Parametric Response Mapping of Apparent Diffusion Coefficient (ADC) as an Imaging Biomarker to Distinguish Pseudoprogression from True Tumor Progression In Peptide-Based Vaccine Therapy for Pediatric Diffuse Intrinsic Pontine Glioma

Rafael Ceschin1,6,7, Brenda F. Kurland8,9, Shira R. Abberbock8, Benjamin M. Ellingson10, Hideho Okada3,4,5,8, Regina I. Jakacki2,7,8, Ian F. Pollack4,7,8, and Ashok Panigrahy1,6,7,8

1Department of Radiology, University of Pittsburgh, Pittsburgh, PA, USA
2Department of Pediatrics, University of Pittsburgh, Pittsburgh, PA, USA
3Department of Surgery, University of Pittsburgh, Pittsburgh, PA, USA
4Department of Neurosurgery, University of Pittsburgh, Pittsburgh, PA, USA
5Department of Immunology, University of Pittsburgh, Pittsburgh, PA, USA
6Department of Biomedical Informatics, University of Pittsburgh, Pittsburgh, PA, USA
7University of Pittsburgh School of Medicine, Children's Hospital of Pittsburgh, University of Pittsburgh, Pittsburgh, PA, USA
8University of Pittsburgh Cancer Institute, University of Pittsburgh, Pittsburgh, PA, USA
9Department of Biostatistics, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA
10Department of Radiological Sciences, University of California, Los Angeles, CA, USA

Abstract

Background and Purpose—Immune response to cancer therapy may result in pseudoprogression, which can only be identified retrospectively and which may disrupt an effective therapy. This study assesses whether serial parametric response mapping (PRM, a voxel-by-voxel method of image analysis also known as functional diffusion mapping) analysis of ADC measurements following peptide-based vaccination may help prospectively distinguish progression from pseudoprogression in pediatric patients with diffuse intrinsic pontine gliomas.

Materials and Methods—From 2009–2012, 21 children age 4–18 with diffuse intrinsic pontine gliomas were enrolled in a serial peptide-based vaccination protocol following radiotherapy.
was acquired before immunotherapy and at six week intervals during vaccine treatment. Pseudoprogression was identified retrospectively based on clinical and radiographic findings, excluding DWI. Parametric response mapping was used to analyze 96 scans, comparing ADC measures at multiple time points (from first vaccine to up to 12 weeks after the vaccine was halted) to pre-vaccine baseline values. Log-transformed fractional increased ADC (fiADC), fractional decreased ADC (fdADC), and parametric response mapping ratio (fiADC/fdADC) were compared between patients with and without pseudoprogression, using generalized estimating equations with inverse weighting by cluster size.

**Results**—Median survival was 13.1 months from diagnosis (range 6.4–24.9 months). Four of 21 children (19%) were assessed as experiencing pseudoprogression. Patients with pseudoprogression had higher fitted average log-transformed parametric response mapping ratios (p=0.01) and fiADCs (p=0.0004), compared to patients without pseudoprogression.

**Conclusion**—Serial parametric response mapping of ADC, performed at multiple time points of therapy, may distinguish pseudoprogression from true progression in patients with diffuse intrinsic pontine gliomas treated with peptide-based vaccination.

**Keywords**

brainstem glioma; diffusion imaging; immunotherapy; pediatric brain tumor; vaccine therapy

**INTRODUCTION**

Diffuse intrinsic pontine gliomas (DIPG) are highly malignant brainstem tumors affecting primarily children. One-year progression-free survival is less than 25% with a median overall survival of 9–10 months. Despite multiple clinical trials, irradiation is the only therapy that is of proven clinical benefit. Cancer peptide vaccines work by administering epitopes from antigens which are overexpressed in tumor cells to trigger the patient’s immune response. The results of a pilot clinical trial targeting three glioma-associated antigens (GAA), IL13Rα2, EphA2, and survivin, in children with newly diagnosed malignant brainstem gliomas have been recently published. Pseudoprogression was observed in parallel to immunological responses. Pseudoprogression, defined radiologically as a transient increase in the size of contrast-enhancing tumor on structural MRI, is thought to result from local tissue inflammation due to vasogenic edema and abnormal vessel permeability. Thus, assessment of pseudoprogression in peptide-based immunotherapy of pediatric brainstem gliomas presents a challenge for clinical management. Pseudoprogression can currently only be determined retrospectively after a period of time during which treatment is potentially halted, thus creating the evident problem of stopping treatment at a time where it is maybe at its highest efficacy.

Since structural MRI cannot reliably differentiate inflammation from recurrent tumor, advanced neuroimaging techniques such as DWI have been evaluated to assess brain tumor therapeutic response, including discriminating between pseudoprogression and true progression. We evaluated DWI as a potential tool to discriminate between tumor response and true tumor progression, using information available close to the time of suspected progression. The apparent diffusion coefficient (ADC) is a quantitative measure reflecting
the observed net movement of water calculated from DWI and has been shown to correlate with tissue cellularity in tumors5–12 likely due to restriction of extracellular water motion in tightly packed tumor cells. Modulation of diffusion measurements has been previously observed in both preclinical and human studies of immunotherapy13–15 While mean tissue ADC may be a useful measure for distinguishing tumor from other masses, it may be problematic for quantifying change over time. Opposing heterogeneous responses (i.e. different areas of tumor with increasing and decreasing diffusion) may neutralize each other with no change in overall mean ADC16. To overcome this limitation, we applied parametric response mapping (PRM)6,17–19, formerly known as functional diffusion mapping, to evaluate response to immunotherapy over time by quantifying voxel-wise changes in ADC20. Our study differs from prior studies by evaluating immunotherapy, by its exclusive focus on pediatric brain tumors, and by using information from >2 time points in PRM. We hypothesized that serial PRMs calculated at multiple time points during immunotherapy could differentiate pseudoprogression from true progression in pediatric brainstem gliomas (DIPG).

MATERIALS AND METHODS

Demographics, Clinical Characteristics and Study Design

The cohort consisted of the 21 children (9 males) with DIPG enrolled on our institutional glioma vaccine trial (ClinicalTrials.gov #NCT01130077)3. Prior to enrollment, patients had completed 5000 to 6000 cGy involved field fractionated radiotherapy, with or without concurrent chemotherapy; post-irradiation chemotherapy precluded enrollment. Adequate organ function, absolute lymphocyte count ≥500, performance status ≥60, and HLA-A2+ status were required for vaccine treatment initiation. Patients with increased edema or mass effect after irradiation did not start vaccination until this had resolved (up to 12 weeks after completion of irradiation).

Signed IRB-approved informed consent was required for HLA screening and initiation of therapy. Patients received subcutaneous injections of GAA-derived HLA-A*0201-restricted peptides and a tetanus toxoid peptide (TetA830) emulsified in Montanide ISA-51 (Seppic) and concurrent intramuscular injections of 30 µg/kg of the toll-like receptor (TLR) ligand, poly-ICLC (Hiltonol, Oncovir, Inc), every 3 weeks × 8 followed by a Maintenance phase, every 6 weeks.3 Participants were evaluated with neurologic exams and laboratory testing as previously described.3 MR imaging (including DWI) was performed prior to initiating vaccine therapy (Week 0) and at Weeks 6, 15, 21, and q12 weeks after initiating vaccine therapy. More frequent scans were obtained if clinically warranted. Between May 2009 and October 2012, 21 newly diagnosed patients were enrolled: 15 with DIPG treated with irradiation alone, 6 with DIPG treated with irradiation and concurrent chemotherapy (Supplemental Table 1). Patients received 2–11 doses of vaccine (median 7). Mean age at diagnosis was 9 years (SD=4.0) and median survival was 56.3 weeks (range 6.4 – 24.9 months).
Pseudoprogression

Because the development of pseudoprogression is an area of concern in immunotherapy studies, the trial incorporated detailed guidelines for managing possible pseudoprogression. If tumor enlargement and/or increased enhancement was noted on structural MRI, and the patient was neurologically worse, sufficient to warrant initiation of corticosteroid administration or increase in corticosteroid dose, subsequent doses of vaccine and poly-ICLC were held. Imaging and clinical assessments were performed at 4 week intervals thereafter, until it was determined whether the clinical and imaging changes reflected pseudoprogression or true progression. If the subject improved clinically on declining corticosteroid doses that could be weaned to ≤0.1 mg/kg/day dexamethasone for ≥1 week, and the MRI changes improved or resolved, the patient was presumed to have had pseudoprogression and could restart vaccine treatment with 67% of the poly-ICLC dose (i.e. 20 µg/kg). Conversely, if the repeat MRI scan was unchanged or worse, and the patient’s clinical status had not improved despite increased corticosteroid doses, the patient was taken off study due to presumed true tumor progression.

Magnetic Resonance Imaging and Diffusion-Weighted Imaging

Imaging was conducted on 1.5T MR systems with the majority of the studies performed on a 1.5T GE HDx system. Diffusion-weighted images were acquired at slice thicknesses of 4–5 mm (1 mm gap), and TR ranging from 6000 to 8000 ms, b= 0 and 1000 s/mm² per clinical protocol. In order to register every time point onto a common space for subsequent analysis, we chose the earliest time point available with volumetric imaging (T1- or T2-weighted which in most cases was a 3D T2-Cube) after completion of radiation therapy and prior to vaccine therapy as a structural reference. A minimum of three diffusion imaging time points (pre- or post- initial vaccine) were required for analysis. GRE or SWI imaging was also available for assessment of blood products.

Image Registration

A semi-automated processing pipeline was developed using Nipype. Tumor area was manually delineated for each patient at each time point. We excluded regions with blood product that might cause EPI distortion. Tumor volume delineation was consistently done for every patient in diffusion space, using the B0 and ADC images to avoid any bias related to variations in institutional protocol. FLAIR imaging was also used to confirm the margin of the tumor. We performed a two-step registration method in order to minimize potential registration errors – first the diffusion-weighted images were brain extracted and pre-registered to a medium resolution T2-weighted image acquired at the same time point using a 6 degree of freedom rigid body registration. The medium resolution images were then registered to the chosen high resolution structural image, and the resulting registration matrix applied to the pre-registered diffusion images. Linear registration was performed with FSL’s FLIRT linear registration tool using an affine registration algorithm, followed by a fine fourier registration with AFNI. We generated an aggregate tumor ROI by adding all registered delineated tumor areas in common space and only including regions present in at least 10% of all time points.
Serial PRM Postprocessing

Parametric response maps (PRM) were generated by an operator blinded to pseudoprogression diagnosis for every time point in reference to the baseline scan by calculating the voxel-wise difference in apparent diffusion coefficient (ADC) within the aggregate tumor ROI (Figure 1 and Figure 2). We chose a significant change threshold of $+/-0.4\ mm^2/s$, as empirically determined by Ellingson et al.\textsuperscript{25} to represent the 95% confidence interval of temporal ADC variation in normal brain tissue. Patient-level summary measures were created following generation of PRMs. Fractional increased ADC (fiADC) measured by the percent of voxels above this threshold reflects a decrease in cellularity and potentially indicates an inflammatory response or necrotic tissue.\textsuperscript{19, 26} Fractional decreased ADC (fdADC) reflects the relative degree of hypercellularity, and potentially indicates true tumor progression. We also looked at the ratio of fiADC to fdADC (PRMratio), calculated as fiADC/(fdADC + 0.01)\textsuperscript{27} (to account for instances where fdADC = 0) as a potential marker for overall trend of tissue progression. Whole tumor volume and mean ADC were also extracted, from the same ROI as for PRM analysis.

Statistical Analysis

At the time of analysis, all patients in this study were deceased, and can therefore be presumed to have had true tumor progression as an overall disease outcome. We therefore categorized patients without confirmed pseudoprogression as experiencing true progression (in contrast to patients whose eventual tumor progression was preceded by pseudoprogression). We tested for average differences in fiADC, fdADC, and PRMratio values between these two groups, with log-transformation of each to limit the influence of large values. The analysis was restricted to PRM values measured from scans performed no later than 12 weeks following a subject’s final vaccination, since later scans are relevant only for retrospective assessment of pseudoprogression. Associations between each measure and pseudoprogression status were modeled using weighted generalized estimating equations (WGEE) with independence working correlation. Since patients with rapid disease progression undergo fewer scans, the cluster size (number of scans per person) is informative. Regression analysis used inverse weighting by cluster size, and adjusted inference to “typical” PRM results for each patient rather than the full set of PRM results (which would implicitly contain information about prognosis).\textsuperscript{26, 28} Statistical analyses were performed using SAS/STAT statistical software version 9.4 (SAS Institute, Cary, NC) and R version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Pseudoprogression Cases and Overall Survival Time

Four children (19%) developed acute neurologic worsening associated with increased tumor size and/or enhancement several months after beginning vaccination with subsequent clinical and radiographic improvement on corticosteroids, consistent with pseudoprogression (Supplemental Figure 1). One of these cases experienced a prolonged objective response, maintained until 19.5 months post-diagnosis as previously reported.\textsuperscript{3} Median survival from the time of diagnosis among DIPG patients with pseudoprogression was 19.1 months compared to 12.5 months in those without pseudoprogression.
Differences in Serial PRM Metrics and standard measures (mean ADC, tumor volume) between Pseudoprogression vs Non-Pseudoprogression Cases

A total of 151 MR imaging time points for 21 patients had ADC maps available, having excluded three scans due to image registration failure, and an additional 2 due to artifacts in the diffusion imaging. Although the patients were on a treatment trial with scheduled follow-up, imaging time points varied due to scheduling windows and use of DWI. Serial PRM metrics for each patient are shown in Figure 3, with colored lines connecting PRM results for each subject's non-baseline time points. The 3 rows display 3 PRM metrics (fiADC, fdADC, and the fiADC/fdADC or PRM ratio) as the Y axis for each plot. The X axis for each plot is the number of weeks after the first vaccine treatment (in contrast to time from diagnosis, which is used for survival analysis). The three columns are panels created for ease of presentation, with patients sorted by increasing survival time. Each patient appears in all 3 rows, but in only one column. There is one pseudoprogression case in the second column, and three in the third column (dashed lines), reflecting the longer survival for pseudoprogression cases. Figure 3 suggests that patients with pseudoprogression (dashed lines) had a higher fiADC and higher PRM ratio compared to patients whose vaccine therapy was halted due to true progression (solid lines), for most post-baseline scans. These trends are examined further in Figure 4, which shows the same PRM metrics for the same patients (with the same color coding across both Figure 3 and Figure 4) for pseudoprogression and true progression cases but without information about scan timing. To compare PRM metrics assessed earlier than the current (retrospective) standards for pseudoprogression, Figure 4 shows only the serial diffusion data used for statistical modeling, which is limited to time points from baseline until 12 weeks after the vaccine was halted (96 scans, 2–8 scans per patient, median of 4 scans per patient). Assessed using WGEE models accounting for informative clustering, patients with pseudoprogression on average had higher log-transformed PRM ratios (p=0.01) and fiADCs (p=0.0004), and no statistically significant difference for lower log-transformed fdADCs (p=0.12), than patients without pseudoprogression. The fitted average fiADC/fdADC or PRM ratio for a scan compared to baseline was 0.4 for patients without pseudoprogression (95% CI 0.3, 0.6) and 3.7 for patients with pseudoprogression (95% CI 0.8, 18.0).

There was no significant difference in mean ADC or tumor volume between cases of pseudoprogression and true progression. In the 4 pseudoprogression cases, the greatest percentage change in mean ADC from the baseline measurement ranged from 24% decrease to 86% increase (median 33% increase), compared to −25% to 36% (median 5%) for the 17 remaining patients. Raw data for change in both mean ADC and tumor volume are found in Supplemental Table 1. Using the same timeframe (post-vaccine scans until 12 weeks after the last vaccine dose) and same analysis approach (WGEE), we explored the association between mean ADC and tumor volume with pseudoprogression, controlling for baseline values. Neither mean ADC (p=0.55) nor tumor volume (p=0.44) was associated with pseudoprogression.

As a post-hoc sensitivity analysis, we examined PRM comparing baseline measures only to the time points most proximal to decisions about continuing vaccine therapy when progression (or pseudoprogression) was suspected. We defined these time points as up to 6
weeks before the last vaccine, and up to 3 weeks after the last vaccine (allowing for no missed vaccines if pseudoprogression was identified). Twenty-seven scans with DWI met these criteria, 1–2 scans in 18 patients. Again the magnitude and direction of effects for fiADC and fdADC were maintained (and statistical significance strengthened) comparing pseudoprogression versus true progression; however, 2 of the 4 pseudoprogression cases did not have scans within this timeframe. Other exploratory analyses examined robustness of our results to selection of tumor ROI and to excluding patients treated with bevacizumab (Supplement and Supplemental Figure 2).

**DISCUSSION**

This study, to our knowledge, is the first demonstration of the use of serial diffusion weighted imaging and parametric response mapping (PRM) in distinguishing between pseudoprogression and true progression in immunotherapy trials for pediatric brain tumors. Childhood brainstem tumors treated with peptide-based vaccination had a notable rate of pseudoprogression, all with transient increases in tumor size or enhancement, with new or worsening neurological deficits, and subsequent clinical improvement and MRI stabilization or improvement after administration of corticosteroid and suspension of vaccine therapy. Accurately identifying and managing such patients is essential to avoid both premature termination of therapy and unacceptable neurological decline, a particular concern in children with DIPG who may develop significant neurologic deterioration with changes in mass effect. Our results suggest using PRM to characterize temporal diffusion profiles is better able to distinguish pseudoprogression from true progression than mean ADC measurement or tumor volume. This is likely related to treatment-related heterogeneity, in which there may be a mix of viable tumor (low ADC), necrosis (high ADC) and vasogenic edema (high ADC) within the tumor ROI. When measuring change in the mean ADC value of the tumor ROI, the potentially lower ADC values of active tumor foci likely blended in with the higher ADC values found in areas of edema and necrosis.

While these results are promising clinically, further study is required for greater understanding of the mechanisms underlying advanced MR manifestations of immunotherapy-induced inflammatory response in the brain. One hypothesis is that immunotherapy effects on the tumor microenvironment lead to transient vasodilation, increased vessel permeability, and local inflammation, with a resultant increase in contrast enhancement and edema that mimics early tumor progression. An increase in ADC may correspond with tissue hypocellularity due to either treatment-related inflammation and/or tumor reduction. Animal models have demonstrated fractional increase in ADC by PRM as early as 24 hours following introduction of 1,3-bis(2-chloroethyl)-1-nitrosourea, and a detectable increase in ADC within 2 days following IL-13Ra2 T-cell injection. Progressive separation observed in long-term diffusion profiles between some patients with confirmed pseudoprogression versus true tumor progression in our study supports the use of parametric response maps as supplementary imaging biomarkers for monitoring tumor response in the setting of peptide-based immunotherapy. In particular, fiADC and the PRM ratio appear to be the strongest candidates as potential early biomarkers for determining pseudoprogression.
PRMs have been shown to predict treatment response and survival in the setting of adult GBM. However, these studies only used two imaging time points, in contrast to our study, in which multiple PRMs were analyzed per patient. Some limitations of the use of PRM in adult tumors are related to poor image registration of lesions resulting from changes in mass effect and tumor contour, which was less of an issue in our pediatric brainstem gliomas. Given that PRM measurements can be confounded by normal tissue, we used weighted PRM techniques to control for changes in tumor size from each time point, without substantive changes in study results. Study limitations include a small number of pseudoprogression cases, and lack of biopsy confirmation for pseudoprogression. (Biopsy is a high-risk procedure for DIPG lesions.) The peak period of pseudoprogression following RT for DIPG is generally within the first 3 months. Anything after that time is presumed to be true tumor progression, unless the patient has received vaccine-related immunotherapy, as in our study. The peak period of pseudoprogression related to radiotherapy had likely passed before initiation of vaccine therapy, and the observed cases of pseudoprogression occurred after several doses of vaccine. Furthermore, patients with increased edema or mass effect after irradiation did not start vaccination until this had resolved (up to 12 weeks after completion of irradiation). Regardless, the objective of our study was not to elucidate mechanisms for pseudoprogression using PRM, but to explore its utility in characterization of pseudoprogression in pediatric DIPG.

CONCLUSION

In conclusion, our study is the first to suggest that serial PRM may be useful to identify pseudoprogression in children with DIPG receiving peptide-based immunotherapy. The valuable properties of diffusion imaging with PRM analysis as an in vivo imaging biomarker include: its translatability to the clinical arena; its quantitative nature, and its ease of use and cost effectiveness. The accurate identification of pseudoprogression versus true tumor progression is crucial in determining the optimal management of this novel treatment. We have identified three strong candidates (fiADC, fdADC, and PRMratio) for development of a predictive model of pseudoprogression, in conjunction with other types of biomarkers that may assist in the treatment of children undergoing immunotherapy. We believe that combining diffusion imaging metrics with clinical information and standard MR imaging will allow timely discrimination of pseudoprogression and true progression, enabling optimal use of immunotherapy. Our preliminary observations, which analyzed 96 scans in 21 patients, should be validated in a planned multi-institutional clinical trial before being used to guide clinical management.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

UPCI Clinical Research Services for regulatory management, Andres Salazar, Oncovir, Inc., for provision of poly-ICLC, physicians who referred their patients, and the patients and families who participated in this trial. We also thank Angela K. Connelly, Sharon Dibridge, Fern Wasco, and Melanie Gieraltowski for research coordination.
**Funding:** This clinical trial was supported by National Institutes of Health grants R21CA149872, P01NS40923, and the UPCI Immunological Monitoring Core and Biostatistics Shared Resource Facility, supported in part by NIH award P30CA47904; grants from the Pediatric Low-Grade Glioma Initiative via the National Brain Tumor Society and the Ellie Kavaliers Fund of the Children’s Hospital of Pittsburgh Foundation; and the Pediatric Clinical and Translational Research Center, supported by the NIH through Grant Numbers UL1 RR024153 and UL1TR000005. The imaging postprocessing was supported by the Ian’s (Ian Yagoda) Friends Foundation Grant, Society of Pediatric Radiology Pilot Award and a NLM Grant ST15LM007059-27.

Hideho Okada is an inventor in the U.S. Patent Application No. 60,611,797 (Utility Patent Application) “Identification of An IL-13 Receptor Alpha2 Peptide Analogue Capable of Enhancing Stimulation of Glioma-Specific CTL Response”. An exclusive licensing agreement has been completed on this application between University of Pittsburgh and Stemline, Inc.

**Abbreviation**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIPG</td>
<td>Diffuse intrinsic pontine gliomas</td>
</tr>
<tr>
<td>PRM</td>
<td>Parametric response mapping</td>
</tr>
<tr>
<td>fADC</td>
<td>Fractional increased ADC</td>
</tr>
<tr>
<td>fdADC</td>
<td>Fractional decreased ADC</td>
</tr>
</tbody>
</table>

**References**


26. Pavlou M. Analysis of clustered data when the cluster size is informative. University College London. 2012


Figure 1.
A) Tumor ROI for patient with confirmed pseudoprogression (above) and patient with true tumor progression without pseudoprogression (below). Color scale indicates the proportion of scans in which each voxel was classified as tumor tissue (voxel weights). B) Sample serial PRM maps at time Weeks 7, 24, and 30 as compared to baseline scan prior to vaccine therapy. Plots show co-registered voxels at baseline compared to indicated time point. Green voxels indicate no significant change above or below the predefined threshold of +/- 0.4 mm²/ms. Red voxels show a significant increase in ADC and blue voxels a decrease in ADC over time. Point opacity is proportional to the voxel weight (i.e. how much does the voxel contributes to the PRM metric calculation in the weighted model).
Figure 2.
Sample PRM snapshots for patient with confirmed pseudoprogression (above) and patient with true tumor progression without pseudoprogression (below) give a spatiotemporal reference to tumor characterization. ADC maps are co-registered onto a common space and voxel-wise subtraction is calculated between each subsequent time point and the baseline scan. Green voxels indicate no significant change above or below the predefined threshold of $\pm 0.4 \text{mm}^2/\text{s}$. Red voxels show a significant increase in ADC and blue voxels a decrease in ADC compared to baseline. There is evidence of spatial heterogeneity of diffusion within the brainstem tumor of both patients.
Figure 3. Serial PRM metric and disease trajectories for 21 pediatric brainstem glioma patients. Although the patients were on a treatment trial with scheduled follow-up, imaging time points varied due to scheduling windows and use of DWI. Serial PRM metrics for each patient are shown, with colored lines connecting PRM results for each subject's non-baseline time points. Columns divide patients into groups by increasing overall survival from the start of vaccine therapy (14–27 weeks, 28–56 weeks, 57–93 weeks). Rows display fractional increased ADC (fiADC), fractional decreased ADC (fdADC), and fiADC/fdADC (PRM_Ratio) compared to the baseline (pre-vaccine) scan. Each PRM measurement is indicated with a circle, connected by solid lines for patients without pseudoprogression and dashed lines for patients with eventual diagnosis of pseudoprogression. Vertical lines (|) indicate the date of last vaccine for each patient. For two patients with psedoprogression, vaccine treatment was restarted (date shown as ×), 8 and 13 weeks after the initial halt. One of these patients underwent a second treatment stoppage (date shown as ○). Examining the time from the last vaccine dose (vertical line |, or ○ for the patient who restarted therapy) to death (♦), patients survived 4–56 weeks after halting vaccine therapy.
Figure 4.
Boxplots of log fractional increased ADC (log(\(\text{fiADC}\)), log fractional decreased ADC (log(\(\text{fdADC}\)) and log ratio of \(\text{fiADC}/\text{fdADC}\) (log (PRM_Ratio)). Values are obtained from PRMs from 75 post-baseline scans no more than 12 weeks after last vaccine date, each compared to the patient’s baseline scan. Cohorts are confirmed pseudoprogression (n=4 patients) and true tumor progression (no pseudoprogression, n=17 patients). Datapoints of the same color are the same patient’s PRM metrics for multiple scans, each compared to baseline. Figure 3 uses the the same coloring scheme (but includes time points >12 weeks after last vaccine date).