

When the MRI is misleading:

How to evaluate tumour response, progression vs pseudoresponse and pseudoprogression

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Outline

- Importance of response assessment (RA)
- RA criteria in neuro-oncology
- Pseudoprogression
- Pseudoresponse
- Future of RA in neuro-oncology



Why is RA critical in neuro-oncology

- Clinical decisions:
 - Proceed effective treatments
 - Stop non-beneficial treatments
 - Avoid unnecessary toxicity and cost
- Evaluation of new strategies for brain tumors
 - Identify promising novel treatments
 - Abandon inactive new treatments



What are the ideal RA criteria

- Accurate
- Reliable
- Predictive
- Easy to use



Evolution of RA criteria in Neuro-oncology

- RECIST criteria
- Macdonald criteria
- RANO criteria



- RECIST criteria
 - Response Evaluation Criteria in Solid Tumors
 - Introduced in 2000. Updated in 2009
 - Single lesion: longest diameter in the axial plane
 - Multiple lesions: sum of individual diameters
 - Nonmeasurable: Cystic or necrotic tumor foci



- RECIST criteria
- Concordance with two-dimensional and volumetric measurements in high-grade gliomas.

Table 3. Concordance among the different criteria in assessing the type of progression

	RECIST	RECIST + F	Macdonald	RANO
RECIST		0.83 (0.72–0.95)	0.98 (0.93-1.00)	0.76 (0.62-0.92)
RECIST + F	61/68 (90%)		0.81 (0.69-0.93)	0.92 (0.84–1.00)
Macdonald	67/68 (99%)	60/68 (88%)		0.78 (0.65–0.91)
RANO	58/68 (85%)	65/68 (96%)	59/68 (87%)	

Upper values represent the kappa statistic and its 95% confidence interval. Lower values represent the observed frequency and percent.



Fig 2. Kaplan-Meier estimates of progression-free survival according to the different criteria.

Gállego Pérez-Larraya J, etal. Response assessment in recurrent glioblastoma treated with irinotecan-bevacizumab: comparative analysis of the Macdonald, RECIST, RANO, and RECIST + F criteria. Neuro-oncology. 2012, 14(5): 667-673.



- RECIST criteria
 - No prospective validation in high-grade gliomas
 - Rarely used in practice and clinical trials



- Macdonald criteria
 - Two-dimensional
 - Tumor size:

Maximum cross-sectional area of <u>enhancing</u> tumor on CT or MRI

- Corticosteroids and neurologic status





Macdonald criteria

• Limitations

- Measures enhancing component only
- Does not address non-enhancing tumors
- Pseudoprogression
- Anti-angiogenic treatments
 - * Pseudoresponse
 - * Non-enhancing progression



RANO criteria

- General principles of RANO criteria
 - Two-dimensional
 - Enhancing and non-enhancing tumor areas evaluated
 - Durability of response (> 4 wks)
 - Steroid dose and clinical status must be recorded

Criterion	CR ^a	PR ^a	SD	PD ^b
T1-Gd+	None	$\geq 50\% \downarrow$	< 50% ↓ to < 25% ↑	$\geq 25\% \uparrow^{\ddagger}$
T2/FLAIR	Stable or \downarrow	Stable or \downarrow	Stable or ↓	↑ [‡]
New lesion	None	None	None	Present [‡]
Corticosteroids	None	Stable or ↓	Stable or ↓	NA ^c
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	\downarrow^{\ddagger}
Requirement for response	All	All	All	Any [‡]

^a Must be sustained for 4 weeks

^b Progression occurs when any criteria marked with a *double dagger* is present

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

 \downarrow —decrease; \uparrow —increase; CR—complete response; FLAIR—fluid-attenuated inversion recovery; Gd+—gadolinium; PD—progressive disease; PR—partial response; SD—stable disease.

Wen PY, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol. 2010, 28(11):1963-72.



- Definition
 - Treatment-related
 - Increase in enhancement and/or edema on MRI
 - Usually occurs within the first 3 months
 - Subsequently stabilizes or decreases
 - Subsides without further treatment or sometimes progresses to radiation necrosis



Male, 39 yrs, biopsy proven GBM



Post RT (75 Gy)



Male, 65 yrs, GBM



Pre-op Post-op Post-RT/TMZ 4 m TMZ 8 m TMZ



• Mechanism





RANO allows for retrospective attribution when changes are equivocal



Wen PY, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol. 2010, 28(11):1963-72.





- Magnetic Resonance Spectroscopy (MRS)
 - Proton-based imaging
 - Identify metabolic compounds

Metabolite	Property	
Choline (Cho)	Cell membrane marker	
N- acetylaspartate (NAA)	Neuronal marker	
Creatine (Cr)	Energy metabolism	
Lactate	Product of anaerobic glycolysis	
Lipid	Products of brain destruction	





- Magnetic Resonance Spectroscopy (MRS)
 - Tumor v.s. Necrosis: higher Cho/Cr and lower NAA/Cr
 - Cho/NAA cut-off: 1.7
 - 3D MRS

Sensitivity: 94.1%

Specificity: 100%

Diagnostic accuracy: 96.2%

Zeng QS, et al. Multivoxel 3D proton MR spectroscopy in the distinction of recurrent glioma from radiation injury. J Neurooncol. 2007, 84(1): 63-9





Male, 46 yrs, GBM



Post treatment



3D MRS

Cho/NAA: 1.35

Cho/Cr: 1.63

NAA/Cr: 1.21



15 m after





Female, 32 yrs, AA





Post treatment

3D MRS

Cho/NAA: 2.91

Cho/Cr: 2.63

NAA/Cr: 0.90

H&E staining





- Limitations
 - Susceptibility to artefact (e.g. posterior fossa)
 - Low spatial resolution
 - Decreased specificity for heterogeneous tissue
 - No universally accepted ratios



Perfusion MRI

• Perfusion MRI

- Evaluate angiogenesis: vascular density, vascular permeability
- Various techniques:
 - Arterial spin labeling (ASL)
 - Dynamic susceptibility contrast-enhanced perfusion imaging (DSC)
 - Dynamic contrast-enhanced T1-weighted imaging (DCE)
- Parameter
 - Absolute cerebral blood flow (CBF)
 - Cerebral blood volume (CBV)
 - relative CBV (rCBV)



Perfusion MRI

Primary GBM



Post-treatment necrosis



Endothelial hyperplasia Glomeruloid vessels

Endothelial hyalinisation Vascular thrombosis

















Perfusion MRI

- Limitations
 - Low resolution: small enhanced lesion
 - DSC-MRI: susceptibility to artefact (e.g. posterior fossa)
 - Contrast leak: fast clearance of gadolinium from blood
 - rCBV distortion: grey and white matter proportion



Positron emission tomography (PET)

• PET

- Molecular imaging
- Tracers targeting metabolic pathways

FDG: glucose metabolism

MET: methionine (essential aminoacide) metabolism

FLT: thymidine kinase-1 activity (DNA synthesis)

FDOPA: dopamine receptors





Advantages

- High tumor-to-background contrast





• Advantages

- Applicable for both high- and low-grade gliomas

MRIT1 FDG-PET MET-PET



WHO II

WHO IV





T1 + C MET FET





Radiation injury





• Limitation

- Low resolution: false negative
- Nonspecific uptake: false positive

FDG: metabolic burst of active inflammatory cells

FET: vascular malformations & dural venous sinuses

FDOPA: corpus striatum







Radiation-induced necrosis



- Definition
 - Observed in anti-VEGF/VEGFR therapy
 - Rapid decrease in enhancement
- Mechanisms
 - Rapid normalization of abnormally permeable blood vessels
 - Reduction of vasogenic edma
 - NOT antitumor effect
 - Infiltrative phenotype



Avastin + CPT-110 cycle7 cycles

T1 + C



T2 FLAIR



- Differentiation tools
 - T2 FLAIR
 - Contrast-enhanced T1-weighted subtraction maps
 - Differential quantitative T2 mapping
 - Diffusion MRI
 - High b-value MR diffusion imaging
 - MR perfusion imaging



Female, 44 yrs, rGBM with BEV



T1 substraction map

Ellingson BM, et al. Recurrent glioblastoma treated with bevacizumab: contrast-enhanced T1-weighted subtraction maps improve tumor delineation and aid prediction of survival in a multicenter clinical trial. Radiology. 2014, 271(1):200-10.





Differential quantitative T2 mapping

Ellingson BM, et al. Quantification of edema reduction using differential quantitative T2 (DQT2) relaxometry mapping in recurrent glioblastoma treated with bevacizumab. J Neurooncol. 2012, 106(1):111-9.



Future of RA in neuro-oncology

- Standardization and ease of implementation
- Novel imaging tools: APT MR, Volumetric analysis
- Combination of multiple techniques: fMRI, PET & SPECT
- Updated guidelines:
 - RANO criteria for high-grade & low-grade gliomas
 - RANO criteria for brain metastases
 - RANO criteria for meningiomas
 - RANO criteria for pediatric brain tumors (RAPNO)

To be continued...



Thank you!