Received: 19 April 2021 | Revised: 19 May 2021 | Accepted: 25 May 2021

DOI: 10.1002/pbc.29178

Pediatric Blood & Cancer | SIOP International Society of Paediatric Oncology | aspho The American Society of Pediatric Hematology/Oncology | WILEY

ONCOLOGY: RESEARCH ARTICLE

Gadolinium is not necessary for surveillance MR imaging in children with chiasmatic-hypothalamic low-grade glioma

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Abstract

Background: Patients with chiasmatic-hypothalamic low-grade glioma (CHLGG) have frequent MRIs with gadolinium-based contrast agents (GBCA) for disease monitoring. Cumulative gadolinium deposition in the brains of children is a potential concern. The purpose of this study is to evaluate whether MRI with GBCA is necessary for determining radiographic tumor progression in children with CHLGG.

Methods: Children who were treated for progressive CHLGG from 2005 to 2019 at Texas Children's Cancer Center were identified. Pre- and post-contrast MRI sequences were separately reviewed by one neuroradiologist who was blinded to the clinical course. Three dimensional measurements and tumor characteristics were evaluated. Radiographic progression was defined as a 25% increase in size (product of two largest dimensions) compared with baseline or best response after initiation of therapy.

Results: A total of 28 patients with progressive CHLGG were identified with a total of 683 MRIs with GBCA reviewed (mean 24 MRIs/patient; range, 11-43 MRIs). Radiographic progression was observed 92 times, 91 (99%) on noncontrast and 90 (98%) on contrast imaging. Sixty-seven progressions necessitating management changes were identified in all (100%) noncontrast sequences and 66 (99%) contrast sequences. Tumor growth > 2 mm in any dimension was identified in 184/187 (98%) noncontrast and 181/187 (97%) with contrast imaging. Metastatic tumors were better visualized on contrast imaging in 4/7 (57%).

Conclusion: MRI without GBCA effectively identifies patients with progressive disease. When imaging children with CHLGG, eliminating GBCA should be considered unless monitoring patients with metastatic disease.

KEYWORDS
gadolinium, hypothalamic-chiasmatic, low-grade glioma, pediatric, surveillance imaging

Abbreviations: ADC, apparent diffusion coefficient; AUC, area under the curve; CHLGG, chiasmatic-hypothalamic low-grade glioma; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; FNR, false-negative rate; FPR, false-positive rate; GBCA, gadolinium-based contrast agents; GRE, gradient echo; MRI, magnetic resonance imaging; pLGG, pediatric low-grade glioma; ROC, receiver operative characteristic; SWI, susceptibility-weighted imaging; T1W, T1 weighted; T2W, T2 weighted.

1 | INTRODUCTION

Gadolinium-based contrast agents (GBCA) are used in magnetic resonance imaging (MRI) in both clinical and research settings. These agents are considered helpful for initial diagnosis and in ongoing surveillance. However, there is concern about the accumulation of these agents throughout the brain parenchyma, with the greatest amount of deposition in the basal ganglia and dentate nuclei. GBCA are chelated to either linear or macrocyclic organic ligands in order to safely administer and eliminate the toxic agent.[1] Gadolinium deposition has been noted with both types of ligands with greater retention observed with chelated to linear ligands.[2] Deposition occurs with even a single administration of GBCA.[2] T1 signal changes on MRI in the dentate nucleus and basal ganglia, specifically globus pallidus, can be seen after as few as four injections of GBCA. Deposition has been reported to be dose and age dependent and can last for months to years.[3–5]

Currently, the clinical implications of gadolinium deposition are unclear. There are rare reports of adverse events, but the evidence does not show strong associations.[6,7] Patients have reported pain, paresthesias, skin changes (rash, edema), headaches, altered mentation. The effects of long-term deposition, especially in young children, are unknown. It is critical that this be investigated to determine if imaging guidelines need to be modified. Pediatric patients with low-grade glioma, particularly those with chiasmatic-hypothalamic low-grade glioma (CHLGG), are a vulnerable population for excessive deposition of gadolinium as MRIs with GBCA are performed for disease surveillance over many years. The required observations for the last eight Children's Oncology Group and Pediatric Brain Tumor Consortium clinical trials for low-grade glioma include GBCA-enhanced MRI and are required 12-17 times within five years of enrollment. Spontaneous changes and variability in enhancement have been reported in low-grade glioma and therefore may not be as consistently reliable in determining disease progression.[8–10] T2-weighted (T2W) imaging has been shown to detect areas of higher cellular activity and therefore can be helpful in detecting tumor progression.[11] T2W and T2 FLAIR sequences have also been valuable in identifying nonenhancing tumor burden, which can be very useful in low-grade glioma patients as many of these tumors do not enhance.[12] T2W imaging in addition to T1-weighted (T1W) and T2 FLAIR sequences may be sufficient to monitor for tumor progression of patients with low-grade glioma. We aimed to evaluate whether a noncontrast MRI can identify radiographic progression as accurately as a contrast-enhanced MRI for patients with CHLGG. Our hypothesis is that contrast-enhanced MRIs, in conjunction with noncontrast MRIs, are not necessary to identify disease progression in all patients with progressive CHLGG.

2 | MATERIALS AND METHODS

2.1 | Study population

This retrospective study was approved by the Institutional Review Board at Baylor College of Medicine. Patients with progressive CHLGGs from birth to 22 years of age were identified using the electronic medical records at Texas Children's Hospital, from 2005 until 2019. Progressive CHLGG was defined as patients requiring more than one type of tumor-directed intervention due to clinical and/or radiographic progression. A retrospective chart review was conducted to collect patient information including age, gender, age at diagnosis, pathology including molecular data when available, surgical intervention if any, chemotherapy, radiation therapy, dates of all treatment modalities, evidence of metastases on presentation, number of GBCA exposures. Imaging characteristics were assessed at diagnosis and at all subsequent follow-up MRIs including post treatment or diagnostic intervention, at time of clinical and radiographic progression and at change in treatment or initiation of new treatment. Patients who had a diagnosis of neurofibromatosis type 1 were excluded from this study to avoid evaluating focal areas of T2 hyperintensity commonly seen on MRI in these patients.

2.2 | MRI analyses

Pre- and post-contrast MRIs on 1.5 and 3 Tesla MRIs were separately reviewed by one neuroradiologist who was blinded to the clinical course. Patients with progressive CHLGG had MRIs reviewed at multiple time points, including times when no disease progression was identified. This information was used as a control. The manual measurement tool on the PACS workstation was used to measure tumors on noncontrast sequences. Following a two-week delay, tumors were measured on the T1W post-contrast images. For noncontrast images, the neuroradiologist recorded tumor measurements in three dimensions (anteroposterior, craniocaudal, transverse) from the T1W noncontrast, T2W, or T2 FLAIR sequences depending on which sequence provided greatest visualization of the tumor margins. For contrast-enhanced images, the same three-dimensional measurements were measured on T1-weighted images with contrast. Measurements in all planes were obtained from imaging with 3 mm or less slice thickness for both noncontrast and post-contrast sequences. 3D imaging, which obtains 1 mm image slice thickness, was not available for all MRI scans but was utilized when available. Cystic components of the tumor were included in tumor measurements. The product of the two largest dimensions were used to assess for response. Changes in tumor size were recorded as being attributable to change in cystic, solid, or both solid and cystic portions. Other information collected included changes on diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC), new cystic or solid areas, evidence of metastatic disease, and changes in enhancement pattern, if 3D sequences were used. On ADC sequences, signal hyperintensity of the solid portion of the tumor was assessed as a percentage, 0%-25%, 25%-50%, 50%-75%, and 75%-100%. New susceptibility within the tumor was recorded on gradient echo or susceptibility-weighted imaging when available. Tumor progression was defined as development of new lesions and/or 25% increase in size compared with baseline/best response after initiation of therapy. We also separately looked at 2 mm differences in any dimensional measurements to help identify tumor growth, stability, or

regression. The neuroradiologist documented their assessment of tumor stability, progression, or regression blindly and independently following the completion of the measurements for the noncontrast sequences and at a later time upon completion of contrast sequences.

2.3 | Statistical analyses

Individual measurement correlations between noncontrast and contrast scans: All analyses were conducted in the latest version of R (v 3.6.1; R Development Core Team, 2003). To examine the correlations between measurements from MRI sequences with and without contrast, measurements with a nonnormal distribution (based on having a skew or kurtosis greater than −1 and less than +1, and a visual inspection of the histograms) were transformed to normality using a rank-based inverse normal transformation, a mathematical technique to achieve a normal distribution.[13] To account for some patients having multiple measures of the outcome (progression vs nonprogression), the repeated measured correlation was computed, with 95% confidence intervals ascertained via bootstrapping (1000 resamples).[14]

Diagnostic abilities of MRIs without contrast: To examine the accuracy of MRI sequences without contrast to diagnose tumor progression, a receiver operating characteristic (ROC) analysis was run, using the method by Obuchowski (1997) to adjust the standard errors for the within-person effect (i.e., the presence of tumor progression was measured at more than one occasion for each patient).[15,16] Tumor progression was identified using sequences of MRI with contrast. The diagnostic ability of MRIs without contrast to identify tumor progression was quantified using area under the curve (AUC) representing the trade-off between sensitivity (detecting every case of progression) and specificity (detecting every case of no progression) of MRIs without contrast. AUCs are scored between 0.5 (diagnostic ability no better than chance) and 1.0 (perfect diagnostic ability), and should be interpreted as the probability of a randomly selected pair of a true positive and a true negative being ranked as such by the diagnostic test.[16] The false-positive rates (FPR; the proportion of MRI scans diagnosing tumor progression where there was no progression) and false-negative rates (FNR; the proportion of MRI scans not diagnosing tumor progression where there was progression) were calculated as described by Fleiss et al.[17]

3 | RESULTS

3.1 | Patient and tumor characteristics

Twenty-eight patients with progressive CHLGG were identified (Table 1). Median age at diagnosis was 23 months, and there were 15 females (54%) and 13 males (46%). Seven of 28 (25%) patients had evidence of disseminated disease, five identified at the time of initial diagnosis. Pathology was available for 24 patients. One patient with localized disease died; all other patients are alive at the time of publication. Median follow-up for all patients in our cohort was 6.5

TABLE 1 Patient characteristics

Age at diagnosis	Current age	Gender	Pathology	Disseminated disease	Treatment regimens	Radiotherapy	GBCA studies
Range: 2 months-13 years Mean: 3 years	Range: 4-22 years Mean: 10 years 8 months	F (54%)M (46%)	Pilocytic astrocytoma (78%) Pilocytic astrocytoma with pilomyxoid features (8%) Pilomyxoid astrocytoma (8%) Pilomyxoid astrocytoma with pilocytic astrocytoma (4%) Low-grade glioma not otherwise specified (4%)	7 (25%)	Range: 2-8 Mean: 4	Yes: 7 (25%)No: 21 (75%)	Range: 11-43 Mean: 24

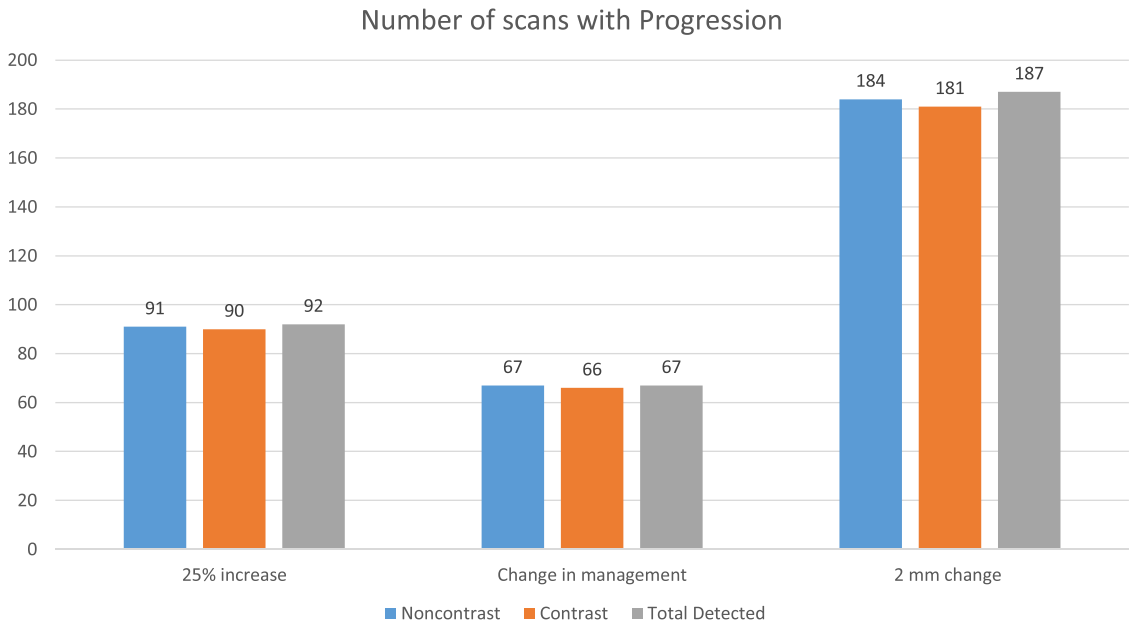

FIGURE 1 Contrast and noncontrast scans identified as progression defined as 25% increase in size, leading to a change in management and 2 mm change in any dimension

years. Twenty-four of 28 patients (86%) had some form of surgical intervention, sometimes more than one: biopsy, subtotal resection, cyst aspiration or fenestration, laser ablation. Twenty-six patients (93%) received at least one chemotherapy regimen and ten (36%) received molecularly targeted therapy. Seven (25%) of 28 patients received radiation therapy. A minimum of two and maximum of eight different tumor-directed therapies were prescribed in our patient cohort, with a median and mean of four different treatments per patient.

3.2 | Imaging analyses

A total of 674 MRIs with GBCA were reviewed, a mean of 24 MRIs per patient and a range of 11-43 MRIs per patient. In the disseminated pilocytic astrocytoma subset, the exposure to MRIs with contrast was similar, range of 15-26, with an average of 22 scans per patient. Of the 674 MRI scans, 643 were evaluated for progression; initial diagnostic scans were not included in these evaluations. Five hundred and nineteen (77%) MRI scans were completed on 1.5 Tesla and 155 (23%) on 3 Tesla. 3D T1 without contrast or 3D T2 FLAIR sequences were available for 112 (17%) scans and 3D T1 with contrast sequences were available for 318 (47%) of the 674 scans. One hundred eighty-seven (28%) of the MRIs with contrast had a change in enhancement pattern. Changes in DWI were evaluated in 605 scans; DWI changes were seen in 71 scans (12%). New areas of susceptibility were seen in 40 scans (6%). ADC signal hyperintensity was identified as 0%-25% in 220 (35%), 25%-50% in 63 (10%), 50%-75% in 98 (15%), and 75%-100% in 251 (40%) scans.

Progression, defined as 25% increase in size compared with baseline or best response after initiation of therapy, was observed 92 times in total (Figure 1). Ninety-one of the 92 progressions (99%) were identified on noncontrast imaging and 90 (98%) were identified on contrast imaging. Of the 92 progressions that were noted, 67 of those progressions led to a change in therapy. All 67 (100%) of those progressions were identified on noncontrast sequences and 66 of 67 (99%) on contrast sequences. Tumor growth greater than 2 mm in any dimension was identified 187 times, 184 of 187 (98%) identified on noncontrast imaging and 181 of 187 (97%) identified on contrast imaging. Disseminated disease was seen in 7 of 28 patients (25%), was identified in all (100%) patients on contrast-enhanced imaging, six out of seven patients (86%) on noncontrast imaging, and was better visualized on contrast imaging in four of seven patients (57%). Progressive disease was not detected on noncontrast imaging in total three times and in all three instances was identified on contrast imaging. For contrast imaging, progressive disease was not detected a total of six times and in all six instances was identified on noncontrast imaging.

Individual measure correlations between scan types: For all 3D measurements, the MRI sequences with and without contrast were significantly and highly correlated (all $r \geq 0.87$; Table 2).

Diagnostic MRIs without contrast: The diagnoses of progression between MRI sequences with and without contrast were highly concordant (Table 3), yielding an AUC for an MRI without contrast of AUC = 0.986 (95% confidence intervals; CI: 0.974-0.998; Figure 2). The false-positive rate was 0.03, indicating that 2.6% of the diagnoses of progression from a noncontrast MRI had not progressed, according to an MRI with contrast. The false-negative rate was 0.01, indicating that 0.7% of the diagnoses of "no progression" by noncontrast MRI were judged as showing progression according to MRI with contrast (Table 3). The sensitivity and specificity of MRI sequences without contrast to detect tumor progression are 98% and 99%, respectively. Identification of stability and regression of disease on MRIs without and with contrast were concordant in 96% and 97% of scans, respectively.

TABLE 2 Results from multiple measurement correlations between MRI scans ascertained with and without contrast

	r (± 95% confidence intervals)	*P*
AP	0.91 (0.89-0.93)	$5.55*10^{-240}$
Transverse	0.88 (0.86-0.90)	$1.45*10^{-206}$
Craniocaudal	0.87 (0.84-0.89)	$1.02*10^{-192}$

TABLE 3 Diagnoses of tumor progression from MRI sequences without contrast compared with MRI sequences with contrast

	MRI with contrast	
	Progression	**No progression**
MRI without contrast		
Progression	187	5
No progression	3	436

4 | DISCUSSION

MRI with GBCA have been used as the standard for disease monitoring in pediatric patients with central nervous system tumors. In patients with non-neurofibromatosis type 1–related low-grade gliomas, the utility of gadolinium to identify disease progression is less clear, and there is increasing concern for potential adverse effects from gadolinium deposition. This is especially concerning for pediatric patients with CHLGG who require long-term monitoring of their tumors with MRI. Our results indicate that contrast-enhanced imaging is not necessary to identify tumor progression as the false-negative rate for MRI sequences without contrast was 0.01 and the false-positive rate was 0.03. However, contrast sequences were superior in identifying patients with disseminated disease in our small sample and therefore should be used at initial diagnosis and in patients with disseminated disease.

Our study cohort's clinical characteristics well represented children with CHLGG. The age at diagnosis, gender, pathology, and number of treatment regimens completed are all similar to other progressive CHLGG patients.[9,10]

In patients with central nervous system tumors, the utility of gadolinium in identifying disease progression has been evaluated in pediatric tuberous sclerosis patients with subependymal giant cell astrocytomas, adults with meningiomas and prolactinomas, and children with optic pathway gliomas.[18–23] For all of these tumor types, MRI sequences without gadolinium were reported to be sufficient for tumor surveillance, similar to what our results indicate for CHLGG.

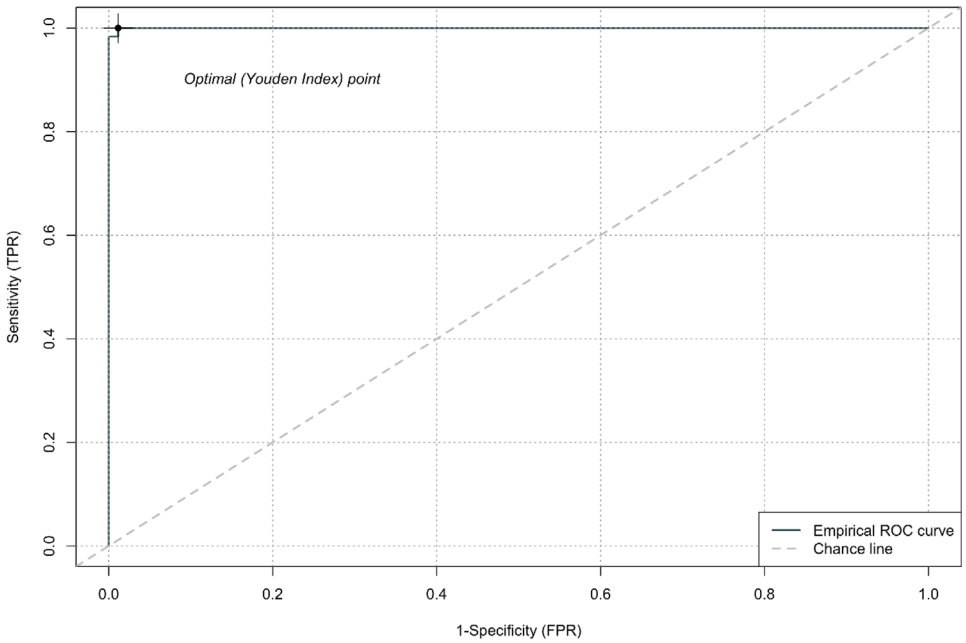

FIGURE 2 AUC for an MRI without contrast to diagnose tumor progression (defined from an MRI with contrast) from ROC analysis

In our patient population, all time points of tumor progression leading to management change were identified by noncontrast MRI sequences, highlighting the fact that contrast-enhanced sequences are not necessary for management decisions. Volumetric analysis of low-grade gliomas can be sufficiently completed using T2-weighted and T2 FLAIR imaging with 2D sequences (or 3D sequences, when available). These sequences and T1W noncontrast imaging are adequate to detect tumor progression to allow for appropriate changes in management.

The Response Assessment in Pediatric Neuro-Oncology working group subcommittee for pediatric low-grade gliomas (pLGG) recently published imaging guidelines to assess tumor response.[24] The recommended sequences to evaluate for disease response included sequences that were identified in our study, T1W, T2W, T2 FLAIR, in addition to DWI/ADC sequences and contrast-enhanced imaging. The subcommittee acknowledged that contrast-enhanced imaging for disease assessment in pLGG has remained controversial due to the variability of enhancement patterns and concerns for gadolinium deposition, but due to the lack of data of T1 contrast-enhanced imaging in response assessment for pLGG, the recommendation was to include this sequence. Our study provides data on the utility of contrast-enhanced imaging in tumor response assessment for a subset of metastatic pLGG. Spontaneous changes and variability in contrast enhancement can occur as seen in 28% of the contrast-enhanced MRIs in our cohort. In addition, treatment-related changes in enhancement pattern can occur; therefore, this sequence alone should not be used for tumor assessment and may not be the most effective sequence to use.[8–10]

In addition to identifying progression, recognition of stability and regression on noncontrast and contrast imaging was concordant in 96% and 97% of scans, respectively, highlighting that noncontrast scans can identify these tumor responses as well. Detection of these changes is just as important in tumor surveillance for CHLGG. DWI, ADC signal of the solid component of the tumor and susceptibility changes on susceptibility-weighted images (SWI) and gradient echo (GRE) sequences were analyzed in our cohort. Changes on gradient echo sequences were assessed to see if tumor enlargement was secondary to new intratumoral hemorrhage. In our patient cohort, only 6% of MRIs had new susceptibility on SWI and GRE sequences, confirming that intratumoral hemorrhage was minimal and did not contribute to tumor growth. DWI and ADC changes were analyzed to determine if there was any correlation between findings on these sequences and tumor progression. Our findings suggest that more progressive tumors had greater percentages of solid tumor ADC hyperintensity. In our patient cohort, 25% had disseminated disease, of which 57% were better visualized on post-contrast imaging. Leptomeningeal disease in low-grade gliomas is rare but is best seen on contrast-enhanced MRI sequences.[25,26] For this reason, we recommend that the initial diagnostic MRI brain and spine should include macrocyclic GBCA, as there is less retention seen with these agents.[27,28] Patients with disseminated disease or suspicion of metastatic disease should obtain contrast-enhanced MRIs for surveillance. Even with this approach, patients with CHLGG will have less exposure to GBCA and hopefully less deposition, decreasing the potential long-term risks.

There are several limitations to this study. This was a retrospective review completed by one neuroradiologist at a single institution; therefore, provider and institutional bias may have influenced results. In addition, imaging was reviewed from 2005 until 2019, on different types of machines, with variability in image quality, due to limitations of the potential sequences available. Only 23% of scans were completed on a 3 Tesla MRI, 17% had 3D T2 FLAIR sequences, and 47% had 3D T1 with contrast sequences. There are noteworthy strengths to this study as well. To our knowledge, our study has analyzed the largest number of MRIs evaluating if GBCA is necessary for determining radiographic tumor progression, a total of 674 scans for patients with CHLGG. Another strength is that all scans underwent a blinded review process. The results of our research could change overall management of patients with CHLGG and can truly make a significant impact on quality of life.

5 | CONCLUSION

Gadolinium may not be necessary to determine tumor progression in patients with CHLGG. Tumor size best visualized on T1W, T2W, and FLAIR sequences without contrast is sufficient in identifying disease progression for these patients. MRI with macrocyclic GBCA would only be indicated at the time of initial diagnosis and in surveillance of disseminated disease. A prospective clinical trial should be considered to confirm that noncontrast imaging is sufficient in identifying tumor progression for patients with CHLGG as well as to determine optimal timing of contrast imaging to assess for leptomeningeal disease in this patient population.

FUNDING

Dr. Wood's role on this project was funded, in part, by USDA/ARS cooperative agreement #58-3092-1-001. The contents of this publication do not necessarily reflect the views or policies of the U.S. Department of Agriculture, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

DATA AVAILABILITY STATEMENT

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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How to cite this article: Malbari F, Chintagumpala MM, Wood AC, et al. Gadolinium is not necessary for surveillance MR imaging in children with chiasmatic-hypothalamic low-grade glioma. *Pediatr Blood Cancer*. 2021;e29178. https://doi.org/10.1002/pbc.29178