Glioblastoma Treatment Response Versus Pseudoresponse: A Crash Course on the RANO, iRANO, and Modified RANO Assessment Criteria in Dealing with a Pseudo-friend

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Background

- Glioblastoma (GBM, WHO grade IV) is the most common primary brain malignancy in the United States, with an *annual incidence of 4-5 per 100,000 people*
- Since 2005, the **Stupp protocol** [maximal safe tumor resection followed by radiotherapy + temozolomide] has been standard of care for the initial treatment of GBM
- Newer **anti-angiogenic agents** and **immunotherapies** have since been tested in recent and ongoing clinical trials
- However, these agents can **confound tumor surveillance imaging**, creating a diagnostic dilemma for radiologists and neurooncologists

RANO criteria (2010)

- The **response assessment in neuro-oncology (RANO)** criteria was developed in 2010 as a detailed set of imaging and clinical criteria to determine treatment outcomes (replaces the *Macdonald criteria*)
- Addresses:

Pseudoprogression

Completed chemoRT

Worsened imaging appearance followed by stability/improvement without change in therapy
Associated with chemoradiation, immunotherapy

Pseudoresponse

Rapid improvement in imaging appearance without significant benefit to overall survival, may be followed by stable/progressive disease
Associated with anti-angiogenics (bevacizumab, cediranib)

RANO Rules

Baseline MRI should be performed 24-48hrs post-op, with DWI
Measurement = product of max. cross-sectional *enhancing* component

- margins must be clearly defined and $\geq 10\text{mm}$
- do not include cystic/surgical cavity
- multiple lesions: measure 2 largest (min.) and up to 5 (max.), then sum up

(ie. $12.6\text{mm} \times 13.3\text{mm} = 167.6\text{mm}$)

Non-measurable disease: unidimensional, $< 10\text{mm}$, ill-defined margins, nonenhancing component (T2/FLAIR)

* PD should not be diagnosed radiographically within 3 months following completion of concomitant TMZ + RT (when pseudoprogression is most prevalent), unless there is:
1) New enhancement outside the radiation field
2) Pathologic confirmation of unequivocal progression

Important considerations:

- CR or PR must be confirmed on follow-up imaging ≥ 4 weeks later
- If equivocal (stable vs PD), observe patient closely and re-image at 4 week intervals

Exclude:

- Nonenhancing T2/FLAIR changes caused by comorbid events
- Clinical deterioration from seizures, adverse therapy/medication effects, CVA, infection

iRANO criteria (2015)

- The **immunotherapy response assessment in neuro-oncology (iRANO)** criteria was proposed in 2015 to decrease the likelihood of premature discontinuation of potentially beneficial immunotherapies
- Revises criteria to account for immunotherapy pseudoprogression

- * Immunotherapies do not show pseudoresponse, therefore any decrease in tumor size = treatment response
- * Any changes in corticosteroid dose within 2 weeks of imaging makes the MRI non-evaluable

Modified RANO criteria (2017)

- The **modified response assessment in neuro-oncology (modified RANO)** criteria attempts to address deficiencies of the 2010 criteria:
1. *Bidirectional measurements tend to overestimate tumor volume*
2. *Thresholds based on "% change" are biased toward small tumors*
3. *Evaluation of non-enhancing (T2/FLAIR) component is subjective and does not accurately predict overall survival*

Modifications: use post-radiation MRI as baseline, volumetrics when available, decreased importance of T2/FLAIR component, introduces "preliminary response" and "preliminary progression" terms for initial imaging that is then "confirmed" ≥ 4 weeks later

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Nothing to disclose

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RANO Criterion	Complete response (CR)	Partial response (PR)	Stable disease (SD)	Progressive disease (PD)
T1 gadolinium enhancing disease	None	$\geq 50\% \downarrow$	$< 50\% \downarrow$ but $< 25\% \uparrow$	$\geq 25\% \uparrow$
T2/FLAIR	Stable or $\downarrow$	Stable or $\downarrow$	Stable or $\downarrow$	Significant $\uparrow$
New lesion	None	None	None	Present
Corticosteroids	None	Stable or $\downarrow$	Stable or $\downarrow$	N/A
Clinical status	Stable or $\uparrow$	Stable or $\uparrow$	Stable or $\uparrow$	$\downarrow$
Requirement for response	All	All	All	Any