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# Neuroimaging assessment of brain metastases in the targeted therapy era

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# Overview

- RANO for HGG
- Proposed RANO for BM
- Remaining problems
  - Radiation Necrosis
  - New imaging techniques
- MR-Imaging: What is on the horizon?



# RANO for HGG



- Introduced in 2010
- Work in progress



# Macdonald Criteria

Response	Criteria
<b><u>Complete response (CR)</u></b>	Requires all of the following: <ul style="list-style-type: none"><li>• Complete disappearance of all enhancing measurable and nonmeasurable disease</li><li>• No new lesions</li><li>• No corticosteroids</li><li>• Stable or improved clinically</li></ul>
<b><u>Partial response (PR)</u></b>	Requires all of the following: <ul style="list-style-type: none"><li>• <math>\geq 50\%</math> decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions</li><li>• No new lesions</li><li>• Stable or reduced corticosteroid dose</li><li>• Stable or improved clinically</li></ul>
<b><u>Stable disease (SD)</u></b>	Requires all of the following: <ul style="list-style-type: none"><li>• Does not qualify for CR, PR or PD</li><li>• Stable clinically</li></ul>
<b><u>Progressive disease (PD)</u></b>	Defined by any of the following: <ul style="list-style-type: none"><li>• <math>\geq 25\%</math> increase in sum of the products of perpendicular diameters of enhancing lesions</li><li>• Any new lesion</li><li>• Clinical deterioration</li></ul>



# Major Changes in RANO HGG Criteria

- Definition of Measurable lesions
- Inclusion of T2 progress
- Inclusion of Pseudoprogression/  
Pseudoregression

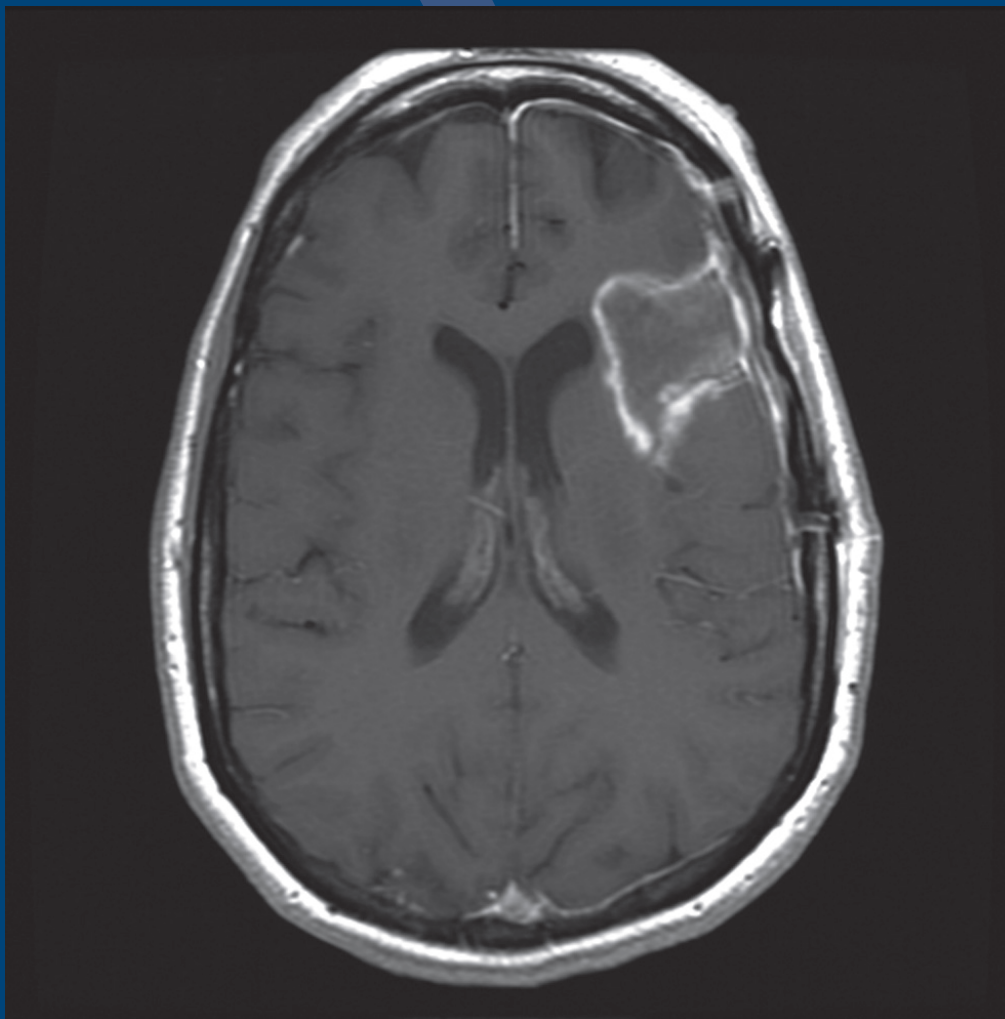
# Measurable lesions

Measurable lesions:

- bidimensionally contrast enhancing lesions with clearly defined margins by CT or MRI scan,
- **two perpendicular diameters** of at least 10 mm, visible on two or more axial slices that are 5 mm apart with 0-mm skip.
- As with RECIST version 1.1, if MRI is performed with thicker slices, size of a measurable lesion at baseline should be two times the slice thickness.

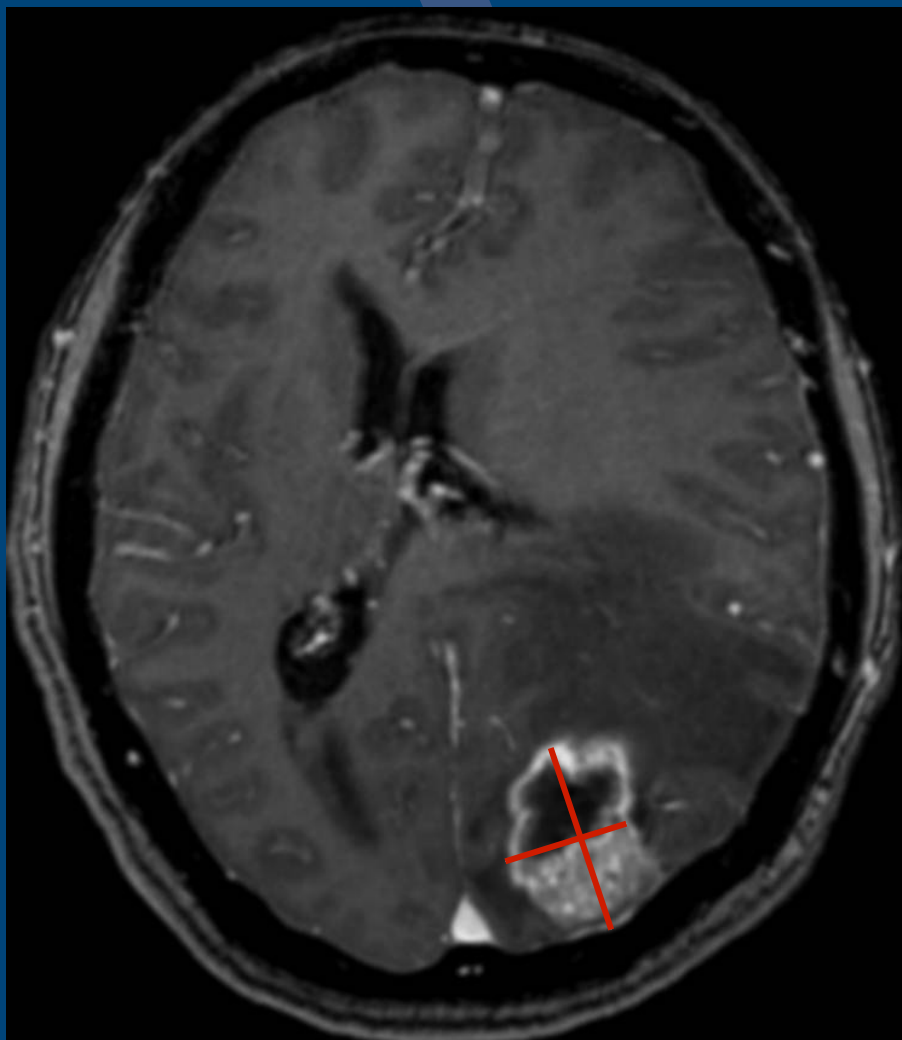
# Non-measurable lesions

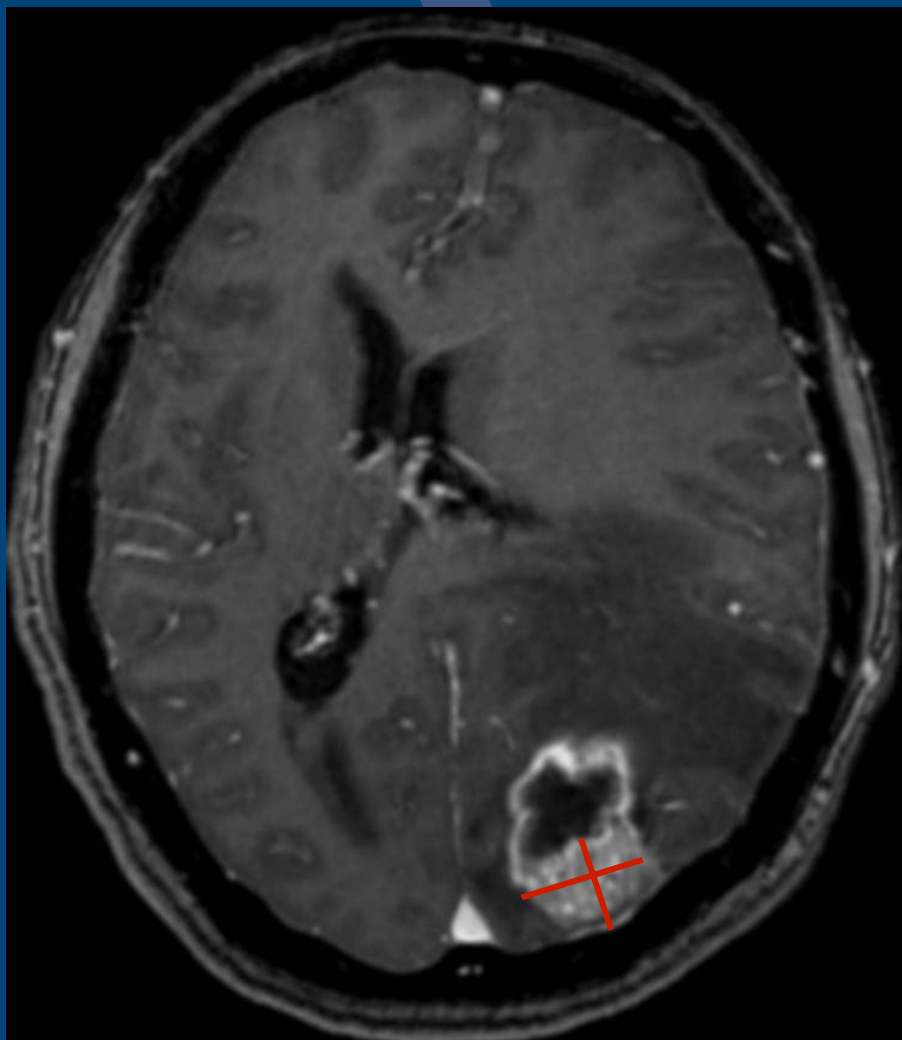
- Unidirectional lesions
- Lesions without sharp delineation
- Lesions with a size less than 2x of the slice thickness



**No measurable lesion**

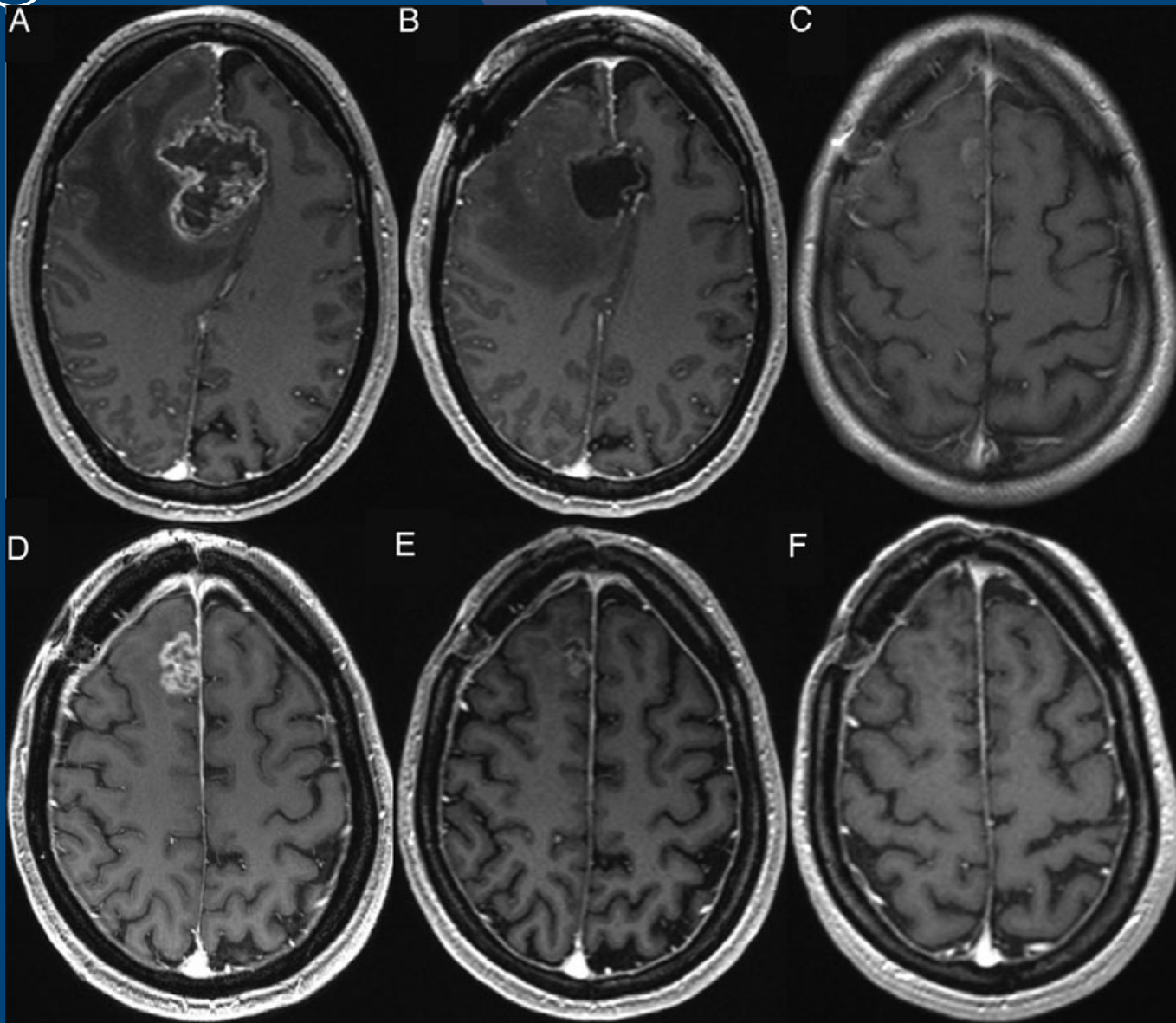






# Pseudoprogression (PsP)

- **Up to 50 %** of patients undergoing their first postradiation MRI show increased contrast enhancement that eventually subsides without any change in therapy.



# Pseudoprogression in RANO HGG

- Within the first 12 weeks of completion of radiotherapy, when pseudoprogression is supposed to be most prevalent, progression can only be determined
  - if the majority of the new enhancement is outside of the radiation field
  - if there is pathologic confirmation of progressive disease
- Otherwise: confirmatory scan in 4 weeks

# Inclusion of T2 Progress/ Pseudoregression

- PD is considered:
  - Increase of enhancement on T1-weighted images of at least 25 %
  - **Significant T2-signal increase**, even if there is stable or decreasing enhancement on T1-weighted images

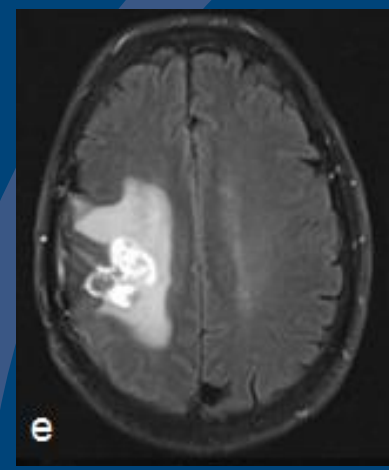
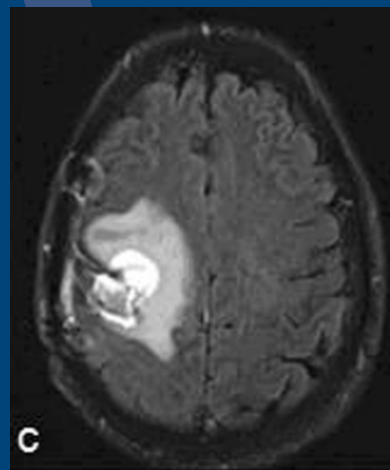
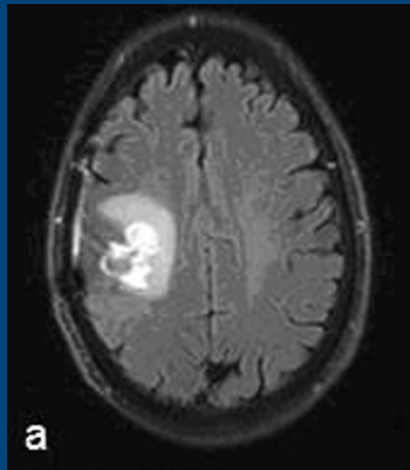


Baseline

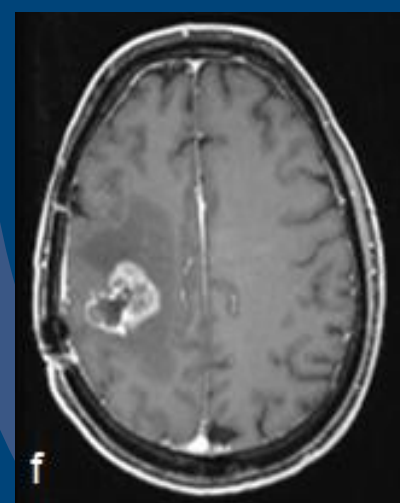
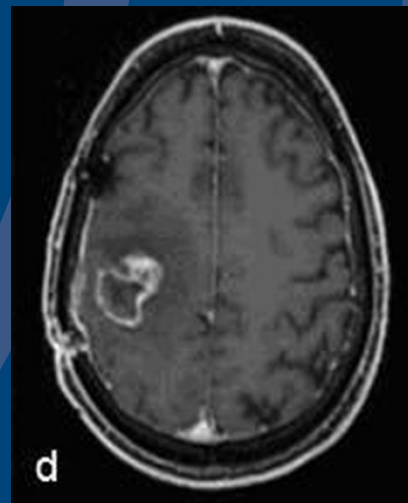
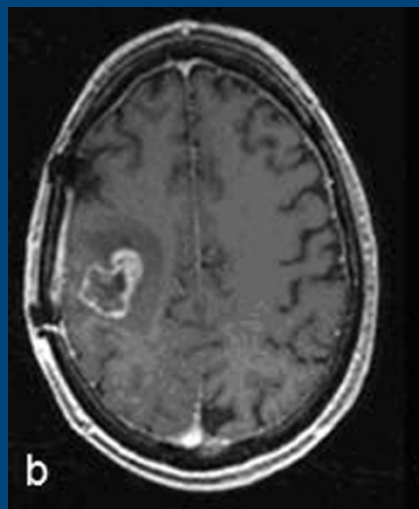
follow up after 3  
months

follow up after 6  
months

Flair



ce-T1





# Summary: RANO Criteria for HGG

Criterion	CR	PR	SD	PD
<b>T1 gadolinium enhancing disease</b>	none	$\geq 50\% \downarrow$	$< 50\% \downarrow$ but $< 25\% \uparrow$	$\geq 25\% \uparrow^*, **$
<b>T2/FLAIR</b>	stable or $\downarrow$	stable or $\downarrow$	stable or $\downarrow$	$\uparrow^*$
<b>New lesions</b>	none	none	none	<b>present*</b>
<b>Corticosteroids</b>	none	stable or $\downarrow$	stable or $\downarrow$	<b>NA <math>\uparrow</math></b>
<b>Clinical status</b>	stable or $\uparrow$	stable or $\uparrow$	stable or $\uparrow$	$\downarrow^*$
<b>Requirement for response</b>	<b>all</b>	<b>all</b>	<b>all</b>	<b>any*</b>

\* Progression occurs when this criterion is present.

$\uparrow$  Increase in corticosteroids alone will not be taken into account in determining progression in absence of persistent clinical deterioration.

\*\*No PD in case of enhancement increase  $\geq 25\%$  in the radiation field within 12 weeks after completion of RCT.



# Starting Point Proposed RANO BM

- welcome trend away from automatic exclusion of patients with BM from clinical trials
- irregular response criteria for assessment of CNS metastases has made interpretation of trial results challenging

# Proposed RANO BM Criteria

- RANO Metastatic Working Group convened 2011: medical oncologists, neuro-oncologists, radiation oncologists, neurosurgeons, neuroradiologists, neuropsychologists, biostatistics
- RANO BM Criteria cover only evaluation of parenchymal brain metastases NOT leptomeningeal metastases, dural metastases or bone metastases invading the brain

# Proposed RANO BM Criteria

- RECIST 1.1 and the RANO response assessment criteria for high-grade gliomas (HGG)
- Gaps were identified; areas of controversy were resolved: evidence-based approach or expert opinion and consensus
- RANO BM: Work in Progress

# Measurable disease according to RANO BM

- contrast enhancing lesion with a minimum size of 10 mm in **one dimension**, visible on two or more axial slices that are at most 5 mm apart with 0-mm skip
- if MRI is performed with thicker slices, size of a measurable lesion at baseline should be two times the slice thickness
- Cavities or cysts are considered non-measurable unless there is a nodular component measuring  $\geq 10$  mm in longest diameter and  $\geq 5$  mm in the perpendicular plane

## Non-Measurable disease according to RANO BM

- All other lesions, including lesions with longest dimension  $< 10$  mm, lesions with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, and leptomeningeal disease.

# Tumor Response Evaluation according to RANO BM

- Only patients with measurable CNS disease at baseline should be included in protocols where objective CNS tumor response is the primary endpoint.
- Baseline documentation: When more than one measurable lesion is present at baseline, all lesions **up to a maximum of five** will be identified as target lesions
- A sum of the diameters for all target lesions will be calculated and reported as the baseline sum of longest diameters (sum LD)

# Evaluation of Target Lesions

- **Complete response (CR):**  
Disappearance of all CNS target lesions sustained for at least 4 weeks; no new lesions; no corticosteroids; stable or improved clinically

# Evaluation of Target Lesions

- **Partial response (PR):** At least a 30% decrease in the sum LD of CNS target lesions, taking as reference the baseline sum LD sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.



# Evaluation of Target Lesions

- **Progressive disease (PD):** At least a 20% increase in the sum LD of CNS target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study).

# Evaluation of Target Lesions

- **Stable disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the small sum LD while on study.



# Summary of RANO BM

Criterion	CR	PR	SD	PD
<b>Target lesions</b>	None	$\geq 30\%$ decrease in sum LD relative to baseline	$< 30\%$ decrease relative to baseline but $< 20\%$ increase in sum LD relative to nadir	$\geq 20\%$ increase in sum LD relative to nadir
<b>Non-target lesions</b>	None	Stable or improved	Stable or improved	Unequivocal PD
<b>New lesion(s)**</b>	None	None	None	Present
<b>Corticosteroids</b>	None	Stable or decreased	Stable or decreased	NA
<b>Clinical status</b>	Stable or improved	Stable or improved	Stable or improved	Worse
<b>Requirement for response</b>	All	All	All	Any



# Corticosteroid Use and Clinical Deterioration

- An increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor does not qualify for PD.



# Treatment of Non-CNS (Extracranial) Disease

- Preclinical and clinical data demonstrate a differential response in intracranial versus extracranial metastases.
- Many systemic agents are not expected to have CNS activity, e.g. due to drug penetration
- Vice versa, local CNS therapies (e.g. radiosurgery) do not affect extracranial sites

# Approach of RANO GBM

- CNS is a separated compartment, scored irrespective of extracranial response



# CNS and non-CNS Response Assessment

CNS (by RANO-BM)	Non-CNS (by RECIST 1.1)	Response
CR, PR, or SD	CR, PR, or SD	Log as CNS CR, PR, or SD  Log as non-CNS CR, PR, or SD
CR, PR, or SD	PD	Log as CNS CR, PR, or SD  Log as non-CNS PD
PD	CR, PR, or SD	Log as CNS PD  Log as non-CNS CR, PR, or SD
PD	PD	Log as both CNS and non-CNS PD



# Recommendations for Minimum Requirements for Brain Imaging

MR Scanners: 1.5T and 3T MR scanners only

Localizer/Scout

## 3D T1w pre-contrast (MPRAGE, 3D IR SFPGR T1w)

minimum TE  
TI, TR and flip angle according to manufacturer specific / field strength specific recommendations for optimum image quality  
Slice/3D slab orientation: sagittal or transverse  
FOV: 256 mm x 256 mm  
Matrix: 256x256  
Slice thickness:  $\leq 1.5$  mm  
Full brain coverage

## DWI

single shot EPI sequence  
b: 0 and 1000 s/mm<sup>2</sup> (3 directions)  
Slice orientation: transverse  
Slice thickness: 5mm  
Slice gap: 0  
Number of slices: Full brain coverage  
FOV: 240 mm x 240 mm  
Matrix: 128 x 128 or higher  
Postprocessing: Calculation of ADC maps

## 2D FLAIR, transverse

Turbo Spin Echo (TSE) / Fast Spin Echo (FSE) sequence  
Slice orientation: transverse  
Slice thickness: 5mm  
Slice gap: 0  
Number of slices: same as sequence 2  
FOV: 240 mm x 240 mm  
Matrix: 256 x 256 or higher  
Slice positioning as in sequence 2

## 3D FLAIR (OPTIONAL)

Contrast agent injection  
0.1 mmol/kg BW of a Gd-based contrast agent

## T2w-TSE

Turbo Spin Echo (TSE) / Fast Spin Echo (FSE) sequence  
Slice thickness: 5mm  
Slice gap: 0  
Number of slices: same as sequence 2  
FOV: 240 mm x 240 mm  
Matrix: 256 x 256 or higher  
Slice positioning as in sequence 2

## 3D T1w post-contrast (MPRAGE, 3D IR FSPGR T1w)

Sequence parameters and slice positioning as in sequence 1

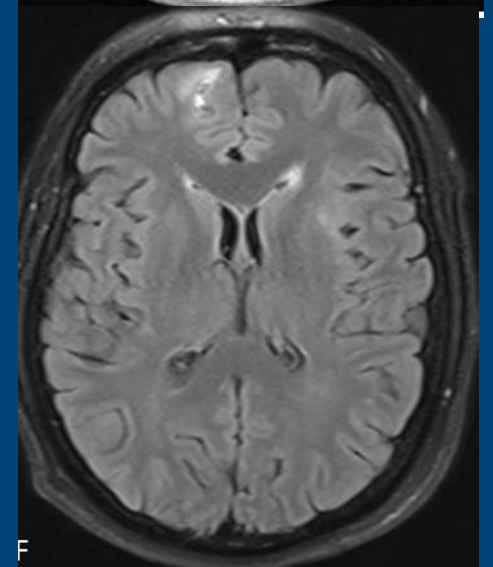
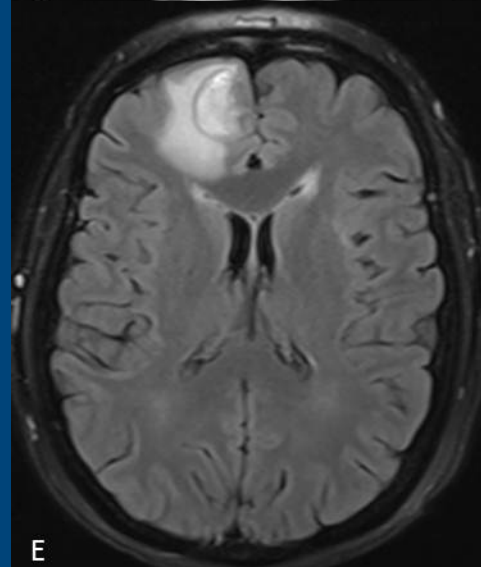
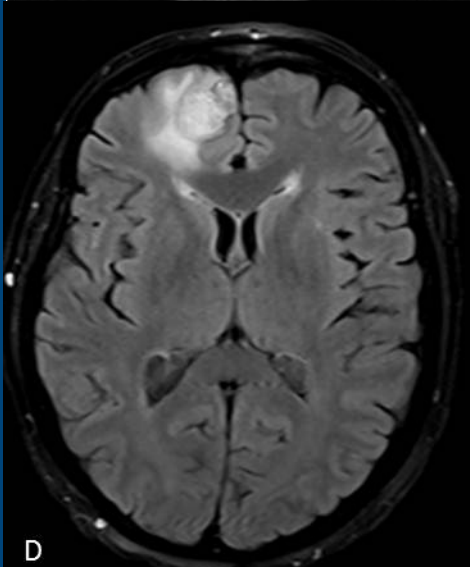
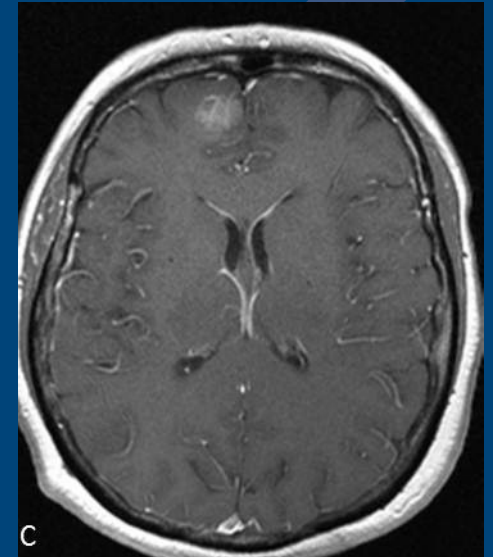
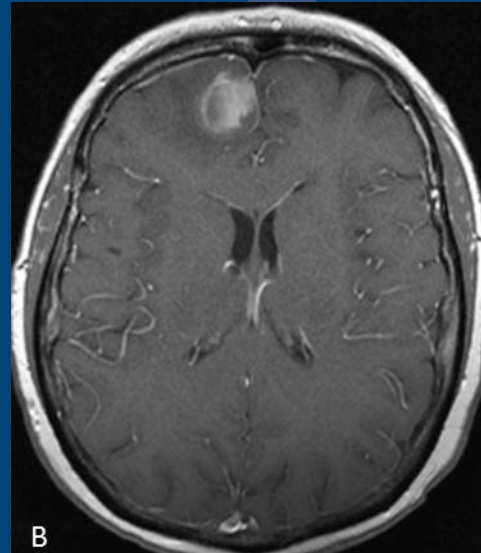
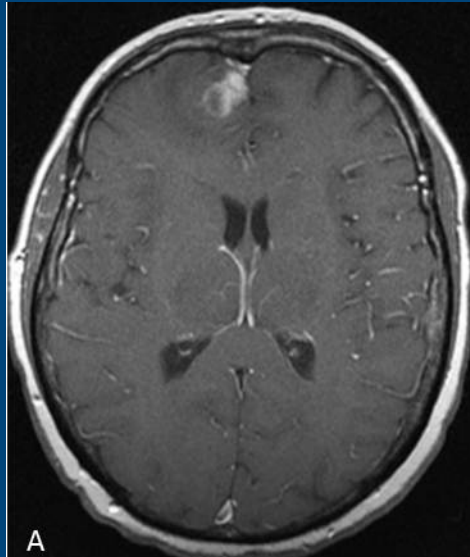


# Guidance in the case of uncertain attribution of radiographic findings and/or equivocal cases

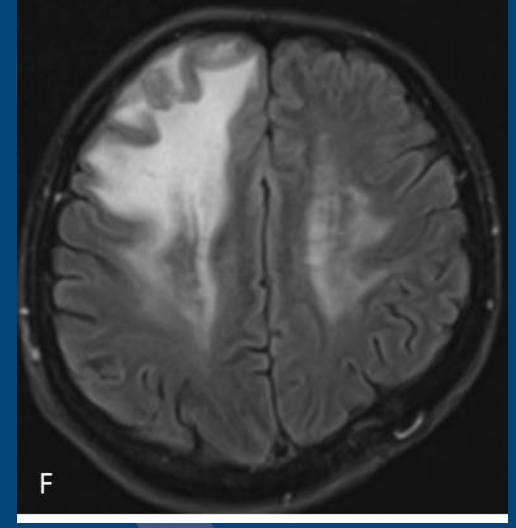
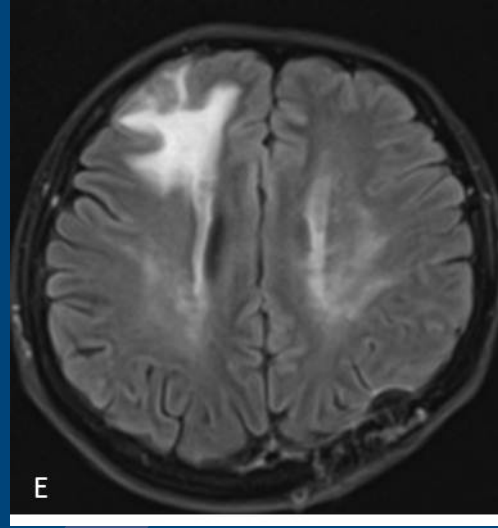
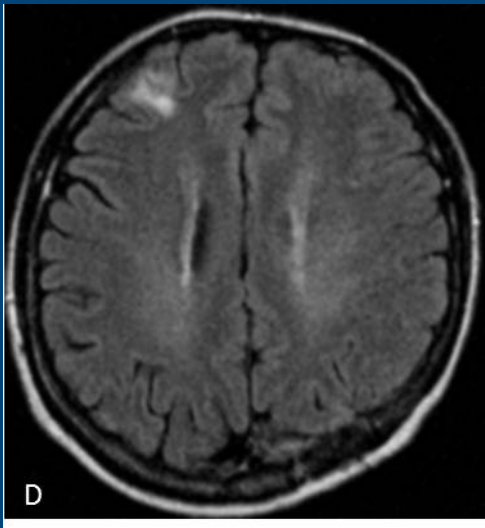
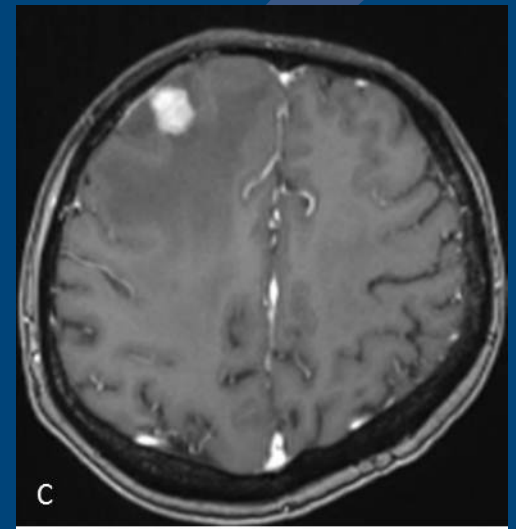
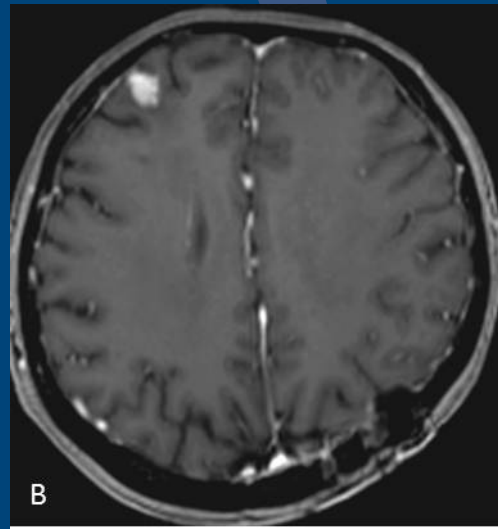
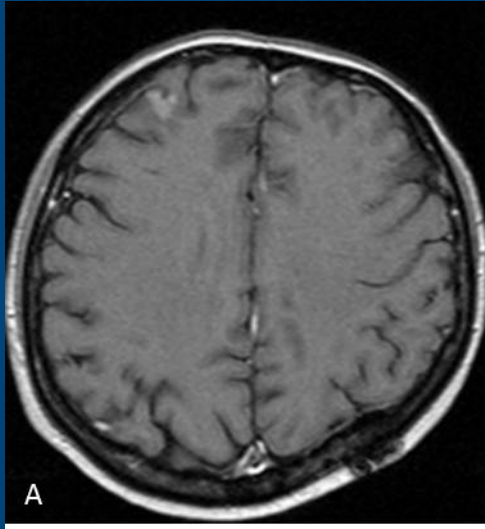
Methods used to distinguish between radiation necrosis and true progression should be specified prospectively in the clinical protocol

1. Repeat the scan at the next protocol scheduled evaluation
2. Histopathological evaluation
3. Advanced MR/PET Imaging techniques

# Pseudoprogression of a Melanoma BM



# True Progression of a Melanoma BM





# RANO HGG vs proposed RANO BM

## RANO HGG

- Bidimensionally measured
- Exclusively CNS assessment
- T2-progress qualifies for PD
- Enhancement within 12 weeks after RCT in radiation field does not qualify for PD

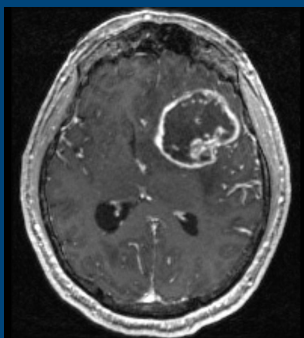
## RANO BM

- Unidimensionally measured
- CNS and Non-CNS assessment independent
- T2-signal not considered
- No clear recommendation for treatment related effects such as radiation necrosis

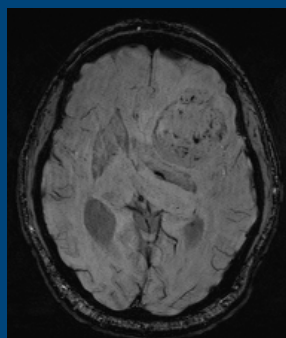
**New Imaging Methods are needed!!**



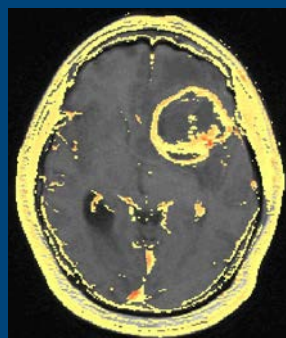
# Advanced MR Imaging



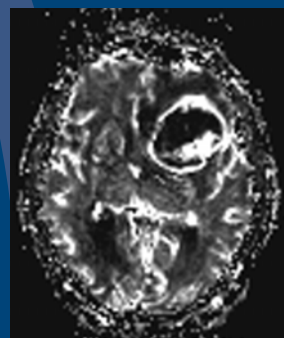
ce-T1



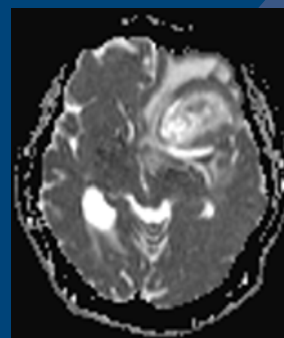
SWI



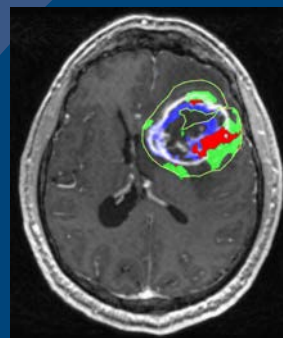
DCE-  
Perfusion



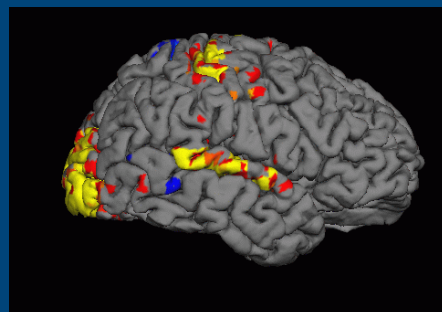
DSC-  
Perfusion



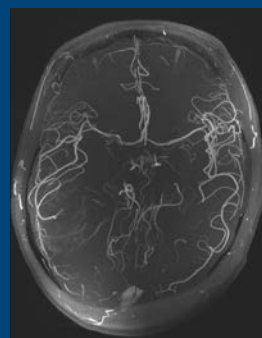
Diffusion



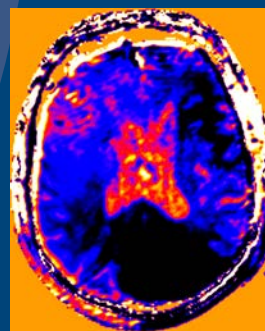
Advanced  
Postprocessing



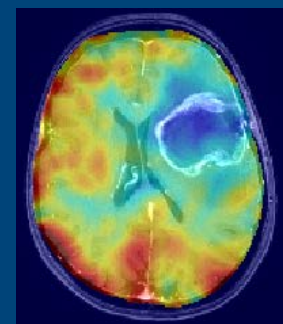
FMRI



Ultra High  
Field: 7 Tesla



CEST (pH  
Imaging?)



X-Nuclei  
Imaging (O17)

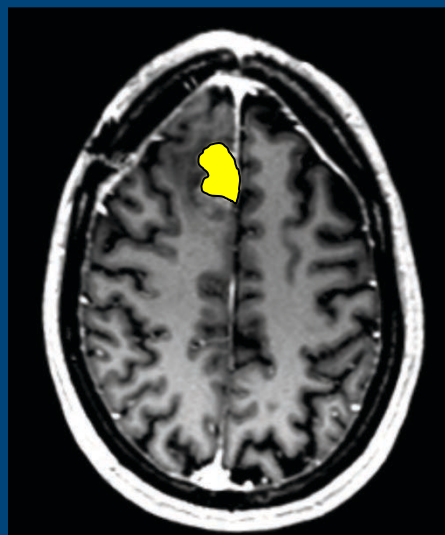


# Diffusion MR Imaging for DD True Progression and Pseudoprogression (PsP)

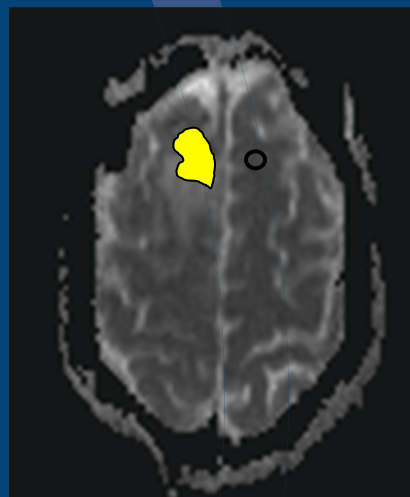
- ADC – possible parameter – Hypothesis:
  - low ADC values – high cellularity – True Progression
  - high ADC values – low cellularity – PsP
- Postprocessing of ADC maps:
  - **Region of Interest Analysis does not reflect the heterogeneity of GBM**
  - Parametric Response Maps\*: Voxelwise analysis of changes in ADC values

\*Galban et al, The Parametric Response Map: An Imaging Biomarker for Early Cancer Treatment Outcome, Nat Med 2009 15(5): 572–576

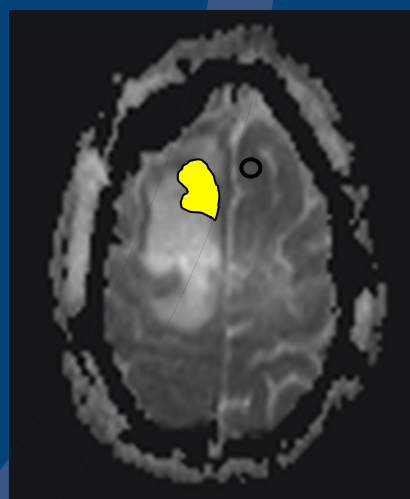
# Workflow: 1. step



new enhancement at  
3 months



baseline ADC



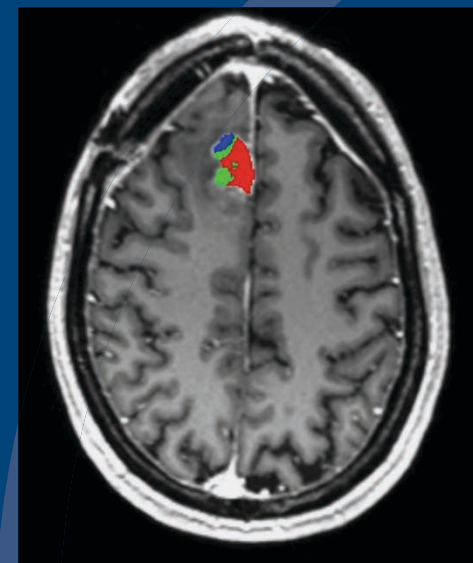
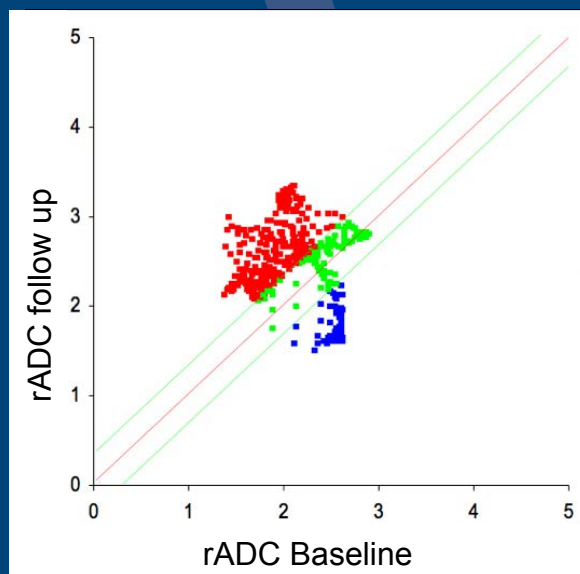
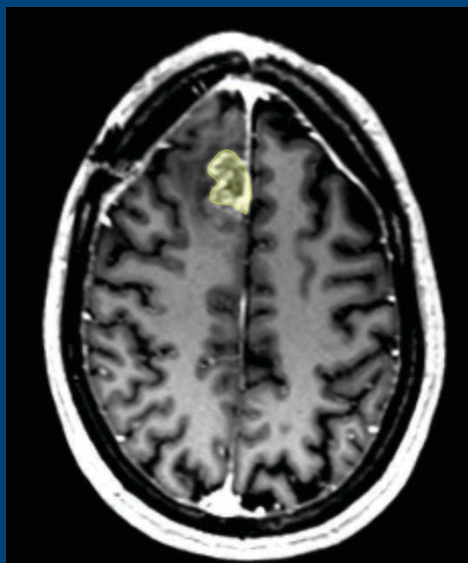
3 months ADC

1. Segmentation of  
contrast enhancement on  
ce-T1

2. coregistration and  
transfer of ROI to ADC  
baseline and ADC f/u

3. calculation of rADC  
values by division of ROI  
with contralateral  
reference-ROI

# Workflow: 2. step



Voxelwise Subtraction of rADC values at baseline and follow up, presentation with scatter plott

Visualization on follow up ce-T1

Quantification of voxels

- 1)  $\text{rADC (baseline)} - \text{rADC (follow up)} > 0.25$
- 2)  $\text{rADC (baseline)} - \text{rADC (follow up)} < -0.25$

(Decrease of rADC)

(Increase of rADC)



# Patients and Methods

## Patients

- 36 Patients with histologically proven GBM
- Postoperative baseline MRI with 72 hours including DWI
- Standard therapy with temozolomide and RCT
- New Enhancement in 1st follow up after completion of RCT
- 7 Pseudoprogression, 29 true progression

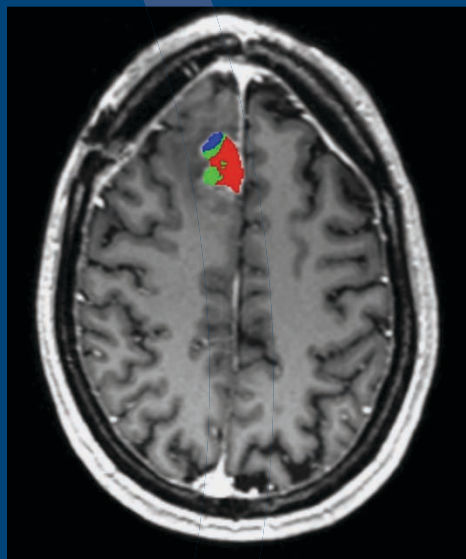
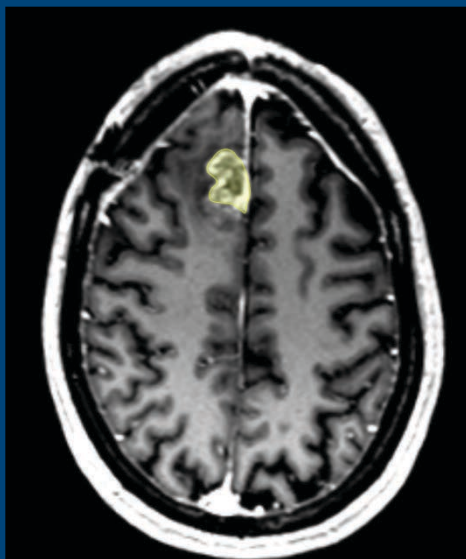
## MRI

- 3 Tesla Siemens Trio or Verio
- ce-T1 (0.1 mmol / kg body weight DOTAREM); DWI: TE = 90 ms, TR = 5300 ms, flip angle = 90°, slice thickness = 5 mm,  $b$ -values of 0 and 1200 s/mm<sup>2</sup>

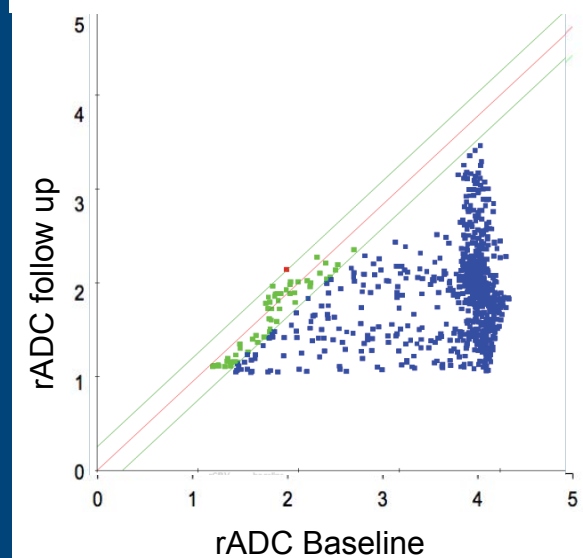
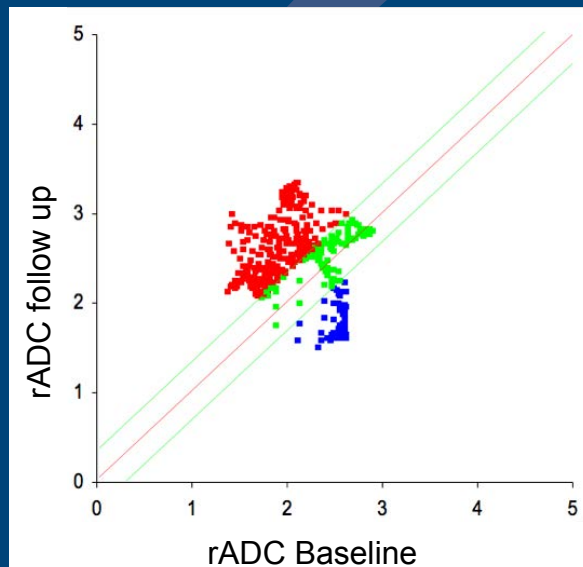
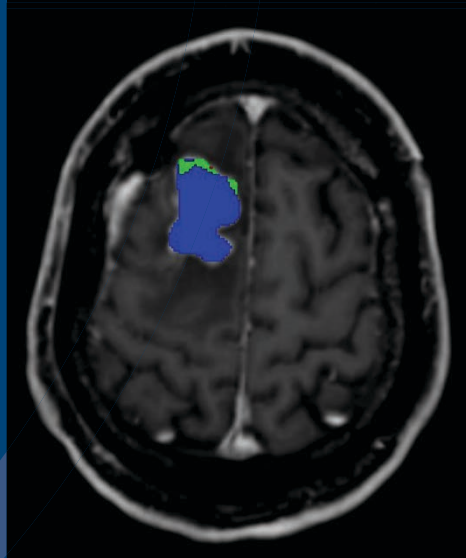
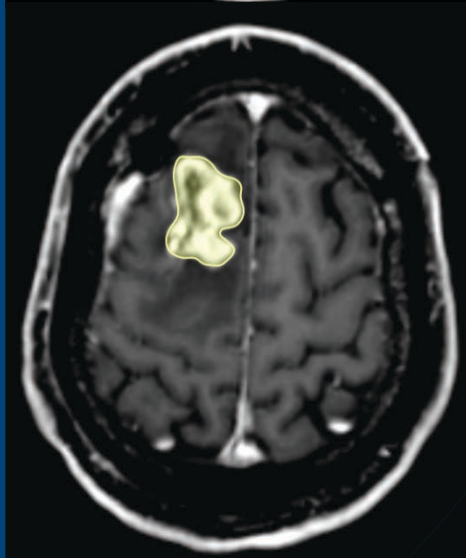


# Results

Example:  
Pseudo-  
progression

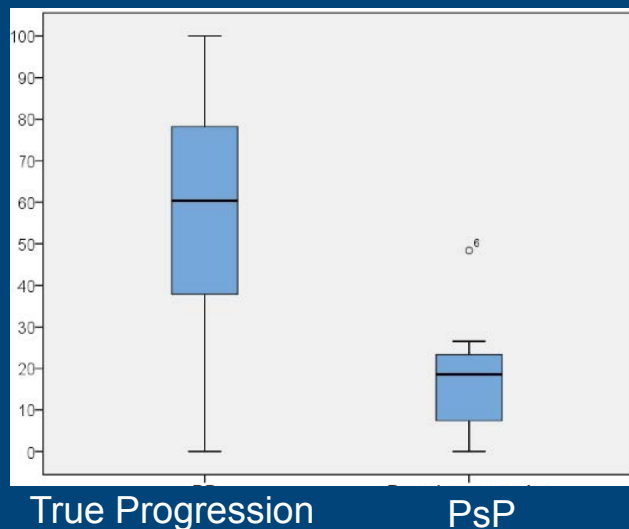


Example:  
True  
Progression



# Results

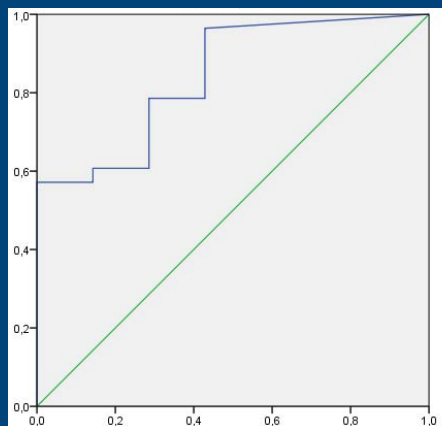
Percentage of voxels with  
rADC  
**decrease**



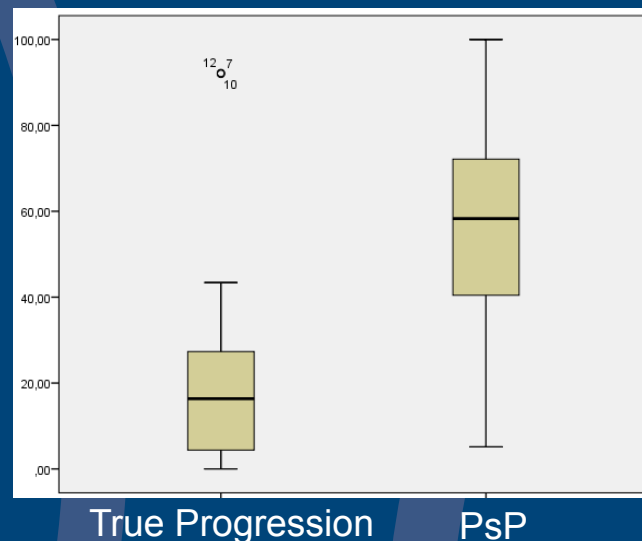
$p < 0.01$

ROC analysis  
(threshold of  
30 % rADC  
decrease)

AUC=0.84



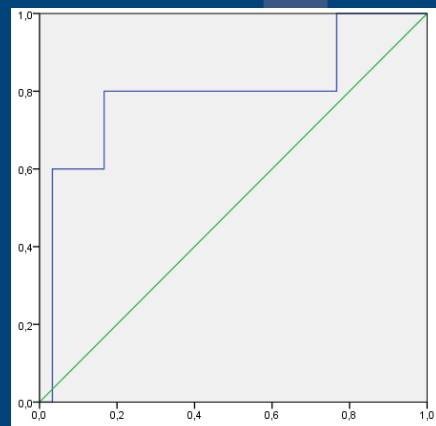
Percentage of voxels with  
rADC  
**increase**



$p < 0.01$

ROC analysis  
(threshold of  
30 % rADC  
increase)

AUC=0.79

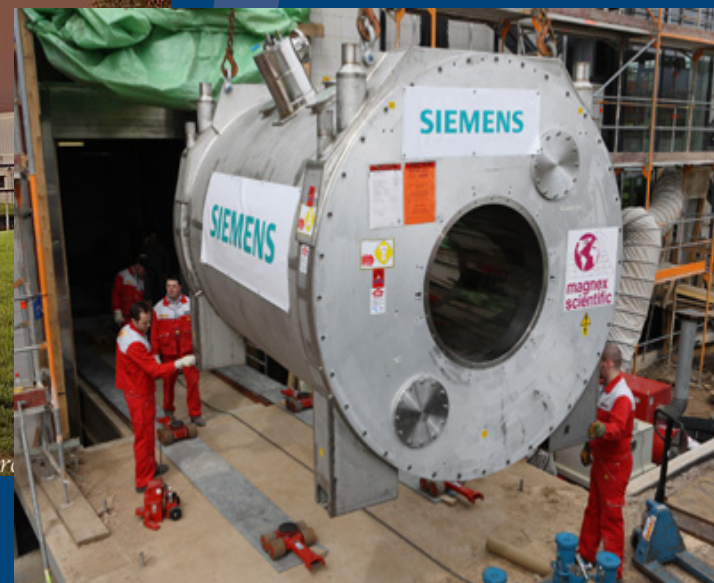


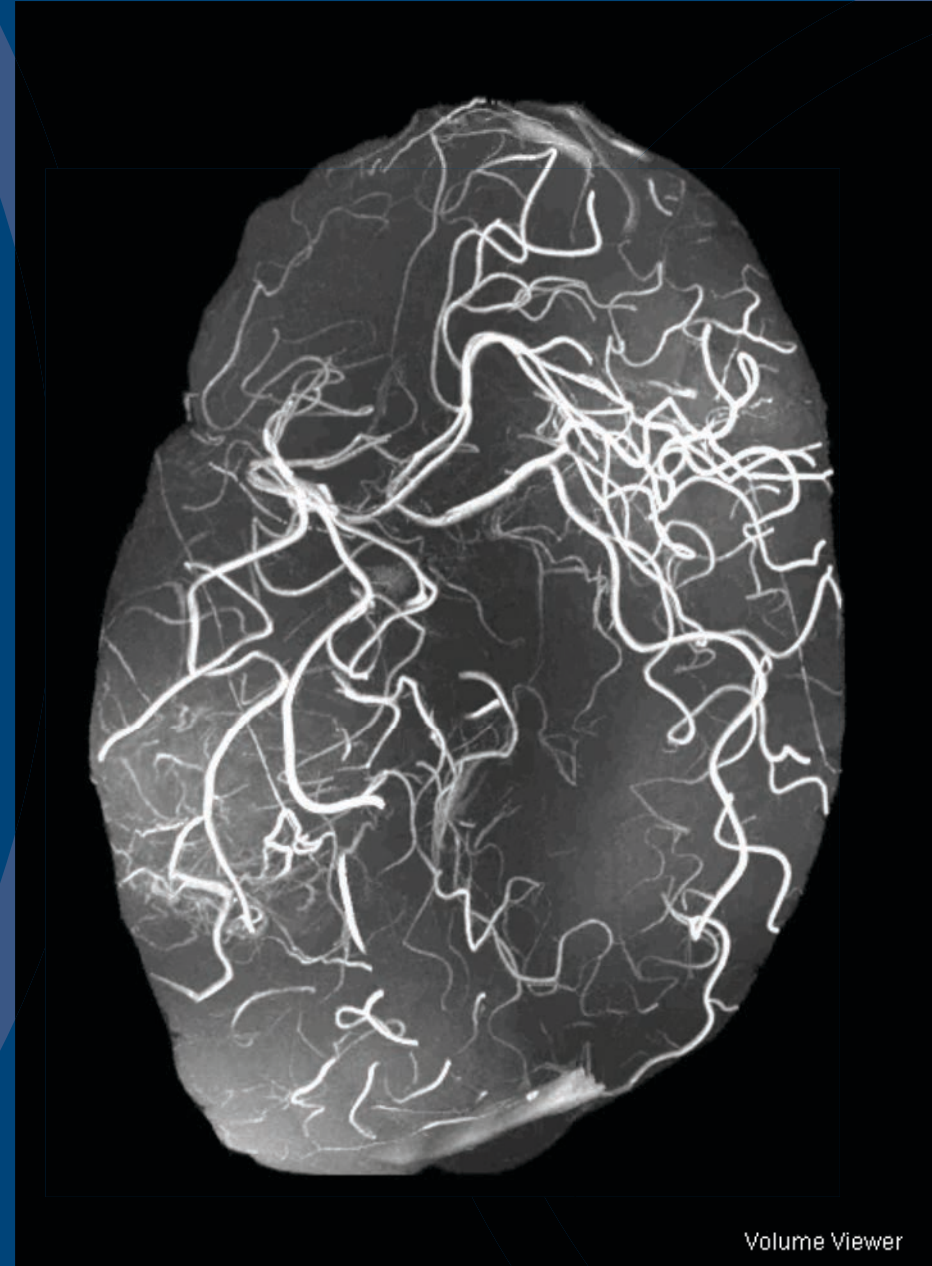
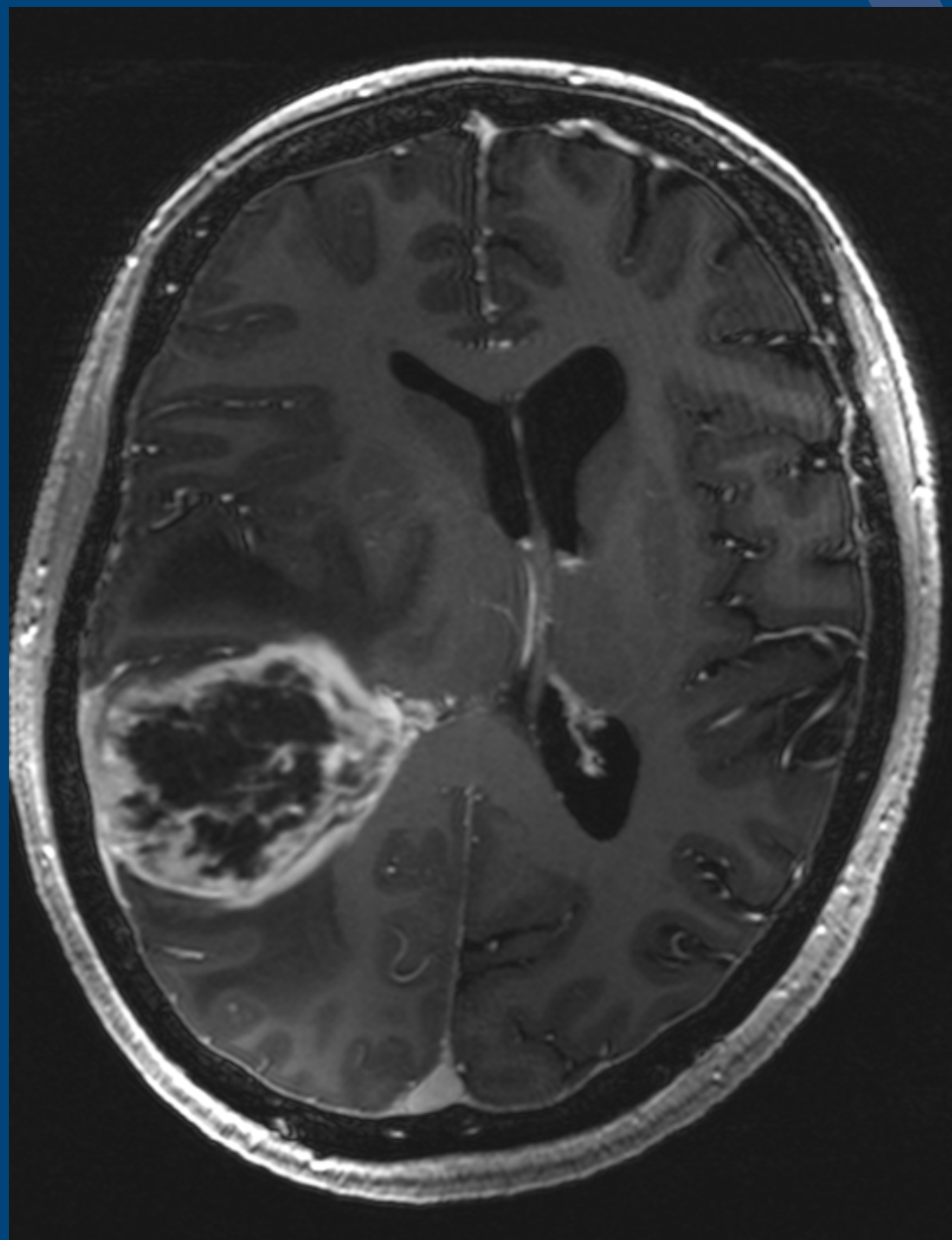
What is on the horizon?



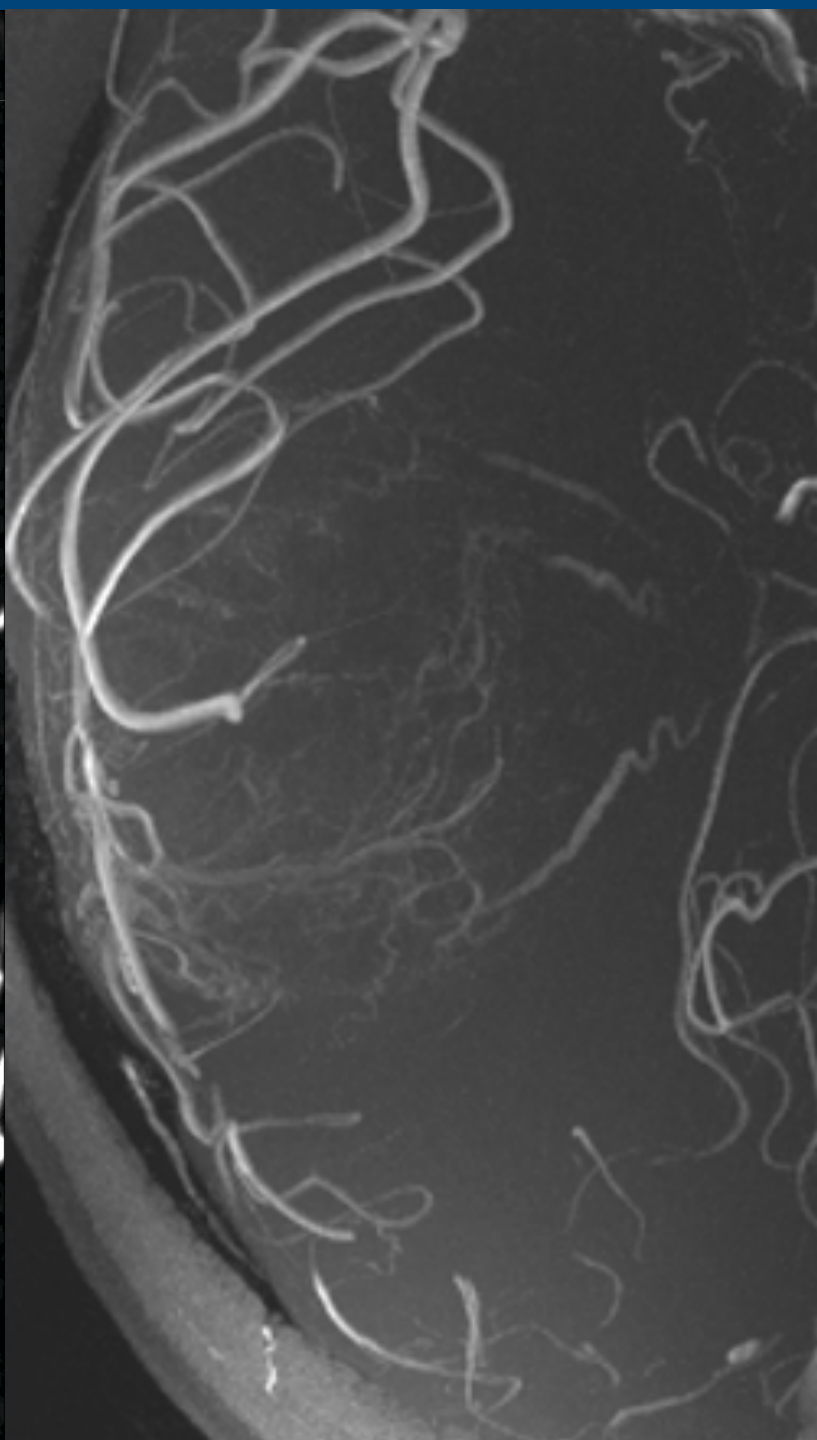
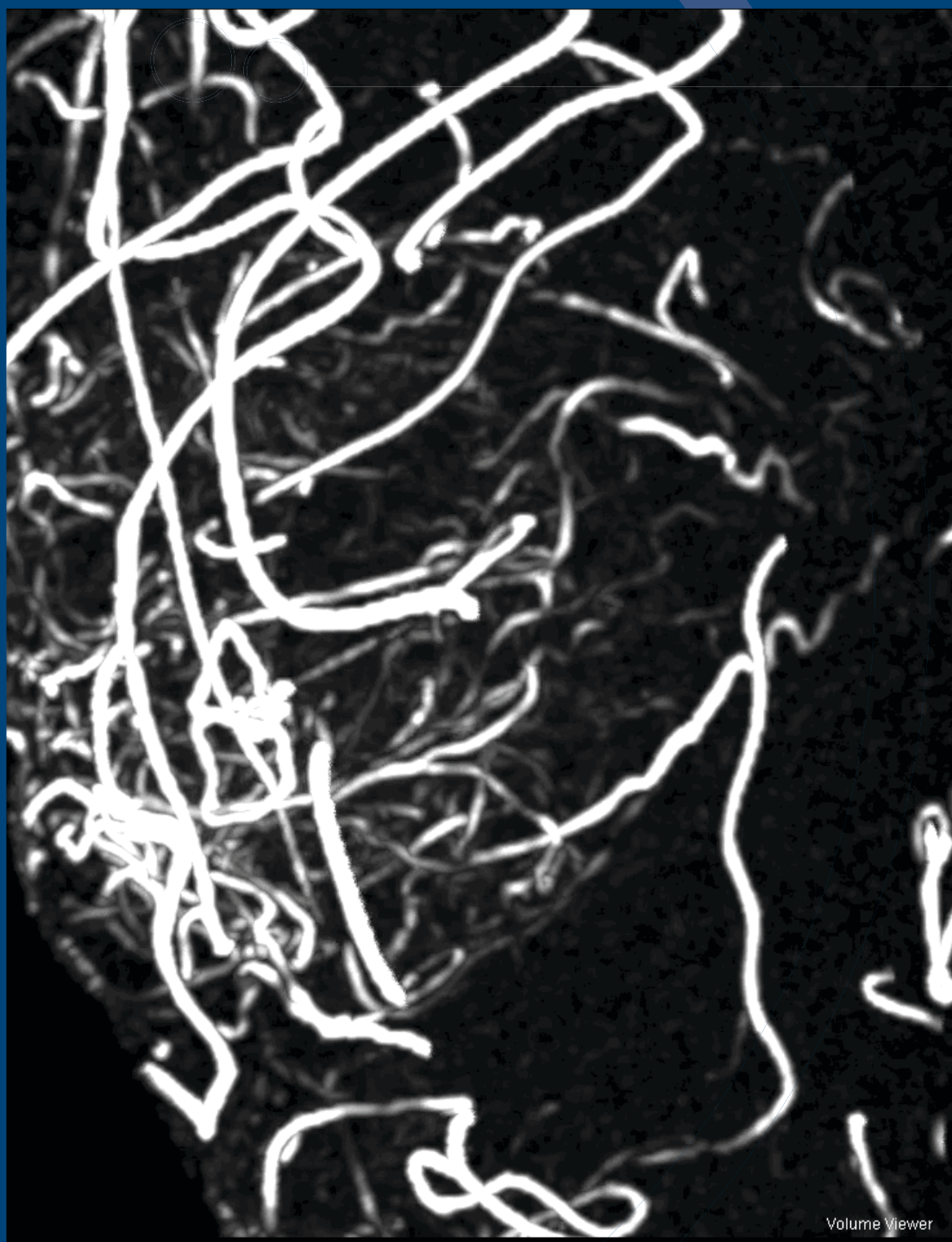


# Ultra-High-Field: 7 Tesla

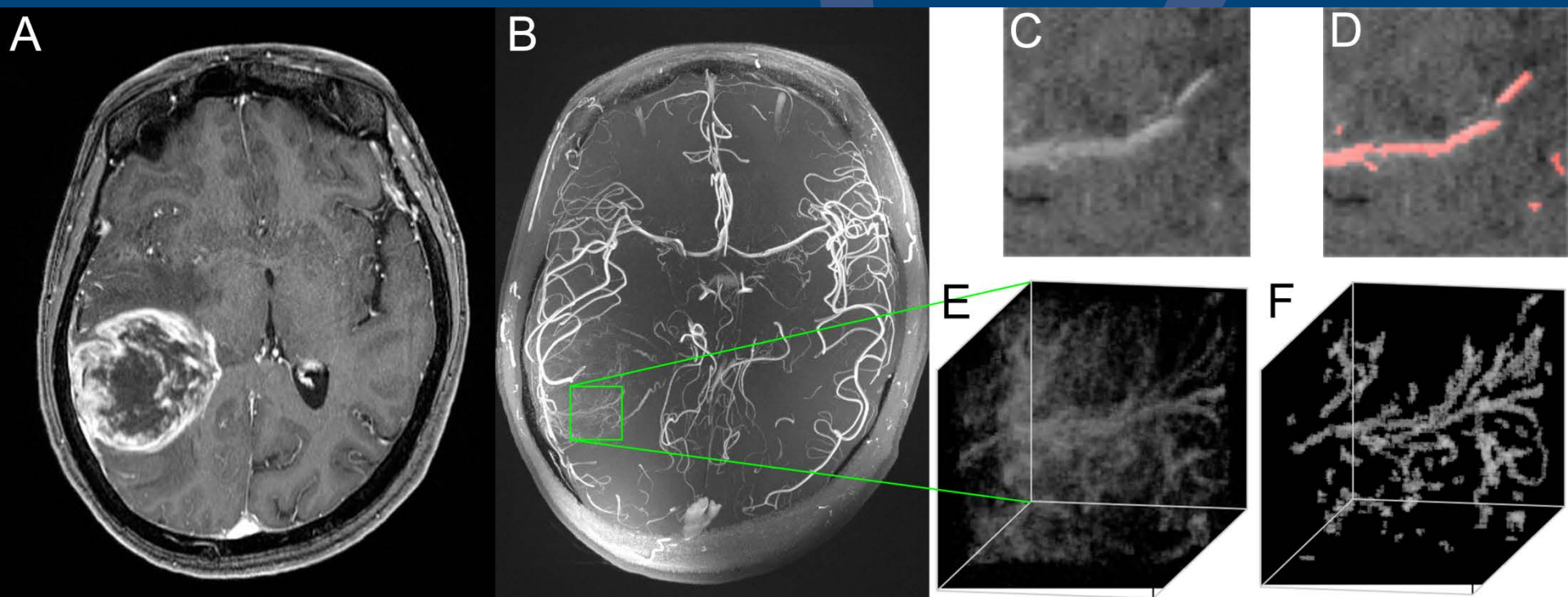








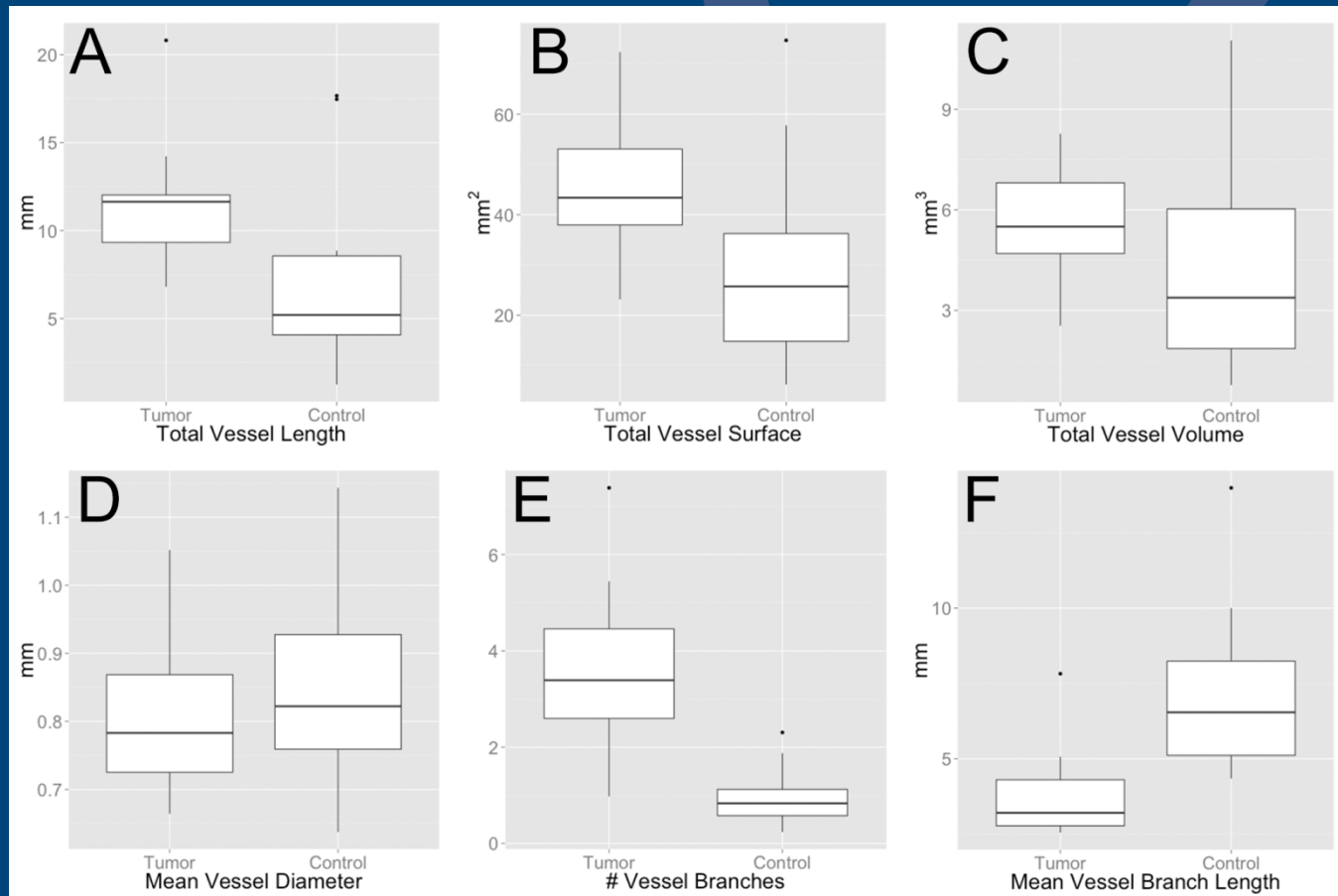
# Quantification of Tumor Vessels at 7 Tesla



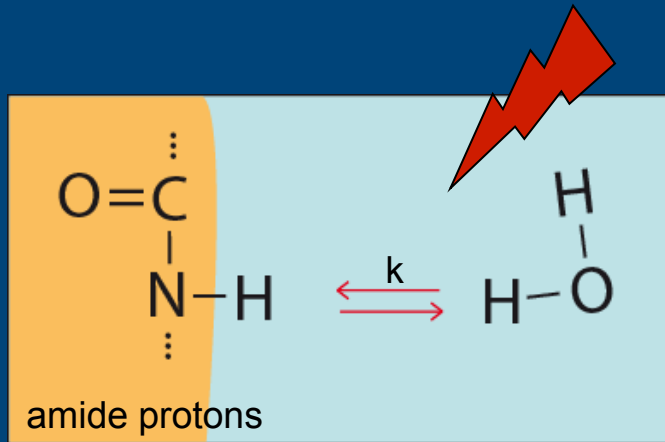




# Quantification of Tumor Vessels at 7 Tesla



# Chemical Exchange Saturation Transfer (CEST)



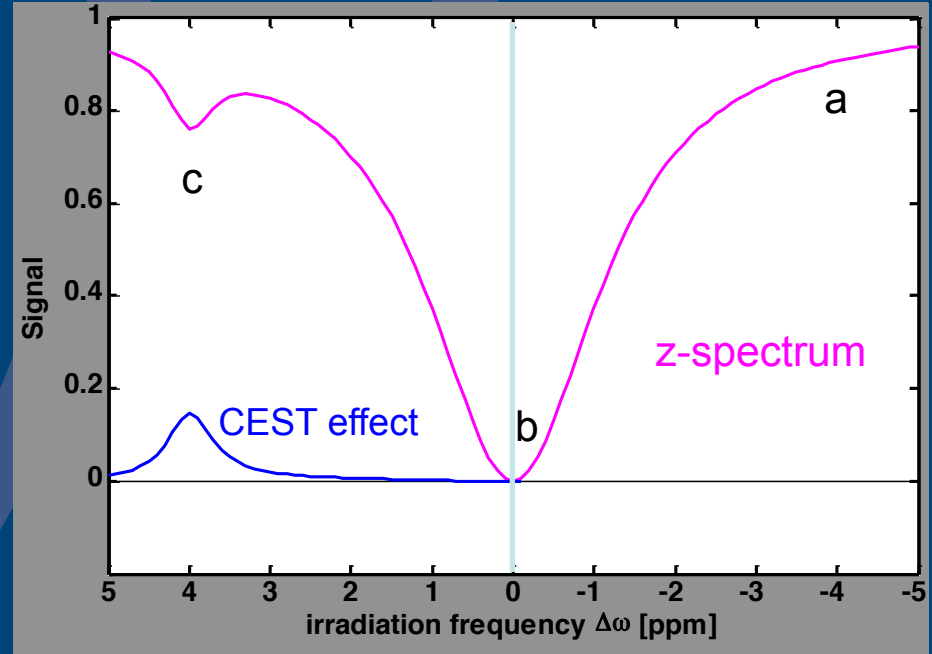
- Amide proton transfer imaging
- Exchangeable solute protons that resonate at a frequency different from the bulk water protons are selectively saturated using RF irradiation
- Transfer of saturation to bulk water – water signal becomes attenuated

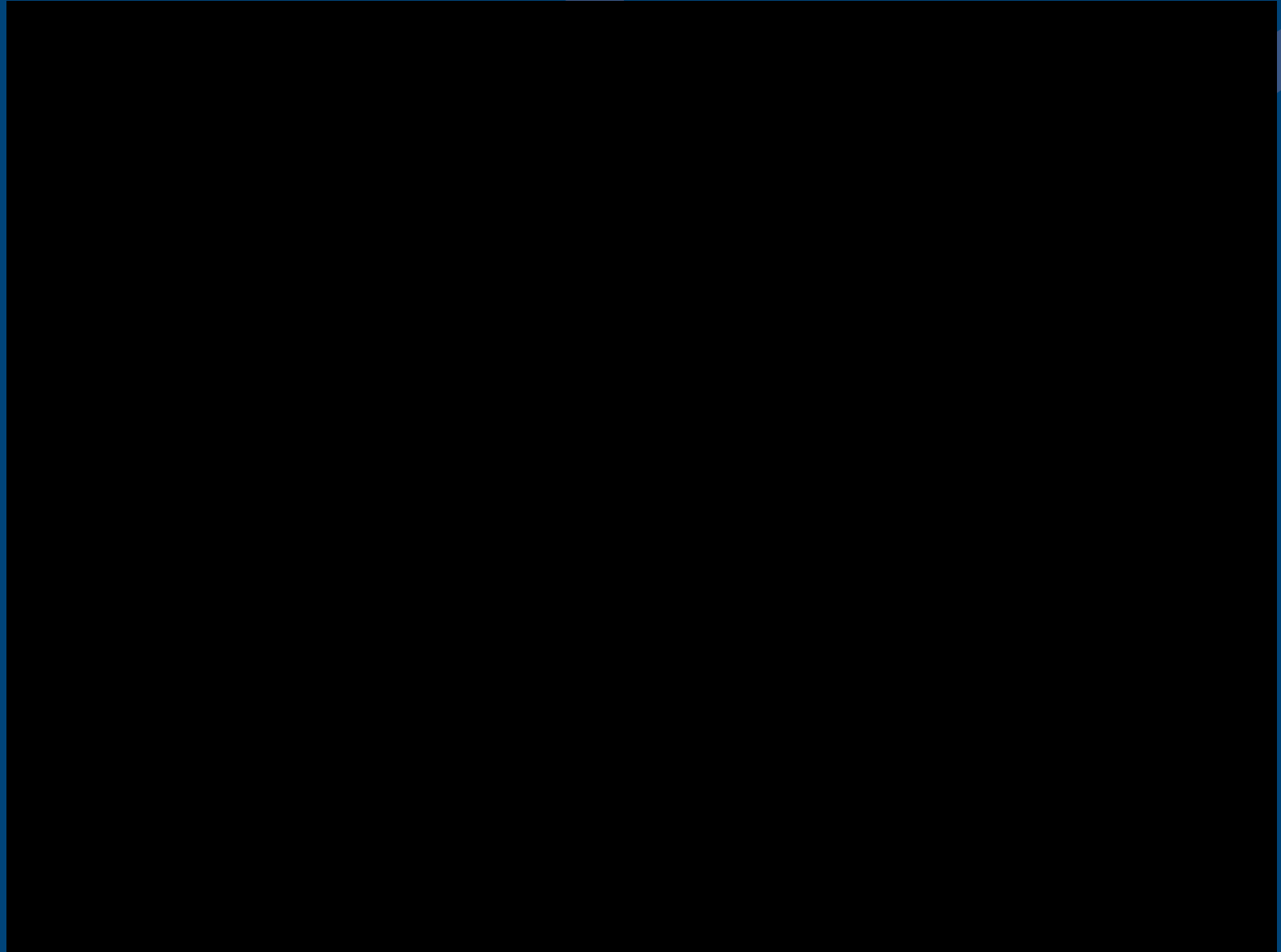
- off-resonant: full water signal
- on-resonant water: no water signal
- CEST-resonant: decreased w. signal

Asymmetry analysis

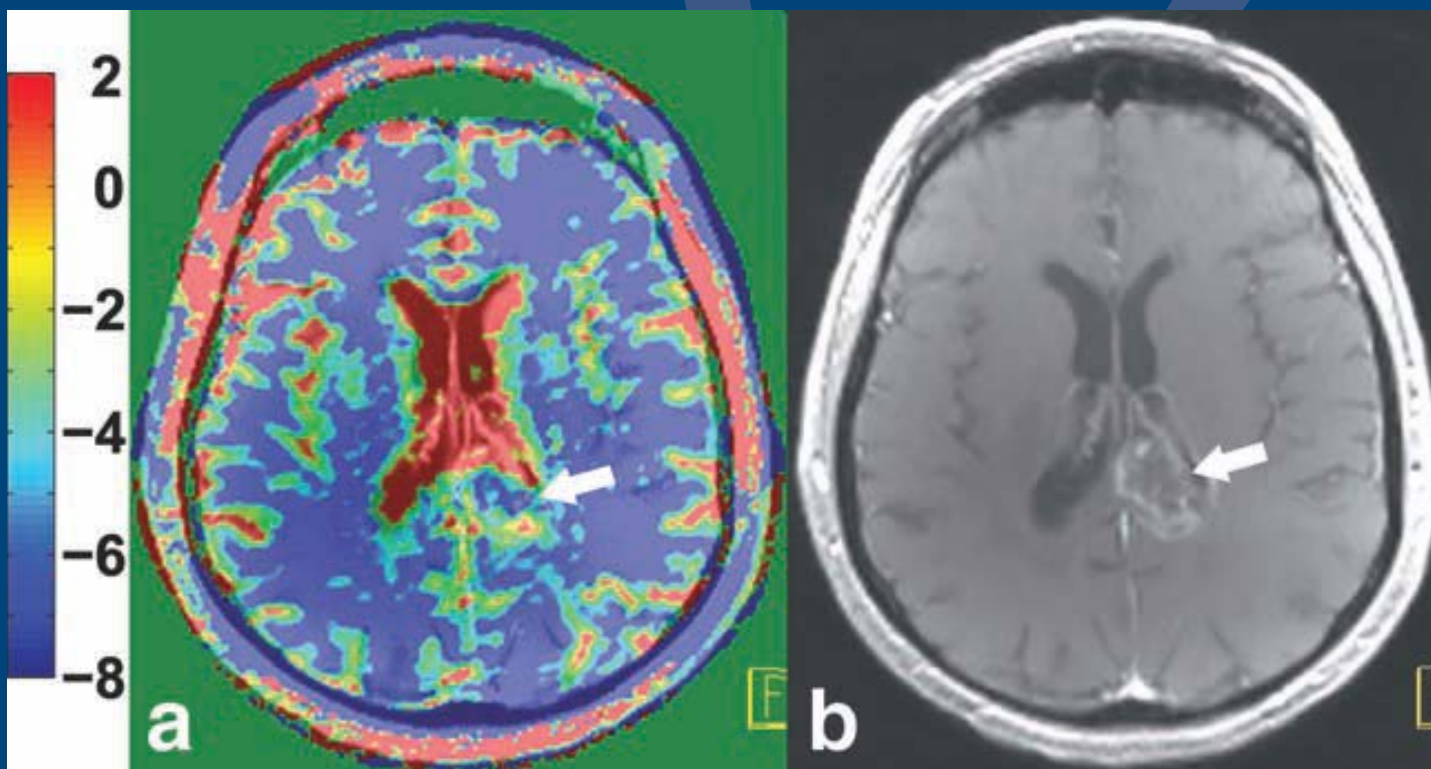
$$\text{CEST}_{\text{asym}} = S(a) - S(c) \approx \text{PTR}$$

pH-Imaging??





# Identification of PsP with CEST





# Advanced CEST

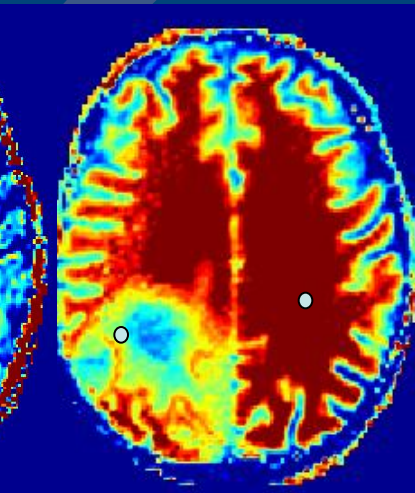
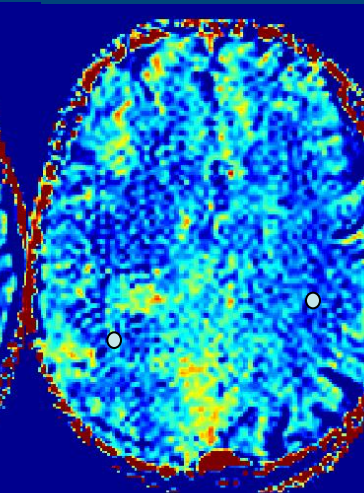
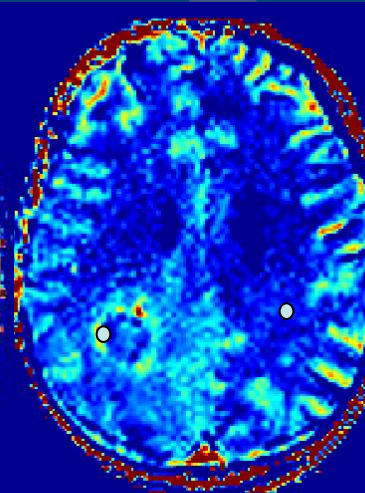
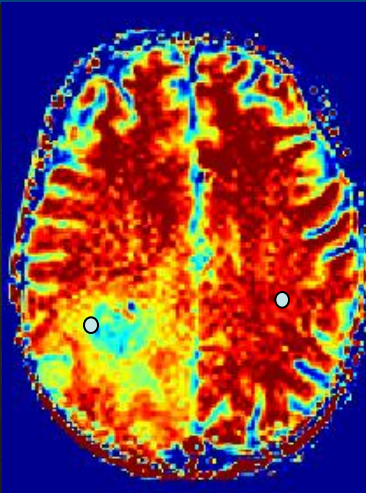
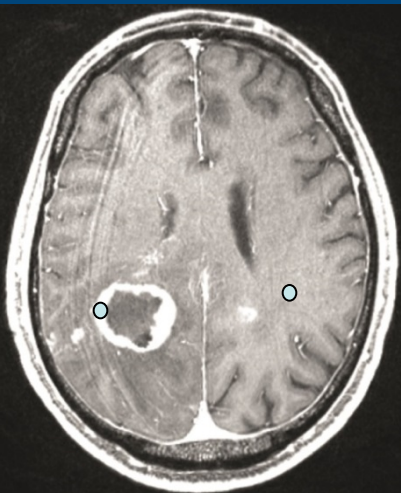
ce-T1

NOE

Amide

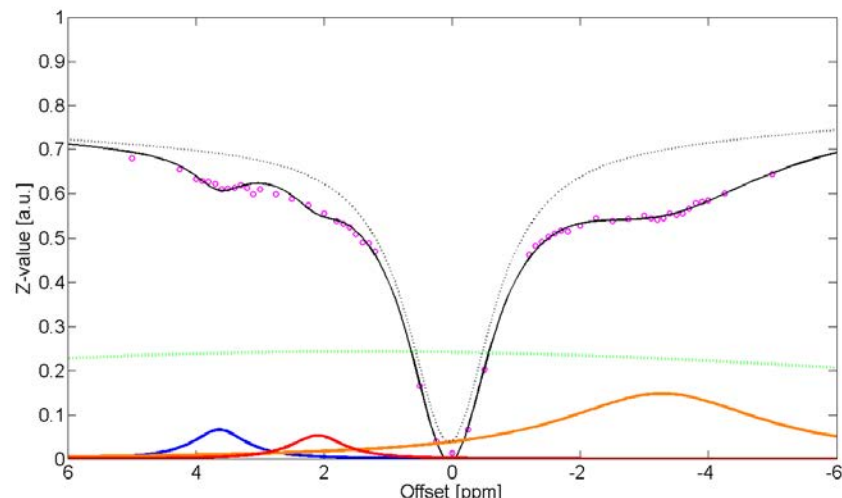
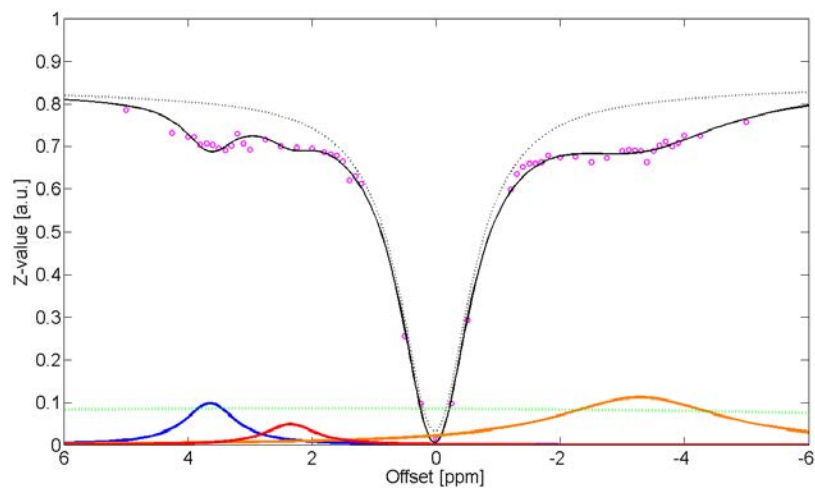
Amine

MT



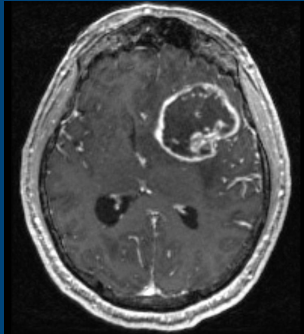
Tumor Enhancement

Contralateral White Matter

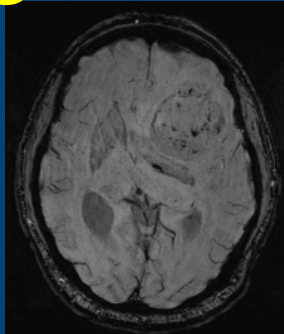




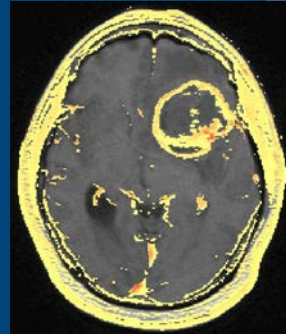
# „Dangers“ of Advanced MR Imaging



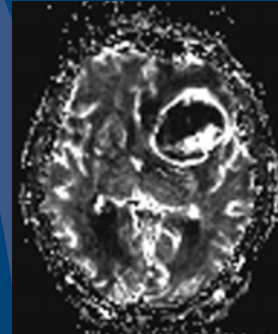
ce-T1



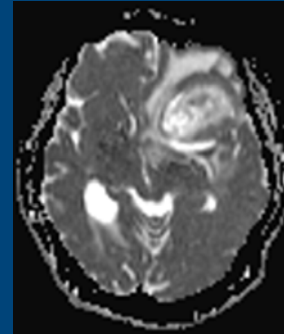
SWI



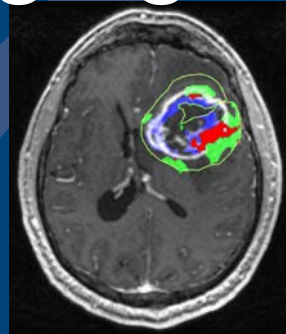
DCE-Perfusion



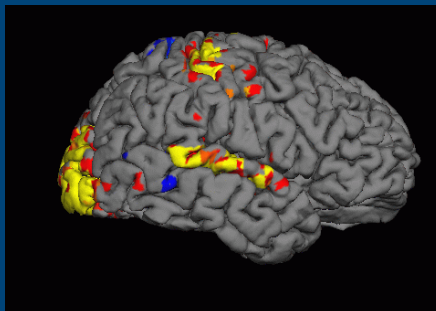
DSC-Perfusion



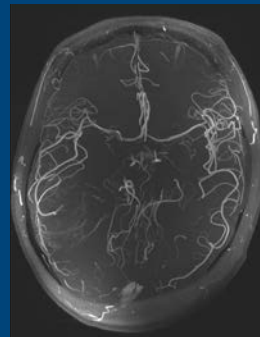
Diffusion



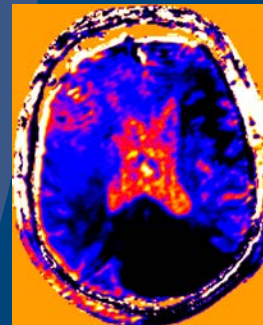
Advanced Postprocessing



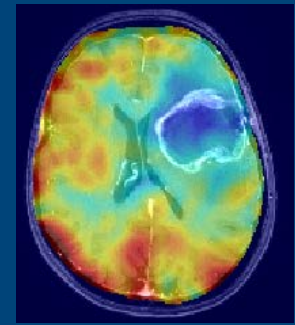
FMRI



Ultra High Field: 7 Tesla



CEST (pH Imaging?)



X-Nuclei Imaging (O17)

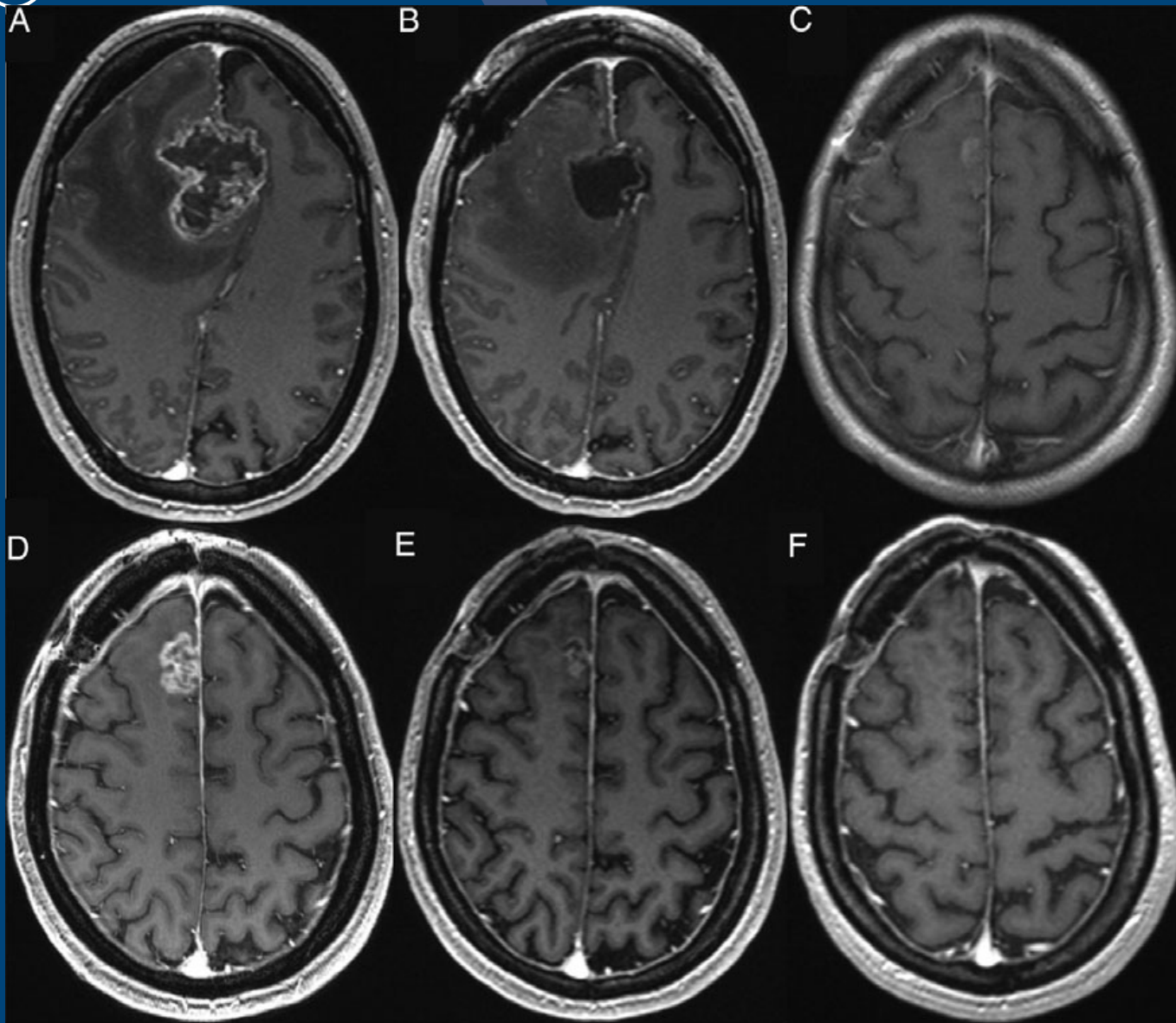
Do not loose sight of the clinical relevance in MR Imaging



# Incidence of Pseudoproggression

Scan	True Progression	Pseudoproggression				Total
		Stable	Decrease < 50 % of enhancement	Decrease > 50 % of enhancement	Complete Resolution of enhancement	
<b>1<sup>st</sup> Post-Radiation Scan</b> Average scan date after initial diagnosis 34.0±18.0 d, median 28 d	39=86.67%	3=6.67%	1=2.22%	2=4.44%	-	45
<b>2<sup>nd</sup> Post-Radiation Scan</b> Average scan date after initial diagnosis 113.3 ±15.2 d, median 111.5 d	15=88.24%	-	1=5.88.3%	-	1=5.88%	17
<b>3<sup>rd</sup> Post-Radiation Scan</b> Average scan date after initial diagnosis 187.8±23.5 d, median 193 d	8=88.89%	-	-	1=11.11%	-	9
<b>4<sup>th</sup> Post-Radiation Scan</b> Average scan date after initial diagnosis 305.0 ± 53.6 d, median 302.5 d	8=100%	-	-	-	-	8
<b>Total</b>	70=88.61%	2=2.53%	4=5.06%	2=2.53%	1=1.27%	79

**Incidence of PsP was heavily overestimated!!!**





# Conclusion

- RANO BM first step to a harmonization for therapy assessment within clinical trials
- Still a long way to go to include advanced imaging methods
- Urgently needed: large multi-center clinical trials with harmonized imaging parameters and postprocessing techniques





Thank you for your attention!