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S.E.N.R
Sociedad Española de Neurorradiología

Protocolo de RM en el diagnóstico y seguimiento tumoral. Nuevas recomendaciones RANO.

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Neuro-Oncology

189

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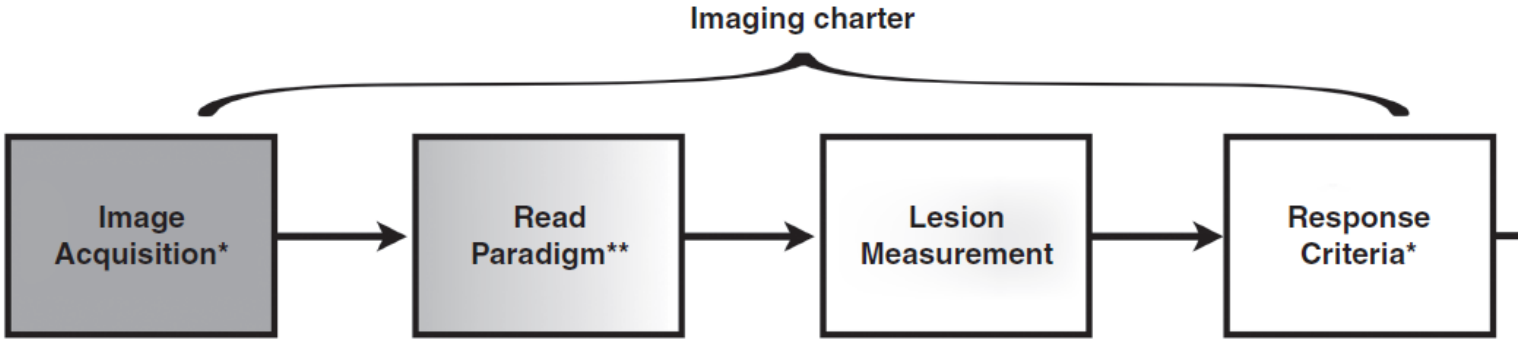
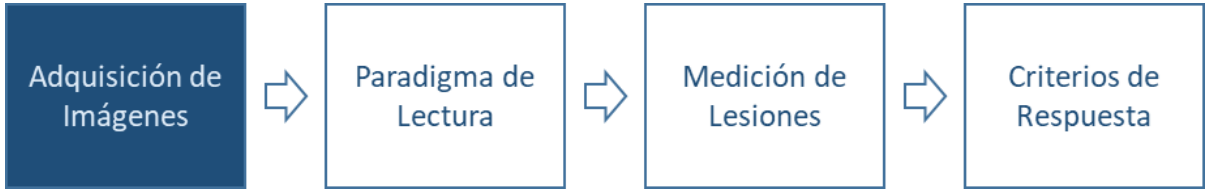
Radiographic read paradigms and the roles of the central imaging laboratory in neuro-oncology clinical trials

Benjamin M. Ellingson, Matthew S. Brown, Jerrold L. Boxerman, Elizabeth R. Gerstner, Timothy J. Kaufmann, Patricia E. Cole, Jeffrey A. Bacha, David Leung, Amy Barone, Howard Colman, Martin J. van den Bent, Patrick Y. Wen, W. K. Alfred Yung, Timothy F. Cloughesy, and Jonathan G. Goldin





Protocolo de RM:

- Protocolo de Diagnóstico.
- Protocolo de Seguimiento:

  Brain Tumor Imaging Protocol (BTIP).

Protocolo de RM. Diagnóstico

MR Imaging of Neoplastic Central Nervous

REVIEW ARTICLE

M. Essig
N. Anzalone
S.E. Combs
A. Dörfler
S.-K. Lee
P. Picozzi
À. Rovira
M. Weller
M. Law

Table 3: Standard protocol for brain tumor imaging based on expert panel discussion following the framework of the ACRIN 6686 component of the RTOG 0825 protocol[73]

Standardized MR imaging protocol
3-Plane localizer/scout (in order of acquisition)
T1-weighted precontrast (spin-echo)
T2-weighted axial
FLAIR (optional to perform after contrast)
T1 map (quantitation) for DCE MR imaging—3D gradient-echo T1 or 2D TSE/FSE T1[a]
DWI and/or DTI (can extract DWI data trace/ADC from DTI)[a]
T2* DSC MR imaging (after presaturation DCE MR imaging sequence)[a]
T1-weighted postcontrast (spin-echo)
Functional language, auditory, visual, motor testing, and MRS[a]
Can do FLAIR before DSC MR imaging
SWI, gradient-echo, additional optional sequences[a]
General parameter recommendations
Section thickness not greater than 5 mm
Delay is recommended, which can be built in by performing DWI and/or DTI before acquiring T1 sequences. Another option is to perform FLAIR (or even T2) before T1 sequences, which may give additional sensitivity for leptomeningeal disease[74]
Target duration ≤30 minutes (maximum, 1.5–2.0 hr)

Note:—ACRIN indicates American College of Radiology Imaging Network; SWI, susceptibility-weighted imaging; RTOG = Radiation Therapy Oncology Group.
[a] Part of the ACRIN 6686 protocol but can be used as an adjunct in the clinical brain tumor protocol.

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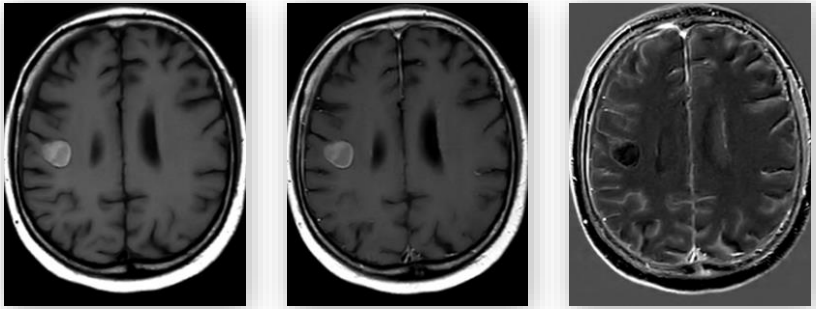
- Secuencias T1 pre y postcontraste, T2/FLAIR, DWI.
- Grosor de corte ≤ 5mm.
- Contraste dosis única (0.1mM/Kg)
- Retraso de hasta 20 min post-contraste.
- Técnicas adicionales optativas.

T1+Gad − T1 = Captación



Protocolo de RM. Seguimiento. BTIP

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Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials

Benjamin M. Ellingson, Martin Bendszus, Jerrold Boxerman, Daniel Barboriak, Bradley J. Erickson, Marion Smits, Sarah J. Nelson, Elizabeth Gerstner, Brian Alexander, Gregory Goldmacher, Wolfgang Wick, Michael Vogelbaum, Michael Weller, Evanthia Galanis, Jayashree Kalpathy-Cramer, Lalitha Shankar, Paula Jacobs, Whitney B. Pope, Dewen Yang, Caroline Chung, Michael V. Knopp, Soonme Cha, Martin J. van den Bent, Susan Chang, W.K. Al Yung, Timothy F. Cloughesy, Patrick Y. Wen, Mark R. Gilbert, and the Jumpstarting Brain Tumor Drug Development Coalition Imaging Standardization Steering Committee

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See the editorial by Sul and Krainak, on pages 1179–1180.

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Consensus recommendations for a standardized brain tumor imaging protocol for clinical trials in brain metastases

Timothy J. Kaufmann, Marion Smits, Jerrold Boxerman, Raymond Huang, Daniel P. Barboriak, Michael Weller, Caroline Chung, Christina Tsien, Paul D. Brown, Lalitha Shankar, Evanthia Galanis, Elizabeth Gerstner, Martin J. van den Bent, Terry C. Burns, Ian F. Parney, Gavin Dunn, Priscilla K. Brastianos, Nancy U. Lin, Patrick Y. Wen, and Benjamin M. Ellingson

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RM Seguimiento. BTIP (2015)

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See the editorial by Sul and Krainak, on pages 1179–1180.

Protocolo mínimo

Table 1. Minimum standard 1.5 T & 3 T MRI protocol

	3D T1w Pre[b]	Ax 2D FLAIR[c]	Ax 2D DWI	Ax 2D T2w[d,e]	3D T1w Post[b]
Sequence	IR-GRE[a,f]	TSE[c]	SS-EPI[g]	TSE[c]	IR-GRE[a,f]
Plane	Sagittal/axial	Axial	Axial	Axial	Sagittal/axial
Mode	3D	2D	2D	2D	3D
TR [ms]	2100[m]	>6000	>5000	>2500	2100[m]
TE [ms]	Min	100–140	Min	80–120	Min
TI [ms]	1100[n]	2000–2500[h]			1100[n]
Flip angle	10°–15°	90°/≥160°	90°/180°	90°/≥160°	10°–15°
Frequency	≥172	≥256	≥128	≥256	≥172
Phase	≥172	≥256	≥128	≥256	≥172
NEX	≥1	≥1	≥1	≥1	≥1
FOV	256 mm	240 mm	240 mm	240 mm	256 mm
Slice thickness	≤1.5 mm	≤4 mm[i]	≤4 mm[i]	≤4 mm[i]	≤1.5 mm
Gap/spacing	0	0	0	0	0
Diffusion options[j]			$b = 0$, 500, 1000 s/mm^2 ≥3 directions		
Parallel imaging	Up to 2x	Up to 2x	Up to 2x	Up to 2x	Up to 2x
Scan time (approx) (benchmarked on 3 T Skyra)	5–10 min (5:49 for 1 mm isotropic)	4–8 min (3:22 for 2D FLAIR)	2–4 min (1:22 for 3 direction DWI and 3 b-values)	4–8 min (5:10 for dual echo)	5–10 min (5:49 for 1 mm isotropic)

Contrast Injection[k]

Recomendado 1.5T

Table 3. Recommended 1.5T protocol

	3D T1w Pre	Ax 2D FLAIR	Ax 2D DWI	Ax 2D T2w	3D T1w Post[b]
Sequence	IR-GRE[a,e]	TSE[c]	EPI[f]	TSE[c]	IR-GRE[a,e]
Plane	Sagittal/axial	Axial	Axial	Axial	Sagittal/axial
Mode	3D	2D	2D	2D	3D
TR [ms]	2100[g]	>6000	>5000	>3500	2100[g]
TE [ms]	Min	100–140	Min	100–120	Min
TI [ms]	1100[h]	2200			1100[h]
Flip angle	10°–15°	90°/≥160°	90°/180°	90°/≥160°	10°–15°
Frequency	≥172	≥256	128	≥256	≥172
Phase	≥172	≥256	128	≥256	≥172
NEX	≥1	≥1	≥1	≥1	≥1
FOV	256 mm	240 mm	240 mm	240 mm	256 mm
Slice thickness	≤1.5 mm	≤4 mm	≤4 mm	≤4 mm	≤1.5 mm
Gap/spacing	0	0	0	0	0
Diffusion options[i]			$b = 0$, 500, and 1000 s/mm^2 ≥3 directions		
Parallel imaging	No	Up to 2x	Up to 2x	Up to 2x	No
Scan time (approximate)	5–10 min	4–5 min	3–5 min	3–5 min	5–10 min

Contrast Injection[j]

Recomendado 3T

Table 2. Recommended 3T protocol

	3D T1w Pre	Ax 2D FLAIR	Ax 2D DWI	Ax 2D T2w	3D T1w Post[b]
Sequence	IR-GRE[a,e]	TSE[c]	EPI[f]	TSE[c]	IR-GRE[a,e]
Plane	Sagittal/axial	Axial	Axial	Axial	Axial/sagittal
Mode	3D	2D	2D	2D	3D
TR [ms]	2100[g]	>6000	>5000	>2500	2100[g]
TE [ms]	Min	100–140	Min	80–120	Min
TI [ms]	1100[h]	2500			1100[h]
Flip angle	10°–15°	90°/≥160°	90°/180°	90°/≥160°	10°–15°
Frequency	256	≥256	128	≥256	256
Phase	256	≥256	128	≥256	256
NEX	≥1	≥1	≥1	≥1	≥1
FOV	256 mm	240 mm	240 mm	240 mm	256 mm
Slice thickness	1 mm	3 mm	3 mm	3 mm	1 mm
Gap/spacing	0	0	0	0	0
Diffusion options			$b = 0$, 500, and 1000 s/mm^2 ≥3 directions		
Parallel imaging	Up to 2x	Up to 2x	Up to 2x	Up to 2x	Up to 2x
Scan time (approx)	5–8 min	4–5 min	3–5 min	3–5 min	5–8 min

Contrast Injection[j]

RM Seguimiento. BTIP-BM (2020)

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Consensus recommendations for a standardized brain tumor imaging protocol for clinical trials in brain metastases

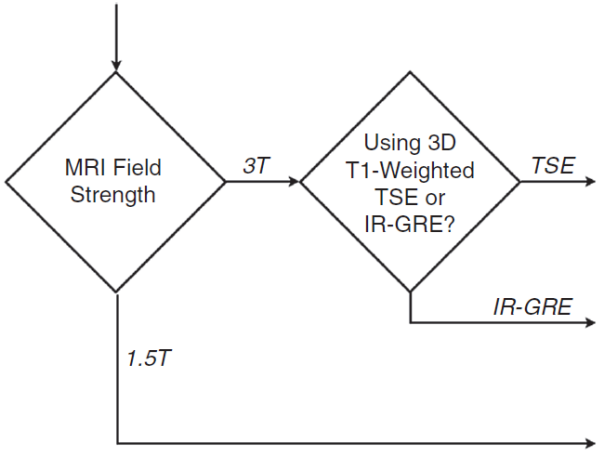


Table 1: "Ideal" Recommended 3T Protocol
- *Use 3D T1w TSE in place of 3D T1w IR-GRE*
- *1mm isotropic resolution on 3D scans*
- *Optional DSC Perfusion*

Table 2: Minimum Standard 3T Protocol
- *Use 3D T1w IR-GRE + Additional 2D SE Scans*
- *1mm isotropic resolution on 3D scans*

Table 3: Minimum Standard 1.5T Protocol
- *Use 3D T1w IR-GRE + Additional 2D SE Scans*
- *≤1.5mm isotropic resolution on 3D scans*

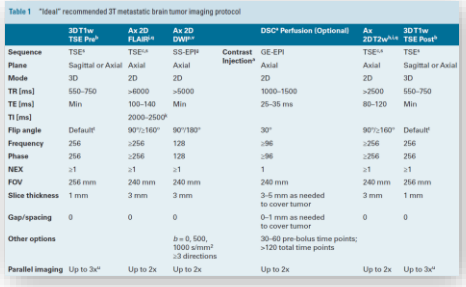


Table 1 "Ideal" recommended 3T metastatic brain tumor imaging protocol

	3D T1w TSE Pre[b]	Ax 2D FLAIR[c,d]	Ax 2D DWI[e,n]		DSC[f] Perfusion (Optional)	Ax 2DT2w[h,i,k]	3D T1w TSE Post[b]
Sequence	TSE[k]	TSE[c,d]	SS-EPI[e]	Contrast Injection[a]	GE-EPI	TSE[c,k]	TSE[k]
Plane	Sagittal or Axial	Axial	Axial		Axial	Axial	Sagittal or Axial
Mode	3D	2D	2D		2D	2D	3D
TR [ms]	550–750	>6000	>5000		1000–1500	>2500	550–750
TE [ms]	Min	100–140	Min		25–35 ms	80–120	Min
TI [ms]		2000–2500[d]					
Flip angle	Default[c]	90°/≥160°	90°/180°		30°	90°/≥160°	Default[c]
Frequency	256	≥256	128		≥96	≥256	256
Phase	256	≥256	128		≥96	≥256	256
NEX	≥1	≥1	≥1		1	≥1	≥1
FOV	256 mm	240 mm	240 mm		240 mm	240 mm	256 mm
Slice thickness	1 mm	3 mm	3 mm		3–5 mm as needed to cover tumor	3 mm	1 mm
Gap/spacing	0	0	0		0–1 mm as needed to cover tumor	0	0
Other options			b = 0, 500, 1000 s/mm² ≥3 directions		30–60 pre-bolus time points; >120 total time points		
Parallel imaging	Up to 3x[m]	Up to 2x	Up to 2x		Up to 2x	Up to 2x	Up to 3x[d]

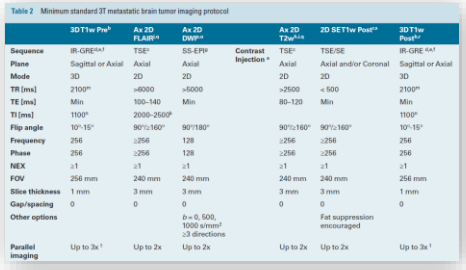


Table 2 Minimum standard 3T metastatic brain tumor imaging protocol

	3D T1w Pre[b]	Ax 2D FLAIR[c,d]	Ax 2D DWI[e,n]		Ax 2D T2w[h,i,k]	2D SE T1w Post[c,k]	3D T1w Post[b,c]
Sequence	IR-GRE[c,e,k,l]	TSE[c]	SS-EPI[e]	Contrast Injection [a]	TSE[c]	TSE/SE	IR-GRE [c,e,l]
Plane	Sagittal or Axial	Axial	Axial		Axial	Axial and/or Coronal	Sagittal or Axial
Mode	3D	2D	2D		2D	2D	3D
TR [ms]	2100[m]	>6000	>5000		>2500	< 500	2100[m]
TE [ms]	Min	100–140	Min		80–120	Min	Min
TI [ms]	1100[n]	2000–2500[d]					1100[n]
Flip angle	10°-15°	90°/≥160°	90°/180°		90°/≥160°	90°/≥160°	10°-15°
Frequency	256	≥256	128		≥256	≥256	256
Phase	256	≥256	128		≥256	≥256	256
NEX	≥1	≥1	≥1		≥1	≥1	≥1
FOV	256 mm	240 mm	240 mm		240 mm	240 mm	256 mm
Slice thickness	1 mm	3 mm	3 mm		3 mm	3 mm	1 mm
Gap/spacing	0	0	0		0	0	0
Other options			b = 0, 500, 1000 s/mm² ≥3 directions			Fat suppression encouraged	
Parallel imaging	Up to 3x[f]	Up to 2x	Up to 2x		Up to 2x	Up to 2x	Up to 3x[f]

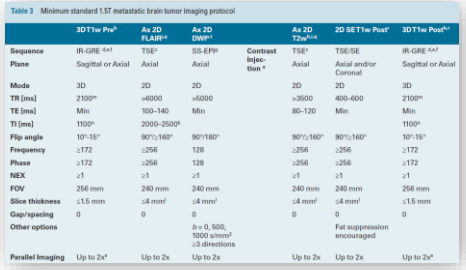
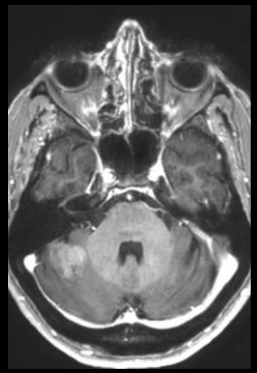


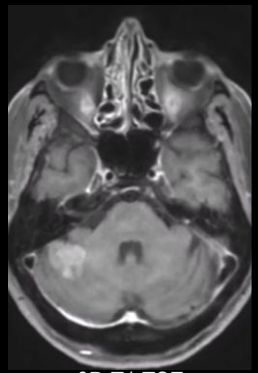
Table 3 Minimum standard 1.5T metastatic brain tumor imaging protocol

	3D T1w Pre[b]	Ax 2D FLAIR[c,d]	Ax 2D DWI[e,f]		Ax 2D T2w[h,i,k]	2D SE T1w Post[c]	3D T1w Post[b,c]
Sequence	IR-GRE [c,e,l]	TSE[c]	SS-EPI[e]	Contrast Injection [a]	TSE[c]	TSE/SE	IR-GRE [c,e,l]
Plane	Sagittal or Axial	Axial	Axial		Axial	Axial and/or Coronal	Sagittal or Axial
Mode	3D	2D	2D		2D	2D	3D
TR [ms]	2100[m]	>6000	>6000		>3500	400–600	2100[m]
TE [ms]	Min	100–140	Min		80–120	Min	Min
TI [ms]	1100[n]	2000–2500[d]					1100[n]
Flip angle	10°-15°	90°/≥160°	90°/180°		90°/≥160°	90°/≥160°	10°-15°
Frequency	≥172	≥256	128		≥256	≥256	≥172
Phase	≥172	≥256	128		≥256	≥256	≥172
NEX	≥1	≥1	≥1		≥1	≥1	≥1
FOV	256 mm	240 mm	240 mm		240 mm	240 mm	256 mm
Slice thickness	≤1.5 mm	≤4 mm[j]	≤4 mm[j]		≤4 mm[j]	≤4 mm[j]	≤1.5 mm
Gap/spacing	0	0	0		0	0	0
Other options			b = 0, 500, 1000 s/mm² ≥3 directions			Fat suppression encouraged	
Parallel Imaging	Up to 2x[g]	Up to 2x	Up to 2x		Up to 2x	Up to 2x	Up to 2x[g]

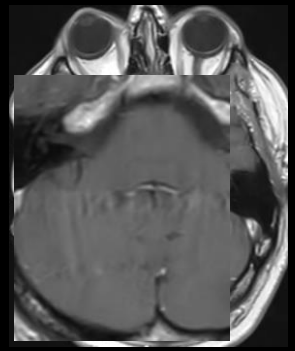
Secuencias 3D-T1 TSE (VISTA, CUBE, SPACE..)



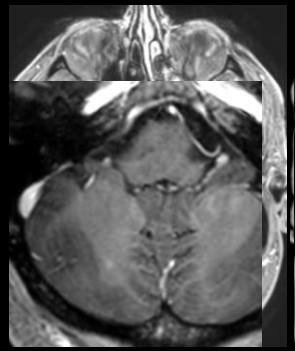
3D T1 IR-GRE



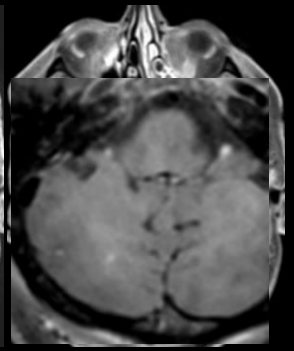
3D T1 TSE



T1 TSE



3D T1 IR-GRE



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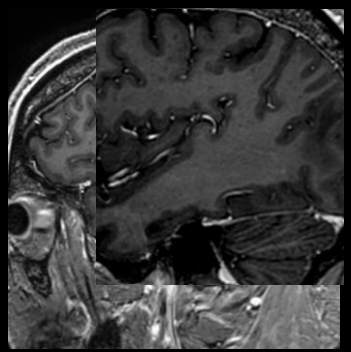
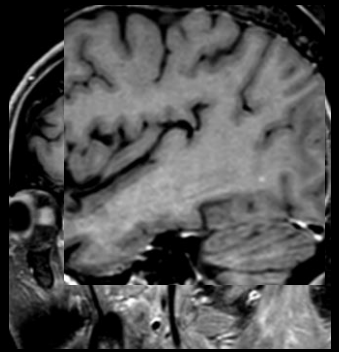


3D T1 IR-GRE



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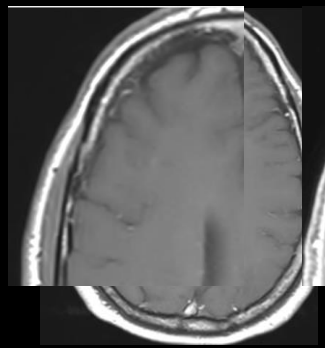
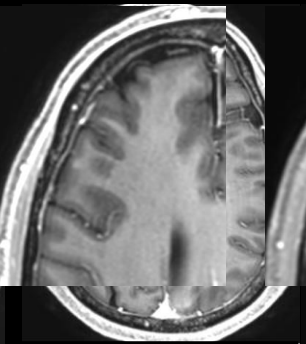


T1 TSE



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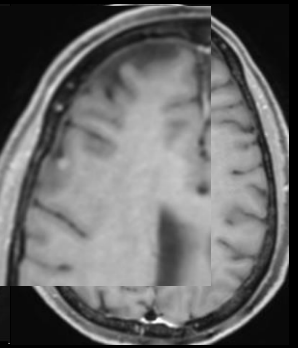


3D T1 TSE

BTIP. Comparativa 3D-T1

	BTIP 2015			BTIP-BM 2020		
	Mínimo 1.5T	Recomendado 1.5T	Recomendado 3T	Mínimo 1.5T	Mínimo 3T	Recomendado 3T
Secuencia	IR-GRE	IR-GRE	IR-GRE	IR-GRE	IR-GRE	FSE
Plano	Sagital/axial	Sagital/axial	Sagital/axial	Sagital/axial	Sagital/axial	Sagital/axial
Modo	3D	3D	3D	3D	3D	3D
TR	2100	2100	2100	2100	2100	550-750
TE	Mínimo	Mínimo	Mínimo	Mínimo	Mínimo	Mínimo
TI	1100	1100	1100	1100	1100	
Flip Angle	10º-15º	10º-15º	10º-15º	10º-15º	10º-15º	Default
Resolución	≥172 x 172	≥172 x 172	256x256	≥172 x 172	≥256x256	256x256
FOV	256 mm	256 mm	256 mm	256 mm	256 mm	256 mm
Grosor	≤1.5 mm	≤1.5 mm	1 mm	≤1.5 mm	1 mm	1 mm

BTIP. Comparativa 2D-FLAIR

	BTIP 2015			BTIP-BM 2020		
	Mínimo 1.5T	Recomendado 1.5T	Recomendado 3T	Mínimo 1.5T	Mínimo 3T	Recomendado 3T
Secuencia	FSE	FSE	FSE	FSE	FSE	FSE
Plano	Axial	Axial	Axial	Axial	Axial	Axial
Modo	2D	2D	2D	2D	2D	2D
TR	>6.000	>6.000	>6.000	>6.000	>6.000	>6.000
TE	100-140	100-140	100-140	100-140	100-140	100-140
TI	2000-2500	2200	2500	2000-2500	2000-2500	2000-2500
Flip Angle	90º	90º	90º	90º	90º	90º
Resolución	≥256x256	≥256x256	≥256x256	≥256x256	≥256x256	≥256x256
FOV	240 mm	240 mm	240 mm	240 mm	240 mm	240 mm
Grosor	≤4 mm	≤4 mm	3 mm	≤4 mm	3 mm	3 mm

BTIP. Comparativa 2D-T2

	BTIP 2015			BTIP-BM 2020		
	Mínimo 1.5T	Recomendado 1.5T	Recomendado 3T	Mínimo 1.5T	Mínimo 3T	Recomendado 3T
Secuencia	FSE	FSE	FSE	FSE	FSE	FSE
Plano	Axial	Axial	Axial	Axial	Axial	Axial
Modo	2D	2D	2D	2D	2D	2D
TR	>2.500	>3.500	>2.500	>3.500	>2.500	>2.500
TE	80-120	100-120	80-120	80-120	80-120	80-120
Flip Angle	90º	90º	90º	90º	90º	90º
Resolución	≥256x256	≥256x256	≥256x256	≥256x256	≥256x256	≥256x256
FOV	240 mm	240 mm	240 mm	240 mm	240 mm	240 mm
Grosor	≤4 mm	≤4 mm	3 mm	≤4 mm	3 mm	3 mm

Table 4 Reader paradigm and adjudication design*

Paradigm	Description	Uses in Neuro-Oncology	Pros/Cons
Consensus Read	3+ readers work together and discuss the exam, coming to a single consensus interpretation.	Phase 0/I/II	*Pros*: No adjudication or ambiguity. Useful for rare or complex tumors, or small studies. *Cons*: Logistically difficult to get 3+ readers to discuss a case.
Paired Read with No Adjudication	R1 and R2 perform independent reads. Reader results are averaged or 2 sets of results are provided. Common when reporting both "site determined" and "centrally determined" results.	Phase 0/I	*Pros*: Efficient and cost-effective. *Cons*: High discordance rates can cause confusion about results.
Paired Read with Forced Adjudication$^{\Psi}$	R1 and R2 perform independent reads. R3 adjudicates any differences between R1 and R2 by choosing the best read,$^{\Psi}$ R1 or R2.	Phase II/III	*Pros*: Unbiased *Cons*: Expensive and time consuming
Paired Read with Open Adjudication	R1 and R2 perform independent reads. R3 adjudicates any differences between R1 and R2 by independently reading the exam or series. Results from R3 are final and can be different from R1 and R2.	Phase II/III	*Pros*: Unbiased *Cons*: Expensive and time consuming
Central Confirmation of Local Reads Using Single Read with (Forced or Open) Adjudication	R1 performs independent reads. R2 adjudicates any differences between R1 and the local site reads through either forced or open adjudication.	Phase 0/I/II	*Pros*: Efficient and cost effective. *Cons*: Depends heavily on experience of core lab neuroradiologists with disease and treatment mechanism.

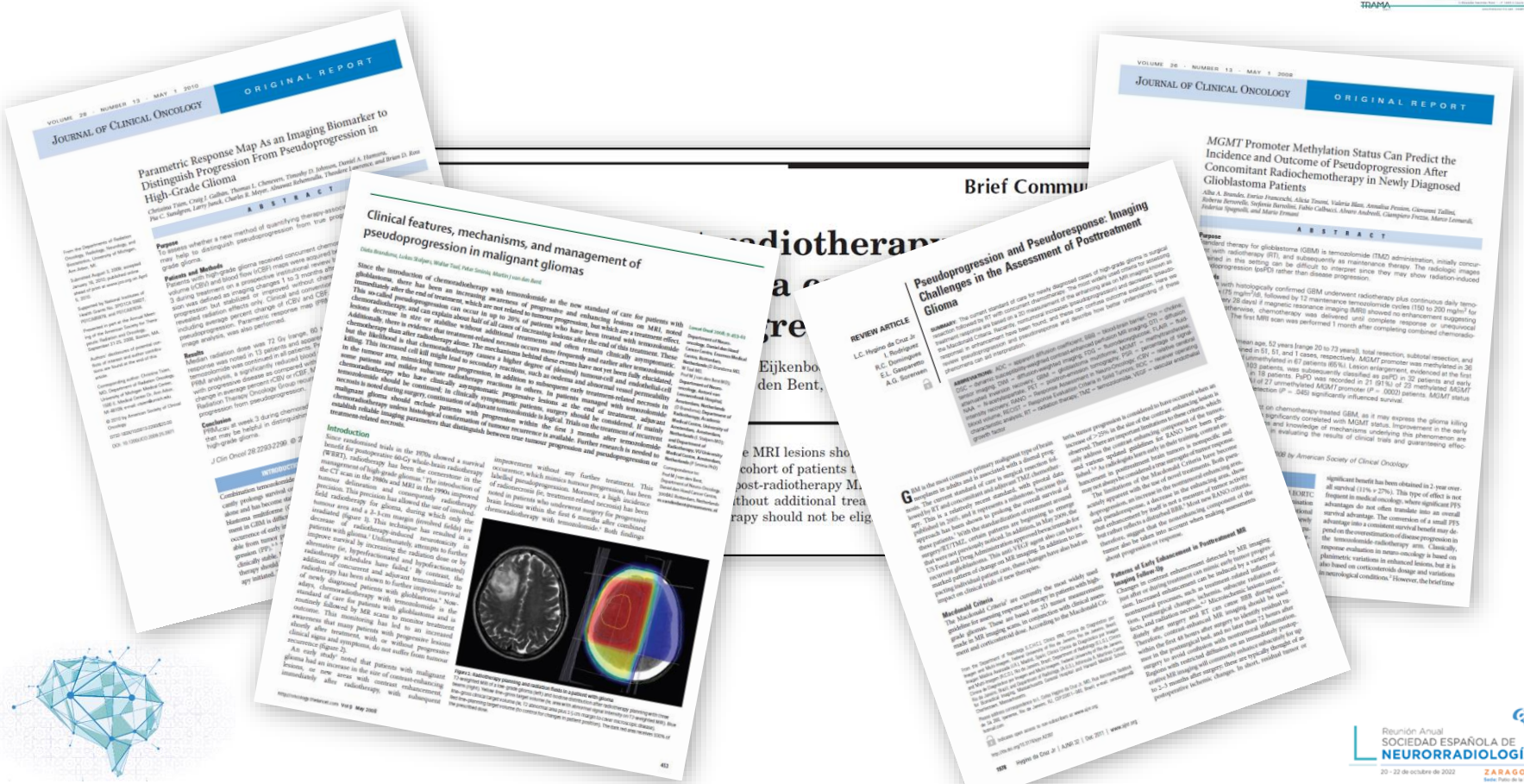
Table 3 Reading queue procedures

Reading Queue Procedure	Description
Locked Time-Sequential Presentation*	A patient's complete image set from baseline to current evaluation is presented in the chronological order in which the images were acquired. Unless specified in the Charter, the reader is blinded to the total number of time points per patient. This is the current standard for reading queue procedures in general oncology.
Simultaneous Image Presentation	All of a patient's image set is displayed simultaneously. There is no blinding to total number of time points or date of exams.
Simultaneous, Randomized Temporal Image Presentation	All of the patient's image set is displayed simultaneously, but presented in random order with reader blinded to the date of exam but not to the total number of time points.
Hybrid Randomized Image Presentation**	A patient's image set is presented in random order with reader blinded to the date of exam. Once measurements are locked, the readers are allowed to unlock and review all images in chronological order. Changes from the randomized assessments are tracked.
Hybrid Locked Time-Sequential Image Presentation**	A patient's image set is presented in a locked, time-sequential fashion. The readers are then allowed to unlock and review all images at the same time with no blinding to total number of time points or date of exams. Changes from the randomized assessments are tracked.

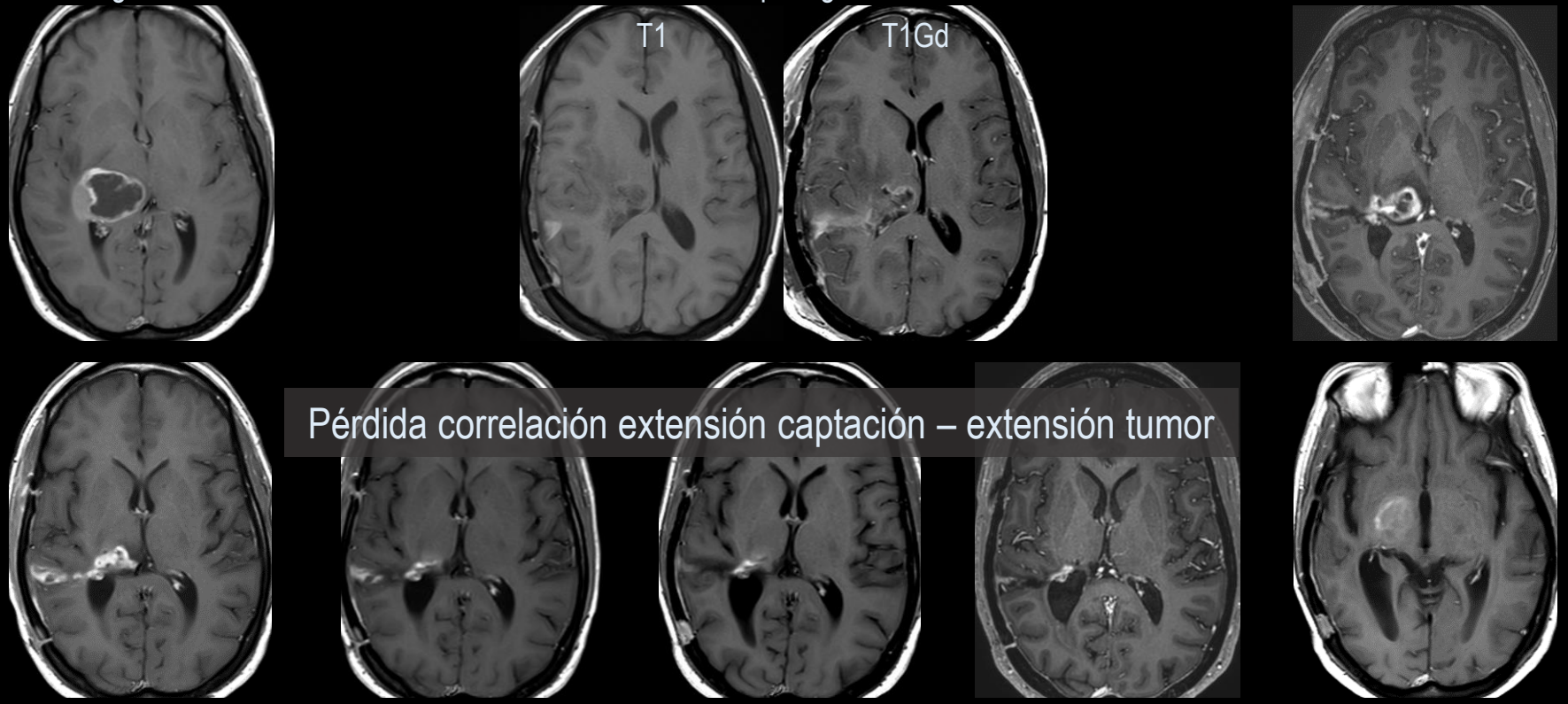
Adquisición de Imágenes → Paradigma de Lectura → Medición de Lesiones → **Criterios de Respuesta**

- RANO-HGG (2010)
- RANO-LGG (2011)
- RANO-BM (2015)
- iRANO (2015)
- mRANO (2017)
- RANO PRO(2018)

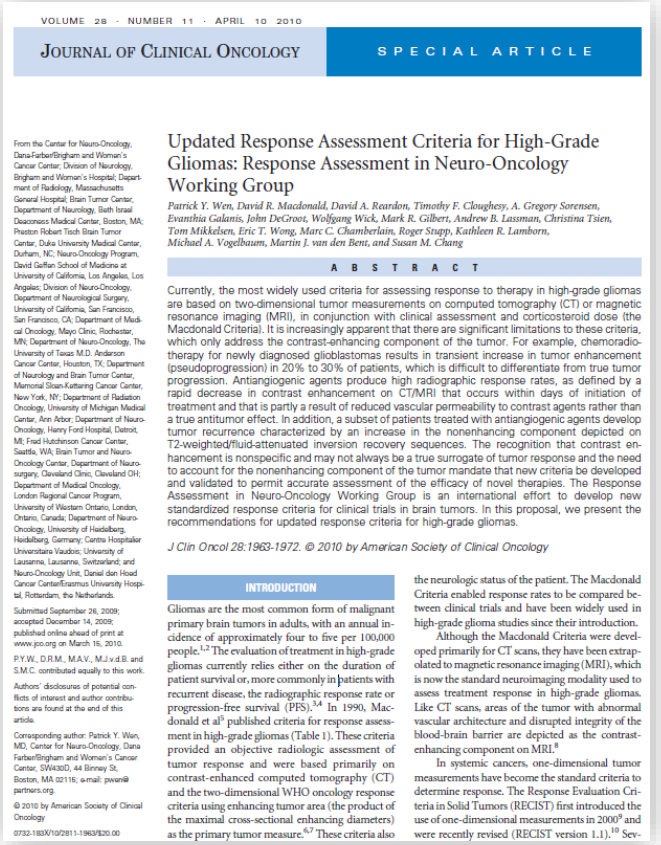
Criterios RANO. Introducción (2004)



Pseudoprogresión



RANO-HGG (2010)



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JOURNAL OF CLINICAL ONCOLOGY — SPECIAL ARTICLE

Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/10/2811-1963/$20.00

A B S T R A C T

Currently, the most widely used criteria for assessing response to therapy in high-grade gliomas are based on two-dimensional tumor measurements on computed tomography (CT) or magnetic resonance imaging (MRI), in conjunction with clinical assessment and corticosteroid dose (the Macdonald Criteria). It is increasingly apparent that there are significant limitations to these criteria, which only address the contrast-enhancing component of the tumor. For example, chemoradiotherapy for newly diagnosed glioblastomas results in transient increase in tumor enhancement (pseudoprogression) in 20% to 30% of patients, which is difficult to differentiate from true tumor progression. Antiangiogenic agents produce high radiographic response rates, as defined by a rapid decrease in contrast enhancement on CT/MRI that occurs within days of initiation of treatment and that is partly a result of reduced vascular permeability to contrast agents rather than a true antitumor effect. In addition, a subset of patients treated with antiangiogenic agents develop tumor recurrence characterized by an increase in the nonenhancing component depicted on T2-weighted/fluid-attenuated inversion recovery sequences. The recognition that contrast enhancement is nonspecific and may not always be a true surrogate of tumor response and the need to account for the nonenhancing component of the tumor mandate that new criteria be developed and validated to permit accurate assessment of the efficacy of novel therapies. The Response Assessment in Neuro-Oncology Working Group is an international effort to develop new standardized response criteria for clinical trials in brain tumors. In this proposal, we present the recommendations for updated response criteria for high-grade gliomas.

J Clin Oncol 28:1963-1972. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Gliomas are the most common form of malignant primary brain tumors in adults, with an annual incidence of approximately four to five per 100,000 people.[1,2] The evaluation of treatment in high-grade gliomas currently relies either on the duration of patient survival or, more commonly in patients with recurrent disease, the radiographic response rate or progression-free survival (PFS).[3,4] In 1990, Macdonald et al[5] published criteria for response assessment in high-grade gliomas (Table 1). These criteria provided an objective radiologic assessment of tumor response and were based primarily on contrast-enhanced computed tomography (CT) and the two-dimensional WHO oncology response criteria using enhancing tumor area (the product of the maximal cross-sectional enhancing diameters) as the primary tumor measure.[6,7] These criteria also the neurologic status of the patient. The Macdonald Criteria enabled response rates to be compared between clinical trials and have been widely used in high-grade glioma studies since their introduction.

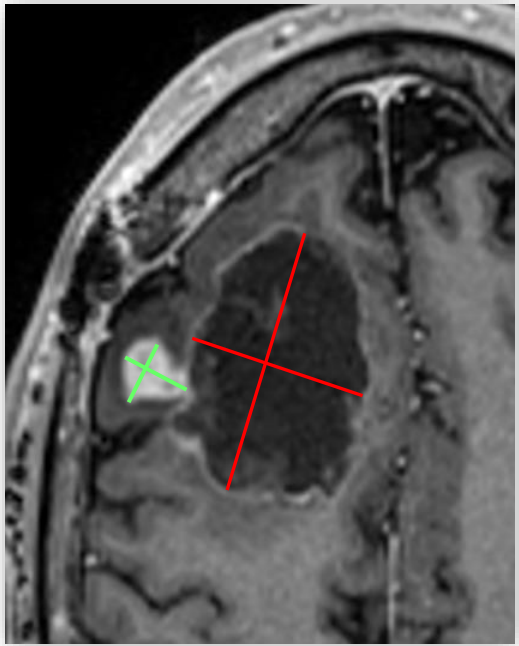
Although the Macdonald Criteria were developed primarily for CT scans, they have been extrapolated to magnetic resonance imaging (MRI), which is now the standard neuroimaging modality used to assess treatment response in high-grade gliomas. Like CT scans, areas of the tumor with abnormal vascular architecture and disrupted integrity of the blood-brain barrier are depicted as the contrast-enhancing component on MRI.[8]

In systemic cancers, one-dimensional tumor measurements have become the standard criteria to determine response. The Response Evaluation Criteria in Solid Tumors (RECIST) first introduced the use of one-dimensional measurements in 2000[9] and were recently revised (RECIST version 1.1).[10] Sev-

- Grupo multidisciplinar.
- Enfermedad medible y carga tumoral.
- Criterios de respuesta.
- Manejo pseudoprogresión.
- Valoración FLAIR.

https://www.senr.org/wp-content/uploads/2015/05/Criterios_respuesta_Neuroon2011.pdf

RANO-HGG. Lesión medible



1. Lesión captante.
2. Márgenes bien definidos.
3. Bidimensional (10 x 10 mm).
4. Visible en dos o mas cortes axiales.
5. Cuantificada como producto de diámetros perpendiculares máximos.
6. Cálculo carga tumoral en caso de varias lesiones: suma de áreas de 2-5 lesiones.

RANO-HGG. Criterios de respuesta

Table 4. Summary of the Proposed RANO Response Criteria

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑*
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA†
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for response	All	All	All	Any*

Abbreviations: RANO, Response Assessment in Neuro-Oncology; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FLAIR, fluid-attenuated inversion recovery; NA, not applicable.
*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.

RANO-HGG. Definición de progresión

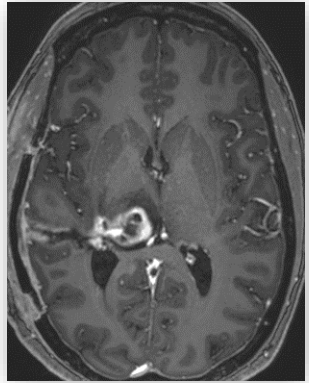
Tiempo transcurrido desde el fin del tratamiento con quimioradioterapia concomitante:

A. Más de 3 meses:

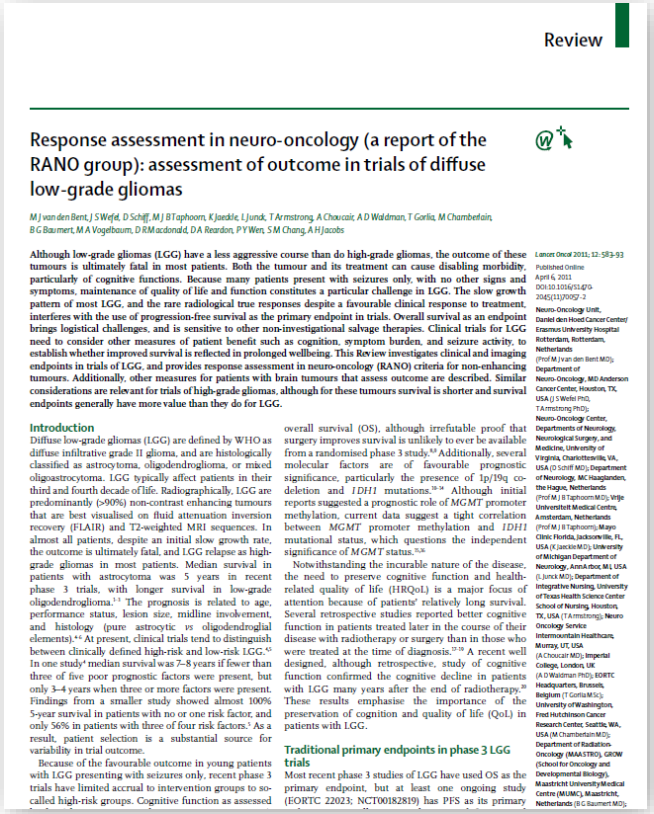
- Criterios RANO: Aparición de nueva lesión, crecimiento en FLAIR, o crecimiento >25% lesión diana.

B. Menos de 3 meses:

- Aparición de nueva lesión **fuera del campo de radioterapia**.
- Presencia inequívoca de tumor en muestra anatomopatológica.



RANO-LGG (2011)



Review

Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas

M J van den Bent, J S Wefel, D Schiff, M J B Taphoorn, K Jaeckle, L Junck, T Armstrong, A Choucair, A D Waldman, T Gorlia, M Chamberlain, B G Baumert, M A Vogelbaum, D R Macdonald, D A Reardon, P Y Wen, S M Chang, A H Jacobs

Although low-grade gliomas (LGG) have a less aggressive course than do high-grade gliomas, the outcome of these tumours is ultimately fatal in most patients. Both the tumour and its treatment can cause disabling morbidity, particularly of cognitive functions. Because many patients present with seizures only, with no other signs and symptoms, maintenance of quality of life and function constitutes a particular challenge in LGG. The slow growth pattern of most LGG, and the rare radiological true responses despite a favourable clinical response to treatment, interferes with the use of progression-free survival as the primary endpoint in trials. Overall survival as an endpoint brings logistical challenges, and is sensitive to other non-investigational salvage therapies. Clinical trials for LGG need to consider other measures of patient benefit such as cognition, symptom burden, and seizure activity, to establish whether improved survival is reflected in prolonged wellbeing. This Review investigates clinical and imaging endpoints in trials of LGG, and provides response assessment in neuro-oncology (RANO) criteria for non-enhancing tumours. Additionally, other measures for patients with brain tumours that assess outcome are described. Similar considerations are relevant for trials of high-grade gliomas, although for these tumours survival is shorter and survival endpoints generally have more value than they do for LGG.

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Introduction

Diffuse low-grade gliomas (LGG) are defined by WHO as diffuse infiltrative grade II glioma, and are histologically classified as astrocytoma, oligodendroglioma, or mixed oligoastrocytoma. LGG typically affect patients in their third and fourth decade of life. Radiographically, LGG are predominantly (>90%) non-contrast enhancing tumours that are best visualised on fluid attenuation inversion recovery (FLAIR) and T2-weighted MRI sequences. In almost all patients, despite an initial slow growth rate, the outcome is ultimately fatal, and LGG relapse as high-grade gliomas in most patients. Median survival in patients with astrocytoma was 5 years in recent phase 3 trials, with longer survival in low-grade oligodendroglioma.[1–3] The prognosis is related to age, performance status, lesion size, midline involvement, and histology (pure astrocytic *vs* oligodendroglial elements).[4–6] At present, clinical trials tend to distinguish between clinically defined high-risk and low-risk LGG.[4,5] In one study[4] median survival was 7–8 years if fewer than three of five poor prognostic factors were present, but only 3–4 years when three or more factors were present. Findings from a smaller study showed almost 100% 5-year survival in patients with no or one risk factor, and only 56% in patients with three of four risk factors.[5] As a result, patient selection is a substantial source for variability in trial outcome.

Because of the favourable outcome in young patients with LGG presenting with seizures only, recent phase 3 trials have limited accrual to intervention groups to so-called high-risk groups. Cognitive function as assessed overall survival (OS), although irrefutable proof that surgery improves survival is unlikely to ever be available from a randomised phase 3 study.[4,5] Additionally, several molecular factors are of favourable prognostic significance, particularly the presence of 1p/19q co-deletion and *IDH1* mutations.[7–14] Although initial reports suggested a prognostic role of *MGMT* promoter methylation, current data suggest a tight correlation between *MGMT* promoter methylation and *IDH1* mutational status, which questions the independent significance of *MGMT* status.[15,16]

Notwithstanding the incurable nature of the disease, the need to preserve cognitive function and health-related quality of life (HRQoL) is a major focus of attention because of patients' relatively long survival. Several retrospective studies reported better cognitive function in patients treated later in the course of their disease with radiotherapy or surgery than in those who were treated at the time of diagnosis.[17,18] A recent well designed, although retrospective, study of cognitive function confirmed the cognitive decline in patients with LGG many years after the end of radiotherapy.[19] These results emphasise the importance of the preservation of cognition and quality of life (QoL) in patients with LGG.

Traditional primary endpoints in phase 3 LGG trials

Most recent phase 3 studies of LGG have used OS as the primary endpoint, but at least one ongoing study (EORTC 22023; NCT00182819) has PFS as its primary

Criterios de respuesta RANO-LGG:

- Medición en FLAIR.
- Captación como criterio de progresión.
- Respuesta minor (reducción 25-50%).
- Necesidad estandarizar otras medidas de respuesta.

RANO-MET (2015)

Review

Response assessment criteria for brain metastases: proposal from the RANO group

Nancy U Lin*, Eudocia Q Lee*, Hidefumi Aoyama, Igor J Barani, Daniel P Barboriak, Brigitta G Baumert, Martin Bendszus, Paul D Brown, D Ross Camidge, Susan M Chang, Janet Dancey, Elisabeth G E de Vries, Laurie E Gaspar, Gordon J Harris, F Stephen Hodi, Steven N Kalkanis, Mark E Linskey, David R Macdonald, Kim Margolin, Minesh P Mehta, David Schiff, Riccardo Soffietti, John H Suh, Martin J van den Bent, Michael A Vogelbaum, Patrick Y Wen, for the Response Assessment in Neuro-Oncology (RANO) group

CNS metastases are the most common cause of malignant brain tumours in adults. Historically, patients with brain metastases have been excluded from most clinical trials, but their inclusion is now becoming more common. The medical literature is difficult to interpret because of substantial variation in the response and progression criteria used across clinical trials. The Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group is an international, multidisciplinary effort to develop standard response and progression criteria for use in clinical trials of treatment for brain metastases. Previous efforts have focused on aspects of trial design, such as patient population, variations in existing response and progression criteria, and challenges when incorporating neurological, neuro-cognitive, and quality-of-life endpoints into trials of patients with brain metastases. Here, we present our recommendations for standard response and progression criteria for the assessment of brain metastases in clinical trials. The proposed criteria will hopefully facilitate the development of novel approaches to this difficult problem by providing more uniformity in the assessment of CNS metastases across trials.

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See Online for interview with Nancy Lin

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Introduction

Brain metastases are the most common cause of malignant brain tumours in adults. Of the nearly 1·5 million patients in the USA who received a primary diagnosis of cancer in 2007, about 70 000 of these primary diagnoses are estimated to eventually relapse in the brain.[1,2] Despite the frequency of brain metastases, prospective trials in this patient population are limited, and the criteria used to assess response and progression in the CNS are heterogeneous.[3] This heterogeneity largely stems from the recognition that existing criteria sets, such as RECIST,[4,5] WHO,[6] or Macdonald Criteria,[7] are themselves distinct and have gaps and limitations in their ability to address issues specific to the assessment of patients with brain metastases (table 1).[3] Key issues in the imaging of CNS metastases include the modality and frequency of assessment, the method of measurement (linear, bidimensional, volumetric), the magnitude of change that defines response or progression, differentiation between tumour-related and treatment-related changes, the inclusion (or exclusion) of corticosteroid use and clinical signs and symptoms with imaging definitions of progression and response, and the inclusion (or exclusion) of systemic disease status into the definition of CNS response and progression.

Scope and purpose of the proposed RANO-BM criteria

Prospective clinical trials to assess new treatments for patients with active brain metastases are becoming increasingly common. Additionally, we welcome the trend away from automatic exclusion of patients with brain metastases from clinical trials of novel therapies. The concurrent proliferation of response criteria for

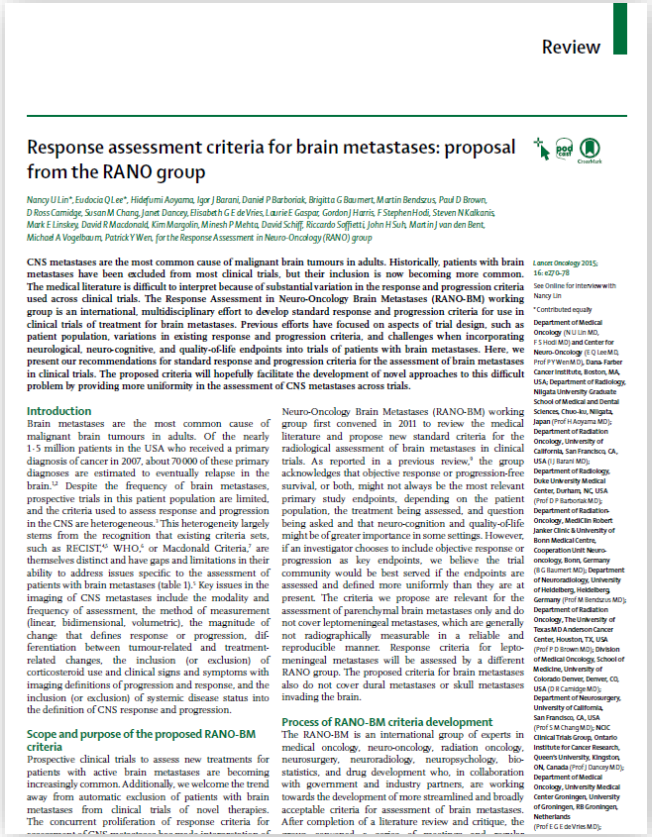
Neuro-Oncology Brain Metastases (RANO-BM) working group first convened in 2011 to review the medical literature and propose new standard criteria for the radiological assessment of brain metastases in clinical trials. As reported in a previous review,[8] the group acknowledges that objective response or progression-free survival, or both, might not always be the most relevant primary study endpoints, depending on the patient population, the treatment being assessed, and question being asked and that neuro-cognition and quality-of-life might be of greater importance in some settings. However, if an investigator chooses to include objective response or progression as key endpoints, we believe the trial community would be best served if the endpoints are assessed and defined more uniformly than they are at present. The criteria we propose are relevant for the assessment of parenchymal brain metastases only and do not cover leptomeningeal metastases, which are generally not radiographically measurable in a reliable and reproducible manner. Response criteria for leptomeningeal metastases will be assessed by a different RANO group. The proposed criteria for brain metastases also do not cover dural metastases or skull metastases invading the brain.

Process of RANO-BM criteria development

The RANO-BM is an international group of experts in medical oncology, neuro-oncology, radiation oncology, neurosurgery, neuroradiology, neuropsychology, biostatistics, and drug development who, in collaboration with government and industry partners, are working towards the development of more streamlined and broadly acceptable criteria for assessment of brain metastases. After completion of a literature review and critique, the

- Intención de facilitar introducción pacientes con M1 cerebrales en ensayos clínicos.
- Diferenciar respuesta compartimentos intracraneal y extracraneal.
- PFS o OS puede no ser el endpoint primario mas relevante.
- Basado en criterios RANO-HGG y RECIST.

RANO-MET (2015)



Review

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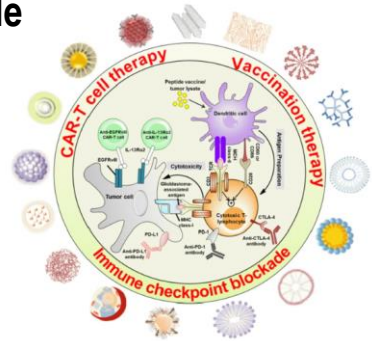
Criterios de respuesta RANO-MET:

- Medición unidimensional.
- Lesión medible > 10 x 5 mm.
- Seguimiento cada 6 – 12 semanas.
- RM basal < 4 semanas inicio tratamiento.
- PR: reducción carga tumoral > 30%.
- PRO: aumento carga tumoral >20%.
- Definir los criterios para distinguir PRO de efectos RT definidos prospectivamente.
- Valoración multidisciplinar

Inmunoterapia. Valoración radiológica

- La inmunoterapia induce respuestas inmunes anticáncer o modifica las ya existentes.
- Requiere más tiempo para actuar.
- Induce respuesta inflamatoria acentuada.
- **Crecimiento inicial no descarta posibilidad de beneficio clínico (no es criterio de progresión)**:
- Posible **aumento de tamaño** inicial por:
    - Retardo de respuesta.
    - Respuesta inflamatoria acentuada.
- Posible **nueva captación** por reacción inflamatoria en lesiones inicialmente silentes.



La inmunoterapia puede requerir mayor tiempo para respuesta

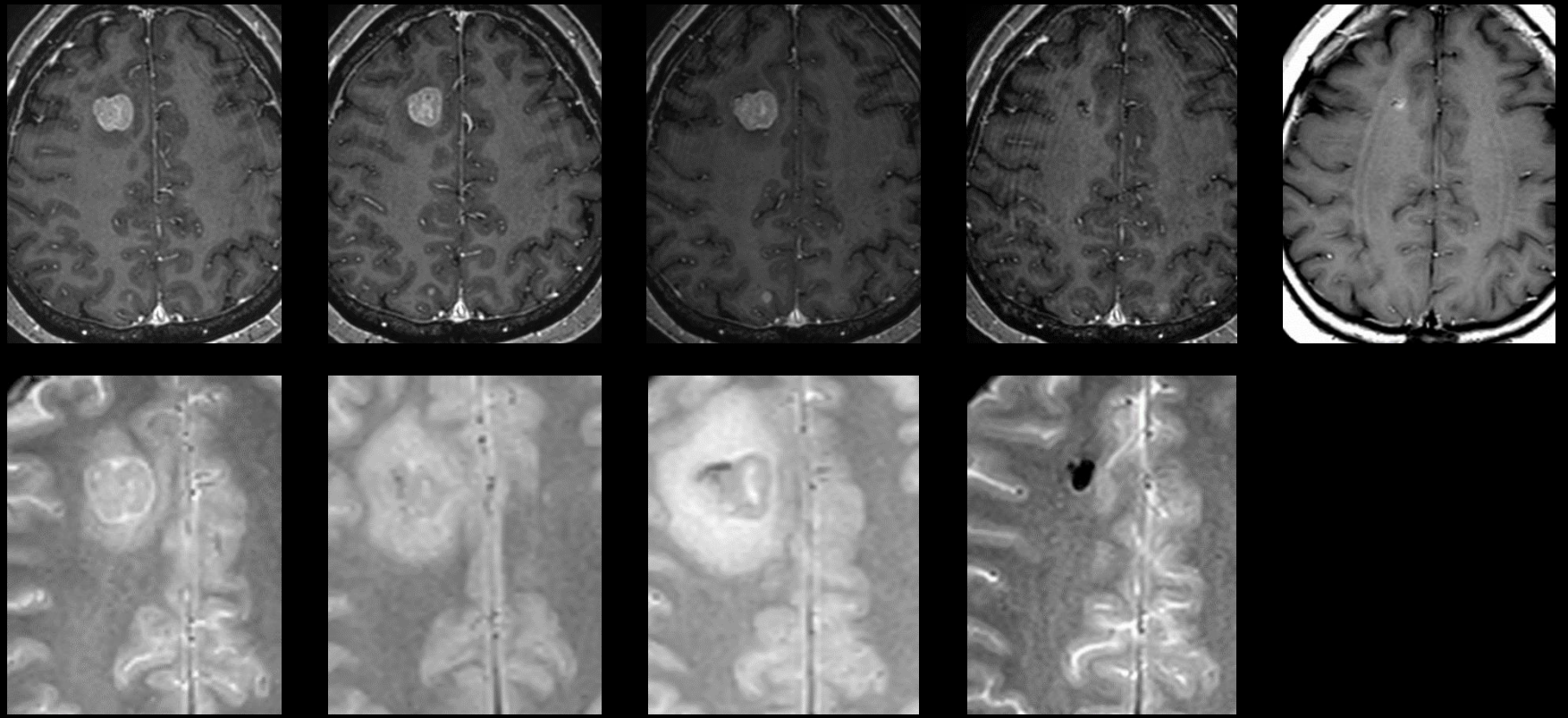
Basal

+1 mes

+6 meses

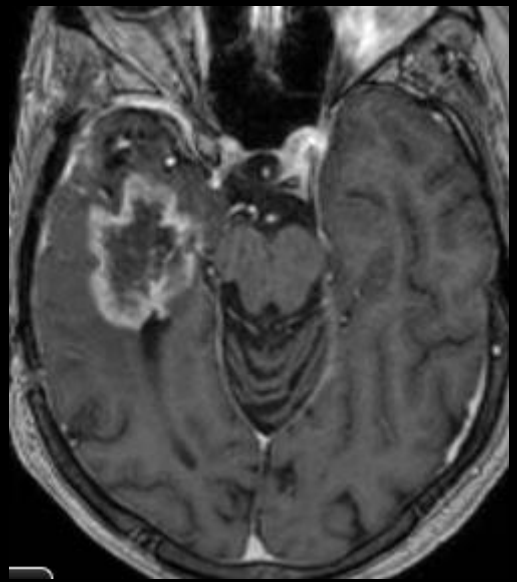
+17 meses

+25 meses

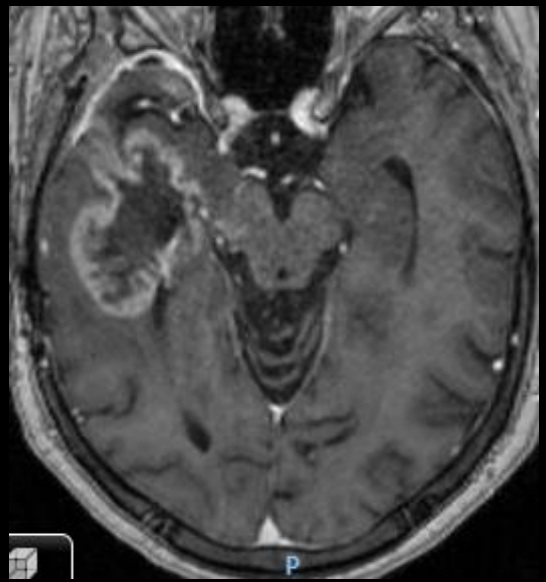


Crecimiento en tto con inmunoterapia no siempre es criterio de PRO

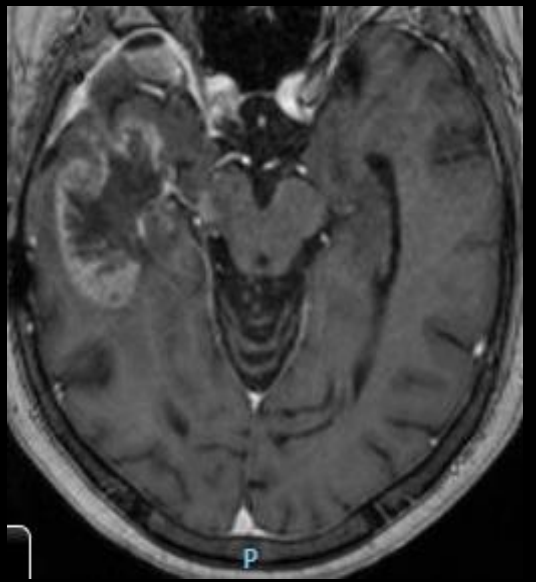
Basal



+1 mes

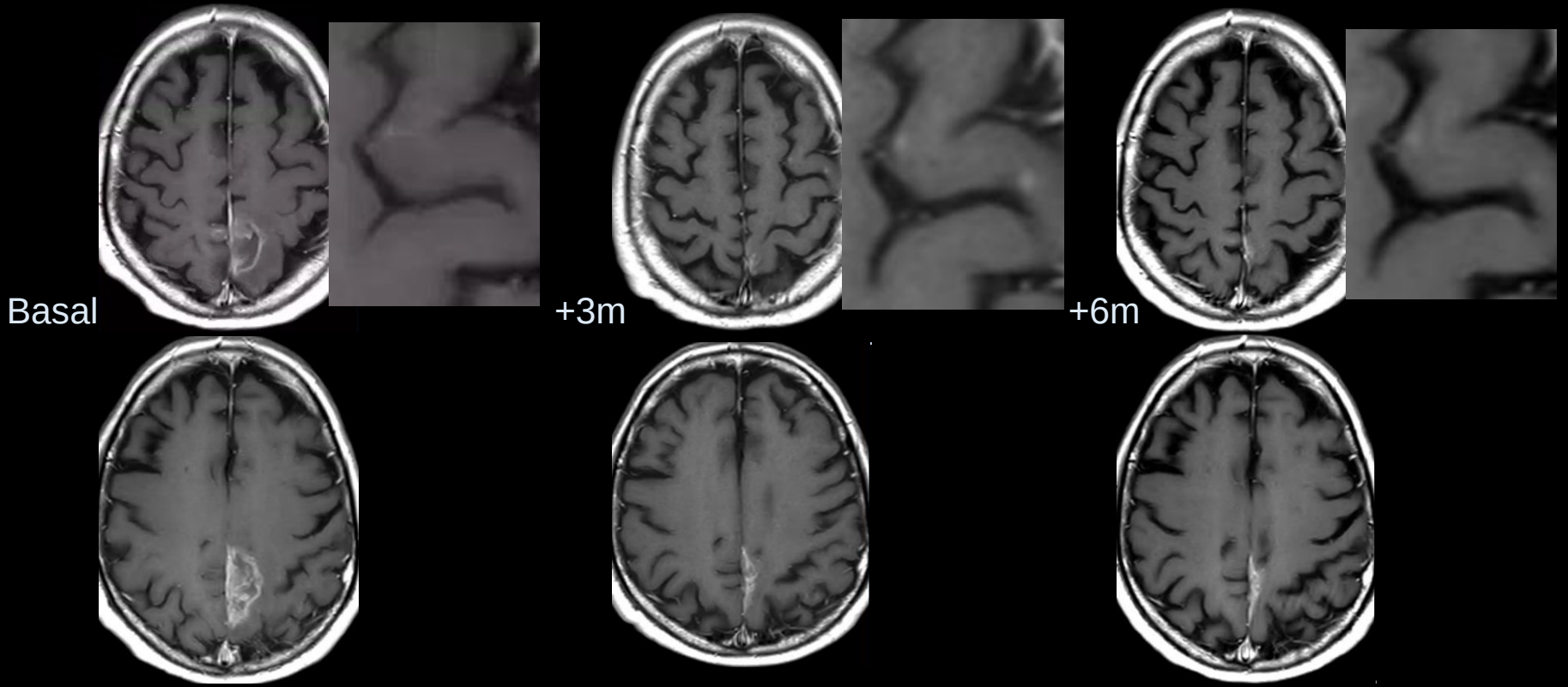


+3 meses

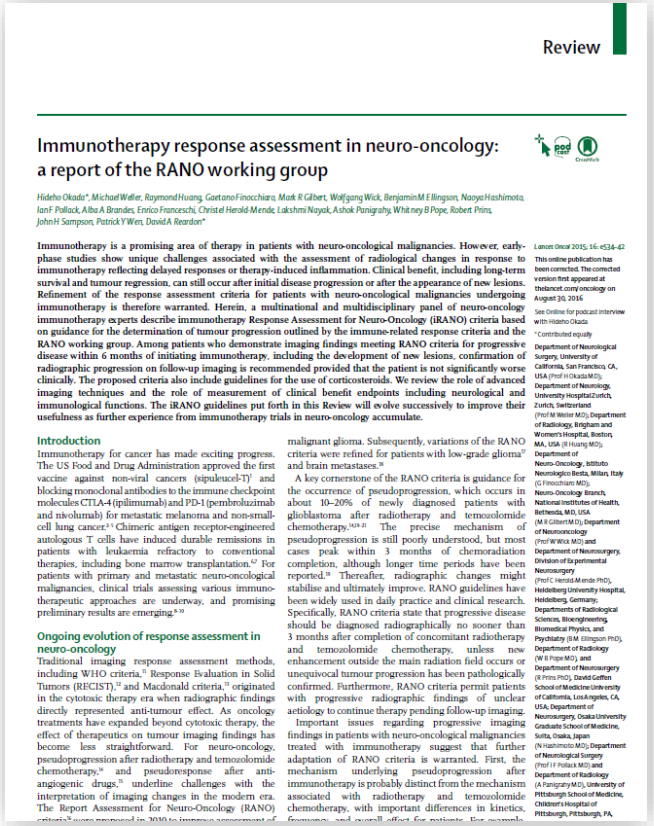


Cortesia Dr. José Mateos. IEC (Instituto Ensayos Clínicos). H Quirón Barcelona.

Aparición de nueva lesión no siempre es criterio de PRO



iRANO (2015)



Review

Immunotherapy response assessment in neuro-oncology: a report of the RANO working group

Hideho Okada*, Michael Weller, Raymond Huang, Gaetano Finocchiaro, Mark R Gilbert, Wolfgang Wick, Benjamin M Ellingson, Naoya Hashimoto, Ian F Pollack, Alba A Brandes, Enrico Franceschi, Christel Herold-Mende, Lakshmi Nayak, Ashok Panigrahy, Whitney B Pope, Robert Prins, John H Sampson, Patrick Y Wen, David A Reardon*

Immunotherapy is a promising area of therapy in patients with neuro-oncological malignancies. However, early-phase studies show unique challenges associated with the assessment of radiological changes in response to immunotherapy reflecting delayed responses or therapy-induced inflammation. Clinical benefit, including long-term survival and tumour regression, can still occur after initial disease progression or after the appearance of new lesions. Refinement of the response assessment criteria for patients with neuro-oncological malignancies undergoing immunotherapy is therefore warranted. Herein, a multinational and multidisciplinary panel of neuro-oncology immunotherapy experts describe immunotherapy Response Assessment for Neuro-Oncology (iRANO) criteria based on guidance for the determination of tumour progression outlined by the immune-related response criteria and the RANO working group. Among patients who demonstrate imaging findings meeting RANO criteria for progressive disease within 6 months of initiating immunotherapy, including the development of new lesions, confirmation of radiographic progression on follow-up imaging is recommended provided that the patient is not significantly worse clinically. The proposed criteria also include guidelines for the use of corticosteroids. We review the role of advanced imaging techniques and the role of measurement of clinical benefit endpoints including neurological and immunological functions. The iRANO guidelines put forth in this Review will evolve successively to improve their usefulness as further experience from immunotherapy trials in neuro-oncology accumulate.

Introduction

Immunotherapy for cancer has made exciting progress. The US Food and Drug Administration approved the first vaccine against non-viral cancers (sipuleucel-T)[1] and blocking monoclonal antibodies to the immune checkpoint molecules CTLA-4 (ipilimumab) and PD-1 (pembrolizumab and nivolumab) for metastatic melanoma and non-small-cell lung cancer.[2,3] Chimeric antigen receptor-engineered autologous T cells have induced durable remissions in patients with leukaemia refractory to conventional therapies, including bone marrow transplantation.[4,5] For patients with primary and metastatic neuro-oncological malignancies, clinical trials assessing various immuno-therapeutic approaches are underway, and promising preliminary results are emerging.[6–10]

Ongoing evolution of response assessment in neuro-oncology

Traditional imaging response assessment methods, including WHO criteria,[11] Response Evaluation in Solid Tumors (RECIST),[12] and Macdonald criteria,[13] originated in the cytotoxic therapy era when radiographic findings directly represented anti-tumour effect. As oncology treatments have expanded beyond cytotoxic therapy, the effect of therapeutics on tumour imaging findings has become less straightforward. For neuro-oncology, pseudoprogression after radiotherapy and temozolomide chemotherapy,[14] and pseudoresponse after anti-angiogenic drugs,[15] underline challenges with the interpretation of imaging changes in the modern era. The Report Assessment for Neuro-Oncology (RANO) criteria[16] were proposed in 2010 to improve assessment of malignant glioma. Subsequently, variations of the RANO criteria were refined for patients with low-grade glioma[17] and brain metastases.[18]

A key cornerstone of the RANO criteria is guidance for the occurrence of pseudoprogression, which occurs in about 10–20% of newly diagnosed patients with glioblastoma after radiotherapy and temozolomide chemotherapy.[9,19–21] The precise mechanism of pseudoprogression is still poorly understood, but most cases peak within 3 months of chemoradiation completion, although longer time periods have been reported.[19] Thereafter, radiographic changes might stabilise and ultimately improve. RANO guidelines have been widely used in daily practice and clinical research. Specifically, RANO criteria state that progressive disease should be diagnosed radiographically no sooner than 3 months after completion of concomitant radiotherapy and temozolomide chemotherapy, unless new enhancement outside the main radiation field occurs or unequivocal tumour progression has been pathologically confirmed. Furthermore, RANO criteria permit patients with progressive radiographic findings of unclear aetiology to continue therapy pending follow-up imaging.

Important issues regarding progressive imaging findings in patients with neuro-oncological malignancies treated with immunotherapy suggest that further adaptation of RANO criteria is warranted. First, the mechanism underlying pseudoprogression after immunotherapy is probably distinct from the mechanism associated with radiotherapy and temozolomide chemotherapy, with important differences in kinetics, frequency, and overall effect for patients. For example,

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This online publication has been corrected. The corrected version first appeared at thelancet.com/oncology on August 26, 2016
See Online for podcast interview with Hideho Okada

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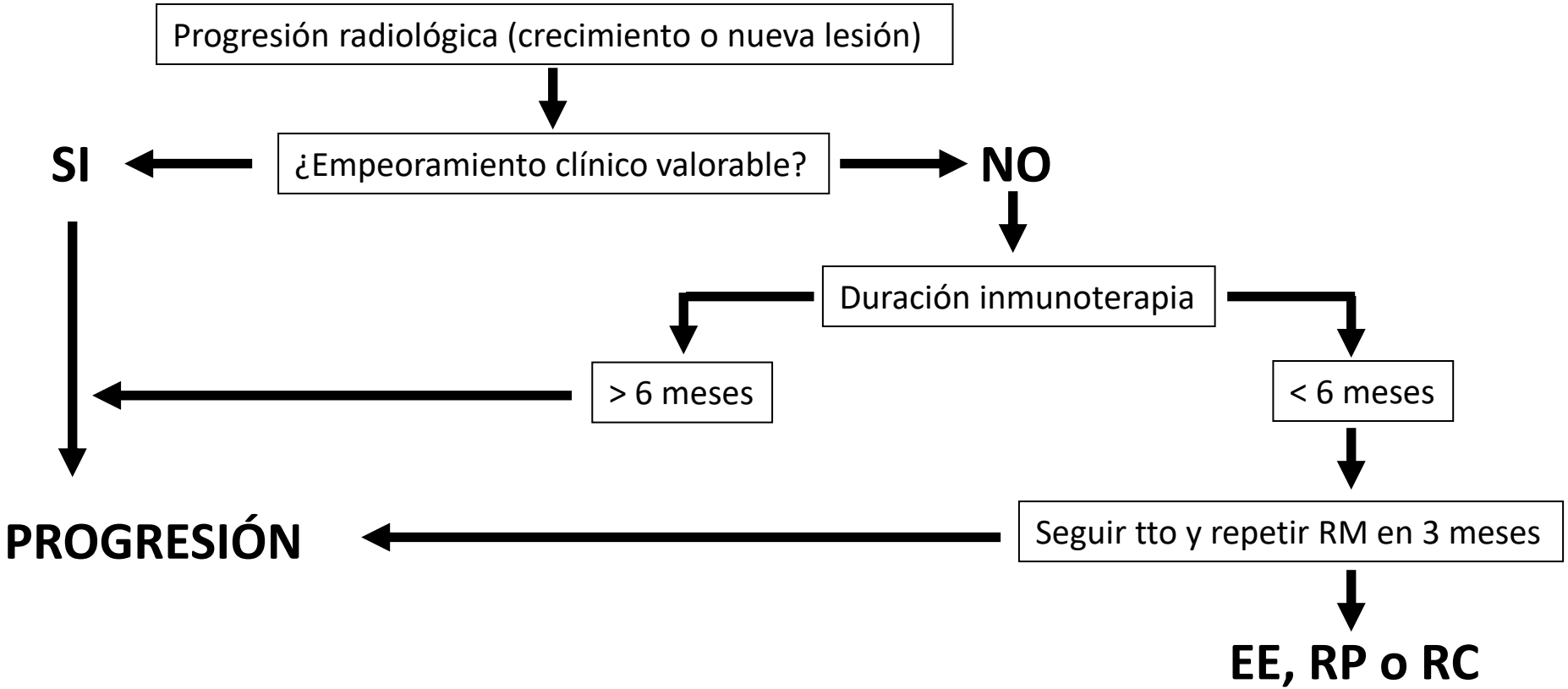
- Criterios aplicables a RANO-HGG, RANO-LGG y RANO-BM.
- Empeoramiento del estatus neurológico es el criterio más potente de progresión.
- Una nueva lesión no es criterio de progresión por si sola.
- Si aumento carga tumoral dentro de los 6 meses desde el inicio del tratamiento: repetir RM en 3 meses.

iRANO (2015)


Progresión radiológica (crecimiento o nueva lesión)
¿Empeoramiento clínico valorable?
SI
NO
Duración inmunoterapia
> 6 meses
< 6 meses
PROGRESIÓN
Seguir tto y repetir RM en 3 meses
EE, RP o RC

Conclusiones

- Considerar todo el proceso de valoración de respuesta.
- Hay protocolos de imagen recomendados para diagnóstico y seguimiento.
- Adaptar a la realidad local.
- Criterios RANO definen lesión medible y criterios de respuesta.
- Tener en cuenta estado del paciente y corticoides.
- Complejidad valoración de respuesta en LGG.
- RANO-MET distingue compartimentos intra/extracerebral para valorar respuesta.
- Crecimiento o aparición de nueva lesión no necesariamente es criterio de PRO según criterios iRANO.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