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Advanced imaging techniques in the diagnosis of Atypical Teratoid Rhabdoid Tumor in pediatric patients

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Abstract

Atypical Teratoid Rhabdoid Tumor (AT/RT) is a highly invasive malignant embryonal tumor that is characterized by its low survival rate among pediatric patients. AT/RT spreads through the cerebral spinal fluid (CSF) and white matter tracts (WMTs) to other parts along the brain. Due to its rarity, AT/RT affects only a small number of pediatric patients, therefore studies on the tumor have been limited. While standard Magnetic Resonance Imaging (MRI) techniques offer valuable insight to characterize and detect AT/RT, incorporating advancing imaging techniques such as Diffusion Weighted Imaging (DWI), Diffusion Tensor Imaging (DTI), MR Spectroscopy (MRS), and Perfusion Weighted Imaging (PWI) significantly improves diagnostic accuracy, facilitates early detection of tumor spread, and overcomes the limitations of standard imaging techniques. This paper examines and provides clinical recommendations on how advanced imaging techniques can be used with standard imaging techniques to diagnose AT/RT and identify recurrence in pediatric patients. Additionally, this paper proposes that artificial intelligence (AI) powered Machine Language algorithms be used to statistically recreate DWI, DTI and PWI from conventional MRI scans for use in resource-constrained healthcare settings so as to diagnose AT/RT as well as to distinguish between AT/RT and other brain tumors. It also proposes creation of synthetic pediatric MRI images from adult MRI counterparts so as to expand pediatric MRI image database paucity. Genetic and epigenetic approaches to further improve detection and treatment of AT/RT are also discussed.

Keywords

Atypical Teratoid Rhabdoid Tumor, White Matter Tracts, Cerebral Spinal Fluid, Diffusion Weighted Imaging, Diffusion Tensor Imaging, MR Spectroscopy, Perfusion Weighted Imaging, Artificial Intelligence, Epigenetics, Pediatric patients

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1. Introduction

Atypical Teratoid Rhabdoid Tumor (AT/RT) is a rare aggressive embryonal tumor that is commonly found in pediatric patients aged three and under (1). Embryonal tumors are characterized by the uncontrolled growth of cells that are left over from fetal development (2). Common symptoms of AT/RT include headaches, loss of balance, increased head size for pediatric patients, vomiting, and changes in activity levels (3). According to the World Health Organization (WHO) grading system, brain tumors can be organized into four grades. Grade 1 tumors are the lowest grade version of a tumor and are usually intervened through surgery. Grade 4 tumors are the most malignant and usually require aggressive forms of therapy to mitigate their detrimental effects (4). AT/RT are WHO grade 4 tumors, classifying them as extremely invasive and fast-growing (3).

Classified as an embryonal tumor, AT/RT spreads through the cerebrospinal fluid (CSF) to other parts of the brain and the spinal cord (2). Hence, patients often need emergency treatment of intracranial hypertension or hydrocephalus until doctors can surgically decompress the tumor (1). Additionally, AT/RT has the potential to dissect and invade White matter tracts (WMTs), using them as pathways to spread to other areas of the brain (5).

The prognosis of AT/RT in pediatric patients is severe, with a median overall survival (OS) rate of 6-11 months (6). The 5-year survival rate for children with AT/RT is 50%, though this varies based on the patient's age. Children under 3 years of age, especially those with advanced disease spread, tend to have the poorest prognosis (7). Compared to other tumors, AT/RT requires more aggressive forms of therapy, which is uncommon for most other types of pediatric tumors. Additionally, stem cell transplant, a type of treatment for high-grade tumors, is preferentially used in cases of AT/RT (8).

AT/RT represents a subsection of a group of tumors known as rhabdoid tumors. Rhabdoid tumors are aggressive tumors commonly seen in pediatric patients and distinguished by mutations in the tumor suppressor gene SMARCB1/INI1/hSNF5 (9). AT/RT is correlated with a loss of SMARCB1 located on chromosome 22q. It is less frequently related to the deletion of the SMARCA4 gene, which is also a tumor suppressor gene that is involved in the remodeling of chromatin. Disruption to the chromatin remodeling factors is known to change the transcription process into a cancerous state (6). AT/RT can originate anywhere in the Central Nervous System (CNS) and are most seen in the cerebrum and cerebellum. Since AT/RT affects different genes when compared to similar tumors, treatment for AT/RT requires a specific regimen for pediatrics with the tumor, especially when focusing on epigenetic therapy. Failure to appropriately diagnose AT/RT has been shown to result in significantly worse outcomes for patients (10)

The current standard of care for patients with AT/RT includes surgery, chemotherapy, and radiation therapy (multimodality therapy) (3). Imaging modalities such as Magnetic Resonance Imaging (MRI) are also used to assist with the diagnosis of brain tumors. Imaging is a non-invasive method of visualizing the tumor and related edema (11). The current protocol for standard imaging includes 3-dimensional (3-D)

T1 weighted (T1) imaging, 3-D gadolinium contrast-enhanced T1 (T1C) weighted imaging, gadolinium contrast enhanced T2 weighted imaging, and FLuid-Attenuated Inversion Recovery (FLAIR), which are performed on a minimum 1.5 Tesla MRI (11) (Figure 1).

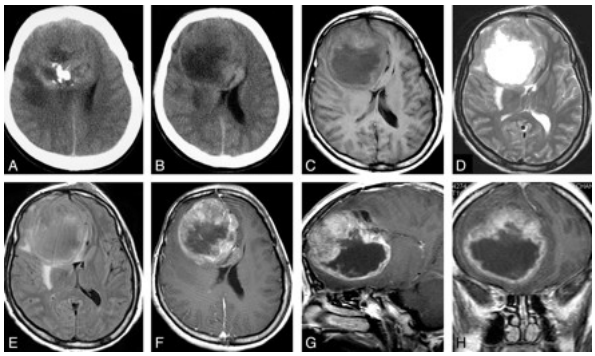

Figure 1. A. a T1-weighted MR image, shows a necrotic area. This necrotic area is hypointense, and the solid area is isointense. **D**. T2-weighted MR image, shows a hyperintense cystic area and an isointense solid area. **E**. FLAIR MR image, demonstrates isointense and hyperintense signal intensity with mild peritumoral edema.

Despite the use of standard MRI protocols, accurate differentiation of AT/RT from other pediatric brain tumors remains difficult. Identifying early recurrence can be challenging with conventional imaging alone. Contrast agents, for example, provide critical diagnostic information, but can also increase the risks of Nephrogenic Systemic Fibrosis (NSF) in patients with preexisting kidney issues, limiting their use in children with renal complications (12). In addition, there are limited studies of standard MRI techniques and AT/RT due to the rarity of the tumor and lack of biopsies for analysis (13).

Due to AT/RT's overlapping radiologic features with other tumors such as medulloblastoma, ependymomas, and even less common conditions such as gliomas, clinicians often face difficulty distinguishing it from more prevalent pathologies (14). Recently, there has been growing interest in using advanced imaging techniques to supplement diagnosis and research in various types of brain tumors, as they can increase diagnostic accuracy (15).

To address these gaps, this review proposes the use of advanced imaging techniques – Including Diffusion Weighted Imaging (DWI), Diffusion Tensor Imaging (DTI), Magnetic Resonance Spectroscopy (MRS), and Perfusion Weighted Imaging (PWI) – for initial diagnosis and early detection of recurrence. Additionally, this review also examines emerging research into artificial intelligence (AI) and epigenetics, and their potential to improve the detection and treatment of AT/RT.

2. Methods

A literature review was performed using the key phrases "Atypical Teratoid Rhabdoid Tumor" and "MRI." More specifically, phrases such as "Standard Weighted imaging," "Diffusion weighted imaging," "Diffusion Tensor Imaging," "MR spectroscopy," "Perfusion weighted imaging," and "AI technology in

MRI" were used to narrow available data to specific MRI techniques. This review focused on pediatric studies; however, adult population studies were also used due to a lack of pediatric information for some diagnostic measures. Databases were searched for articles from PubMed and Google Scholar from February 2025 to September 2025. Articles from alternative sources (Radiopedia, Mayoclinic, NEJM, AJR) were also included. Papers that were published before 2005 were omitted, and papers that examined Atypical Teratoid Rhabdoid Tumor specifically on the spinal cord were also excluded due to a lack of relevance. Furthermore, this review only used articles that were written in the English language.

3. Discussion

3.1 Diffusion Weighted Imaging (DWI) and Diffusion Tensor Imaging (DTI)

DWI is sensitive to microstructural changes such as shifts in water molecules from extracellular to intracellular spaces, restriction of cell membrane permeability, cellular density, and a disruption of cellular membrane depolarization, all of which are associated with malignant tumors (14). AT/RT may spread through the CSF, and a key property of DWI is being able to track the diffusion of the spinal fluid to determine diagnosis or tumor progression.

DWI uses a computational b-value to determine the degree of diffusion sensitivity. A higher b value increases sensitivity to restricted diffusion, making it easier to detect highly cellular regions such as tumors (15). Additionally, DWI generates an Apparent Diffusion Coefficient (ADC) map, which provides quantitative measurements of water diffusion, helping differentiate between normal and pathological issues (16). The ADC value is found using MRI data acquired with specific b-values.

DTI builds upon DWI by measuring not only the diffusion of water molecules in tissues, but specifically the direction of diffusion in WMTs in the brain. DWI provides detailed information about the directionality and integrity of neural pathways, allowing for better visualization of the WMTs (17).

An extension of DWI, DTI, has been used to further evaluate brain tumors in WMTs. DTI uses the Fractional Anisotropy (FA) value, which is a scalar value from 0 to 1 that characterizes the diffusion of water molecules. A FA value of 0 implies that the water directionality is isotropic, meaning that water molecules diffuse equally in all directions. A FA value of 1 implies that the water diffusion is anisotropic, or the water molecules diffuse exclusively in one direction (18). A higher FA value suggests organized axonal fibers, dense myelination, and coherent fiber orientation (19). A lower FA value indicates demyelination, axonal loss, or crossing fibers, all of which can correspond to a brain tumor (20). The FA value that is calculated by using equation 1.

$$FA = \sqrt{\frac{(\lambda_1-\lambda_2)^2+(\lambda_1-\lambda_3)^2+(\lambda_2-\lambda_3)^2}{2(\lambda_1^2+\lambda_2^2+\lambda_3^2)}} \qquad \text{(eq.1)}$$

where λ_1, λ_2 and λ_3 are the diffusion tensor eigenvalues. DTI also uses a Mean Diffusivity (MD) value, which is a scalar value used to measure the average magnitude of water diffusion within a tissue regardless of the directionality of diffusion (21). A higher MD value is associated with pathological changes such as multiple sclerosis, Alzheimer's disease, traumatic brain injuries, or Creutzfeldt–Jakob disease (22). The MD value is calculated using the equation, $MD = (D_{xx}+D_{yy}+D_{zz})/3$ (eq.2), where D_{xx}, D_{yy}, and D_{zz} are the three diagonal elements of the 3x3 diffusion tensor matrix. They quantify the diffusion coefficients along the left-right (x), anterior-posterior (y), and superior-inferior (z) directions, respectively, in the scanner's reference frame.

Tractography is another form of DTI that can be useful in diagnosing AT/RT. Tractography is a computational method used in DTI to visualize and model the WMTs of the brain (23). A key characteristic of AT/RT is that it spreads through WMTs. For this reason, DTI can be useful beyond conventional imaging to diagnose and determine recurrence for AT/RT because of its added anatomical analyses.

Since AT/RT is known to spread through the WMTs of the brain and via the CSF, DWI and DTI can be useful to diagnose AT/RT in pediatric patients. DWI typically shows hyperintense signal intensity in pediatric patients, and a hypointense signal intensity on ADC images, which indicates restricted diffusion for the tumor (24). Medulloblastoma can often be confused with AT/RT due to many similar pathological features, such as small round blue tumors, necrosis, being hyperdense, and showing restricted diffusion on DWI (24) (Figure 2).

However, AT/RT and Medulloblastoma can be distinguished apart with the ADC value. AT/RT has a lower ADC value when compared to Medulloblastoma (25). Moreover, DWI was able to detect leptomeningeal dissemination, a common feature of AT/RT, since tumor deposits along CSF pathways exhibit restricted diffusion (26).

When compared to traditional MR imaging, DWI demonstrated a 96% accuracy rate in detecting an embryonal tumor relapse for lesions, which is significantly greater compared to standard MR imaging techniques, which were able to detect a relapse 77% of the time (27). The findings suggest that DWI should be integrated into routine surveillance protocols for embryonal tumors, extending its application beyond initial diagnosis to longitudinal monitoring of tumor infiltration and treatment response. This could optimize therapeutic strategies by providing real-time insights into cellular changes and disease progression, ultimately improving long-term patient outcomes.

DWI is able to differentiate between visible tumor tissue and radiation necrosis; i.e., necrosis caused by radiotherapy; which a task standard MRI technique may not be able to classify as accurately (28). Compared to DWI, however, DTI was able to provide a better diagnosis due to its characterization of WMTs. As part of DTI, FA mapping was able to differentiate AT/RT from other more common brain tumors by highlighting areas of anisotropy loss near the tumor margins or areas with associated infiltrated WMTs (29).

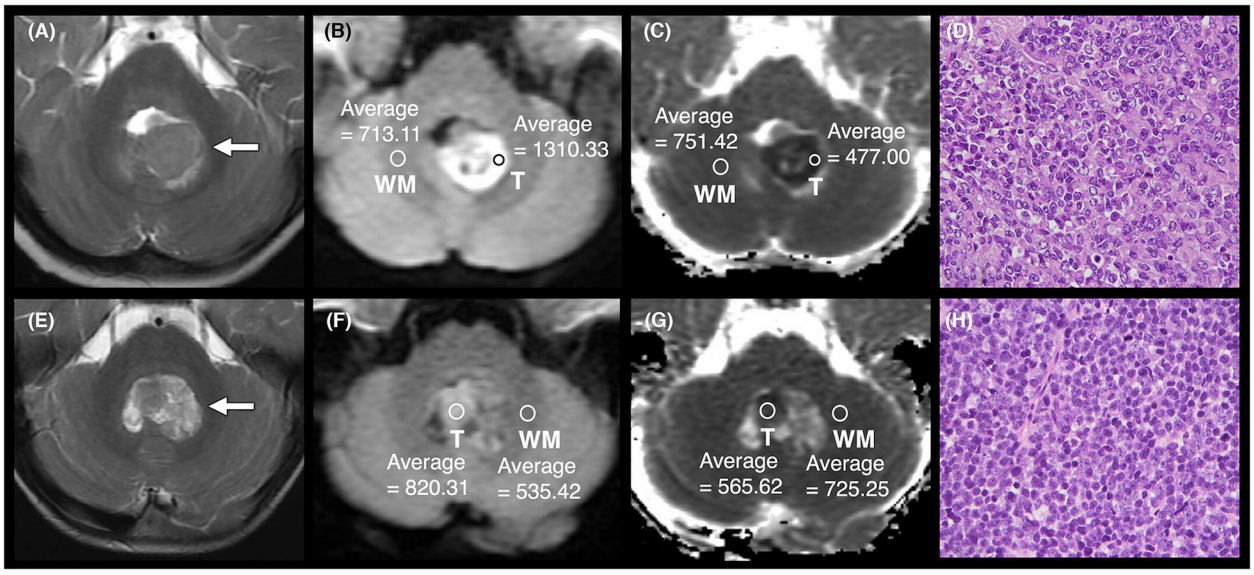

Figure 2. A-D. depict a pediatric patient with AT/RT under a DWI scan. **E-H.** show a pediatric patient with medulloblastoma under a DWI scan. Both images showed similar imaging features on a T2W scan. AT/RT **(A-D)** depict tumor cells that had a prominent nucleolus. Medulloblastoma shows tumor cells with small blue round cells.

These advanced imaging techniques can assist physicians in surgery and in determining further treatment. DTI is useful in surgical navigation because it is able to reconstruct 2D/3D maps of critical WMTs, enabling surgeons to identify their proximity to tumors (30). In AT/RT cases, tumors may push WMTs aside rather than infiltrate them, allowing the surgeons to navigate around displaced tracts. It has been noted that multiple surgical plans were adjusted after DTI revealed unexpected tract proximity to tumors, hence reducing the risk of motor or sensory iatrogenesis (30). Given these findings, DTI may help guide more personalized surgical planning in AT/RT patients.

AT/RT tumors are often located in vital brain regions, such as near motor pathways or optic radiations. Tractography allows surgeons to identify and map key WMTs, such as the corticospinal tract or geniculo-calcarine tract, ensuring that these critical areas are preserved during surgery (31). In addition, AT/RT tumors often cause edema or hemorrhage that can distort WMTs. Tractography helps visualize these changes and in adapting surgical plans accordingly (32).

However, DWI and DTI do have limitations when determining the diagnosis for AT/RT. For example, AT/RT often contains intratumoral hemorrhage (47% of cases) and necrosis, which can distort ADC measurements and mimic other tumors on DWI (25). Additionally, although DWI can distinguish AT/RT from medulloblastoma and other high-grade tumors, it is not correct 100% of the time. Both tumors exhibit restricted diffusion on DWI with hyperintensity and similar ADC values. For example, AT/RT (mean ADC: $0.55 \pm 0.06 \times 10^{-3}$ mm^2/s) and medulloblastoma (mean ADC: $0.47 \pm 0.16 \times 10^{-3}$ mm^2/s) show no statistically

significant difference in ADC values (33). Overall, DWI and DTI offer valuable tools for improving the diagnosis, differentiation, and overall survival of AT/RT in pediatric patients, particularly in cases where conventional MRI lacks specificity and sensitivity.

3.2 MR Spectroscopy

MR Spectroscopy (MRS) detects and quantifies biochemical changes in tissues by analyzing specific metabolites. Unlike MRI, which provides only anatomical details, MRS offers a molecular-level view by revealing the biochemical composition of tissues. An added advantage of MRS is that it does not require any contrast agent, which can be especially harmful for pediatric patients (34).

Some of the most common metabolites are choline, N-acetyl-L-aspartic acid (NAA), creatine (Cr), Lactate, Lipids, and myoinositol, among others. Elevated levels of choline, lactate, and lipids, combined with decreased NAA and creatine, form a metabolic signature characteristic of AT/RT. Higher levels of choline are associated with tumoral development, progression, and high-grade tumor malignancy (35). A characteristic of AT/RT is its cellular proliferation, which can be measured by analyzing choline levels. When choline levels are distinct, physicians can differentiate between AT/RT and other high-grade tumors such as medulloblastomas (36).

NAA is a metabolite that is used to assess neuronal integrity. Low levels of NAA are associated with tumor cells because these cells replace neurons as they start to deteriorate (34). AT/RT tumors consist primarily of poorly differentiated cells rather than neurons. As a result, they lack the neuronal components necessary for producing NAA. AT/RT tumors are highly aggressive and infiltrating, leading to the destruction or displacement of normal neuronal tissue. This results in significantly reduced or absent NAA levels in affected regions (34).

Creatine levels are associated with energy levels and are typically reduced in cases of AT/RT (36). This is why symptoms of tiredness and lethargy are often reported in pediatric cases of AT/RT (37).

MRS is also able to detect high levels of lactate and lipids, which can be indications of necrosis and anaerobic metabolism within the tumor. Additionally, these metabolites are extremely common to be seen in short TE MRS scans (36). Lactate is rarely seen in healthy brain tissues, and its elevation is typically associated with high-grade tumors, making it a valuable marker for malignancy. Elevated lipid levels are linked to cell necrosis or hypoxia (35), which are common in many high-grade tumors, including AT/RT. This is because the mutation of the SMARCB1 gene disrupts the SWI/SNF chromatin remodeling complex. The disruption in the chromatin remodeling complex leads to dysregulation, uncontrolled cell growth, and poor differentiation (38).

Minimal levels of myoinositol peaks have also been associated with AT/RT. This is important as the low amount of these peaks can be a differentiating factor between AT/RT and glial tumors, another common grade 4 tumor (36). Additionally, the the Cho/NAA ratio is increased in AT/RT, often showing increased values than those seen in other high-grade

tumors like medulloblastomas or glioblastomas (39). The Cho/Cr can also be used to differentiate AT/RT from other high-grade tumors; however, this ratio often overlaps with some tumors, requiring additional markers for a definitive diagnosis (40).

Lipid and lactate peaks are commonly observed in AT/RT due to necrosis and anaerobic metabolism within the tumor. These peaks are less common in some other high-grade tumors such as medulloblastomas (39)

MRS can also be used to differentiate between recurrence and radiation injury. For example, elevated Cho/NAA ratios are indicative of tumor recurrence due to increased cellular proliferation and membrane turnover in active tumor tissue. On the other hand, lower Cho/NAA ratios suggest radiation necrosis, reflecting reduced neuronal integrity and metabolic activity (41). High Cho/Cr ratios are associated with tumor recurrence, while lower ratios favor radiation necrosis. A reduced NAA/Cr ratio can be indicative of radiation injury, since NAA is a marker of neuronal health (40).

However, there are some factors that can limit the reliability of MRS findings. MRS data can be affected by motion artifacts, magnetic field inhomogeneities, and other technical challenges, which may limit its reliability in diagnosing AT/RT. Moreover, MRS is more time-consuming compared to conventional imaging techniques, which can be a drawback in urgent clinical scenarios such as suspected cases of AT/RT (42).

MRS is particularly valuable in AT/RT diagnosis because of its unique metabolic measurement profile, elevated choline, lactate, and lipids alongside reduced NAA and creatine, which distinguishes it from other pediatric brain tumors (43). These patterns highlight the potential of MRS as a non-invasive tool for early diagnosis, tumor characterization, and treatment planning in AT/RT.

3.3 Perfusion Weighted Imaging

Perfusion weighted imaging (PWI) is an imaging technique that measures the flow of blood through brain tissues to assess perfusion and vascular characteristics (44). There are several subtypes of PWI techniques. Dynamic susceptibility contrast MRI (DSC-MRI) uses gadolinium-based contrast agents to track changes in signal intensity as the contrast bolus passes through the brain, estimating parameters such as relative cerebral blood volume (rCBV). Dynamic contrast-enhanced MRI (DCE-MRI) also uses contrast but focuses on vascular permeability rather than blood volume (45). The rCBV value can be useful to determine malignancy and depict AT/RT and support diagnosis. These tumors often exhibit increased angiogenesis, which contributes to higher perfusion values. This vascular signature helps distinguish AT/RT from less aggressive lesions and may also provide prognostic information.

AT/RTs often exhibit increased vascularity. Perfusion imaging quantifies rCBV, which reflects blood volume in tumor tissue. Elevated rCBV values correlate with tumor angiogenesis, or the growth of new blood cells that supply the tumor. Elevated tumor vascularity can help differentiate AT/RT from more benign or lower-grade tumors (46).

AT/RT and medulloblastoma may appear similar on conventional MRI; however, perfusion metrics, like rCBV, can assist in differentiating between the two. For example, AT/RT's higher cellular density and necrosis may alter perfusion patterns compared to other embryonal tumors (25). Moreover, rCBV lesion volumes can be used to guide professionals in therapeutic intensity, as higher rCBV lesion volumes are associated with poorer outcomes in high-grade tumors (47).

The rCBV value can also be used to distinguish between pseudo-progression and recurrence. Elevated rCBV values (>2.6) are indicative of increased angiogenesis and active tumor progression. This reflects the higher vascular density in recurrent tumors. Lower rCBV values (<0.6) suggest treatment-related changes, such as inflammation or radiation-induced injury, rather than active tumor growth (48). Additionally, tumor progression shows higher peak height and lower signal recovery percentages compared to pseudo progression, which is associated with less vascular disruption (49) (Table 1).

Table 1. Metabolite profile and Diagnostic implications

Metabolite	Biological Significance	Diagnostic Significance	Level in AT/RT
Choline (Cho)	Increase Cell proliferation	Present in high grade tumors	High
Lactate	Anaerobic Metabolism	Hypoxia and necrosis in high grade tumors	High
Lipids	Hypoxic environment, necrosis, and vascular leakage	Aggressive or necrotic tumor	High
Creatine (Cr)	Cellular energy metabolism levels	Symptoms of lethargy in AT/RT patients	Low
NAA	Neuronal integrity	Low levels indicate neuronal damage	Low

While elevated rCBV is a helpful marker of tumor aggressiveness, it is not specific to AT/RT and may overlap with other high-grade tumors such as glioblastoma or anaplastic tumors. Therefore, perfusion imaging should be interpreted in conjunction with other advanced MRI techniques for accurate diagnosis (25). Despite this, PWI has had few studies tailored specifically towards AT/RT in pediatric patients. The relative lack of AT/RT-specific rCBV case reports attests to its rarity, technical challenges in pediatric imaging, and research priority on more common tumors. The current PWI principles derived from gliomas and metastases provide a starting point, but AT/RT-specific studies are needed to validate and apply these findings (50). Therefore, future research should focus on rCBV specific to AT/RT and use the marker to differentiate AT/RT.

3.4 AI-based inference of imaging modalities

Advanced imaging is a useful tool for initial diagnosis and early detection; however, advanced imaging modalities have some notable limitations in the hospital setting. For one, they can be expensive to install, making it hard for resource constrained, lower-level and developing facilities to incorporate. Advanced

imaging machines can range from $3 million to $5 million to install and maintain, and use up a substantial amount of power to perform brain scans (51).

Additionally, to keep the MRI machine operable, resources would have to be appropriated other critical healthcare services (52). Therefore, hospitals may incorporate a few advanced MRI machines or not use them at all.

AI presents an affordable solution to use advanced imaging techniques for initial diagnosis and early detection. Using generative adversarial networks (GANs), AI can transform standard MRI sequences (e.g., T1, T2W, and FLAIR) into advanced imaging sequences by learning complex mappings between different modalities.

GANs are trained on paired datasets, enabling them to generate missing or advanced sequences (like DWI or PWI) from available standard scans (53). For example, studies have shown that GANs can synthesize realistic FLAIR images from T2W and pre-contrast T1W from post-contrast T1W, with segmentation results on synthetic images closely matching those obtained from original scans (54).

The same AI approach shows promise for inferring advanced sequences such as DWI and PWI from standard MRI. By training on datasets that include both standard and advanced sequences, GANs could learn to predict microstructural or hemodynamic information, creating DWI or PWI from T1W, T2W, or FLAIR inputs (55). This could make advanced imaging more accessible in settings where specialized hardware or protocols are unavailable, allowing access to high-quality diagnostics.

Another challenge that advanced MRI modalities face is the long scan times that can make it difficult for specialists to obtain accurate images, especially in pediatric patients who have a tendency to move during scans. To help solve this problem, researchers have used AI to lower scanning times and improve patient scans.

AI can reduce MRI scan times for brain tumor imaging using advanced image reconstruction and enhancement algorithms. Learning models can reconstruct high-quality images from significantly less raw data, allowing for faster acquisition without compromising diagnostic accuracy. AI has been shown to reduce brain MRI scan times by up to 45% (56).

Additionally, AI not only shortens the time patients spend in the scanner, improving comfort and reducing motion artifacts, but also increases the output of MRI machines, allowing for more patients to be scanned at a given time (57). FDA-cleared AI tools like SubtleHD™ have reduced scan times by upto 80%, highlighting the potential of these technologies in clinical practice (58).

Using complex machine learning models such as Convolutional Neural Networks (CNNs), as well as Graph Neural Network (GNN) methods, AI can improve the accuracy and speed with which tumors are detected from conventional MRI scans. These algorithms can automatically segment tumor regions, identify AT/RT among brain tumors, and recognize subtle imaging characteristics that are likely to go unnoticed by the human eye, thereby improving accuracy and

early diagnosis (59). MRI-focused AI frameworks that integrate MRI data with other imaging techniques can contribute to a better diagnosis for pediatrics with AT/RT.

Research has shown that AI has the potential to predict certain traits that would be effective against AT/RT that have mutations in the SMARCB1 or SMARCA4 genes. Using large-scale data sets, such as gene expression and mutations, along with drug response datasets, Lantern Pharma's (Dallas, TX) anticancer drug candidate LP-184 was predicted by their RADR® AI platform to be effective against AT/RT. This was validated using a culture of mice and demonstrated a regression in AT/RT of that sample (60). Although this study has not yet been demonstrated in humans, it still shows the value of AI predictions to not only identify tumors but also to identify potential treatments for AT/RT. However, the rarity of AT/RT makes it difficult for AI to obtain comprehensive information, leading to a relative lack of datasets. This lack of data can restrict the training and validation of AI models (61).

Additionally, most AI models use data from adult patients, not pediatric ones. Their direct application to pediatric patients with AT/RT can lead to a reduced accuracy because of the anatomical and physiological differences between adults and pediatric patients (61).

Other investigators have advocated for the creation of synthetic data sets to train AI and create a potential solution to this lack of AI datasets. A benefit to this approach is that AI data sets can overcome the ethical concerns and logistical hurdles of gathering any AT/RT data for AI (62,63). More synthetic data sets can also be created by training AI to identify differences between pediatric and adult MRI data, and then be presented with an adult MRI brain scan to be able to create a pediatric version from it. This was explored in a study where AI was utilized to transform images across adult and pediatric patients. The paper demonstrated the potential for AI given adult MRI scans to mimic anatomy to generate more pediatric data (64). Although the creation of synthetic data sets is new and few studies have completely explored it, synthetic data sets for AT/RT hold value for the future diagnostic techniques. In conclusion, AI has the potential to be useful in diagnosing pediatrics with AT/RT while overcoming the limitations that standard imaging techniques have and setbacks that some advanced imaging have as well.

Finally, AI faces certain general and ethical challenges with neuroimaging in pediatric patients. There have been concerns about the interpretability and explainability of AI decisions regarding MRI, as well as concerns about privacy and sensitive pediatric information (59). Nevertheless, in the face of acceptable accuracy, precision, recall and F1 metrics, using AI to statistically recreating DWI, DTI and PWI images from conventional MRI scans should prove extremely valuable in the differential diagnosis of AT/RT; as should using AI to statistically recreate pediatric MRI scans from adult ones. These, as yet under-researched areas hold much promise in resource constrained and information (database) constrained health-care settings; not only for AT/RT but also for diseases with analogous challenges.

3.5 Emerging therapeutics and gene-based

approaches

Recent advances in AT/RT therapy have focused on targeting epigenetic vulnerabilities, particularly through Enhancer of Zeste Homolog 2 protein (EZH2) inhibitors, which use the loss of SMARCB1 to disrupt tumor growth by reactivating tumor suppressor pathways and immune responses (65). For example, EZH2 inhibitors can reactivate tumor suppressor pathways and trigger immune responses, making them viable for clinical development.

Additionally, chromatin remodeling therapies extend beyond EZH2 inhibitors, with increasing attention on targeting other components of the SWI/SNF complex and related epigenetic regulators. Studies have indicated that combination epigenetic therapies, such as pairing EZH2 inhibitors with Bromodomain and Extra-Terminal (BET) or (Histone DeACetylase) HDAC inhibitors, could overcome treatment resistance and improve anti-tumor effects in rhabdoid tumors (66). These techniques aim to restore normal chromatin states and reactivate silenced tumor suppressor genes, offering a way toward more favorable response.

Gene therapy and advanced molecular interventions show a future in AT/RT research. Recent studies have discussed the potential of gene editing technologies, such as CRISPR, to restore SMARCB1 function or correct underlying genetic defects (67). Additionally, delivery systems, which include nanoparticles and viral vectors, are being explored to enhance the effectiveness and safety of these approaches (68).

However, the use of gene therapy is largely experimental and still remains as part of preclinical trials and not as a standard of care for patients with AT/RT. There have been very few studies that have focused specifically on gene therapy in pediatrics with AT/RT (67).

Furthermore, there can be a potential for adverse effects when using gene therapy to treat AT/RT, leading to possible unwanted mutations or even secondary malignancies (68). Therefore, future research should focus on utilizing more clinical trials specific to pediatrics with AT/RT in order to implement gene therapy as a standard procedure. Additionally, research into integrating gene therapy with epigenetic and chromatin remodeling therapies, as well as using molecular profiling to create specific treatment plans for pediatrics with AT/RT should be pursued.

4. Conclusion

AT/RT is a rare invasive malignant tumor that can occur in pediatric populations. The aggressiveness and high mortality of AT/RT make it a significant health concern that warrants future research. Although much research has been geared towards AT/RT and its mortality in pediatrics, there remain gaps in the advanced diagnostic measures that can be utilized to identify AT/RT. This review emphasizes the need for rapid, accurate and differential diagnoses of pediatrics with AT/RT. Four advanced diagnostic measures are proposed here, alongside standard measures to achieve a better AT/RT diagnosis: DWI, DTI, MRS, and PWI. Additionally, this review proposes that AI be used to statistically recreate DWI, DTI and PWI images from conventional MRI images for use in resource-constrained

healthcare settings as well as to generate synthetic pediatric AT/RT MRI images from their adult counterparts, to expand datasets and increase generalizability. Such Machine Language algorithms and architecture; when used with acceptable accuracy, precision, recall and F1 metrics will enable AT/RT to be distinguished from other brain tumors, such that specific treatment protocols can be started early and patient outcomes and – ultimately, survival - can be improved.

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