Glioblastoma and Response Assessment in Neuro-Oncology (RANO) Criteria

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1. What is Glioblastoma (GBM)?

Glioblastoma (GBM) is the most common and aggressive type of brain cancer, representing 45% of all malignant brain and spinal cord tumors [1]. GBMs can be characterized as either primary or secondary tumors [2]. The majority of GBMs are primary brain tumors, that is, they develop spontaneously without prior indication that a tumor is present. In contrast, secondary GBMs begin as low-grade tumors which evolve to higher-grade over a longer time course, yet they still advance quite aggressively.

Brain tumors are named for the cell types from which they originate. Tumors originating from glial cells (such as a GBM), are termed gliomas. Gliomas that arise from astrocytes, a specific type of glial cell, are termed astrocytomas and the most advanced astrocytomas are GBMs. Therefore, it is common to hear GBMs referred to as astrocytomas or more generically as gliomas.

2. Prognosis and Treatment of GBM

Unfortunately, GBM carries a grim prognosis. The median duration of patient survival is between 12 to 18 months [3] and fewer than 10% of patients will survive past 5 years of their initial diagnosis [4].

The current treatment plan for newly diagnosed GBM patients includes open skull surgery followed by radiotherapy with concomitant chemotherapy [5]. Although the goal of surgery is to remove as much of the tumor as possible, resection of the entire tumor can be difficult because of the tentacle-like fingers that allow GBMs to imbed into brain tissue. Additionally, surgery may not be possible if the tumor is inaccessible or encompasses vital brain tissue. After surgical removal (if possible) patients receive multiple sessions of radiotherapy in which radiation is used to kill remaining tumor cells. Additionally, patients receive temozolomide, a chemotherapy agent that triggers tumor cell death [5]. Despite providing maximal treatment, the propensity for a GBM to return after treatment is high. The dismal outlook for patients with GBM serves as the impetus to develop new therapeutic drugs.
3. Imaging GBM

GBMs can be detected using contrast-enhanced computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI). Although both modalities provide a high degree of confidence for evaluating GBM, lower grade tumors may go undetected with CT imaging. As such, MRI, which is more sensitive to the presence of GBM, is the recommended imaging modality for the detection, delineation, and evaluation of response to drug therapies for GBM [5].

MRI performed with contrast agents that shorten the T1 relaxation time constant are used to image GBMs. Since GBMs are typically innervated with abnormally leaky blood vessels, the contrast is able to pass through the vessels, penetrate the blood-brain barrier and pool in the non-cellular space of the tumor. When this occurs the tumor region becomes bright on T1 weighted images as shown in left panel of Figure 1. Tumors showing contrast-enhancement are referred to as enhancing lesions. Enhancing lesions are thought to represent the most aggressive portion of the tumor [6].

![Figure 1. MRI images showing enhancing and non-enhancing GBM lesions. The left panel is an axial T1-weighted contrast-enhanced MRI image showing multifocal GBMs. The right panel is a T2/FLAIR image showing non-enhancing lesions. Figure adapted from [7].](image)
Although GBMs can invade surrounding brain tissue they do not always disrupt the blood brain barrier and thus the full tumor burden may not show contrast enhancement on T1-weighted images. Instead the non-enhancing tumor can be visualized with T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI. The FLAIR sequence suppresses the effects of fluid in order to intensify lesions on the resulting image (Figure 1, right panel). Although a tumor may show a reduction in the enhancing component, the non-enhancing component can still progress [8], as shown in Figure 2, and lead to neurological decline. Thus it is important to image both enhancing and non-enhancing lesions (using T1-weighted and T2-weighted/FLAIR MRI, respectively) when evaluating changes in GBM.

Figure 2. A patient with recurrent GBM shows non-enhancing lesion progression after therapy. Axial contrast-enhanced, T1-weighted images show (A) multifocal right frontal GBM; (B) decreased contrast enhancement after 7 months of therapy (arrow) (C) T2/FLAIR image of non-enhancing lesions at baseline and (D) after 7 months of therapy showing that the frontal non-enhancing tumor has progressed into the left frontal lobe (arrow). Figure taken from [7].
4. **Response Assessment in Neuro-Oncology (RANO) Criteria**

In order to evaluate the efficacy of a GBM drug, tumor responses are objectively assessed using a set of standard criteria. In 2010, a group of neuro-oncologists, neurosurgeons, radiation oncologists, neuro-radiologists, and experts in quality-of-life measures, in collaboration with government and industry, convened to evaluate, modify, and improve the assessment criteria used to define response in brain tumors. The group reformed the prior MacDonald criteria [9] and provided updated Response Assessment in Neuro-Oncology (RANO) criteria for evaluating high grade gliomas in clinical trials [7].

4.1. **Measurable and Non-measurable Contrast Enhancing Lesions**

To evaluate changes in GBM using the RANO criteria, up to 5 enhancing lesions identified on baseline T1-weighted images are measured and monitored for response over time. In general, the largest enlarging lesions that lend themselves to repeated measurements are selected as target lesions. To be selected, a lesion should demonstrate contrast enhancement, have clearly defined margins, have two perpendicular diameters of at least 10 mm, and be visible on two or more axial slices that are at most 5 mm apart with no interslice gap. If the slices are thicker than 5 mm, the selected lesions should measure two times the slice thickness on the baseline scan. To perform the size measurement, the maximal tumor diameter is obtained and then a second diameter is obtained at a right angle to the first. The product of these measurements is then used for purposes of comparison between imaging timepoints.

Non-measurable lesions are generally those that do not meet the above criteria. Tumors around a cyst or surgical cavity are also considered non-measurable unless a nodular component measuring 10 mm or greater in diameter is present.

4.2. **Non-enhancing Lesions**

In addition to enhancing lesions, non-enhancing lesions on T2/FLAIR images are reviewed when evaluating GBM response. Non-enhancing lesions are not measured but instead are monitored for changes in size. It is important to note that the extent of the non-enhancing component of the tumor can be difficult to determine since localized swelling and damage caused by radiation have a similar radiographic appearance. Changes in T2/FLAIR signal that suggest presence of an infiltrating tumor include mass effect, infiltration of the cortical ribbon, and location outside of the radiation field.

4.3. **Response Definitions**

GBM response to therapy is categorized into one of four categories: complete response, partial response, stable disease, or progression.
Complete response is achieved if all enhancing (measurable and non-measurable) lesions have disappeared for at least 4 weeks, there are no new lesions, and non-enhancing lesions have either improved or remain stable. Clinically, subjects must be off corticosteroids (or be receiving only physiological replacement doses) and show stable or improved clinical symptoms.

Partial response is achieved when all of the following requirements are met: the sum of the products of perpendicular diameters of all enhancing lesions is reduced by 50% or more (from baseline) for at least 4 weeks, there are no new lesions, there is no progression in non-measurable lesions, and non-enhancing lesions have either improved or remain stable. Clinically, subjects must be on a corticosteroid dose no greater than the dose they were receiving at the time of the baseline scan and they must show stable or improved clinical symptoms.

A subject is considered to have stable disease if all of the following are met: the subject does not qualify for complete response, partial response, or progressive response (described below), and non-enhancing T2/FLAIR lesions are stable. Subjects must be on either a lower dose of corticosteroids or be maintaining the same dose level as baseline. Clinical symptoms must also be stable.

Progressive disease is defined by the occurrence of any of the following:

- The sum of the products of perpendicular diameters of enhancing lesions is increased by 25% or more compared with the smallest tumor measurement obtained either at baseline or the timepoint with the best response for patients receiving either stable or increasing doses of corticosteroids.
- There is a significant increase in T2/FLAIR non-enhancing lesions compared to baseline or best response scans for patients receiving either stable or increasing doses of corticosteroids. The increase in T2/FLAIR non-enhancing lesions should not be attributable to other non-tumor causes (e.g., radiation therapy, demyelination, ischemic injury, etc.).
- Appearance of new lesions.
- Clear progression of non-measurable lesions.
- There is clear clinical deterioration that is not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, etc.) or changes in corticosteroid use.
- The subject does not return for evaluation due to death or deteriorating health.

A summary of these response definitions are provided in Table 1.
Table 1. Summary of RANO Response Criteria [7]

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Complete Response</th>
<th>Partial Response</th>
<th>Stable Disease</th>
<th>Progressive Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 enhancing disease</td>
<td>None</td>
<td>≥ 50% ↓</td>
<td>&lt; 50% ↓ but &lt; 25% ↑</td>
<td>≥ 25% ↑*</td>
</tr>
<tr>
<td>T2/FLAIR</td>
<td>Stable or ↓</td>
<td>Stable or ↓</td>
<td>Stable or ↓</td>
<td>↑↑</td>
</tr>
<tr>
<td>New lesion</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Present*</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>None</td>
<td>Stable or ↓</td>
<td>Stable or ↓</td>
<td>NA↓</td>
</tr>
<tr>
<td>Clinical status</td>
<td>Stable or ↑</td>
<td>Stable or ↑</td>
<td>Stable or ↑</td>
<td>↓*</td>
</tr>
<tr>
<td>Requirement for response</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>Any*</td>
</tr>
</tbody>
</table>

* Progression occurs when this criterion is present.
† Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

5. VirtualScopics Analysis of GBM

Our 21 CFR Part 11 and HIPAA compliant image analysis platform provides semi-automated tools for identifying enhancing lesion boundaries and automatically extracting structural measurements (longest diameter, shortest diameter) to facilitate RANO evaluations. Our system is human interactive allowing radiologists to view all frames of multi-framed image datasets and switch series within the same timepoint in order to identify target lesions and follow non-enhancing and non-measurable disease. Following the RANO criteria described above, VirtualScopics is able to deliver highly reproducible data and reliable response assessments that can be used to evaluate the efficacy of new therapeutics for GBM treatment.
6. References


