Posttreatment Evaluation of Central Nervous System Gliomas

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KEYWORDS
- Glioma
- Glioblastoma
- MacDonald criteria
- Response assessment
- Radiation necrosis
- Pseudoresponse
- MR imaging
- Imaging biomarkers

INTRODUCTION

Gliomas represent the most common adult primary brain malignancy with an annual incidence of about 4 to 5 per 100,000.1 The prognosis for glioblastoma in particular remains dismal. Postoperative radiation therapy has been an integral part of the treatment of high-grade gliomas (HGGs) since the 1970s.2 Over the next 2 decades, innovations in computed tomography (CT) and magnetic resonance (MR) imaging improved both brain tumor characterization and radiotherapy techniques.3 However, further attempts using...
alternative methods of radiotherapy failed to improve outcomes. In 2005, Stupp and colleagues showed improved survival with the addition of concurrent and adjuvant temozolomide (TMZ) to radiotherapy and this regimen, combined with maximal surgical resection, has since become the current standard of care for newly diagnosed glioblastoma. In 2009, the antiangiogenic agent bevacizumab received US Food and Drug Administration approval for the treatment of recurrent/progressive glioblastoma. Therapeutic assessment of high-grade gliomas (HGGs) relies on patient survival or, in cases of recurrent tumor, often the radiographic response rate or progression-free survival (PFS). The adoption of chemoradiation with TMZ and antiangiogenic agents into the therapeutic armamentarium has resulted in a reevaluation of conventional contrast-enhanced MR imaging and response criteria.

The most widely used method to assess therapeutic response in HGGs has been to examine changes in contrast-enhancing area, typically on conventional contrast-enhanced MR imaging. Progression on imaging is defined as either a 25% increase in the size of enhancement or new foci of enhancement. This schema is known as the MacDonald criteria. When proposed in 1990, these criteria represented a shift from a subjective evaluation of clinical and radiologic data toward a more objective, image-based methodology.

LIMITATIONS OF THE MACDONALD CRITERIA

Since their introduction, several limitations of the MacDonald criteria have been identified. These limitations include interobserver variability, failure to measure nonenhancing portions of tumor (particularly significant for evaluation of low-grade gliomas [LGGs]), difficulty in measuring tumors with irregular shapes, lack of guidance in the evaluation of multifocal tumors, assessment of progression after gross total resection of all enhancing tumor, and difficulties with measuring enhancing lesions in the walls of cysts/surgical cavities because the cysts/cavities may be incorporated into the tumor size measurement.

The most critical limitation rests on the MacDonald criteria’s reliance on contrast enhancement as a criterion of therapeutic response. Although contrast enhancement is a sensitive marker of blood-brain barrier (BBB) disruption, it is not a specific finding of active tumor, and can be the result of many other processes including treatment-related effect, ischemia, seizure, inflammation, and postoperative changes.

**Table 1**

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>All of the following are required:</td>
</tr>
<tr>
<td></td>
<td>Complete disappearance of all enhancing measurable and nonmeasurable</td>
</tr>
<tr>
<td></td>
<td>disease that is sustained for a minimum of 4 wk</td>
</tr>
<tr>
<td></td>
<td>No new lesions</td>
</tr>
<tr>
<td></td>
<td>No use of corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Stable or improved clinically</td>
</tr>
<tr>
<td>Partial response</td>
<td>All of the following are required:</td>
</tr>
<tr>
<td></td>
<td>≥50% decrease compared with baseline in the sum of products of perpendicular</td>
</tr>
<tr>
<td></td>
<td>diameters of all measurable enhancing lesions sustained for a minimum of</td>
</tr>
<tr>
<td></td>
<td>4 wk</td>
</tr>
<tr>
<td></td>
<td>No new lesion</td>
</tr>
<tr>
<td></td>
<td>Stable or reduced corticosteroid dose</td>
</tr>
<tr>
<td></td>
<td>Stable or improved clinically</td>
</tr>
<tr>
<td>Stable disease</td>
<td>All of the following are required:</td>
</tr>
<tr>
<td></td>
<td>Does not qualify for complete response, partial response, or progression</td>
</tr>
<tr>
<td></td>
<td>Stable clinically</td>
</tr>
<tr>
<td>Progression</td>
<td>Any of the following:</td>
</tr>
<tr>
<td></td>
<td>≥25% increase in sum of the products of perpendicular diameters of enhancing</td>
</tr>
<tr>
<td></td>
<td>lesions</td>
</tr>
<tr>
<td></td>
<td>Any new lesion</td>
</tr>
<tr>
<td></td>
<td>Clinical deterioration</td>
</tr>
</tbody>
</table>

addition, corticosteroid dosage can complicate assessment in that this can physiologically decrease the amount of contrast enhancement.\textsuperscript{17,18} In particular, the recent recognition of the entities of pseudoprogression (PsP) and pseudoresponse (PsR) associated with chemoradiation with temozolomide and antiangiogenic agents, respectively, has emphasized the need to reevaluate traditional imaging criteria of treatment response.

THERAPEUTIC EVALUATION AFTER CHEMORADIATION WITH TMZ IN HGG-RADIATION NECROSIS AND PSP

Radiation necrosis (RN), and the recently recognized PsP, are forms of treatment-related enhancement mimicking tumor progression that can occur following chemoradiation with TMZ. They pose significant problems for treating physicians because they are essentially indistinguishable from tumor progression using conventional MR imaging methods (Fig. 1).\textsuperscript{12,16,19,20} Further complicating matters is the possibility to have both coexisting tumor and therapy-induced necrosis in the same enhancing lesion.\textsuperscript{21}

**RN**

Radiation-induced injury represents not a single instantaneous event but a dynamic, complex process that develops over time, with a significant amount of tissue damage occurring hours to days after the initial injury.\textsuperscript{22} These processes can include vascular injury with vasogenic edema, glial and white matter damage, effects on the fibrinolytic enzyme system, and immune mechanisms.\textsuperscript{12} Radiation effects are usually divided into acute, subacute, and late effects. Vasodilatation, damage to the BBB, and edema are thought to underlie both acute and subacute types of radiation injury.\textsuperscript{23}

Late radiation effects include RN as well as other processes such as leukoencephalopathy, vascular lesions such as moyamoya syndrome and lacunar infarcts, parenchymal calcifications, and enhancing white matter lesions.\textsuperscript{24} RN typically occurs months to years following therapy and may be progressive and irreversible.\textsuperscript{12,25–27} The incidence of RN is unclear, but may be as high as 24%.\textsuperscript{28} Both the volume of brain irradiated as well as the radiation dose delivered are important factors, particularly when doses are higher than 65 Gy in fractions of 1.8 to 2.0 Gy.\textsuperscript{24} In RN, blood vessels show fibrinoid necrosis with surrounding perivascular parenchymal coagulative necrosis.\textsuperscript{12,25,26} Endothelial injury from radiation results in fibrinoid necrosis of small vessels, endothelial thickening, hyalinization, and vascular thrombosis. In contrast, recurrent tumor shows vascular proliferation and angiogenesis without vascular luminal obliteration.\textsuperscript{21} Patterns described as “soap bubble” or “Swiss cheese” have been described on conventional contrast-enhanced MR imaging in RN; however, these appearances cannot reliably differentiate between tumor recurrence and RN.\textsuperscript{12,29,30} Advanced MR imaging techniques (discussed later) have been examined to better characterize RN. However, no technique is widely accepted and this remains an active area of research.

The treatment of RN ranges from observation to medical and surgical therapy. Medical treatment incorporates corticosteroids because of their ability to counteract BBB disruption from radiation-induced vascular endothelial injury.\textsuperscript{29} Because there seems to be increased vascular endothelial growth factor (VEGF) and microvascular permeability in RN, there is some evidence

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Fig. 1. PsP. Axial T1 contrast-enhanced MR imaging (A) after surgery, (B) 2 months after chemoradiation showing increased enhancement in the right temporo-occipital region, and (C) a significant decrease in enhancement is seen 2 months later without a change in therapy.
to suggest that RN may be responsive to bevaci- 
zumab treatment. Hyperbaric oxygen treatment 
has also been explored as a treatment option 
because it may stimulate angiogenesis and restore 
the vascular supply injured by radiation.29 Med- 
cially intractable cases may require surgical resec- 
tion if the lesion is surgically accessible and will not 
result in significantly increased morbidity.

PsP

While PsP may occur following radiotherapy 
alone, there has been a greater focus on PsP since 
the recent adoption of chemoradiation with TMZ 
as the standard of care for glioblastoma.9 Al- 
though PsP currently lacks a strict definition, in 
general it refers to an increase in contrast en- 
hancement within the first 3 to 6 months after che- 
moradiation that is the result of treatment-induced 
changes rather than true early progression 
(TEP).19,27 The time period of its occurrence is 
earlier than after radiotherapy alone and, as 
such, it may represent a mild, self-limiting variant 
of RN.19 However, there is evidence to suggest 
that PsP and RN are distinct entities with PsP rep- 
senting a combination of treatment effect on 
residual tumor cells and disruption of the BBB, 
whereas RN represents radiation damage to the 
peritumoral white matter.29 As such, some have 
argued that the term PsP should replace the 
outdated term early radionecrosis.31,32

Without a change in therapy, PsP may improve 
or disappear, although in some cases it may 
remain persistent. Although most patients with 
PsP are asymptomatic, as many as one-third 
may need surgery, increased steroids, or possibly 
antiangiogenic therapy because of symptoms 
from mass effect.33

PsP seems to be a common occurrence, with 
incidence estimates of approximately 20% to 30% 
and seems to be more frequent in patients with 
a methylated O6-methylguanine–DNA methyltrans- 
f erase (MGMT) promoter.11,19,34 More recent anal- 
yses seem to support this incidence estimate.35,36 
However, because of varying definitions, uncer- 
tainities in image interpretation, as well as variations 
in the quality and design of studies, the true inci- 
dence of PsP is still not clear.32,37 Clarke and 
Chang27 estimate that about half of all patients 
with glioblastoma develop worrisome contrast- 
 enhancing lesions on follow-up MR imaging after 
chemoradiation and that many are the result of 
PsP rather than TEP. In 2011, a retrospective study 
of the first postradiotherapy scans in 321 patients 
with glioblastoma treated with chemoradiation 
with TMZ was reported from a major brain tumor 
referral center.20 The investigators reported that 
this was, to date, the largest cohort of patients 
examined to determine whether conventional MR 
imaging could distinguish PsP from TEP. Suspi- 
cious new or enlarging enhancing lesions were 
found in 93 patients. Of these, 30 patients (32.3%) 
were determined to have PsP (confirmed patholog- 
ically in 6 cases). This incidence is consistent with 
several prior reports.34,38–40 Eleven conventional 
MR imaging signs were evaluated and only sube-
 pendymal enhancement could predict TEP with 
38.1% sensitivity, 93.3% specificity, and 41.8% 
negative predictive value. The remaining 10 signs 
were not predictive and there was not a sign with 
a sufficiently high negative predictive value for 
PsP. As such, the investigators concluded that 
conventional MR imaging signs have limited useful- 
ness to diagnose PsP and that an alternative 
imaging biomarker is needed.

PsP and MGMT promoter methylation status

The MGMT enzyme is a DNA repair protein that 
provides resistance to the alkylating drug TMZ by 
removing alkyl groups (such as those placed by 
chemotherapeutic alkylating agents) from the O6 
position of guanine.41 Epigenetic silencing of the 
MGMT gene by promoter methylation causes 
a loss of its expression, thus inhibiting the DNA 
repair mechanism and resulting in chemotherapy-
 induced cytotoxicity and apoptosis.41–43 The 
status of the MGMT promoter represents a poten- 
tially useful marker to complement imaging 
because PsP is more frequently seen in cases 
with a methylated promoter than in those with an 
unmethylated promoter.34 Numerous studies 
have also shown that methylated MGMT promoter 
status is associated with improved survival with 
TMZ treatment.24,34,41,44

Clinical implications of PsP

The inability of conventional MR imaging methods 
to differentiate PsP from TEP limits the validity of 
PFS as a primary end point (unless pathologic 
confirmation of TEP is made) and confounds the 
design of salvage clinical trials.9,11,27 If a patient 
does not respond to initial therapy with TMZ then 
treatment should be changed quickly, often into 
a clinical trial. However, if a patient has developed 
PsP, then altering management prematurely termi- 
nates an effective therapy, and, because PsP 
tends to improve on its own, can result in a falsely 
high response rate and PFS as well as lending a 
false attribution of efficacy to the new agent.

ANTIANGIOGENIC THERAPY AND PSR

Cancers grow beyond their initial local blood 
supply by developing deregulated angiogenesis, 
which allows tumors to acquire an abnormal
vasculature composed of dilated, tortuous, and hyperpermeable vessels.\textsuperscript{45} This results in irregular, inefficient perfusion of tumors, and ultimately hypoxia and necrosis.\textsuperscript{46} At first, the mechanism of antiangiogenic agents against tumors was thought to be via reduction or elimination of tumor vasculature, effectively starving the tumor.\textsuperscript{45,47–49}

However, clinical studies have shown an absence of a clear dose-response relationship as well as a lack of benefit without concomitant cytotoxic therapy. In addition, the resulting hypoxia caused by elimination of blood vessels should result in decreased effectiveness of chemotherapy. However, this has also not been seen in clinical studies.\textsuperscript{45,47} As a result, an alternative mechanism termed vascular normalization has been proposed. In vascular normalization, antiangiogenic agents cause a decrease in vessel diameter and permeability as well as thinning of the abnormally thick basement membrane.\textsuperscript{50,51}

Treatment with antiangiogenic agents directed against VEGF, such as bevacizumab, can cause a rapid decrease in enhancement caused, at least in part, by a decrease in microvascular permeability secondary to vascular normalization, rather than a true antitumoral effect.\textsuperscript{52} This process has become known as PsR.\textsuperscript{19} A decrease in contrast enhancement has been documented as early as 24 hours following a single dose of the pan-VEGF tyrosine kinase inhibitor cediranib, and discontinuing the drug leads to a rapid reversal in enhancement, which lends credence to this notion.\textsuperscript{48}

Some patients treated with angiogenic agents may also experience nonenhancing tumor progression manifesting as increasing T2/FLAIR signal abnormality (Fig. 2).\textsuperscript{53,54} Antiangiogenesis therapy may stimulate tumor progression through vascular cooption and develop an invasive, nonenhancing phenotype.\textsuperscript{55–57} This process could help explain the large disparity between high response rates in recurrent glioblastoma and modest, if any, survival benefit.\textsuperscript{48,53}

Regardless of whether there is a PsR or true antitumoral response, vascular normalization with an associated decrease in vasogenic edema may result in decreased morbidity and steroid usage.\textsuperscript{19,48}

**Clinical Implications of PsR**

There are currently no validated predictive biomarkers for any antiangiogenic agent in cancer.\textsuperscript{58} Radiologic responses in patients being treated with antiangiogenic agents must be viewed with skepticism. As with PsP, the possibility of PsR limits the usefulness of PFS as a primary end point in clinical trials.\textsuperscript{5} Furthermore, changes in T2/FLAIR signal abnormality have not been explicitly addressed by the traditional MacDonald criteria and should be addressed in updated criteria.

**RANO CRITERIA**

The Response Assessment in Neuro-Oncology (RANO) Working Group is a multidisciplinary, international collaborative effort whose goal is to provide expert consensus opinion regarding the development of new standardized response criteria for brain tumor clinical trials.\textsuperscript{10} In 2010, given concerns raised by PsP and PsR, the RANO Working Group attempted to address some of the limitations of the MacDonald criteria.\textsuperscript{11}

![Fig. 2. PsR. Recurrent HGG on axial T1 contrast-enhanced MR imaging (A) and axial FLAIR (B). The patient was treated with a combination of bevacizumab and VP-16, but clinically worsened significantly despite treatment. Follow-up imaging 2 months later: axial T1 contrast-enhanced MR imaging (C) and axial FLAIR (D) show decreased enhancement but marked progression of infiltrative FLAIR abnormalities, suggesting nonenhancing tumor progression. (Reproduced from Clarke JL, Chang S. Pseudoprogression and pseudoresponse: challenges in brain tumor imaging. Curr Neurol Neurosci Rep 2009;9(3):241–6; with permission.)](image-url)
Despite many advances in functional MR imaging techniques (discussed later), there is currently insufficient evidence to incorporate them into routine response criteria for use in clinical trials/practice and, therefore, conventional follow-up contrast-enhanced MR imaging remains the standard-of-practice imaging technique. As a result, the determination of PsP by MR imaging alone is inherently a retrospective process. Furthermore, other end points such as quality-of-life measures and neuropsychological testing may be incorporated into response criteria as these metrics are developed and validated.

A summary of the proposed RANO response criteria is given in Tables 2–4.

PsP

Because of the possibility of PsP, the RANO recommendations state that patients within 12 weeks of the completion of chemoradiation should be excluded from clinical trials for recurrent glioma unless TEP is shown as new enhancement outside of the radiation field or there is unequivocal evidence of tumor at tissue sampling (see Table 2). If patients remain clinically stable and/or are thought to have PsP based on functional imaging, then therapy should remain unchanged. Pope and Hessel raised concern that these new recommendations may exclude the most malignant tumors that progress rapidly, and that, because these patients were not excluded from many prior clinical trials, a bias may be introduced when the therapeutic efficacy of a new drug is compared with historical controls. Furthermore, the RANO guidelines do not account for the possibility of PsP occurring at time later than 3 months. The risk of excluding TEP must be considered against the risk of including PsP in clinical trials.

Table 2
RANO criteria for determining first progression based on time from initial chemoradiation

<table>
<thead>
<tr>
<th>First Progression</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Progressive disease &lt;12 wk after completion of chemoradiation</strong></td>
<td>Progression can only be defined using imaging if:</td>
</tr>
<tr>
<td></td>
<td>There is new enhancement outside the radiation field (beyond the</td>
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<td></td>
<td>high-dose region or 80% isodose line) or if there is unequivocal</td>
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<td></td>
<td>evidence of viable tumor on histopathologic sampling (eg, solid</td>
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<tr>
<td></td>
<td>tumor areas, ie, greater than 70% tumor cell nuclei in areas; high</td>
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<tr>
<td></td>
<td>or progressive increase in MIB-1 proliferation index compared</td>
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<tr>
<td></td>
<td>with prior biopsy; or evidence for histologic progression or</td>
</tr>
<tr>
<td></td>
<td>increased anaplasia in tumor)</td>
</tr>
<tr>
<td></td>
<td>Because of the difficulty of differentiating TEP from PsP, clinical</td>
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<tr>
<td></td>
<td>deterioration alone, in the absence of histologic or radiographic</td>
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<tr>
<td></td>
<td>confirmation of progression, is not sufficient for definition of</td>
</tr>
<tr>
<td></td>
<td>progressive disease in the first 12 wk after completion of</td>
</tr>
<tr>
<td></td>
<td>concurrent chemoradiation</td>
</tr>
<tr>
<td><strong>Progressive disease ≥12 wk after completion ofchemoradiation</strong></td>
<td>1. New contrast-enhancing lesion outside radiation field on</td>
</tr>
<tr>
<td></td>
<td>decreasing, stable, or increasing corticosteroid doses</td>
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<tr>
<td></td>
<td>2. Increase by ≥25% in the sum of the products of perpendicular</td>
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<tr>
<td></td>
<td>diameters between the first postradiotherapy scan, or a subsequent</td>
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<tr>
<td></td>
<td>scan with smaller tumor size, and the scan at 12 wk or later on</td>
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<tr>
<td></td>
<td>stable or increasing corticosteroid doses</td>
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<tr>
<td></td>
<td>3. Clinical deterioration not caused by concurrent medication or</td>
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<tr>
<td></td>
<td>comorbid conditions is sufficient to declare progression on</td>
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<tr>
<td></td>
<td>current treatment but not for entry onto a clinical trial for tumor</td>
</tr>
<tr>
<td></td>
<td>recurrence</td>
</tr>
<tr>
<td></td>
<td>4. For patients receiving antiangiogenic therapy, significant</td>
</tr>
<tr>
<td></td>
<td>increase in nonenhancing T2/FLAIR lesion may also be</td>
</tr>
<tr>
<td></td>
<td>considered progressive disease. The increase must have occurred</td>
</tr>
<tr>
<td></td>
<td>while on stable or increasing corticosteroid doses compared with</td>
</tr>
<tr>
<td></td>
<td>baseline scan or best response following initiation of therapy</td>
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<tr>
<td></td>
<td>and not be a result of comorbid events (such as radiation therapy</td>
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<tr>
<td></td>
<td>effects, demyelination, ischemic injury, infection, seizures,</td>
</tr>
<tr>
<td></td>
<td>postoperative changes, or other treatment effects)</td>
</tr>
</tbody>
</table>

Given the possibility of PsR, the RANO Working Group has issued new recommendations for patients with recurrent glioblastoma on antiangiogenic therapy (see Tables 2–4). These recommendations now state that disease progression can be manifested by a significant increase in the amount

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>All of the following are required:</td>
</tr>
<tr>
<td></td>
<td>Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for a minimum of 4 wk</td>
</tr>
<tr>
<td></td>
<td>No new lesions</td>
</tr>
<tr>
<td></td>
<td>Nonenhancing (T2/FLAIR) lesions stable or improved</td>
</tr>
<tr>
<td></td>
<td>No use of corticosteroids (or on physiologic replacement doses only)</td>
</tr>
<tr>
<td></td>
<td>Clinically stable or improved</td>
</tr>
<tr>
<td></td>
<td>Those with nonmeasurable disease only cannot have a complete response. The best possible response is stable disease</td>
</tr>
<tr>
<td>Partial response</td>
<td>All of the following are required:</td>
</tr>
<tr>
<td></td>
<td>≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for a minimum of 4 wk</td>
</tr>
<tr>
<td></td>
<td>No progression of nonmeasurable disease</td>
</tr>
<tr>
<td></td>
<td>No new lesions</td>
</tr>
<tr>
<td></td>
<td>Nonenhancing (T2/FLAIR) lesions stable or improved on same or lower dose of corticosteroids compared with baseline scan</td>
</tr>
<tr>
<td></td>
<td>Corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan</td>
</tr>
<tr>
<td></td>
<td>Clinically stable or improved.</td>
</tr>
<tr>
<td></td>
<td>Those with nonmeasurable disease only cannot have a partial response. The best possible response is stable disease</td>
</tr>
<tr>
<td>Stable disease</td>
<td>All of the following are required:</td>
</tr>
<tr>
<td></td>
<td>Does not qualify for complete response, partial response, or progression</td>
</tr>
<tr>
<td></td>
<td>Nonenhancing (T2/FLAIR) lesions stable on same or lower dose of corticosteroids compared with baseline scan</td>
</tr>
<tr>
<td></td>
<td>If the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on imaging, and subsequent imaging follow-up shows that this increase in corticosteroid dose was needed because of disease progression, the last scan thought to show stable disease is the scan obtained when the corticosteroid dose was equivalent to the baseline dose</td>
</tr>
<tr>
<td>Progression</td>
<td>Any of the following:</td>
</tr>
<tr>
<td></td>
<td>≥25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response</td>
</tr>
<tr>
<td></td>
<td>Stable or increasing corticosteroids doses&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Significant increase in nonenhancing T2/FLAIR lesion on stable or increasing corticosteroids doses&lt;sup&gt;a&lt;/sup&gt; compared with baseline scan or best response after initiation of therapy&lt;sup&gt;a&lt;/sup&gt; that is not the result of comorbid events such as radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects</td>
</tr>
<tr>
<td></td>
<td>Any new lesion</td>
</tr>
<tr>
<td></td>
<td>Obvious clinical deterioration with no causes other than the tumor (such as seizures, adverse effects of medications, therapeutic complications, cerebrovascular events, infection), or corticosteroid dose changes</td>
</tr>
<tr>
<td></td>
<td>Failure to return for follow-up evaluation because of deteriorating condition or death</td>
</tr>
<tr>
<td></td>
<td>Obvious progression of nonmeasurable disease</td>
</tr>
</tbody>
</table>

<sup>a</sup> Stable corticosteroid doses include patients not taking corticosteroids.

of nonenhancing T2W/FLAIR signal while the patient is on stable/increasing corticosteroid dose compared with the baseline scan or best response after the start of therapy.11 For this reason, the RANO criteria have been referred to as MacDonald plus FLAIR.59 However, these criteria contain some ambiguity because the definition of a significant increase in T2W/FLAIR signal was not explicitly defined.59 Another difficulty rests in the recommendation that nonenhancing T2/FLAIR tumor progression must be differentiated from radiation effects, demyelination, infection, decreased corticosteroid dosing, ischemic injury, other treatment effects, and seizures. Imaging findings that would suggest nonenhancing tumor include mass effect, infiltration of the cortical ribbon, and location beyond the radiation field. The RANO criteria also recommend retrospective backdating of the time when nonenhancing progression was first suspected, and although this could increase sensitivity for progression, there is concern that comparison with historical controls could again be difficult.59 Discordant interpretations can be common in antiangiogenic therapy drug trials and inconsistent progression dating is an issue. Pope and Hessel59 advocate that making note of suspicious regions of possible nonenhancing progression that are retrospectively confirmed as tumor progression could decrease the discrepancy or adjudication rate.

Other concerns regarding the RANO criteria include issues relating to corticosteroid dosage and lack of validated measures of neurologic function.11,59 Regarding corticosteroid dosing, what qualifies as a significant change in steroid dose, over what time period before imaging should steroid status be considered relevant, and whether total daily dose or average daily dose should be considered are also unclear. Both the MacDonald and RANO criteria also consider neurologic function in their assessment criteria. However, a precise definition currently cannot be provided given the lack of validated measures of neurologic function. In RANO, whether a patient is suffering from neurologic deterioration is left to the discretion of the treating physician. They do recommend consideration of a decrease in Karnofsky performance score, Eastern Cooperative Oncology Group performance status or World Health Organization performance score to determine clinical decline.

**SURGICALLY DELIVERED THERAPIES**

The Surgery Working Group of RANO recently proposed new guidelines regarding response/progression measures following surgically delivered therapies.10 A summary of their recommendations is given in Box 1.

1. **Imaging after surgery for both HGG and LGG.** Because improved outcomes are seen following maximal resection of tumor, recommendations have been set forth regarding the timing of baseline postoperative contrast-enhanced MR imaging to better assess completeness of resection. As was stated by Wen and colleagues,11 the recent guidelines stressed that, for HGGs, baseline postoperative MR imaging should occur ideally within 24 to 48 hours after surgery, and no later than 72 hours after surgery, because increased enhancement can develop in the wall of the resection cavity 48 to 72 hours after surgery. This postsurgical enhancement can be mistaken for residual or new enhancing tumor. LGGs typically do not

### Table 4
Summary of proposed RANO response criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhancing disease</td>
<td>None</td>
<td>≥50% ↓</td>
<td>&lt;50% ↓but &lt;25% ↑</td>
<td>&gt;25% ↑ a</td>
</tr>
<tr>
<td>T2/FLAIR</td>
<td>Stable or ↓</td>
<td>Stable or ↓</td>
<td>Stable or ↓</td>
<td>↑ a</td>
</tr>
<tr>
<td>New lesion</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Present a</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>None</td>
<td>Stable or ↓</td>
<td>Stable or ↓</td>
<td>NA b</td>
</tr>
<tr>
<td>Clinical status</td>
<td>Stable or ↑</td>
<td>Stable or ↑</td>
<td>Stable or ↑</td>
<td>↑ a</td>
</tr>
<tr>
<td>Requirement for response</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>Any a</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease.

a Progression occurs when criterion present.
b Corticosteroid dose increase alone is not considered in determining disease progression when there is no persistent clinical deterioration.

show significant contrast enhancement and so a delay of up to 12 weeks for postoperative MR imaging may be needed to differentiate nonenhancing tumor from edema. This study should be compared with the appearance of T2/FLAIR hyperintensity on the preoperative MR imaging. For both HGG and LGGs, intraoperative assessment of completeness of resection is thought to be an unreliable measure compared with postoperative MR imaging. The importance of DWI to document possible perioperative ischemia caused by microvascular compromise at the surgical resection margins was emphasized. These regions may go on to show contrast enhancement on follow-up imaging that could be misinterpreted as recurrent tumor, and so comparison with the postoperative DWI images may be critical.

2. Updated terminology for completeness of surgical resection. Traditional terminology to describe completeness of surgical resection included descriptors such as gross total resection, near-total resection, subtotal resection, and partial resection. These terms were thought to be subjectively determined and inconsistently used depending on glioma grade, so a set of alternative terms has been suggested. This updated terminology may allow improved design of prospective clinical trials that use a specific extent of tumor debulking for entry and for retrospective studies examining impacts of surgical resection on clinical outcome (see Box 1).

3. To determine disease progression, completeness of surgical resection and use of local therapies, if applicable, should be taken into consideration.

4. Clinical trials should allow retrospective evaluation of disease progression.

5. Blinded central review should be considered for use in clinical trials.

6. Volumetric assessment of tumor size and response should be used as these techniques become more widely available.


<table>
<thead>
<tr>
<th>Box 1</th>
<th>Summary of RANO surgery task force recommendations</th>
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<tbody>
<tr>
<td>1. Imaging after surgery for HGG and LGG</td>
<td></td>
</tr>
<tr>
<td>a. Should be performed within 72 hours after surgery to determine extent of resection of enhancing tumors (eg, HGG)</td>
<td></td>
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<tr>
<td>b. For nonenhancing tumors (eg, LGGs), final determination of extent of resection may require a delay of up to 12 weeks to allow for edema resolution</td>
<td></td>
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<tr>
<td>c. Diffusion-weighted imaging (DWI) should be used to determine regions of perioperative ischemia that could subsequently develop nonspecific areas of enhancement</td>
<td></td>
</tr>
<tr>
<td>2. Updated terminology for completeness of surgical resection</td>
<td></td>
</tr>
<tr>
<td>a. When enhancing tumor is present, removal of all enhancing tissue should be called complete resection of enhancing tumor rather than gross total resection</td>
<td></td>
</tr>
<tr>
<td>b. Resection of all enhancing tumor (if present) and all nonenhancing tumor tissue (ie, T2/FLAIR hyperintensity) should be called complete resection of detectable tumor</td>
<td></td>
</tr>
<tr>
<td>c. Partial resections can also be referred to as partial resection of enhancing tumor or partial resection of detectable tumor</td>
<td></td>
</tr>
<tr>
<td>3. To determine disease progression, completeness of surgical resection and use of local therapies, if applicable, should be taken into consideration</td>
<td></td>
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<tr>
<td>4. Clinical trials should allow retrospective evaluation of disease progression</td>
<td></td>
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<tr>
<td>5. Blinded central review should be considered for use in clinical trials</td>
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</tr>
<tr>
<td>6. Volumetric assessment of tumor size and response should be used as these techniques become more widely available</td>
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Posttreatment Evaluation of CNS Gliomas
biopsy remains an option, there is a concern regarding its ability to determine prognosis in treated glioblastoma. However, tissue sampling may be needed if a clinical trial uses an entry criterion or end point of tumor progression.

4. **Clinical trials should allow retrospective evaluation of disease progression.** Given that there are no validated imaging methods to distinguish tumor progression from treatment effects (i.e., PsP), serial follow-up conventional MR imaging should be allowed to determine whether there is disease progression. An indeterminate designation may be used if tumor progression is suspected but treatment effects still cannot be excluded. If it is borne out that the patient does have tumor progression, then the date of an indeterminate designation is deemed to be the true date of progression.

5. **Use of blinded central review in clinical trials.** PFS is often used as a surrogate for overall survival (OS) in clinical trials. PFS has the advantage that it can shorten trial duration and is not affected by subsequent salvage treatment. However, its reliance on subjective interpretation of MR imaging studies can be problematic, whereas OS can be assessed objectively. The incorporation of a blinded central review of MR imaging studies into the design of a clinical trial should be considered to address this issue.

6. **Volumetric assessment of tumor size and response.** Given concerns about current nonvolumetric measuring techniques such as poor accuracy and reliability, lack of comparability between studies given different slice positioning, and difficulty in documenting how measurements were made, consideration should be given to the use of volumetric analysis of whole tumor volumes. There is preliminary evidence to suggest that volumetric analysis is effective and this may become realized as the requisite software becomes more widely available. Volumetric techniques may then be applied toward routine assessment of residual enhancing or nonenhancing tumor volume.

**LGGs**

Although HGGs are the primary focus of this article, a brief overview of response criteria for LGGs is also given. Recent RANO guidelines have also been published regarding assessment criteria in trials of LGG (Table 5). The MacDonald criteria are not well suited for use with LGGs because these tumors generally show little to no enhancement. Although LGGs show a less aggressive clinical course than HGGs, most ultimately relapse as HGG, with poor outcome. Conventional contrast-enhanced CT or MR imaging seems to be insensitive to detect early malignant degeneration. Low or even absent radiographic responses have been seen in several LGG trials despite clinical benefit, including a reduction in seizures and prolonged disease control. The posttherapeutic imaging evaluation of LGG is difficult because T2-weighted signal abnormalities following successful therapy cannot be differentiated from tumor. As a result, the category of minor response has been created. Further confusing evaluation is the possibility of radiation-induced leukoencephalopathy, which also shows T2-weighted signal abnormalities. The use of PFS as primary end point in clinical trials is problematic in LGG because of the slow growth rate of LGG and the rare radiological true responses despite favorable response to therapy. At the same time, the use of OS as an end point presents logistical challenges and is also prone to the effect of other noninvestigational salvage treatment at recurrence. Regardless of whether PFS or OS is used as a primary end point, RANO also recommends that ancillary measures such as measures of cognition, seizure activity, symptom severity and burden, quality of life, and neurologic deterioration be considered. Response to radiotherapy should be performed with MR imaging 3 to 4 months following the end of radiotherapy given the possibility of PsP in LGG.

**ADVANCED IMAGING TECHNIQUES IN THE POSTTREATMENT SETTING**

Advanced imaging techniques such as perfusion (dynamic susceptibility contrast and arterial spin labeling [ASL]) MR imaging, permeability (dynamic contrast-enhanced) MR imaging, diffusion MR imaging, MR spectroscopy, and positron emission tomography (PET) are active areas of clinical research and have shown promise when used to assess therapy, predict survival time, and differentiate tumor recurrence from treatment-induced changes. However, these methods require further rigorous clinical validation before they can be incorporated into routine imaging assessment of gliomas. An overview of some recent developments is provided.

**Perfusion MR Imaging**

Dynamic susceptibility contrast-enhanced (DSC) MR perfusion, sometimes called perfusion-weighted or bolus tracking MR imaging, is a technique in which the first-pass of a bolus of a gadolinium-based contrast agent (GBCA)
through the brain parenchyma is monitored by a series of T2-weighted or T2*-weighted MR images.\textsuperscript{67} Relative cerebral blood volume (rCBV) is the most robust and commonly used perfusion metric derived from DSC MR imaging and seems to be the most useful parameter in patients with brain tumors.\textsuperscript{68,69} rCBV seems to be increased in tumor progression secondary to increased vascular proliferation, whereas, in RN, rCBV seems to be decreased because of extensive fibrinoid necrosis, vascular dilatation, and endothelial injury (Fig. 3).\textsuperscript{21,68,70–76}

In addition to finding higher rCBV in recurrent glioblastoma compared with RN, Barajas and colleagues\textsuperscript{70} also found that peak height (PH), defined as difference in precontrast T2*-weighted signal intensity and minimum T2*-weighted signal intensity, was also higher in recurrent glioblastoma than RN. Furthermore, recurrent glioblastoma also showed lower relative percentage signal recovery (PSR), a reflection of increased vascular permeability, although a large degree of overlap was seen between the 2 groups, making this a less robust predictor of progression of tumor. A recent

<table>
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<th>Table 5</th>
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<td>RANO response criteria for LGG</td>
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<table>
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<tr>
<th>Response</th>
<th>Criteria</th>
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<tr>
<td>Complete response</td>
<td>All of the following are required compared with the baseline scan: Complete disappearance of the lesion on T2/FLAIR imaging (if enhancement had been present, it must have completely resolved) No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement Patients must not be taking corticosteroids or only on physiologic replacement doses Patients should be stable or improved clinically</td>
</tr>
<tr>
<td>Partial response</td>
<td>All of the following are required compared with the baseline scan: ( \geq 50% ) decrease in the product of perpendicular diameters of the lesion on T2/FLAIR imaging sustained for a minimum of 4 wk compared with baseline No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement Patients should be on a corticosteroid dose that is not greater than the dose at time of baseline scan, and should be stable or improved clinically</td>
</tr>
<tr>
<td>Minor response</td>
<td>Requires the following criteria compared with baseline: Decrease of the area of nonenhancing lesion on T2/FLAIR imaging between 25% and 50% compared with baseline No new lesions, no new T2/FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically</td>
</tr>
<tr>
<td>Stable disease</td>
<td>If the criteria do not qualify for complete, partial, or minor response or progression, then stable disease is present. It requires: Stable area of nonenhancing abnormalities on T2/FLAIR imaging No new lesions, no new T2/FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement Patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically</td>
</tr>
<tr>
<td>Progression</td>
<td>Defined by any of the following: Development of new lesions or increased enhancement (imaging evidence of malignant transformation) A 25% increase of the T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not caused by radiation effect or comorbid events Clear clinical deterioration not from causes other than the tumor, or decrease in corticosteroid dose Failure to return for follow-up evaluation because of deteriorating condition or death, unless caused by documented nonrelated causes</td>
</tr>
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study addressed the confounding effects of GBCA leakage in rCBV determination and found that a 0.1 mmol/kg preload dose of GBCA with 6 minutes of incubation time along with baseline subtraction techniques seemed to improve the diagnostic accuracy of rCBV to differentiate recurrent glioma from radiation effect. The use of ASL perfusion MR imaging in the posttherapeutic setting is emerging and a recent pilot study using ASL found that it may be more accurate than DSC MR imaging to distinguish RN from progressive HGG, especially in areas of mixed radiation necrosis in which leakage of GBCA could result in underestimation of rCBV.

Like in the case of RN, DSC MR imaging seems to be a promising technique to distinguish PsP from TEP, with several recent studies showing lower rCBV in PsP compared with TEP. A recent prospective study by Kong and colleagues examined 90 patients with glioblastoma who were treated with chemoradiation. They found new or enlarging contrast-enhancing lesions in 59 of these patients, with 26 and 33 patients subsequently being classified as PsP and TEP, respectively (based on either imaging follow-up or histopathology). Using the maximum rCBV ratio based on color overlay maps, there was a significantly lower mean rCBV in patients with PsP versus TEP with an rCBV ratio greater than 1.47 demonstrating a sensitivity of 81.5% and specificity of 77.8%. The MGMT promoter methylation was also examined and the unmethylated group had a significant difference in the mean rCBV between PsP and TEP, whereas those with a methylated promoter did not. The investigators postulated that this difference could be a reflection of a higher probability of TEP in tumors with an unmethylated promoter and, if a patient has an unmethylated promoter, that rCBV may be more useful to determine TEP, which suggests that correlation with MGMT promoter status could improve the validity of the rCBV value. A retrospective study in 36 patients with glioblastoma by Mangla and colleagues reported that, at 1 month after chemoradiation with TMZ, a greater than 5% increase in rCBV seemed to be a strong predictor of less than 1-year survival. In 53% of their patients, an increase in contrast enhancement was noted on posttreatment MR imaging and 37% of these patients were determined to have PsP based on follow-up imaging. The patients with PsP had a mean decrease in rCBV of 41%, whereas those with TEP had a mean increase in rCBV of 12%. To differentiate TEP from PsP, receiver operating characteristic (ROC) analysis was used in which percent change in rCBV greater than 0% or 0% or lower was used. This analysis showed an area under the ROC curve of 0.85 with 76.9% sensitivity and 85.7% specificity.

A 2012 retrospective study by Baek and colleagues of 135 patients with newly diagnosed glioblastomas who were treated with chemoradiation found 79 patients with new or enlarging contrast-enhancing lesions concerning for TEP versus PsP. They found that changes in the shape (percent change of skewness and kurtosis) of normalized rCBV histograms between the first and second postchemoradiation MR imaging may be a potential technique to differentiate TEP from PsP. Four categories were created based on whether the histograms derived from a region of interest (ROI) of the contrast-enhancing lesion showed negative or positive skewness and

Fig. 3. RN. (A) Axial postcontrast T1 MR imaging shows an enhancing mass adjacent to the surgical bed and an axial T2-weighted image (B) shows a significant amount of edema with mass effect. (C) Gradient-echo axial DSC MR imaging with rCBV color overlay map shows reduced perfusion throughout the lesion. Surgical resection showed this lesion to be RN. (Reproduced from Lacerda S, Law M. Magnetic resonance perfusion and permeability imaging in brain tumors. Neuroimaging Clin N Am 2009;19(4):527–57; with permission.)
leptokurtic or platykurtic kurtosis. The histogram pattern of normalized rCBV represented the largest area under the ROC curve of 0.934 and a sensitivity of 85.7% and a specificity of 89.2%. This method outperformed quantitative continuous variables using each percent change in skewness and kurtosis.

In 25 patients with glioblastoma undergoing surgical resection for newly developed or enlarging lesions on follow-up MR imaging, Hu and colleagues recently showed that a DSC perfusion thresholding metric called perfusion MR imaging–fractional tumor burden (pMRI-FTB) was strongly correlated with histologic tumor fraction and seemed to be correlated with OS. This type of approach could be significant because virtually all studies view contrast-enhancing MR imaging lesions as either tumor or posttreatment radiation effect (PsP and RN), even though most lesions are an admixture with variable amounts of tumor fraction. Using stereotactic coregistration, they showed that an rCBV threshold of 1.0 could differentiate posttreatment radiation effect from tumor with 100% accuracy. This threshold was higher than what the same group had reported earlier, which could be because of technical differences in perfusion data postprocessing. The results of this study suggest that using pMRI-FTB to noninvasively quantify tumor burden relative to posttreatment radiation effect could prove useful to predict tumor progression and survival.

To account for the heterogeneity of DSC perfusion MR imaging values within tumors, parametric response mapping (PRM) was introduced by Galban and colleagues as a voxel-wise method for analyzing perfusion maps. It differs from traditional whole-tumor ROI analysis methods in that it retains spatial alteration in perfusion metrics after the start of therapy. They measured the change in coregistered rCBV on a voxel-wise basis, designated as PRM\(_{rCBV}\), before treatment and 1 and 3 weeks after treatment initiation. These values were then compared with standard whole-tumor ROI analysis for their accuracy in predicting OS. Percentage change of ROI-based mean rCBF and rCBF did not predict survival, probably because of varying changes in these parameters throughout the tumor that desensitizes the measurement. However, PRM\(_{rCBV}\) predicted OS, probably because of its ability to detect and quantify variations of increased, decreased, and unchanged voxels following treatment initiation. This finding held true even when accounting for baseline rCBV, which is also known to be prognostic. The investigators acknowledged a potential limitation that accurate image registration is required, which could introduce error if large changes in tumor volume occur between examinations.

A follow-up study by the same group also evaluated PRM in PsP and seemed to show a significant difference in PRM\(_{rCBV}\) in patients with PsP compared with TEP at week 3 during chemoradiation. However, percent change in whole tumor rCBV or rCBF, extent of resection MR tumor volume changes, and Radiation Therapy Oncology Group recursive partitioning analysis classification could not make this distinction. This study found significantly decreased rCBV based on PRM in those with TEP compared with PsP at 3 weeks, which is counterintuitive. Decreased perfusion could result in hypoxia and treatment resistance, although it is unclear to what extent underestimation of rCBV caused by T1 GBCA leakage effects could have influenced these results. None-theless, this technique seems to be promising and more validation of this method is necessary.

A prospective study in 14 patients by Gahramanov and colleagues compared the GBCA gadoteridol (without leakage correction) with the blood pool agent ferumoxytol, an ultra-small superparamagnetic iron oxide nanoparticle, in determining rCBV in patients with HGG following chemoradiation. Because of its larger molecular size, the leakage rate of ferumoxytol is lower than that of GBCAs and their results suggest that a low rCBV derived from ferumoxytol may be a better discriminator of PsP than an rCBV derived with a GBCA. A high ferumoxytol rCBV may similarly be a better indicator of TEP. They also suggest that the use of a blood pool agent may be a simpler and more reliable method to minimize GBCA leakage effect compared with other proposed methods.

In a retrospective study of 16 patients with recurrent glioblastoma treated with bevacizumab, Sawlani and colleagues examined mean rCBV, mean leakage coefficient \(K_2\), and hyperperfusion volume (HPV), defined as the fraction of tumor with an rCBV greater than a predefined threshold, as potential imaging biomarkers of therapeutic response. A statistically significant hazard ratio of 1.077 was found that correlated with time to progression when examining the percent change in HPV (rCBV threshold of 1.00). Given the small sample size and that hazard ratio was just greater than 1, further validation and modification of this technique may be needed.

Although OS or duration of response or PFS may be a better indicator of true antitumoral effect of antiangiogenic agents, the amount of initial response may also correlate with survival. Changes in microvascular permeability (volume transfer constant \([k^{\text{trans}}]\), rCBV, and circulating
collagen IV were recently combined to produce a vascular normalization index in 31 patients with recurrent glioblastoma following a single dose of the antiangiogenic agent cediranib.49 This index was closely associated with both PFS and OS in these patients.

In theory, the vascular normalization produced by antiangiogenic agents should result in improved perfusion and improved oxygenation and drug delivery. However, until now, clinical evidence for this has been lacking.45,46 A recent study by Sorensen and colleagues46 found a durable increase in perfusion for at least 1 month and longer survival in 7 out of 30 patients with recurrent glioblastoma treated with cediranib. These results suggest that decreases in permeability from vascular normalization could result in increased perfusion in some patients, with consequently improved antitumoral effect of cediranib caused by improved drug delivery.

In a longitudinal study of 13 patients with biopsy-proven LGG who were treated conservatively, Danchaivijitr and colleagues65 noted that rCBV values at baseline were not significantly different between transformer and nontransformer groups. However, a significant increase in consecutive rCBV was found in patients who transformed to HGG. An increase in rCBV was noted up to 1 year before contrast enhancement was evident in those undergoing malignant degeneration. Law and colleagues89 performed retrospective analysis in 189 patients with LGG and HGGs to determine whether baseline rCBV could predict clinical outcome. They concluded that both patients with HGG and LGG with increased rCBV (>1.75) had significantly more rapid time to progression compared with those with low rCBV, independent of pathologic findings. The development and validation of rCBV threshold values in the future may result in an earlier diagnosis of progression, or stage migration, the clinical significance of which is unclear.62 Oligodendrogliomas, especially the 1p/19q loss of heterozygosity genotype, may be problematic with this approach given their propensity to show increased rCBV regardless of grade because of their chicken-wire vasculature.69,90 Because of the low rCBV of nontransforming LGG, it is unlikely to be a sensitive biomarker of treatment response because of this floor effect.62

Permeability MR Imaging

Permeability dynamic contrast-enhanced (DCE) MR imaging is a technique that can measure the integrity and leakiness of tumoral microvasculature.51 By assuming a 2-compartment model composed of intravascular and extravascular space, common variables reported using pharmacokinetic modeling, variables including the Ktrans, blood plasma volume (Vp), and volume of extravascular-extracellular space (Ve) can be measured.67,92,93 Semiquantitative model-free parameters include initial area under the curve (iAUC), time to peak (TTP), and slope of the initial phase or washout curve. Although iAUC is easier to calculate and correlated with the quantitative variables Ktrans, Ve, and Vp, it is less physiologically specific and seems to represent a combination of the three parameters.91

Most DCE MR imaging studies have focused on Ktrans and, although it seems that Ktrans represents a potentially intractable combination of microvascular permeability, blood flow, and endothelial surface area, it seems to be reproducible.94,95 There are comparatively few studies using DCE MR imaging to diagnose RN compared with DSC MR imaging. Early work by Hazle and colleagues86 in 1997 seemed to indicate that RN had lower permeability than recurrent tumor. A recent study by Biswas and colleagues97 used DCE MR imaging in 18 patients with HGG who developed postradiation enhancement questionable for recurrent tumor or RN. Both Ktrans and iAUC were significantly higher for the recurrent glioma group, with Ktrans showing a superior sensitivity and specificity compared with iAUC. Another recent study by Narang and colleagues98 found that iAUC at both 60 and 120 seconds, maximum slope of enhancement in the initial vascular phase (MSIVP), and normalized MSIVP (nMSIVP) were all significantly higher in the recurrent tumor group, whereas normalized slope of the delayed equilibrium phase (nSDEP) was significantly lower. nMSIVP seemed to be the single best predictor of recurrent tumor, with a sensitivity of 95% and specificity of 78%. They postulated that semiquantitative, non–model-based metrics derived from DCE MR imaging could serve as alternatives to more complex pharmacokinetic-based methods.

Diffusion MR Imaging

Diffusion MR imaging is commonly performed in both academic and community settings. Compared with DCE and DSC MR imaging, it has some advantages in that it does not require the use of an exogenous contrast agent and may be easier to implement and more reproducible.99,100 It can allow insight into cellular architecture at the millimeter scale by being sensitive to thermally driven molecular water motion.101 In vivo, water motion is thought to be impeded by cellular packing, membranes, intracellular elements, and macromolecules, although there is still an
incomplete understanding and consensus regarding the biophysical basis of apparent diffusion coefficient (ADC) values.  

In general, increases in ADC following therapy can be seen as evidence of successful therapy in most malignancies, including brain tumors. However, the cellular processes resulting from successful therapy, particularly antiangiogenic/cytostatic rather than cytotoxic/radiotherapies that kill tumor cells, can produce variable, occasionally opposing, effects on ADC. Early cellular swelling in cell death mediated by necrosis can produce diffusion restriction, whereas later cell lysis can result in increased water diffusion. Early cell shrinkage associated with apoptosis can also result in increased ADC. Tumor progression may manifest as a decrease in ADC caused by an increase in tumor cell density, although an increase in ADC could also be seen in tumor progression secondary to vasogenic edema that accompanies tumor cell infiltration along intact white matter tracts.

There is currently limited and conflicting evidence regarding the use of diffusion MR imaging to differentiate RN or PsP from recurrent tumor. A recent preclinical diffusion tensor imaging (DTI) study by Wang and colleagues used rat models of RN as well as 2 orthotopic glioma models. Compared with viable glioma, RN had significantly lower ADC in the central zone of necrosis and lower fractional anisotropy (FA) in the peripheral zone of necrosis. These changes were thought to be caused by coagulative necrosis in the central zone and random microstructures of necrosis in the peripheral zone. Parallel diffusivity ($\lambda_p$) in the central and peripheral zone and perpendicular diffusivity ($\lambda_\perp$) in the central zone were also significantly lower in RN compared with glioma; in addition, their diagnostic powers seemed to be nearly equal to those of ADC and higher than those of FA, although further validation in clinical cases is needed. An earlier clinical study in 28 patients by Sundgren and colleagues found lower ADC, $\chi_\parallel$, and $\lambda_\perp$ in RN compared with tumor recurrence and no difference in FA. Other reports have suggested that ADC may be increased and that FA may be decreased in RN compared with recurrence.

A recent study in 15 patients with recurrent glioblastoma showed that a change in any direction in mean ADC in the FLAIR signal abnormality region after bevacizumab and irinotecan therapy was associated with decreased survival. This finding suggests the importance of disease stability to be a favorable prognostic factor and that an increase or decrease of ADC could correspond with tumor progression. Another study in 20 patients with recurrent/progressive glioblastoma treated with bevacizumab alone or with concurrent chemotherapy found that those with tumor progression showed a trend of decreasing ADC in both the contrast-enhancing and FLAIR hyperintense signal regions, whereas those without progression seemed to show a trend of stable to slightly progressive increase over time.

Histogram analysis is an alternative to traditional ROI analysis that allows documentation of tumor heterogeneity, although no spatial specificity can be extracted. In 2 separate studies, Pope and colleagues showed that ADC histogram analysis derived from contrast-enhancing tumor and fitted to a 2 normal distribution curve seemed to show that the mean ADC from the lower curve (ADC-L) and the mean lower curve proportion (LCP) were able to predict PFS and OS. The Pope and colleagues study from 2012 is notable because it was performed in a multicenter setting in 97 patients without standardization of imaging technique. The longest surviving patients (living more than 600 days) were all identified with their method.

Functional diffusion maps (fDMs) were proposed in 2005 in which multiple ADC maps are generated at multiple time points and coregistered with a first-scan baseline. Then, voxel-wise changes are isolated and computed according to the magnitude of their change. As opposed to conventional ROI analysis, in which the ADC values are averaged over the ROI, fDM does not assume homogeneity within the lesion, a factor that is critical because many tumors show quite a bit of spatial heterogeneity.

This technique has been shown to be a sensitive early biomarker for brain tumor responses to therapy and specific to progression of HGG. Different degrees of cell density change may be reflected by using graded thresholds in fDM. This modification of fDM allows quantification and tracking of the volume of tissue showing changes between different ADC thresholds and this may be more predictive of OS than traditional fDMs in patients with recurrent glioblastoma treated with bevacizumab.

Like the potential difficulties seen with PRM-based perfusion MR imaging, fDM is limited by the proper registration of diffusion MR images from subsequent scans. Slight misregistration between the datasets caused by image distortion or edema may confound quantification and interpretation of the fDM-classified tumor regions.

At present, only linear image registration techniques have been used to match the DWI sets. Ellingson and colleagues hypothesized that an additional nonlinear (elastic) registration step after
linear registration could improve the clinical sensitivity and reduce misregistration and misclassification of fDMs (Fig. 4). In patients undergoing antiangiogenic therapy, nonlinear fDMs provide improved clinical predictability, sensitivity, and specificity for PFS and OS compared with the linear fDMs.\(^{126}\) The significance of new diffusion restriction lesions in patients with glioblastoma during therapy is unclear. Gupta and colleagues\(^{127}\) reported that some patients with glioblastoma who develop a new focus of nonenhancing diffusion restriction during therapy (chemoradiation with TMZ or bevacizumab with or without chemotherapy) may evolve into a region of enhancing tumor, although histopathologic correlation was lacking. Gerstner and colleagues\(^{128}\) described a case report of pathologically confirmed diffusion-restricting, nonenhancing tumor in a patient with recurrent glioblastoma treated with bevacizumab, possibly reflecting vascular cooperation by tumor. Rieger and colleagues\(^{129}\) showed the presence of persistent diffusion-restricting lesions in 13 out of 18 patients with recurrent glioblastoma treated with bevacizumab. In the 1 patient for whom pathologic confirmation was available, only atypical necrosis and upregulation of hypoxia-inducible factor 1 alpha without recurrent tumor was found. A recent retrospective study by Mong and colleagues\(^{130}\) found that 20 patients with malignant glioma treated with bevacizumab had significantly greater time to progression, time

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**Fig. 4.** Linear and nonlinear fDM calculations. Top row: linear (traditional) fDMs consisting of a linear registration algorithm to align posttreatment ADC maps to pretreatment ADC maps. Middle row: before to after nonlinear fDMs consisting of nonlinear registration of pretreatment ADC maps to posttreatment ADC maps. Bottom row: after to before nonlinear fDMs consisting of nonlinear registration of posttreatment ADC maps to pretreatment ADC maps. For fDMs, blue voxels represent a significant decrease in ADC (beyond 0.4 mm\(^2\)/ms), red voxels represent a significant increase in ADC (beyond 0.4 mm\(^2\)/ms), and green voxels are those with no significant change in ADC. (Reproduced from Ellingson BM, et al. Nonlinear registration of diffusion-weighted images improves clinical sensitivity of functional diffusion maps in recurrent glioblastoma treated with bevacizumab. Magn Reson Med 2012;67(1):237–45; with permission.)
to survival from bevacizumab initiation, and OS compared with matched controls. Gelatinous necrotic tissue was found in the 1 diffusion-restricting patient in whom surgical resection was performed and, where available, perfusion MR imaging and 3,4-dihydroxy-6-[18F]fluoro-phenylalanine (18F-FDOPA) PET scans also were not consistent with tumor. The investigators concluded that these persistent diffusion-restricting lesions may be related to atypical necrosis rather than active tumor.

Smith and colleagues reported that diffusion restriction can occur in or around the resection cavity in patients with glioma immediately following surgery. The diffusion restriction typically resolves and is followed by contrast enhancement on follow-up imaging. Over time, this region of contrast enhancement evolves into encephalomalacia. Therefore, it seems that contrast enhancement that is preceded by diffusion restriction is more consistent with postreresction injury than with tumor recurrence. As stated earlier, routine inclusion of DWI has been recommended by the Surgery Working Group of RANO.

**PET**

PET imaging can provide quantitative metabolic information about gliomas. Various radiotracers can be used to characterize different molecular processes within glioma, most of which are concerned with increased metabolism and cell proliferation. Some disadvantages of PET imaging relate to its increased expense as well as its decreased availability compared with MR imaging.

The first onologic application of PET was in the imaging of brain tumors with 18F-fluorodeoxyglucose (FDG). To date, there is little known regarding use of 18F-FDG and PsP directly. However, literature does exist on attempts to use 18F-FDG to differentiate RN from tumor progression. These studies typically display low or disputed sensitivities and specificities, largely because of high background activity within the brain parenchyma. A study by Ricci and colleagues found that 18F-FDG had a sensitivity of 73% and specificity of 56% when the contralateral gray matter was used as reference standard. Using contralateral white matter as a reference, sensitivity was 86% and specificity was 22%, respectively. Based on their study, nearly one-third of patients would have been treated inappropriately if 18F-FDG were the sole determinant of treatment response.

A recent meta-analysis by Nihashi and colleagues examined the diagnostic accuracy of various PET radiotracers to diagnose recurrent glioma. They conducted database searches of Scopus and PubMed from inception until June 30, 2011. Their analysis found wide-ranging sensitivities and specificities for the 2 radiotracers that satisfied their search criteria: 18F-FDG (16 studies) and the amino acid–based 11C-methionine (11C-MET) (7 studies). Results were based primarily on visual assessment of 18F-FDG and quantitative assessment of 11C-MET. Various thresholds and diagnostic criteria were used across studies. For 18F-FDG in HGG, sensitivities ranged between 18% and 100% and specificity ranged between 25% and 100%. For 11C-MET, sensitivity ranged between 44% and 93% and specificity ranged between 50% and 100%. When summary estimates of sensitivity and specificity with their 95% confidence intervals (CIs) were calculated by using bivariate random effects meta-analysis with the exact binomial likelihood, 18F-FDG had a summary sensitivity of 77% (95% CI, 66%–85%) and specificity of 78% (95% CI, 54%–91%) for any glioma histology, whereas 11C-MET had a summary sensitivity of 70% (95% CI, 50%–84%) and specificity of 93% (95% CI, 44%–100%) for HGG. The investigators concluded that both 18F-FDG and 11C-MET had moderately good accuracy for detecting recurrent glioma as add-on tests for diagnosing recurrent glioma. However, they cautioned that these estimates may not be replicable or relevant to other clinical settings given that most studies had limited internal and external validity. Other limitations were that the number of studies was small and few studies used current standard-of-care therapies. Their study also revealed limited data on other radiotracers such as 18F-FLT, 18F-fluoroethyl-L-tyrosine (18F-FET), and 18F-boronophenylalanine. They also found few direct comparison studies examining different PET radiotracers and of PET versus other non-PET imaging modalities.

Numerous novel radiotracers have been developed because of the limitations of 18F-FDG-PET in the brain. Amino acid–based PET, such as 11C-MET or 18F-FET, seem to be more useful in brain imaging because of lower baseline uptake. Both of these modalities have been promising in determining tumor progression from RN, and may be potentially useful to diagnose PsP. 11C-MET is the most widely used non-18F-FDG-PET radiotracer in use because of its localization precision and higher sensitivity than 18F-FDG. However, its major limitation is the requirement of an on-site cyclotron because of its short half-life. Terakawa and colleagues examined the diagnostic accuracy of 11C-MET in 77 patients with metastatic brain
tumors (n = 51) and glioma (n = 26) and determined that uptake of $^{11}$C-MET tended to be increased for tumor recurrence compared with RN. Using a lesion to normal to mean ratio (L/N$_{\text{mean}}$) of mean standardized uptake values, ROC analysis found that, for metastatic tumor, an L/N$_{\text{mean}}$ cutoff value greater than 1.41 had a sensitivity of 79% and specificity of 75%, whereas, for glioma, an L/N$_{\text{mean}}$ greater than 1.58 had a sensitivity of 75% and specificity of 75%. A limitation of $^{11}$C-MET that was raised by this study was that a reduction of specificity could result from accumulation of $^{11}$C-MET in necrotic tissue because of disruption of the BBB. Potzi and colleagues$^{148}$ studied both $^{18}$F-FDG and $^{11}$C-MET in 28 patients with glioblastoma following surgery and/or conservative treatment and found that $^{11}$C-MET was able to show increased uptake in tumor in 24 patients compared with only 2 for $^{18}$F-FDG. However, neither radiotracer correlated with survival. Focusing on volumetric data, Gallidiakis and colleagues$^{149}$ found that $^{11}$C-MET may be able to show that the volume of recurrent glioblastoma may be underestimated by contrast-enhanced MR imaging. $^{11}$C-MET may offer complementary information to MR imaging, which can be helpful for therapeutic planning.

As discussed previously, the major disadvantage of $^{11}$C-MET relates to its short half-life of 20 minutes, making it unavailable in PET centers without a cyclotron. $^{18}$F-amino acid analogs such as $^{18}$F-FDOPA with longer half-lives may be attractive alternatives to $^{11}$C-MET. Becherer and colleagues$^{150}$ compared $^{18}$F-FDOPA with $^{11}$C-MET and found that $^{11}$C-MET was able to show increased uptake in brain tumors compared with $^{18}$F-FDG. However, neither radiotracer correlated with survival. Focusing on volumetric data, Gallidiakis and colleagues$^{149}$ found that $^{11}$C-MET may be able to show that the volume of recurrent glioblastoma may be underestimated by contrast-enhanced MR imaging. $^{11}$C-MET may offer complementary information to MR imaging, which can be helpful for therapeutic planning.

In a retrospective study comparing conventional MR imaging and $^{18}$F-FET during routine posttreatment follow-up, $^{18}$F-FET had a sensitivity of 100% and specificity of 92.9% to distinguish treatment response versus recurrent glioma, compared with conventional MR imaging’s specificity of 50%.$^{147}$ Another study using $^{11}$C-MET on a patient population that, on average, was almost 7 months after treatment resulted in a sensitivity of 100% and accuracy of 82% to differentiate recurrent glioma and RN, although specificity was 60%.$^{143}$ Grosu and colleagues$^{146}$ found that $^{18}$F-FET and $^{11}$C-MET had equal efficacy when performed on the same day, with an equal sensitivity of 91% and specificity of 100%. The lack of congruence among these studies could be caused by variations in the timing of posttreatment imaging and variations in technique, underscoring the need for a large multicenter trial focusing on PsP. A study of 24 patients with HGG who underwent intracavitary radioimmunotherapy found that nodular foci of uptake of $^{18}$F-FET indicated recurrent glioma, as opposed to slightly increased, homogeneous uptake around the resection cavity that seemed to indicate benign, therapy-related changes.$^{152}$

$^{18}$F-FLT is a newer PET alternative that also shows promise. It is thought to show cellular proliferation by tracking DNA synthesis; however, its analysis can be complicated by the status of the BBB.$^{153}$ It seems to be advantageous compared with $^{18}$F-FDG in that there is minimal uptake and retention in normal brain tissue.$^{154}$ In a prospective study of 25 patients, Chen and colleagues$^{155}$ performed side-by-side comparison of $^{18}$F-FLT with $^{18}$F-FDG in newly diagnosed or treated patients with glioma and found that $^{18}$F-FLT may have greater sensitivity than $^{18}$F-FDG to detect recurrent glioma, likely secondary to the low background uptake of $^{18}$F-FLT in normal brain tissue. $^{18}$F-FLT was also better correlated with Ki-67 proliferation index values and was also a better predictor of tumor progression and survival. There were limited data on the specificity of $^{18}$F-FLT PET in the differential diagnosis of RN versus tumor because they did not have a case of RN in their study group. A later prospective study by the same group in 19 patients with recurrent gliomas treated with irinotecan and bevacizumab found that $^{18}$F-FLT PET responses seemed to be significant predictors of OS and outperformed conventional MR imaging.$^{156}$ In LGGs, there is preliminary evidence to suggest that $^{18}$F-FET may be able to show metabolic responses earlier than changes seen on MR imaging in patients treated with TMZ. This finding may prove to be significant given the slow growth rate of LGG.$^{157}$

A recent study by Laymon and colleagues$^{154}$ investigated treatment response by imaging patients with glioblastoma before, during, and after therapy with voxel-wise analysis of $^{18}$F-FLT PET, (23Na) sodium MR imaging, and 3-T MR imaging. Sodium MR imaging may be useful for brain tumor imaging because an increase in intracellular and total 23Na concentration caused by depolarization of the cell membrane precedes increased cell division. However, analysis is complicated because the 23Na signal is a result of a combination of both intracellular and extracellular regions. The investigators found that both $^{18}$F-FLT and (23Na) MR imaging were promising for evaluating tumor progression/response and
may provide complementary information because, unlike $^{18}$F-FLT, $^{23}$Na MR imaging is not affected by changes in the BBB.

In tumors, structurally and functionally abnormal microvasculature, impaired ability of oxygen to diffuse through tissues, competition between different regions within a tumor, and decreased oxygen carrying capacity of blood caused by treatment-related or disease-related anemia results in hypoxia.\textsuperscript{158} Hypoxia has been linked to tumor progression and treatment resistance, with much attention in the literature devoted to hypoxia within head and neck tumors.\textsuperscript{139} $^{18}$F-Fluoromisonidazole (MISO) is probably the most widely used PET radiotracer that has been used to quantify hypoxia in tumors.\textsuperscript{158,159} Uptake of $^{18}$F-MISO has been seen in HGG but not in LGG and a significant relationship was seen between $^{18}$F-MISO or $^{18}$F-FDG and expression of VEGF-R1 and Ki-67 expression and $^{18}$F-MISO.\textsuperscript{160} It also seemed to be prognostic of treatment outcomes in most of their patients. Bruehlmeier and colleagues\textsuperscript{161} showed that, in 11 patients with various brain tumors, $^{18}$F-MISO could depict hypoxic regions in tumors independently of BBB disruption or tumor perfusion. The investigators suggest that the development of hypoxia in glioblastomas may occur regardless of the magnitude of perfusion. There is also some evidence to show that $^{18}$F-MISO may be beneficial before surgery and radiotherapy to quantify tumor volume and degree of hypoxia and following therapy to predict outcome.\textsuperscript{139} Although the full potential of $^{18}$F-MISO has yet to be realized, there is a search for other hypoxia imaging radiotracers because $^{18}$F-MISO is not widely available and it also exhibits slow clearance from normoxic tissues. Other radiotracers that are in development include Cu-diacetyl-bis(N4-methylthiosemicarbazone) ($^{64}$Cu-ATSM), $^{99m}$Tc-labeled and $^{68}$Ga-labeled metronidazole (MN), $^{99m}$Tc-labeled iminodiacetic acid (IDA) derivative of 2-methyl-5-nitroimidazole and 1-[2-$^{18}$F fluoro-1-[hydroxymethyl]ethoxy] methyl-2-nitroimidazole, an $^{18}$F-labeled 2-nitroimidazole analog.\textsuperscript{158}

**MR Spectroscopy**

Although different heteronuclei such as sodium ($^{1}$Na) and phosphorus ($^{31}$P) MR spectroscopy have been used to evaluate brain tumor metabolism, the most common method involves use of proton ($^{1}$H) MR spectroscopy.\textsuperscript{162} $^{1}$H MR spectroscopy is capable of assessing membrane turnover and proliferation (choline), energy homeostasis (creatine), glioneural structures (N-acetyl-aspartate), and necrosis (lactate or lipids).\textsuperscript{152} It has been used in both adult and pediatric brain tumor populations to distinguish recurrent tumor from RN. Multiple studies have shown that tumor recurrence can be suggested in the presence of increased Cho signal (ie, Cho levels relative to Cho signal in normal-appearing tissue, Cho/Cr or Cho/NAA ratios), whereas reduced Cho (and Cr) levels suggest RN.\textsuperscript{163–171} However, there can be difficulty in determining whether increased choline is caused by membrane production or degradation, which can lead to temporary choline peaks after treatment.\textsuperscript{172} False-positive results for recurrent tumor can occur from radiation-induced inflammation, demyelination, or gliosis, whereas false-negatives are typically secondary to partial-volume effects (such as small tumor cell clusters within nonneoplastic tissues).\textsuperscript{164} A substantial limitation of MR spectroscopy is its inability to properly evaluate masses composed of mixed tumor and RN.\textsuperscript{167,173} The addition of ADC measurements does not seem to improve the ability to distinguish between mixed-tissue versus pure tumor or RN, although it can improve the distinction between pure tumor versus RN.\textsuperscript{168,173} The grade of glioma may also influence the accuracy of spectroscopy. A recent study reported that $^{1}$H MR spectroscopy seems to be more accurate when predicting tumor recurrence versus RN for LGG, whereas FDG-PET seemed to be more accurate than MR spectroscopy in HGG recurrences.\textsuperscript{174} Fink and colleagues\textsuperscript{175} recently compared both single-voxel and multivoxel MR spectroscopy in a multiparametric evaluation of patients with suspicion for recurrent glioblastoma using 3-T MR imaging. They found that single-voxel MR spectroscopy parameters could not reliably differentiate tumor recurrence compared with posttreatment effects, whereas multivoxel MR spectroscopy Cho/Cr peak area and Cho/NAA PH ratios seemed to show good diagnostic performance (Fig. 5). The differentiation between PsP and TEP is likely to be challenging in most clinical settings given that both may present with increased choline, decreased NAA, and increased lipid/lactate.\textsuperscript{32}

Changes in metabolite signatures may be able to predict changes in tumor volume. A decrease in Cho may suggest response to treatment, whereas stable or increased Cho may indicate progression.\textsuperscript{12,170,171,176–180} Increases in Cho/NAA may also predict areas of new contrast enhancement on MR imaging following chemoradiation in patients with glioblastoma.\textsuperscript{181} For patients undergoing Gamma knife radiosurgery for recurrent glioblastoma, MR spectroscopy may be able to predict survival.\textsuperscript{182} There was significantly shorter survival in patients whose metabolic lesion was outside the Gamma knife
target compared with those whose lesions were confined to the target. These results suggested that MR spectroscopy could be used to define the Gamma knife target and that alternative forms of therapy such as chemotherapy or surgical resection should be considered in Gamma knife candidates who possessed very large metabolic lesions.

Emerging MR imaging techniques
In addition to the more familiar advanced imaging methods mentioned previously, a few newer imaging methods such as molecular MR imaging and radiogenomics have gained recent attention. A brief overview is provided.

Molecular MR imaging
Nuclear medicine techniques such as PET have traditionally been the dominant method of clinical molecular imaging. Although MR imaging has been thought of as a less-than-ideal molecular imaging technique because of its inherently low sensitivity to depict contrast agents (orders of magnitude lower than PET), advances in MR imaging contrast agents have made molecular MR imaging a viable technique.\(^{183}\)

The functional MR imaging techniques mentioned earlier can generally be thought of as indirect approaches to measuring changes in molecular processes in tissues. However, more direct molecular imaging using MR imaging are in
development and have been reviewed recently. General approaches to detecting molecular MR imaging probes involve the use of direct detection of a nuclear species that is a component of an imaging probe or indirect detection through the effects of an agent on the large signal from the hydrogen protons in tissue water, either by introducing new pathways for magnetization transfer or altering the water relaxation rate.

The direct approach is most analogous to radio-nuclear techniques. However, using MR imaging is less sensitive than detecting high-energy photons. The most promising nuclear species without hyperpolarization seems to be $^{19}$F (found in perfluorocarbons) because it has the greatest gyromagnetic ratio following hydrogen and so produces stronger signals than any other species at a given field strength and concentration. Also, under normal physiologic conditions, no background fluorine signal exists, and so detection only requires that the signal be greater than ambient noise.

The indirect approach can use either paramagnetic or superparamagnetic (ie, iron oxide nanoparticle) agents that alter T1, T2, or T2* (the basis of conventional MR imaging contrast agents) or manipulation of the water signal magnitude using radiofrequency irradiation to label one species of protons, which then transfers the label to water through magnetization exchange. Examples include paramagnetic chemical exchange saturation transfer (PARACEST) and chemical exchange saturation transfer (CEST) agents. Amide proton transfer (APT) MR imaging is a new molecular MR imaging technique based on CEST. APT MR imaging allows indirect detection of the amide proton signals in the backbone of endogenous proteins and peptides. In preclinical work by Zhou and colleagues, APT MR imaging was able to distinguish between viable glioma and RN in rat models. Increased APT signal in tumors is thought to be caused by a highly cellular environment with increased cytosolic protein and peptide content, whereas the decreased APT signal in RN is probably the result of the absence of mobile cytosolic proteins and peptides caused by loss of the cytoplasm.

Radiogenomics The diagnosis of glioblastoma is still primarily based on histopathology and immunohistochemistry. Histologically grouped tumors often similarly display widely variant clinical behavior and methods to better characterize the molecular differences between tumors may improve diagnosis and individualize therapy. High-throughput methods such as microarray analysis of gene expression are now able to provide a wealth of molecular information about cancer. Current conventional imaging techniques are histopathologically based and provide anatomic and morphologic information. Much of the information in MR imaging of a tumor remains unaccounted for and incompletely understood on a molecular level. Radiogenomics is a developing field that seeks to associate specific imaging traits with specific gene expression patterns to gain a better understanding of cellular and molecular disorders. Recent work by Zinn and colleagues, Diehn and colleagues, Pope and colleagues, and Barajas and colleagues has been published examining the relationship between gene expression and its influence on both conventional and physiologic imaging parameters such as edema, contrast enhancement, mass effect, perfusion, and diffusion metrics in glioblastoma. In a radiogenomic approach, specific radiological tumor phenotypes referred to as radio-phenotypes may serve as surrogates for gene expression to provide an accurate, but noninvasive, diagnosis of tumor subtype and molecular biology.

SUMMARY

Although conventional contrast-enhanced MR imaging remains the standard-of-care imaging method in the posttreatment evaluation of gliomas, recent developments in therapeutic options such as chemoradiation and antiangiogenic agents have caused the neuro-oncology community to rethink traditional imaging criteria. This article highlights the latest RANO Working Group recommendations, with particular attention to PsP and PsR. These recommendations should be viewed as works in progress. As more is learned about the pathophysiology of glioma treatment response, quantitative imaging biomarkers will be validated within this context. There will likely be further refinements and modifications to glioma response criteria, although the lack of technical standardization in image acquisition, postprocessing, and interpretation also need to be addressed.

REFERENCES

3. Heesters MA. Brain tumor delineation based on CT and MR imaging. Implications for radiotherapy...


73. Hopewell JW. Microvasculature and radiation damage. Recent Results Cancer Res 1993;130:1–16.


90. Cha S. Differentiation of low-grade oligodendrogliomas from low-grade astrocytomas by using quantitative blood-volume measurements derived
118. Asao C. Diffusion-weighted imaging of radiation-induced brain injury for differentiation from tumor


129. Mong S. Persistent diffusion-restricted lesions in bevacizumab-treated malignant gliomas are associated with improved survival compared with matched controls. AJNR Am J Neuroradiol 2012;33(9):1763–70.


146. Grosu AL. An interindividual comparison of O-(2-[18F]fluoroethyl)-l-tyrosine (FET) and l-[methyl-11C)methionine (MET)-PET in patients with brain


