Published in final edited form as:

J Neurooncol. 2019 May ; 143(1): 79–86. doi:10.1007/s11060-019-03133-y.

Quantifying Radiation Therapy Response using Apparent Diffusion Coefficient (ADC) Parametric Mapping of Pediatric Diffuse Intrinsic Pontine Glioma: A report from the Pediatric Brain Tumor Consortium

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Conflict of Interest:

There are no actual or potential conflicts of interest. Raf Ceschin and Dr. Ashok Panigrahy had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

There are no actual or potential conflicts of interest. Rafael Ceschin declares that he has no conflict of interest. Mehmet Kocak declares that he has no conflict of interest. Sridhar Vajapeyam declares that he has no conflict of interest. Ian F. Pollack declares that he has no conflict of interest. Arzu Onar-Thomas declares that she has no conflict of interest. Ira J. Dunkel declares that he has no conflict of interest. Tina Young Poussaint declares that she has no conflict of interest. Ashok Panigrahy declares that he has no conflict of interest.

Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent:

Informed consent was obtained from all individual participants included in the study.

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Abstract

Background and Purpose: Baseline diffusion or apparent diffusion coefficient (ADC) characteristics have been shown to predict outcome related to DIPG, but the predictive value of post-radiation ADC is less well understood. ADC parametric mapping (FDM) was used to measure radiation-related changes in ADC and compared these metrics to baseline ADC in predicting progression-free survival and overall survival using a large multi-center cohort of DIPG patients (Pediatric Brain Tumor Consortium -PBTC).

Materials and Methods: MR studies at baseline and post-RT in 95 DIPG patients were obtained and serial quantitative ADC parametric maps were generated from diffusion-weighted imaging based on T2/FLAIR and enhancement regions of interest (ROIs). Metrics assessed included total voxels with: increase in ADC (iADC); decrease in ADC (dADC), no change in ADC (nADC), fraction of voxels with increased ADC (fiADC), fraction of voxels with decreased ADC (fdADC), and the ratio of fiADC and fdADC (fDM Ratio).

Results: A total of 72 patients were included in the final analysis. Tumors with higher fiADC between baseline and the first RT time point showed a trend toward shorter PFS with a hazard ratio of 6.44 (CI = 0.79, 52.79, $p = 0.083$). In contrast, tumors with higher log mean ADC at baseline had longer PFS, with a hazard ratio of 0.27 (CI = 0.09, 0.82, $p = 0.022$). There was no significant association between fDM derived metrics and overall survival.

Conclusions: Baseline ADC values are a stronger predictor of outcome compared to radiation related ADC changes in pediatric DIPG. We show the feasibility of employing parametric mapping techniques in multi-center studies to quantitate spatially heterogeneous treatment response in pediatric tumors, including DIPG.

Keywords

pediatric; brain tumor; brainstem glioma; MR diffusion; ADC parametric mapping

Introduction

Diffuse Intrinsic Pontine Glioma (DIPGs) are a subset of brainstem tumors that primarily affect children. Median progression-free survival (PFS) after diagnosis without any treatment is only 5-8 months,¹ with radiation therapy (RT) being the only known treatment

to effectively increase PFS (median PFS of 9-10 months with RT).² Imaging criteria are a primary source of diagnosis and treatment guidance. Multiple prior studies have shown that diffusion imaging is able to provide useful adjunct information about (1) baseline characteristics of DIPG tumors that reflect cellularity; (2) portend the response of these tumors to radiation.³⁻⁶ Most quantitative diffusion studies of pediatric DIPG have measured spatial distribution of ADC at one time point of imaging using either manual ROI or histogram analyses.⁶

A complementary approach to quantitating diffusion characteristics in tumors is functional diffusion maps (fDMs).^{4,7,8} fDMs look at the spatio-temporal profile of a tumor over a treatment course between two time points of imaging, rather than a single time-point's spatial profile. This is done by performing voxel-wise calculations in the change in diffusion at each voxel between each time point of interest. fDMs have been used extensively in adult brain tumors,^{4,8-10} but to date very limited studies have been performed in pediatric brain tumors, including DIPG. fDM analyses have been previously used to predict pseudo-progression in a cohort of children diagnosed with DIPGs who were enrolled in an immunotherapy clinical trial.¹¹ Here, we perform fDM analysis on a larger population of children with DIPGs who underwent RT, to quantitate FDM metrics in DIPG tumors between baseline and radiation therapy and to compare these FDM metrics with baseline ADC values in predicting outcome in pediatric DIPG. As a secondary objective, we compared FDM metrics in relation to a second time point of imaging after radiation and ADC histogram metrics previously performed in this cohort⁶ to characterize heterogeneous treatment response in pediatric DIPG.

Methods

Patients and Treatment

Imaging was acquired from a total of 95 patients enrolled in Pediatric Brain Tumor Consortium (PBTC) diffuse intrinsic brainstem glioma clinical trials PBTC-006, -007, -014, -021, and -030 who had undergone pre- and post-radiation treatment (RT) MRIs with diffusion weighted imaging. This is a subset of the 140 total patients used in our previous analysis (67.9%).⁶ All patients were diagnosed using standard MRI criteria,¹² and no biopsies were acquired. Institutional Review Board approval was obtained at each participating institution. Informed consent was obtained for all patients. Patients on PBTC-006 were treated with imatinib twice a day during irradiation at doses of 200-800 mg/m². Patients on PBTC-007 phase I and II received gefitinib at doses of 100-375 mg/m² and 250 mg/m², respectively, with concurrent RT. Patients on PBTC-014 phase I received tipifarnib at 100-150 mg/m² with concurrent RT, while patients on PBTC-014 phase II received 125 mg/m²/dose twice a day with concurrent RT. Patients on PBTC-021 phase I received capecitabine with concurrent RT at doses of 375 mg/m², and patients on PBTC-030 phase II received capecitabine with concurrent RT at doses of 650 mg/m²/dose twice a day. All patients received treatment with local irradiation 5 days a week to a total dose of 5580 cGy, using conventional or conformal volume-based delivery techniques. A summary of the imaging intervals in these patients is provided in supplemental table 1.

Imaging

We retrospectively obtained the MR imaging from the PBTC Operations, Biostatistics and Data Management Core (OBDMC) imaging archive for available patients. Patients had the first imaging time point prior to start of RT, at the end of RT, and at every 2-3 subsequent courses of therapy. While imaging was done at multiple institutions, the protocol was standardized across all sites. 15 studies were acquired at a 3.0T magnet, with the remaining done at 1.5T. Imaging acquisition parameters were as follows: Axial T2 FLAIR were obtained using a 4-mm slice thickness (no gap) using sequence repetition time (TR) of 10000, time of inversion of 2200 and echo time (TE) of 162 ms; reconstruction matrix was 256×192, field of view (FOV) of 18–24 cm, and number of excitations (NEX) of 1. Axial T2-weighted FSE were obtained with TR/effective TE = (4000–6000)/80–100, echo train length of 10–16, rf band of +16 kHz, FOV of 18–24 cm, slice thickness of 4 (no gap) acquired interleaved, NEX = 2, matrix = 256×192, with flow compensation option and A-P frequency direction. DWI were acquired with single-shot echoplanar spin echo images with TR of 2000 and TE of 80 ms, reconstruction matrix 128×128, b-factor of 5/1000 s/mm², over 3 directions for trace imaging, receiver bandwidth of +64 kHz, and frequency direction R-L with a slice thickness of 4 mm (no gap). Post-gadolinium axial T1-weighted spin echo images were acquired in 4-mm contiguous slices through the whole head using TR of 500-700 ms and TE minimum full; using a NEX of 2 and reconstruction matrix 256×192.

Image Analysis

We generated functional diffusion maps for each patient's time course using a previously published pipeline.¹³ ROIs were drawn using co-localized axial T2 FSE and FLAIR images at each time point. The b0 image of the DWI was then linearly registered to the T2 FSE using FSL's linear registration tool (FLIRT)¹⁴ and a final fine Fourier registration using AFNI¹⁵, with the resulting transformation matrix applied to the ADC image to bring it into the same space. We used the pre-RT time point as the baseline image, and linearly co-registered every subsequent time point into the baseline image space. This allowed us to generate fDMs between each time point within one spatially consistent volume. This sets the pre-RT time point as the frame of reference for subsequent changes within the tumor volume. fDMs were generated by calculating the voxel-wise change in ADC between each time point. We chose to set the threshold of significance at $\pm 0.4 \text{ mm}^2/\text{ms}$ as empirically derived by Ellingson et al.⁷, estimated to be the 95% confidence interval of normal ADC fluctuations in normal tissue. From each fDM, we calculated the following derived metrics: total voxels with increase in ADC (iADC), total voxels with decrease in ADC (dADC), total voxels with no change in ADC (nADC), fraction of voxels with increased ADC (fiADC), fraction of voxels with decreased ADC (fdADC), and the ratio of fiADC and fdADC (fDM Ratio). The fDM results for each patient were matched with ADC histogram metrics as previously published in this cohort to measure agreement between these complementary techniques.⁶

Statistical Approach

Descriptive statistics were provided for baseline and post-RT fDM measures. Survival distributions were estimated using Kaplan-Meier method and compared using the log-rank

test. Cox Proportional Hazards Models was utilized to investigate possible associations of diffusion histogram measures with Progression-Free Survival (PFS) and overall survival (OS) distributions. Failure (i.e., event) in PFS was defined as any progression or death that occurred while the patient was being followed according to the protocol. PFS was measured from Treatment Start Date to the event date for patients who failed. For patients who did not experience a failure, PFS was measured from “Treatment Start Date” to the “Off Study Date” or to the date of last follow-up. OS was defined from ‘treatment start date’ to the date of death for subjects who died and to the date of last follow-up for subjects who were alive. Spearman rank correlations were calculated to describe the rank correlations between each of the derived fDM metrics and pre- and post-treatment histogram metrics (mean, median, mode, standard deviation, skewness and kurtosis) as calculated from both FLAIR and contrast enhanced delineated ROIs. A p-value threshold of 0.05 was used to declare significance without adjusting for multiplicity. Due to several statistical tests performed, results reported in this manuscript should be considered exploratory and confirmed by other independent studies. Further exploratory analysis is described in the Supplemental Methods.

Results

Patients

Of the 95 patients in which imaging data were obtained, a total of 72 patients were included in the final analysis. Among the 23 patients who were excluded, 1 patient did not have a post RT-scan and the remaining 22 had scans with poor image quality or motion artifact resulting in inadequate image registration when generating the fDMs. Of the 72 patients in our cohort 5 patients were enrolled in PBTC-006, 27 in PBTC-007, 21 in PBTC-014, 5 in PBTC-021, and 14 in PBTC-030. There were 38 female patients (52.78%) and 34 male patients (47.22) with a median age at start of therapy of 6.4 years. The median time from treatment initiation to first Post-RT scan was 58 days. 32 patients had two post-RT scans, with a median interval between the first and second post-RT scan of 56 days. 176 total time points were used. The 1-year PFS and OS for this cohort were 13.9% $\pm$ 4.1% and 42.8% $\pm$ 5.9%, respectively.

fDM characteristics of pediatric DIPG (first time point of imaging after radiation):

We saw no significant differences in response metrics between trial-specific protocols. Patients showed a higher fraction of voxels with decreased ADC (fdADC) compared to the fraction of voxels with increased ADC (fiADC) after the first RT time point, with a median of 24.1% voxels showing decreased ADC compared to 17.5% showing increase (Table 1). Figure 1 shows an example of a patient with overall decrease in ADC between baseline and post-RT, with the inverse shown in Figure 2. As expected, mean tumor ADC at baseline shows a strong correlation with post-RT fDM metrics (Table 2). Notably, however, fdADC between the first post-RT time point and baseline shows a stronger Spearman rank correlation coefficient of 0.702 ($p < 0.0001$) with mean ADC at baseline, similarly observed with the fDM Ratio ($r_s = -0.700$, $p < 0.0001$), compared to fiADC ($r_s = -0.516$, $p < 0.0001$).

Correlation of baseline ADC and fDM metrics with outcome (PFS and OS):

Table 3 shows the association between the fDM derived metrics and progression free survival. Patients with higher fiADC between baseline and the first post-RT time point

showed a trend toward shorter PFS with a hazard ratio of 6.44 (CI = 0.79, 52.79, $p = 0.083$). Additionally, the total number of voxels with no change in ADC (nADC) at the first post-RT time point compared to baseline showed shorter PFS, albeit with a lower hazard ratio of 1.02 (CI = 1, 1.03, $p\text{-value} = 0.06$). In contrast, patients with higher log mean ADC at baseline had longer PFS, with a hazard ratio of 0.27 (CI = 0.09, 0.82, $p = 0.022$). We observed no significant association between tumor volume or fDM derived metrics and overall survival in this cohort.

Additional Secondary Analysis:

As a secondary analysis, we calculated the fDM characteristics of pediatric DIPG using a second time point of imaging after radiation (see Supplemental Table 2 and 3). When measuring ADC changes between the second post-RT time point and baseline, a further increase in fdADC was observed (median 32.9%), with a decrease in fiADC (median 15.8%) relative to the first post-RT time point. The same metrics comparing the second post-RT time point and baseline showed a similar pattern as the first post-RT time point, but weaker correlation with mean ADC at baseline, and no significant correlation with tumor volume at baseline. We also explored the relationship between ADC histogram analysis and fDM, and observed strong association between these metrics (Supplemental Results for details). There was no correlation between fDM metrics and other ADC histogram metrics, including skewness and kurtosis.

Discussion

In this study, we used fDM metrics to measure spatial-temporal changes before and after RT in patients with DIPG and we demonstrate that baseline ADC values have a relatively stronger predictive value of PFS compared to FDM metrics of radiation-related ADC changes. We did see a pattern of decreased ADC within the tumor volume after RT, with fewer voxels showing increase in ADC. This pattern was also noted after the second RT time point, with a further voxel-wise decrease in ADC and fewer voxels showing increase in ADC. We hypothesize that the decrease in diffusivity after RT reflects treatment response which has been noted in other studies⁶. This is further supported by tumors with higher fiADC and nADC showing less favorable PFS. We have also previously demonstrated that higher ADC at baseline is indicative of more favorable outcome.¹⁶ These results are supported by findings by Clerk-Lamallice et al., where the authors suggest that a T2 hyperintense lesion with high ADC prior to RT is indicative of treatable vasogenic edema due to leaky angiogenic vessels, while a T2 hypointense lesion accompanied by low ADC may correspond to focal anaplasia prior to RT.¹⁷ This is consistent with our observations comparing post-RT ADC measures.

Our study does show the feasibility of employing fDM or parametric techniques in a pediatric brain tumor multi-center consortium setting. We have recently used fDMs to characterize pseudoprogression in pediatric DIPG treated with peptide-based vaccine therapy ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01130077) No. [NCT01130077](https://clinicaltrials.gov/ct2/show/study/NCT01130077)).¹¹ fDMs were shown to be a potential biomarker for detecting pseudo-tumor progression in this population. Here, we also secondarily showed correlates between fDM and ADC histogram techniques in the same

pediatric DIPG cases. The application of ADC histogram analysis has been previously reported in this cohort⁶, and here we use these findings to evaluate the fDM derived metrics. Histogram analysis looks at the distribution of the measured metric across the tumor volume. This allows us to measure the characteristic tissue heterogeneity inherent in DIPGs at each time point. We noted significant correlations between selected fDM and ADC histogram metrics providing further evidence that histogram analysis has potential to also characterize heterogeneous treatment response in DIPG. We observed lower values for tumor ADC mean, median, and mode post-RT on FLAIR compared with pre-RT. Furthermore, we found that tumors with lower pre-RT ADC values had significantly shorter PFS and significantly higher skewness and kurtosis compared with those with higher ADC values. Additionally, we note a negative correlation between gadolinium enhancement specific ROI's at baseline and an increase in ADC at the second time point post RT, which may be secondary to the subsequent development of necrosis post radiation. Other studies applying ADC histogram analyses support these findings^{18,19}.

Our FDM analysis adds to the growing body of literature utilizing advanced neuroimaging acquisition and post-processing techniques to characterize baseline and post-therapy related changes of DIPG tumors. The value of these techniques in clinical treatment stratification needs future work. While conventional imaging is used to make the diagnosis of DIPG, characterized by an enlarged pons greater than 50% of the brainstem, diffuse T2/FLAIR signal and minimal gadolinium enhancement¹² – advanced neuroimaging techniques show promise in providing additional information in relation to predicting outcome.¹ Lober et al. used an ADC based threshold to partition DIPG patients into overall survival subgroups.²⁰ Hipp et al. have used multi-parametric imaging to show that increased enhancement, perfusion and MRS choline/NAA ratio were predictive of shorter survival.²¹ Jansen et al. developed a prognostic model comprised of 5 predictive variables of overall survival, with ring contrast enhancement within the tumor at diagnosis being an unfavorable predictor. Histological studies have found DIPGs to be comprised of a heterogeneous mixture of diffuse infiltrating astrocytoma grades 2, 3 and 4 (i.e., GBMs).^{12,22,23} There is evidence to suggest that this is reflected in imaging. Conway et al. found that increased average cerebral blood volume correlates with areas of occult post-contrast enhancement, which may be a marker for angiogenesis.²⁴ Lobel et al have found that T2 hyperintensities and heterogeneity observed within the tumor may represent areas of focal anaplasia.⁵ Recent molecular profiling of DIPGs found a potential target for subtyping in a histone mutation, with H3F3A and HIST1H3B/C mutations showing markedly different treatment response to RT, with strong correlation with imaging markers.²⁵ The HIST1H3B/C variant showed worse response to RT, lower survival, higher relapse frequency, and increased metastases compared to H3F3A. The HIST1H3B/C showed overall higher ADC, and higher variance in ADC measured by histogram analysis. This body of evidence suggests that advanced imaging techniques capable of measuring local tumor properties similar to that of fDM and parametric mapping have value in characterizing DIPG tumors in relation to genomics which can be addressed in future work. Further studies are also needed to determine if fDM of pediatric midline tumors have the potential to distinguish atypical DIPG from tumors that might have better prognosis (i.e. non-K27M midline tumor or pilocytic astrocytomas).

This study has several limitations. The use of a linear registration algorithm to register each time point to the baseline image poses the problem of potentially mismatched voxel-wise tissue comparison. As the tumor grows or diminishes, subsequent time points may compare normal tissue values to tumor values. The alternative to this problem is to use a non-linear deformation algorithm. However, the drawback of using this method is that the non-linear registration invalidates the assumption of measuring the same anatomical region across time. We feel that due to the confined nature of the location of these tumors and short interval between time points, limited tissue distortion is expected, and a linear algorithm provides better confidence in a voxel-wise analysis. Our previous histogram study performed an additional analysis utilizing ROIs measuring only areas of contrast enhancement and found that the presence of enhancement was associated with lower survival. As DIPGs present with minimal enhancement, the FLAIR signal ROIs provided a more consistent volume for spatio-temporal registrations. However, future work may incorporate the gadolinium enhancement ROIs as an added covariate in the fDM analysis. An additional limitation is the exploratory nature of the analyses conducted where a large number of imaging variables were considered. No multiplicity adjustment was employed due to the hypothesis generating nature of this work. The observed significant associations will need to be confirmed in an independent cohort to be considered inferential. Furthermore, our historical control cohort contained an inherent bias for the second post RT endpoint in that only patients who were progression free at that time could be included. The exclusion of a significant portion of studies due to image quality further limits our findings. This inherent limitation may be overcome by advances in motion correction and fast image acquisition, as well as prioritization of diffusion imaging in the clinical protocol if these methods prove to have significant diagnostic utility. Finally, we do not have ground truth in tissue subtyping, as needle biopsies were not performed in this cohort. More recently, the morbidity and mortality rates of stereotactic biopsies have been re-evaluated to be safe and beneficial,²⁶ and with more institutions performing this procedure we hope to incorporate molecular subtyping in future studies.

Conclusion

In this study, we demonstrate the feasibility of functional diffusion parametric mapping techniques in a large cohort of pediatric diffuse intrinsic pontine gliomas prospectively recruited to a series of trials by the multi-center Pediatric Brain Tumor Consortium. We show that baseline ADC is a stronger predictor of outcome compared to post-radiation ADC values derived from fDM analysis. Further work is needed to determine the value of parametric mapping techniques in the evaluation of novel targeted therapy of pediatric brain tumors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding:

This study was funded by: National Institute of Health (NIH) [U01 CA81457]; National Library of Medicine (NLM) Grant 5T15LM007059-27; Memorial Sloan Kettering Cancer Center (MSKCC) [P30 CA008748]; The Pediatric Brain Tumor Consortium Foundation; the Pediatric Brain Tumor Foundation of the United States; the American Lebanese Syrian Associated Charities and Ian's Friends Foundation.

Abbreviations:

fDM	functional Diffusion Map
iADC	increase in ADC
dADC	decrease in ADC
nADC	no change in ADC
fiADC	fraction of voxels with iADC
fdADC	fraction of voxels with dADC
RT	Radiation Treatment
OS	Overall Survival
PFS	Progression Free Survival

References

1. Pollack IF, Jakacki RI. Childhood brain tumors: epidemiology, current management and future directions. *Nat Rev Neurol*. 2011;7(9):495–506. doi:10.1038/nrneurol.2011.110. [PubMed: 21788981]
2. Donaldson SS, Laningham F, Fisher PG. Advances Toward an Understanding of Brainstem Gliomas. *J Clin Oncol*. 2006;24(8):1266–1272. doi:10.1200/JCO.2005.04.6599. [PubMed: 16525181]
3. Holodny AI, Makeyev S, Beattie BJ, Riad S, Blasberg RG. Apparent diffusion coefficient of glial neoplasms: correlation with fluorodeoxyglucose-positron-emission tomography and gadolinium-enhanced MR imaging. *AJNR Am J Neuroradiol*. 2010;31(6):1042–1048. doi:10.3174/ajnr.A1989. [PubMed: 20150307]
4. Ellingson BM, Cloughesy TF, Zaw T, et al. Functional diffusion maps (fDMs) evaluated before and after radiochemotherapy predict progression-free and overall survival in newly diagnosed glioblastoma. *Neuro Oncol*. 2012.
5. Löbel U, Sedlacik J, Reddick WE, et al. Quantitative Diffusion-Weighted and Dynamic Susceptibility-Weighted Contrast-Enhanced Perfusion MR Imaging Analysis of T2 Hypointense Lesion Components in Pediatric Diffuse Intrinsic Pontine Glioma. 2011;32(2). doi:10.3174/ajnr.A2277.
6. Poussaint TY, Vajapeyam S, Ricci KI, et al. Apparent diffusion coefficient histogram metrics correlate with survival in diffuse intrinsic pontine glioma: a report from the Pediatric Brain Tumor Consortium. *Neuro Oncol*. 2015;18(7):1–10. doi:10.1093/neuonc/nov256.
7. Ellingson BM, Malkin MG, Rand SD, et al. Validation of functional diffusion maps (fDMs) as a biomarker for human glioma cellularity. *J Magn Reson Imaging*. 2010;31(3):538–548. [PubMed: 20187195]
8. Moffat BA, Chenevert TL, Lawrence TS, et al. Functional diffusion map: a noninvasive MRI biomarker for early stratification of clinical brain tumor response. *Proc* 2005;102(15):5524–5529.
9. Jain R, Ellika S, Scarpace L, et al. Role of functional diffusion maps as an imaging biomarker for treatment response assessment in recurrent/progressive malignant gliomas treated with bevacizumab. In: *Proceedings 17th Scientific Meeting, International Society for Magnetic Resonance in Medicine* ; 2009:3471.

10. Grech-Sollars M, Saunders DE, Phipps KP, et al. Challenges for the functional diffusion map in pediatric brain tumors. *Neuro Oncol.* 2013;(4):1–8. doi:10.1093/neuonc/not197. [PubMed: 23284031]
11. Ceschin R, Kurland BF, Abberbock SR, et al. Parametric Response Mapping of Apparent Diffusion Coefficient as an Imaging Biomarker to Distinguish Pseudoprogression from True Tumor Progression in Peptide-Based Vaccine Therapy for Pediatric Diffuse Intrinsic Pontine Glioma. *AJNR Am J Neuroradiol.* 9 2015. doi:10.3174/ajnr.A4428.
12. Cohen KJ, Heideman RL, Zhou T, et al. Temozolomide in the treatment of children with newly diagnosed diffuse intrinsic pontine gliomas: a report from the Children's Oncology Group. *Neuro Oncol.* 2011;13(4):410–416. doi:10.1093/neuonc/noq205. [PubMed: 21345842]
13. Ceschin R, Panigrahy A, Gopalakrishnan V. Sfdm: Open-source software for temporal analysis and visualization of brain tumor diffusion mr using serial functional diffusion mapping. *Cancer Inform.* 2015;14:1–9. doi:10.4137/CIn.s17293.
14. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. FSL. *Neuroimage.* 2012;62(2):782–790. [PubMed: 21979382]
15. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res.* 1996;29(3):162–173. [PubMed: 8812068]
16. Poussaint TY, Kocak M, Vajapeyam S, et al. MRI as a central component of clinical trials analysis in brainstem glioma: A report from the Pediatric Brain Tumor Consortium (PBTC). *Neuro Oncol.* 2011;13(4):417–427. doi:10.1093/neuonc/noq200. [PubMed: 21297126]
17. Clerk-Lamalice O, Reddick WE, Li X, et al. MRI evaluation of non-necrotic T2-hyperintense foci in pediatric diffuse intrinsic pontine glioma. *Am J Neuroradiol.* 2016;37(10):1930–1937. doi: 10.3174/ajnr.A4814. [PubMed: 27197987]
18. Chen HJ, Panigrahy A, Dhall G, Finlay JL, Nelson MD, Bluml S. Apparent Diffusion and Fractional Anisotropy of Diffuse Intrinsic Brain Stem Gliomas. *Am J Neuroradiol.* 2010;31(10): 1879–1885. doi:10.3174/ajnr.A2179. [PubMed: 20595371]
19. Zukotynski K, Vajapeyam S, Fahey FH, et al. Correlation of ¹⁸F-FDG PET and MR Apparent Diffusion Coefficient (ADC) Histogram Metrics with Survival in Diffuse Intrinsic Pontine Glioma: A Report from the Pediatric Brain Tumor Consortium. *J Nucl Med.* 3 2017:jnumed.116.185389. doi:10.2967/jnumed.116.185389.
20. Lober RM, Cho Y-J, Tang Y, et al. Diffusion-weighted MRI derived apparent diffusion coefficient identifies prognostically distinct subgroups of pediatric diffuse intrinsic pontine glioma. *J Neurooncol.* 2014;117(1):175–182. doi:10.1007/s11060-014-1375-8. [PubMed: 24522717]
21. Hipp SJ, Steffen-Smith E, Hammoud D, Shih JH, Bent R, Warren KE. Predicting outcome of children with diffuse intrinsic pontine gliomas using multiparametric imaging. *Neuro Oncol.* 2011;13(8):904–909. doi:10.1093/neuonc/nor076. [PubMed: 21757444]
22. Lapin DH, Tsoli M, Ziegler DS. Genomic Insights into Diffuse Intrinsic Pontine Glioma. *Front Oncol.* 2017;7:57. doi:10.3389/fonc.2017.00057. [PubMed: 28401062]
23. Diaz AK, Baker SJ. The genetic signatures of pediatric high-grade glioma: No longer a one-act play. *Semin Radiat Oncol.* 2014;24(4):240–247. doi:10.1016/j.semradonc.2014.06.003. [PubMed: 25219808]
24. Conway AE, Reddick WE, Li Y, et al. “Occult” post-contrast signal enhancement in pediatric diffuse intrinsic pontine glioma is the MRI marker of angiogenesis? *Neuroradiology.* 2014;56(5): 405–412. doi:10.1007/s00234-014-1348-9. [PubMed: 24626721]
25. Castel D, Philippe C, Calmon R, et al. Histone H3F3A and HIST1H3B K27M mutations define two subgroups of diffuse intrinsic pontine gliomas with different prognosis and phenotypes. *Acta Neuropathol.* 2015;130(6):815–827. doi:10.1007/s00401-015-1478-0. [PubMed: 26399631]
26. Hamisch C, Kickingeder P, Fischer M, Simon T, Ruge MI. Update on the diagnostic value and safety of stereotactic biopsy for pediatric brainstem tumors: a systematic review and meta-analysis of 735 cases. *J Neurosurg Pediatr.* 2017;20(3):261–268. doi:10.3171/2017.2.PEDS1665. [PubMed: 28621573]

Figure 1.

4-year-old girl with DIPG who had progression on Day 217 and died on Day 252 from therapy start date. Functional Diffusion maps of voxelwise change in apparent diffusion coefficient (ADC) show a marked decrease in ADC between pre-RT time point, and both 57 days post-RT and 113 days post-RT. Images are linearly co-registered into a common space. Red voxels show an increase in ADC compared to baseline, green voxels show no change in ADC compared to baseline, and blue voxels show a decrease in ADC compared to baseline.

Figure 2.

16-year-old girl with DIPG who had progression on Day 258 and died on Day 348 from therapy start date. Functional Diffusion maps of voxelwise change in apparent diffusion coefficient (ADC) show a marked increase in ADC between pre-RT time point, and 69 days post-RT with very few voxels showing decreased ADC. Images are linearly co-registered into a common space. Red voxels show an increase in ADC compared to baseline, green voxels show no change in ADC compared to baseline, and blue voxels show a decrease in ADC compared to baseline.

Table 1.

Descriptive Statistics for Post-RT (Time-1 and Time-2) fDM metrics

	N	Min	Q1	Median	Q3	Max
First post-RT Time Point Compared to Baseline						
Fraction of increased ADC (fiADC)	71	0.006	0.112	0.175	0.236	0.522
Fraction of decreased ADC (fdADC)	71	0.005	0.115	0.241	0.468	0.753
Ratio of fiADC to fdADC (FDM ratio)	71	0.009	0.29	0.629	1.643	23.804
Total voxels with increased ADC (iADC)	71	173	1576	4371	7008	51885
Total voxels with decreased ADC (dADC)	71	39	2338	5268	13711	32921
Total voxels with no change in ADC (nADC)	71	1809	6127	12385	21816	80202

Table 2.**Rank Correlation of Baseline Mean ADC and Volume ADC with Post-RT fDM metrics.**

	Baseline Mean ADC		Baseline Tumor Volume	
	r_s	$p <$	r_s	$p <$
First post-RT Time Point Compared to Baseline				
Fraction of increased ADC (fiADC)	-0.5161	0.0001	0.1572	0.1904
Fraction of decreased ADC (fdADC)	0.7027	0.0001	0.0003	0.9978
Ratio of fiADC to fdADC (FDM ratio)	-0.7004	0.0001	0.1110	0.3568
Total voxels with increased ADC (iADC)	-0.4195	0.0003	0.2820	0.0172
Total voxels with decreased ADC (dADC)	0.4934	0.0001	0.1554	0.1957
Total voxels with no change in ADC (nADC)	-0.3215	0.0063	0.2616	0.0275

Table 3.

Univariable Association of fDM measures with PFS

Covariate	N(N_{event})	Hazard Ratio (95% CI)	P <
Log of Baseline Mean ADC	72 (68)	0.27 (0.09, 0.82)	0.022
Log of Baseline Volume of ADC	72 (68)	1.02 (0.64, 1.62)	0.93
Fraction of increased ADC (fiADC)	71 (67)	6.44 (0.79, 52.79)	0.083
Fraction of decreased ADC (fdADC)	71 (67)	0.51 (0.16, 1.65)	0.26
Ratio of fiADC to fdADC (FDM ratio)	71 (67)	1.01 (0.96, 1.07)	0.66
Total voxels with increased ADC (iADC)	71 (67)	1.02 (0.98, 1.06)	0.37
Total voxels with decreased ADC (dADC)	71 (67)	1.01 (0.98, 1.04)	0.57
Total voxels with no change in ADC (nADC)	71 (67)	1.02 (1, 1.03)	0.06