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Pros and cons of current brain tumor imaging

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Over the past 20 years, very few agents have been approved for the treatment of brain tumors. Recent studies have highlighted some of the challenges in assessing activity in novel agents for the treatment of brain tumors. This paper reviews some of the key challenges related to assessment of tumor response to therapy in adult high-grade gliomas and discusses the strengths and limitations of imaging-based endpoints. Although overall survival is considered the "gold standard" endpoint in the field of oncology, progression-free survival and response rate are endpoints that hold great value in neuro-oncology. Particular focus is given to advancements made since the January 2006 Brain Tumor Endpoints Workshop, including the development of Response Assessment in Neuro-Oncology criteria, the value of T2/fluid-attenuated inversion recovery, use of objective response rates and progression-free survival in clinical trials, and the evaluation of pseudoprogression, pseudoresponse, and inflammatory response in radiographic images.

Keywords: clinical trials, endpoints, MRI, RANO, response assessment.

Need for Radiographic Measures of Tumor Response to Therapy

Approximately 327 000 new primary brain or CNS tumors are diagnosed each year in the United States, which constitutes ~21 people per 100 000.[1] Of these newly diagnosed tumors, ~28% are gliomas, which constitute 80% of all malignant tumors.[1] Glioblastoma multiforme (GBM), the most common and aggressive type of glioma, is the focal point in this document for 2 reasons. First, it is the most common and aggressive form of malignant glioma, accounting for 54% of all gliomas and 45% of all malignant primary brain and CNS tumors,[1] thus it is a high priority area for therapeutic development. Second, GBM is one of the most complex, adaptive, and drug-resistant brain tumors. Therefore, improvements to drug development and measurement of tumor response to therapy in GBM may provide added benefits to other types of brain tumors.

GBM carries a dismal prognosis, with a median survival of around 14 months,[2] and fewer than 10% of patients survive beyond 5 years after diagnosis.[3] Despite the modest increase in survival observed with the addition of temozolomide to radiotherapy,[2] this dismal prognosis has not changed substantially in the past 30 years. Currently, the standard of care for newly diagnosed GBM patients consists of maximum safe surgical resection, followed by radiotherapy plus concomitant and adjuvant temozolomide. At recurrence, however, very few therapeutic options exist. A careful review of the clinical trials from 2006–2012 involving recurrent GBM has shown that only a minority of patients are eligible for a second surgery or reirradiation. At relapse, temozolomide-pretreated patients show progression-free survival (PFS) rates at 6 months of 20%–30% with nitrosoureas, temozolomide rechallenge, or bevacizumab.[4] Thus, there is an urgent need for drug development in the setting of recurrent GBM.

Although overall survival (OS) is considered the gold standard for determining whether a cancer treatment is effective, in certain situations OS may not directly reflect the impact of a specific regimen because of potential confounding effects of prognostic factors, additional therapies, and other factors. Therefore, PFS and in particular response rate (RR) are considered valuable endpoints for isolating the relative value of a given treatment.[5] Determining response and progression using surrogate measures of tumor burden, however, suffers from issues associated with

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imaging characteristics (enhancement), measurement variability, false positives, and discordance in radiographic interpretation between observers.[6] Therefore, there is a need for refinement of response assessment in neuro-oncology with the objective of minimizing intrinsic errors and enhancing the accuracy of predicting true response to a particular therapy.

Brief History of Glioma Response Assessment

MRI used with the addition of contrast agents that shorten T1 relaxation time constants is the standard for detection, delineation, and response assessment of brain tumors. Using this approach, the tumor region becomes bright on T1-weighted images due to the passing of contrast agent out of abnormal vasculature, through the blood–brain barrier, and into the extracellular space.[7] Thus, regions of hyperintensity (brightness) on post-contrast T1-weighted images are thought to reflect the most aggressive portion of the tumor, which has subsequently been confirmed with biopsy observations.[8,9]

The response criteria proposed by Macdonald and colleagues[10] in 1990 attempted to improve upon earlier response assessments, including the Levin criteria[11] and the World Health Organization systemic oncology response criteria, which used bidirectional measurements,[12] by accounting for corticosteroid use and changes in neurologic status. Similar to its predecessors and the Response Evaluation Criteria in Solid Tumors (RECIST),[13] the "Macdonald criteria" used measurements of contrast-enhancing tumor burden to determine tumor response and progression, categorizing response into 4 categories: complete response, partial response, stable disease, and progressive disease. For nearly 20 years the Macdonald criteria, based on contrast enhancement as a surrogate of tumor burden, were used for the evaluation of new therapies. The Macdonald criteria were effectively used for the approval of temozolomide in recurrent anaplastic astrocytoma, where there was a response rate of 35% (8% complete response, 27% partial response) in a single-arm trial. The Macdonald criteria also allowed for the identification of the chemotherapy responsiveness of anaplastic oligodendroglioma, which was subsequently confirmed in OS benefit in phase III trials.[14,15]

In an effort to acknowledge the need for new agents to treat brain tumors and to address methodological challenges associated with brain tumor clinical trial design, the FDA cosponsored a public workshop on brain tumor clinical trial endpoints with the American Association for Cancer Research and the American Society of Clinical Oncology in January 2006. This workshop focused on clinical trial endpoints intended to support the approval of new drugs for brain cancer and sought debate on the analytic validity of the instrument (eg, imaging or patient-reported outcomes) and on how well individual endpoints reflect clinical benefit. Several issues were discussed and conclusions made:

(1) Objective response: Objective response rates can be reliably assessed in single-arm studies, but the magnitude of response is important given interreviewer variability.
(2) Time to event endpoints (PFS): Need to be evaluated within randomized studies. Future consideration would be given to a landmark-based PFS (ie, 6-mo PFS) if it could be established as a reliable surrogate endpoint, or one that is reasonably likely to predict clinical benefit.

What Is New Since 2006 and What Is the Status of Brain Tumor Imaging Today?

Over the last 10 years, the routine implementation of newer imaging techniques, including T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI,[16,17] which allows for better visualization of vasogenic edema, surgical and radiation-induced gliosis and infiltrating tumor, and new therapies that drastically change vascular permeability (eg, anti-angiogenic agents and immunotherapies) resulted in the need to evolve the Macdonald response criteria.[18,19] The largest differences between these new, evolving response criteria and the standard Macdonald criteria revolve mainly around the identification of nonenhancing, infiltrative tumor.[20] Although contrast-enhancing tumor is thought to represent the most aggressive portion of the tumor,[8,9] and a large percentage of high-grade gliomas have a significant enhancing component,[21] these tumors are known to contain proportions of both neovascularized and infiltrative tumor,[22,23] and the relative proportions are thought to reflect different biological phenotypes.[21,24,25] In addition to containing nonenhancing tumor at presentation, a substantial proportion of treated tumors can have nonenhancing tumor progression,[22,26] and progression of nonenhancing tumor can lead to neurologic decline. These issues, combined with the high incidence of "pseudoresponse" during anti-angiogenic therapy, drove the need for reevaluation of the response criteria in neuro-oncology. The inclusion of evaluating nonenhancing parts of the tumor would be particularly valuable if overall tumor burden (and ultimately patient benefit) would improve prediction of overall outcome better than changes in contrast enhancement. In 2010, the Response Assessment in Neuro-Oncology (RANO) criteria were developed[27] to comprehensively reform the Macdonald criteria using the evolving principles and conditions outlined in previous work.[18–20] Although one of the main changes was the inclusion of the evaluation of nonenhancing tumor progression, RANO also attempted to correct a number of deficiencies in the Macdonald criteria. These included definitions of measurable and nonmeasurable disease, definitions of progression for patients being considered for enrollment into clinical trials, recommendations to address pseudoprogression (PsP) and pseudoresponse, the requirement of confirmatory scans for response, and recommendations for dealing with patients with equivocal imaging changes. The details of the current RANO criteria and other modifications to RANO are now well documented in various review articles.[28–34] Importantly, inherent within RANO is the ability to be fluid and adjust the criteria to new and evolving data.

Anti-angiogenic Therapy, Pseudoresponse, and Infiltrative Tumor Recurrence

Clinical studies examining the efficacy of anti-angiogenic agents in patients with GBM note a dramatic reduction in the amount of contrast enhancement,[35–44] translating into very high response rates with bevacizumab (28%–38%,[45] 63%,[46] and 57%[47]) and cediranib[44] (~50%) compared with response rates of 10% or less using irinotecan at recurrence.[48–51] These response rates tend to translate into prolonged PFS but into only a modest change in OS compared with historical series.[44,45] It was hypothesized that this was due to the use of the Macdonald response criteria,

which are based primarily on change in contrast enhancement and not on change in actual tumor size assessment. Therefore, the phenomenon of pseudoresponse,[52] in which contrast agent uptake is reduced due to changes in vascular permeability independent of antitumor effect, potentially represents a significant limitation for early response assessment of anti-angiogenic treatments in recurrent GBM. The awareness of this phenomenon is also the reason for the need to control steroid dose when calling response or progression.

In addition to increased response rates, studies examining tumor relapse/progression while on anti-angiogenic agents note a tendency for growth of nonenhancing, infiltrative tumor prior to emergence or increase of contrast enhancement.[38] Approximately 30%–40% of patients are estimated to experience nonenhancing tumor progression prior to changes in contrast enhancement.[26] In one study 40% of patients treated with bevacizumab experienced nonenhancing tumor progression, including a subgroup of 21% of patients with circumscribed T2 progression who had an especially poor median survival of 5 months, comparable to patients who never responded to bevacizumab.[53]

This observation is further supported by preclinical[54] and clinical[55–57] evidence showing that escape from anti-angiogenic therapy results in tumor invasion into normal brain and upregulation of genes associated with invasion, including those associated with metalloproteinases and insulin-like growth factor binding protein–2. Utilizing a modified Macdonald criteria that integrated qualitative changes in nonenhancing tumor into the response criteria, the BRAIN study (AVF3708g) provided response rate data,[45,58] confirmed in NCI06-C-0064E,[45] which led to the accelerated approval of bevacizumab for recurrent/progressive glioblastoma. Additionally in the BRAIN study, independent radiology review of objective response utilizing modified Macdonald criteria incorporating change in nonenhancing tumor was similar to the determination by an independent radiologic evaluation by the FDA: 28.2% versus 25.9% (Table 2). These observations helped consolidate incorporation of a definition for nonenhancing tumor progression into the current RANO criteria. This was, however, inserted as a qualitative change, without a quantitative threshold for progressive disease or partial response because of the often complex irregular shape of T2/FLAIR abnormalities making routine measurement an issue.

Clinical and Biological Evidence for Incorporating FLAIR Into RANO

Currently, accurate assessment of nonenhancing tumor burden and tumor progression is the most difficult, time-consuming, and expensive portion of RANO evaluation, even though this is to be rated on a subjective scale. While evaluation of nonenhancing tumor burden has been incorporated into a number of registration trials, there remains debate as to whether it provides added value. A bevacizumab-irinotecan study reported by Gallego Perez-Larraya et al[26] indicated that RECIST, Macdonald, and RANO had similar estimates of response rate. Also, despite 1/3 of patients experiencing nonenhancing tumor progression during stable or improved contrast enhancement,[26] there was no significant difference in PFS (RANO median PFS ¼ 11.7 wk compared with Macdonald PFS ¼ 12.7 wk). Regardless, incorporation of nonenhancing tumor progression did not translate into a significant difference in PFS, and all measures of PFS (including those based on T1 with contrast) were shown to correlate with OS.[26] Similar findings were recently reported by Schaub et al[59] in a small study of 26 patients showing that recurrence of nonenhancing tumor did not necessarily predict shorter survival. Additionally, a recent study by Radbruch et al[60] showed that ~24% of their 144 patients had T2 recurrence that preceded recurrence via contrast enhancement when T2 progression was defined as . 15% increase in bidirectional measurements on T2-weighted images. Of these patients, 62% had contrast enhancement on the subsequent follow-up.[60]

Consistent with the hypotheses that T2/FLAIR progression is of limited value to predict patient benefit and that early measures of tumor progression via contrast enhancement are still a surrogate of survival even in the presence of anti-angiogenic therapy, recent results from ACRIN-6677/RTOG-0625, a prospective, randomized, phase II multicenter trial by Boxerman et al[61] compared bevacizumab with either irinotecan or temozolomide treatment in recurrent GBM. This study demonstrated that response rate at 8 and 16 weeks measured using the Macdonald criteria or 3D enhancing volumes using a central reader paradigm predicted OS in recurrent GBM treated with bevacizumab, whereas T2/FLAIR progression rates alone did not predict OS.[62]

Preliminary results from Huang et al[62] using the BRAIN trial dataset with 160 evaluable patients showed that the RANO criteria reduced median PFS by an average of 1.3 months (5.52 mo with Macdonald; 4.21 mo with RANO; log-rank, P ¼ .0423) but produced no significant difference in overall RR. Tumor progression by Macdonald and RANO at 2, 4, and 6 months predicted OS, but the difference between the 2 criteria was not statistically significant.

It is not clear whether any observed differences in PFS between Macdonald and RANO criteria may account for very different patient reported outcomes and neuropsychological testing data from the 2 phase III trials evaluating the role of bevacizumab in newly diagnosed GBM, AVAglio and RTOG-0825. One potential explanation for the decline in patient reported outcomes and neuropsychological function observed in patients enrolled in RTOG-0825, but not in AVAglio, may be that RTOG-0825 did not include assessment of nonenhancing progression, allowing patients to stay on study longer while they were in fact progressing. Evaluation of the RTOG and other datasets using RANO should help determine the potential utility of nonenhancing tumor progression as a measure of a clinically relevant change in neurologic functioning. If true, this would support the evaluation of T2/FLAIR images as part of outcome assessment.

Biologically, there is some preclinical and clinical evidence to suggest that anti-angiogenic therapy results in a more "infiltrative phenotype"[54–57]; however, other studies have compelling evidence to suggest that this is not unique to anti-angiogenic therapy[63–65] and hypothesize that this is an inherent phenotype to the tumor that exists prior to anti-angiogenic therapy, and/or this phenotype may be relatively common among recurrent GBM regardless of therapy. Additionally, studies examining preclinical response to anti-angiogenic therapy have tangentially noted that prolonged therapy eventually results in reactivation of angiogenesis through upregulation of pro-angiogenic pathways or autocrine vascular endothelial growth factor signaling.[54] In summary, the literature suggests that progression may be first via nonenhancing tumor, but tumors will eventually relapse on anti-angiogenic therapy and manifest as an increase in contrast

Table 1. Summary of current studies focusing on incidence of PsP and actual progression in newly diagnosed malignant gliomas treated with radiation or radiochemotherapy

Publication	Window for Early Progression	Number of Early Progressors	Number of Confirmed PsP	Total Number of Patients	Early Prog.	PsP in Early Prog.	PsP in All Patients	Criteria for Progression	Treatment
Brandes et al, J Clin Oncol, 2008	1 mo	50	32	103	48.54%	64.00%	31.07%	Macdonald	Radiochemotherapy
Taal et al, Cancer, 2008	1 mo	36	15	85	42.35%	41.67%	17.65%	Macdonald	Radiochemotherapy
Mangla et al, Radiology, 2010	1 mo	19	7	36	52.78%	36.84%	19.44%	Macdonald	Radiochemotherapy
Gerstner et al, J Neurooncol, 2009	1 mo	24	13	45	53.33%	54.17%	28.89%	Macdonald	Radiochemotherapy
de Wit et al, Neurology, 2004	1 mo	9	3	32	28.13%	33.33%	9.38%	Macdonald	Radiation therapy
Total	**1 mo**	**138**	**70**	**301**	**45.85%**	**50.72%**	**23.26%**		
Sanghera et al, Can J Neurol Sci, 2010	2 mo	27	7	104	25.96%	25.93%	6.73%	RECIST	Radiochemotherapy
Clarke et al, J Clin Oncol, 2008 (Abstr)	2 mo	33	8	80	41.25%	24.24%	10.00%	Increased T1 + contrast	Radiochemotherapy
Young et al, Neurology, 2011	2 mo	63	33	93	67.74%	52.38%	35.48%	Increased T1 + contrast	Radiochemotherapy
Chu et al, Radiology, 2013	2 mo	30	15	52	57.69%	50.00%	28.85%	Increased T1 + contrast	Radiochemotherapy
Total	**2 mo**	**153**	**63**	**329**	**46.50%**	**41.18%**	**19.15%**		
Jefferies et al, Clin Oncol, 2007	6 mo	9	3	15	60.00%	33.33%	20.00%	Not specified	Radiochemotherapy
Chaski et al, Surg Neurol, 2009	6 mo	25	3	54	46.30%	12.00%	5.56%	Increased T1 + contrast	Radiochemotherapy
Kumar et al, Radiology, 2000	6 mo	14	3	92	15.22%	21.43%	3.26%	Increased T1 + contrast	Radiochemotherapy
Total	**6 mo**	**48**	**9**	**161**	**29.81%**	**18.75%**	**5.59%**		

Table 2. Summary of recent recurrent GBM studies

	Study Name	Year	No. of Patients	No. Recurr	Multicenter?	Central Review?	Time Post XRT	Meas (M) vs Eval (E)	ORR	Durability	PFS	PFS-6	OS	Criteria for Response
VEGF Drug Studies														
Friedman et al, J Clin Oncol, 2009	BRAIN Bev	2006–07	85	1–2	Yes	Yes	8 wk	M	28.2	5.6	4.2	42.6	9.2	Modified Macdonald
	BRAIN Bev Only (FDA)	2006–07		1–2	Yes				25.9	4.2		36	9.3	WHO
Friedman et al, J Clin Oncol, 2009	BRAIN Bev/ CPT-11	2006–07	82	1–2	Yes	Yes	8 wk	M	37.8	4.3	5.6	50.3	8.7	Modified Macdonald
Gilbert et al, J Clin Oncol, 2009	RTOG-0625 Bev/TMZ	2007	60		Yes		6 wk		21			39.3		Macdonald
Gilbert et al, J Clin Oncol, 2009	RTOG-0625 Bev/CPT11	2007	57		Yes		6 wk		28			38.6		Macdonald
Boxerman et al, Neuro Oncol, 2013	RTOG-0625	2007	107										9	
Kreisl et al, J Clin Oncol, 2009	NIH	2006–07	48	1+	No	No			35		3.7	24%	7.2	Macdonald
	NIH (FDA)	2006–07	56	1+	No	Yes			19.6	3.9				WHO
Wen et al, J Clin Oncol, 2010	XL-184		151	1–2	Yes	Yes			15.2		3.7–4.7	22.3–41.7	7.7 to 10.2	RANO
Batchelor et al, J Clin Oncol, 2013	Cediranib	2008–09	131	1	Yes	Yes	12 wk	E	15.3		3.1	16.2	8	Macdonald
de Groot et al, J Clin Oncol, 2011	VEGF Trap	2007–08	42	1	Yes	Yes		M	18		2.8	7.7	9.1	Modified Macdonald
Iwamoto et al, Neuro Oncol, 2010	Pazopanib	2007–08	35	1–3	Yes			M&E	5.9		2.8	3	8.2	Macdonald

Continued

Table 2. *Continued*

	Study Name	Year	No. of Patients	No. Recurr	Multicenter?	Central Review?	Time Post XRT	Meas (M) vs Eval (E)	ORR	Durability	PFS	PFS-6	OS	Criteria for Response
Non-VEGF Drug Studies														
Batchelor et al, J Clin Oncol, 2013	CCNU	2008–09	65	1	Yes	Yes	12 wk	E	8.9		2.7	25	9.8	Macdonald
Wick et al, J Clin Oncol, 2010	Enzastaurin	2006–07	174	1–2	Yes	Yes	12 wk	M	2.9		1.5	11	6.6	Levin w/ confirm.
Wick et al, J Clin Oncol, 2010	CCNU	2006–07	92	1–2	Yes	Yes	12 wk		4.3		1.6	19	7.1	Levin w/ confirm.
Yung et al, Br J Cancer, 2000	TMZ		112	1	Yes				5.4			21	7.5	Macdonald
Yung et al, Br J Cancer, 2000	PCB		113	1	Yes				5.3			8	6	Macdonald
Ballman et al, Neuro Oncol, 2007	NCCTG		345		Yes				NA		1.8	9	5	
Lamborn et al, Neuro Oncol, 2008	NABTC		437	1–3	Yes	No	4 wk	M	7		1.9	16	7	Macdonald
Lamborn et al, Neuro Oncol, 2008	NABTC TMZ		146	1–3	Yes		4 wk	M	NA		3.5	28	9.3	Macdonald
Lamborn, et al, Neuro Oncol, 2008	NABTC No TMZ		291	1–3	Yes		4 wk	M	NA		1.6	9	6.1	Macdonald
Yung et al, J Clin Oncol, 1999	TMZ (AG)		162	1	Yes	Yes		M	35		5.4	46	13.6	Macdonald

Abbreviations: XRT, external beam radiotherapy; PFS-6, 6-mo PFS; ORR, overall response rate; Bev, bevacizumab; WHO, World Health Organization; CCNU, lomustine; TMZ, temozolomide; PCB, procarbazine; NCCTG; North Center Cancer Treatment Group; NABTC, North American Brain Tumor Consortium; AG, anaplastic glioma; VEGF, vascular endothelial growth factor. This summary indicates that RR is never . 10% regardless of the drug (non-VEGF agents only) in multicenter, centrally read, first or second recurrence with the inclusion of a 4–12 weeks postradiotherapy window for study entry.

enhancement. Nonenhancing tumor may become apparent prior to changes in contrast enhancement in an individual patient, but this lag is only ~1 to 2 months on average. There remains significant debate in the field regarding whether this contributes to a substantial difference in PFS, whether it should be evaluated as part of the standard imaging criteria moving forward, and what criteria (improved correlation with OS?) should be used to decide on that issue.

Treatment-Related Changes, the Inflammatory Response, and Pseudoprogression

During cytotoxic or radiation therapy, damage to epithelial cells[66,67] and local tissue inflammation are believed to result in edema and abnormal vessel permeability, which in turn can cause an increase in edema on T2-weighted images and/or new or increased contrast enhancement on MRI or CT.[68–70] This process of treatment-related early increases in contrast enhancement mimicking tumor progression (ie, PsP) can be defined as subacute radiographic changes mimicking tumor progression, but in retrospect is likely associated with tissue damage, remodeling, and/or inflammatory response. Although the precise mechanisms of radiation-induced CNS changes are not completely understood to date and are quite complex,[71] many consider PsP to represent a part of a continuum of treatment-related changes ranging from early subacute inflammation to frank radionecrosis that typically occurs only months after the end of radiotherapy.[68] This hypothesis is supported by a study by Chamberlain et al[72] in which 7 of 15 patients (51%) who went to surgery after recurring prior to 6 months following radiotherapy were shown to have histopathological signs of radiation necrosis with no evidence of tumor. Described as early as the early 1990s by Fiegler et al,[69] Watne et al,[70] and Griebel et al,[73] differentiation of PsP from true tumor progression continues to be one of the major diagnostic challenges in the response assessment of malignant gliomas. It also has implications for treatment at relapse, in which the resolution of PsP may suggest activity of inactive agents.[74]

The true incidence of PsP during standard therapy with radiation/temozolomide is unclear. This limitation is primarily due to the small number of studies on PsP, along with the small number of patients evaluated in these studies. Further, the definition of early progression and PsP are highly variable across studies, and there is an increasing tendency to treat patients at the first signs of radiographic progression, leading to increasing difficulty in verifying whether PsP has indeed occurred. Studies have estimated the occurrence of PsP to range anywhere from 3% to 35% in patients treated with radiochemotherapy[72,74–85] (Table 1).[76] The rate of PsP incidence is believed to increase with increasing radiation dose and timing[86] and the addition of concurrent chemotherapy.[76,77] In one of the first well-designed systematic studies involving PsP, de Wit and colleagues[74] described a 9% incidence of PsP in patients with malignant gliomas treated with radiation only as part of a phase III clinical trial. This is consistent with a large retrospective evaluation by Ruben et al,[87] which noted incidences of radiation necrosis of 2.9%, 5.1%, 9.3%, and 13.3% at 6, 12, 24, and 36 months, respectively, after radiotherapy in 352 glioma patients. However, in a study by Taal et al[77] examining radiation therapy with the addition of temozolomide, the incidence of PsP was estimated at around 21% of patients. This higher proportion of PsP in patients treated with radiochemotherapy was also verified by a large study by Brandes et al[76] involving 103 patients, ~31% of whom showed characteristics of PsP.

Advanced imaging techniques have shown some promise in differentiating PsP from true tumor recurrence in recurrent malignant gliomas. For example, studies have shown that relative cerebral blood volume estimated using dynamic susceptibility contrast perfusion MRI is elevated in tumor progression compared with PsP.[88–91] However, the particular threshold recommended for best stratification varies widely (from 0.71 to 2.6) and appears highly dependent on acquisition parameters, postprocessing, and how the measurements are performed (eg, spherical regions of interest vs contoured enhancing tumor). Additionally, PET imaging of neutral amino acids including [^{11}C-methyl]-methionine (^{11}C-MET), L-1-[^{11}C]-tyrosine (^{11}C-TYR), O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (^{18}F-FET), and 3,4-dihydroxy-6-[^{18}F]-fluoro-L-phenylalanine (^{18}F-FDOPA) has shown the ability to identify treatment-related changes from tumor growth.[92] Although this is promising, large trials with standardized image acquisition are necessary to properly verify the added value of advanced imaging in terms of differentiating PsP from recurrent disease.

Conclusions

In general, changes in contrast enhancement follow change in tumor burden in recurrent glioblastoma, with a few exceptions. First, contrast enhancement is altered by changes in corticosteroid dose. This is mitigated by the RANO requirements for stable steroid dosage at baseline and limiting objective response determination if steroid dose is increased. Second, increased contrast uptake on scans obtained during the first 12 weeks postradiotherapy may reflect only treatment-related changes, reducing the ability for contrast enhancement to serve as an accurate surrogate for tumor burden in this situation. This is mitigated by the RANO requirement that limits enrollment of patients into recurrent studies who have progressive lesions 12 weeks or later following external beam radiotherapy. (Important to note, however, is that several studies have suggested that PsP can occur several months after the end of radiotherapy. Hence, this criteria does not fully mitigate PsP as a potential confounding factor.) Third, the RANO criteria require that durable response be demonstrated on subsequent MRI scans in order to identify true response from a transient permeability effect. Lastly, the use of agents that directly impact vascular permeability (eg, anti–vascular endothelial growth factor therapies) may also reduce the accuracy of contrast enhancement as a surrogate for tumor burden in recurrent glioblastoma. This is currently mitigated by the RANO requirement of nonenhancing tumor evaluation; however, it is conceivable that the overall RR threshold for determining success may need to be adjusted for these agents.

Additionally, there is significant uncertainty regarding the value of nonenhancing tumor assessment via T2/FLAIR images in recurrent glioblastoma. While 30%–40% of tumors initially develop nonenhancing tumor after anti–vascular endothelial growth factor therapies, most tumors subsequently develop enhancing disease that may be more easily measured. Currently, quantitative evaluation of nonenhancing tumor is not performed, leading to concerns regarding the reproducibility of determining

nonenhancing tumor progression with no specific guidelines. Evaluation of nonenhancing tumor remains intuitively meaningful; however, there is little evidence in the current literature to support the added value of nonenhancing tumor assessment.

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Conflict of interest statement. B.M.E. is a consultant for Genentech/Roche and Siemens Healthcare. P.Y.W. is a consultant and on the advisory boards of Genentech/Roche, Sigma Tau, Celldex, Momenta, Vascular Biogenics, and Meditech, is a speaker for Merck, editor-in-chief of *Neuro-Oncology*, and the editor of the Neuro-Oncology section of *Up-to-Date*. M.J.v.d.B is a consultant and a research supporter at Roche and Abbvie, a consultant at Celldex, Amgen, and Actelion, a consultant and on the speakers bureau of Merck Ag, and has received honoraria from *Up-to-Date*. T.F.C. is a consultant and on the advisory board of Genentech/Roche, Tocagen, Lpath, Newgen, Celegene, and Amgen.

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