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**Impacto da sequência ponderada em difusão (DWI) nos
estudos controle para caracterização de recidivas de tumores
embrionários no sistema nervoso central**

Tese apresentada à Faculdade de Medicina da
Universidade de São Paulo para obtenção do título de
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Orientadora: Profa. Dra. Claudia da Costa Leite

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Dedicatória

À minha esposa **Andressa** e minha filha **Cecília**, pelo amor, compreensão e carinho incondicionais.

Aos meus pais, **Célio** e **Vânia**, e à minha irmã, **Amanda**, que sempre estiveram ao meu lado, e que com amor, carinho e sabedoria nortearam a minha vida e marcaram minha personalidade

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*"Cada pessoa deve trabalhar para o seu aperfeiçoamento
e, ao mesmo tempo, participar da responsabilidade coletiva
por toda a humanidade."*

(Marie Curie)

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Lista de abreviaturas, símbolos e siglas

Apparent Diffusion Coefficient (ADC)

Células gigantes / anaplásico (CGA)

Diffusion weighted imaging (DWI)

Desmoplásico (DESM)

Fluid Attenuation Inversion Recovery (FLAIR)

Irradiação craniospinal (ICS)

Intervalo de confiança (IC)

Institution Review Board (IRB)

Intraclass correlation coefficient (ICC)

Lesão radioinduzida (LRI)

Líquido cefaloraquidiano (LCR)

Organização Mundial da Saúde (*OMS*)

Ressonância magnética (RM)

Sistema nervoso central (SNC)

Sonic hedgehog (*SHH*)

Sensibilidade (SE)

T1 weighted (T1W)

T2 weighted (T2W)

Tempo de eco (TE)

Tempo de repetição (TR)

Tomografia computadorizada (TC)

Tumor embrionário de múltiplas rosetas (TEMR)

Tumor embrionário - sem outras especificações (TE-SOE)

Tumores neuroectodérmicos primitivos (PNETs)

Tumor teratóide rabdóide atípico (TTRA)

Valor preditivo positivo (VPP)

Valor preditivo negativo (VPN)

Wingless tumor (WNT)

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Resumo

Alves CAPF. *Impacto da sequência ponderada em difusão (DWI) na avaliação de estudos controle para caracterização de recidivas de tumores embrionários no sistema nervoso central*[thesis]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2021.

A ressonância magnética tem papel fundamental no diagnóstico dos tumores do sistema nervoso central. Singular ênfase é dada à sequência ponderada em difusão, a qual tem destacado auxílio no diagnóstico dos tumores embrionários do sistema nervoso central, particularmente na faixa etária pediátrica. No entanto, a efetiva relevância desta sequência para a diferenciação dos diversos subtipos de tumores primários do encéfalo, bem como a sua utilidade diagnóstica na detecção de recidiva dos tumores embrionários não é, ainda hoje, bem estabelecida. Assim, os objetivos deste estudo foram (1) criar um fluxograma que colabore no diagnóstico inicial de tumores embrionários, com auxílio da sequência de difusão, particularmente quando localizados no cerebelo e na faixa etária pediátrica, (2) comparar a sequência de difusão e as demais sequências da ressonância magnética convencional para a detecção de recidiva dos tumores embrionários do sistema nervoso central e (3) avaliar as propriedades da sequência de difusão e da sequência T1 após o uso do agente de contraste paramagnético nas lesões induzidas por radiação. Duas análises retrospectivas e distintas foram realizadas neste trabalho. A primeira análise incluiu a avaliação dos estudos de ressonância magnética em cento e quarenta e oito (148) crianças com diagnóstico histológico e molecular de tumores cerebelares pediátricos. Os respectivos tumores foram avaliados por diferentes sequências de imagem, bem como análise demográfica, seguindo um fluxograma previamente instituído, que incluiu a sequência ponderada em difusão como o núcleo da diferenciação desses tumores para obtenção de um diagnóstico final mais preciso. Com base na análise destes casos, o

fluxograma apresentou uma relativa adequada acurácia na identificação da maioria dos diagnósticos dos tumores cerebelares. Um segundo fluxograma (fluxograma modificado) foi então por nós proposto, baseado nos resultados obtidos pela nossa casuística, que apresentou um significativo aumento da acurácia quando comparado ao anterior, incluindo também uma excelente razão de verossimilhança para a diferenciação da maioria dos grupos histológicos e moleculares dos tumores embrionários cerebelares, entre outros. A segunda análise do nosso estudo incluiu a avaliação retrospectiva dos exames de ressonância magnética em cinquenta e seis (56) pacientes com tumor embrionário do sistema nervoso central. Esses estudos foram avaliados por meio da análise separada das sequências (1) ponderadas em difusão, (2) conjunto de sequências convencionais (T1, T2 / FLAIR e T1 pós-contraste) e (3) sequências ponderadas em T1 pós-contraste de forma isolada. A sensibilidade para detecção de recidiva foi calculada para cada um dos grupos de imagem pré-estabelecidos. Uma análise descritiva por paciente também foi realizada. A sensibilidade de detecção de recidiva nodular focal pela sequência ponderada em difusão (96%) foi significativamente maior que as demais sequências da ressonância magnética convencional (77%) e que a sequência pós-contraste isolada (51%) ($p = 0,0003$ e $p < 0,0001$). Na análise de recidiva por paciente, nenhum diagnóstico foi perdido pela avaliação da sequência de difusão. As demais sequências de ressonância magnética convencional perderam dois (2) diagnósticos e a sequência pós-contraste isolada perdeu oito (8). Em conclusão, o estudo de ressonância magnética, em especial a sequência ponderada em difusão, mostrou-se essencial para diferenciação dos diversos subtipos de tumores encefálicos pediátricos, na detecção aprimorada de recidiva focal em pacientes com tumores embrionários do sistema nervoso central e fundamental em auxiliar na diferenciação entre as lesões decorrentes de recidiva tumoral e as lesões radioinduzidas no contexto de tumores embrionários.

Descritores: 1. Neuroimagem 2. Pediatria 3. Encéfalo 4. Neoplasias do sistema nervoso central 5. Meduloblastoma 6. Diagnóstico por imagem

Summary

Alves CAPF. *Role of the diffusion-weighted sequence (DWI) in the imaging surveillance for the characterization of recurrences of embryonal tumors in the central nervous system* [thesis]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2021.

Magnetic resonance imaging has a fundamental role in the diagnosis of tumors of the central nervous system. Singular emphasis is given to the diffusion-weighted sequence, which has an essential role in the diagnosis of embryonal tumors, particularly in the pediatric age group. However, the real relevance of this sequence in differentiating the subtypes of primary brain tumors, as well as its diagnostic utility in detecting recurrence of embryonal tumors, is still not well-established. The aims of this study are (1) to create a flowchart that improves the capability of a correct diagnosis of brain tumors, particularly those affecting the cerebellum during childhood, with the support of the diffusion-weighted sequence, (2) compare the diffusion sequence with the other conventional magnetic resonance sequences in detecting the recurrence of embryonal tumors of the central nervous system, and (3) to evaluate the properties of the diffusion and T1 sequence after injection of the paramagnetic agent in the analysis of radiation-induced lesions. For these purposes, two retrospective analyses were performed from two different pediatric cohorts. The first one included magnetic resonance imaging of 148 children with cerebellar tumors confirmed molecularly and histologically. These tumors were evaluated by separate imaging and demographic analysis following a pre-designed step-by-step flowchart which includes diffusion-weighted imaging sequence as the core of the stratification of these tumors to obtain a correct final diagnosis. Based on analysis of our cohort, we have confirmed that the pre-designed flowchart was reliable in identifying most diagnoses. However, a few discrepancies between literature and our results were also observed. In order to obtain a more accurate flowchart, our group has submitted modifications in the flowchart, and, subsequently, a modified flowchart with

an overall increased accuracy was created. The modified flowchart showed a good likelihood ratio for most of the histologic and molecular groups of embryonal tumors among others. The second imaging analysis of our study included a retrospective review of fifty-six patients with the diagnosis of an embryonal tumor of the central nervous system. These tumors were evaluated by separate sequences of magnetic resonance imaging including (1) diffusion-weighted sequences, (2) set of conventional sequences (T1, T2 / FLAIR, and T1 post-contrast), and (3) post-contrast T1 sequence alone. The sensitivity for detecting recurrence was calculated for each of the pre-established image groups. A descriptive analysis per patient was also performed. Sensitivity of detection of focal nodular recurrence by the diffusion-weighted sequence (96%) was significantly higher than the other conventional magnetic resonance sequences (77%) and the post-contrast sequence alone (51%) ($p = 0.0003$ ep <0.0001). In the analysis of recurrence per patient, no diagnosis was missed by assessing the diffusion sequence. The other conventional MRI sequences missed two diagnoses and the isolated analysis of the post-contrast sequence missed eight diagnoses. In conclusion, the magnetic resonance study, particularly, the diffusion-weighted image sequence, proved to be essential in the differentiation of the diverse subtypes of pediatric brain tumors, particularly embryonal tumors; improves the detection of focal recurrence in patients with embryonal tumors of the central nervous system; and can assist in the differentiation between tumor recurrence and radioinduced lesions.

Descriptors: Neuroimaging; Pediatrics; Brain; Central nervous system neoplasms; Medulloblastoma; Diagnostic imaging.

1- Introdução

1.1 Tumores do Sistema Nervoso Central na Faixa Etária Pediátrica

Os tumores do sistema nervoso central (SNC) são os tumores de órgãos sólidos mais comuns em crianças e incluem tumores malignos e benignos. Em crianças (faixa etária de 0 a 14 anos), os tumores primários do encéfalo apresentam uma prevalência nos Estados Unidos da América (EUA) de 5,74 por 100.000 (Ostrom et al. 2019). O câncer infantil do SNC também é considerado uma das principais razões de morte por câncer em crianças em todo mundo (de Blank et al. 2015).

Diferentemente das neoplasias em outras localizações, os tumores primários do encéfalo não são estadiados, mas categorizados de acordo com a Classificação da Organização Mundial da Saúde (OMS) 2016, que, atualmente, se baseia principalmente em parâmetros moleculares para definir os diversos subgrupos de tumores que afetam o SNC (Louis et al. 2016).

Essa recente reformulação na classificação dos tumores do SNC decorre, principalmente, do fato que alguns perfis moleculares de neoplasias no SNC, incluindo as neoplasias pediátricas, permitem a completa separação de alguns subtipos de tumores histologicamente homólogos. Por exemplo, podemos citar, o glioma difuso da linha média *H3 K27M* – mutante, uma entidade nova e única que foi recentemente reclassificada por conta do seu perfil genético e, previamente, era discriminada em grupos diferentes de tumores de linha média, incluindo, como principal representante, o glioma intrínseco difuso da ponte. A identificação deste conjunto de tumores definidos

fenotipicamente e molecularmente fornece uma base lógica para terapias direcionadas contra os efeitos dessas mutações (Korshunov et al. 2011; Zhang et al. 2013; Khuong-Quang et al. 2012).

1.2 Tumores Embrionários do Sistema Nervoso Central

Os tumores embrionários do SNC compreendem um subgrupo biologicamente heterogêneo de neoplasias malignas pediátricas do encéfalo. Estas neoplasias são compostas histologicamente por um condensado de células compactas e hipercromáticas (pequenas células azuis) com escassa quantidade de citoplasma e alto índice mitótico (Board and Others 2008).

Os tumores embrionários do SNC apresentam grande índice de recidiva e de disseminação por meio do líquido cefalorraquidiano (LCR) (Sabel et al. 2016). A doença pode recorrer no sítio do tumor primitivo ou mesmo de forma disseminada com lesões à distância. As localizações de metástases à distância incluem lesões focais intraparenquimatosas e lesões decorrentes de disseminação leptomeníngea intracraniana e/ou espinal, podendo ser de forma isolada ou concomitante (Sébastien Perreault et al. 2014; Warmuth-Metz et al. 2011; Sébastien Perreault et al. 2013).

De acordo com a última classificação revisada da *OMS* 2016 (Louis et al. 2016) os tumores embrionários são genericamente categorizados como grau IV; e os seus subtipos neoplásicos incluem: meduloblastomas; tumores embrionários de múltiplas rosetas (TEMR, *C19-MC* mutado); meduloepiteliomas; tumores embrionários - sem outras especificações (TE-SOE) e tumores teratóides rabdóides atípicos (TTRA).

Várias mudanças foram impostas à subdivisão dos tumores embrionários de acordo com a última revisão atualizada da *OMS (Louis et al. 2016)*. Destacam-se a elas, a nova subdivisão dos meduloblastomas, que passam a ser definidos principalmente por seus quatro principais perfis moleculares (meduloblastoma-*SHH*; meduloblastoma-*WNT*; meduloblastoma-grupo 3; meduloblastoma-grupo 4), e não mais pelas suas características histológicas; a remoção do léxico atual da subcategoria de tumores neuroectodérmicos primitivos (PNETs); e a adição de uma nova entidade, (TEMR, *C19-MC*-mutado).

Da mesma forma que para muitos outros grupos de tumores do SNC, a justificativa para a redistribuição e reagrupamento desses tumores foi impulsionada, principalmente, pela percepção de que, em geral, essas neoplasias podem compartilhar um perfil molecular semelhante, que mais frequentemente sobrepõe às suas características histológicas, no que concerne à distribuição demográfica, agressividade, e resposta a tratamento.

1.3 Relevância dos Estudos de Imagem no Diagnóstico dos Tumores do Sistema Nervoso Central na Faixa Etária Pediátrica

A avaliação por imagem de tumores primários do SNC é fundamental para a construção de tratamentos adequados. A padronização da aquisição de imagens é um pré-requisito essencial, não apenas para um diagnóstico mais acurado, mas também para permitir estudos comparativos em um mesmo indivíduo ao longo do seu período de tratamento e para viabilizar análises comparativas entre exames realizados em serviços diferentes. No que tange a uma análise mais precisa, a ressonância magnética (RM) é,

indubitavelmente, o melhor método de auxílio diagnóstico, tendo se mostrado útil não apenas no auxílio para diferenciação histológica desses tumores, mas também para a diferenciação dos seus aspectos moleculares, os quais hoje representam a base diagnóstica e de direcionamento para tratamentos mais eficazes.

Dentro da faixa etária pediátrica, a importância da RM se acentua, visto que os tumores pediátricos primários do encéfalo têm apresentações clínicas e de imagem extremamente variáveis, o que pode representar um verdadeiro desafio diagnóstico. Ademais, a capacidade de identificar os fenótipos de imagem mais comuns e as características de agressividade dos tumores pediátricos abrem caminho para um diagnóstico precoce, com maior possibilidade de um prognóstico clínico favorável e, conseqüentemente, um aumento na sobrevivência dessas crianças.

1.4 Relevância dos Estudos de Imagem no Diagnóstico de Recidiva Tumoral

A caracterização da recidiva e recorrência tumoral dos tumores embrionários no SNC é considerada crucial e um dos principais indicadores prognósticos a longo prazo da doença (Zeltzer et al. 1999).

Os estudos de tomografia computadorizada (TC) e RM são os métodos de imagem mais utilizados e capazes de fornecer informações sobre o parênquima encefálico, permitindo a identificação de alterações estruturais, que sugiram a presença de recidiva tumoral.

Entretanto, embora a TC seja considerada um método de baixo custo, de fácil acesso e rápido (Blaser and Harwood-Nash 1996), a sua baixa sensibilidade diagnóstica para avaliação de recidivas e o seu relativo baixo detalhamento estrutural, quando

comparados ao estudo de RM, associados à presença de artefatos de imagem, notadamente observados na fossa posterior, podem dificultar ou mesmo impedir o diagnóstico precoce e a avaliação correta das recidivas tumorais (Barajas and Cha 2012).

1.5 Ressonância Magnética (RM) no Diagnóstico de Recidiva Tumoral

A RM é o método estrutural mais amplamente utilizado para o controle dos tumores do SNC. Isto se deve ao fato desta modalidade de imagem apresentar alta sensibilidade diagnóstica e fornecer um grande detalhamento estrutural do parênquima encefálico (Byrne 1994; Leeds e Jackson 1994). Particularmente, as sequências de RM pós-contraste são atualmente recomendadas como padrão para avaliar a extensão do tumor e sua disseminação (Koeller e Rushing 2003). Entretanto, enquanto a maioria das neoplasias do SNC tipicamente apresentam impregnação pelo agente de contraste paramagnético, os tumores embrionários do SNC demonstram, como particularidade, um grau variável de impregnação pelo contraste. Neste contexto, merecem destaque os meduloblastomas. De acordo com a literatura, essas neoplasias não impregnam pelo agente de contraste em cerca de 11-25 % dos casos (Erdem et al. 2001; Yeom et al. 2013; S. Perreault et al. 2014; Rollins et al. 1990).

Adicionalmente, nos exames controle desses pacientes, apesar das lesões nodulares intraparenquimatosas ou piaais serem descritas como fundamentais para o diagnóstico de recidiva da doença (Meyers et al. 1994), a impregnação pós-contraste pode resultar de alterações relacionadas ao tratamento, como a radioterapia (Weintraub et al. 2014; Spreafico et al. 2008). Este achado pode promover uma grande dificuldade de interpretação e afetar diretamente o diagnóstico correto e o tratamento precoce desses pacientes (Cassia et al. 2018).

1.6 Ressonância Magnética- DWI no Diagnóstico de Recidiva Tumoral

A DWI (sigla do inglês: *diffusion weighted imaging*) é uma sequência capaz de fornecer informações sobre a difusibilidade das moléculas de água, sobre as quais o valor quantitativo, conhecido como coeficiente de difusão aparente ADC (sigla do inglês: *Apparent Diffusion Coefficient*) pode ser calculado.

No contexto das neoplasias, a DWI permite uma estimativa não invasiva da diferença de densidade celular, bem como da estrutura do tecido avaliado, sendo amplamente utilizada em todos os tumores pediátricos do SNC (Rossi et al. 2010; Gauvain et al. 2001). Particularmente, no que concerne à análise diagnóstica dos tumores embrionários do SNC, o fato dessas neoplasias partilharem algumas características histológicas semelhantes, como o grande condensado celular e o baixo componente citoplasmático, determinam o seu achado mais clássico e frequente por imagem - a presença de componente lesional com restrição à movimentação das moléculas de água na sequência DWI, confirmada no mapa ADC (Rumboldt et al. 2006; S. Perreault et al. 2014). No entanto, embora a importância da sequência DWI no diagnóstico dos tumores embrionários do SNC seja amplamente reconhecida, a exata relevância desta na caracterização de recidiva dos tumores embrionários, bem como na sua diferenciação com lesões de outras naturezas, em particular aquelas relacionadas ao tratamento radioterápico (LRI), não é, ainda hoje, bem estabelecida na literatura.

2 – Texto Sistematizado

2.1 Organização do texto sistematizado

Considerando a importância dos tumores do SNC na faixa etária pediátrica, entre eles os tumores embrionários e as suas características de imagem por RM, em especial a sequência de difusão, desenvolvemos esta tese baseada na publicação de dois artigos científicos relacionados ao diagnóstico destes tumores e de suas recidivas.

O texto sistematizado se refere à duas publicações, agrupadas na temática abaixo:

- **Tumores cerebrales na faixa etária pediátrica**

Publicação 1: Alves et al., 2021

- **Recidivas dos tumores embrionários no encéfalo**

Publicação 2: Morana and Alves et al., 2017

2.2 Fluxograma diagnóstico para os tumores cerebrales na faixa etária pediátrica

Publicação 1:

C.A.P.F. Alves, U. Löbel, J.S. MartinSaavedra, S. Toescu, M.H. Tsunemi, S.R. Teixeira, K. Mankad, D. Hargrave, T.S. Jacques, C. da Costa Leite, F.G. Gonçalves, A. Vossough, F. D'Arco. American Journal of Neuroradiology Mar 2021, DOI: 10.3174/ajnr.A7057

Nos últimos 10 anos, houve um aumento exponencial no conhecimento das características moleculares dos tumores pediátricos do SNC. Esse conhecimento foi incorporado, em parte, à última atualização da Classificação de Tumores do Sistema Nervoso Central da *OMS* (Louis et al. 2016). Mesmo após à publicação desta classificação em 2016, uma série de recentes estudos continuam identificando outros novos subgrupos moleculares, que envolvem os tumores pediátricos, de forma particularmente relevante, os tumores embrionários, com possíveis implicações prognósticas. Essas mudanças envolvem os grupos dos meduloblastomas (Ramaswamy et al. 2016) e os tumores teratóides rabdóides atípicos (TTRA), ambos tumores embrionários (Nowak et al. 2018), bem como o grupo dos ependimomas (Pajtler et al. 2015). Em paralelo a esse contínuo avanço molecular houve, também, uma ascensão na capacidade diagnóstica dos métodos de imagem, assim como na sua translação diagnóstica a esses resultados moleculares obtidos. Esse constante e vasto conteúdo de dados disponibilizados na literatura científica sobre diferentes padrões de imagem ligados a perfis moleculares ampliou, ainda mais, a importância dos métodos de imagem no diagnóstico e conduta desses pacientes, porém, em contrapartida, trouxe um desafio ainda maior na capacidade do médico radiologista se manter atualizado e qualificado para aplicar esse conhecimento na sua prática diária. Um exemplo típico dessa recente modificação e da sua aplicabilidade na área da medicina diagnóstica são os já estabelecidos 4 subgrupos principais de meduloblastoma, principal neoplasia do grupo dos tumores embrionários, hoje denominados pelo seu perfil molecular e que incluem: meduloblastomas-*WNT*, meduloblastomas-*SHH*, com ou sem a mutação *p53*, meduloblastomas-grupo 3 e meduloblastomas-grupo 4. Embora estes grupos possam parecer, muitas vezes, semelhantes na microscopia, estas categorias têm perfis

moleculares, epidemiologia, prognóstico e origem embriológica distintas (Taylor et al. 2012). No que concerne à imagem diagnóstica, historicamente, desde o advento e “popularização” das sequências ponderadas em difusão, no início dos anos 2000, os tumores embrionários, em particular os meduloblastomas, têm como descritor de imagem mais importante a presença de restrição na sequência DWI o que, indiretamente, denota o seu padrão de distribuição e morfologia celular. No entanto, apesar desta característica singular para este grupo de tumores, a emergência dos diferentes perfis moleculares, associados a prognósticos por vezes distintos, impôs ao radiologista, em particular o pesquisador neurorradiologista, explorar novas associações do padrão molecular com outros diferentes fenótipos da imagem. Dentro do contexto de estratificação diagnóstica, a RM mostra-se uma técnica de imagem cada vez mais promissora para distinção dos tumores pediátricos, seja pelas características histológicas, como pelos perfis moleculares diferentes dessas neoplasias. Essa capacidade diagnóstica é resultante, não apenas da variabilidade das características de sinal ou padrões de impregnação pelo contraste paramagnético desses tumores na RM, mas também da sua capacidade de fornecer um profundo detalhamento anatômico, que permite, de forma precisa, determinar a localização e extensão espacial desses tumores.

Uma nova possibilidade de abordagem para transpor esse contínuo desafio diagnóstico é a utilização/ associação da inteligência artificial aos métodos de imagem. A inteligência artificial tem como um dos seus objetivos ramificar e “compreender” diversos padrões de imagem que se repetem com alta frequência, direcionando-os para possíveis diagnósticos mais precisos. No entanto, apesar das grandes expectativas para essa inovação de características extremamente promissoras, a dificuldade na capacidade de identificar corretamente a localização de um tumor do SNC, aliada às inúmeras

variáveis relacionadas às características de sinal, contraste, infiltração, entre outros, fazem com que seu uso como um elemento diagnóstico seja ainda limitado no contexto dos tumores pediátricos do SNC e, consequentemente, o diagnóstico seja ainda centrado na perícia de um radiologista experiente.

Anteriormente ao trabalho aqui apresentado, com intuito de facilitar e difundir o conhecimento radiológico no diagnóstico de tumores pediátricos, D'Arco e cols. (D'Arco et al. 2018) propuseram um fluxograma (Figura 1) para o diagnóstico diferencial de tumores da fossa posterior em crianças. O fluxograma previamente proposto possui, como suporte para seu modelo, dados unicamente oferecidos na literatura sobre as características epidemiológicas, de imagem e de distribuição dessas neoplasias. Entretanto, ainda que criado com amplo sustento científico, o fluxograma previamente apresentado não dispõe de qualquer validação crítica fundamentada em pacientes direcionados para a sua apreciação. Adicionalmente, posterior à sua criação, novos avanços na análise molecular dos tumores pediátricos que influenciaram significativamente na classificação desses tumores, culminaram, mesmo que em um curto espaço de tempo, na necessidade de uma validação e ajuste desse fluxograma. Realizamos, então, no nosso trabalho um processo de validação e ajuste desse fluxograma diagnóstico.

Para a validação do fluxograma, nosso processo de análise revisou cento e quarenta e oito (148) estudos de RM realizados em campos de 1.5T e 3.0T em crianças com tumores cerebelaes, obrigatoriamente, confirmados sob base histológica e molecular. Dados mínimos necessários incluíram a necessidade das sequências de DWI, T1W, T2W e sequências T1W pós-contraste, bem como dados demográficos mínimos do paciente, como data de nascimento e idade no momento do exame e, também, a não

realização de nenhum tratamento prévio à RM adquirida para a avaliação do tumor. Seguiu-se, então, uma análise numérica sequencial do fluxograma, na qual cada um dos números designados e à sua ordem foram estabelecidos em relação a cada uma das características de imagem pré-estabelecidas para cada tumor analisado, com o intuito de obter uma correlação direta entre o conjunto único de numerações e o diagnóstico final desses tumores. Exemplificando, quando diante de um paciente com um tumor localizado no hemisfério cerebelar, associado a baixo valor no mapa ADC, e a morfologia multinodular na sequência T1 pós-contraste, os números referidos são, 1, 1 e 2, nessa respectiva ordem, e esse conjunto numérico (112) designa-se ao diagnóstico do grupo de meduloblastomas-*SHH*.

Figura 1.

Fluxograma radiológico pré-projetado criado de acordo com a literatura antes da análise de precisão diagnóstica. (Modificado de D'Arco et al., 2018) (D'Arco et al. 2018)

O asterisco (*) indica tumores do tronco encefálico excluídos da análise. Os asteriscos duplos (**) indicam a comparação da intensidade de sinal em relação à substância cinzenta.

Os diversos resultados do nosso estudo foram capazes de validar estatisticamente uma série de informações pré-determinadas pelo fluxograma inicial e, também, capazes de acrescentar e remover informações previamente estabelecidas na literatura.

Com base nos nossos resultados, observamos, por exemplo, que a distinção da maioria dos meduloblastomas grupo 3 e grupo 4 é possível de ser feita em relação demais grupos de meduloblastomas, com uma excelente especificidade (86-96%) e alto valor preditivo negativo (88-97%). Em contrapartida, não observamos dados que suportam algumas informações relativamente bem estabelecidas na literatura e, previamente designadas no fluxograma como, por exemplo, a distinção dos meduloblastomas- *WNT* dos demais meduloblastomas fundamentado na sua localização de origem, previamente descrita como centrada no forame de Luschka.

Não surpreendente e consoante aos nossos resultados, Stock e cols., recentemente, demonstraram que meduloblastomas- *WNT* não são tão lateralizados como descrito anteriormente em estudos feitos com menores casuísticas (Northcott et al. 2012). Devido às poucas, mas substanciais modificações diagnósticas realizadas no fluxograma pré-desenhado, propusemos, então, um fluxograma modificado que permite, de forma mais acurada e com base em resultados estatísticos obtidos da nossa casuística, o auxílio diagnóstico dos tumores cerebelares em crianças (Figura 2).

Figura 2.

Fluxograma radiológico criado de acordo com a nossa casuística de 148 crianças com tumores cerebelares confirmados por resultado histológico e molecular. (Modificado de Alves et al., 2021) (Alves et al. 2021)

O asterisco (*) indica tumores do tronco encefálico excluídos da análise. Os asteriscos duplos (**) indicam a comparação da intensidade de sinal em relação à substância cinzenta. Asteriscos triplos (***) indicam baixo VPP e sensibilidade para qualquer grupo histológico de tumor.

Acreditamos que essa publicação oferece amplo apoio à radiologistas de diferentes níveis de expertise na prática clínica diária, com intuito de auxílio na formulação de hipóteses diagnósticas para os tumores pediátricos cerebelares. Outro

mérito deste trabalho baseia-se no fato que os resultados obtidos em nossa pesquisa servem como substancial base de dados para o alicerce de técnicas de *machine learning* no diagnóstico de tumores pediátricos no SNC.

2.3 Recidiva dos tumores embrionários no encéfalo

Publicação 2:

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O acompanhamento estabelecido para os tumores embrionários do SNC inclui exames de neuroimagem e avaliações clínicas em intervalos regulares. O controle dos estudos de imagem é feito acreditando-se que a detecção precoce da recorrência do tumor pode, potencialmente, permitir uma intervenção imediata e, assim, melhorar o prognóstico do paciente. Entretanto, o rastreamento e o diagnóstico de recorrências tumorais representam, ainda, um desafio significativo e, do ponto de vista do controle por imagem, a identificação precoce da recidiva do tumor, na maioria das vezes, é baseada na identificação de uma lesão no SNC que apresenta impregnação pelo gadolínio (quebra da barreira hematoencefálica).

No que concerne, por sua vez, à análise por imagem da recidiva dos tumores embrionários do SNC, a aplicabilidade da avaliação da sequência T1W pós-contraste, isoladamente ou mesmo em conjunto às outras sequências convencionais (T1W, T2W e FLAIR), deve ser questionada. Este questionamento baseia-se em resultados provenientes de estudos anteriores que demonstraram que as recidivas de meduloblastomas tendem a apresentar uma impregnação menor quando comparadas ao seu local primário de origem (Bühning et al. 2002) e cerca de 36% das recorrências de meduloblastomas podem não impregnar pelo gadolínio (Rollins et al. 1990) com até 20% de doença leptomeníngea secundária não detectada pela RM convencional (Fouladi et al. 1999). Estes resultados trazem atenção obrigatória ao radiologista para uma avaliação por imagem diferenciada

na busca de recidiva tumoral neste subgrupo de tumores. Estudos recentes também demonstraram que, dependendo do subgrupo molecular, os meduloblastomas podem apresentar maiores ou menores graus de quebra da barreira hematoencefálica (Guerit and Liebner 2016). Como exemplo, lesões com ausência de impregnação pelo gadolínio foram demonstradas, de forma significativa, em maior número nos meduloblastomas-grupo 4 (S. Perreault et al. 2014).

Em paralelo à dificuldade de caracterização das recidivas nos estudos de RM associa-se, muitas vezes, a complexidade em se diferenciar a recidiva tumoral de outras entidades, como as lesões radioinduzidas (LRI). Estes fatores podem determinar um diagnóstico equivocado de recidiva tumoral e, conseqüentemente, impactar negativamente no prognóstico do paciente.

Realizamos, então, com o intuito de aumentar a acurácia diagnóstica das recidivas dos tumores embrionários, um estudo baseado na análise da sequência ponderada em difusão. A justificativa e embasamento científico do nosso estudo fundamentaram-se na evidência fornecida pela literatura da presença de restrição à difusão na vasta maioria dos tumores embrionários primários do SNC (Yeom et al. 2013; S. Perreault et al. 2014; Rumboldt et al. 2006; Jaremko et al. 2010; Chawla et al. 2007).

O aumento da celularidade, a diminuição do espaço extracelular e a alta relação núcleo/ citoplasma são as explicações mais comuns das características da restrição observadas na sequência DWI para esses tumores. Relatos de casos e pequenas séries de casos sugerem um possível papel da DWI para estudos controle dos meduloblastomas. Shubert e colg., (Schubert et al. 2006) avaliaram a utilidade diagnóstica da DWI em três pacientes com meduloblastomas, sugerindo um papel relevante para DWI na detecção precoce da doença metastática. Observações semelhantes foram relatadas por Rasalkar e

col. (Rasalkar et al. 2011) e por Amene e col. (Amene, Yeh-Nayre, and Crawford 2013) mostrando em casos isolados a utilidade da DWI na detecção de recorrência de meduloblastomas. No entanto, na literatura, com exceção dos dados esparsos acima mencionados, nenhum estudo sistemático foi realizado com o objetivo de avaliar e validar o valor diagnóstico da DWI no controle de crianças com tumor embrionário do SNC.

Foi feita, então, uma análise retrospectiva de cento e oitenta (180) pacientes pediátricos com tumores embrionários do sistema nervoso central, com a inclusão final de cinquenta e seis (56) crianças nesse estudo. Um total de 125 lesões focais foram identificadas de acordo com o estudo-referência. Dessas, 103 foram diagnosticadas como recidivas/ recorrências locais e 22 como LRI

Devido a impossibilidade de confirmação histológica para todas as lesões avaliadas com suspeitas de recidiva, a análise do estudo completo oferecido ao coordenador do estudo, bem como o acesso aos dados clínicos e laboratoriais, tratamento prescrito e acesso a exames controle foi estipulado como padrão-ouro/ estudo-referência. Lesões com crescimento contínuo em estudos subsequentes e confirmação clínico-laboratorial foram determinadas como recidiva. Lesões que impregnavam após três meses do tratamento radioterápico, mas que desapareceram sem o advento de nenhum novo tratamento foram determinadas com LRI (Sugahara, T. et al. 2000).

Todos pacientes eram menores que 18 anos no momento diagnóstico, apresentavam confirmação de tumores embrionários do SNC e foram acompanhados no Instituto Giannina Gaslini em Genova-Itália entre os anos de 2005 e 2015. O estudo foi aprovado pela IRB (sigla do inglês: *Institution Review Board*) e a coleta de dados foi feita durante o ano de 2016 sob a supervisão e orientação do chefe do Departamento da Neurorradiologia Pediátrica, Dr. Andrea Rossi.

A inclusão de cada indivíduo neste estudo foi regularizada de acordo com os preceitos da Declaração de Helsinque e do Código de Nuremberg, respeitadas as Normas de Pesquisa Envolvendo Seres Humanos (Res. CNS 196/96) do Conselho Nacional de Saúde.

Os dados clínicos, laboratoriais, resultado de histopatologia e de análise genético-molecular foram obtidos por meio do prontuário eletrônico dos pacientes.

Detalhadamente, foram incluídos na pesquisa, (1) pacientes com diagnóstico histológico confirmado de tumor embrionário do SNC que apresentaram durante a sua evolução confirmação de recidiva tumoral; (2) pacientes com LRI não neoplásicas, porém inicialmente consideradas como recidivas pelo estudo de RM e (3) pacientes sem evidência de recidiva ou LRI após acompanhamento de pelo menos três anos.

Nos subgrupos 1 e 2, foram incluídos apenas pacientes que haviam feito pelo menos um estudo controle com diagnóstico de lesões suspeitas para recidiva neoplásica. Para evitar resultados falso positivos pela sequência DWI relacionados às alterações pós-cirúrgicas (hemorragia e contusões), somente os pacientes com suspeita de recidiva de tumor embrionário a partir de 3 meses do procedimento cirúrgico foram incluídos nos subgrupos 1 e 2.

Foram excluídos pacientes cuja qualidade de imagem não permitia uma análise adequada do estudo e pacientes que continham dados clínicos e laboratoriais insuficientes durante o estudo controle.

Nossos resultados mostram que a DWI foi capaz de identificar um número significativamente maior de recidivas focais de tumor embrionário do SNC quando comparada às sequências da RM convencional (Figura 3).

Figura 3.

Gráfico de barras mostrando lesões focais recidivantes identificadas (cinza) e perdidas (branco pontilhado) pela avaliação isolada do agente de contraste paramagnético (CE), pela avaliação conjunta das sequências convencionais (T2W / FLAIR e T1W pós-contraste) (CONV) e pela avaliação isolada da imagem ponderada por difusão (DWI). A DWI identificou 19,42% mais recidivas focais quando comparada a todas as sequências convencionais (CONV) e 44,66% mais lesões quando comparada a sequência pós-contraste T1W isolada (CE).

Ao considerarmos uma análise por indivíduo, a DWI foi capaz de adicionar informações diagnósticas à RM convencional em oito (32%) dos pacientes com recidiva nodular focal, identificar um maior número de lesões recidivadas em 13 (52%) pacientes quando comparada à sequência pós-contraste e foi a única capaz de identificar recidiva em dois (8%) pacientes. Ao mesmo tempo, todas lesões, exceto uma que apresentava restrição à difusão, foram confirmadas como lesões secundárias, com consequente valor preditivo positivo (VPP) muito alto (99%). A alta sensibilidade e o VPP sugerem que a

DWI é uma excelente sequência para identificação de recidivas focais de tumor embrionário no encéfalo, de modo que um achado positivo na DWI é altamente preditivo de recidiva.

Outro ponto importante do nosso trabalho foi a avaliação das lesões radioinduzidas. A presença de LRIs é amplamente reconhecida no contexto dos estudos controle dos tumores embrionários do SNC (Spreafico et al. 2008; Helton et al. 2005; Fouladi et al. 2004; Muscal et al. 2009). Entretanto, a análise destes estudos baseia-se apenas nas características das sequências convencionais da RM e no padrão de imagem da evolução temporal das LRIs, sem uma avaliação direcionada para a sequência DWI. O padrão de imagem frequentemente encontrado e descrito nas LRIs em crianças com tumor embrionário no SNC, tratadas com radioterapia e quimioterapia, é a presença de pequenos focos de impregnação pelo contraste paramagnético distribuídos pelo parênquima encefálico, quase sempre associados à hiperintensidade de sinal focal nas sequências T2 / FLAIR. Essas lesões são frequentemente observadas em crianças tratadas com radioterapia acelerada hiperfracionada (HART) e são consideradas uma forma mais branda de lesão encefálica, que podem ser causadas pela presença de edema vasogênico transitório ou desmielinização com ruptura da barreira hematoencefálica sendo, dessa forma, diferentes da necrose clássica por radiação. Há, geralmente, distribuição preferencial dessas lesões pela substância branca, com localização variável em relação ao tumor primário e com intervalos variáveis após o término do tratamento, variando de poucos meses a anos (Spreafico et al. 2008; Kumar et al. 2000). No estudo controle, as LRI geralmente regridem de tamanho, embora o aumento das suas dimensões durante os intervalos nas avaliações iniciais, seguido por diminuição subsequente possa também ocorrer. O diagnóstico de radionecrose deve ser suspeito nos casos em que a lesão

aumenta progressivamente em suas dimensões e se associa à presença de edema e efeito expansivo (Pružincová et al. 2009).

Os resultados obtidos no nosso estudo demonstram que todas as lesões, exceto uma LRI com realce de contraste focal, não apresentaram restrição à difusão, sugerindo que a ausência de restrição à difusão favorece uma lesão não neoplásica nesse contexto. De fato, os valores quantitativos mínimo e a médio do mapa ADC das recidivas focais e das LRI evidenciaram diferenças significativas entre os dois grupos. Vale salientar que todos os nossos pacientes com recidivas foram selecionados com base em confirmação patológica ou determinação radiológica (de acordo com os critérios radiológicos atuais) (Sébastien Perreault et al. 2013). Com a exceção de dois pacientes, por razões clínicas e éticas, todos os demais obtiveram confirmação histológica das recidivas e LRI.

Em relação ao envolvimento leptomeníngeo difuso das recidivas, nossos dados confirmam que a imagem pós-contraste é a sequência que apresenta maior sensibilidade em relação às demais e é, portanto, a base para o diagnóstico de recidivas leptomeníngeas. No entanto, mesmo neste padrão de disseminação, a sequência DWI pode ser útil no diagnóstico, sendo capaz, por vezes, de demonstrar a presença de extensas áreas de restrição da superfície pial do parênquima acometido, mesmo na ausência de impregnação pelo contraste nas sequências ponderadas em T1.

A análise direcionada para recidiva de meduloblastomas, segundo seu padrão histológico, demonstrou que em indivíduos com a variante histológica clássica, a DWI contabilizou um número maior de lesões focais quando comparada à sequência T1W pós-contraste isolada. As recidivas do subtipo histológico clássico dos meduloblastomas, também, apresentaram ausência de realce pelo contraste com maior frequência. Ao mesmo tempo, a ausência de realce dos meduloblastomas primário foi documentada

principalmente em variantes clássicas (6 dos 7 tumores da nossa casuística não impregnavam pelo gadolínio). Curiosamente, uma observação semelhante em relação às lesões primárias foi relatada por Fruehwald-Pallamar J e colg. (Fruehwald-Pallamar et al. 2011), que observaram tênue realce ou realce linear apenas no MB clássico, enquanto todas as outras variantes de meduloblastomas apresentaram realce acentuado. Um resultado semelhante foi, também, documentado pelo estudo de Yeom KW e colg. (Yeom et al. 2013), em que 8 de 9 meduloblastomas primários sem realce pertenciam ao grupo clássico. Em um outro estudo mais recente de Łastowska M e colg., (Łastowska et al. 2015) avaliando o padrão de impregnação pelo contraste nos tumores com subtipos moleculares meduloblastomas não- *WNT* / *SHH*, foi observada a impregnação pelo gadolínio em todos os casos desses subgrupos (29 de 60 indivíduos), dos quais 25 eram meduloblastomas clássicos. Este aspecto destaca o papel da DWI na imagem de controle do meduloblastomas clássico.

Curiosamente, embora o meduloblastoma aparentemente não mude o seu grupo molecular na recidiva e permaneça estável entre os compartimentos primário e metastático (Ramaswamy et al. 2013; Wang et al. 2015), os subtipos histológicos de meduloblastomas podem mudar com a recidiva, como demonstrado por Pöschl J e colg. (Pöschl, Koch, and Schüller 2015) em uma série de 16 recidivas de meduloblastomas, na qual 7 de 16 casos (44%) apresentaram alteração no subtipo histológico. Nesse estudo, a maioria dos casos de meduloblastoma desmoplásico / nodular (57%) recidivou como meduloblastoma clássico, enquanto todos os meduloblastomas clássicos, exceto um, permaneceu no mesmo grupo molecular. Esta observação pode, potencialmente, dar uma explicação da evidência de neuroimagem sobre a ausência de realce em recidivas de meduloblastomas quando comparada aos tumores primários e pode reforçar, ainda mais,

o papel da DWI no controle do meduloblastomas dada a alta frequência de tumores que se incluam como variantes clássicas.

Como o diagnóstico do subgrupo molecular de meduloblastomas não estava disponível para todos os nossos pacientes, as conclusões definitivas sobre possíveis correlações entre as características da DWI nas recidivas e os subgrupos moleculares foram limitadas. Destaca-se, porém, a clara discrepância entre restrição e impregnação para alguns subtipos moleculares, sendo este último menos observado nos grupos *WNT*, *SHH* e no grupo 4, contrapondo os meduloblastomas- grupo 3 que impregnaram mais frequentemente. Novos estudos com casuísticas maiores são necessários para avaliar se exames de imagem controle nos subgrupos moleculares específicos de meduloblastomas podem ser aprimorados pela avaliação detalhada da DWI.

Devido à algumas limitações do nosso estudo, os nossos resultados devem ser interpretados com cautela. Primeiro, dada a natureza retrospectiva do estudo, o viés de amostragem não pode ser excluído. Também, estamos cientes da amostra relativamente pequena de pacientes. No entanto, a análise por lesão permitiu avaliar um número significativo de lesões. Não avaliamos a imagem FLAIR pós-contraste em nosso estudo, uma vez que nosso protocolo de controle de tumores cerebrais de rotina não inclui essa sequência após injeção de contraste.

Reconhecemos que a imagem FLAIR pós-contraste pode adicionar informações significativas à imagem ponderada em T1 pós-contraste convencional para a avaliação de doença leptomeníngea, melhorando a detecção de metástase leptomeníngea em crianças (Ercan et al. 2004; Griffiths et al. 2003). Acreditamos que pesquisas adicionais com o objetivo de comparar o valor diagnóstico da DWI e imagens de FLAIR pós-contraste no

acompanhamento de tumor embrionário do SNC pode trazer informações relevantes e uma significativa contribuição destas sequências neste contexto.

Como o diagnóstico detalhado do grupo molecular dos meduloblastomas não estava disponível para todos os pacientes da nossa casuística, as conclusões definitivas sobre possíveis correlações entre as características da DWI nas recidivas e os subgrupos moleculares dos meduloblastomas foram limitadas. Destaca-se, porém, a clara discrepância entre restrição à difusão e impregnação de alguns subtipos moleculares, sendo a impregnação menos observada nos grupos *WNT*, *SHH* e no grupo 4 contrapondo os meduloblastomas- grupo 3. Esses resultados são concordantes a estudos que avaliam as características desses tumores quando primários à sua origem (Colafati et al. 2018) e ao padrão de imagem da sua recorrência (Aboian et al. 2018). No entanto, acreditamos que novos estudos, preferencialmente longitudinais e com casuísticas maiores, são necessários para melhor avaliar a potencial relação das sequências da DWI na diferenciação das recidivas de meduloblastomas.

3- Conclusões

1. Os tumores pediátricos do sistema nervoso central apresentam uma ampla variabilidade de representações por imagem, sendo algumas das suas características de imagem observadas no estudo de ressonância magnética, muito úteis para sua diferenciação diagnóstica. Dessa forma, a utilização de formulações sistematizadas de análise, como por exemplo o uso de fluxograma, são úteis para estabelecer métodos de leitura uniformizados. Destaca-se dentro do grupo de tumores pediátricos a alta acurácia diagnóstica de um fluxograma que utiliza às características de restrição à DWI para o diagnóstico dos tumores embrionários, em especial meduloblastomas e TTRA, que apresentam quase que obrigatoriamente restrição à difusão.

2. A DWI representa uma importante ferramenta diagnóstica dentre às diversas sequências obtidas na ressonância magnética para o acompanhamento de tumores embrionários pós-tratamento e detecção de metástases leptomeningeas, podendo fornecer informações essenciais para o manejo desses pacientes. Em particular, a DWI pode aumentar a detecção de recidivas focais e auxiliar na diferenciação de doenças recidivadas das lesões induzidas por radiação com impregnação pelo gadolínio. A avaliação cuidadosa de imagens DWI é, portanto, altamente recomendável para esses pacientes. Adicionalmente, crianças com meduloblastomas da variante histológica clássica, com perfis moleculares dos grupos *SHH*, *WNT* e grupo 4, devem ser reconhecidas como potenciais formas de apresentação de recidivas com maior frequência de lesões sem impregnação, e com restrição à difusão.

4- Anexos

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ORIGINAL RESEARCH
PEDIATRICS

A Diagnostic Algorithm for Posterior Fossa Tumors in Children: A Validation Study

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ABSTRACT

BACKGROUND AND PURPOSE: Primary posterior fossa tumors comprise a large group of neoplasias with variable aggressiveness and short and long-term outcomes. This study aimed to validate the clinical usefulness of a radiologic decision flow chart based on previously published neuroradiologic knowledge for the diagnosis of posterior fossa tumors in children.

MATERIALS AND METHODS: A retrospective study was conducted (from January 2013 to October 2019) at 2 pediatric referral centers, Children's Hospital of Philadelphia, United States, and Great Ormond Street Hospital, United Kingdom. Inclusion criteria were younger than 18 years of age and histologically and molecularly confirmed posterior fossa tumors. Subjects with no available preoperative MR imaging and tumors located primarily in the brain stem were excluded. Imaging characteristics of the tumors were evaluated following a pre-designed, step-by-step flow chart. Agreement between readers was tested with the Cohen κ , and each diagnosis was analyzed for accuracy.

RESULTS: A total of 148 cases were included, with a median age of 3.4 years (interquartile range, 21–61 years), and a male/female ratio of 124. The pre-designed flow chart facilitated identification of pilocytic astrocytoma, ependymoma, and medulloblastoma *sonic hedgehog* tumors with high sensitivity and specificity. On the basis of the results, the flow chart was adjusted so that it would also be able to better discriminate atypical teratoid/rhabdoid tumors and medulloblastoma groups 3 or 4 (sensitivity = 75%–79%; specificity = 92%–99%). Moreover, our adjusted flow chart was useful in ruling out ependymoma, pilocytic astrocytomas, and medulloblastoma *sonic hedgehog* tumors.

CONCLUSIONS: The modified flow chart offers a structured tool to aid in the adjunct diagnosis of pediatric posterior fossa tumors. Our results also establish a useful starting point for prospective clinical studies and for the development of automated algorithms, which may provide precise and adequate diagnostic tools for these tumors in clinical practice.

ABBREVIATIONS: AT/RT = atypical teratoid/rhabdoid tumor; LR = likelihood ratio; NPV = negative predictive value; PA = pilocytic astrocytoma; PPV = positive predictive value; WNT = wingless; SHH = *sonic hedgehog*.

In the past 10 years, there has been an exponential increase in knowledge of the molecular characteristics of pediatric brain tumors, which was only partially incorporated in the 2016 World Health Organization Classification of Tumors of the Central Nervous System.¹ The main update in the 2016 Classification was the introduction of the molecular profile of a tumor as an

important factor for predicting different biologic behaviors of entities which, on histology, look very similar or even indistinguishable.² A typical example is the 4 main groups of medulloblastoma: *wingless* (WNT), *sonic hedgehog* (SHH) with or without the p53 mutation, group 3, and group 4. Although they may appear similar on microscopy, these categories have distinct molecular profiles, epidemiology, prognosis, and embryologic origin.³

Subsequent to the publication of the 2016 World Health Organization Classification, further studies have identified even more molecular subgroups of medulloblastoma with possible prognostic implications⁴ and also at least 3 new molecular subgroups of atypical teratoid/rhabdoid tumor (AT/RT)⁵ and several subgroups of ependymoma.⁶ MR imaging shows promise as a technique for differentiating histologic tumors and their molecular subgroups. This capability relies on not only various imaging characteristics but also the location and spatial extension of the tumor, evident on MR imaging, which can be traced to the embryologic origin of the neoplastic cells.^{5,7–10}

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FIG 1. Predesigned radiologic flow chart created according to the literature before diagnostic accuracy analysis. The asterisk indicates brain stem tumors excluded from the analysis. Double asterisks indicate relative to gray matter. Modified with permission from D'Arco et al.¹¹

One approach to the challenge of identifying imaging characteristics of different tumors in children is to use artificial intelligence. Yet despite this exciting innovation, correctly identifying the location of the mass and its possible use as an element for differential diagnosis still requires the expertise of an experienced radiologist. Previously, D'Arco et al.¹¹ proposed a flow chart (Fig 1) for the differential diagnosis of posterior fossa tumors in children based on epidemiologic, imaging signal, and location characteristics of the neoplasm. The aims of the current study were the following: 1) to validate, in a retrospective, large cohort of posterior fossa tumors from 2 separate pediatric tertiary centers, the diagnostic accuracy of that flow chart, which visually represents the neuroradiologist's mental process in making a diagnosis of posterior fossa tumors in children, 2) to describe particular types of posterior fossa lesions that are not correctly diagnosed by the initial flow chart, and 3) to provide an improved, clinically accessible flow chart based on the results.

MATERIALS AND METHODS

Setting and Subjects

A retrospective, cross-sectional study from 2 large tertiary referral pediatric hospitals in 2 countries (Children's Hospital of Philadelphia, United States, and Great Ormond Street Hospital, London, United

Kingdom) was performed on the basis of patient records spanning January 2013 to October 2019 in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.¹² This study was conducted under 2 research protocols (IRB No. 18-015588 and CA Reg No. 2504), approved by the respective institutional review boards at each center.

Subjects were identified by electronic search of brain MR imaging reports and the electronic health record systems. The following terms/diagnoses were used for the search: "brain tumor," "posterior fossa tumor," "brain neoplasia," "posterior fossa neoplasia," "cerebellar tumor," "cerebellar neoplasia," "medulloblastoma," "AT/RT," "atypical teratoid/rhabdoid tumor," "ependymoma," "pilocytic astrocytoma." Results were screened, and subjects younger than 18 years of age with a histologically and genetically confirmed diagnosis of posterior fossa tumor, according to the 2016 World Health Organization classification, were selected.² Subjects with no available preoperative MR imaging study, those with low-quality MR imaging studies, and those without diffusion imaging on their MR imaging study were excluded. Subjects with tumors located primarily in the brain stem were also excluded.

Variables

Age at first MR imaging (before histologic/pathologic confirmation of the tumor), sex, and histologic and genetic/molecular results

were obtained from the electronic medical records. Two experienced pediatric neuroradiologists independently reviewed these initial MR imaging studies at each institution (C.A.P.F.A., A.V., F.D., and U.L.), blinded to the final diagnosis. Imaging characteristics were evaluated following a step-by-step numeric flow chart, with a digit assigned to each level and subsequent branch, providing a flow chart and a 3-digit numeric sequence code for each diagnosis end point to be used in the analysis (Fig 1). The flow chart took into account the following: 1) tumor location, 2) ADC map signal intensity in comparison with gray matter, 3) internal architecture, 4) contrast enhancement, and 5) the patient's age. The flow chart was designed before the initiation of the study; it was based on a review on the topic by D'Arco et al.¹¹ Before starting the blinded analysis of the cohort, one of the readers (C.A.P.F.A.) performed a pilot evaluation using the first 8 cases from each institution (16/148; 10.8%) to confirm the applicability of the flow chart multiple weeks before the formal evaluation.

Statistical Analysis

Visual inspection of the histogram showed non-normal distribution, which was confirmed with the Shapiro-Wilk test ($P < .001$) for all numeric variables. Categorical variables are described with percentage and frequency, and numeric variables, with median and interquartile range. Statistical analysis was performed using R statistical and computing software, Version 3.5.3 for Windows (<http://www.r-project.org/>).

Diagnostic accuracy of the flow chart was verified through a 2×2 contingency table and calculation of sensitivity, specificity, positive predictive values (PPV), and negative predictive value (NPV). To estimate accuracy and effect size, we estimated 95% CIs for sensitivity, specificity, PPV, and NPV. The diagnostic accuracy analysis was performed for each diagnosis, with molecular/histologic diagnosis as the criterion standard comparison. Because flow chart numeric sequences 312 and 311 of the predesigned flow chart would not provide a single unique final tumor molecular diagnosis, we later adjusted the sequences according to the most prevalent diagnosis. The modified flow chart reflects these adjustments. Last, we recalculated diagnostic accuracy tests on the basis of the adjustments for these 2 flow chart modifications. The clinical applicability of findings was further explored with positive and negative likelihood ratios (LR+ and LR-, respectively), and on the basis of changes in probability from the LR described by McGee.¹³ Clinical applicability to rule in diagnosis was considered if the 95% CI of LR+ was above 10. Clinical applicability to rule out diagnosis was considered if the 95% CI of LR- was below 0.5.

RESULTS

Histologic Diagnosis and Demographics

One hundred forty-eight subjects were included. The median age at MR imaging was 3.4 years, (interquartile range = 2.1–6.1 years), and the male/female ratio was 1.24. Fifty-four (36.5%) patients had a histologic diagnosis of medulloblastoma, 56 (37.5%) had pilocytic astrocytoma (PA), 12 (8.1%) had AT/RT, and 19 (12.8%) had ependymoma. Medulloblastomas were also subclassified according to molecular subtypes including 14/54 (26%) *SHH*; 7/54 (13%) *WNT*; 5/54 (9%) group 3; 9/54 (17%) group 4; and 19/54 (35%) group 3 or 4 (separation of groups 3 and 4 was not always

easily possible). Seven cases (5%) had a diagnosis of other tumors not covered by the flow chart (2 low-grade diffuse astrocytomas not otherwise specified, 1 hemangioblastoma, 2 gangliogliomas, 1 case of Langerhans cell histiocytosis, and 1 meningioma). Agreement between readers at each institution was very high ($\kappa = 0.96$ for both institutions, $P < .001$). Because both institutions had almost perfect agreement, we did a pooled analysis without differentiating per institution. The same diagnosis using the predesigned flow chart was reached for 86% of the cohort. In the 14% of cases in which the same diagnosis was not reached by the 2 readers, disagreement was solved through consensus between the readers.

Diagnosis Using the Flowchart

By means of the predesigned flow chart (Fig 1), the most common diagnosis was PA (numeric sequence 123) ($n = 53$, 36%), followed by medulloblastoma all subgroups (numeric sequence 312) ($n = 35$, 24%), ependymoma (numeric sequence 323) ($n = 17$, 11%), medulloblastoma *SHH* (numeric sequence 111) ($n = 10$, 7%), medulloblastoma group 4 or AT/RT (numeric sequence 311) ($n = 5$, 3%), AT/RT (numeric sequence 411) ($n = 7$, 5%), ependymoma (numeric sequence 423) ($n = 7$, 5%), desmoplastic medulloblastoma *SHH* (numeric sequence 112) ($n = 6$, 4%), desmoplastic medulloblastoma *SHH* (numeric sequence 313) ($n = 3$, 2%), and medulloblastoma *WNT* (numeric sequence 412) ($n = 5$, 3%). Figure 2 and Table 1 show the statistical results of the sensitivity, specificity, PPV, and NPV of the flow chart per diagnosis.

In cases that followed sequence 311 (medulloblastoma group 4 or AT/RT), 3/5 (60%) were AT/RT, 1/5 (20%) was an ependymoma, and 1/5 (20%) was a medulloblastoma group 4. This finding suggested that sequence 311 catches more tumors in the AT/RT category than in medulloblastoma group 4, so we recalculated the diagnostic accuracy tests considering both 311 and 411 as AT/RTs. As can be appreciated in Fig 2 and Table 1, diagnostic accuracy for cases of AT/RT improved when combining sequences 311 and 411. Of the 35 cases under sequence 312 (medulloblastoma all subgroups), 26/35 (74%) were confirmed as group 3 or 4 (3 confirmed as group 3, eight confirmed as group 4, and 15, as group 3 or 4). The remaining cases under sequence 312 were 3/35 (9%) *SHH*, 5/35 (14%) *WNT*, and 1/35 (3%) AT/RT. Figure 3 shows the diagnostic accuracy of sequence 312 to identify medulloblastoma *SHH*, *WNT*, and group 3 or 4. For this sequence, the NPV and specificity were higher than the PPV and sensitivity for all other sequences. Table 2 shows the LR analysis per diagnosis and the recommended sequences for the diagnosis. After our analysis and on the basis of Table 1 results, we modified the predesigned flow chart with more precise categorization of the types of tumor. We recommend this new flow chart (Fig 4) for the diagnosis of posterior fossa tumors in children.

Some examples of differentiating posterior fossa tumors from our cohort, diagnosed on the basis of the new flow chart here presented, can be seen in Figs 5 and 6.

DISCUSSION

The 2016 introduction of the new classification of brain tumors based on histologic and molecular characteristics dramatically changed the management of pediatric brain tumors.^{1,2,14,15} Tumors with similar histologic appearance being related to

FIG 2. Diagnostic accuracy of a predesigned radiologic flow chart to identify different types of cerebellar tumors.

Table 1: Statistical analysis of the radiologic flow chart to discriminate different types of cerebellar tumors

Diagnosis Equivalent	Flowchart Sequence	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Ependymoma	323/423	89 (67–99)	95 (89–98)	71 (49–87)	98 (94–100)	94 (89–97)
Pilocytic astrocytoma	123	88 (76–95)	96 (89–99)	92 (82–98)	93 (85–97)	93 (87–96)
AT/RT	411	50 (21–79)	99 (96–100)	86 (42–100)	96 (91–98)	99 (96–100)
AT/RT	411/311	75 (43–95)	98 (94–100)	75 (43–95)	98 (94–100)	91 (96–98)
Medulloblastoma SHH	111/112/313	71 (42–92)	93 (88–97)	53 (29–76)	97 (92–99)	72 (64–79)
Medulloblastoma WNT	412	14 (0–58)	97 (93–99)	20 (1–72)	96 (91–98)	88 (93–97)

completely different cellular populations with different molecular profiles and different embryologic origins implies that they develop along different cellular paths. Thus, tumors that were previously considered as a single group can now be differentiated on imaging by location, age, and/or the patient's signal characteristics, resulting in a more accurate prognosis.^{16–18}

In light of the crucial role of molecular profiling in tumor diagnosis and management, we found that the predesigned flow chart was very useful for categorizing and better understanding pediatric brain tumors. The importance of molecular profiling in the pediatric neuro-oncology clinical practice was first studied in medulloblastomas but is now recognized for ependymomas, low-grade astrocytomas, AT/RTs, and all previously classified primitive neuroectodermal tumors.^{6,18–22}

Yet, since the 2016 classification update, several newly identified radiologic markers have been proposed as surrogates for the molecular diagnosis. The role of these radiologic markers may be limited by the constant evolution of the molecular characterization of brain tumors.^{8,11} However, we believe that a standardized method of evaluating images, such as the proposed flow chart, may facilitate increased diagnostic accuracy.

The initial predesigned diagnostic flow chart has proved reliable and consistently accurate in this validation study, with an almost perfect agreement between 2 blinded neuroradiologists at 2 different institutions. Our results showed high coefficients of specificity and NPV for all diagnoses included in the predesigned flow chart. Sensitivity coefficients were high (>87%) for diagnosing pilocytic astrocytoma and ependymomas, the 2 most common diagnoses in

FIG 3. Diagnostic accuracy of sequence 312 (all types of medulloblastomas) of the predesigned radiologic flow chart to identify different types of medulloblastomas.

Table 2: Likelihood ratio analysis of the radiologic flow chart to discriminate different types of cerebellar tumors

Diagnosis	Flow Chart Sequence	LR+ (95% CI)	LR- (95% CI)
AT/RT	411/311	34 (10.6–109) ^a	0.26 (0.1–0.7)
Ependymoma	323/423	16.5 (7.9–35)	0.11 (0.03–0.4) ^a
Medulloblastoma SHH	111/112/313	10.6 (5.2–21.7)	0.3 (0.1–0.7)
Medulloblastoma group 3 or 4	312	10.07 (5.3–19.3)	0.23 (0.12–0.45) ^a
Pilocytic astrocytoma	123	2.0 (7.7–52.8)	0.13 (0.13–0.26) ^a

^aClinically applicable confidence intervals.

our cohort. Moreover, PA and ependymoma tumors had the smallest 95% CIs, suggesting reliability in the diagnosis of these 2 types of tumors. This was especially true for PA, in which the lower 95% CI limit for sensitivity was 76%, and for PPV, it was 82%.

After analyzing results from the initial flow chart created on the basis of more recently published literature, we modified it to improve diagnostic accuracy. Our modifications (see Figs 1 and 4 for comparison) successfully improved the sensitivity coefficient for identification of AT/RTs to 75%, but the confidence interval remained wide. The second modification to flow chart sequence 312 made possible the identification of most cases of medulloblastoma

group 3 or 4, with fair-to-good sensitivity (61%–91%) and PPV (57%–88%) and good-to-excellent specificity (86%–96%) and NPV (88%–97%). The modified flow chart (Fig 4) proved to be more clinically relevant. The modified flow chart proved capable of discriminating AT/RTs, ependymomas, medulloblastomas SHH, medulloblastoma groups 3 and 4, and PA, which together constitute 90.5% of tumors in our cohort.

Clinically, the flow chart demonstrates great performance in ruling out group 3 or 4 medulloblastomas, PAs, and ependymomas and ruling in AT/RTs.

However, when it came to correctly identifying WNT medulloblastoma (numeric sequence 412, Fig 2), diagnostic accuracy was poor. In the predesigned flow chart, the authors designated a tumor in the pontocerebellar angle/foramen of Luschka with high cellularity (ie, low ADC) and patient age older than 3 years as suggestive of WNT. The rationale was that the cellular path of embryologic precursors, which can transform into neoplastic WNT cells, arises from the fourth ventricle down and laterally into the foramen of

FIG 4. Modified radiologic flow chart (flow chart 2) after diagnostic accuracy analysis. The asterisk indicates brain stem tumors excluded from the analysis. Double asterisks indicate relative to gray matter. Triple asterisks indicates low PPV and sensitivity for any particular molecular/histological group of tumor.

Luschka.⁷ The only other tumor with striking diffusion restriction in the Luschka area is AT/RT, but this is typical of younger children.²³ These results can be explained by several factors: the small number of WNT tumors present in our series (10% of all medulloblastomas), most cases in our series being in the fourth ventricle (which is understandable given that the path of the WNT cells is thought to start from the fourth ventricle), and the presence of anaplastic ependymomas showing diffusion restriction (therefore simulating WNT medulloblastoma on imaging).²⁴ More recently, a study of a larger cohort of WNT medulloblastomas has shown that they are not as lateralizing as previously reported in smaller cohorts.²⁵

This study has some limitations, the main one being its retrospective nature. However, we controlled potential biases by doing a blinded review of images by only including cases with images obtained before surgical intervention and creating the baseline flow chart before data collection. Another important limitation is the relatively small number of cases for some types of tumor, which explains the larger confidence intervals for certain tumors. Nevertheless, many pediatric cerebellar tumors are relatively rare, and this is perhaps one of the largest cohorts available in the literature.²⁶ Moreover, we were able to gather a large enough cohort to allow diagnostic accuracy tests for the most common types of pediatric cerebellar tumors, with reliable results for most diagnoses.

Because this was planned as a validation study, we consider it successful in providing results that show that the modified flow chart can be used, is reliable, and has clinical applicability.

More research is still desired, with a larger consistency analysis evaluating results from multiple blinded readers. A larger prospective study would be needed to evaluate the diagnostic efficacy of the modified flow chart with higher precision. Such a study could provide an initial decision model for potential deep learning studies. Artificial intelligence is already being used to predict the molecular profile of brain tumors, most commonly in adult populations, but with recent important studies emerging in pediatric populations.^{27,28} The main limitation for the application of machine learning in posterior fossa tumors may be the identification of tumor location,²⁹ because we know that signal characteristics (which reflect at least partially histologic appearances) can be similar for different molecular groups with similar tissue features. Currently, artificial intelligence is not able to differentiate tumors with the necessary level of precision, though this may be possible in the future.

CONCLUSIONS

A flow chart for the diagnosis of posterior fossa tumors in children has been validated through a retrospective analysis of 148 patients with confirmed diagnoses. On the basis of analysis of these

FIG 5. Differential diagnoses in cases of posterior fossa tumors originating from the cerebellar hemisphere. Axial T2WI (A) and axial ADC map (B) show SHH medulloblastoma (flow chart 2, number 11) in a typical peripheral location within the cerebellar hemisphere due to its origin from ganglionic cell precursors. Note very low ADC values (ie, diffusion restriction). Axial T2WI (C) and axial ADC map (D) show the typical appearance of a pilocytic astrocytoma (flow chart 2, number 123) originating from the cerebellar hemisphere. Note the typical nodule and appearance of cysts and much higher ADC values in comparison with the medulloblastoma.

FIG 6. Differential diagnoses in posterior fossa tumors involving the foramen of Luschka and cerebellopontine angle. Axial T2WI (A) and ADC map (B) in a child with ependymoma (flow chart 2, number 423). Note the presence of internal vessels (arrow) and intermediate ADC values. Axial T2 (C) and ADC maps (D) in a 2-year-old boy with an AT/RT (new flow chart number 411). Note very low values of ADC, suggesting an embryonal tumor and peripheral cysts.

results, the predesigned flow chart was accurate in identifying most diagnoses, and with our subsequent modifications, the overall accuracy improved. The modified flow chart showed a good

likelihood ratio for most of the histologic and molecular groups of tumors. Furthermore, it may offer an important starting point for prospective analysis using machine learning techniques. As new molecular subgroups emerge in the classification of pediatric brain tumors, there is the potential for further modifications to the flow chart to aid in diagnosis.

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Research Paper

Added value of diffusion weighted imaging in pediatric central nervous system embryonal tumors surveillance**Giovanni Morana^{1,*}, Cesar Augusto Alves^{1,2,*}, Domenico Tortora¹, Mariasavina Severino¹, Paolo Nozza³, Armando Cama⁴, Marcello Ravegnani⁴, Gabriella D'Apolito⁵, Alessandro Raso⁴, Claudia Milanaccio⁶, Claudia da Costa Leite², Maria Luisa Garre⁶ and Andrea Rossi¹**¹Neuroradiology Unit, Istituto Giannina Gaslini, Genova, Italy²Radiology Institute, Hospital das Clinicas, Sao Paulo, Brazil³Pathology Unit, Istituto Giannina Gaslini, Genova, Italy⁴Neurosurgery Unit, Istituto Giannina Gaslini, Genova, Italy⁵Neuroradiology Unit, Ospedale M. Bufalini, Cesena, Italy⁶Neuro-Oncology Unit, Istituto Giannina Gaslini, Genova, Italy

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ABSTRACT

Diffusion weighted imaging (DWI) has an established role in primary CNS embryonal tumor (ET) characterization; however, its diagnostic utility in detecting relapse has never been determined. We aimed to compare DWI and conventional MRI sensitivity in CNS ET recurrence detection, and to evaluate the DWI properties of contrast-enhancing radiation induced lesions (RIL).

Fifty-six patients with CNS ET (25 with disease relapse, 6 with RIL and 25 with neither disease relapse nor RIL) were retrospectively evaluated with DWI, conventional MRI (including both T2/FLAIR and post-contrast images), or contrast-enhanced MR imaging (CE-MRI) alone. MRI studies were independently reviewed by two neuroradiologists for detection and localization of potential brain relapses. Sensitivity for focal relapse detection was calculated for each image set on a lesion-by-lesion basis. A descriptive per subject analysis was also performed. Evaluation of follow-up MRI studies served as standard of reference.

Focal recurrence detection sensitivity of DWI (96%) was significantly higher than conventional MRI (77%) and CE-MRI alone (51%) ($p=0.0003$ and $p<0.0001$). On per subject analysis there were not missed diagnoses for DWI. At the time of DWI relapse detection, conventional MRI missed 2 diagnoses, and CE-MRI 8. Analysis of medulloblastoma relapses revealed that DWI identified a higher number of focal lesions than CE-MRI in subjects with classic variant. All but one RIL did not show restricted diffusion.

In conclusion, DWI is a valuable complementary technique allowing for improved detection of focal relapse in CNS ET patients, particularly in children with classic medulloblastoma, and may assist in differentiating recurrence from RIL.

INTRODUCTION

Central nervous system (CNS) embryonal tumors (ET) comprise a biologically heterogeneous group of malignant neoplasms occurring predominantly in children, generally composed of densely packed poorly differentiated cells (small blue cell tumors) with scant cytoplasm and high mitotic index [1]. According to the revised fourth edition of the WHO classification [2], the most common entities in this group include medulloblastomas (MB) (genetically or histologically defined), atypical teratoid/rhabdoid tumors (AT/RT), embryonal tumors with multilayered rosettes (ETMR), C19MC-altered and CNS embryonal tumors, NOS (replacing the CNS primitive neuroectodermal tumors of the fourth edition of the WHO classification).

ET demonstrate an increased tendency to recur and disseminate throughout the nervous system via cerebrospinal fluid pathways. Disease may recur at the primary site or may be disseminated at the time of relapse. Sites of distant relapse include the spinal leptomeninges and intracranial sites, in isolation or in any combination [3-5].

Contrast-enhanced MRI is the recommended standard to assess tumor spread and recurrence on imaging [6]. However, while the majority of primary CNS ET typically show contrast enhancement, the degree of enhancement can be variable, and considering only MB, approximately 11% to 25% do not enhance [7-10]. In addition, although MRI findings of pia-arachnoidal or focal nodular brain enhancement were previously described as highly specific in the diagnosis of recurrent disease [11], contrast enhancement may occur as a result of radiation therapy [12, 13], thus posing a major diagnostic challenge.

Diffusion weighted imaging (DWI) provides information regarding diffusion of water molecules in the section studied, from which quantitative values, the so-called apparent diffusion coefficient (ADC), can be calculated. DWI provides non-invasive estimation of differences in cell density and tissue structure and has been widely used in the diagnosis of pediatric brain tumors [14]. In particular, it has been demonstrated that CNS ET usually show decreased diffusivity in keeping with their common cellular features [9, 15, 16]. Nevertheless, even though the role of DWI in primary CNS ET characterization is well known, the diagnostic utility of DWI in detecting CNS ET relapse has not been conclusively established to our knowledge.

On the basis of these considerations, the aim of this study was to assess and compare DWI and conventional MRI sensitivity in CNS ET recurrence detection, and to evaluate the DWI properties of contrast-enhancing radiation induced lesions (RIL).

RESULTS

Among 56 subjects enrolled in the study, 25 with disease relapse and 31 without relapse (6 with RIL and 25

without RIL) (Table 1), a total of 125 focal brain lesions were identified according to our standard of reference. In detail, there were 103 focal brain relapses and 22 radiation induced lesions. Nine subjects with focal disease relapse presented also with diffuse linear secondary pathological involvement. Isolated local relapse occurred in 4 patients (1 MB, 1 ETMR and 2 ATRT), combined local and distant relapse in 6 (all patients with MB) and isolated distant relapse in 15 (9 MB, 2 CNS ET, NOS, 4 ATRT). Distribution of focal relapsing lesions is reported in Table 2. Distribution of focal radiation-induced lesions was as follows: 13 local (11 cerebellar hemispheres, 2 middle cerebellar peduncles) and 9 distant (4 ependymal supratentorial, 5 thalami).

Time to relapse ranged between 4.8 and 118 months after disease onset (median 18 months). Time to RIL onset ranged from 5 to 10 months (median 7.5 months) after the end of treatment.

Of 103 focal relapses, DWI correctly detected 99 lesions (96.1%), conventional MRI 79 (76.6%) and contrast-enhanced (CE)-MRI alone 53 (51.4%) at the blinded reading session. DWI identified 19.42% more focal relapses than conventional MRI (95% CI, 18.56-25.24, $p=0.0003$) and 44.66% more lesions than CE-MRI (95% CI, 9.42-24.99, $p<0.0001$). Conventional MRI identified 25.24% more focal relapses than CE-MRI (95% CI, 18.56-25.24, $p<0.0001$) (Figure 1).

Of 22 focal radiation induced contrast enhancing lesions, only 1 demonstrated decreased diffusion whereas the remainder showed increased diffusivity or diffusivity similar to normal parenchyma.

Interobserver agreement was excellent for every image set: DWI (ICC, 0.986; 95% CI, 0.972-0.993), conventional MRI (ICC, 0.989; 95% CI, 0.978-0.995) and CE-MRI (ICC, 0.994; 95% CI, 0.988-0.997).

A statistically significant difference was demonstrated between sensitivity of DWI (96%), conventional MRI (77%) and contrast enhanced (CE)-MRI (51%) ($p=0.0003$ and $p<0.0001$, respectively). A statistically significant difference was also demonstrated between conventional MRI and CE-MRI ($p<0.0001$). The positive predictive value (PPV) of DWI was 99%.

The average minimum and mean ADC values across relapsing lesions were $0.540 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.128$ (SD) and $0.642 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.145$ (SD), respectively. The average minimum and mean ADC values across RIL were $1.086 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.698$ (SD) and $1.201 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.751$ (SD). A significant difference was demonstrated between minimum and mean ADC of relapsing lesions and RIL ($p<0.001$ and $p=0.001$, respectively). The average minimum and mean ADC values across primary lesions were respectively $0.515 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.063$ (SD) and $0.676 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.090$ (SD). Evaluation of the contrast enhancement pattern of primary lesions revealed 10 non-enhancing tumors: 7 MB (6 classic, 1 anaplastic), 2 AT/RT and 1 CNS ET, NOS.

Table 1: Summary of subjects characteristics

No. of subjects		56			
Sex					
Male		35 (62.5%)			
Female		21 (37.5%)			
Age at diagnosis					
Median		5.4			
Range		0-14.3			
No. of subjects with relapse		25			
Histology					
MB	16	LCA 6	Group 3	2	
			Group 4	1	
			SHH	2	
			Not available	1	
		Classic 9	Group 3	2	
			Group 4	2	
			WNT	1	
			Not available	4	
		Desm/Nod 1	SHH	1	
ATRT		6 (4 supratentorial, 2 infratentorial)			
CNS ET, NOS		2 (supratentorial)			
ETMR		1 (supratentorial)			
No. of subjects with RIL		6			
Histology					
MB	6		LCA 2		
			Classic 4		
No. of subjects with neither relapse nor RIL		25			
Histology					
MB	19		LCA 4		
			Classic 9		
			Desm/Nod 6		
CNS ET, NOS		4 (supratentorial)			
ATRT		2 (1 supratentorial, 1 infratentorial)			
Treatment					
CSI + Chemo		47 (84%)			
Chemo only		9 (16%)			
Time to recurrence (months)					
Median		18			
Range		4,8-118			
Time to RIL (months since the end of RT)					
Median		7,5			
Range		5-10			

(Continued)

No. of subjects	56
Site of recurrence	
Local	4
Distant	15
Combined	6
Pattern of recurrence	
Focal nodular	16
Focal nodular and diffuse linear	9
Survival in pts with recurrence	
Dead	21
Alive	4

MB: medulloblastoma, ATRT: atypical teratoid rhabdoid tumor, CNS ET, NOS: central nervous system embryonal tumor, not otherwise specified, ETMR: embryonal tumor with multi-layered rosette, LCA: large cell anaplastic, Desm: desmoplastic, RIL: radiation induced lesions, CSI: craniospinal irradiation.

On per subject analysis, focal relapse was solely identified by DWI in two patients (8%) (1 MB, and 1 CNS ET, NOS). In 6 patients (24%) (all with MB), DWI identified a higher number of focal relapses when compared to conventional MRI. In 5 patients (20%) (2 MB, 1 ETMR, 2 ATRT), focal relapses were equally identified by DWI and conventional MRI, but lesions were non-enhancing on post-contrast imaging, thus in 13 out of 25 subjects with relapse (52%) DWI identified more

focal lesions than CE-MRI alone. In 2 patients (2 MB), however, CE-MRI identified more focal relapses than DWI (8%). Finally, in 10 patients (40%) (5 MB, 1 CNS ET, NOS, and 4 ATRT) all imaging modalities identified the same number of lesions. Overall, there were no missed diagnoses for DWI, whereas conventional MRI missed 2, and CE-MRI missed 8 diagnoses at the time of DWI relapse detection. Lack of enhancement of relapsing lesions was demonstrated in 4 out of 16 patients with MB

Figure 1: Bar chart showing identified (grey) and missed (dotted white) focal relapsing lesions for contrast enhanced (CE) MRI alone, conventional MRI (T2/FLAIR and post-contrast imaging) (CONV), and diffusion weighted imaging (DWI). DWI identified 19.42% more focal relapses than conventional MRI and 44.66% more lesions than CE-MRI alone. Conventional MRI identified 25.24% more focal relapses than CE-MRI.

(3 classic and 1 large-cell/anaplastic), in the patient with ETMR, in 1 out of 2 patients with CNS ET, NOS and in 2 out of 6 patients with AT/RT.

When only considering MB, DWI identified a higher number of focal relapses than CE-MRI alone in 9 out of 16 subjects (56%). Of these, histology of primary lesions consisted of 7 classic, 1 desmoplastic, and 1 large-cell/anaplastic, whereas molecular subgrouping revealed two group 4, two SHH, one group 3, and one WNT (molecular subgrouping unavailable in 3 subjects). In those subjects (7 out of 16) in whom CE-MRI identified an equal (5 subjects) or higher (2 subjects) number of focal lesions than DWI, histology revealed 5 large-cell/anaplastic and 2 classic MB (three group 3, one SHH and one group 4; molecular subgrouping unavailable in 2 subjects). A significant difference was demonstrated between histological variant distribution and detection rate of DWI and CE-MRI images ($p=0.043$).

Regarding diffuse linear leptomeningeal or ependymal relapse, CE-MRI was positive in 7 out of 9

patients (78%) (4 MB and 3 ATRT) whereas DWI in 3 out of 9 patients (33%) (1 MB, 1 CNS ET, NOS and 1 ATRT). Of note, in 2 patients (1 MB and 1 CNS ET, NOS) CE-MRI was negative at the time of DWI diffuse linear relapse detection.

Representative images of relapsing and radiation induced lesions are shown in Figures 2-6.

DISCUSSION

Standard surveillance for CNS ET includes neuroimaging and clinical evaluations at regular intervals. The rationale behind surveillance imaging is that early detection of tumor recurrence may potentially allow for prompt intervention and thus improved outcome. However, screening for and diagnosing recurrent disease poses significant challenges. Early identification of tumor relapse can be influenced by the contrast-enhancing pattern of the lesion. Of note, not all CNS ET present with contrast enhancement, and prior studies have demonstrated that

Figure 2: Brain MRI findings in an 8-year-old boy with focal distant medulloblastoma relapse detected earlier by DWI. Axial FLAIR (A, B) and post-contrast T1-weighted (C) images reveal a small focal gliotic area in the head of the left caudate nucleus (arrowheads, A, B). DWI (D) and corresponding ADC (E) map show facilitated diffusion (short thin arrow, E). This sequela was stable for 2 years without evidence of disease relapse. Subsequent brain MRI (F-J) does not reveal significant changes when compared to the prior study on both FLAIR (F, G) and post-contrast T1-weighted images (H). At that time conventional pre- and post-contrast MRI were considered negative for relapse. On the contrary DWI (I) and ADC (J) map clearly show a change in signal intensity of the left caudate head nucleus focal lesion, demonstrating decreased diffusivity (long thin arrows, I, J); evaluation of DWI/ADC images was considered positive for relapse. Follow-up MRI (K-O) shows increased volume of the focal lesion, with persistent lack of contrast enhancement (open arrow, M) and decreased diffusivity (N, O), confirming focal relapse.

metastases of MB tend to display a weaker enhancement than the initial neoplasms [17]; in addition, up to 36% of MB recurrences can be non-enhancing [10] with up to 20% of secondary leptomeningeal diseases missed by conventional MRI [18]. Recent studies have also demonstrated that depending on the molecular subgroup, MBs can present with higher or lower degrees of blood brain barrier breakdown [19]. For instance, lack of enhancement has been demonstrated in a significant subset of group IV MB [9]. AT/RT and others CNS ET can also be non-enhancing.

At the same time, on conventional MRI, it may be difficult to differentiate tumor recurrence from other entities, such as radiation-induced contrast-enhancement, and misdiagnosing recurrent lesions can have a significant impact on patient's outcome. Despite these shortcomings, conventional post-contrast MRI is presently considered the standard of reference for evaluating recurrent disease on neuroimaging.

The rationale of this work was based on the known evidence of decreased diffusivity of these tumors, so far reported in the vast majority of cases [8, 9, 15, 20, 21].

Increased cellularity, decreased extracellular space, and high nuclear-to-cytoplasmic ratio are the most common explanation of the DWI features of CNS ET. Isolated reports or small case series have also suggested a potential role of DWI in MB surveillance. Shubert et al. [22] evaluated the diagnostic utility of DWI in 3 patients with MBs suggesting a role for DWI in early detection of metastatic disease and warranting a formal study. Similar observations were reported by Rasalkar et al. [23] and by Amene et al. [24] showing in isolated case reports the utility of DWI in detecting recurrent MBs. Nevertheless, with the exception of the sparse above-mentioned data, no systematic studies aimed at evaluating the diagnostic value of DWI in the surveillance of children with CNS embryonal tumors are as yet available to our knowledge.

Our results show that DWI was able to pick up a significantly higher number of focal CNS ET relapses when compared to conventional MRI. Sensitivity for focal relapsing lesions raised from 77% of conventional MRI to 96% of DWI ($p=0.0003$). When considering a per subject analysis, DWI added diagnostic information to conventional MRI in 32% of patients with focal

Figure 3: Brain MRI findings in a 12-year-old girl with multiple focal distant medulloblastoma relapsing lesions better depicted by DWI. DWI images (A, B) and corresponding ADC maps (C, D) reveal multiple leptomeningeal and ependymal focal nodular lesions with decreased diffusivity. FLAIR (E, F) images show a lower number of lesions, and only few of them demonstrate contrast enhancement (G, H). On follow-up MRI, DWI (I, J) and post-contrast T1-weighted images (K, L) demonstrate increased number and volume of focal lesions, confirming multifocal disease relapse.

Table 2: Distribution of focal relapsing lesions

	TOTAL N patients 25 /N lesions 103	MB N patients 16 /N lesions 94	ATRT N patients 6 / N lesions 6	CNS ET, NOS N patients 2 / N lesions 2	ETMR N patients 1 / N lesions 1
Local	4/4	1/1	2/2	/	1/1
Distant	15/61	9/55	4/4	2/2	/
Leptomeningeal	14/53	8/47	4/4	2/2	/
Leptomeningeal and ependymal	1/8 (2 leptomeningeal 6 ependymal)	1/8 (2 leptomeningeal 6 ependymal)	/	/	/
Combined	6/38	6/38	/	/	/
Local and ependymal	2/10 (2 local, 8 ependymal)	2/10 (2 local, 8 ependymal)	/	/	/
Local and parenchymal	1/2 (1 local, 1 parenchymal)	1/2 (1 local, 1 parenchymal)	/	/	/
Local and leptomeningeal	3/26 (3 local, 23 leptomeningeal)	3/26 (3 local, 23 leptomeningeal)	/	/	/

MB: medulloblastoma, ATRT: atypical teratoid rhabdoid tumor, CNS ET, NOS: central nervous system embryonal tumor, not otherwise specified, ETMR: embryonal tumor with multi-layered rosette.

nodular disease relapse, being the sole diagnostic tool to show early tumor recurrence in two subjects (8%) and showing a higher number of lesions than CE-MRI in 13 out of 25 subjects (52%). At the same time, all but one lesion with decreased diffusivity turned out to be

secondary lesions, yielding a very high PPV (99%). The high sensitivity and positive predictive value suggest that DWI is a good test in identifying focal brain CNS ET relapses, so that a positive finding on DWI is highly predictive of relapse.

Figure 4: Brain MRI findings in a 7-year-old girl with AT/RT relapse and linear leptomeningeal involvement not visible on DWI. Post-contrast T1-weighted images show a distant focal nodular contrast enhancing relapsing lesion in the left temporal lobe (arrowhead, A); there is also diffuse linear leptomeningeal enhancement along cerebellar folia and in the basal cistern (long thin arrows, A, B). FLAIR images do not reveal evident lesions (C, D). DWI and corresponding ADC maps clearly show the nodular lesion with decreased diffusivity in the left temporal lobe (thick arrows, E, G) but are unable to demonstrate linear leptomeningeal involvement (F, H).

Focal radiation induced contrast-enhancing lesions in the setting of CNS ET surveillance have been widely documented [13, 25-27] but almost all studies have focused on conventional MRI characteristics and temporal evolution of lesions, rather than on DWI. The most common pattern of RIL in children with CNS ET treated with concurrent radiotherapy and chemotherapy is characterized by small foci of contrast enhancement within the brain parenchyma, almost always associated with focal T2/FLAIR hyperintensity. These lesions are more frequent in children treated with hyperfractionated accelerated radiotherapy (HART) and are considered a milder form of brain injury due to transient vasogenic edema or demyelination with blood brain barrier (BBB) breakdown, different from classic radiation necrosis; they usually occur within the white matter at variable distances from the primary tumor and at variable intervals after the end of treatment, ranging from few months to years [13, 28]. On follow-up, they usually regress in size, although interval increase can be detected on initial evaluations, followed by subsequent decrease; progression to radiation necrosis should be suspected if they progressively increase in size or are accompanied by edema and mass effect [29]. Our findings show that all but one focal contrast-enhancing RIL did not present with decreased diffusion, suggesting that lack of decreased diffusion favors a non-tumoral lesion. Indeed, average minimum and mean

ADC values of focal relapses and contrast-enhancing RIL demonstrated significant differences among the two groups. Our study also confirms that a distant intra-axial parenchymal relapse is extremely uncommon in CNS ET, as all but one distant focal parenchymal enhancing lesions turned out to be radiation induced lesions.

Regarding diffuse linear leptomeningeal involvement, our data confirm that post-contrast imaging is the mainstay to evaluate this pattern of relapse due to higher sensitivity. However, even on DWI linear leptomeningeal involvement can sometimes be appreciated resulting in a diffuse DWI highlighting of the pial surface of involved brain areas.

Analysis of relapsing MB demonstrated that in subjects with the histologically defined classic variant, DWI picked-up a higher number of focal lesions when compared to CE-MRI alone; classic MB relapsing lesions also presented lack of contrast enhancement with higher frequency. At the same time lack of enhancement of primary MB was documented mainly in classic variants (6 out of 7 non-enhancing tumors). Interestingly, a similar observation (regarding primary lesions) was reported by Fruehwald-Pallamar J et al. [30], who documented subtle or linear enhancement only in classic MB, whereas all other MB variants presented marked enhancement. A similar pattern can be inferred by the study of Yeom KW et al. [8] in which 8 out of 9 non-enhancing primary MB belonged to the classic group. In a more recent study by

Figure 5: Brain MRI findings in a 12-year-old boy with CNS ET, NOS relapse and linear leptomeningeal involvement visible only on DWI. DWI (A, B) and corresponding ADC (C, D) maps show two adjacent focal nodular ependymal relapsing lesions with decreased diffusivity located in the right posterolateral recess of the IV ventricle and along the nodule of vermis (arrowheads, A, C). There is also linear decreased diffusivity along the ventral margin of the brainstem in keeping with linear leptomeningeal involvement (short thin arrows, B, D). FLAIR images (E, F) show a reduced representation of the right posterolateral recess of the IV ventricle and focal prominence of the nodule of vermis (thick arrow, E). Post-contrast T1-weighted images (G, H) do not reveal enhancing lesions.

Lastowska M et al. [31] evaluating contrast enhancement pattern of patients with non-WNT/SHH MB, none to weak enhancement was demonstrated in 29 out of 60 subjects, of which 25 were classic MB. This aspect highlights the role of DWI in surveillance imaging of classic MB. Intriguingly, although MB does not change molecular subgroup at recurrence [32] and remains stable among primary and metastatic compartments [33], histological subtypes of MB may change upon recurrence [34]. However, as demonstrated by Pöschl J et al. [34] in a series of 16 relapsing medulloblastomas in which 7 out of 16 cases (44 %) showed change in the histological subtype, the majority of desmoplastic/nodular medulloblastoma cases (57 %) relapsed as classic medulloblastoma, whereas all classic medulloblastoma but one remained stable among primary and relapsing

compartment. This observation may potentially give an explanation of the neuroimaging evidence of weaker contrast enhancement of relapsing MB lesions when compared with primary tumors, and may further strengthen the role of DWI in MB surveillance given the high frequency of tumors that relapse as classic variants which, as previously demonstrated, tend to be more frequently non-enhancing.

Our results should be interpreted with awareness of certain limitations. First, given the retrospective nature of the study, sampling bias cannot be excluded. We are also aware of the relatively small sample of patients; however, per lesion analysis allowed to evaluate a significant number of lesions. We did not evaluate post-contrast FLAIR imaging in our study since our routine Institutional brain tumor surveillance protocol does not include this

Figure 6: Brain MRI findings in a patient with non-neoplastic radiation induced focal lesion. (A-D). Post-operative MRI 3 months following surgery. Post-contrast T1-weighted (A) and FLAIR (B) images demonstrate a post-surgical cavity along the left posterolateral margin of the fourth ventricle without evidence of residual/recurrent disease (thin arrows, A, B). DWI (C) and corresponding ADC map (D) show increased diffusion. **(E-H)** Follow-up MRI 5 months after the end of combined CT and RT. Brain MRI shows a new area of contrast-enhancement (E) with minimal mass effect and FLAIR hypersignal (F) along the posterolateral margin of the fourth ventricle (open arrows, E, F). DWI (G) and corresponding ADC map (H) show increased diffusion. **(I-L)** Follow-up MRI 7 months after the end of combined CT and RT. Post-contrast T1-weighted (I) and FLAIR (J) images show increased extension of the lesion with perilesional edema. On DWI and ADC there still is facilitated diffusion (thick arrows, K, L). The lesion was surgically removed and histology revealed gliosis and hemosiderin-laden macrophages in keeping with therapy-induced reactive changes.

sequence following gadolinium administration. We recognize that post-contrast FLAIR imaging can add significant information to conventional post-contrast T1-weighted imaging for the evaluation of leptomeningeal diseases, improving detection of leptomeningeal metastasis in children [35, 36]; further investigations aimed at comparing the diagnostic value of DWI and post-contrast FLAIR imaging in ET surveillance are awaited to specifically evaluate the contribution of these sequences.

Since molecular subgrouping of MBs was not available for all patients, we were unable to draw definite conclusion regarding possible correlations between DWI characteristics of relapsing lesions and molecular subgroups; further studies with larger cohorts are thus needed to evaluate whether surveillance imaging of particular subgroups of MB may be improved by careful evaluation of DWI.

With the exception of two subjects, histological confirmation of relapsing and radiation induced lesions was not obtained for both clinical and ethical reasons, and radiographic evaluation was the standard of reference; however, MRI represents a common standard in clinical practice and current standard of care does not require histological confirmation of relapsing lesions.

In conclusion, DWI represents a valuable diagnostic tool for the surveillance of embryonal tumors after treatment and can provide helpful information for clinical management of these patients. In particular, DWI may improve the detection of focal recurrent disease and assist in differentiating recurrent disease from contrast-enhancing radiation induced lesions. Careful evaluation of DWI images is therefore strongly recommended. Among children with MB, particular attention should be paid to subjects with classic variant who present a higher frequency of non-enhancing lesions, better evaluable with DWI.

MATERIALS AND METHODS

This retrospective single-center study was institutional review board-approved. Informed consent was waived by the local institutional review board.

Subjects

We screened the tumor registry and radiology report database of our Institution for patients with histologically confirmed CNS ET aged less than 18 years at initial diagnosis, and for whom MRI data including DWI at diagnosis and on serial follow-up were available in our Picture Archive and Communication System (PACS). Patients were categorized in three main groups: i) those with a brain disease relapse, ii) those without relapse, presenting with contrast-enhancing radiation-induced brain lesions, and iii) those without evidence of disease relapse or of radiation induced brain lesions. Specifically,

patients with disease relapse were selected on the basis of a pathologic confirmation or radiologic determination (according to current standard radiological criteria) [5] and clinical evolution; subjects with contrast enhancing RIL were selected on the basis of a pathologic confirmation or after revision of the radiological reports, describing new onset of cerebral focal contrast enhancing lesions following radiotherapy, that demonstrated spontaneous regression on follow-up without treatment. Absence of brain RIL and disease relapse proved at MR imaging follow-up of at least 3 years was the selection criteria for the last group of subjects.

Fifty-six subjects (34 males and 22 females) were identified. There were 25 patients with disease relapse, and 31 without relapse (6 with RIL and 25 without RIL). Among 25 patients with disease relapse there were 16 MB, 1 ETMR (previously designated as embryonal tumor with abundant neuropil and true rosettes), 2 CNS embryonal tumors, NOS (previously designated as PNET), and 6 AT/RT. All patients with RIL had MB (5 out of 6 treated with Hyperfractionated Accelerated Radiotherapy). Among patients with neither disease relapse nor RIL there were 19 MB, 4 CNS embryonal tumors, NOS and 2 AT/RT. The main characteristics of subjects and their brain lesions are summarized in Table 1.

MRI protocol

All MRI studies were performed on a 1.5 Tesla magnet (Intera Achieva; Philips, Best, the Netherlands). Conventional imaging included 4-mm-thick axial Fluid Attenuated Inversion Recovery (FLAIR), T2- and T1-weighted images. Following gadolinium compound bolus administration (0.1 mmol/kg, macrocyclic ionic agent), 4-mm-thick axial, coronal, and sagittal T1-weighted images were acquired in all patients.

DWI was performed using a single-shot spin-echo (SE) echo-planar sequence with the following parameters: TR/TE= 5.050/63 ms, 90° flip angle, NEX=2, 30 transverse sections, SENSE factor= 2.5, slice thickness/gap=4 mm/1mm, FOV= 160 mm, 100×160 matrix, and imaging time of 69 s. Diffusion sensitizing gradients were applied in the x, y, and z directions with b factors of 0 and 1000 s/mm².

Study design, image evaluation and analysis

Since the main objective of the study was to evaluate the recurrence detection rate of DWI in comparison with pre- and post-contrast MRI, an independent pre-evaluation of all MRIs performed during follow-up of each patient with documented disease relapse was carried out by the principal investigator (AR, 24 years of experience) in order to select the studies corresponding to radiographic relapse onset. Radiographic relapse was defined as new onset of local disease, brain metastasis, or both. In detail,

considering the purpose of our analysis, studies were considered positive for tumor relapse in case of new onset of at least one of the following: i) focal nodular (minimum diameter on transverse plane of 3 mm) or diffuse linear intracranial contrast enhancement, ii) focal lesion on T2/FLAIR images, even without contrast enhancement, clearly distinguishable from comorbid events (eg, demyelination, ischemic injury, infection, bleeding, etc), iii) focal nodular or diffuse linear hyperintense signal relative to the surrounding normal brain on DWI and hypointense signal on the corresponding ADC map (decreased diffusion) [37], clearly distinguishable from artifactual images, ischemic or haemorrhagic lesions. When evaluating MRI scans, both conventional imaging and DWI were available to the principal investigator. Findings were compared with follow-up MRI studies and clinical data in order to establish and confirm the date of radiographic relapse.

Then, he evaluated the MRI scans of patients with focal contrast enhancing RIL and the examination date corresponding to RIL onset was recorded.

Finally, he reviewed all MRI studies of patients with absence of disease relapse and RIL and selected an intermediate follow-up study.

In a following image reading session, two different neuroradiologists with 12 and 3 years of experience, respectively (GM and CAA), were asked to independently review all the selected MRI studies (patients with and without relapse, including RIL). These observers were blinded to the final diagnosis. Three sets of images were analysed for each patient: conventional MRI (axial FLAIR, T1 and T2-weighted images) including axial contrast enhanced (CE) T1-weighted images (image set A), only axial CE T1-weighted images (image set B), and only DWI/ADC images (image set C). To minimize any recall bias, the readings of each image set were separated by 2 weeks and images were analysed in a random order. These observers were asked to determine potential tumor relapses utilizing the same criteria used by the principal investigator. Each image set was evaluated in comparison with the corresponding image set of the prior MRI study performed by each patient. For each image set the two readers independently recorded the number and location of potential tumor relapses (local or distant leptomeningeal, ependymal or parenchymal) along with the MRI pattern (focal nodular or diffuse linear). Confluent lesions were counted as one. Potential local relapse was defined as recurrence within the tumor primary area. Potential distant relapse was defined as recurrence outside the primary tumor area. The same 2 neuroradiologists jointly reviewed all the image sets with discordant evaluation. They were asked to reach a consensus on the number and location of lesions for each patient. This consensus reading was considered for statistical analysis.

After the blinded reading was completed, the DWI along with pre-and post-contrast MRI images were reviewed

together by all three readers in consensus; they compared the results of the blinded reading with the standard of reference. During this final verification, region of-

interest-based ADC analysis of focal brain relapsing lesions and primary lesions was performed as previously described [8]. Minimum and mean ADC values of RIL were also calculated by manually drawing a region of interest (ROI) onto the obtained ADC maps in the area corresponding to the T1-enhancing region. ROIs were shaped to the contour of contrast enhancement.

Presence or absence of contrast-enhancement of primary lesions was finally evaluated.

Standard of reference

Because histological proof was not available in all but one relapsing lesion and one RIL, evaluation of all combined image sets and follow-up MRIs were considered the image comparator. Any identified lesion increasing in size on follow-up serial MR examinations or decreasing following treatment was considered positive for relapse [38]. Enhancing lesions following radiotherapy that disappeared or decreased in subsequent MR examinations without any treatment were considered radiation injury related and negative for relapse [39].

Statistical analysis

Statistical analysis was performed by using SPSS Statistics for Mac, Version 21.0 (IBM, Armonk, New York). A p value of .05 was used to define nominal statistical significance. Differences among the three image sets were evaluated on a per lesion and per subject analysis. Intraclass correlation coefficients (ICCs) were used to study the agreement between the 2 readers in identifying the number and location of potential relapsing lesions. An ICC < 0.40 indicated a poor agreement; 0.40–0.75, fair-to-good (moderate); and 0.76–1.00, excellent agreement [40]. A McNemar test was used to evaluate the differences in detection score of relapsing lesions among the three image sets. Sensitivity (SE) for all image sets and positive predictive value (PPV) for DWI were calculated by comparing the blinded reading results with the standard of reference.

Recurrence and RIL groups were compared by using Mann-Whitney U test for average minimum and mean ADC values.

Chi-squared test was performed to assess differences between DWI and CE images focal relapse detection rates among MB variants.

Author contributions

G.M.: conceived, designed the study, data analysis and interpretation, drafted the manuscript, and corresponding author; C.A.A.: conceived, designed

the study, data analysis and interpretation, drafted the manuscript; D.T.: statistical data analysis and interpretation, collaborated to draft the manuscript; M.S.: collaborated to design the study, collected and assembled radiological data, contributed to draft the manuscript; P.N.: histopathology review, drafted and revised the manuscript; A.C., M.R.: collected and assembled clinical and surgical data, reviewed the manuscript; G.D.A.: collaborated to design the study, performed radiological data analysis, contributed to draft the manuscript; A.R.: provided molecular data, collaborated to draft the manuscript; C.M., C.C.L.: collected and assembled clinical and radiological data, contributed to draft the manuscript; M.L.G.: clinical interpretation of analysis, reviewed the manuscript; A.R.: coordinated the study design, data review, analysis and interpretation, and reviewed the manuscript.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

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