Assessment of treatment response in high grade gliomas: RANO criteria usage for an accurate radiology report.

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Learning objectives

1. Describe the key points of a structured radiology report to assess treatment response in high grade gliomas (Fig. 1), using the Response Assessment in Neuro-Oncology (RANO) criteria.
2. Explain the method for data gathering and analysis.
3. Specify how radiology reports based on RANO criteria provide an accurate evaluation of treatment response.

Images for this section:

**Fig. 1:** A 64 year old patient with right occipital high-grade glioma showing enhancement in a T1W C+ MRI.
Background

High grade gliomas are rapidly progressive brain tumours. Appropriate management requires the determination of whether the patient is responding to therapy or is progressing. Since 1990, the primary criteria used for the assessment of response to therapy in high-grade gliomas were those developed by Macdonald and colleagues. Those criteria incorporated 2-dimensional area measurements of contrast-enhancing tumour regions, corticosteroid dose at the time of the study, and assessment of patient clinical status in order to arrive at a designation of complete or partial response, stable disease or progression.

Improvements in imaging technology, use of radiotherapy, chemotherapy and antiangiogenic agents have prompted the need to change the response assessment. In 2010, the Response Assessment in Neuro-Oncology (RANO) Working Group published updated criteria to standardize response assessment and incorporated relevant clinical and treatment information as to arrive at a designation of complete or partial response, stable disease, progression and pseudoprogression.

The current treatment for newly diagnosed high-grade gliomas remains a surgical resection followed by radiotherapy with concurrent temozolamide (RT/TMZ) and then maintenance temozolamide for 6 months. The introduction of new treatments raised issues regarding pathophysiological and biological response of the tumour and the surrounding tissue. Wit et al in 2004 described the phenomenon known as pseudoprogression, which refers to subacute imaging changes in human gliomas subsequent to radiochemotherapy suggestive of progression, with or without associated clinical deterioration and which resolves spontaneously. Up to 30% of patients in their first MRI post radiochemotherapy will show increased contrast enhancement. The mechanisms why this occurs are still not fully understood. Some believe it is due to inflammatory tissue reaction secondary to vascular and oligodendroglial injury and others explain it as an exaggerated response to effective treatment. The phenomenon occurs in the first 3 months after radiochemotherapy and can persist up to 6 months after the treatment. This treatment related effect has implications for patient management and may result in premature discontinuation of effective adjuvant therapy.

Increased enhancement also occurs with surgery and other therapies. The surgical cavity can present enhancement in the 48 to 72 hours after surgery. In addition this enhancement can also be explained by the administration of local therapies. These include chemotherapy wafers, immunotoxins, regionally administered gene and
viral therapies, immunotherapies, brachytherapy, and stereotactic surgery\textsuperscript{3}. To avoid the misinterpretation of this enhancement as residual disease, a baseline MRI is recommended within 24 to 72 hours after surgery.

Another challenge for response criteria is the use of antiangiogenic agents, especially those targeting vascular endothelial growth factor (VEGF), such as bevacizumab, and the VEGF receptor, cediranib, which can produce a marked decrease in contrast enhancement as early as 1 or 2 days after the initiation of therapy. This phenomenon is known as pseudoresponse and can mislead to a false positive high radiological response rate. This agents affect vascular permeability, which in turn, influences the leakage of gadolinium into the brain and extent of contrast enhancement on imaging\textsuperscript{1,3}. Increasing evidence also suggests that antiangiogenic agents may increase the tendency of tumour the cell to take in existing blood vessels, which will in turn result in a non-enhancing phenotype.

For this reasons the inclusion of contrast enhancement changes and fluid-attenuated inversion recovery (FLAIR)/T2 hyperintensity into the RANO criteria increases the sensitivity in the detection of high-grade gliomas true progression\textsuperscript{9,10}.

**Images for this section:**

![Fig. 2: A 57 year old patient diagnose of pseudoprogresion after radiochemotherapy: coronal T1-contrast enhance MRI.](image-url)
Findings and procedure details

The application of RANO criteria enables:

- Standardization of protocols for planning, acquiring and interpreting MRI studies in the assessment of treatment response of high grade gliomas.
- Greater accuracy in the interpretation of MRI within the current clinical state, received treatments and time intervals between relevant clinical events of the patient with uniform and clinically-focused criteria.
- Reduction of false positive diagnosis of progression post radiochemotherapy and false positive diagnosis of response to treatment in patients receiving antiangiogenic drugs.

It is important to mention that the RANO criteria do not apply to dynamic studies with IV contrast or non-conventional MRI sequences like DWI, perfusion, ERM among others and the use of PET scan due to the fact there are still no extensive studies into these techniques and technologies to validate their use in patients with high grade gliomas.

We outline a series of issues to understand the process by which these criteria can be adapted and implemented in the radiological and clinical setting. It must be clear that the application of RANO criteria is for MRI only, and not for CT, unlike the Macdonald criteria.

What variables to take into account:

- MRI: T1WI C+ and T2WI/FLAIR.
- New enhancing lesions.
- Corticosteroid dose, and also any recent increase or reduction in patient’s dose.
- Clinical status. The RANO working group suggest using the Karnofsky status performance (KSP) scale, Eastern Cooperative Oncology Group performance status or WHO performance score to measure patient clinical deterioration. We prefer the use of KSP.
- Radiotherapy, chemotherapy and antiangiogenic agents being used by the patient. It is also important to know the last dose the patient received before the MRI imaging procedure.

How should the MRI be programmed?

- The MRI slice thickness should be less than 5mm and without any gaps. As for sequencing T1 pre and post contrast, and T2/FLAIR and as part of the study. The same protocol must be used with each patient, with the same
planes for contrast-enhanced T1 WI and FLAIR. It is preferable to acquire them in axial view.

- Patients should be imaged in the same MRI scanner or at least with the same magnet strength to reduce differences only related to these conditions, and if possible all the MRI studies of the same patient should be reviewed by the same radiologist.

**When to program the studies?**

- The baseline MRI study should correspond to the post-surgical MRI, and should ideally be performed in the first 48 hours after the surgery, no later than 72 hours after. There are some exceptions to this rule, which will be reviewed later.
- If a patient is under radiotherapy treatment a MRI study should be scheduled for 3 to 4 weeks after he has finished the treatment.
- Every 2 or 3 cycles of chemotherapy, each patient should undergo a MRI study to assess treatment response.
- Whenever the possibility that a response to treatment (either partial or complete) is the outcome of an MRI study, a confirmatory MRI should be performed no sooner than 4 weeks after.
- If possible, a standardised protocol should be planned in every hospital; it should integrate the workforce of the radiology department alongside with the neurosurgeons and neuro-oncologists who treat patients with high-grade gliomas.

**How to measure the lesions?**

- Measurable disease corresponds to contrast enhancing lesions at least 10mm long in 2 orthogonal diameters and visible in at least 2 slices with well-defined borders. (Fig. 3) If slice plus gap thickness equal more than 5mm the minimum lesion size would be 2 times the total. Areas of necrosis, cyst or cavity are not included within the diameter being measured.
- Non-measurable disease includes lesions that are too small (e.g. 13x7mm), have poorly defined margins or lesions that do not enhance or are only seen in T2WI/FLAIR (Fig. 4, 5 and 6).
- For measurable disease we have to select target lesions at the baseline study, to assess treatment response in every follow-up MRI study. The target lesions should be the largest preferred, no more than five, and suitable for reproducible measurements (Fig. 7).
- The measurements should not be made in strict anatomical axis, but measuring the largest diameter in any orientation and the second one orthogonal to this one. If the orientation of the maximal diameters of the lesions changes between the following MRI’s of the same patient, this is of no consequence, and the largest diameter in each MRI study will still be measured (Fig. 8).
• When there is more than one measurable lesion the variable to use is the sum of the products of diameters (SPD). To obtain it the products of the maximal diameters of each lesion must be added (Fig. 9).

**How to compare each new RM with to the previous studies of the patient?**

• We have already explained how the baseline MRI should be performed, but we also need to define what the nadir MRI is. The nadir episode is the previous MRI that shows the best response in the whole current line of treatment of the patient.

• When we are suspecting response to treatment we use the baseline MRI or the MRI before any treatment was started. When progression is what we suspect we compare it with the nadir MRI. The immediately previous MRI study is never taken as a reference for comparison unless it is the baseline or the nadir episode.

• When a new line of treatment is started the reference MRI changes also. The baseline MRI will no longer be the post-surgical, but the MRI previous to the beginning of the second line treatment. And the new nadir MRI will be the one with the best response during the course of the second line treatment.

• In every baseline/nadir MRI there is a corresponding baseline clinical status and corticosteroid dose.

• Frequently, in the first line treatment the baseline and nadir MRI are the same.

• In cases of pseudoprogression the post-surgical MRI is not taken into account for response assessment, but the first post-radiotherapy MRI instead.

• (Fig 10-13).

**How to register the clinical status and deterioration?**

• Like mentioned above we use the KPS scale (Table. 1).

• To assess clinical deterioration we need to compare the current KPS to the KPS in the nadir MRI. If in the nadir the KPS was of 100, a decrease of 30 or more points is needed to consider deterioration. Between 90 to 70, a decrease of 20 points or more would be needed, and if KPS is 60 points or less, clinical deterioration is established with a decrease of at least 10 points.

**Table 1. Karnofky Scale**

<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease.</td>
</tr>
</tbody>
</table>
90  Able to carry on normal activity; minor signs or symptoms of disease.
80  Normal activity with effort; some signs or symptoms of disease.
70  Cares for self; unable to carry on normal activity or to do active work.
60  Requires occasional assistance, but is able to care for most of his personal needs.
50  Requires considerable assistance and frequent medical care.
40  Disabled; requires special care and assistance.
30  Severely disabled; hospital admission is indicated although death not imminent.
20  Very sick; hospital admission necessary; active supportive treatment necessary.
10  Moribund; fatal processes progressing rapidly.
0   Dead

How to register the corticosteroid dosage?

- Corticosteroid dosage has to be compared with dosage administered at baseline or nadir MRI, just like clinical status has.
- An isolated increase in the dosage of corticosteroids without changes in any other variable is not considered as a criterion for disease progression. To be considered as progression it has to be associated with clinical deterioration or signs of radiological progression on MRI.
- The diagnosis of radiological disease progression must be made in a context of stable or increased corticoid doses from the nadir MRI dosage.

How to make a radiological conclusion?

- There are six possible conclusions we can come to when reporting a patient MRI with a high-grade glioma: complete response, partial response, stable disease, progression, pseudoprogression and pseudoresponse. Complete response (CR) means all target and non-target lesions have disappeared. Partial response (PR) is concluded when SPD decreases more than 50% from the value at baseline MRI. Stable disease diagnosis is made when the SPD variation is between less than 50% decrease and less than 25%
increase. And when the SPD increase is greater than or equal to 25% from the value at nadir MRI we conclude progression. If the MRI reported is within 12 weeks of radiation and/or chemotherapy pseudoprogression must be considered.

- Due to technical factors some target lesions cannot always be evaluated in the following MRI’s and these lesions should be termed "unable to assess" lesions.

- Patients with non-measurable disease cannot get a CP or PR diagnosis. The best option in these cases of apparent response is SD.

- To come to the best possible radiological conclusion, radiologists need to know under which line of treatment the patient is, meaning: radiotherapy, chemotherapy or antiangiogenic agents and the date of the last treatment episode.

- If the current MRI is prior to the conclusion of radiochemotherapy treatment or before the conclusion of 12 weeks post-radiochemotherapy we suspect:
  - Pseudoprogression if there is a growth of existing lesions, appearance of new lesions or enhancement that simulates tumour growth on the MRI. Subsequent follow-up imaging will help determine whether the initial lesion growth was true progression or pseudoprogression (Fig. 14). It is believed that diffusion weighted imaging, MRI perfusion and spectroscopy can help distinguish pseudoprogression from true tumour growth, but they are still experimental.

- Progression can only be diagnosed when new enhancing lesions appear outside the radiotherapy radiation field (for example, under the high-dose region or 80% isodose line) or there is histological progression by biopsy in comparison to previous pathological sample. One exception to this rule are patients under antiangiogenic therapy alone, in these cases any increase is SPD greater than or equal to 25% from the value at nadir MRI, arising of new enhancing lesions or significant T2/FLAIR signal growth will also be considered as progression.

- We do not conclude progression if there is clinical deterioration alone without radiographic or histologic signs of progression.

- If patients are being treated with antiangiogenic agents it is possible to see a pseudoresponse in the first 4 weeks after the conclusion of the treatment, an MRI should be performed in 4 weeks to see if the response to treatment persists. In this case we confirm CR, PR or pseudoresponse as the diagnosis, depending on the result of the second MRI (Fig. 15).

To summarize this section, in a follow-up MRI visit you must:

1. Measure the previously defined target lesions and calculate the SPD, if it is the case.
2. Qualitatively assess non-target lesions, if there is any. Including enhancing non-target lesion and lesions only seen on T2/FLAIR.

3. Search for new lesions.

4. Determine if the current MRI is before or after the 12 week period post-radiochemotherapy conclusion.

5. If patient is under antiangiogenic treatment.

6. Combine lesion assessment with neurological and steroid dose information.

7. Come to a response assessment conclusion (Table 2).

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**Table 2. Summary of the Proposed RANO Response Criteria**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1 gadolinium enhancing disease</strong></td>
<td>None</td>
<td>Decrease</td>
<td>&lt;50%</td>
<td># 25% increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50%</td>
<td>decrease, but &lt; 25% increase</td>
<td></td>
</tr>
<tr>
<td><strong>T2/FLAIR</strong></td>
<td>Stable or #</td>
<td>Stable or #</td>
<td>Stable or #</td>
<td>#</td>
</tr>
<tr>
<td><strong>New lesion</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td>None</td>
<td>Stable or #</td>
<td>Stable or #</td>
<td>Stable or #</td>
</tr>
<tr>
<td><strong>Clinical Status</strong></td>
<td>Stable or #</td>
<td>Stable or #</td>
<td>Stable or #</td>
<td>Stable or #</td>
</tr>
<tr>
<td><strong>Requirement for response</strong></td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>Any</td>
</tr>
</tbody>
</table>


* Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

**Images for this section:**
Fig. 3: Axial contrast enhanced T1W MRI that shows an example of measurable disease.
Fig. 4: Axial T1-contrast enhanced MRI that shows irregular enhancement of wall cavity an example of non-measurable disease.
Fig. 5: Axial T1-contrast enhanced MRI that shows two foci of enhancement in the occipital lobe. The lesions would be non-measurable disease since its longest diameters are smaller than 10mm.
**Fig. 6:** Axial T1-contrast enhanced MRI shows a nodular enhancing right sided lesion of more than 10mm (measurable disease) and posterior to it a linear irregular enhancing lesion that corresponds to non-measurable disease.

**Fig. 7:** Choosing target lesions algorithm
**Fig. 8:** Axial T1-contrast enhanced MRI showing enhancing tumour with measurable and non-measurable disease on the left side. Same image on the right with draw lines of how take the correct measurements of the tumor.

**Fig. 9:** Sum of the products of the diameters (SPD)
**Fig. 10:** Graphic interpretation of tumor load vs time on how to compare every new RM with the previous studies of the patient and which MRI corresponds to baseline MRI.

**Fig. 11:** Graphic interpretation of tumor load vs time on how to compare every new RM with the previous studies of the patient and how to choose nadir MRI in the case of response to treatment.
**Fig. 12:** Graphic interpretation of tumor load vs time on how to compare every new RM to the previous studies of the patient and how to choose the nadir MRI in the case of 2nd line of treatment.

**Fig. 13:** Graphic interpretation of tumor load vs time on how to compare every new RM with the previous studies of the patient in the case of pseudoprogression.
Fig. 14: Pseudoprogression. A 59-year-old man with GBM. An MR image obtained 1 month after RT-TMZ demonstrates an expansion of the right temporal lesion. Reductions in both the enhancing portion and the surrounding abnormal hyperintense area in the T2-weighted imaging were seen in the follow-up MRI.
Fig. 15: Pseudoresponse is characterized by a marked decreased in the enhancing portion of the lesion after initiation of treatment. In some cases, the FLAIR sequence shows a clear expansion of the lesion.
Conclusion

The integration of clinical and therapeutic variables with MRI parameters offers a more reliable and accurate evaluation of treatment response and the real state of the disease, with clinically relevant outcomes when compared to an evaluation based only on imaging variables. The correct use of RANO criteria requires trained radiologists and proper models to gather the relevant patient information.

Personal information

References