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**Review for PEDIATRIC NEUROSURGERY**

# Advances in Imaging Modalities for Pediatric Brain and Spinal Cord Tumors

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**Running Title**: Advanced imaging in pediatric neurooncology

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**Abstract**

**Background:** Neuroimaging has evolved from anatomical imaging towards a multi-modality comprehensive anatomical and functional imaging in the past decades, important functional data like perfusion weighted imaging, permeability imaging, diffusion weighted and diffusion tensor imaging (DWI, DTI), tractography, metabolic imaging, connectomics, event related functional imaging, resting state functional imaging, and much more is now being offered.

**Summary:** Precision diagnostics has proven to be essential for precision treatment. Many minimal invasive techniques have been developed taking advantage of digital subtraction angiography and interventional neuroradiology. Furthermore, intraoperative CT and/or MRI and more recently MR guided focused ultrasound have complemented the diagnostic and therapeutic armamentarium.

**Key Messages:** In the current manuscript we discuss standard imaging sequences including advanced techniques like DWI, DTI, susceptibility weighted imaging (SWI) and 1H magnetic resonance spectroscopy (MRS), various perfusion

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weighted imaging approaches including arterial spin labeling (ASL), dynamic contrast enhanced (DCE) imaging and dynamic susceptibility contrast (DSC) imaging. Pre-, intra and postoperative surgical imaging including visualize imaging will be discussed. The value of connectomics will be presented for its value in neuro-oncology. Minimal invasive therapeutic possibilities of interventional neuroradiology and image guided laser ablation and MR guided high intensity focused ultrasound will be presented for treatment of pediatric brain and spinal cord tumors. Finally, a comprehensive review of spinal cord tumors and matching neuropathology has been included.

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**Introduction**

During the past decades neuroimaging has evolved from a purely anatomical imaging towards a multi-modality comprehensive anatomical and functional imaging allowing for precision diagnostics. Nowadays in addition to ultra-high resolution anatomical imaging, important functional data like perfusion weighted imaging, permeability imaging, diffusion weighted and diffusion tensor imaging (DWI, DTI), tractography, metabolic imaging, connectomics, event related functional imaging, resting state functional imaging, and much more is being offered. Precision diagnostics has proven to be essential for precision treatment following the classic mantra: Primum non nocere (First do no harm). In addition, many minimal invasive techniques have been developed taking advantage of digital subtraction angiography and interventional neuroradiology. Furthermore, intraoperative CT and/or MRI and more recently MR guided focused ultrasound have complemented the diagnostic and therapeutic armamentarium.

In the current manuscript experts from various backgrounds in neuroimaging and neurosurgery will discuss standard imaging sequences including advanced techniques like DWI, DTI, susceptibility weighted imaging (SWI) and $^{1}H$ magnetic resonance spectroscopy (MRS), various perfusion weighted imaging approaches including arterial spin labeling (ASL), dynamic contrast enhanced (DCE) imaging and dynamic susceptibility contrast (DSC) imaging. Pre-, intra and postoperative surgical imaging including visualize imaging will be discussed. The value of advanced neurofunctional tools, in particular connectomics will be presented for its value in neuro-oncology. Minimal invasive therapeutic possibilities of interventional neuroradiology and image guided laser ablation and MR guided high intensity focused ultrasound will be presented for treatment of pediatric brain and spinal cord tumors. Finally, a comprehensive review of spinal cord tumors and matching neuropathology has been included.

**Standard and advanced imaging techniques (DWI/DTI, SWI, MRS) in Pediatric Neuro-Oncology**

Magnetic Resonance Imaging (MRI) is the modality of choice for diagnosis of brain and spinal tumors, delineate its anatomic extent, narrow the differential diagnosis, plan stereotactic biopsy or surgical resection and distinguish post treatment changes from recurrent tumor [1].MRI protocols vary among institutions, but normally include multiplanar pre- and post-contrast 3D T1-weighted, T2-weighted fast spine echo (T2-FSE), T2-weighted fluid attenuation inversion recovery (T2-FLAIR), Diffusion weighted imaging (DWI) with apparent diffusion coefficient (ADC), and either susceptibility-weighted (SWI) or gradient echo (T2*GRE) imaging.

Volumetric 3D isotropic (x-, y-, z- axis of the voxel are of equivalent dimensions) T1 GRE techniques such as spoiled gradient echo (SPGR) or magnetization-prepared rapid gradient echo (MP-RAGE) provides strong contrast between grey-white matter structures and along with its capabilities to be reformatted in any planes, is very useful for precise localization of any sized pathologies and consequently essential for preoperative purposes.

MRI contrast agents are primarily Gadolinium based and because of its T1 shortening property leads to higher signal intensity on T1 weighted images with areas of gadolinium accumulation appearing bright or “enhanced”. Axial 3D T1 pre and post contrast imaging is ideally performed by gradient echo sequences (e.g., T1 MPRAGE) so as to visualize normal and pathologic tumoral arterial and venous vasculature. T1 black blood techniques which are spin echo based, (e.g., T1 SPACE) suppress vascular enhancement and therefore are not ideal for vascular purposes although may be run in conjunction [2]. If more detail is needed on the location of the vascular inflow and outflow to a mass and proximity of normal regional vasculature CT angiography (CTA) and/or CT venography (CTV) may be needed. CTA is especially helpful in surgical planning of neoplasms near or involving the skull base, sella and suprasellar regions. Alternatively, pre and postcontrast 3D time of flight (TOF) imaging may also be performed of the entire head. The presence of contrast affords the ability to identify distal arterial vasculature as well as the entirety of the venous system on TOF imaging. 3D or high resolution 2D T2 and T2 FLAIR sequences is also paramount in depicting T2 hyperintense target nonenhancing tumor and nontarget peritumoral edema signal. High resolution (2.0 mm -2.5 mm) two-dimensional T2-FSE sequences are especially useful for evaluation of vasogenic and cytotoxic edema, extent of infiltrative tumor, ventricular size and contour delineation. With CSF nulling capability (signal suppression of free wate) of T2-FLAIR images as compared to T2-FSE images, it provides better delineation of tumor margin, intratumoral cystic/necrotic changes, disease spread along the ventricular margin as well as subarachnoid spaces.

If additional 2D T2 sequences are employed, coronal and axial planes are preferable for supratentorial tumors whereas axial and sagittal planes are advantageous for posterior fossa masses. It is preferable that the T2 FLAIR sequence be run postcontrast as it provides excellent depiction of local leptomeningeal invasion and distant leptomeningeal spread given the sequence’s inherent sensitivity to contrast and the contrast afforded by vascular suppression (i.e., black blood).

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Given the high prevalence of cerebro-spinal fluid (CSF)-seeding tumors (e.g. medulloblastoma, ependymoma, germinoma, pineoblastoma) postcontrast imaging of the entire neuroaxis is advised on initial presentation. At our institution, we perform sagittal and axial 2D T1-weighted sequences through the entire spine.

When preoperative imaging is purposefully performed when routine imaging already exists, imaging may be curtailed to those sequences that serve navigational purposes. In pediatrics, given the need for sedation for most patients, standard MRI sequences ought to be modified to navigational compatible ones, ideally under a "new brain tumor" protocol that ensures such sequences are run at the time of diagnosis, avoiding the need for repeat sedation.

The Response Assessment in Neuro-Oncology (RANO) criteria are still primarily based on conventional MRI and includes measurable enhancing lesion and nonenhancing mass-like T2-FLAIR changes as metrics of tumor analysis.

**Diffusion weighted imaging (DWI)**

Diffusion MR imaging is a powerful technique that exploits the diffusion properties of water to generate contrast between normal tissue and pathology. Along with its routine clinical role in stroke imaging, DWI provides important functional and physiological information about brain tumors and the peri-tumoral microenvironment. Direct measurement of water mobility becomes an imaging biomarker of tissue pathology, as water movement is dependent on factors such as cellularity and viscosity. Restricted diffusion, as demonstrated by increased DWI signal and correspondingly reduced ADC values, is caused by decreased free motion of water molecules, either because of high cellular density (e.g. lymphoma and medulloblastoma) or high protein content (e.g. epidermoid cyst). The ADC maps provide quantitative data derived by measuring restriction of water molecules at differing degrees of diffusion weighting, useful for differentiating tumor type and grade. For instance, the degree of lowered ADC values will typically be greater in lymphoma, medulloblastoma as compared to high-grade glioma or metastases and the ADC values will be greater in high-grade glioma or metastases as compared to low grade glioma.

**Diffusion Tensor Imaging (DTI)**

In DTI, the application of a diffusion tensor model onto DWI data determines diffusion along each of three axes of a given voxel and produces a three-dimensional ellipsoid, known as the diffusion tensor. The diffusion tensor provides more complete anisotropic and structural data of each voxel, yielding fractional anisotropy images which clearly delineate white matter tracts by coding left–right (red), anterior–posterior (green), and superior–inferior (blue) diffusion. Neuroradiology-generated preoperative mapping of eloquent white matter tracts helps the neurosurgeon to reduce morbidity by resecting as much tumor as possible while preserving or avoiding important white matter tracts which correlates with improved quality of life and patient survival. At our institution, two white matter tracts most frequently requested to be mapped/identified by our neurosurgical colleagues are the corticospinal tracts (CST) for motor function and the arcuate fasciculus (AF) for language.

**Susceptibility weighted imaging (SWI)**

SWI is a high-spatial-resolution, three-dimensional (3D), fully velocity compensated, gradient-echo MRI technique which accentuates the magnetic properties (susceptibility effects) of various substances such as blood products, calcification and iron. A total of four images are generated in a SWI sequence dataset. An original magnitude image and a filtered phase or phase mask is initially obtained. The original magnitude and phase data multiplied by each other produces a combined SWI processed magnitude image. Finally, a minimum intensity projection (minIP) image is used to display the combined processed magnitude data using contiguous sections of thickness from 8 to 16 mm in the axial plane. SWI is more sensitive than T2*-GRE in detecting microhemorrhages and differentiating them from calcification. SWI is also useful in the demonstration of abnormal vascularity within tumors. This information put together with the conventional MR sequences and clinical setting may yield vital information in the diagnosis and prognosis, mostly in evaluating the tumor grade. Calcifications are typical of low-grade tumors, whereas hemorrhages and an increased vascularity are common in high-grade tumors.

**$^{1}$H MR Spectroscopy (MRS)**

Magnetic resonance spectroscopy (MRS) can aid in the evaluation of pediatric brain tumors by providing metabolic information complementary to neuroanatomical imaging. (Table 1) MRS is typically performed as independent acquisitions using a short time-to-echo (TE) (30 milliseconds), a long TE (244 milliseconds) and an intermediate TE (135 milliseconds). At our institution for Neuro-oncology imaging, we perform multi-voxel long TE MRS which constitute the dominant peaks in the MR spectrum, including N-acetyl aspartate (NAA), choline (Cho), and creatine (Cr). In addition to these high concentration metabolites characterized in the MRS spectrum by large peaks, the single

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voxel short TE acquisition may also demonstrate peaks from smaller molecules, such as taurine, glutamine and glutamate, myoinositol, and alanine.

Semi-quantitative analysis using ratios of various metabolites is used to better predict the grade. Commonly used ratios are Cho/Cr, Cho/NAA, and NAA/Cr. Typical pattern in high grade gliomas (HGGs) are elevated Cho/Cr, Cho/NAA ratios and reduced NAA/Cr ratio. Wang and colleagues in a large meta-analysis, looked at 30 articles comprising 1228 patients and analyzed utility of various metabolite ratios in predicting the malignancy grade of gliomas and capability of distinguishing low-grade gliomas (LGGs) from HGGs [1]. Quantitative synthesis of studies showed that the pooled sensitivity/specificity of Cho/Cr, Cho/NAA and NAA/Cr ratios was 0.75/0.60, 0.80/0.76 and 0.71/0.70, respectively. The area under the curve values for these metabolites were 0.83, 0.87, and 0.78, respectively. In this analysis, all 3 ratios had comparable performance and Cho/NAA ratio showed the highest accuracy.

**Perfusion weighted imaging including DSC, ASL and DCE**

The utility of MRI perfusion imaging of pediatric brain tumors is based on the correlation between neovascularization and tumor grade. MRI perfusion techniques provide hemodynamic information of the brain tumor that cannot be otherwise determined from the conventional imaging as the contrast enhancement of a tumor is affected by both the vascularity and the degree of blood brain barrier disruption. MRI perfusion techniques have been shown to improve radiological diagnosis of pediatric brain tumors, correlate with tumor histopathology, and can be easily integrated into routine imaging protocol. The most common MRI perfusion techniques utilized are dynamic susceptibility contrast (DSC), arterial spin labeling (ASL), and dynamic contrast enhanced (DCE) perfusion. MRI perfusion data has shown utility in differentiating low grade and high grade pediatric tumors, however the determination of a specific pathology by perfusion techniques is limited largely due to the wide range of pathologies encountered. When implementing and evaluating MRI perfusion imaging in pediatric brain tumors, it is important to be cognizant that changes in imaging parameters can affect perfusion results and that perfusion results should always be interpreted in conjunction with conventional imaging (Figures 1-3).

MRI DSC perfusion technique involves acquiring a T2* echoplanar sequence before and after rapid administration of intravenous contrast and can be acquired in ~ 2 minutes. Post processing of DSC data results in DSC parameters/maps including relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF), and mean transit time (MTT). Advantages of DSC perfusion are the rapid acquisition and high signal to noise. Disadvantages of DSC include the use of intravenous contrast, rapid rate of contrast administration, large bore intravenous access, and results can be affected by parenchymal contrast leakage (impaired blood brain barrier), hemorrhage and calcification. The CBV parameter/maps from DSC has been most often studied in pediatric brain tumors and is measured as a ratio to an internal control to produce a relative CBV (rCBV) [3-5]. A rCBV cutoff of 1.38 demonstrated a sensitivity and specificity of 92% and 40% indicating that rCBV from DSC performed well for excluding high grade pathology when the tumor has a low rCBV [4]. Reasons for the lower specificity of rCBV in grading of pediatric brain tumors include the parenchymal leakage of contrast in some low grade tumors, particularly pilocytic astrocytomas, which can falsely elevate the rCBV. This can be offset by evaluating the leakage pattern obtained from DSC perfusion. Normally, the signal intensity decreases after contrast administration but then returns to the baseline signal intensity. A T2* leakage pattern occurs when the signal intensity does not return to baseline or a T1 leakage pattern if the signal intensity rises above baseline. A T1 contrast leakage pattern demonstrated high specificity for low grade tumors indicating this additional information can assist in diagnosis [3]. Alternatively, a small volume of intravenous contrast can be administered as a preload to limit the effect of leakage on the determination of the rCBV. Lastly, DSC rCBV data has also been shown to correlate with survival metrics in patients with diffuse pontine gliomas. Patients with pontine gliomas that had higher baseline rCBV as well as those with an increase in rCBV over time had shorter progression free survival and overall survival [6].

MRI arterial spin labelling (ASL) perfusion technique is a noncontrast enhanced imaging technique that acquires images of the brain in a tagged/labeled and untagged/unlabeled state of blood within inflowing arteries and subsequent subtraction to generate a cerebral blood flow images of the brain. Advantages of ASL include the lack of intravenous contrast injection requirement. Disadvantages of ASL are the slower acquisition time, sensitivity to motion and susceptibility artifacts, low signal to noise ratio, and CBF is affected by choice of post label delay, hydrocephalus and sedation. High grade pediatric brain tumors demonstrate a higher CBF than low grade tumors [7, 8]. Using a CBF cut off of > 50 mL/min/100 g demonstrates a sensitivity and specificity of 90% and 93% for cerebral hemispheric tumors, 100% and 80% for thalamic tumors, and 65% and 94% for posterior fossa tumors [8]. When the

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ASL CBF data is combined with the contrast enhancement pattern, the CBF-to–contrast enhancement ratio improved sensitivity and specificity for posterior fossa tumors to 96% and 97% [8]. Using an algorithm approach with ASL perfusion and contrast enhancement, an accuracy of 93% was shown for differentiation of pediatric low grade and high grade tumor [8]. Lastly, the ASL CBF has been shown to correlate with microvascular density measured in tumor samples (Spearman R value, 0.66) indicating that ASL CBF represents a biomarker for pediatric brain tumors [8]. Lastly, ASL CBF allows to differentiate pseudoprogression from true progression in pediatric patients with diffuse pontine gliomas which may prove useful in the event that newer treatments emerge [9].

MRI DCE perfusion technique involves imaging with a T1W sequence before and after rapid administration of intravenous contrast and can be acquired in ~ 4-5 minutes. Advantages of DCE are the high signal to noise ratio and the fact that permeability parameters can be acquired. Disadvantages of DCE are the slower acquisition time, and need for intravenous contrast injection. Following post processing of the DCE data, DCE parameters/maps obtained include $K_{trans}$ and $K_{ep}$ which reflect permeability, and $V_p$, and $V_e$ which reflect blood volume. Relatively limited data on DCE perfusion for pediatric brain tumors has shown mixed results [10, 11]. In one study, pediatric high grade tumors demonstrated higher $K_{trans}$ and $K_{ep}$, and lower $V_e$ compared to low grade tumors [11]. However, another study showed only differences in the DCE $V_p$ parameter between low grade and high grade pediatric brain tumors [10].

Further research with combination of DSC, ASL, and DCE perfusion parameters in conjunction with conventional MRI findings as well as correlation with molecular data will be useful for further understanding the utility of MRI perfusion data as biomarkers in pediatric brain tumors. Lastly, further developments in MRI techniques that allow for assessment of spinal tumor perfusion may allow for better differentiation of tumor pathology when combined with conventional imaging.

**Intraoperative imaging**

Intraoperative imaging is safe and may increase the likelihood of gross total resection and decrease the need for repeat operation [12, 13]. Intraoperative imaging is typically performed while the surgical field remains open such that repeat interrogation of the field is possible should the need for repeat resection be identified. Intraoperative imaging is best employed by targeted, efficient high resolution imaging (Figure 4) with limited imaging through the remainder of the brain parenchyma. The imaging protocol ought to be optimized to mitigate against susceptibility effects introduced by air and blood products in the surgical field. High resolution (<3 mm) axial T1 FSE and axial T2 FSE are common although some institutions may still prefer 3D T1 imaging [13]. DWI is helpful in evaluating for residual hypercellular tumor but to also evaluate for untoward complications such as regional infarct. Intraoperative DWI ought to employ non echo planar (EPI) imaging such as spin echo DWI or sequences like readout segment EPI DWI that mitigate against susceptibility effects. High resolution or 3D SWI is also valuable in distinguishing blood products. DWI and SWI in combination are especially useful in evaluating what regions of the field have been surgically interrogated. High resolution 2D T1 FSE and 3D T1 postcontrast are accepted postcontrast methodologies.

If intraoperative imaging demonstrates expected resection results, formal postoperative imaging is not necessary [13]. Postoperative imaging is otherwise preferably performed immediately after surgery (conveniently possible when intraoperative MRI is available even if intraoperative MRI was not used) during the same sedation. Previous literature has promoted the notion that imaging after 48-72 hours may significantly confound residual tumor identification due to postsurgical enhancement. While this may be true, such studies have not been reproduced in the modern era with 3T MRI, with modern contrast agents and in the pediatric population. Contrast enhancement in everyday practice is often seen immediately postoperative well prior to 48-72 hours [14]. Routine follow up surveillance imaging commonly consists of precontrast DTI/DWI with ADC maps, isotropic 3D T1, 2D or 3D T2 and T2 FLAIR, SWI and postcontrast 3D T1 imaging either via conventional T1 SPGR sequences or 3D T1 black blood imaging (e.g., T1 SPACE). 3D T1 imaging precontrast and postcontrast imaging is especially important in the postoperative setting so as to differentiate T1 hyperintense blood from true enhancement. Conventional single plane 2D T1 (fast spin echo) is also helpful as a complementary post contrast sequence. Many institutions also perform T2 FLAIR imaging postcontrast for reasons as noted above.

**Connectomics in the evaluation of pediatric intracranial tumors**

While conventional neuroimaging is limited to the description of local/regional morphological changes in patients with intracranial tumors, more advanced neuroimaging approaches, such as structural connectomics e.g the study of the connectome, can reveal more global changes. The connectome is a comprehensive map of the structural and functional inter-regional connections within the brain. It is, therefore, an ideal tool to study structural and functional

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brain networks implicated in neurocognitive and behavioral functions [15]. Connectomics is evolving into a powerful neurosurgical application, for example in glioma and posterior fossa tumor surgery (Figure 5) [16, 17].
As previously suggested, glioma is not a focal disease but rather a network-related disease [18-20]. The evaluation of the presurgical connectome has the potential to elucidate disease mechanism at a network level and improve patient's outcome after surgery [21, 17].
Posterior fossa tumors deserve special mention in pediatric oncology, as tumors located in the posterior fossa represent 50-70% of solid tumors in children. Posterior fossa syndrome (PFS), also known as cerebellar mutism, is a well-recognized complication that occurs in approximately 25% of children who undergo posterior fossa surgery for tumors. A number of pre-surgical conventional radiographic findings such as location and size of the tumor have been associated with development of PFS, but not in a consistent manner. The brain network analysis of pre-operative and post-operative MRI offers a unique opportunity to study the effect of midline posterior fossa tumors on cerebello-cerebral networks and provide new insights into the structural plasticity and compensatory mechanisms after surgery. The connectome has the potential to help address what the neurosurgeon needs to know to potentially prevent this syndrome.
A previously published study by Meoded et al [17] evaluated differences in pre-operative and post-operative structural brain connectivity in children with PFS. Findings from this work revealed significant differences in pre-operative brain networks involving the cortico-thalamic and other pathways among children who "did" versus "did not" develop PFS post-operatively. Connectomics offers a unique opportunity to study the effect of brain oncologic surgery and provide new insights into the mechanism of the structural plasticity/reorganization after surgery.

**Preoperative embolization for pediatric intracranial tumors**

Hypervascular intracranial tumors in the pediatric population can produce rapid intraoperative blood loss precluding safe, complete resection. Added to that, lower systemic blood volumes in these smaller pediatric patients decrease the margin of acceptable blood loss [22]. Therefore, pediatric tumors pose a unique challenge to the surgeon. Fortunately, advances in catheter and embolic material technology have enabled the neurointerventionalist to reliably devascularize tissues in a safe and specific manner resulting in greater application of percutaneous preoperative embolization (PPE) to reduce morbidity and mortality from incomplete resection, repeat surgery, or excessive blood loss [23]. According to PPE guidelines from the Society for Neurointerventional Surgery, choroid plexus tumors, hemangioblastomas, and juvenile nasopharyngeal angiofibromas are ideal candidates for preoperative embolization due to: surgically inaccessible arterial feeders, long operative times, blood loss, potential for damage to adjacent normal tissue, and incomplete resection [24]. PPE has enabled complete resection of tumors where prior surgery was aborted due to excessive blood loss [25-27] and has thus become, a useful surgical adjunct to reduce tumor recurrence [28] and increase overall survival [29, 30]. Studies have also reported improved visualization of the surgical field, likely from improved hemostasis and tumor softening. Thus, PPE has shown utility as a surgical adjunct to decrease morbidity and mortality in certain pediatric brain tumors. However, the literature on PPE for brain tumors, particularly in the pediatric population, is limited to institutional case series and small cohorts which will be reviewed and summarized in this section.

**Choroid plexus tumors**

Choroid plexus tumors (CPT) are rare neuroectodermal neoplasms with a slight male predominance, accounting for 2-4% of all intracranial pediatric tumors but 12% of children younger than 3 years old. Recently, CPT have been categorized into three histologic types: papilloma, atypia, and carcinoma. Atypia (aCPP) is associated with a recurrence at 5 years that is five-fold that of choroid plexus papillomas (CPP).[31] Gross total resection (GTR) is needed to maximize patients' overall survival, but intraoperative blood loss poses a significant challenge to that end [29].
In the largest reported series, overall survival for CPP is 99% vs 59% for choroid plexus carcinomas (CPC).[30] CPC are more vascular and associated with greater intraoperative blood loss (317% vs 132% average percent blood loss) compared to CPP [29, 32] which can limit the surgeons' ability to achieve GTR [29, 32, 33]. Thus, GTR rates are lower in CPC (41-71% CPC vs 65-92% CPP) [34, 30, 33]. It follows then that decreasing extent of resection (EOR) in CPC is associated with decreased five-year overall survival 73% vs 46% vs 38% (GTR vs subtotal resection (STR) vs no surgery, respectively) [30]. EOR in CPP also varies with 5 year overall survival: 100% vs 56% *(GTR vs STR, respectively) [29, 35]. If GTR is the goal, it is interesting to note that historically 29% of cases were aborted due to excessive bleeding [32]. Thus, an aggressive approach with PPE has been proposed to maximize chances for GTR [30].

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Embolic agents for CPT include n-Butyl cyanoacrylate (nBCA) [22, 36], histoacryl[32], onyx [37] and PVA [38, 22]. Choice of embolic should take into consideration the effect of catheterization on the parent vessel and risk of non-target embolization. Baro et al describe a case of PPE with nBCA where the parent artery is not seen on control angiography but reappeared on delayed angiography suggestive of spasm [36]. This is an example of the need to minimize catheter dwell time as well as the benefit of fast polymerizing embolic agents. In the largest published series of CPT undergoing embolization, Haliosos et al reported complications were seen in 20% and included seizure, intratumor hemorrhage, and asymptomatic stroke but none with permanent sequela [32].

Numerous case reports demonstrate that PPE can be safely executed to facilitate GTR. Because of the relatively high risk of mortality and morbidity associated with resection, PPE will likely continue to be liberally employed in the multidisciplinary management of CPT.

**Hemangioblastoma**

Hemangioblastomas (HB) are hypervascular tumors that comprise about 2.5% of central nervous system (CNS) neoplasms [39] and present most commonly in the posterior fossa and less commonly in the spinal cord and brainstem [40]. HB are more common in adults; however, childhood HB have 5-year survival rates greater than 95%.[40] About 20-43% of HB are associated with von Hippel Lindau disease, where multiple lesions are more common [41, 42, 40]. Multiple HB are associated with decreased overall survival (hazard ratio (HR) 1.715 $p < 0.001$) compared to solitary HB due to development of new lesions or regrowth of resected lesions [40]. The classic presentation on MRI is that of a cystic lesion of the posterior fossa with an enhancing mural nodule, but HB may present as solid lesions in 29% of cases [43]. Solid HB is an independent prognostic factor for poor patient outcomes [43, 44]. Unlike cystic HB where the cyst is internally decompressed to facilitate removal of the smaller solid and highly vascular component (i.e., the enhancing mural nodule), solid HB cannot be decompressed and are removed en bloc,[45, 44] making them appropriate candidates for PPE.

Support for PPE of HB in the literature is mixed. Historically, these tumors had a high mortality of 30%, although in later years this has been trending down to 20-24% [43]. Early reports demonstrating significant decreases in intraoperative blood loss,[26, 46] transfusion rates and operative times[47] support PPE in the treatment of HB. Other advantages include easier identification of the dissection plane[48] as well as the ability to accomplish GTR in patients whose initial operations were aborted due to blood loss [25-27, 49]. GTR is important because residual tumor was found to be the source of post-operative of hemorrhage [44]. These results have supported the use of PPE as an adjunct to surgical management [25, 26, 50]. However, a 2016 systematic review of 111 patients aged 12-72 years found that PPE was not associated with any operative benefit including increased rates of GTR, decreased blood loss, or decreased complications compared to 392 non-embolized controls. Moreover, it found significant procedural risks and discouraged use of PPE in the treatment for intracranial HB [51].

Post embolization complications of PPE are well reported, including non-target embolization resulting in cerebellar infarctions[52, 47, 53] and intracranial hemorrhage after embolization with onyx,[47] PVA,[52] nBCA,[46] and embospheres [27]. Interestingly, choice of embolic agent may be a factor. Cornelius noted that particles used for spinal HB are associated with lower rates of post embolization intratumoral hemorrhage than that for cerebellar HB, 5.6 vs 43% [27]. The authors cleverly hypothesized that the mechanism stemmed from cerebellar capillaries being larger than spinal cord capillaries so that embolic particles were inadvertently deposited on the venous side causing congestion and intratumoral rupture.

Other studies support PPE only in the setting complete devascularization [52]. However, this is a difficult task given that 100% complete devascularization in any series is rare, with rates ranging from 0-78% [26, 46, 47]. Other instances for declining PPE are when lesions are supplied by multiple small arterial pedicles or if the main supply can be easily ligated in the surgical approach [41]. In these cases, the risk associated with the procedure does not confer substantial surgical benefit. Some surgeons simply find it unnecessary for successful operative management [54, 34, 55]. Because HB comprise a small subset of primary CNS tumors, larger reviews like that by Ampie et al provide valuable insight into the efficacy of PPE.

There are two pediatric case series of hemangioblastomas in the cerebellum, brainstem, and spinal cord [56, 57]. In the largest and more recent, gross total resection was achieved in all 25 patients [57]. Only four of which underwent PPE for large solid HB. They reported a 4% rate of long-term surgical complications which consisted of a cervical cord HB patient with worsened sensory deficits without improvement at long term follow up. They reported short-term complications including lower cranial nerve dysfunction, worsened motor deficits, mutism, cerebrospinal fluid leak,

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and pneumonia, all of which recovered by 3 months. In their series, four patients underwent PPE for large solid HB without complications. Still, the authors acknowledge that PPE requires careful risk-benefit evaluation. Vougioukas et al also reported transient neurologic deficits including hemiparesis and cranial nerve IX and X paresis requiring tracheostomy but with no long-term complications. The majority of the work on PPE of HB has been reported in modest sized series composed predominately of adults [43, 26, 54, 45, 44, 53] and in small pediatric specific case reports [22]. These studies report a low rate of post-operative complications in children with a positive association of overall survival with younger age,[42] which has made the literature's equivocal support for PPE even more tenuous in the pediatric population.

**Juvenile Nasopharyngeal Angiofibroma**

According to the Kids' Inpatient Database, amongst 473 juvenile nasopharyngeal angiofibroma (JNA) treated in the United States from 1997-2016, no cases underwent PPE in 1997 but in 2006, two-thirds of all cases utilized PPE [58]. This practice pattern is surprising given that studies published as early as 1979 and 1984, respectively, noted benefit of PPE over surgery alone[59] and arterial ligation prior to surgery[60] in reducing intraoperative blood loss by more than half.

JNA are uncommon hypervascular tumors centered in the sphenopalatine foramen comprising 0.5% of all head and neck tumors [61]. They are found almost exclusively in young men (97.5%) and commonly present with nasal obstruction or epistaxis [62]. Similar to CPT and HB, operative management is challenging due to the high risk of significant hemorrhage, need to pre-emptively abort surgery leading to higher rates of residual tumor, and ultimately, disease recurrence due to incomplete extent of resection [28]. Tumors are typically supplied by the sphenopalatine branch of the internal maxillary artery and ascending pharyngeal artery. When the tumor extends into the sphenoid sinus or toward the cribriform plate, ethmoidal perforators arising from the ophthalmic artery and artery of the vidian canal arising from the petrous segment of the internal carotid artery will also supply the tumor [63].

Because JNA are supplied by external carotid artery (ECA) branches, complications may result from non-target embolization of the vasa vasorum of cranial nerves supplied by the petrosquamosal branch of the middle meningeal artery[64] or neuromeningeal branch of the ascending pharyngeal artery[63] which also anastomoses with the vertebral artery via the odontoid arcade [65]. The most feared complication is stroke[66] from dangerous ECA – internal carotid artery (ICA) anastomoses, which should be on the forefront of the neurointerventionalists mind during embolization [67, 68, 65]. Other complications stem from aggressive embolization of the superficial temporal artery, resulting in temporalis or scalp pain [59]. The highly redundant nature of the facial vascular supply means that super selective catheterization is required to achieve meaningful devascularization. Proximal embolization proves ineffective due to ready collateralization from the contralateral internal maxillary artery.

Overall, the literature supports the use of PPE as a surgical adjunct. PPE significantly decreases operative blood loss (385 vs 1215 ml $p<0.001$) and operative time (205 vs 266 min $p<0.064$) compared to non-embolized controls,[69] a finding echoed in multiple studies [70-72]. Gelfoam,[70, 71, 73] polyvinyl alcohol (PVA) particles with[74] and without coils[71] and liquid embolics[75] are commonly used agents. More aggressive techniques such as balloon assisted occlusion of the ICA to embolize inferolateral trunk pedicles can achieve high degrees of tumor devascularization [76] Figure 6 illustrates the use of ethylene vinyl alcohol copolymer in PPE of a right sided JNA. Direct puncture embolization has also been successfully employed[77] in combination with PPE [78]. Gao et al found that direct puncture significantly decreased intraoperative blood loss compared to transarterial particulate embolization. In short, there is role of PPE in the surgical management of JNA with a variety of intravascular agents available for one armed with a thorough understanding of the vascular anatomy and its potential pitfalls.

**Other tumors**

In addition to the three main pathologies discussed above, CPT, HB, and JNA, case reports of PPE abound in rare pediatric entities including: rhabdomysaroma,[79] acoustic neuroma,[80] cavernous angioma,[81] solitary fibrous tumor (hemangiopericytoma),[82] cranial giant cell granuloma,[83] and scalp hemangioma [84]. There is a relatively sizeable body of literature on PPE for meningiomas in adults, given that they comprise 34% of adult primary CNS tumors; however, they account for less than 5% of primary CNS tumor in children.

The use of PPE for meningiomas is less compelling than hypervascular lesions although significant decreases in estimated blood loss for skull base meningiomas less than 6 cm have been reported [85]. Taking on the added risk of PPE for what can be an otherwise relatively safe resection in terms of blood loss and intraoperative hemostasis requires careful consideration of the neurosurgical team's concerns, ECA supply, tumor location, presumed pre-

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operative diagnosis (meningioma vs solitary fibrous tumor (hemangiopericytoma)) and tumor size,[67] as oftentimes the surgical approach provides early access to the tumor's arterial supply since most meningeal feeders are superficial to the meningioma. PPE may be best suited for meningiomas of the skull base where dural supply arises deep and medial to the tumor. PPE may be utilized for convexity meningiomas as central devascularization results in softening of the tumor allowing the surgeon to separate tumor from cortex more easily and ligate pial branches supplying the tumor capsule [67].

Another pathology where PPE has been shown to play a role is in hemangiomas. While hemangiomas are considered slow flow non-surgical vascular lesions, in rare cases they can produce congestive heart failure refractory to medical management [84]. In these specific cases, surgeons may encounter increased blood loss and may elect for preoperative embolization. Figure 7 demonstrates an example of a scalp hemangioma that underwent preoperative embolization after the first attempt was aborted due to an unacceptable volume of blood loss. The versatility of PPE affords neurointerventionalists limitless applications when benefits outweigh the risks to assist surgeons dealing with hypervascular masses.

**Pediatric spinal cord tumors**

Since the introduction of the WHO classification of CNS tumors in 2016 and the latest version of 2021, new tumor groups are discovered and some tumor entities are abandoned. Most changes concern the brain tumors but several changes apply to pediatric spinal cord tumors.

Looking into the epidemiology, spinal tumors remain rare lesions. Of all CNS tumors, 0.5-1% are spinal tumors of which 35% are intrinsic. They present more frequently towards the end of the first and beginning of the second decade of life, but all age groups may be affected, without gender predilection.

The clinical presentation is often non-specific. Children usually present (very) late, with a long history of exacerbations and remissions of neurological symptoms including back pain due to the fluctuation of spinal cord edema. But red flags of possible spinal cord neoplasms include: progressive motor weakness, progressive scoliosis, gait disturbance, rigidity/paraspinal muscle spasm. Back pain is present in 25-30% of cases. Sensory deficits are less common, but vague, burning pain with paresthesia may occur. Important to note, 15% of children with spinal cord neoplasms may present with symptoms of increased intracranial pressure due to elevated CSF protein resulting in impaired CSF resorption, due to blockage of foramen magnum (cervical cord tumor) or subarachnoid tumor hemorrhage and subarachnoid seeding.

MRI is the primary imaging modality of choice for spinal cord tumors. The vast majority of lesions show contrast enhancement. Cysts are frequently seen in spinal tumors. Tumoral and non-tumoral "cysts" can be noted. Non-tumoral "cysts" are more at the poles of the solid tumor, can be produced by the tumor, do not enhance and can be a reactive dilatation of the central canal. Whereas tumoral cysts are within the tumor and show peripheral enhancement and should be resected.

Despite the new WHO 2021 classification, no drastic refinement of spinal cord subtypes is implemented. The majority of the spinal cord tumors are glial (90-95%) including pilocytic astrocytoma (60%), ependymoma (30%) and diffuse midline glioma H3K27 altered (<5%). Non-glial tumors account for 5-10%, of which multiple different tumors are to be considered like hemangioblastoma, ganglioglioma, neurocytoma, paraganglioma, metastasis, and lymphoma.

Glial spinal cord tumor

Based on WHO 2021 classification glioma of the spinal cord consist of pilocytic astrocytoma (histologically often with myxoid features), diffuse midline glioma, diffuse leptomeningeal glioneuronal tumor (DLGNT) and high-grade astrocytoma with piloid features.

As pilocytic astrocytoma is the most common spinal tumor in children, some imaging characteristics will be mentioned. In children the location is more rostrally compared to adults and commonly extending over a small number of segments, though total spinal cord pilocytic astrocytoma do occur.

In 50% of cases the location is at the cervico-(thoracic) level and in 20-40% tumor cysts (polar and intratumoral) are present, as well as syrinxes (caudal and rostral).

On imaging the tumor is difficult to separate from normal spinal cord tissue, they rarely show hemorrhage and often have an eccentric location and asymmetric expansion. A higher incidence of pilocytic astrocytomas are observed in NF1 patients.

Spinal ependymoma is the second most frequent spinal cord tumor, most frequently seen in the cervical cord. They are more centrally located and therefore present with sensory symptoms due to involvement of the spinothalamic

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tracts. In the WHO2021 classification 4 subgroups can be identified; spinal ependymoma (associated with NF2 mutation), spinal ependymoma MYCN amplified, myxopapillary ependymoma and spinal subependymoma.
On imaging, the tumor is typically centrally located in close proximity to the ependymal lining of the central canal, commonly present with polar cysts, tumor and less frequently with tumoral cyst. Small feeding vessels can be noted as well as strong enhancement. High vascularity may result in intra-tumoral and subarachnoid hemorrhage. Often a "cap sign", rim of hemosiderin at tumor poles due to hemorrhages can be seen. If the tumor is located at the conus medullaris and filum terminale, myxopapillary ependymoma is the most likely diagnosis, especially in a male child. The tumor is often polylobulated.
Also gliomas that commonly occur in the brain can rarely present in the spine, like PXA's, astroblastoma, MN1-altered and rosette-forming glioneuronal tumor.
Non-glial spinal cord tumors
Meningiomas do occur in the spine, most common clear cell meningioma due to SMARCE mutation. Of the mesenchymal, non-meningothelial tumors involving the CNS, hemangioblastoma is most common (1-7% of all spinal cord neoplasms), but chordoma and hemangioma can be seen. Typically, hemangioblastoma are intramedullary, with extension to intra- and extradural space and highly vascular. Prominent dilated feeding arteries and draining pial veins can be noted and they may present with subarachnoid hemorrhage or hematomyelia. Edema and cap sign may be seen. If a patient presents with multiple hemangioblastomas one has to rule out von Hippel-Lindau disease.
Embryonal tumors in the spine do occur but are rare. In the newest classification CNS tumor with BCOR ITD has rarely been described in the spinal cord.
Melanocytic tumors, like meningeal melanocytosis and melanomatosis, involve the leptomeninges and can potentially involve the spinal cord. Meningeal melanocytomas occur mostly in the cervical and thoracic spine. They can be dural based or associated with nerve roots or spinal foramina. Meningeal melanomas may occur throughout the neuroaxis, but, like melanocytomas, they show a predilection for the spinal canal and posterior fossa. A purely intraparenchymal location of a melanoma in the CNS is highly indicative of metastatic disease.
Metastases
Intramedullary metastases are rare, extramedullary and intradural metastases are seen more frequently. They do occur due to hematogenous (arteries) spread, direct extension from leptomeninges or through CSF-seeding (intracranial neoplasms). The most common CNS tumors with tendency to metastasize are embryonal tumors like medulloblastoma and atypical teratoid / rhabdoid tumor (ATRT), germ cell tumors and pineal gland tumors. Also glial tumors like ependymoma and astrocytoma can give drop metastases. Finally, choroid plexus tumors and pituitary gland adenoma (then called carcinoma). Also non-CNS tumors, like malignant rhabdoid tumors, chordoma and neuroblastoma may spread to the spinal canal.
In case of intramedullary metastasis, imaging will show nodular and irregular thickening of thecal sac, and coating of surface of cord. Nerve roots may be thickened and the lumbosacral region is most commonly affected. Contrast-enhanced sequences are mandatory and in case of suspected embryonal tumor intracranially, DWI and heavily T2 weighted 3D sequence can be added. Preferably, staging has to be performed preoperatively.
Non-described spinal tumors in WHO 2021
Some spinal cord tumors are not yet classified in the WHO 2021, either as tumor entity or as location in the spine. Examples are gliofibroma with FGFR1 tyrosine kinase domain duplication (TKDD) which has never been described, or pediatric type high grade glioma, H3 and IDH wildtype of which location in the spine is not yet described.
Differential diagnosis
Several non-neoplastic diseases, like transverse myelitis, multiple sclerosis, acute disseminated encephalomyelitis (ADEM), Devic disease, Erdheim Chester/ juvenile xanthagranuloma as to be considered within the differential diagnosis of primary spinal cord tumors. Also, vascular abnormalities, like AV-fistula is part of the differential diagnosis.

**Future of image guided minimally invasive neurosurgery in pediatrics**

Advances in MRI imaging have led to novel treatment approaches for children with CNS tumors. Stereotactic laser ablation (SLA) has emerged as a promising, minimally invasive neurosurgical technique for treating tumors located in challenging deep locations of the brain, where traditional open surgery entails the potentially increased risk of corridor and access related morbidity. Adult patients with recurrent glioblastoma multiforme comprised the cohort initially treated with SLA, but the indications have expanded over the last several years to include other grades of

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adult glioma, metastatic lesions, and a variety of pediatric brain tumors [86-90]. Two systems are currently in clinical use, and are FDA approved: the Visualase system, in 2009 (Medtronic), and NeuroBlate, in 2013 (Monteris). Significant progress in MRI thermometry facilitated the practical use of laser ablation in patients. The advantages of this minimally invasive MRI-based neurosurgical approach include obviating the need for large incisions and craniotomy, and any associated shaving of hair, enabling easy and less traumatic access to deep seated and remote regions of the brain that previously would have required exposure by open microsurgery, with all the inherent risk, shorter length of hospital stay, and enhanced overall patient experience. More recently, this technique has been used to ablate epileptogenic lesions in the brain, as an alternative to open resection [91, 92]. Although this technique is being used with increasing frequency at many centers, the published literature on laser ablation to date is limited to small retrospective series demonstrating safety and efficacy. Therefore, prospective clinical trials are needed to elucidate the optimal indications for SLA in the clinical setting.

Another recent novel neurosurgical intervention, also based on MRI guidance, is high intensity focused ultrasound, a completely non-invasive technology that utilizes ultrasound energy to target deep lesions in the brain. Insightec's focused ultrasound system was FDA approved to treat essential tremor (2016) and tremor-dominant Parkinson's disease (2018) [93-95]. Several clinical trials are underway examining its role in the management of brain tumors, epilepsy, and other functional neurological conditions.

**Conclusion**

There have been significant advances in the imaging of the central nervous system. The results of these imaging tests can provide relative information that influences subsequent treatment decisions. The recent technological advances in these modalities provides the neurosurgeon or neuro-oncologist with the most comprehensive images to share with the family, treatment team and provide the most current treatment for a particular pathology. These advances in technology have changed how we treat brain tumors with laser ablation therapy and focused ultrasound therapy.

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**Figure legends:**

**Figure 1:** A 2-year-old with medulloblastoma demonstrating homogeneous enhancement centered in the fourth ventricle on axial T1W+C image (a) and elevated rCBV on DSC perfusion (b).

**Figure 2:** An 18-month-old with embryonal tumor with multilayered rosettes (ETMR) in the right parietal lobe without contrast enhancement on T1W+C imaging (a) but with elevated Ktrans (b) and Kep (c) from DCE imaging.

**Figure 3:** A 27-month-old with ATRT centered in the pineal region seen on T2W imaging (a) and demonstrates heterogeneous CBF with scattered areas of elevated CBF from ASL perfusion imaging (b).

**Figure 4:** A 14-year-old female with recurrent medulloblastoma. Sagittal and axial 3D T1 postcontrast at multiple time points. Preoperative MRI (a, top row) demonstrated enhancing mass lesion along the inferior left margin of the historical resection cavity consistent with recurrent neoplasm. After initial resection, intraoperative MRI (b, top middle row) demonstrated small residual enhancing neoplasm at the site of the original neoplasm. Patient was immediately returned to the operating room for repeat resection. Repeat intraoperative MRI (c, bottom middle row) post repeat resection demonstrated gross total resection. Note that the minimal linear T1 hyperintense signal along the margins of the resection were benign postsurgical in nature. Postoperative MRI (d, bottom row) performed the following day confirms gross total resection.

**Figure 5:** 3D tractography with a sagittal brain surface (a) and graph visualization of the pre-surgical PFS network (b), showing the connectome of patients with PFS. Depicted white matter tracts with decreased connectivity in PFS vs. patients with intact language include the corpus callosum, right corticothalamic pathway, and right corticostriatal pathway.( Meoded A, Jacobson L, Liu A, et al. Diffusion Tensor Imaging Connectomics Reveals Preoperative Neural Connectivity Changes in Children with Postsurgical Posterior Fossa Syndrome. J Neuroimaging 2020;30:192-197 )

**Figure 6:** AP (a) and lateral (c) digital subtraction angiographic (DSA) views of the right ECA before embolization. Post embolization AP (b) and lateral (d) views of the right ECA after 255-350 micron PVA particle and ethylene vinyl alcohol copolymer (Onyx 18) embolization of the sphenopalatine and descending palatine branches of the right internal maxillary artery.

**Figure 7:** Lateral left ECA DSA pre (a) and post (b) embolization of a left temporal scalp hemangioma using 20% n-Butyl cyanoacrylate (nBCA) dilated with lipiodol. The embolic cast is visualized on the unsubtracted lateral view (c) and at the margin of the operative field (white arrow, d).

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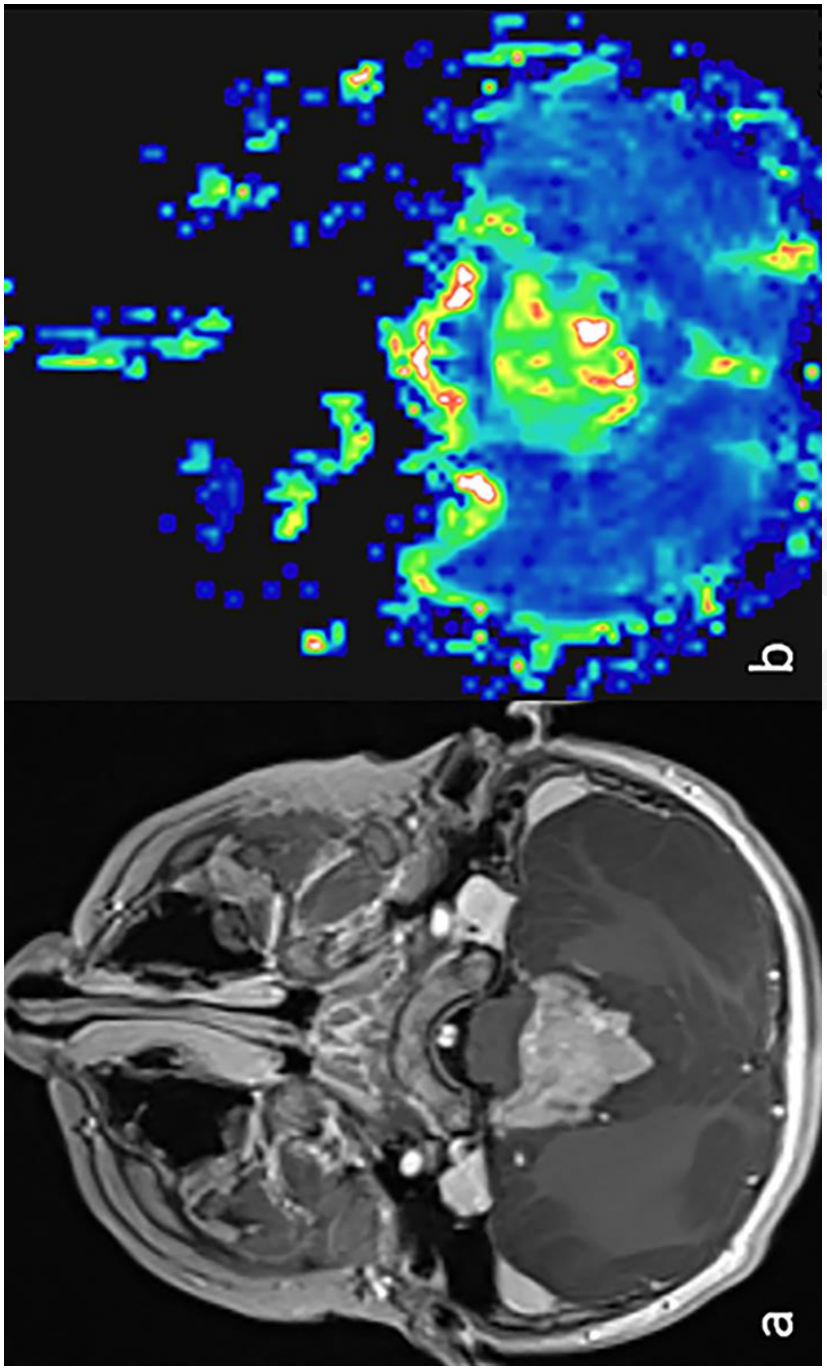


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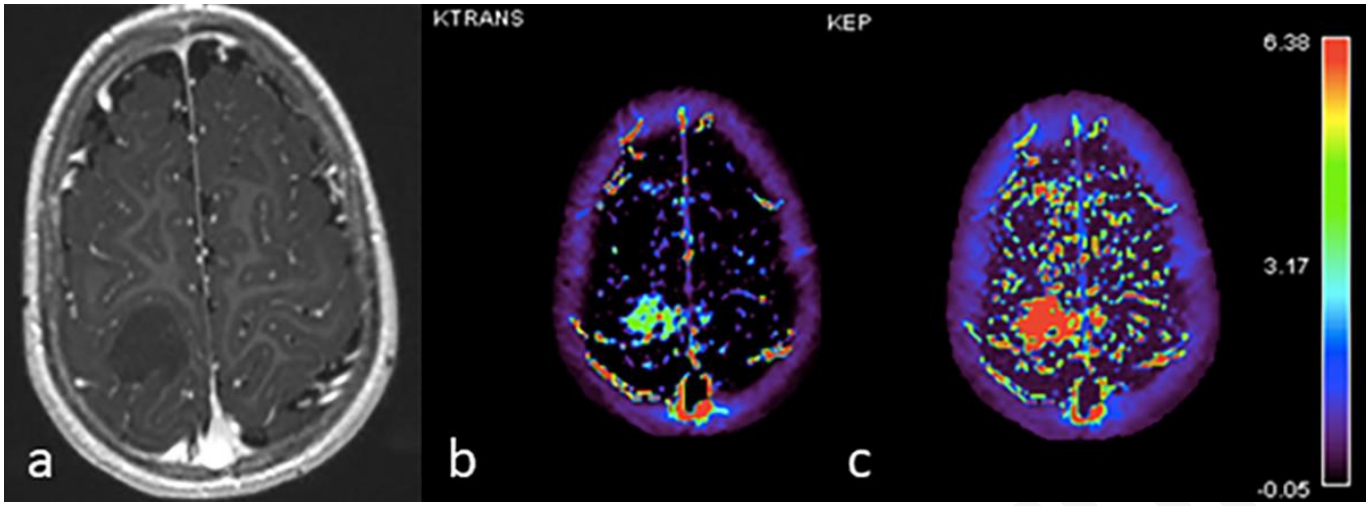


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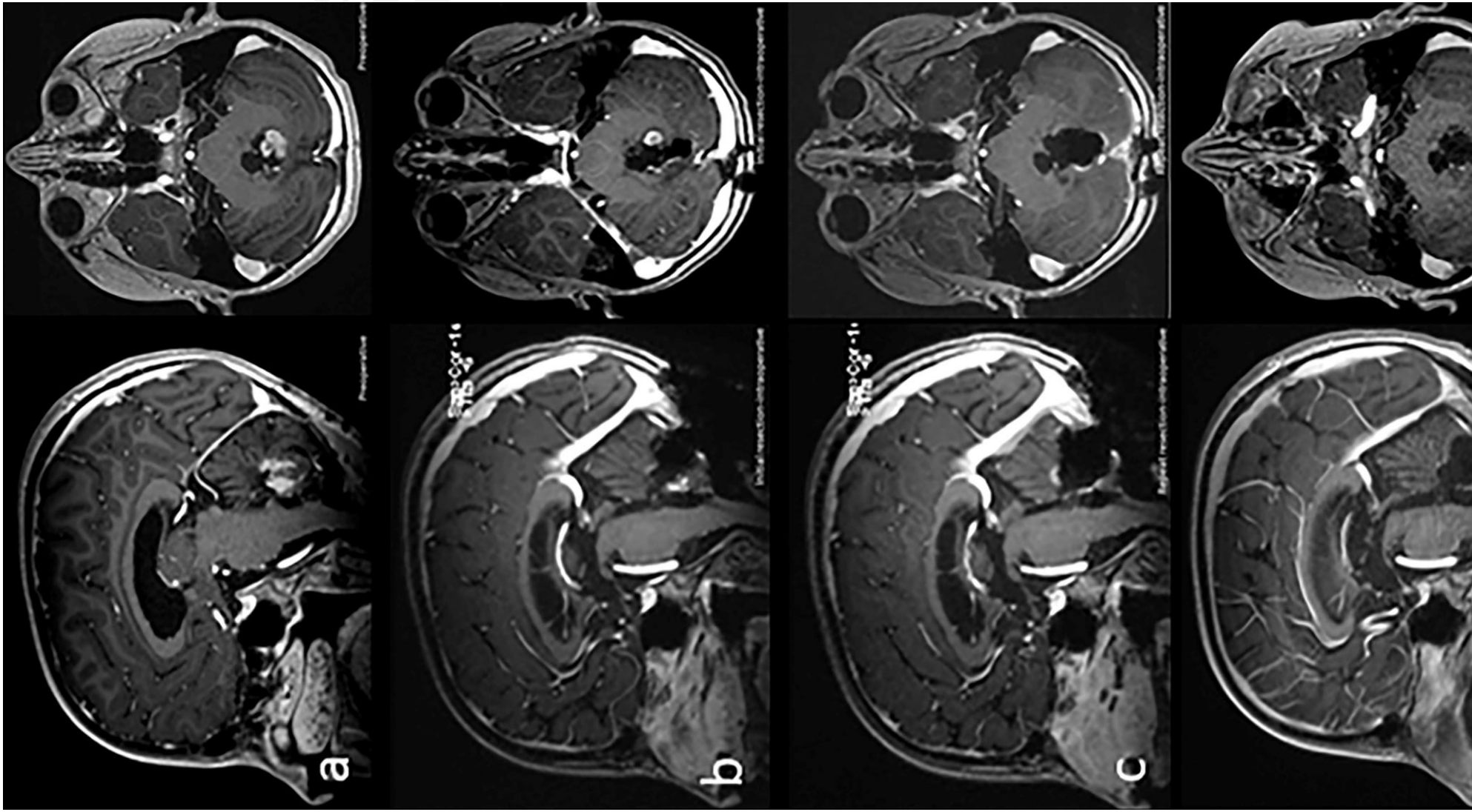

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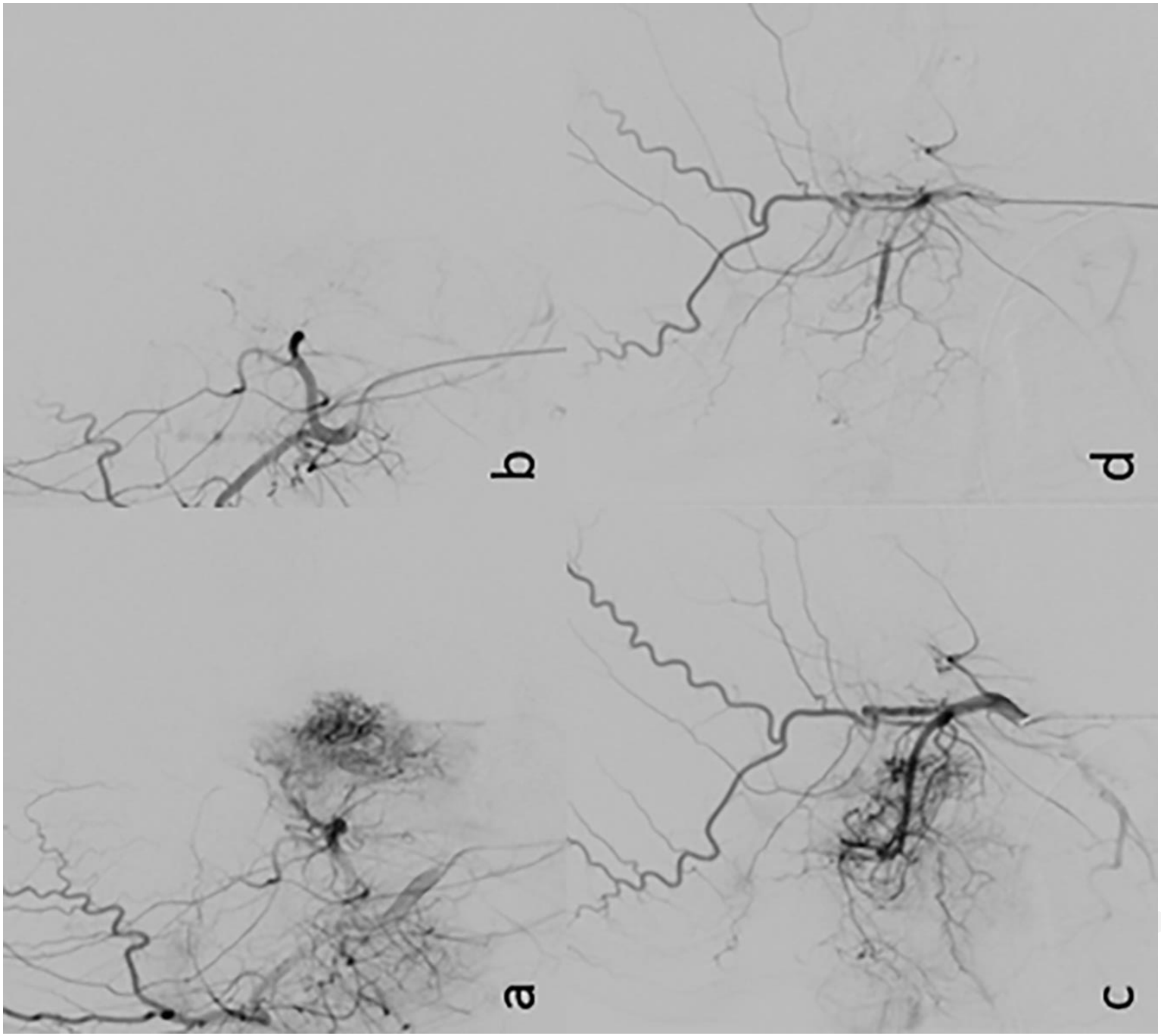

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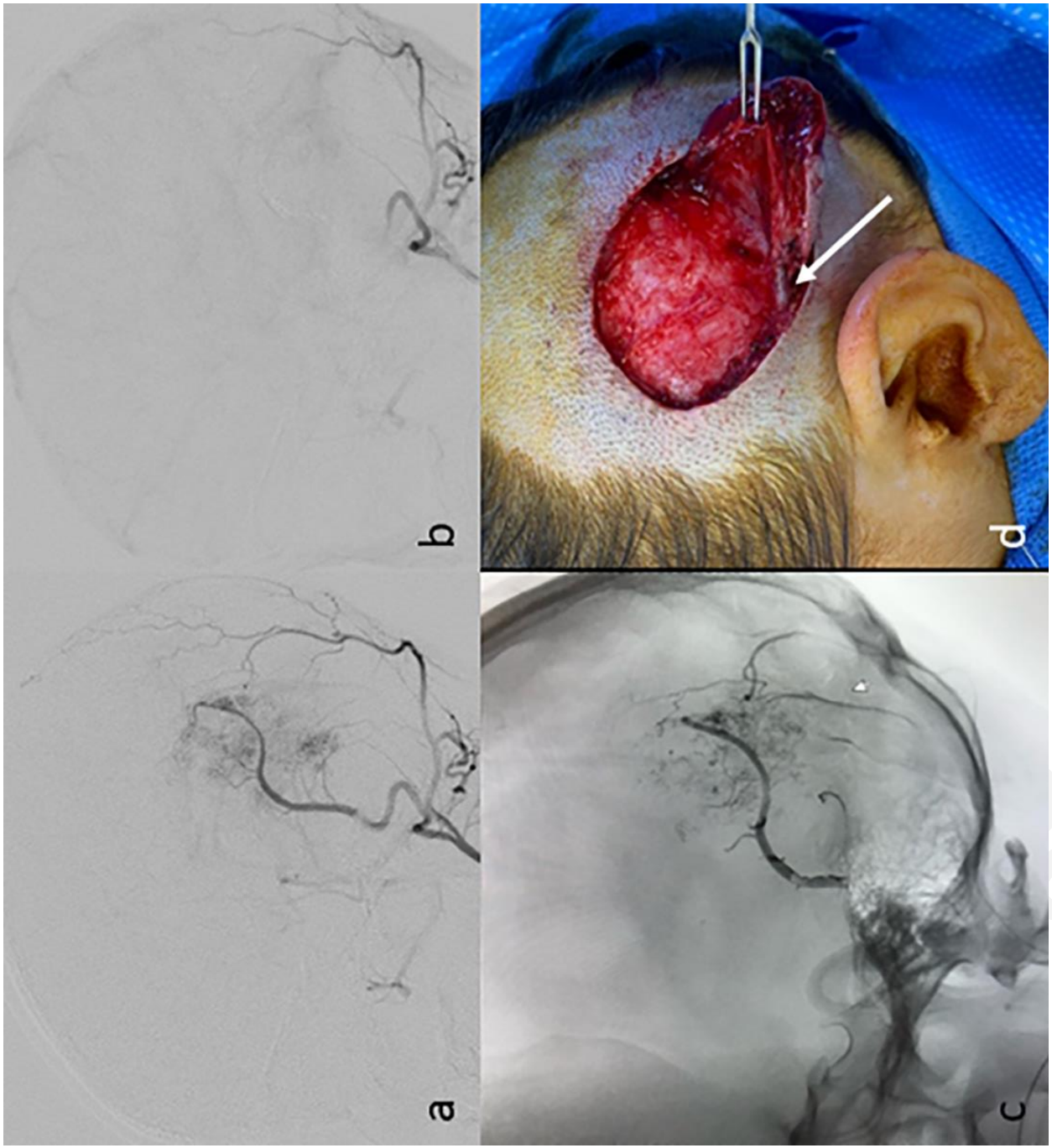

| Metabolite | ppm | Marker | Increased | Decreased | Importance in Brain Tumor Imaging |
|---|---|---|---|---|---|
| **N-acetyl aspartate (NAA)** | 2.0 | Marker of Neuronal Viability | | High grade gliomas<br>Radiation necrosis<br>Metastases<br>Lymphoma | Grading of gliomas<br>Distinguishing gliomas from metastases |
| **Creatine (Cr)** | 3.0 | Marker of Energy Metabolism | | High grade gliomas<br>Necrosis | Grading of gliomas<br>Distinguishing metastases from Glioblastoma |
| **Choline (Ch)** | 3.2 | Marker of Cellular Turn over | Neoplasms<br>Inflammation | Necrosis | Grading gliomas<br>Distinguishing glioblastomas from metastases<br>Differentiating tumor progression versus pseudo-progression/ Radiation necrosis |
| **Lactate** | 1.33 inversion at intermediate TE | Marker of Anerobic Metabolism | Glioblastoma<br>Abscesses | | Grading of gliomas |
| **Lipids** | 1.3 | | Glioblastoma<br>Abscess<br>Lymphoma | | Grading of gliomas |
| **2-Hydroxy glutarate (2-HG)** | 2.25 | | IDH-1 positive tumors | | Detection of IDH-1 positive tumors |
| **Myo-Inositol** | 3.5 | | Low grade gliomas<br>Progressive multifocal encephalopathy (PML) | High grade gliomas | Grading of gliomas |

**Table 1. Magnetic resonance spectroscopy findings in brain tumor imaging**

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