resolution and cannot be used to better define the extent of a brain tumor, especially in brain tumors known to spread easily, like high-grade gliomas. Some brain tumors on imaging and histology are heterogeneous, and, therefore, SV spectroscopy cannot be used to map regional metabolic variations. Therefore, SV spectroscopy alone cannot reliably define the highest-grade components of the tumor. It may also involve significant averaging with low-grade parts of a tumor or even with adjacent normal brain tissue.

**Multivoxel technique**

Multivoxel MRS, a chemical shift technique (CSI) using either a short or long TE, can be used to further characterize different regions of a tumor and to assess the brain parenchyma around or adjacent to the tumor. This method is best for detection of infiltrating malignant cells beyond the enhancing margins of tumors. Particularly in the case of cerebral high-grade gliomas, increased choline levels are frequently detected in edematous regions of the brain outside the enhancing mass (Fig. 6). CSI can also be used to assess the response to therapy and to search for tumor recurrence. It is possible to scan in a two-dimensional (2D) or three-dimensional (3D) mode. The 3D CSI method is especially sensitive for detecting small areas of recurrence. A major drawback is its long scanning time (in children it may result in a higher portion of MR scanning under general anesthesia) and its low signal/noise ratio caused by its smaller voxel size, resulting in less reliable MR spectra. Also, acquisitions from larger volumes increase the risk for inhomogeneity of the magnet field and inadequate water suppression. 2D CSI MRS has also been used to help biopsy planning by showing areas of highest choline levels.

Quantitative rather than qualitative, MRS has been recently suggested for the assessment of
the metabolic profiles of pediatric brain tumors. Although absolute concentrations and concentration ratios of the prominent metabolites of the 1H-MR spectrum (NAA, Cr, tCho [total Choline], ml) provide important diagnostic information, less prominent spectral features, such as increased Tau in medulloblastomas or reduced guanidinoacetate in astrocytomas, also proved to be relevant for the discrimination of different tumors (Fig. 7). This quantitative MRS may help improve preoperative diagnosis of specific tumors. However, in daily practice, MRS should be used with standardized acquisition and processing methods, and easy-to-follow rules for quality control. Also, the interpretation is complex and requires expert knowledge to have an impact on clinical decision making (Fig. 8). Fully automated processing and quantitation can be helpful but in inexperienced hands it is cumbersome.

In summary, our suggested protocol in pediatric patients suspected to have a brain tumor is:

1. Initial diagnosis, SV MRS with short TE (35 milliseconds) in suspected brain tumor area and 2D CSI for defining the preferable area for biopsy. On both MRS sequences, the area with contrast enhancement should be included and areas with cerebrospinal fluid, hemorrhage, and calcifications should be avoided (Fig. 9).
2. Postoperative 24-hour to 72-hour MR scan. Depending on the amount of residual tumor seen on the conventional images and what the surgeon suspects to have left behind, SV, 2D CSI, or 3D CSI with short TE can be done. Because of landmark changes and other postoperative alterations, like bleeding, hemostasis material, and infarction of surrounding brain parenchyma, interpretation of the MRS spectra can be challenging. SV is less sensitive for postoperative changes and therefore, for routine postoperative scanning, the best choice. However, if the suspected residual tumor area is small, then 2D or 3D CSI may be better options.

3. Follow-up MRS can be included in the scanning protocol if treatment response seems to be inadequate. Some clinicians advocate using 3D CSI in every follow-up scan to detect small tumor recurrence. In brainstem gliomas, SV is the best method because of interpretation problems with CSI spectra caused by magnetic field inhomogeneity at the skull base.

All metabolites that are detectable with MRS and that could help in differentiating among pediatric brain tumors are summarized in Tables 1 and 2. Therapeutic response assessment, radiation necrosis, and differential diagnosis for focal brain tumor are discussed briefly. Extensive

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Fig. 7. A 5-year-old boy presents with a midline tumor. Conventional MR sequences (A–C) and ADC (D) suggest medulloblastoma. Single-voxel MRS (E) shows high choline and increased taurine, favoring the diagnosis of medulloblastoma and closely related to high risk of cerebrospinal fluid spread. This diagnosis was confirmed on the spinal MR.
description of possible brain tumor types in the posterior fossa and supratentorial are addressed in other articles.

**Therapeutic response assessment**

As stated earlier, 2D or 3D CSI is the best technique to assess a small recurrence within the surgical bed, especially when MRS can detect an increase in the Cho peak. Second, clinicians must take into account whether radiation therapy has been given, because this may result in low NAA peaks in the surrounding gray and white matter, compared with normal NAA levels in healthy controls. In the case of medulloblastomas, a higher total choline and taurine level may suggest metastatic disease, which may have a different therapeutic response (see Fig. 7). In brainstem glioma, if the citrate peak is reduced compared with the pretreatment situation, this may indicate malignant transformation, or result from chronic steroid administration, radiotherapy, and/or chemotherapy.\(^{14}\) Also, increased total choline and lipid levels can suggest malignant transformation. In grade II astrocytomas, a citrate peak may indicate a more aggressive behavior and higher chance for recurrence and metastases, and therapeutic response assessment should be tailored for patients with this kind of tumor.

**Radiation necrosis**

Radiation necrosis could be a diagnostic challenge for neuroradiologists. Most of the time conventional imaging is inconclusive and advanced MR imaging techniques are necessary (Figs. 10 and 11). Typically, radiation necrosis develops months to several years after radiation therapy.

Besides perfusion-weighted imaging, MRS can be helpful to differentiate between tumor progression and radiation necrosis. On MRS, a high lipid/lactate peak, low NAA peak, and a low choline peak compared with the spectra of normal-appearing brain parenchyma and with the spectra of the pretreatment brain tumor are suggestive of radiation necrosis.

High choline peaks may be shown after radiation therapy because of tumor cell death. In these cases, information obtained from other advanced MR imaging techniques, such as perfusion-weighted MR...
imaging, as well as follow-up with MRS, may be helpful in characterizing the lesion.

**Pseudoprogression**

In the pediatric population, pseudoprogression is less an issue than in the adult population, because of a lower occurrence of high-grade brain tumors.

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**Table 1**

Peaks of metabolites in infratentorial brain tumors

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*Abbreviations:* ATRT, atypical teratoid rhabdoid tumor; BSG, brainstem glioma; CPC, choroid plexus carcinoma; CPP, choroid plexus papilloma; Lac, lactate; Lip, lipids; MB, medulloblastoma.
Table 2
Peaks of metabolites in supratentorial brain tumors

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Abbreviations: Dаци, desmoplastic astrocytoma of infancy; ДИГ, desmoplastic infantile ganglioglioma; DНET, dysembryoplastic neuroepithelial tumor; PNET, primitive neuroectodermal tumor; SEGа, subependymal giant cell astrocytoma.

Fig. 10. Glioblastoma in a 14-year-old girl. The lesion in the right parietal lobe shows solid and cystic components on T2 (A) and T1 (B) and nearly no enhancement (C). Some areas in the tumor show low ADC values (D). On ASL there is moderate perfusion (E). Spectrum suggests high-grade tumor with increased choline and lipid peaks and reduced NAA and creatine peaks (F).
treated with postoperative adjuvant radiation therapy and temozolomide chemotherapy. Pseudoprogression often appears several weeks to months after radiation therapy. The causative factor is a transient interruption of myelin synthesis secondary to damage to oligodendrocytes as a result of radiation injury.

Accurate distinction between tumor recurrence and treatment effects can also be difficult in children. DWI and PET scans (with 11C-methionine) may provide the answer in many cases, but sometimes MRS can give additional information. Because of new treatment strategies, radiologists can no longer rely on changes in enhancement within the old tumor region. Enlargement of an enhancing lesion may represent pseudoprogression.

Although perfusion and permeability may help distinguish pseudoprogression from true tumor progression, follow-up MR imaging with contrast is the only established technique to confidently distinguish these lesions.

**Pseudoresponse**

To date, MRS has not provided any additional value in the diagnosis of pseudoresponse. Pseudoresponse has been noticed since the introduction of antiangiogenic therapies targeting vascular endothelial factor (VEGF), such as bevacizumab, a recombinant humanized monoclonal antibody to VEGF-A, or the VEGF receptor, such as cediranib, a pan-VEGF receptor tyrosine kinase inhibitor normalization of leaky tumor blood vessels. These agents can cause reduction in enhancement within 1 to 2 days after administration, with a radiographic response observed in 25% to 60% of patients. However, this impressive radiographic response does not translate into increased overall survival. It is thought that

**Fig. 11.** Same patient as in Fig. 10. First column: 48-hour postoperative MR with small enhancing nodule without hyperperfusion on ASL (A). Two weeks later, another enhancing lesion more lateral-anterior to the postoperative cavity. Recurrence or pseudoprogression? (B, second column) Three months later, enhancing lesion caudomedial without hyperperfusion, probably fibrotic tissue. Previous hyperperfused area lateral-anterior no longer visible, so it was pseudoprogression (C).
the rapid radiographic response represents a direct action on blood vessel permeability rather than a true antitumor effect; a phenomenon termed pseudoresponse. A further confounder in radiographic assessment of therapy response is the tendency for antiangiogenic agents to promote progression of nonenhancing disease by selecting for an invasive tumor phenotype capable of co-opting existing blood vessels and no longer relying on angiogenesis.  

**Differential diagnosis**

It may be difficult or even impossible to distinguish between a necrotic tumor and an abscess,
even with contrast-enhanced MR imaging. Most of the time DWI can give the answer and in some cases MRS can be of additional help (Figs. 13 and 14). If in the cystic/necrotic part of the mass acetate, succinate, and amino acid (valine, alanine, leucine) peaks are visible, a pyogenic abscess is the most likely diagnosis.17

Fig. 13. An 8-year-old boy presents with a deviation of the head and eyes to the left. Upper row shows the conventional MR sequence characteristics on the initial MR scan (A–C). Differential diagnoses include brain abscess, tumor, or vascular malformation. Second row MR scan 3 days later with T2 (D) and with ADC (E) showing no restricted diffusion except for a rim in the enhancing lesion (F). SV MRS (35 milliseconds) shows a normal spectrum (G). No increased choline peak suggesting tumor. No clear lactate peak suggesting abscess. Cavernous hemangioma with some internal bleeding?
Fig. 14. MR 12 days later in the same patient as Fig. 13 shows enlargement of the brainstem lesion (A, B). MRS shows a change in the spectra (C). Now there is a prominent choline peak favoring brain tumor. Susceptibility-weighted image (D) shows no bleeding in the tumor and no other bleeding ruling out a cavernous hemangioma. ASL shows high CBF (cerebral blood flow), suggesting high-grade tumor (E). On the MR 9 days later, MRS shows high choline peak, lower NAA, and a high lipid/lactate, characteristic of a high-grade brain tumor (F). On histology it was a primitive neuroectodermal tumor.

Fig. 15. Supratentorial anaplastic ependymoma: 6-year-old boy with irritability, and signs of high intracranial pressure. There is a large lesion with perifocal edema on T2 (A) in the left frontal lobe, with heterogeneous enhancement (B, C). The ADC map (D) shows restriction in the tumor wall. The DSC shows low perfusion (E). Spectra show increase of the Cho peak, presence of lipids, along with reduction of the NAA and Cr peaks (F).
In pseudotumoral demyelinating lesions, MRS may show increased choline, lactate, and lipid levels, caused by inflammatory response, mimicking neoplasm. Increase of glutamate and glutamine levels shown with short-TE MRS favors demyelination rather than tumor.¹⁸

**Contrast Perfusion MR Imaging (Dynamic Susceptibility Contrast MR Imaging, Dynamic Contrast-Enhanced MR Imaging, and Arterial Spin Labeling; A Noncontrast Technique)**

**Dynamic susceptibility contrast MR imaging**
Imaging the passage of an injected MR imaging contrast bolus can be used to investigate the perfusion characteristics of brain tumors. With DSC MR imaging the passage of the MR imaging contrast agent is used to investigate tumor characteristics based on the T2* effects, in which the (relative) cerebral blood volume (CBV) is the most important parameter used for the characterization of brain tumors. A higher (relative) CBV is correlated with a higher tumor grade both in adults and in children. In a recent DSC perfusion study of 63 pediatric patients with brain tumors, the relative CBV was a good method to exclude high-grade tumors in patients with low relative CBV values. However, the specificity in this study was low because a subgroup of low-grade tumors also showed higher relative CBV values.¹⁹

Interesting findings may be shown in pediatric brain tumors such as medulloblastomas and pilocytic astrocytomas (PAs). Despite being aggressive grade IV tumors, medulloblastomas may not present with high blood volumes in the perfusion study. In contrast, PAs, which are low grade (grade I tumors), often present with very high blood volumes.

Knowledge of these unexpected findings is helpful in order to consider the appropriate diagnosis.

**Dynamic contrast-enhanced MR imaging**
With DCE MR imaging, permeability characteristics of brain tumors can be assessed based on dynamic imaging of changes using T1 in the brain tumor regions. With DCE MR imaging, vascular permeability parameters such as the transfer coefficient (K-trans) can be determined. At present, most DSC perfusion MR imaging studies are reported for brain tumor evaluation in children (Figs. 15 and 16).

![Fig. 16. A 7-year-old girl presents with temporal epileptic focus on the left. Conventional MR images show a high-signal-intensity lesion on T2 (A), hypointense on T1 (B), subcortical, in the left temporal lobe. No enhancement (C), no restricted diffusion (D), hypoperfused on the DSC study (E). Histology confirmed a dysembryoplastic neuroepithelial tumor.](image-url)
**Arterial spin labeling MR imaging**

ASL MR imaging is a noncontrast method to assess the perfusion in brain tumors and has been the focus of clinical research of many groups around the world. In general, ASL MR imaging is performed by magnetically labeling the arterial water in the feeding arteries to the brain. After labeling the arterial blood the MR sequence is built in such way that a delay (typically 1–2 seconds) allows the labeled water molecules to flow into the brain tissue and exchange with the brain tissue water. Consequently, a small change (a few percent) occurs in the magnetization of the brain tissue water. In itself this small percentage change is not visible but a control image is also acquired and a subtraction of labeled and control images is performed that results in a perfusion-weighted MR image. Because the signal/noise ratio of a single subtracted label control image is low, typically a series of 20 to 40 labeled and control pairs are acquired, which results in ASL MR imaging scan times of 3 to 5 minutes. Two main flavors of ASL perfusion methods are available on many MR imaging scanners. The first is pulsed ASL and the second is (pseudo) continuous ASL. These methods differ in the way the blood in the neck region is labeled. With pulsed ASL a thick excitation slab labels all the blood in the neck region at 1 point in time (spatial labeling of the blood in the arteries). With (pseudo) continuous ASL a thin excitation slab is used in which the blood in the neck region is labeled during 1.5 to 2.0 seconds (temporal labeling of the blood in the arteries). In a recent article the consensus was that pseudocontinuous ASL with certain labeling and delay parameters provides the best images for use in most clinical scenarios. More recently, a study compared pseudocontinuous ASL with pulsed ASL in a series of 61 children. The result from this study was that pseudocontinuous ASL resulted in a better image quality compared with the pulsed ASL method. Quantitatively both methods resulted in the same cerebral blood flow values. Also interesting from this study was that in 75% of the scans the image quality was good enough for this comparison, which shows that there is a high percentage of patients in whom ASL might result in noninterpretable results; for instance, because of motion artifacts.

Similar to its use in adults, ASL perfusion MR imaging may be a useful method to estimate tumor grade in children. In adults, tumor grade was correlated with higher ASL perfusion signal. In a recent study, Yeom and colleagues showed that high-grade brain tumors (grades 3 and 4) have high ASL MR imaging perfusion signal intensity, whereas low-grade tumors (grades 1 and 2) have low ASL perfusion signal intensity. ASL perfusion MR imaging was performed in 54 children with a mean age of 7.5 years, before treatment. Using region of interest analysis, the maximum relative tumor blood flow was obtained. The largest portions of tumors were astrocytic tumors in this study. ASL perfusion MR imaging was not able to distinguish tumor histologic subtypes, except that there was a higher ASL perfusion signal in posterior fossa medulloblastomas compared with PAs.

However, more research is needed concerning the use of ASL perfusion MR imaging in patients with brain tumors. Areas of interest are the correlation between (pretreatment) ASL perfusion signal and patient prognosis. For instance, Fig. 17 shows ASL perfusion signal in 2 patients with a medulloblastoma. In one patient, ASL perfusion images show low perfusion signal, whereas in the other patient the ASL perfusion signal is high. These differences in perfusion signal may have prognostic consequences. Furthermore, another unexplored area is the use of ASL perfusion signal in the postoperative evaluation of children treated for brain tumors. For instance, being able to discriminate between treatment effects (radiotherapy) and recurrent tumor growth, which may show contrast enhancement on postcontrast T1-weighted MR imaging images. Higher perfusion ASL signal can be expected in high-grade recurrent tumors compared with possibly low ASL perfusion signal in areas where treatments were effective. Another area of future research is the added value of quantification of the cerebral blood flow in regions of interest of the tumor compared with a qualitative assessment of the perfusion signal in the brain tumor region.

Furthermore, on the technical side, ASL comparison studies have to be performed for further improvements in the methods to enhance ASL perfusion measurements. Although the pseudocontinuous ASL is currently most often used because of its high signal/noise ratio, it is possible that the signal/noise ratio may further increase based on optimization of the best possible readout strategy. Furthermore, especially in patients after surgery, surgical material (clips) may cause artifacts, which could be reduced with readout strategies that are less sensitive for MR field distortions.

**Other Advanced MR Imaging Sequences**

**Susceptibility-weighted imaging**

SWI is a 3D fast low-angle shot (FLASH) MR imaging technique that is extremely sensitive
to susceptibility changes. Various paramagnetic, ferromagnetic, or diamagnetic substances, such as air/tissue or air/bone interfaces, can cause these susceptibility changes. Compared with T2*-weighted (ie, gradient-echo) images (Fig. 18), SWI uses not only the magnitude of the signal loss but also the phase information to reveal anatomic and physiologic information about brain tissue and venous vasculature. The underlying contrast mechanism is primarily associated with the magnetic susceptibility difference between oxygenated and deoxygenated hemoglobin, leading to a phase difference between regions containing deoxygenated blood and surrounding tissues, resulting in signal cancellation. Therefore, SWI is sensitive for calcifications and blood products, like T2*-weighted images, but is also sensitive in visualization of venous vessel because of its deoxyhemoglobin concentration (Fig. 19). However, SWI contrast is also affected by other factors like hematocrit, red blood cell integrity, clot structure, molecular diffusion, pH, temperature, field strength, voxel size, previous contrast material use, blood flow, and vessel orientation.

Because of its magnetic susceptibility effects, SWI is extremely sensitive to small changes within brain tissues that are likely not visible.

Fig. 17. ASL perfusion signal in 2 patients with a medulloblastoma. Patient A has a primary tumor, patient B was a local recurrence (A, B). In patient A, ASL perfusion images show low perfusion signal (A) and, in patient B, ASL shows high perfusion signal in the tumor (B).
with conventional MR techniques. Thus, SWI can be used to identify even small alterations in hemorrhage, calcifications, and new vessel growth. SWI can be used to detect calcifications in brain tumors, suggesting a low-grade tumor. Also hemorrhage, often seen in rapidly growing tumors, is easily detected, suggesting a high-grade tumor. In addition, SWI can show areas of neovascularization in the tumor, which may help guiding tumor biopsy. Besides detection of small tumor vessels, SWI can also assess contrast agent uptake and oxygenation of the brain tumor.23,24

Functional MR imaging
fMR imaging uses regional changes in cerebral blood flow and metabolism that are induced by brain activation. During neuronal activation, there is a change in blood oxygenation levels, which results in minor magnetic susceptibility differences. The blood oxygenation level–dependent (BOLD) contrast depends on the differences between the amount of deoxygenated and oxygenated blood present in the brain region being activated. With this technique, radiologists can noninvasively identify important cortical areas, controlling language, motor, and memory functions. This ability could be essential for the decision to undertake neurosurgery or choose another treatment option. If neurosurgery is the best option, fMR imaging can help in presurgical planning, assisting in the decision of the best surgical approach as well as helping to determine the possible extent of the resection (Fig. 20). In addition, fMR imaging may help to select the patients who need an intraoperative cortical stimulation procedure, in cases in which the eloquent cortical areas are adjacent to or within the tumor. A disadvantage is that this procedure can only be performed in cooperative children. An important consideration concerning brain activation with fMR imaging is that it is easier to map the motor cortex using motor tasks than to map language areas (Broca and Wernicke) in children.

To overcome many of the limitations of task-dependent fMR imaging, resting state fMR imaging has been introduced. Several studies show that this method in combination with connectivity analysis is useful in the presurgical
evaluation of pediatric patients with brain tumors. Moreover, it may improve postoperative outcomes. Recently, fMR imaging has been integrated with electroencephalography (EEG) to optimize the information on brain function around the brain tumor. The advantage of this combination is the high temporal resolution of EEG and high spatial resolution of fMR imaging. The EEG changes produced by the tumor depend primarily on lesion size, rate of growth, distance to the cortical surface, and specific structures involved. To date, experience has only been gathered in adult patients.

**Future Perspectives**

As stated earlier, extensive progress is being made in pediatric neuroradiology. Recent discoveries about the genomic characteristics of brain tumors have changed the understanding of tumor genesis and biology, which may have a great impact on the diagnostic power of the conventional and advanced MR methods discussed earlier. Also epigenetic factors, like histone mutations in pediatric high-grade gliomas, add another layer of complexity. However, all these new insights may clarify the previously poor understanding of biological and imaging phenotype features and variations, such as location, prognosis, and therapeutic response.

Future advances in molecular biology will alter neuroradiologic concepts and thinking and add information to that obtained from conventional and advanced MR imaging techniques, which will benefit pediatric patients with brain tumors.
REFERENCES


11. Seo HS, Chang KH, Na DG, et al. High b-value diffusion (b = 3000 s/mm²) MR imaging in cerebral

Fig. 20. In this 14-year-old girl, a total brain tumor work-up is done. The conventional MR sequences show a heterogeneous tumor in the left frontal lobe (A–C). ADC map (D) shows diffusion restriction. DSC study (E) shows hyperperfusion compared with the contralateral brain parenchyma. fMR imaging was performed to localize speech and language areas (F) as well as the motor strip (G). These areas were not involved by the tumor. Also, fMR imaging showed that the tumor was more than 2 cm from the activated areas, which implies good prognosis concerning surgical resection. Histology of the resected tumor was consistent with an anaplastic ependymoma.


