Apparent diffusion coefficient histogram metrics correlate with survival in diffuse intrinsic pontine glioma: a report from the Pediatric Brain Tumor Consortium

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Background. Diffuse intrinsic pontine glioma (DIPG) is associated with poor survival regardless of therapy. We used volumetric apparent diffusion coefficient (ADC) histogram metrics to determine associations with progression-free survival (PFS) and overall survival (OS) at baseline and after radiation therapy (RT).

Methods. Baseline and post-RT quantitative ADC histograms were generated from fluid-attenuated inversion recovery (FLAIR) images and enhancement regions of interest. Metrics assessed included number of peaks (ie, unimodal or bimodal), mean and median ADC, standard deviation, mode, skewness, and kurtosis.

Results. Based on FLAIR images, the majority of tumors had unimodal peaks with significantly shorter average survival. Pre-RT FLAIR mean, mode, and median values were significantly associated with decreased risk of progression; higher pre-RT ADC values had longer PFS on average. Pre-RT FLAIR skewness and standard deviation were significantly associated with increased risk of progression; higher pre-RT FLAIR skewness and standard deviation had shorter PFS. Nonenhancing tumors at baseline showed higher ADC FLAIR mean values, lower kurtosis, and higher PFS. For enhancing tumors at baseline, bimodal enhancement histograms had much worse PFS and OS than unimodal cases and significantly lower mean peak values. Enhancement in tumors only after RT led to significantly shorter PFS and OS than in patients with baseline or no baseline enhancement.

Conclusions. ADC histogram metrics in DIPG demonstrate significant correlations between diffusion metrics and survival, with lower diffusion values (increased cellularity), increased skewness, and enhancement associated with shorter survival, requiring future investigations in large DIPG clinical trials.

Keywords: ADC histogram, brain tumor, brainstem glioma, MR diffusion, pediatric.
Recent work has shown the importance of whole tumor ADC histograms in differentiating tumor types in adults and in predicting response. Pope et al.10 found that the ADC histograms of the enhancing portion of glioblastoma multiforme tumors in adults showed a bimodal distribution and that the change in the mean ADC of the lower peak predicted response to anti-angiogenic therapies in these tumors. Nowoselski et al.11 reported on adult recurrent high-grade gliomas undergoing anti-angiogenic therapy and found that changes in shape characteristics of the ADC histogram of the enhancing and T2 hyperintense regions of the tumors predicted PFS. While these studies were in adults, Bull et al.12 used ADC histograms to successfully discriminate among pediatric brain tumor types; Rodriguez Gutierrez et al.9 analyzed pediatric posterior fossa tumors; and Steffen-Smith et al.10 used diffusion tensor histogram analysis to show intratumoral differences in a cohort of children with DIPG. This study focuses on a large cohort of DIPG patients, and we hypothesized that ADC metrics obtained through volumetric ADC histogram analyses of DIPG at baseline and after radiation would correlate with tumor response and survival.

**Materials and Methods**

**Study Design**

Baseline and post-RT MR exams were obtained from the Pediatric Brain Tumor Consortium (PBTC) diffuse intrinsic brainstem glioma clinical trials PBTC-006, -007, -014, -021, and -030. All DIPG patients were diagnosed on MRI without biopsy. The institutional review boards of each PBTC institution approved these studies in advance of initial patient enrollment; continuing approval was maintained throughout. Patients or legal guardians gave written informed consent; assent was obtained (as appropriate) at the time of enrollment. The effects of RT, combined with molecular targeting agents—imatinib, gefitinib, and tipifarnib—were analyzed in patients enrolled and treated on PBTC-006, PBTC-007 phase I/II, and PBTC-014 phase I/II, respectively. Patients treated on PBTC-006 received imatinib twice daily during irradiation of newly diagnosed brainstem gliomas at doses of 200–800 mg/m². PBTC-007 phase I received gefitinib at doses of 100–375 mg/m², and those from the phase II trial received 250 mg/m² once daily with concurrent RT. Patients on PBTC-014 phase I received tipifarnib at doses of 100–150 mg/m², and those on PBTC-014 phase II received tipifarnib with concurrent RT at 125 mg/m²/dose twice daily. Patients on PBTC-021 phase I received capécitabine with concurrent RT at 375 mg/m²/dose, and those on PBTC-030 phase II received capécitabine with concurrent RT at 650 mg/m²/dose twice daily. Patients received local irradiation using conventional or conformal volume-based delivery techniques, with one treatment 5 days per week to a total dose of 5580 cGy. The gross tumor volume was defined as the abnormal signal on MRI (usually T2 weighted, but a combination of T1 with contrast and T2 was acceptable). The clinical target volume for subclinical disease was defined as a 1.5-cm anatomic margin beyond the gross tumor volume, targeting at least the entire anatomic section of the brainstem within the clinical target volume. This margin was constrained by the anatomic limits of brain structures and within the skull. The planning target volume was an institution-specific geometric margin to allow for daily patient setup uncertainties (typically 3–5 mm). Doses were delivered uniformly to the target volumes and prescribed to the isocenter or to an isodose surface that encompassed the planning target volume (ie, 100% isodose surface for 3D techniques).

Progression was defined by the treating institutions as worsening neurologic status or increasing steroid requirement not explained by causes other than tumor progression, or a >25% increase in tumor bidimensional measurement on MRI, or appearance of new lesions or increasing doses of dexamethasone required to maintain stable neurologic status or imaging.

**MRI Evaluation and Apparent Diffusion Coefficient Histogram Analysis**

Each course was defined as 4 weeks. MRI was done pretreatment; every other course throughout the first year; once every 3 courses thereafter; at the end of treatment (maximum 2 y); and at the time of disease progression. MR studies from the PBTC imaging archive of DIPG clinical trials were obtained, consisting of the baseline and first post-RT MR scans. The scans were randomly sorted, anonymized, and assigned different accession numbers by the Operations, Biostatistics, and Data Management Core of the PBTC to minimize bias in the image analyses. Each site participated in an MR quality assurance program.11,12 All studies were conducted on 1.5-Tesla magnets, with the exception of 15 studies conducted on 3.0T magnets. Imaging parameters were similar for 1.5T and 3.0T magnets. The following parameters were used for the imaging sequences at each site. Axial T2 fluid-attenuated inversion recovery (FLAIR) images were obtained with 4-mm contiguous slice thickness using the sequence repetition time (TR)/time of inversion/echo time (TE) of 10 000/2200/162 ms; matrix = 256 × 192, field of view = 18–24 cm, and number of excitations (NEX) = 1. Axial T2-weighted fast spin echo images were obtained with TR/echo time (TE) = (4000–6000)/80–100 ms, echo train length = 10–16, radiofrequency band = ±16 kHz, field of view = 18–24 cm, slice thickness/gap = 4/0 interleaved, NEX = 2, matrix = 256 × 192, flow compensation option, and frequency direction anterior/posterior. Diffusion images were single-shot echoplanar spin echo images with TR/TE = 2000/80 ms, 128 × 128 matrix, b-factor of 5/1000 s/mm², 3 directions (x, y, z) for trace imaging, receiver bandwidth of ±64 kHz, and frequency direction right/left with a slice thickness/gap of 4/0. Post-gadolinium axial T1-weighted spin echo images were 4-mm contiguous slices through the whole head using TR/TE = 500–700 ms/minimum full; NEX = 2, matrix = 256 × 192.

For ADC histogram analyses, B0 diffusion images were used because of superior anatomic contrast and were registered to the FLAIR images, and the same transformation matrix was applied to the ADC images in order to align them with the FLAIR data. A mutual information algorithm available under FSL in the Functional Magnetic Resonance Imaging of the Brain Software Library13 was used for the registration. FLAIR images were used for ROIs based on the more consistent selection of tumor boundaries. For those studies where FLAIR data were unavailable or unusable, axial T2 data were used instead. A 3D ROI comprising the tumor FLAIR signal was automatically generated using a thresholding feature available in Fiji,14 an Open Source distribution of Java along with ImageJ (National
Institutes of Health. The same 3D ROI was used on the registered ADC maps, and the histogram of the ADC values of all voxels in the ROI was generated. For all studies showing enhancement after contrast injection, the postcontrast images were also registered with the FLAIR data (and hence the ADC data), and the ADC histogram of the enhancing portion of the tumor was generated using the methods described above.

Quantitative histogram analysis of the FLAIR and enhancing portion of the tumors was also done using Fiji. All histograms were first thresholded uniformly with a lower threshold of 600 × 10⁻⁶ mm²/s and an upper threshold of 2600 × 10⁻⁶ mm²/s. The purpose of this step was twofold: (i) the lower threshold eliminated voxels containing hemorrhage, and the upper threshold eliminated voxels containing necrosis, cyst, or CSF; and (ii) using a uniform interval for ADC values allowed us to compare histogram shape descriptors across studies. A uniform bin width of 10 was used. For each histogram calculated using Fiji, the following metrics were assessed on FLAIR and enhancement images: number of peaks, mean ADC, standard deviation (SD), mode, median ADC, skewness (the symmetry of distribution around the mean), and kurtosis (height and sharpness of peak relative to rest of data). For peaks with a bimodal distribution, the ADC values were further delineated using the default thresholding algorithm in Fiji and metrics including lower peak and higher peak mean ADC, SD, mode, and median ADC of the lower peak and higher peak values calculated separately.

Using the Vitrea workstation (Vital Images) and a perimeter technique, we performed volumetric tumor analyses on axial FLAIR sequences and post-gadolinium axial T1 images with user-assisted semi-automated software; tumor volumes on FLAIR, enhancement on T1 gadolinium images, and cyst/necrosis on T1 gadolinium images were then recorded.

Statistical Considerations

Linear associations between continuous variables of interest were described using the Spearman rank correlation coefficient. To compare the distribution of a continuous imaging marker between 2 groups of patients, the Wilcoxon–Mann–Whitney test was used. Distributions of PFS and overall survival (OS) were estimated using the Kaplan–Meier method, and survival distributions were compared between 2 or more groups using the log-rank test. Cox proportional hazards models were used to investigate the associations of continuous ADC histogram variables, or a list of predictors in a multivariable fashion, with PFS and OS. OS was defined as the interval between initiation of treatment and death on study. PFS was defined as the interval between initiation of treatment and the earliest of either progressive disease or death on study for patients. Patients without failure for PFS or OS were censored at the off-study date. When statistically appropriate, log-transformation of covariates was used in survival models.

Results

Patients

One hundred forty patients had newly diagnosed DIPG. Fourteen patients were enrolled in PBTC-006, 45 patients in PBTC-007, 37 patients in PBTC-014, 10 patients in PBTC-021, and 34 patients in PBTC-030. The analysis cohort was defined as patients who had analyzable diffusion data either for FLAIR or for enhancement tumor volume at either baseline or post-RT. Nineteen patients did not satisfy this definition and were excluded, as the diffusion studies were not analyzable. Thus our analysis cohort size was reduced from 140 patients to 121 patients. The median age for the 121 patients was 6.6 years. There were 67 girls (55%) and 54 boys (45%). The 1-year PFS and OS for this cohort were 10.6% ± 2.8% and 42.8% ± 4.6%, respectively. There was no statistical difference in survival between the treatment protocols. For those patients who did not die on study, the follow-up duration was comparable: median time of 4–5 months from the off-therapy date except for PBTC-006, which was the earliest study, with median follow-up of 28 days.

Imaging Evaluation

There were 242 brain MRI scans from the 121 patients. Eighteen patients pre-RT and 17 post-RT were not analyzable. The majority of the brainstem gliomas were T1 hypointense and T2 hyperintense at presentation with variable T2 hypointensity within the tumor. Median tumor volume was 35.3 cc based on FLAIR images (n = 118, range: 6.6–86.2). Out of 55 patients with enhancing tumors based on ADC analysis, the median enhancing volume was 2.2 cc and range 0.12–15.0 cc.

All patients received concurrent RT and molecularly targeted drug. Scans were obtained pre-RT within 2 weeks of therapy initiation, and post-RT at a median of 57 days from the treatment start date (range = 40 to 142 days with 90% of patients having post-RT scans between day 48 and day 80 from the treatment start date). We analyzed neuroimaging variables, including tumor volume on FLAIR and enhancing tumor volume on T1 gadolinium images.

Baseline ADC Histogram Metrics and Associations with PFS and OS (FLAIR)

At baseline on FLAIR, 18 patients did not have analyzable FLAIR data. There were 86 patients with unimodal ADC histogram peaks and 17 patients with bimodal peaks. Those tumors with a unimodal peak had the suggestion of shorter PFS (P = .088) and definitely shorter OS (P = .04) than those with a bimodal peak (Fig. 1). There was no difference between tumor volume size distributions between tumors with unimodal peaks and bimodal peaks at baseline. The baseline FLAIR mean ADC negatively rank-correlated with baseline FLAIR skewness and kurtosis; higher ADC mean values had lower skewness and kurtosis (P < .0001) (Fig. 2). The pre-RT FLAIR mean, mode, and median values were significantly associated with decreased hazard of progression (P < .0001); higher pre-RT ADC values had longer PFS. Pre-RT FLAIR skewness was significantly associated with increased risk of progression (P < .0001); higher pre-RT FLAIR skewness had shorter PFS. For nonenhancing tumors at baseline, there were higher ADC FLAIR mean values (median ADC, 1417 × 10⁻⁶ mm²/s) and lower kurtosis (median nonenhancing, 0.9; P = .027).

Regarding age at diagnosis, ADC distribution for pre-RT FLAIR mean was slightly higher on average for age <7 years (median...
Baseline ADC Histogram Metrics and Associations with PFS and OS (Contrast-Enhancing Tumor T1 Post Gadolinium)

At baseline, 46 patients had a unimodal peak within the tumor enhancement and 9 had bimodal peaks. Enhancing tumors had shorter PFS ($P = .011$) and showed significantly lower ADC FLAIR mean values ($1298.7 \times 10^{-6} \text{ mm}^2/\text{s}$ vs $1417 \times 10^{-6} \text{ mm}^2/\text{s}$ for nonenhancing, $P = .04$) and higher kurtosis (1.9 vs 0.9 for nonenhancing, $P = .027$). In addition for baseline enhancement, skewness and kurtosis were associated with an increased risk of progression, with higher values associated with shorter PFS and OS ($P = .018$ and .024 for skewness and $P = .013$ and .027 for kurtosis).

For enhancing tumors at baseline, those patients with bimodal pre-RT enhancement ADC histograms had much worse OS and PFS than unimodal cases (with $P = .006$ and $P = .074$, respectively). The lower peak metrics in bimodal cases were significantly lower on average (lower peak mean $= 807.61 \times 10^{-6} \text{ mm}^2/\text{s}$ and lower nonenhancing, $P = .04$) and higher kurtosis (1.9 vs 0.9 for nonenhancing, $P = .027$). In addition for baseline enhancement, skewness and kurtosis were associated with an increased risk of progression, with higher values associated with shorter PFS and OS ($P = .018$ and .024 for skewness and $P = .013$ and .027 for kurtosis).

Fig. 1. (A) Correlation of diffusion histogram number of peaks with OS, with longer survival in those tumors with 2 histogram peaks at baseline. (B) Axial FLAIR, axial ADC, and single peak ADC histogram (left to right) based on FLAIR tumor volume with PFS of 40 days and OS of 52 days. (C) Axial FLAIR, axial ADC, and bimodal peak ADC histogram (left to right) based on FLAIR tumor volume with PFS of 455 days and OS of 997 days.
peak mode = \(769.75 \times 10^{-6} \text{ mm}^2/\text{s}\) than the unimodal distribution (mean = \(1233.88 \times 10^{-6} \text{ mm}^2/\text{s}\); mode = 1178.42) with \(P\)-values of .0022 and .031, respectively (Fig. 3).

Regarding age at diagnosis, pre-RT enhancement ADC median values were slightly higher on average for age <7 years (median ADC value, 1287.4 \(\times 10^{-6} \text{ mm}^2/\text{s}\)) compared with age \(\geq 7\) years (median ADC value, 1158.4 \(\times 10^{-6} \text{ mm}^2/\text{s}\)), with \(P = .077\).

**Preradiation versus Postradiation ADC Histogram Metric Differences**

After radiation, there was no correlation of the number of histogram peaks with PFS and OS. There were lower values for tumor ADC mean, median, and mode post-RT on FLAIR compared with pre-RT (\(P < .0001\)) (Fig. 4). There was increased skewness and kurtosis post-RT compared with pre-RT (\(P < .0001\)). In addition, pre-RT FLAIR mean and median values negatively correlated with post-RT volume FLAIR; tumors with higher pre-RT ADC values had smaller post-RT tumor volumes (\(P < .0001\)). There was a positive rank correlation between the change in ADC mean from pre-RT to post-RT assessment and the pre-RT to post-RT change in volume FLAIR (Spearman rank correlation = 0.53, \(P < .0001\)). Those tumors with no change in the number of peaks on FLAIR post-RT, or a change in the number of peaks from unimodal to bimodal peaks, had the suggestion of worse OS (\(P = .096\)) compared with those tumors where the number of peaks decreased from 2 to 1 (Fig. 5). Those patients with tumors that enhanced only after radiation had a shorter PFS than baseline patients with and without enhancing tumors (\(P < .0001\)) (Fig. 6). In enhancing tumors after RT, peaks that changed from bimodal to unimodal had a worse PFS, with \(P = .006\), but this was not significant for OS.

**Discussion**

Diffuse intrinsic pontine gliomas constitute 80% of all cases of brainstem glioma and have a poor prognosis. Imaging plays a crucial role in disease assessment considering that many of these tumors have not been previously biopsied. Advanced imaging techniques such as diffusion imaging, which measures the diffusion of water in tissue, provide physiological assessment of tissue type, tumor cellularity, and tumor response to treatment.

This is the first study to use ADC histogram metrics in DIPG to stratify response and survival in a large cohort. ADC histogram analyses afford a quantitative volumetric assessment of the tumor, reflecting heterogeneity. In our study, we found that there were 2 types of histogram distributions that can be seen with DIPG, a unimodal peak and a bimodal peak. There was worse survival for the pre-RT FLAIR unimodal tumor peaks than the bimodal peak, which may be secondary to increased cellularity in the single peak tumors reflected by increased skewness with more values distributed to the left of the mean; bimodal peaks likely reflect more tumor heterogeneity, with areas of cell density heterogeneity and extracellular edema. This has not been previously described in DIPG, although intratumoral differences in DIPG patients on treatment were described in the report by Steffen-Smith et al. However, in ADC histograms in adults with recurrent high-grade glioma, Nowosielski et al. reported that increasing skewness with anti-angiogenic therapy was associated with more compact hypercellular tumor.

Previous studies have demonstrated the association of diffusion metrics with survival in DIPG. Chen et al reported worse outcome in DIPGs with lower ADC values at baseline. In our study, tumors with lower pre-RT ADC values had significantly shorter PFS and significantly higher skewness and kurtosis compared with those with higher ADC values. The internal milieu of DIPG is likely heterogeneous with focal areas of anaplasia or increased cellularity. Lobel et al. reported T2 hypointense foci within DIPG likely reflecting areas of focal anaplasia associated with low ADC values and elevated cerebral blood volume. Zukotynski et al. reported that increased fluorodeoxyglucose PET uptake was associated with restricted diffusion in DIPG corresponding to increased tumor cellularity. Lobel et al. used diffusion weighted imaging to stratify subsets of DIPG with distinct clinical behavior. They found that a median ADC could be used to partition tumors into low or high diffusion groups with significant and differing median survivals of 3 months and 13 months, respectively.
Previous work by Poussaint et al.\(^4\) showed that enhancement at baseline and over time within DIPG was associated with shorter OS and PFS, with enhancement corresponding to restricted diffusion and increased cellularity. Hipp et al.\(^{23}\) with multiparametric MRI showed that increased enhancement was associated with increased perfusion and increased...
choline/N-acetylaspartate ratio, which was associated with shorter survival. Conway et al.\textsuperscript{24} reported that enhancement within DIPG was associated with elevated regional cerebral blood volume on perfusion imaging and was likely an MR marker of angiogenesis. In a study of a survivor predictor model of DIPG, Jansen et al.\textsuperscript{25} found that ring enhancement was an unfavorable predictor, which we confirmed in this study. Here we report that tumors with enhancement had lower ADC FLAIR mean values and higher skewness and kurtosis, reflecting increased cellularity within the tumor. Within the enhancement, positive skewness and the presence of a bimodal distribution peak was associated with shorter survival, with significantly lower mean ADC of the lower peak compared with mean ADC in unimodal distributions—this suggests markedly increased cellularity, likely reflecting higher tumor grade, with imaging characteristics suggestive of grade IV tumors. Similar results have been reported in adult glioblastoma multiforme in the work of Pope et al.\textsuperscript{26} where lower mean ADC values within the tumors were associated with significantly decreased survival. These findings need to be validated and confirmed within larger pediatric DIPG cohorts.

Radiation therapy is well known to provide short-term radiological response and improvement in symptoms in DIPG.\textsuperscript{2,27} After radiation therapy, there are decreases in extracellular tumor volume and tumor size.\textsuperscript{3,4,28,29} In this study, radiation led to significantly lower ADC mean, median, and mode tumor values, hypothetically secondary to decreased extracellular volume, cellular swelling, and early apoptosis.\textsuperscript{4} We also found increased skewness and kurtosis in the ADC histogram curves post-RT. Those tumors with higher pre-RT FLAIR mean ADC values showed significantly reduced post-RT tumor volumes reflecting less tumor cellularity, leading to better response compared with those with lower ADC values (increased cellularity) who had larger post-RT tumor volumes and thus worse response after RT.

Regarding the change in the number of histogram peaks after RT within the tumor, if there was no change or if the peaks changed from unimodal to bimodal after RT, there was worse survival. In the case of no change in the number of peaks, this may reflect decreased responsiveness to RT and increased cellularity within the tumor. Other prognostic values after RT included the development of enhancement in tumors.

![Fig. 5.](image)

(A) Overall survival by change in FLAIR histogram peaks after radiation therapy. Patients who had no change in number of peaks (denoted with “0”) or with number of peaks increased from 1 to 2 (denoted “1”) had relatively worse OS compared with those whose number of peaks decreased from 2 to 1 (“2”). (B) DIPG with change in ADC histogram peaks from bimodal to unimodal after RT with PFS of 455 days and OS of 997 days. (C) DIPG without change in number of ADC histogram peaks after RT with PFS of 60 days and OS of 137 days. (D) DIPG with change in ADC histogram peaks from unimodal to bimodal with PFS of 186 days and OS of 245 days.

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that did not enhance previously, which may reflect an alteration in the tumor microenvironment leading to increased cellularity. However, this needs to be confirmed in other clinical trials.

One limitation to our study is the potential influence of the different concomitant investigational drugs with different mechanisms of action on post-RT images. In our study, none of the agents came close to meeting the modest threshold for clinical activity, and there was no statistical difference between survival in these patients between the treatment protocols.

In our previous work, we reported the correlations between mean tumor ADC and survival based on mean ADC measured from a 2D ROI drawn manually by a user. This study uses a more robust user-independent technique of 3D ROIs comprising the whole tumor using a semi-automated thresholding technique and is therefore less subjective and more reproducible. While most of our previously reported results have been confirmed in this study regarding a drop in ADC values after RT and associations of tumor enhancement with shorter survival, we found that our current rigorous technique proved an association between baseline FLAIR ADC and survival, which we had been unable to establish previously. This work provides additional valuable prognostic indicators based on the number of histogram peaks at baseline and post-RT as well as the various advanced metrics of the ADC histograms including mean, median, mode, skewness, and kurtosis of ADC histogram peaks.

This study did not have tumor tissue analysis at either biopsy or autopsy, and it is possible that non-DIPG tumors may have been included in this analysis. In the future, we hope that these types of diffusion analyses can be done together with genomic analyses of the tumors at diagnosis with evaluation of activin A receptor type 1 and K27M-H3.1 mutations as have been described in DIPG. In our cohort, we found that in children <7 years of age, there was slightly higher baseline mean ADC on FLAIR and baseline mean ADC tumor enhancement, reflecting less cellularity in these tumors and possibly lower tumor grade. In the study by Buczkowicz et al., there was a significant association of age at diagnosis with tumor grade, where age at diagnosis for the glial tumors increased with tumor grade. These findings require further evaluation in future DIPG treatment protocols. This work provides a valuable template we plan to use in future prospective treatment protocols to monitor response, to understand response in immunotherapy protocols where there can be pseudoprogression, and to correlate with genomic analyses.

Conclusion

Our study is the first to demonstrate the association of ADC histogram metrics with survival in DIPG. Our data support the following: (i) ADC histogram based on FLAIR demonstrates 2 types of ADC distributions in DIPG, with the majority being unimodal, showing increased skewness with greater distribution within lower ADC ranges and shorter survival; (ii) tumors with higher ADC mean values have longer survival than those with lower ADC mean values; (iii) tumor enhancement at baseline and occurring after RT is associated with shorter survival and lower ADC mean tumor values—when the tumor enhancement occurs, bimodal histogram peaks are associated with significantly shorter survival, and the lower peaks had significantly lower ADC mean values; and (iv) baseline mean and median ADC values on FLAIR show significant negative correlation with post-RT FLAIR tumor volume; higher diffusion values correlated with smaller post-RT tumor volumes, which complements previous work showing that patients with higher tumor ADC mean values have longer survival. These observations represent valid imaging surrogates for outcome, which can be confirmed in future DIPG prospective trials. Subsequent incorporation of advanced diffusion analyses within DIPG trials is important, as we continue to learn more about the biology of these tumors, and biological/histological/imaging correlates are needed.

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