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Evaluation of pseudoprogression in patients with glioblastoma multiforme using dynamic magnetic resonance imaging with ferumoxytol calls RANO criteria into question

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Background. Diagnosis of pseudoprogression in patients with glioblastoma multiforme (GBM) is limited by Response Assessment in Neuro-Oncology (RANO) criteria to 3 months after chemoradiotherapy (CRT). Frequency of pseudoprogression occurring beyond this time limit was determined. Survival comparison was made between pseudoprogression and true progression patients as determined by using perfusion magnetic resonance imaging with ferumoxytol (p-MRI-Fe).

Methods. Fifty-six patients with GBM who demonstrated conventional findings concerning for progression of disease post CRT were enrolled in institutional review board-approved MRI protocols. Dynamic susceptibility-weighted contrast-enhanced p-MRI-Fe was used to distinguish true progression from pseudoprogression using relative cerebral blood volume (rCBV) values. rCBV of 1.75 was assigned as the cutoff value. Participants were followed up using RANO criteria, and survival data were analyzed.

Results. Twenty-seven participants (48.2%) experienced pseudoprogression. Pseudoprogression occurred later than 3 months post CRT in 8 (29.6%) of these 27 participants (ie, 8 [14.3%] of the 56 patients meeting the inclusion criteria). Overall survival was significantly longer in participants with pseudoprogression (35.2 months) compared with those who never experienced pseudoprogression (14.3 months; $P < .001$).

Conclusions. Pseudoprogression presented after 3 months post CRT in a considerable portion of patients with GBM, which raises doubts about the value of the 3-month time limit of the RANO criteria. Accurate rCBV measurement (eg, p-MRI-Fe) is suggested when there are radiographical concerns about progression of disease in GBM patients, regardless of any time limit. Pseudoprogression correlates with significantly better survival outcomes.

Keywords: ferumoxytol, GBM, perfusion-MRI, pseudoprogression, RANO criteria.

Glioblastoma multiforme (GBM) is the most common form of malignant primary brain tumors, with an incidence of 3.19 per 100 000 person-years.[1] The current standard medical treatment for a newly diagnosed GBM consists of maximal safe resection of the intracranial lesion followed by fractionated, conformal external beam radiation with concomitant temozolomide (TMZ) chemotherapy over a 6-week period. Further chemotherapy with monthly TMZ for 6 months is given for maintenance treatment.[2]

Response to chemoradiotherapy (CRT) is evaluated by both clinical and radiographic measures. Increased enhancement (>25%) on T1-weighted magnetic resonance imaging (MRI) using gadolinium-based contrast agent (GBCA) after CRT can represent either tumor progression or pseudoprogression for GBM patients. Since the introduction of adjuvant chemotherapy to radiation therapy for treating patients with newly diagnosed GBM, the incidence of pseudoprogression has increased, resulting in substantial clinical attention to this diagnosis.[3–14] Distinguishing between true disease progression (PD) and pseudoprogression is critical for determing appropriate therapy.

Conventional MRI is ineffective for distinguishing pseudoprogression from true PD.[15] Macdonald criteria, the first and most widely used criteria to assess treatment response in patients

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with high-grade glioma (HGG), considers all enhancing lesions as progression without consideration for treatment-related processes such as inflammation or necrosis.[16] The Response Assessment in Neuro-Oncology (RANO) criteria recognizes true PD within 12 weeks post CRT only with pathological confirmation or if new lesions have appeared outside the radiation field; otherwise, pseudoprogression is considered as a possible diagnosis.[17] Other investigators consider a diagnosis of pseudoprogression for up to 6 months following completion of CRT.[5,6,9,18] This arbitrary time limit means that cases of delayed pseudoprogression or early disease progression can be missed. Noninvasive diagnostic imaging techniques, utilizing radiographic biomarkers and various contrast agents, may assist radiologists in differentiating pseudoprogression from true PD.[3,19–35] Perfusion MRI (pMRI) studies have proven promising in resolving this dilemma by utilizing relative cerebral blood volume (rCBV) measurements.[27,28] We have previously shown that rCBV measurements using ferumoxytol (AMAG Pharmaceuticals), as the MRI contrast agent (Fe-MRI) can assist in delineating true tumor progression from pseudoprogression in GBM patients.[22,36]

The purpose of this study was to determine the frequency of pseudoprogression occurring within and beyond 3 months following CRT in patients with GBM. Follow-up MRI studies were reviewed retrospectively to confirm the diagnoses made using Fe-rCBV (ie, pseudoprogression vs PD). The prognostic significance of pseudoprogression was also evaluated.

Materials and Methods

Data Collection

Medical records of 68 consecutive patients with histological diagnosis of GBM (WHO grade IV glioma, primary or secondary, arising from a lower-grade glioma) who were enrolled in one of 4 prospective Oregon Health and Science University (OHSU) institutional review board-approved MRI protocols (2753, 2864, 1562, and 813) using 2 contrast agents (gadolinium-based contrast agent and ferumoxytol) were retrospectively reviewed. Patients had been diagnosed between March 2006 and September 2011, and written informed consent had been obtained from all.

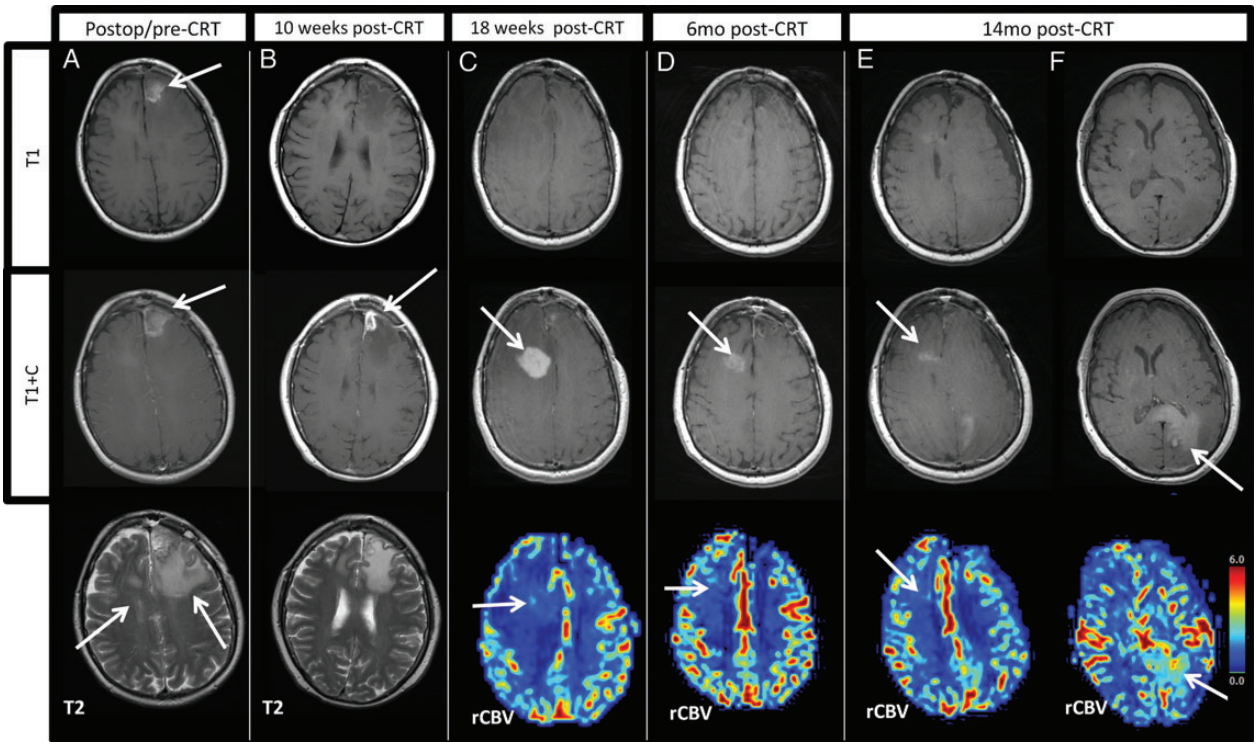

Fig. 1. Delayed pseudoprogression in a 61-year-old female with GBM. (A) MRI of brain after the initial tumor resection revealed postoperative changes including blood products in the resection cavity in the left frontal lobe. T2 hyperintensity around the resection cavity extended to the right frontal lobe, which was covered within the planned radiation field. (B) MRI of brain at 10 weeks post CRT showed decreasing enhancement at the operative site (arrow) compared with the immediate postoperative scan, which was consistent with resolving surgical changes without concern for tumor recurrence. Areas of T2-signal abnormalities remained stable. (C) MRI of brain at 18 weeks post CRT revealed a new area of enhancement in the right frontal lobe within the previously radiated field. rCBV was shown to be low (<1.75) in this area (arrow), suggesting pseudoprogression. Hence, the patient was continued on the treatment plan in place with monthly oral TMZ. (D) MRI of brain at 6 months post CRT showed significant decrease in the enhancing area in the right frontal lobe without any changes in the treatment regimen, confirming the diagnosis of pseudoprogression. rCBV remained low in this area (arrow). (E and F) MRI of brain at 14 months post CRT; the right frontal lobe continued to show minimal area of enhancement with low rCBV, as depicted in column E (arrows). Column F showed a new enhancing lesion in the left parieto-occipital lobe with increased rCBV (arrows), consistent with recurrent disease at a distant site from the initial presentation of disease. *Images in column B were acquired at an outside facility with different protocols than those employed at OHSU. Hence, the angles of slices are different from the rest of the images. Best presentation of the area of interest was chosen.

Patients with inadequate follow-up information, stable disease at the time of this review (10/2011), or who received alternative treatment including antiangiogenic agents (bevacizumab) prior to the first Fe-MRI were excluded from our participant pool.

Inclusion criteria required participants with histological evidence of GBM who had undergone pMRI studies at the time of radiographic worsening (defined by RANO criteria as more than 25% increased enhancement or new enhancing lesion) at any time after completion of CRT. All participants had received CRT at OHSU or an affiliated center with either 60 Gy in 30 fractions or 59.4 Gy in 33 fractions with concomitant oral TMZ at a dose of 75 mg/m^2/day. After completion of CRT, all participants continued on monthly TMZ (150–200 mg/m^2/day for 5 days in every 28 day cycle) for at least 6 months or until PD occurred. Pseudoprogression was defined as increasing or new enhancement with rCBV $\leq$ 1.75, while true PD was defined as rCBV $>$ 1.75 (Figs. 1 and 2). Upon confirmation of PD, participants stopped temozolomide and received second-line treatment based on clinical status, radiographic findings, and their own preference. The type of therapy used at recurrence was analyzed and balanced between the 3 groups. These participants were followed up with a median follow-up of 459 days after completion of CRT.

Clinical MRI exams were retrospectively reviewed including exams obtained prior to resection, prior to initiation of CRT, after completion of CRT, and any follow-up studies available until death.

Overall survival (OS) was calculated as the time between the surgery leading to diagnosis of GBM and the date of the participants death. Survival data were recorded for all participants and analyzed between cases of PD, pseudoprogression developed within 3 months (Ps $\leq$ 3), and beyond 3 months (Ps $>$ 3) after completion of CRT.

Imaging Studies

Participants underwent MRI at 3 Tesla, either using Siemens Tim Trio (Siemens Medical Solutions) or Philips Achieva (Philips

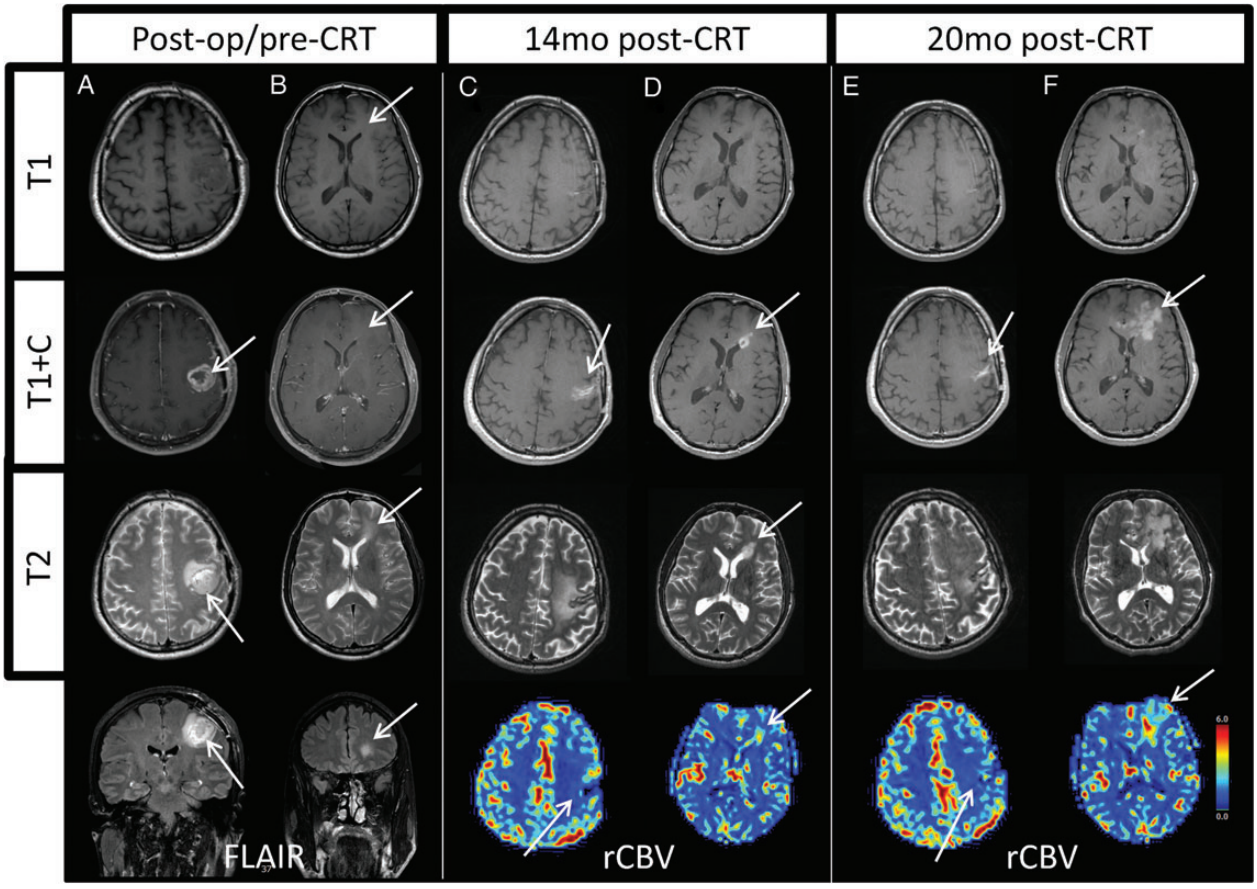

Fig. 2. Progression of disease in a 64-year-old male with GBM. Columns A and B: (A) MRI of brain after biopsy of the left fronto-parietal lesion with residual enhancing tumor and T2/FLAIR hyperintensity that was covered in the planned radiation field. (B) MRI of brain at a lower section demonstrated nonenhancing T2/FLAIR hyperintense lesion in the left frontal lobe, included in the radiation field (arrows). Columns C and D: MRI of brain 14 months after completion of CRT. (C) Residual T1-enhancement in the left fronto-parietal lesion with slight T2 hyperintensity. rCBV appeared to be low (<1.75) in this region (arrows). (D) New area of enhancement in the left frontal lobe. High rCBV was noted, indicating progression of disease (arrows). Columns E and F: Follow-up MRI of brain at 20 months post CRT after 5 doses of i.v. bevacizumab infusion. (E) The left fronto-parietal lesion appeared to be stable with no significant changes in enhancement or the rCBV (arrows). (F) The left frontal lesion showed increased enhancement as well as increased rCBV, confirming progression of his disease (arrows).

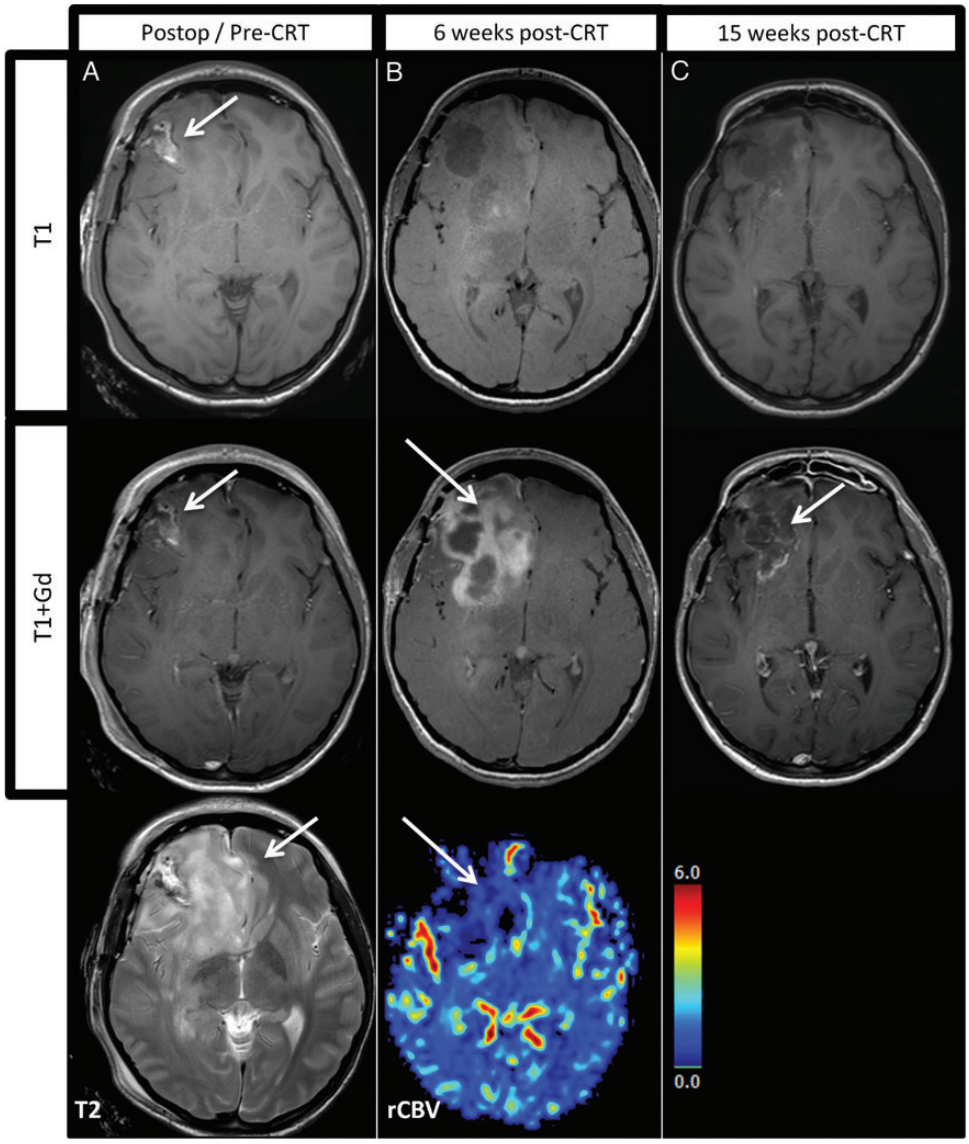

Fig. 3. Early pseudoprogression in a 23-year-old female with GBM. (A) MRI of brain after initial resection of tumor, representing postoperative changes and T2 hyperintensity in the right frontal lobe, included in the planned radiation field (arrows). (B) MRI of brain 6 weeks after completion of CRT showed increased enhancing area in the right frontal lobe (arrow). Patient did not have any clinical symptoms. Low rCBV noted in the area of enhancement, indicating pseudoprogression (arrow). (C) Follow up MRI of brain 15 weeks after completion of CRT revealed significant decrease of the enhancing area (arrow) without any changes in the treatment regimen, confirming the diagnosis of pseudoprogression.

Healthcare) whole-body scanners with multichannel receiver-head coils. All imaging protocols included anatomical and dynamic sequences in the axial plane. Anatomical sequences were acquired with a field of view (FOV) of 240 mm × 240 mm, acquisition matrix 256 × 256, number of slices up to 44, and slice thickness 2 mm, with no interslice gap. Repetition time (TR)/echo time (TE) were 900 milliseconds/10 milliseconds or similar for T1-weighted spin echo scans. T2-weighted turbo spin echo (Siemens) or fast spin echo (Philips) sequences had TR/TE 9000 milliseconds/93 milliseconds or similar, echo train length 9. Dynamic-susceptibility contrast-enhanced (DSC) scans were acquired with FOV 192 mm × 192 mm, acquisition matrix 64 × 64, number of slices 27, 3 mm slice thickness, 0.9 mm interslice gap, TR/TE/flip angle 1500 milliseconds/20 milliseconds/45°. Ninety dynamic phases were scanned with a temporal resolution of 1.5 s/phase. After the seventh phase, a short IV bolus of 1 or 2 mg/kg (~5–10 mL) ferumoxytol was injected at a flow rate of 3 mL/s followed by 20 mL of saline flush at the same rate. A total of ~20 phases were obtained before the contrast reached the brain (7 before injection and 13 after IV injection and before any contrast could be seen in the brain), allowing an accurate baseline signal. To assess anatomical contrast enhancement on T1-weighted scans, IV gadoteridol (Bracco Diagnostic) was administered in a standard clinical dose of 0.1 mmol/kg.

Image Analysis

All DSC-MRI data were processed by S.G. with a dedicated software package (NordicICE; NordicNeuroLab). The rCBV maps were generated by using established tracer kinetic models applied to the first-pass data.[37,38] rCBV maps were created on a pixel-by-pixel basis and were normalized by dividing these rCBV values by normal-appearing white matter rCBV values in the same geographical region of the contralateral hemisphere. The normalized rCBV maps were coregistered and displayed as color overlays on GBCA-enhanced T1-weighted images. A 2×2 pixel (6×6 mm) region of interest with the highest rCBV value was selected on the Fe-rCBV parametric map within the anatomical-enhancing lesion for analysis. Areas showing major vessels, obvious hemorrhage, and visible cystic and necrotic changes were excluded from regions of interest. Patient classification was made based on a binary categorization of rCBV values as high and low and rCBV threshold of 1.75. This threshold value was chosen in part because Law et al.[39] suggested that it provided the optimal sensitivity and specificity for differentiating low-grade gliomas from HGG. Gahramanov et al.[36] further tested different values of rCBV thresholds, and 1.75 appeared to reliably distinguish between pseudoprogression and PD using either ferumoxytol or leakage-corrected GBCA pMRI. Mixed response, indicated by the presence of areas of both high and low rCBV, was considered as PD due to presence of active tumor.

Statistical Analysis

All analyses were conducted using SAS 9.2 (SAS Institute). Patient characteristics were summarized using descriptive statistics. OS was assessed using Kaplan–Meier product-limit estimates and compared between groups of patients with different responses to treatment using the log-rank test. One- and 2-year survival rates were calculated for the different groups. A type I error rate of 0.05 was used to determine the significance of all testing results.

Results

A total of 56 eligible patients met inclusion criteria. Mean age at time of diagnosis was 55 years (SD = 13.8 years). Twenty-nine of the 56 participants (51.8%) had PD based on pMRI after their first radiographic worsening following CRT. At the time of analysis, 48 participants had PD, of whom 41 had died. Key participant characteristics are summarized in Table 1. The remaining (48.2%) participants were diagnosed with pseudoprogression, which was subsequently confirmed with stabilization or decrease of the enhancing lesion on follow-up MRI studies. Nineteen participants presented with pseudoprogression in the first 3 months following CRT, including 11 who presented within 6 weeks following CRT. Eight participants had pseudoprogression diagnosed beyond 3 months post CRT (range, 4–10 months).

Median OS for the entire cohort was 19.3 months (95% CI, 15.1–23.3 months) with one- and 2-year survival rates of 76.8% and 33.4%, respectively (Fig. 4A). Median OS in all participants with pseudoprogression was 35.2 months, and OS of 14.3 months was observed in participants with PD (Table 2, Fig. 4B). Median OS in Ps > 3 was 54.9 months. Participants with Ps ≤ 3 had a median OS of 21.6 months. One-year survival for Ps ≤ 3, Ps>3 and true PD groups were 94.7%, 100%, and 58.6% respectively. Two-year OS for Ps ≤ 3, Ps>3 and true PD groups were 36.7%, 83.3%, and 17.2% respectively (Fig. 4B and C). Significant differences were observed in OS between all pseudoprogression and PD groups ($P < .0001$, Fig. 4B), but not between Ps ≤ 3 and Ps>3 ($P = .15$, Fig. 4C).

Table 1. Demographics

Total number of patients		56
Sex		
Male, *n* (%)		36(64.3%)
Female, *n* (%)		20 (35.7%)
Age		
All mean (SD)		55(13.8)
Younger than 60 years, *n* (%)		32 (57.1%)
60 years or older, *n* (%)		24 (42.9%)
KPS		
All median (IQR)		80 (70–90)
Ps	Within 3 months of CRT	80 (70–100)
	Beyond 3 months of CRT	90 (90–100)
PD		70 (60–90)
≥70		44 (78.6%)
<70		12 (21.4%)
TMZ cycles received		
1–6 months		29
6–12 months		22
More than 12 months		5

Abbreviations: CRT, chemoradiotherapy; IQR, interquartile range; KPS, Karnofskey Performance Status; Ps, pseudoprogression; PD, progression of disease; SD, standard deviation; TMZ, temozolomide.

Discussion

Pseudoprogression was diagnosed in 48% of all participants meeting the inclusion criteria in this report, with 30% of them presenting beyond 3 months post CRT. Occurrence of pseudoprogression throughout the treatment course of participants with GBM was associated with better prognosis and longer OS compared with those who never experienced pseudoprogression prior to progression of their disease. Radiographic worsening on conventional MRI exams beyond 3 months following completion of CRT does not necessarily indicate tumor progression, and changes in therapy at this time may be counterproductive. This finding calls into question the RANO criteria of a 3-month time limit for diagnosis of pseudoprogression.[17]

Pseudoprogression, which was reported for the first time in 1979 by Hoffman,[40] described in 2004 by de Wit,[8] and named by Tall et al.,[4] represents the phenomenon of subacute imaging changes resulting from CRT with or without associated clinical sequelae that resolve or stabilize without any changes in the treatment regimen. Multiple pathological studies have shown that pseudoprogression lesions consist of necrotic tissue and inflammatory cells without evidence of active tumor growth or PD.[4,13] Pseudoprogression is associated with significantly better overall prognosis and longer OS in patients with HGG treated with CRT,[9,10,12–14,41] leading to the hypothesis that pseudoprogression is a marker of better prognosis and therapeutic response.

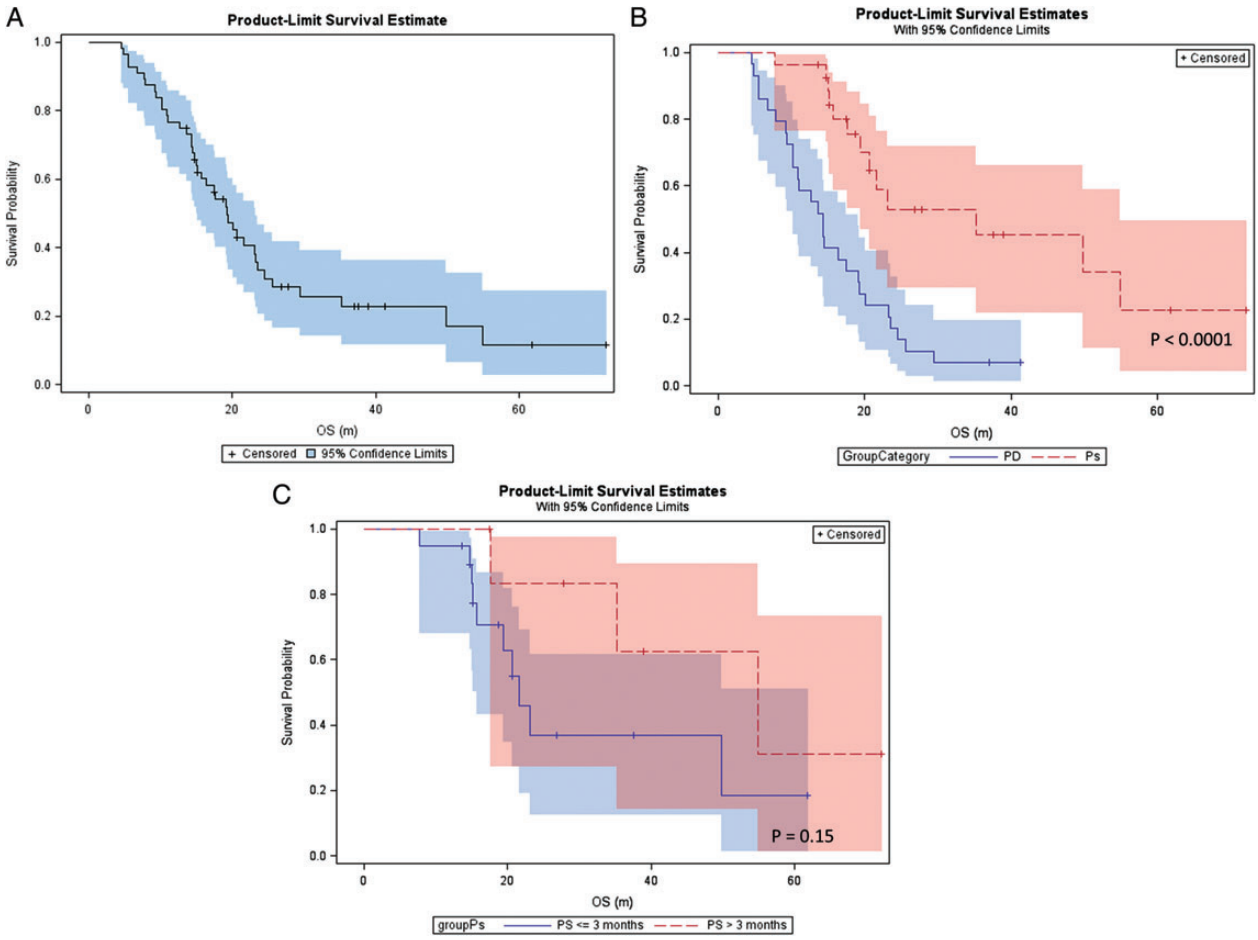

Fig. 4. Overall survival curves. (A) Overall survival in all patients. (B) Comparison of overall survival amongst participants with pseudoprogression (Ps) and progression of disease (PD). Significantly longer overall survival was observed in participants with pseudoprogression when compared with progression of disease ($P < .0001$). (C) The difference in overall survival between participants presenting with pseudoprogression within the first 3 months after CRT and beyond 3 months after CRT was not statistically significant ($P = .15$).

DSC pMRI has been investigated for analyzing and characterizing morphologic features of tissue in attempts to predict time to PD for patients with glioma.[28] Low rCBV values are associated with necrosis in post CRT tissue,[25,28] and this has been confirmed histologically with tissue resection.[21] These measurements have been correlated with OS in patients with recurrent GBM.[11] However, GBCA has certain limitations in serving this purpose due to its physiochemical properties and small size.[22] Leakage of GBCA cannot be monitored very accurately and requires mathematical leakage correction to improve diagnostic accuracy.[22] Gahramanov et al. reported the superiority of ferumoxytol as a contrast agent for pMRI over GBCA due to its larger size and blood-pooling properties, eliminating the need for contrast-agent leakage correction.[22,36,42]

Ultrasmall superparamagnetic particles of iron oxide (eg, ferumoxytol) with their larger molecular size (up to 50 nm compared with the 1 nm gadolinium chelate) and carbohydrate coating tend to extravasate much more slowly, even in areas of severe blood-brain barrier dysfunction (eg, malignant glioma), making them better candidates as blood-pool agents for pMRI.[43] As previously reported by Gahramanov et al., the reliability of the 1.75 cutoff value was reaffirmed by our own work, in which this cutoff also allowed differentiation of pseudoprogression from PD in HGG using either ferumoxytol or leakage-corrected GBCA-based DSC pMRI.[36] However, the ideal threshold with highest sensitivity and specificity is still under debate in the literature. For example, a cutoff point of 1.47 was also reported,[44] although the rCBV values used the average of enhancing area. In our study and other studies,[28] only rCBV values from the hot spots were used. Unlike GBCA-based DSC pMRI, ferumoxytol-based DSC pMRI requires no leakage correction; however its use in imaging remains an off-label indication, and the use of 2 different contrast agents is not FDA approved and needs further study.

Studies have been recently published on high-resolution, steady-state CBV mapping using clinically applicable doses of ferumoxytol. The high spatial resolution and distortion-free CBV maps allow superior assessment of highly vascular areas compared with the DSC technique[45] and could provide quantitative, absolute CBV values.[46] Steady-state CBV maps could be considered in the future to improve the differentiation of true progression from pseudoprogression. The ability to accurately diagnose pseudoprogression at the first signs of increased enhancement

Table 2. Summary of treatment outcomes and survival data

Patients with increased enhancement on T1W + C	*n* (%)
All	56 (100%)
Low rCBV (Ps)	27 (48.2%)
Ps ≤3 months	19 (33.9%)
Ps >3 months	8 (14.3%)
High rCBV	29 (51.8%)
Overall survival (PD)	**Median (95% CI)**
All	19.3 (15.1, 23.3)
Ps	35.2 (19.5–54.9)
Ps ≤3 months	21.6 (15.7–NE)
Ps >3 months	54.9 (17.6–NE)
PD	14.3 (10.2–19.1)

Abbreviations: CI, confidence interval; NE, not estimateable; PD, progression of disease; Ps, pseudoprogression; rCBV, relative cerebral blood volume; T1W +C, post-contrast T1-weighted MRI images of brain

on MRI may avoid delay in diagnosis or compromise in the care and management of GBM patients.

Studies in animal models suggest that ferumoxytol may also diagnose pseudoresponse (a decrease in the enhancing area despite presence of active tumor tissue that occurs frequently with the use of antiangiogenic agents such as bevacizumab) more reliably.[42] Acting as a blood-pool agent, ferumoxytol continues to provide more accurate estimation of blood volume in the areas of active tumor regardless of normalization of vasculature responding to bevacizumab.

Other imaging modalities have also been utilized to aid in distinguishing treatment-induced phenomena versus PD in patients with recurrent GBM, but none have provided adequate diagnostic reliability. Reduced apparent diffusion coefficient values have been associated with tumor progression.[3,19–22,25,26] MR spectroscopy has shown potential in discriminating neoplastic from non-neoplastic tissue; however, variable results, low sensitivity, and low positive predictive values have limited their widespread use.[29,30] 18F-FDG PET, alone or in combination with other imaging modalities such as MRI or CT, has also shown low sensitivity.[31,33,34] PET with labeled amino acids and their analogs, such as L-[methyl-11C]-methionine (11C-MET) and 18F-fluoroethyltyrosine (18)F-FET), have shown higher sensitivity and specificity compared with 18F-FDG PET; however, the availability of these radiotracers is limited to few centers, and clinical experience is limited.[47,48]

Unfortunately, there has not been a large clinical trial to validate the utility of these techniques in distinguishing recurrent tumor from treatment-induced tissue changes. Short of a few small studies,[26,32] direct head-to-head comparison of these imaging modalities in a large systematic study is lacking.

The limitations of this study are the lack of histological confirmation at the time of radiographic progression and the moderate sample size, particularly for Ps>3 cases. Pseudoprogression was confirmed by clinical outcomes, OS, and radiographic changes over time instead of invasive biopsy, which has the potential for patient harm. An increased OS in the Ps>3 group was observed in comparison with the Ps ≤ 3 group, although the difference was not statistically significant; this might have been due to our moderate sample size. This difference could be evaluated in future studies with a larger sample size. In the characterization of the Ps ≤ 3 group, it is widely known that unspecific contrast enhancement is to be seen within 6 weeks after CRT, and it is hard to distinguish between pseudoprogression versus true progression; however, pseudoprogression can occur before 6 weeks. Furthermore, we did try to add an analysis by looking within the Ps ≤ 3 group and comparing <6 weeks versus 6–12 weeks separately, but the sample sizes were too small to produce reliable results. Again, this difference could be evaluated in future studies with a larger sample size.

Conclusion

Pseudoprogression can present beyond 3 months following completion of CRT. Thus, radiographic worsening on conventional MRI beyond 3 months after completion of CRT does not necessarily indicate tumor progression, and changes in treatment strategy at this point may be inappropriate. Therefore, we believe that the 3-month time limit after CRT, as implemented by RANO criteria, is not adequate for delineating between pseudoprogression and true progression. We suggest utilization of dynamic MRI studies to differentiate between these 2 entities upon appearance of radiographic changes concerning for progression of disease, at least within the first year after completion of CRT, and it might be worthwhile to consider including rCBV measurements as part of the RANO criteria.

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Conflict of interest statement. Dr. Neuwelt's studies involving ferumoxytol were entirely funded by Veterans Administration and NIH research grants, with the ferumoxytol USPIO nanoparticles partially donated by AMAG Pharmaceuticals. In 2008, OHSU received and completed a one-time sponsored research agreement with AMAG Pharmaceuticals to conduct clinical trials of MRI with ferumoxytol. This agreement covered only a fraction of the costs of this study (<5%). None of the authors has financial interest in this agent or in its developer, AMAG Pharmaceuticals.

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