Longitudinal DSC-MRI for Distinguishing Tumor Recurrence From Pseudoprogression in Patients With a High-grade Glioma

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Objective: For patients with high-grade glioma on clinical trials it is important to accurately assess time of disease progression. However, differentiation between pseudoprogression (PsP) and progressive disease (PD) is unreliable with standard magnetic resonance imaging (MRI) techniques. Dynamic susceptibility contrast perfusion MRI (DSC-MRI) can measure relative cerebral blood volume (rCBV) and may help distinguish PsP from PD.

Methods: A subset of patients with high-grade glioma on a phase II clinical trial with temozolomide, paclitaxel poliglumex, and concurrent radiation were assessed. Nine patients (3 grade III, 6 grade IV) with a total of 19 enhancing lesions demonstrating progressive enhancement (≥ 25% increase from nadir) on postchemoradiation conventional contrast-enhanced MRI, had serial DSC-MRI. Mean leakage-corrected rCBV within enhancing lesions was computed for all postchemoradiation time points.

Results: Of the 19 progressively enhancing lesions, 10 were classified as PsP and 9 as PD by biopsy/surgery or serial enhancement patterns during interval follow-up MRI. Mean rCBV at initial progressive enhancement did not differ significantly between PsP and PD (2.35 vs. 2.17; P = 0.67). However, change in rCBV at first subsequent follow-up (~0.84 vs. 0.84; P = 0.001) and the overall linear trend in rCBV after initial progressive enhancement (negative vs. positive slope; P = 0.04) differed significantly between PsP and PD.

Conclusions: Longitudinal trends in rCBV may be more useful than absolute rCBV in distinguishing PsP from PD in chemoradiation-treated high-grade gliomas with DSC-MRI. Further studies of DSC-MRI in high-grade glioma as a potential technique for distinguishing PsP from PD are indicated.

Key Words: dynamic susceptibility contrast MRI, pseudoprogression, progressive disease, chemoradiation, relative cerebral blood volume

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Treatment of newly diagnosed high-grade glioma typically includes maximal, safe resection, followed by temozolomide (TMZ)-based chemoradiation. Increased enhancement on posttreatment magnetic resonance imaging (MRI) can represent progressive disease (PD) or it may represent pseudoprogression (PsP) that spontaneously resolves or stabilizes without treatment modification. Discriminating PsP from PD is challenging but critical for avoiding premature removal of patients from trials in case of PsP and selecting timely alternative therapies in case of PD. Standard T2-weighted and postcontrast T1-weighted MRI have proved unreliable for distinguishing PsP from PD, and misinterpretation of PsP has limited the use of progression-free survival as an endpoint in clinical glioma trials and the eligibility of patients for salvage treatment trials.

Dynamic susceptibility contrast MRI (DSC-MRI) tracks the first-pass of an exogenous, paramagnetic, gadolinium-based contrast agent through the brain. Images through the tumor-containing brain are repeatedly acquired in rapid succession during contrast agent bolus passage, and the resulting signal-time curves are processed using physical models to yield voxel-wise measures of cerebral hemodynamics, analogous to classical tracer-kinetic techniques, including relative cerebral blood volume (rCBV). Evidence for the ability of rCBV to distinguish PsP from PD is conflicting, with some studies concluding that specific thresholds are helpful and others asserting the opposite or even dependence of rCBV utility on MGMT promoter methylation status. Heterogenous distributions of rCBV within recurrent enhancing lesions are reported, with overlapping rCBV measurements in PsP and PD, emphasizing the potential limitation of single mean rCBV values in distinguishing PsP from PD.

We hypothesized that longitudinal measures of rCBV within recurrent enhancing lesions would stabilize or decrease for PsP and escalate for PD, and better discriminate PsP from PD compared with absolute mean rCBV at the time of initial progressive enhancement. To test this hypothesis, longitudinal rCBV trends in patients with newly diagnosed high-grade glioma treated with chemoradiation were examined. We previously reported a 25-patient phase II multi-institutional study of patients with high-grade glioma treated with the combination of paclitaxel poliglumex (PPX), TMZ, and concurrent radiation. PPX is a drug conjugate that links paclitaxel to a biodegradable polymer, poly-l-glutamic acid. Preclinically, PPX demonstrated a tumor tissue radiation enhancement factor of ~4.0 as compared with 1.5 to 2.0 for paclitaxel. The regimen of PPX, TMZ, and radiation induced a high rate of PsP as assessed by posttreatment biopsy/surgical resection and interval follow-up, and PPX-treated high-grade gliomas may...
therefore provide an ideal cohort for investigating the ability of DSC-MRI to distinguish PsP from PD. Nine of these patients had sequential DSC-MRI, forming the basis of this analysis.

MATERIALS AND METHODS

Patients and Clinical Treatment

The Brown University Oncology Group previously reported a phase II study of PPX, TMZ, and concurrent radiation for patients with newly diagnosed high-grade glioma. Institutional Review Boards of participating hospitals approved this HIPAA-compliant study. Patients received PPX (40 to 50 mg/m²), TMZ (75 mg/m²/d), and concurrent radiotherapy (2 Gy/d, 5 d/ wk, 60 Gy total dose) over 6 weeks, and adjuvant TMZ (150 to 200 mg/m² × 5 every 28 d) until disease progression. No patients were treated with any alternative chemotherapy before any of the imaging time points acquired herein.

Conventional and Perfusion MRI

MRI was performed 4 weeks after completion of PPX, TMZ, and radiation and every 2 to 3 months thereafter, at 1.5 or 3 T (Esprey or Symphony and Verio, respectively; Siemens Medical Solutions, Malvern, PA). DSC-MRI consisted of gradient-echo EPI (field of view = 24 cm², matrix = 96 × 96 or 128 × 128, flip angle = 90 degrees, TE = 30 ms, TR = 1000 to 1050 ms, slice thickness = 5 mm, interslice gap = variable, 14 slices, 120 acquired time points) with bolus contrast injection at 2.5 mL/s or 5.0 mL/s (Gadavist or Magnevist, respectively; Bayer HealthCare, Whippany, NJ) after acquisition of 50 baseline images. Before dynamic imaging, ¼ to single dose (0.025 to 0.1 mmol/kg) preload of contrast was administered. After dynamic imaging, postcontrast T1-weighted (matrix = 256 × 256, slice thickness = 4 to 5 mm, NEX = 1) FLAIR (TR = 2000 ms, TE = 8.6 ms, TI = 860 ms) or spin echo (TR = 400 ms, TE = 17 ms) images were acquired at slice positions and orientations matching the DSC-MRI images (“exact match” axial postcontrast T1-weighted images).

Identification of Lesions and Determination of Lesion Destiny

For each patient, we identified all enhancing lesions ≥1 cm in minimum diameter at any posttreatment time point and ≥1 cm from other lesions. Lesion destiny was determined by time course of enhancing volume (waxing-waning for PsP; progressive enlargement for PD) or histopathology when available. PsP was defined radiologically as stabilization or improvement of enhancing lesions over time.

CBV Computation

We computed rCBV maps using commercial software (Aycan Osirix Pro v2.0.04; Aycan Medical Systems, LLC, Rochester, NY and IB Neuro v1.1; Imaging Biometrics, LLC, Elm Grove, WI). On a voxel-wise basis, we calculated baseline prebolus mean signal intensity, omitting 5 initial time points to exclude non–steady-state values; converted the truncated signal-time series to relaxation-time series, \( \Delta R_2^* (t) \); estimated CBV using trapezoidal integration of \( \Delta R_2^* (t) \) over postbolus time points (first-pass plus postbolus tail) and a postprocessing leakage correction algorithm, and normalized CBV to mean CBV in a 70 to 80 mm² region of interest (ROI) in contralateral normal-appearing white matter (rCBV) consistently located across all longitudinal studies.

Image Segmentation

For lesion segmentation, we used custom AFNI (http://afni.nimh.nih.gov/afni) scripts and manually defined the region of lesion enhancement, excluding hemorrhage and macrovessels; further constrained regions using empirical thresholds, excluding central necrosis; and edited segmentations to exclude nonlesion voxels. Segmentations were performed on anonymized images by 2 investigators at a different institution from where patients were treated to eliminate possible bias from lesion recognition and familiarity with patient outcomes. Because segmentations were made on the “exact match” T1-weighted postcontrast images naturally coregistered to the DSC-MRI data, no additional registration was performed. Final segmentations consisted of the areas of maximal overlap between the 2 independent segmentations, which did not differ by >5% in volume. All rCBV maps completely covered the lesions in question. Segmented lesion volumes were computed and tracked longitudinally over all posttreatment imaging time points. We defined the time of progressive enhancement for each lesion to be days after PPX, TMZ, and radiation completion when enhancing volume increased by ≥25% compared with nadir and lesion size ≥1 cm, without reduction in steroids within the preceding 4 weeks. Mean lesion rCBVs at post PPX, TMZ, and radiation time points were extracted from rCBV maps naturally coregistered to enhancing lesion segmentations.

Statistical Methods

We used GraphPad Prism 5.0d (GraphPad Software, La Jolla, CA) for statistical analyses. For the PsP versus PD groups, we compared time to initial progressive enhancement, mean rCBV at time of initial progressive enhancement, and both absolute and percent change in rCBV between the time at initial progressive enhancement and first subsequent follow-up. We also investigated the rCBV trend after initial progressive enhancement by comparing the linear regression slopes of rCBV versus days posttreatment beginning at initial progressive enhancement (range, 300 to 400 d) in PsP and PD groups. For all comparisons, we used a 2-tailed, unpaired \( t \) test (statistically significant threshold of \( P = 0.05 \)) and tested the ability of each imaging feature to predict PD using receiver operating characteristic analysis.

RESULTS

Study Cohort

Of the 25 patients in the phase II PPX, TMZ, and radiation study, 19 had postchemoradiation progressive enhancement by standard MRI assessment. Nine of these patients (5 men, 4 women, aged 38 to 70 y, mean age 58 y) had longitudinal DSC-MRI. Of these 9 patients, 3 had WHO grade II tumors (anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic pilocytic astrocytoma) and 6 had glioblastoma multiforme (GBM). In total, 19 lesions from these 9 patients demonstrated postchemoradiation progressive enhancement; 10 lesions were subsequently characterized as PsP (at least 1 occurred in 8 of the 9 patients) by biopsy/resection (4 lesions) or waxing-waning enhancement (6 lesions), and 9 were characterized as PD (at least 1 occurred in 6 of the 9 patients) by biopsy/resection (6 lesions) or monotonically increasing enhancement with clinical deterioration (3 lesions). Of the 9 patients, 5 had both PsP and PD lesions included in this study. Table 1 summarizes the distribution of lesions in the study cohort. Figure 1 illustrates longitudinal postcontrast T1-weighted MRI and corresponding...
TABLE 1. Distribution of PsP and PD Lesions in the Study Cohort

<table>
<thead>
<tr>
<th>Patient</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>Total</th>
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<td>0</td>
<td>0</td>
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<td>1</td>
<td>9</td>
</tr>
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PD indicates distinct lesions characterized as progressive disease; PsP, distinct lesions characterized as pseudoprogression.

rCBV maps for an anaplastic astrocytoma with examples of PsP and PD.

**rCBV at Initial Progressive Enhancement**

At initial progressive enhancement, mean normalized rCBV did not significantly differ \((P = 0.67; \text{Fig. 2A})\) between PsP \((2.4 \pm 0.9 \,[1.4 \text{ to } 4.0])\) and PD \((2.2 \pm 1.0 \,[0.2 \text{ to } 3.9])\). Mean normalized rCBV \(> 2.4\) was only 67% sensitive and 40% specific for PD, with area under the curve \((AUC)\) not significantly different from chance \((P = 0.93)\).

**Change in Normalized rCBV at First Follow-up After Initial Progressive Enhancement**

Absolute change in normalized rCBV from time at initial progressive enhancement to first subsequent follow-up differed significantly \((P = 0.001; \text{Fig. 2B})\) between PsP \((0.8 \pm 0.9 \,[-2.4 \text{ to } 3.3])\) and PD \((0.8 \pm 0.9 \,[0.3 \text{ to } 3.2])\). Percentage change in normalized rCBV was similarly different \((P = 0.02)\) between PsP \((-29.2 \pm 27.0 \,[ -62 \text{ to } 15.1])\) and PD \((70.2 \pm 117.9 \,[11.5 \text{ to } 378.3])\). The mean time interval from initial progressive enhancement to first follow-up was 62 days \((\text{range, 27 to 143})\) for PsP and 56 days \((\text{range, 23 to 83})\) for PD. A positive change in mean normalized rCBV at first follow-up after initial progressive enhancement was approximately 100% sensitive and 85% specific for identifying PD \((AUC = 0.97, P = 0.0006)\). Figures 3A and C demonstrate examples of decreased rCBV at first follow-up after initial progressive enhancement in lesions with increasing enhancement on conventional MRI that were subsequently found to be PsP.

**Trend in Normalized rCBV Over Multiple Time Points After Initial Progressive Enhancement**

The linear regression slopes of normalized rCBV versus days after chemoradiation beginning at initial progressive enhancement differed significantly \((P = 0.04; \text{Fig. 2C})\) between PsP \((-0.003 \pm 0.002 \,[-0.0086 \text{ to } -0.0009])\) and PD \((0.013 \pm 0.023 \,[-0.0025 \text{ to } 0.073])\). A positive regression slope was approximately 83% sensitive and 100% specific for identifying PD \((AUC = 0.94, P = 0.0011)\). Figure 3 provides several sample regression curves depicting normalized rCBV versus days after chemoradiation completion, including 2 of the lesions highlighted in Figure 1, illustrating "downward" rCBV trends over time for PsP, and "upward" for PD. Note that in the 2 examples of PsP (Figs. 3A, C), enhancing lesion volume continued to increase for several time points after initial progressive enhancement before decreasing, whereas rCBV decreased from the outset, showing how changes in rCBV do not simply "mirror" enhancing volume but rather provide an early means for distinguishing PsP in these cases from PD. In Figure 3B, rCBV rises concurrently with enhancing lesion volume, consistent with PD. Although the rCBV regression curve in Figure 3D has a slight downward trend, rCBV increases at the first follow-up after initial progressive enhancement, consistent with PD.

Figure 2D plots change in normalized rCBV from time at initial progressive enhancement to first subsequent follow-up versus change in enhancing volume over the same time interval for lesions evolving like PsP (closed squares) and PD (open squares). Virtually all lesions with increasing rCBV were found to represent true progression with correspondingly increased enhancing volume (right upper quadrant). Nearly all lesions with decreasing rCBV were found to represent PsP, for both increasing (right lower quadrant) and decreasing (left lower quadrant) enhancing volume. Increased enhancing volume at first follow-up can be seen in PD (increased rCBV) or PsP (decreased rCBV), whereas decreased enhancing volume was associated with PsP (decreased or near-decreased rCBV). There is some overlap about the zero line, but initial change in rCBV appears to be helpful for predicting PsP versus PD in the setting of an initial increase in enhancing volume.

**DISCUSSION**

Differentialiation of PsP from PD is challenging but critically important in clinical neuro-oncology.\(^5\) PsP is transient increased contrast enhancement subsequently stabilizing or diminishing without modified treatment,\(^2,3\) and is commonly associated with radiotherapy and TMZ.\(^6,7\) PsP likely reflects increased vascular permeability secondary to proinflammatory mediators, direct endothelial damage, cellular hypoxia,\(^4,24\) and exaggerated radiation-induced reactive changes.\(^13\) Peak incidence occurs 1 to 6 months after chemoradiation\(^2,3,23\) complicating response criteria for radiologic progression during this time.\(^6,25\)

Conventional MRI has largely proved ineffective for prospectively differentiating PsP from PD,\(^2,7,8\) and DSC-MRI is a potential alternative. Our phase II study of PPX, TMZ, and radiation had a high rate of PsP\(^18\) and therefore provided an opportunity to evaluate the potential of DSC-MRI to differentiate PsP from PD. Our results suggest that temporal trends in normalized rCBV may distinguish PD from PsP in chemoradiation-treated high-grade glioma, whereas absolute normalized rCBV at initial progressive enhancement may have limited value. Focusing the analysis on the time of initial progressive enhancement is clinically relevant, as this is the time at which alternative therapeutic options must be considered.

Previous studies evaluating the potential of rCBV to distinguish PsP from PD are limited and focus on initial rCBV. Several studies investigated late-delayed radiation necrosis rather than PsP,\(^6,16,17,26,27\) finding higher mean rCBV in PD compared with radiation necrosis, albeit with variable degrees of overlap. Although PsP may be on a continuum of treatment-related changes ranging from early subacute inflammation to late-delayed radiation necrosis,\(^2\) PsP and radiation necrosis likely have different histologic properties with contrasting clinical implications. Whereas PsP classically occurs within 6 months after radiotherapy, often spontaneously resolves, and potentially indicates higher treatment efficacy, radionecrosis occurs months to years after treatment, often progresses, and is a nonbeneficial complication.\(^25\) The 4 PsP lesions in our study
with histologic confirmation lacked typical features of radio-
necrosis including inflammatory cells, vessel wall thickening,
and hyalinization. Instead, they contained CD68-positive cells,
suggesting a contribution from macrophages and/or activated
microglia, and “quiescent” tumor cells with Ki-67 (cellular
marker for proliferation) typically <5%. Thus, the composi-
tion of PsP in our study appears to reside somewhere between
necrosis and active tumor in a histopathologic spectrum, likely
contributing to the overlapping rCBVs for PsP and PD at initial
progressive enhancement.

FIGURE 1. PPX, TMZ, and radiation-treated anaplastic astrocytoma (WHO III). The radiation field included all pretreatment regions of
FLAIR hyperintensity, including the right frontal opercular source of lesion C. Longitudinal postcontrast T1-weighted MRI and corre-
sponding rCBV maps demonstrate concomitant PsP (lesions A, B) and PD (lesion C). Pseudoprogressive enhancement peaked 172 days
after PPX + TMZ with decreasing rCBV after appearance of enhancement (Fig. 3A). Progressive tumor enhancement appeared later and
monotonically grew with increasing rCBV (Fig. 3B). Note the prolonged course of pseudoprogressive enhancement characteristic of
PPX + TMZ therapy. MRI indicates magnetic resonance imaging; PD, progressive disease; PPX, paclitaxel poliglumex; PsP, pseudo-
progression; rCBV, relative cerebral blood volume; TMZ, temozolomide.
Several previous studies evaluated lesions shortly after treatment and not around the time of initial progressive enhancement when clinical prospective analysis is most vexing. For example, Mangla et al\textsuperscript{11} found change from baseline in mean rCBV 1 month after chemoradiation in 36 GBMs to predict lesion destiny (41\% decrease for PsP vs. 12\% increase for PD), whereas Tsien et al\textsuperscript{13} paradoxically found significantly reduced rCBV in parametric response maps at week 3 of chemoradiation in high-grade glioma destined for PD as compared with PsP, with standard posttreatment ROI-based measures of mean rCBV nondiscriminatory. Although early prediction of lesion destiny is appealing, rCBV evaluation shortly after treatment is not feasible without sufficient pretreatment and posttreatment enhancement for reasonable measures, and such methods may be inapplicable to new lesions appearing after chemoradiation.

In previous studies in which imaging occurred near the time of progressive enhancement, quantitative rCBV is of inconsistent utility. Gahramanov et al\textsuperscript{28} found ferumoxytol-based rCBV measures better than gadolinium-based measures for distinguishing PsP from PD in 36 GBMs. Kong et al\textsuperscript{14} found significantly different mean rCBVs in PsP and PD for GBMs with unmethylated MGMT, but not with methylated MGMT. Young et al\textsuperscript{12} found significantly higher median rCBV compared with baseline in PD versus PsP for 20 GBMs with progressive enhancement on initial postchemoradiation MRI. We found substantial overlap of mean rCBV at initial progressive enhancement between PsP and PD, consistent with heterogenous perfusion patterns reported in studies using parametric maps to evaluate progressive posttreatment enhancement.\textsuperscript{13,15} Histopathologic factors likely explain both the inconsistencies in the literature and our overlapping mean rCBV values. Viable irradiated tumor often coexists with necrosis, radiation-induced occlusive vasculopathy, and altered vascular morphologies including telangiectasia, elongation, and endothelial proliferation,\textsuperscript{29} representing a wide range of vascular volumes. Mean rCBV at initial progressive enhancement may therefore poorly discriminate coexistent tumor and PsP. rCBV trends are more likely to be useful because over time, the tumor-to-PsP ratio increases when PD dominates, with correspondingly increased rCBV, and the converse should be true when PsP dominates.

It is important to note that rCBV trends provide unique information about lesion behavior beyond trends in lesion enhancement. Figure 3 illustrates 2 sample cases of PsP in which enhancing lesion volume continued to increase for

**FIGURE 2.** Comparison of rCBV features in PsP (n = 10) and PD (n = 9), box-and-whisker plots. A, Mean rCBV at initial progressive enhancement did not differ significantly; however, (B) absolute change in rCBV at first subsequent follow-up differed significantly (negative vs. positive), as did (C) slopes of linear regression for rCBV versus days after treatment beginning at initial progressive enhancement (negative vs. positive). D, Change in normalized rCBV from time at initial progressive enhancement to first subsequent follow-up versus change in enhancing volume over the same time interval for lesions evolving like PsP (closed squares) and PD (open squares). Initial change in rCBV appears to be helpful for predicting PsP versus PD in the setting of an initial increase in enhancing volume. PD indicates progressive disease; PPX, paclitaxel poliglumex; PsP, pseudoprogression; rCBV, relative cerebral blood volume.
several time points after initial progressive enhancement before ultimately decreasing, whereas rCBV decreased from the outset, showing how changes in rCBV do not simply “mirror” enhancing lesion volume but rather provide an early means for distinguishing PsP in these cases from PD.

Ideally, a marker for distinguishing PD from PsP as early as possible is desired, and waiting for trends to evolve may be impractical. However, our data suggest that a rise in rCBV at first follow-up after initial progressive enhancement reflects PD, whereas stable or decreasing rCBV reflects PsP (Fig. 2D). Nearly all lesions with decreasing rCBV ultimately represented PsP, with either initially increasing (right lower quadrant) or decreasing (left lower quadrant) enhancing volume, and virtually all lesions with increasing rCBV ultimately represented PD (right upper quadrant). There is some overlap about the zero line, but initial change in rCBV appears to be helpful for predicting PsP versus PD in the setting of an initial increase in enhancing volume. Left upper quadrant lesions (decreased enhancement, increased rCBV) would be seen in the setting of pseudoresponse (antiangiogenics), which did not occur in our PPX/TMZ-treated population. The impact on clinical care of waiting for an additional short-term follow-up must be determined. Further study with a larger number of patients is required to determine specific thresholds for change in rCBV and the shortest possible follow-up time point that can provide reliable discrimination. Although rCBV trend analysis is unnecessary for decreasing lesion enhancement, progressively enlarging enhancement could represent PD or early PsP, and rCBV trend analysis appears to be discriminatory in this setting.

When progressive enhancement is first detected, tumor often coexists with treatment-related enhancement, and measures of intraleision rCBV heterogeneity have been proposed as a better metric than mean rCBV for predicting lesion destiny.13,15 Although mean rCBV ideally reflects the dominant component of the lesion, mixtures of PsP and PD at initial progressive enhancement may yield nondiscriminatory, intermediate-weighted rCBV values. However, lesion destiny eventually becomes apparent through oppositely evolving weighted-mean rCBV trends in PD and PsP. Hotspot analysis would capture the highest rCBV in the enhancing lesion and reflect what would presumptively be the most active or aggressive part of the lesion, but DSC-MRI is inherently noisy, which may introduce spuriously high single-voxel rCBV values, and segmented ROIs may include vessels inadvertently. Histogram analysis is an appealing alternative that is potentially more sensitive to initial and evolving tissue heterogeneity, and may be considered for future studies.

Our study has several limitations. We defined lesion destiny by the temporal evolution of enhancement with or without tissue sampling, which may be limited by lesion heterogeneity and coexistence of tumor and PsP. rCBV estimates are inherently noisy, as reflected by nonmonotonic graphs of rCBV versus days after chemoradiation (Fig. 3). Contributions to noise come from intrasubject and intersubject methodological variations, including potential differences in scanner field strength,

FIGURE 3. Sample rCBV regression curves and corresponding enhancing volume curves plotted against days after PPX for PsP and PD, including lesions A (A) and C (B) of Figure 1. rCBV tends to trend downward over time for PsP, and upward for PD. PD indicates progressive disease; PPX, paclitaxel poliglumex; PsP, pseudoprogression; rCBV, relative cerebral blood volume.
loading dose, and incubation time between preload and dynamic bolus, and segmentation of enhancement, without well-characterized repeatability measures in the literature. Our linear regression results show consistent “downward” and “upward” trending rCBV for PsP and PD, respectively, but there is noise about these trends. Consistent DSC-MRI methodology is recommended to minimize inrasubject rCBV variability and maximize the ability to discern these trends on a point-to-point basis. Nonetheless, data from our cohort suggest that comparison of early time points beginning at initial progressive enhancement is likely to be useful.

Lastly, our pilot study was retrospective, with a small sample size due, in part, to the limited number of patients enrolled in the parent trial that did not include correlative aspects of imaging among its aims. Because a majority of our patients had both PsP and PD, either sequentially in the same lesion (temporally variant) or in different lesions (spatially variant), we analyzed each lesion independently, rather than aggregate enhancement in each patient. The high coincidence of PsP and PD in patients with PPX-treated gliomas makes this cohort attractive and unique for studying the ability of rCBV to discriminate PsP and PD.

In conclusion, at the time of initial progressive enhancement, subsequent temporal trends in mean normalized rCBV may be helpful in distinguishing PD from PsP after chemoradiation for patients with high-grade glioma. Future prospective clinical trials should investigate the potential utility of longitudinal DSC-MRI in assessment of time to disease progression.

REFERENCES