Session II:
Key Issues for Clinical Development for Brain Mets

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Standardizing Brain Mets Response Assessment

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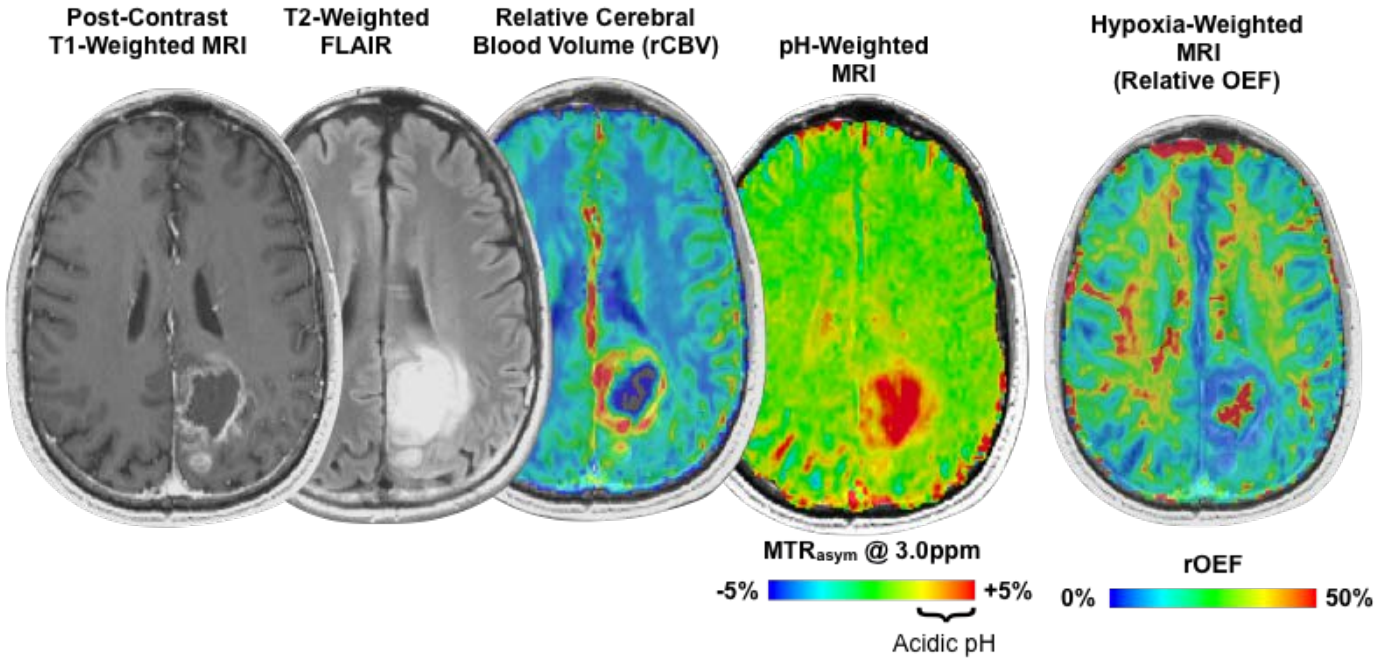
NBTS-FDA Public Workshop: Product Development for Central Nervous System (CNS) Metastases
March 22, 2019

David Geffen School of Medicine

UCLA Health
Radiology
UCLA Brain Tumor Imaging Laboratory

Use of Imaging for Brain Met Response Assessment

- Serial biopsies are not possible or safe (few “pathology-confirmed” responses)
- MRI (and PET) imaging are routinely used for clinical monitoring and response assessment
- MRI has exquisite soft tissue contrast, no ionizing radiation, and a variety of “flavors” for evaluating anatomy *and* physiology



Components of Brain Mets Response Assessment

MRI Image Acquisition

- T2w & T2w FLAIR
- Pre- / Post-Contrast T1w
- Diffusion & Perfusion

Disease Quantification & Interpretation

- Size measurements / Quantification
- Response determination – Clinical “Meaning”

Standards are Critical to Progress…

The New York Times

Opinion

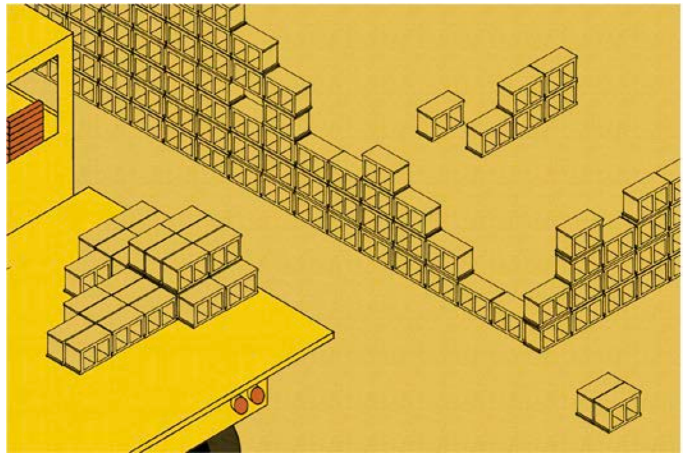
The Joy of Standards

Life is a lot easier when you can plug in to any socket.

By Andrew Russell and Lee Vinsel

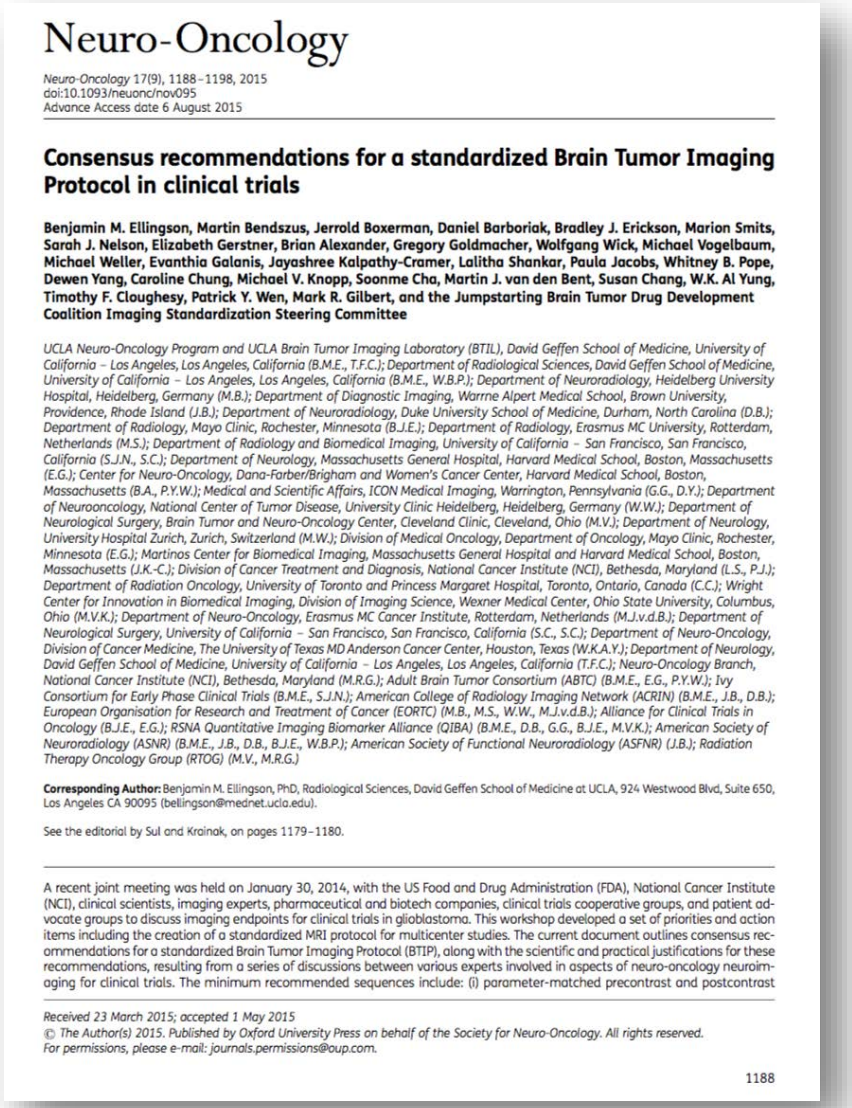
Dr. Russell and Dr. Vinsel study technology.

Feb. 16, 2019



- **We need standards to make meaningful progress…**
  - **Standards are all around us - electrical outlets, gasoline pumps, Bluetooth and even concrete blocks**
  - **Modern laptop >250 standards**
  - **Most standards are voluntary “consensus recommendations”**
  - **Building and improving upon agreed upon standards → Path to tangible progress**

Standardized Brain Tumor Imaging Protocol (BTIP)



Neuro-Oncology

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

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

A recent joint meeting was held on January 30, 2014, with the US Food and Drug Administration (FDA), National Cancer Institute (NCI), clinical scientists, imaging experts, pharmaceutical and biotech companies, clinical trials cooperative groups, and patient advocate groups to discuss imaging endpoints for clinical trials in glioblastoma. This workshop developed a set of priorities and action items including the creation of a standardized MRI protocol for multicenter studies. The current document outlines consensus recommendations for a standardized Brain Tumor Imaging Protocol (BTIP), along with the scientific and practical justifications for these recommendations, resulting from a series of discussions between various experts involved in aspects of neuro-oncology neuroimaging for clinical trials. The minimum recommended sequences include: (i) parameter-matched precontrast and postcontrast

Received 23 March 2015; accepted 1 May 2015

- **Designed for Primary Brain Tumor Clinical Trials (HGGs)**
- **Designed to be used in cooperative group settings including community and academic medical centers**
- **Compatible with most clinical MRI protocols**

Jumpstarting Brain Tumor Drug Development Coalition

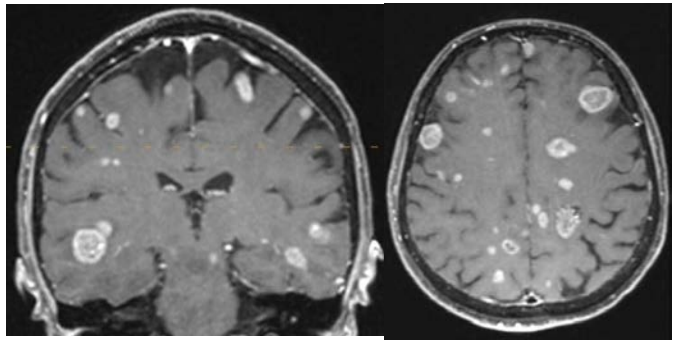
BTIP: Minimum Standard 1.5T and 3T MRI Protocol

	3D T1w Pre[b]	Ax 2D FLAIR[j]	Ax 2D DWI	Contrast Injection [a]	Ax 2D T2w[h,i]	3D T1w Post[b]
Sequence	MPRAGE[e,f]	TSE[c]	SS-EPI[g]		TSE[c]	MPRAGE[e,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[k]				1100[n]
Flip Angle [Degrees]	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
Frequency Direction	A/P	A/P	R/L		A/P	A/P
FOV	256mm	240mm	240mm		240mm	256mm
Slice Thickness	≤1.5mm	≤4mm[l]	≤4mm[l]		≤4mm[l]	≤1.5mm
Gap/Spacing	0	0	0		0	0
Diffusion Options[p]			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 3T Skyra]	5-10 min [5:49 for 1mm 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 1mm isotropic]

- *Pre- and Post-Contrast 3D T1-weighted Images*
  - *1-1.5mm isotropic resolution*
- *2D T2 and FLAIR*
  - *< 4mm slice thickness*
- *Diffusion MRI using ISMRM 2008 consensus recommendations*

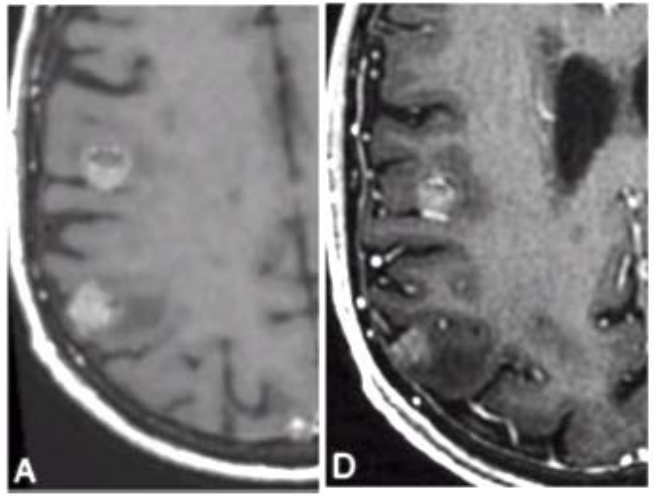
Unique Challenges Associated with Brain Mets

- ***Thin 3D images are absolutely critical to accurately quantify extent of disease***
- ***Better "contrast-to-noise" (CNR) for small mets with turbo spin-echo (TSE) vs. IR-GRE***
  - *Yoon et al., AJNR 2018; 39:1635-41.*
  - *Komada et al., Magn Reson Med Sci 2008; 7(1): 13-21*
  - *Kato et al., AJNR 2009; 30:923-29.*
- ***3D TSE <u>not</u> available on all MRI systems***
  - *Extra $$$ for advanced packages*
  - *Not standardized across vendors (CUBE ≠ SPACE)*
  - *3T >> 1.5T*
- ***3D TSE > 3D IR-GRE > 2D TSE***



Images Courtesy of
Tim Kauffman (Mayo Clinic)x

<u>3D T1w TSE</u> ***<u>3D T1w IR-GRE</u>***



Yoon, AJNR, 2018

Consensus Recommendations for Brain Mets BTIP – *Work in Prog.*

- ***Lead by Tim Kauffman and Ben Ellingson (Part of RANO Effort)***
- ***Builds on to BTIP standard & Integrates RANO-BM recommendations***

	3D T1w Pre	Ax 2D FLAIR	Ax 2D DWI	Ax 2D T2w	DSC-MRI	3D T1w Post	SE/TSE T1w
Sequence	IR-GRE	TSE	EPI	TSE	GRE-EPI 0.1 mmol/kg	IR-GRE	SE or TSE
Plane	Axial	Axial	Axial	Axial	Axial	Axial	Axial
Mode	3D	2D	2D	2D	2D	3D	2D or 3D
TR [ms]	2100	>6000	>5000	>2500	< 1500	2100	
TE [ms]	Min	100-140	Min	80-120	25-35ms	Min	
TI [ms]	1100	2500			N/A	1100	
Flip Angle	10°-15°	90°/≥ 160°	90°/180°	90°/≥ 160°	60°	10°-15°	
Frequency	256	≥ 256	128	≥ 256	≥ 96	256	
Phase	256	≥ 256	128	≥ 256	≥ 96	256	
NEX	≥ 1	≥ 1	≥ 1	≥ 1	1	≥ 1	
Pre-bolus Time Points					30-60		
Total Time Points	N/A	N/A	N/A	N/A	120	N/A	N/A
FOV	256 mm	240 mm	240 mm	240 mm	240mm	256 mm	
Slice thickness	1 mm	3 mm	3 mm	3 mm	As needed for optimal tumor coverage (Typically 3-5mm)	1 mm	≤ 4 mm for 2D
Gap/spacing	0	0	0	0	As needed for optimal tumor coverage (Typically 0-1)	0	0
Diffusion Options	N/A	N/A	B=0, 500, and 1000 s/mm^2 ≥3 directions	N/A	N/A	N/A	N/A
Parallel imaging	Up to 2x	Up to 2x	Up to 2x	Up to 2x	Up to 2x	Up to 2x	Up to 2x

Interpretation → RANO for BM (Lin et al., *Lancet Oncol* 2015)

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*

Lancet Oncology 2015; 16: e270–78

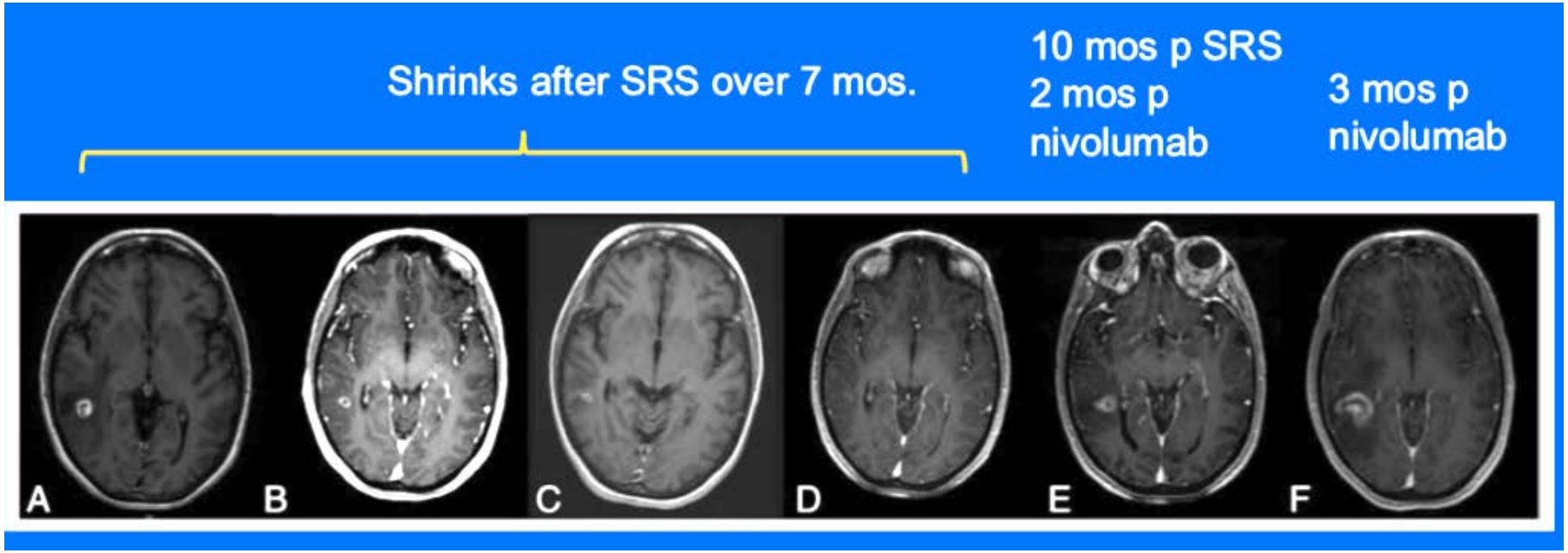
- ***Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group***
- ***Parenchymal mets only***
- ***Based on RECIST 1.1***
  - ***Longest single diameter (LD)***
  - ***Measurable disease ≥ 10mm (≤ 5mm slice thickness)***
  - ***Do not include cyst or cavity***
  - ***Sum up to 5 target lesion diameters at baseline***

Interpretation → RANO-BM (Lin et al., *Lancet Oncol* 2015)

Criterion	Complete Response (CR)	Partial Response (PR)	Stable Disease (SD)	Progressive Disease (PD)
Target lesions	None	≥30% decrease in sum LD relative to baseline	< 30% decrease relative to baseline but < 20% increase in sum LD relative to nadir	≥20% increase in sum LD relative to nadir
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal PD
New lesion(s)	None	None	None	Present
Corticosteroids	None	Stable or decreased	Stable or decreased	NA
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse
Requirement for response	All	All	All	Any

Interpretation → RANO-BM (Lin et al., *Lancet Oncol* 2015)

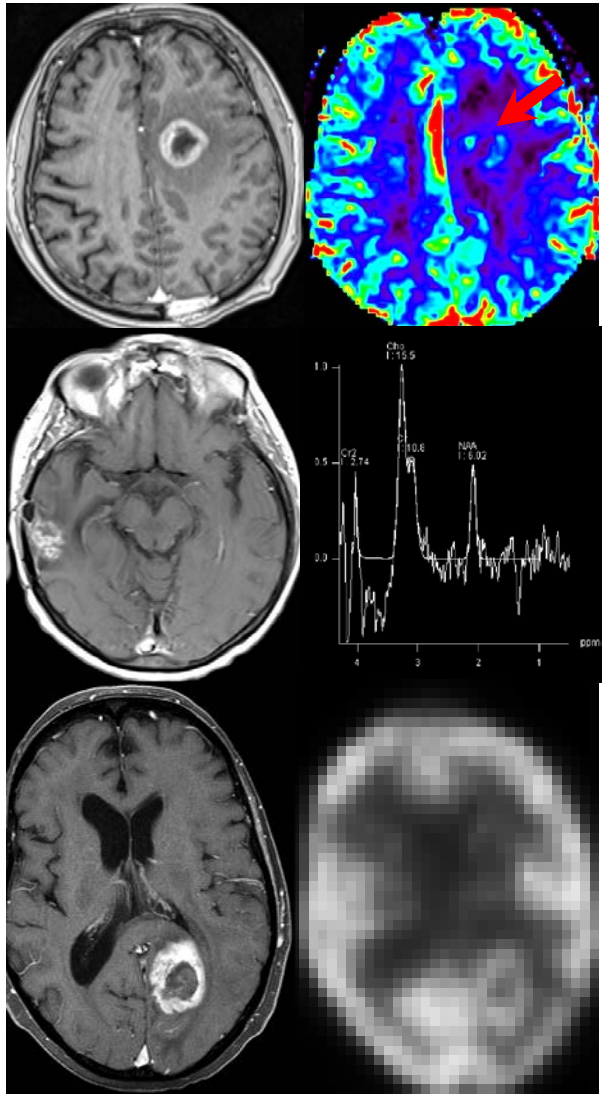
- ***Special considerations:***
  - ***Immunotherapies or SRS – Must verify PD***
    - *iRANO (Okada et al., Lancet Oncol 2015) – 6 mo window*
    - *mRANO (Ellingson et al., Neurotherapeutics 2017) – confirmed sequential PD events – definition for PsP*



Lewis GD et al., Practical Radiation Oncology 2018

Advanced Imaging: *Promising in the Near Future*

- ***DSC Perfusion***
  - *Mitsuya J Neurooncol 2010 (CBV > 2.1 = Tumor)*
  - *Barajas AJNR 2009 (CBV < 1.54 = PsP/RN)*
  - *Hoefnagels J Neurol 2009 (CBV > 2.0)*
- ***MR Spectroscopy*** *(Chernov Minim Invasive Neurosurg 2005; Chernov Acta Neurochir Suppl 2013; Nakajima Neurol Med Chir 2009; Kimura J Neurosurg 2004; Truong Neurosurg 2006; Kamada Biomed Tech 1997)*
  - *Tumor: ↓NAA; ↑Cho; ↑Lip/Lac*
  - *Radiation Necrosis: ↑Cho (early); ↓Cho (late); ↑Lip/Lac*
- ***PET Imaging***
  - *^{18}F-FDG, Amino Acid (^{11}C-MET; ^{18}F-FET; ^{18}F-FDOPA)*
- ***Need for standardization and large, multicenter datasets to determine feasibility and value in RANO-BM.***



Images Courtesy of
Tim Kauffman (Mayo Clinic)
& Caroline Chung (MD Anderson)