Il ruolo delle neuro-immagini nei tumori cerebrali

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Milano

La richiesta di competenza neurologica nel prossimo futuro

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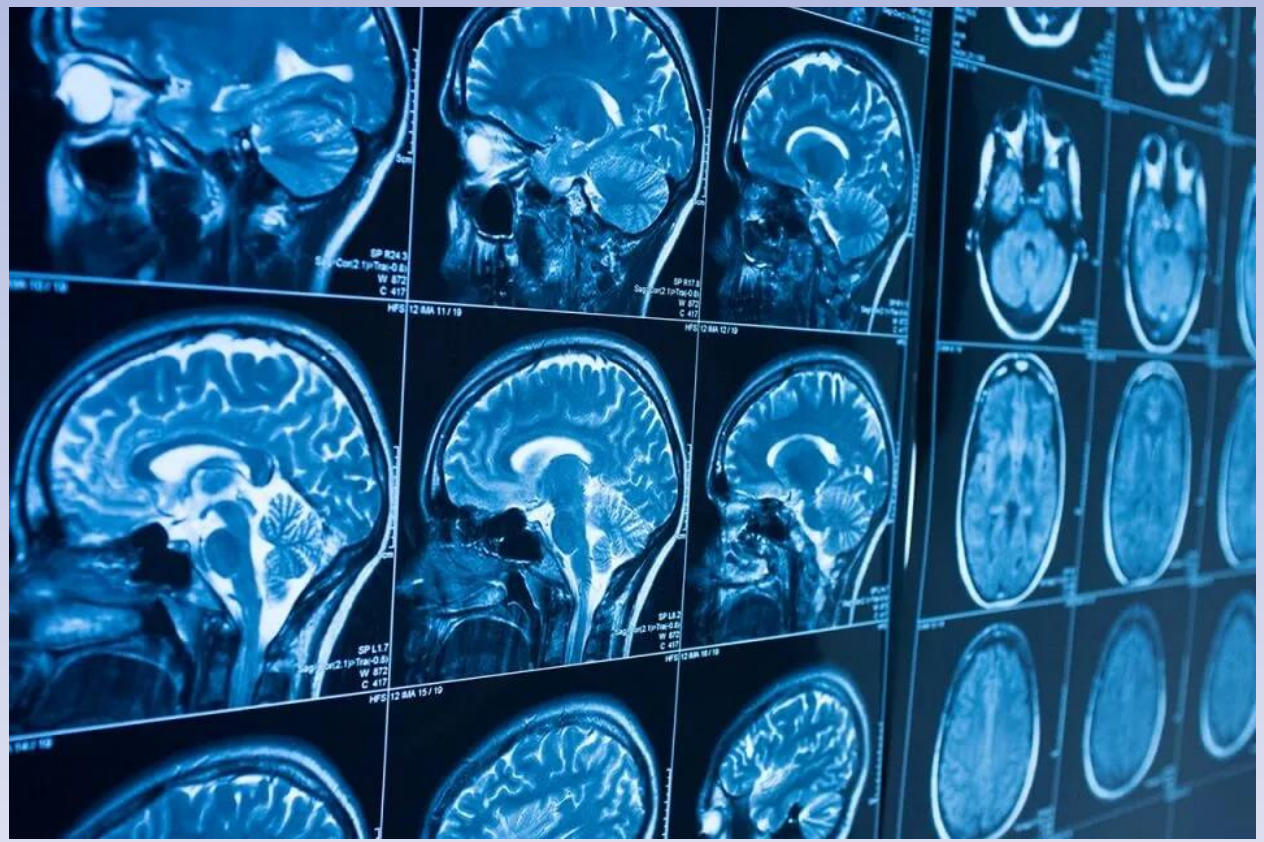
WHAT TO ASK YOUR RADIOLOGIST?



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BRAIN TUMORS

- DIFFERENTIAL DIAGNOSIS
- PRE-TREATMENT ASSESSMENT
- POST-SURGERY ASSESSMENT
- TREATMENT RESPONSE ASSESSMENT
- FOLLOW UP

FIRST OF ALL: «IS IT A BT ?»

- Encephalithis
- Abscess
- Stroke
- Angitis CNS
- Giant plaque MS
- Different tumors (MTS ecc)

DIAGNOSIS

CONVENTIONAL MRI

at least T1, FLAIR, CE-T1 (then T2, T2*-SWI)

Tumor Localization

- Intra-axial
  Infiltrative/mass
- Site- Multifocality
  Extent- issemination

Histology

- Mass effect
  Hemorrages
  Calcifications
- Enhancement
  (extent and pattern: ring, nodular, faint)

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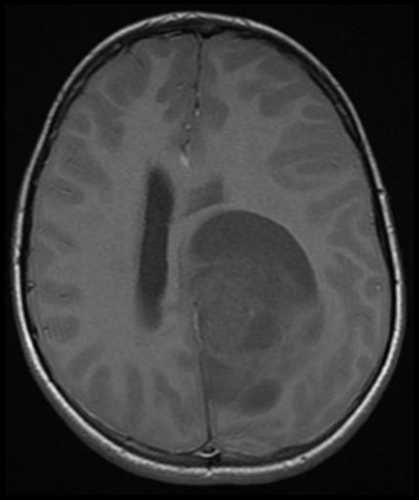
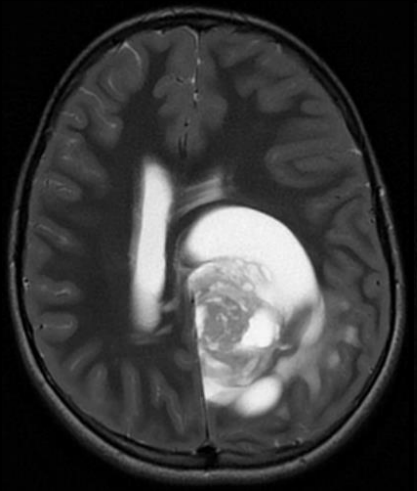
CONVENTIONAL MRI



T1



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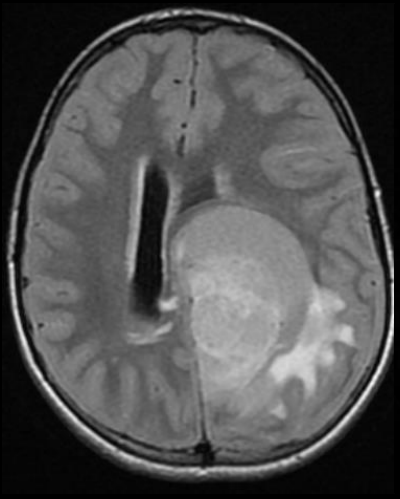
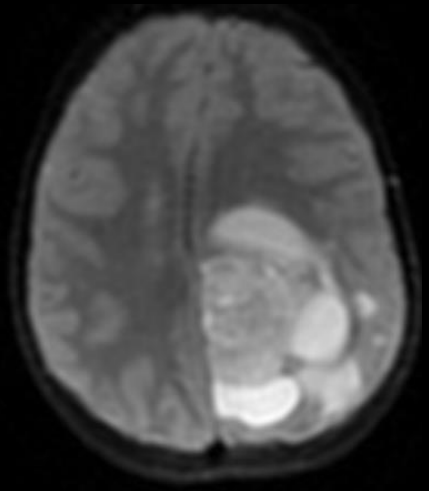
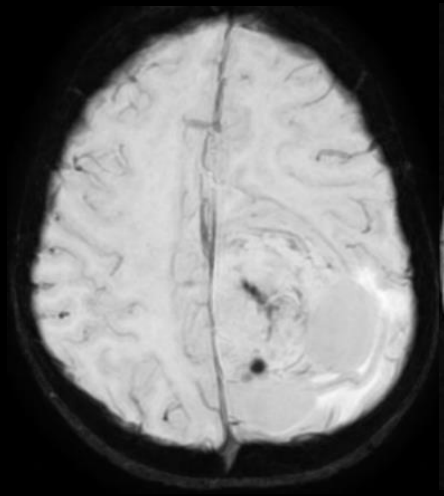


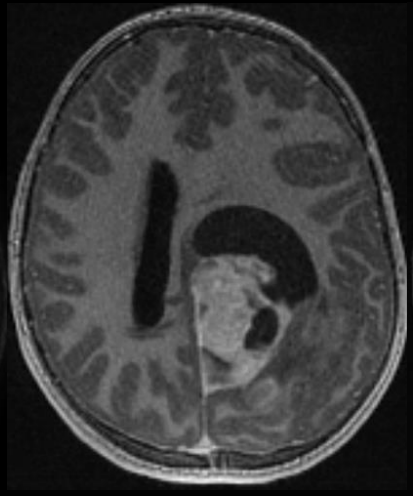
FLAIR



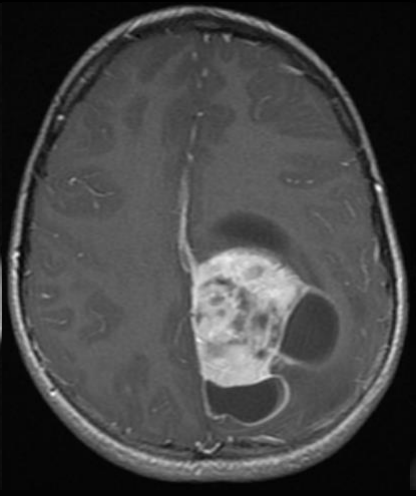
DWI



SW



C+



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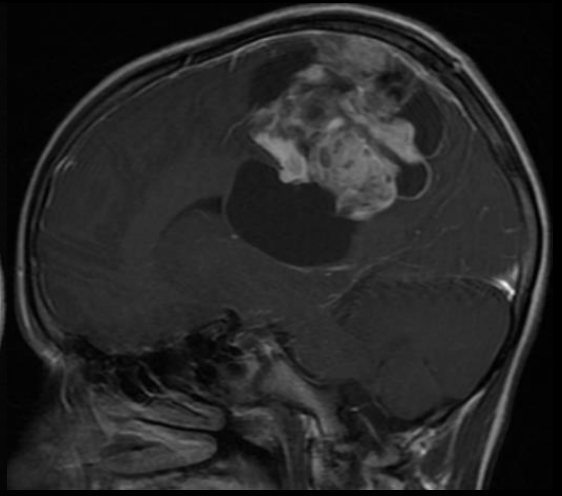

C+

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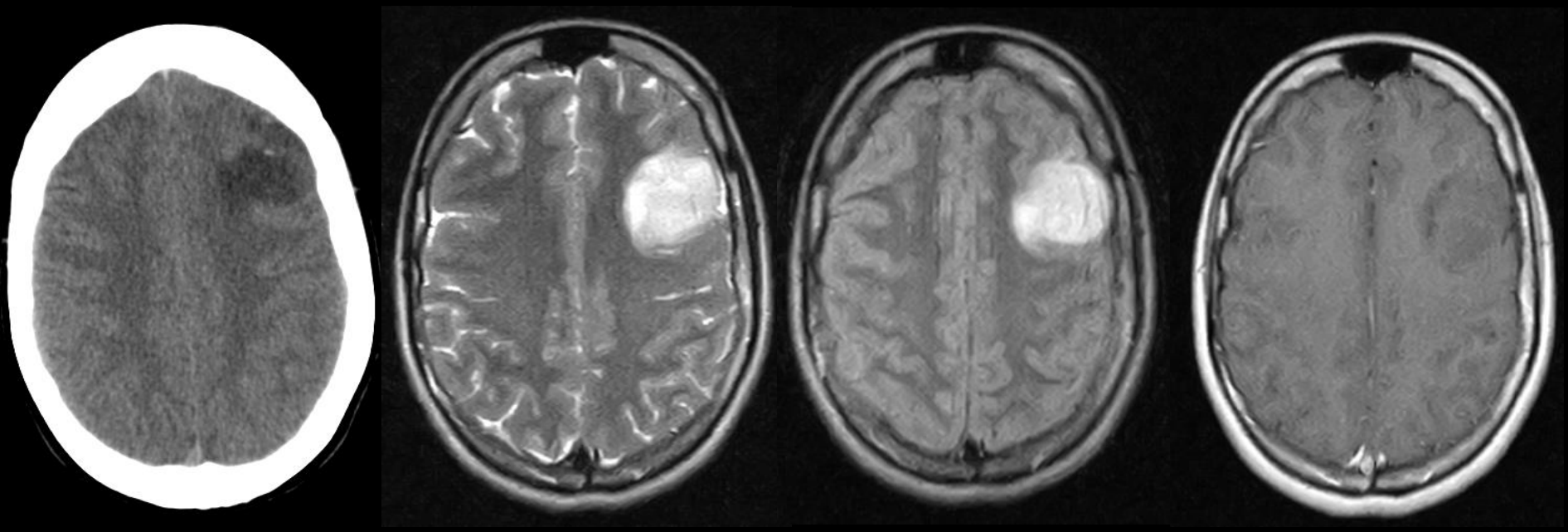
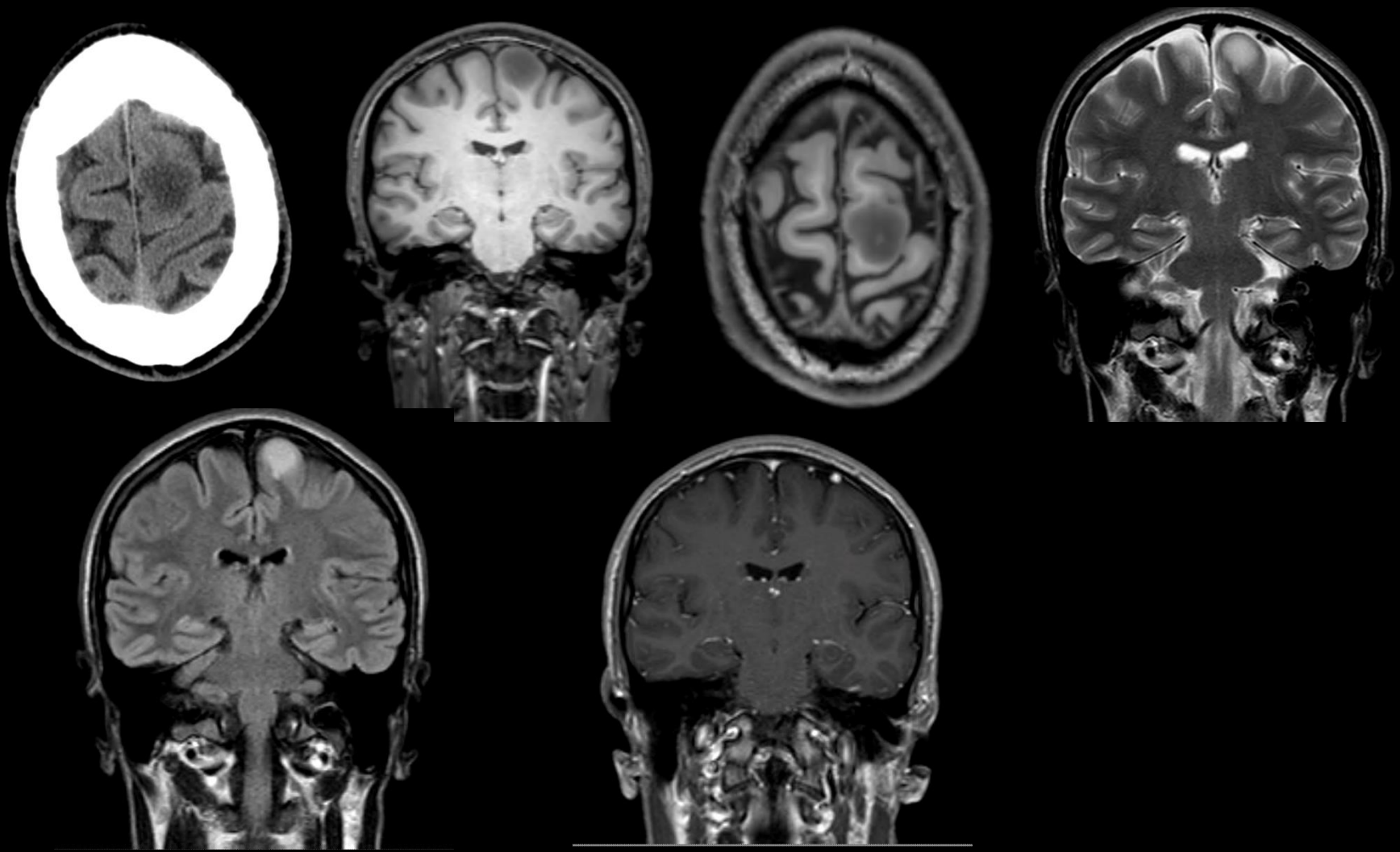
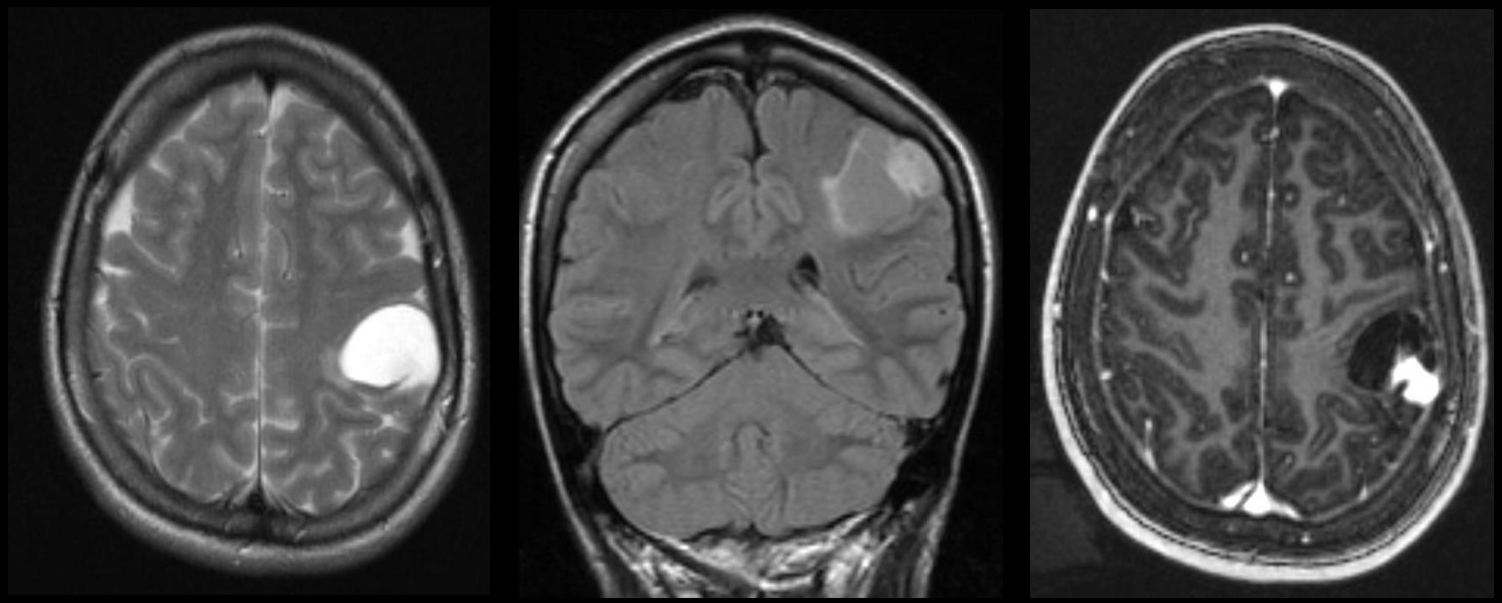
OLIGODENDROGLIOMA GRADE 2



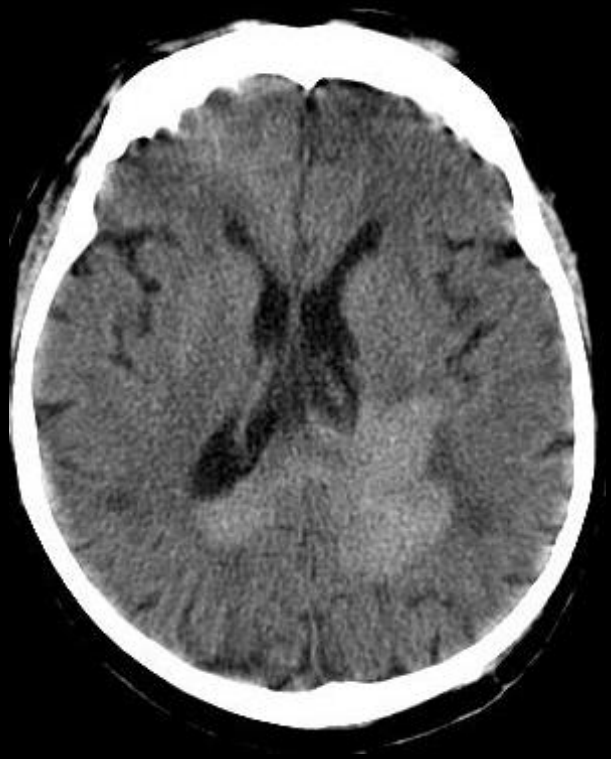
ASTROCYTOMA GRADE 2

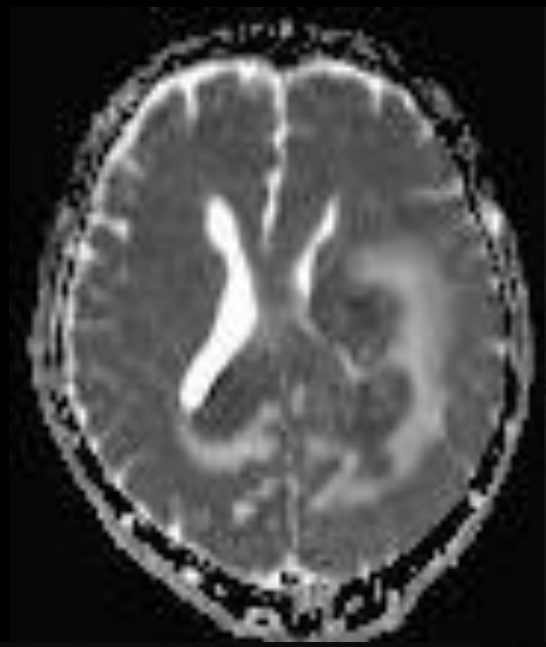


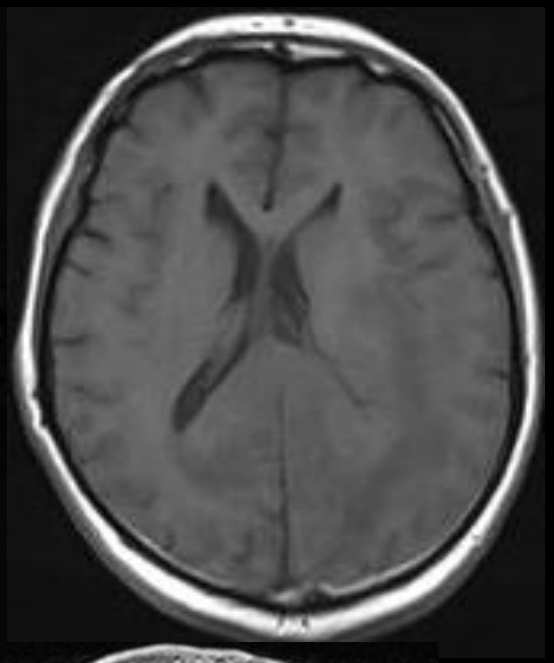
PILOCYTIC ASTROCYTOMA GRADE I

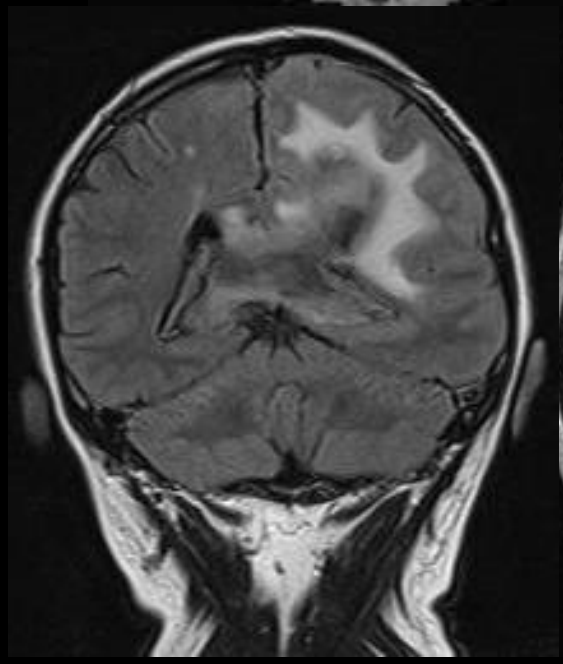


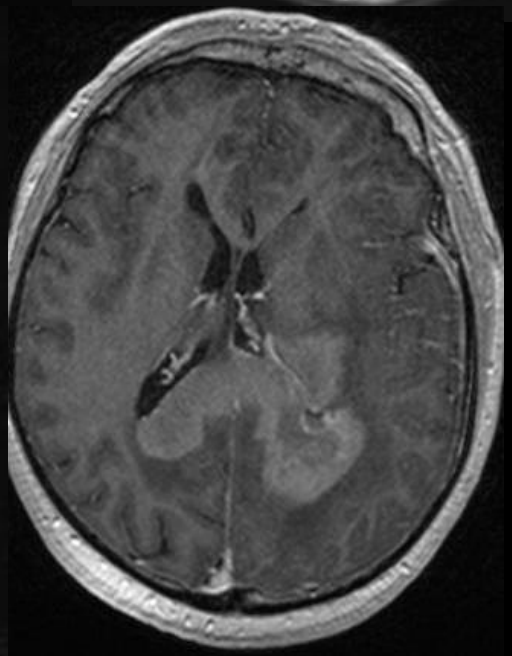
PCNSL

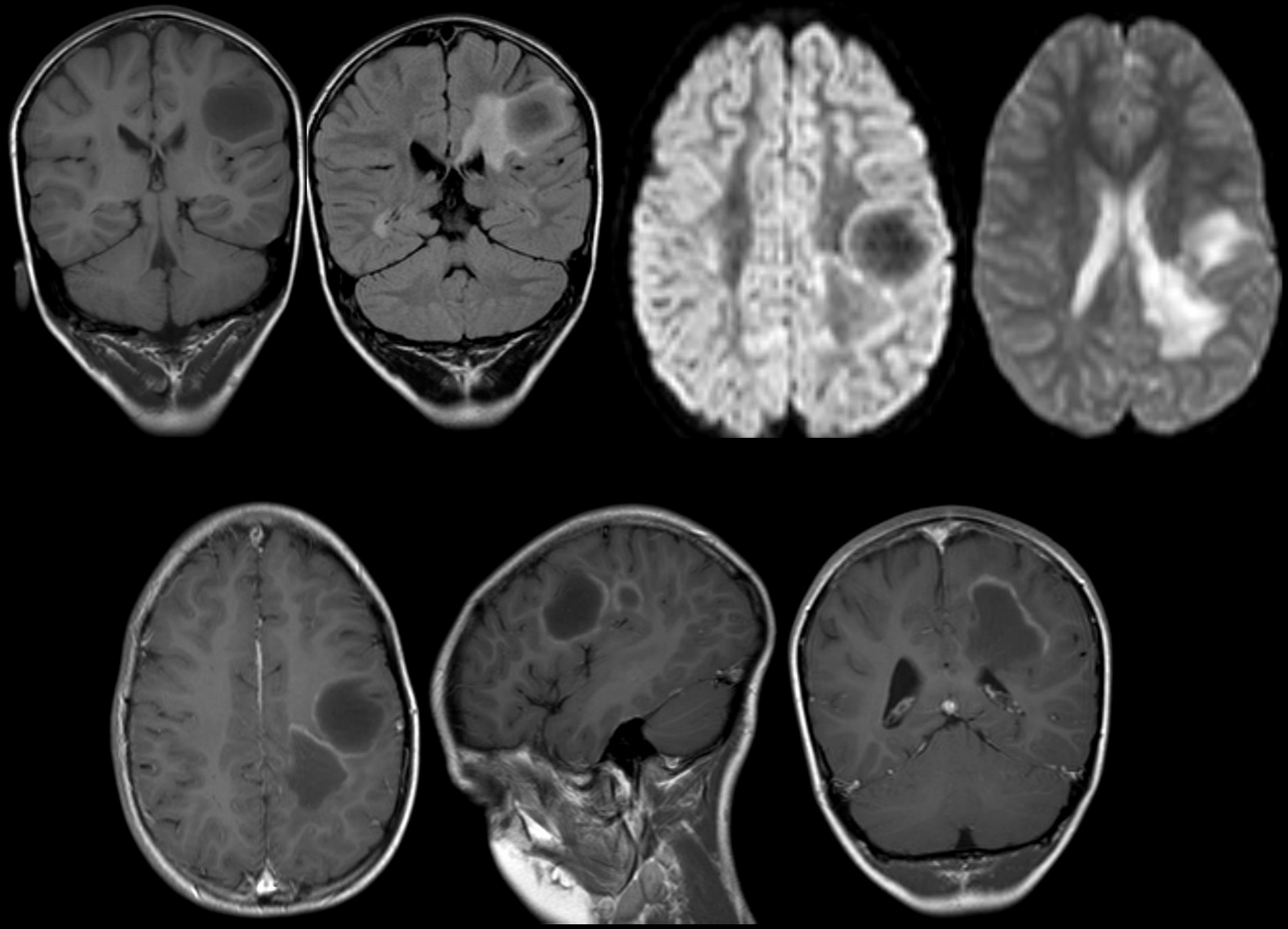


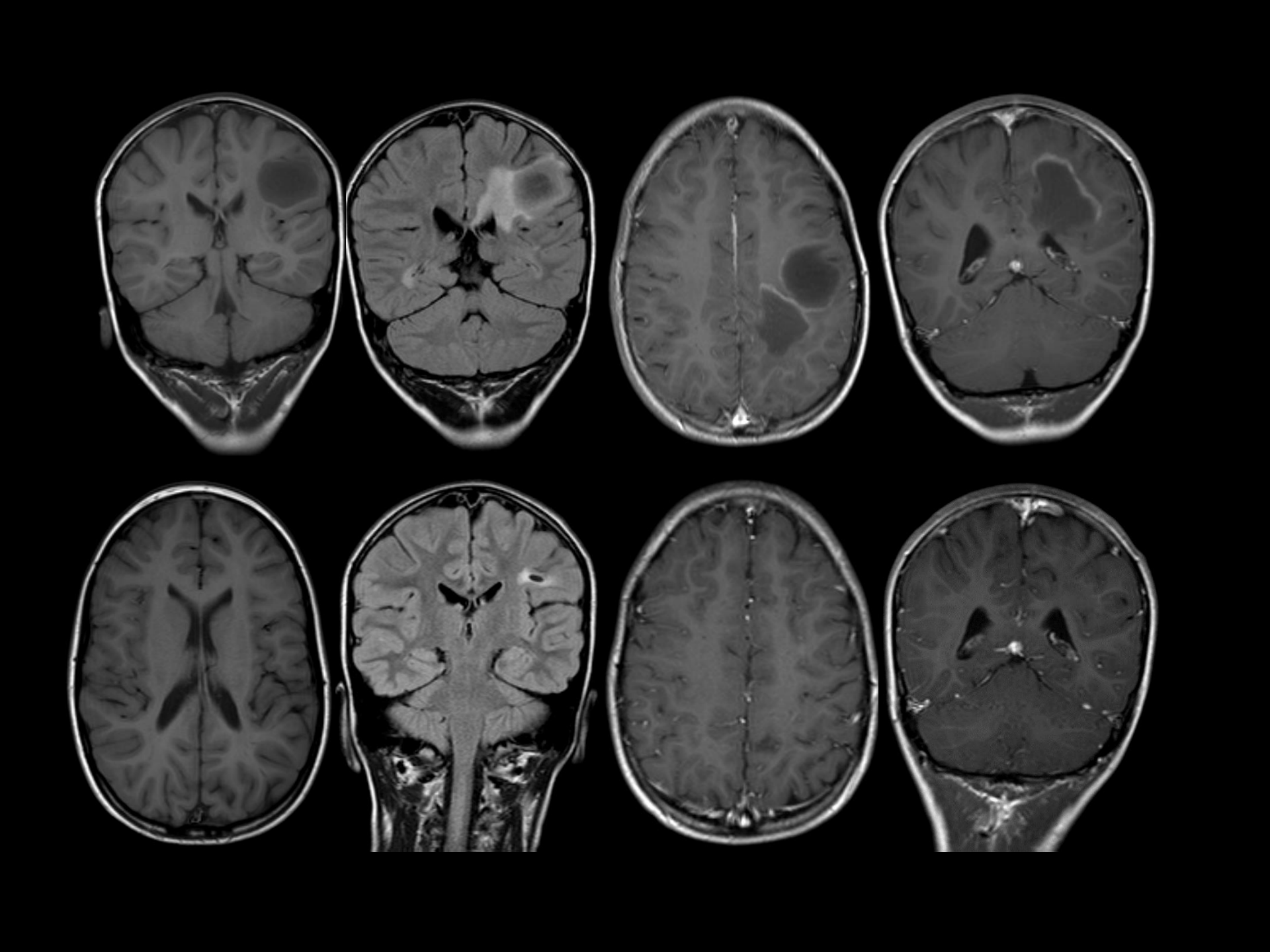






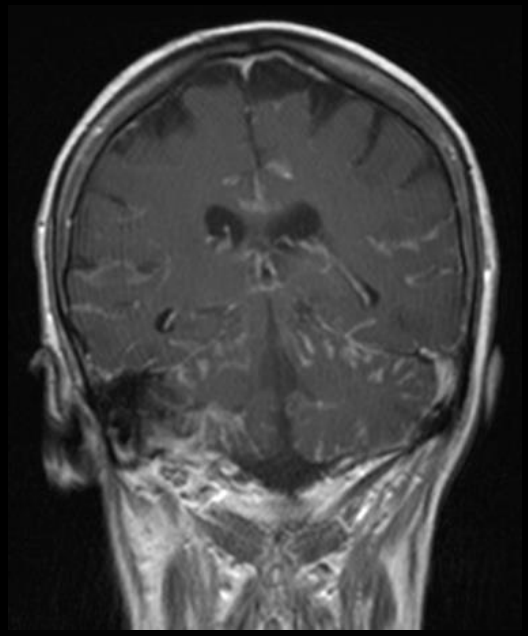


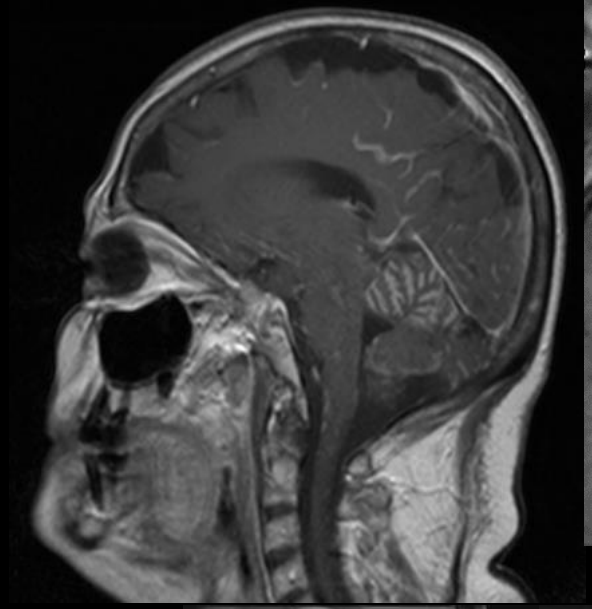


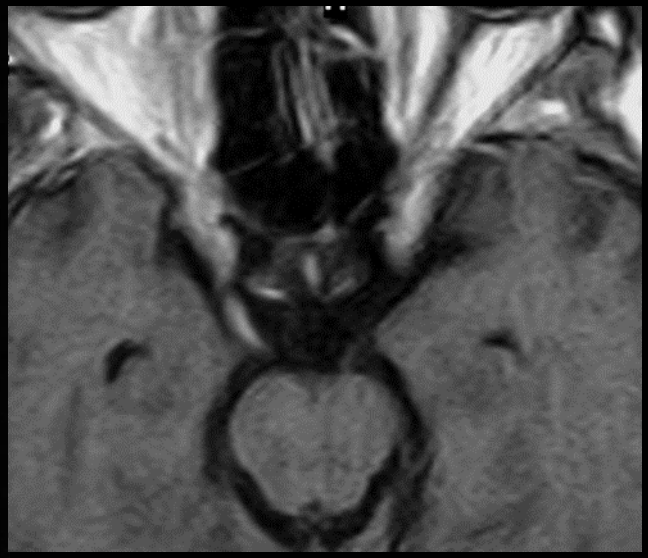


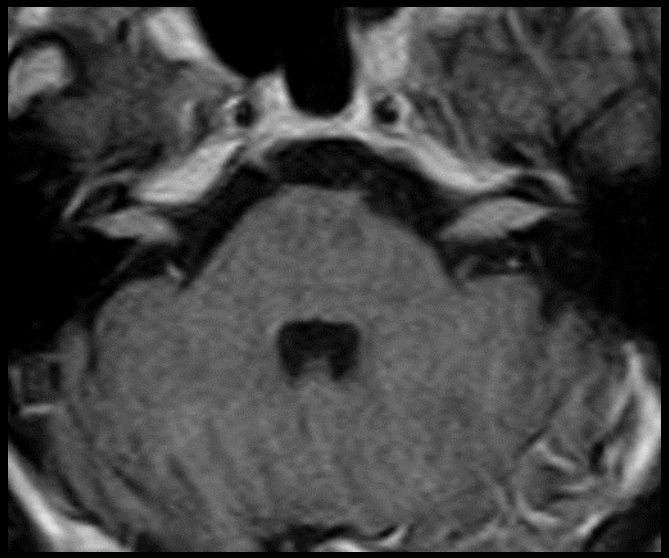
WHO 2021 Classification of Brain Tumours

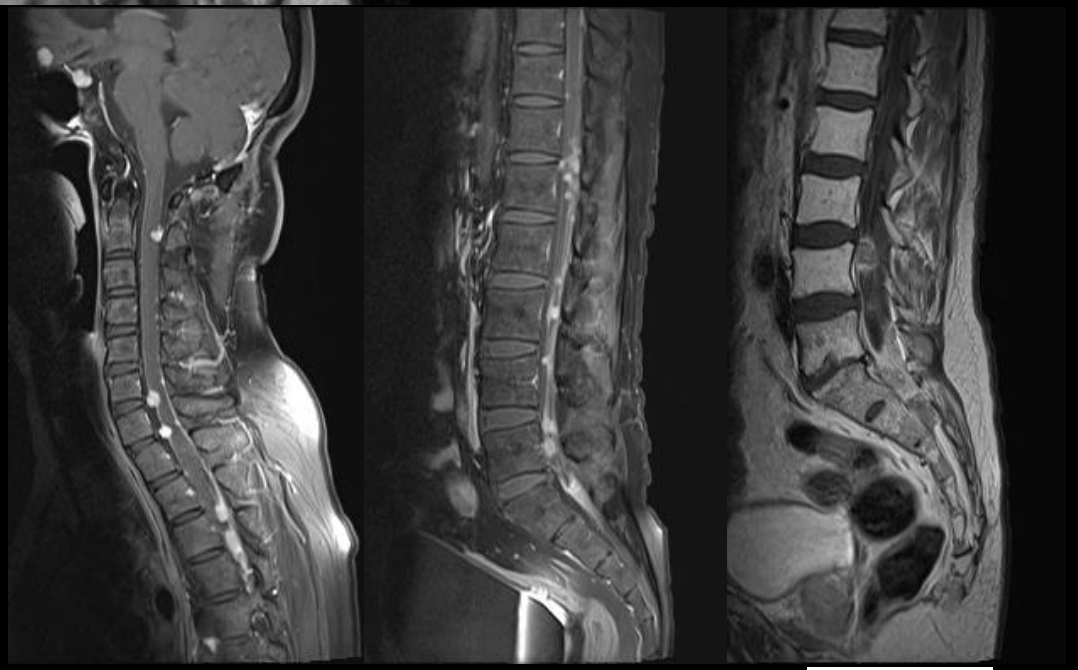
- Our need for biological material has gradually increased with the advent of integrated diagnosis
- The material is essential for molecular analysis
- Only in a few cases, we are treating a patient without histological diagnosis











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Leptomeningeal carcinomatosis

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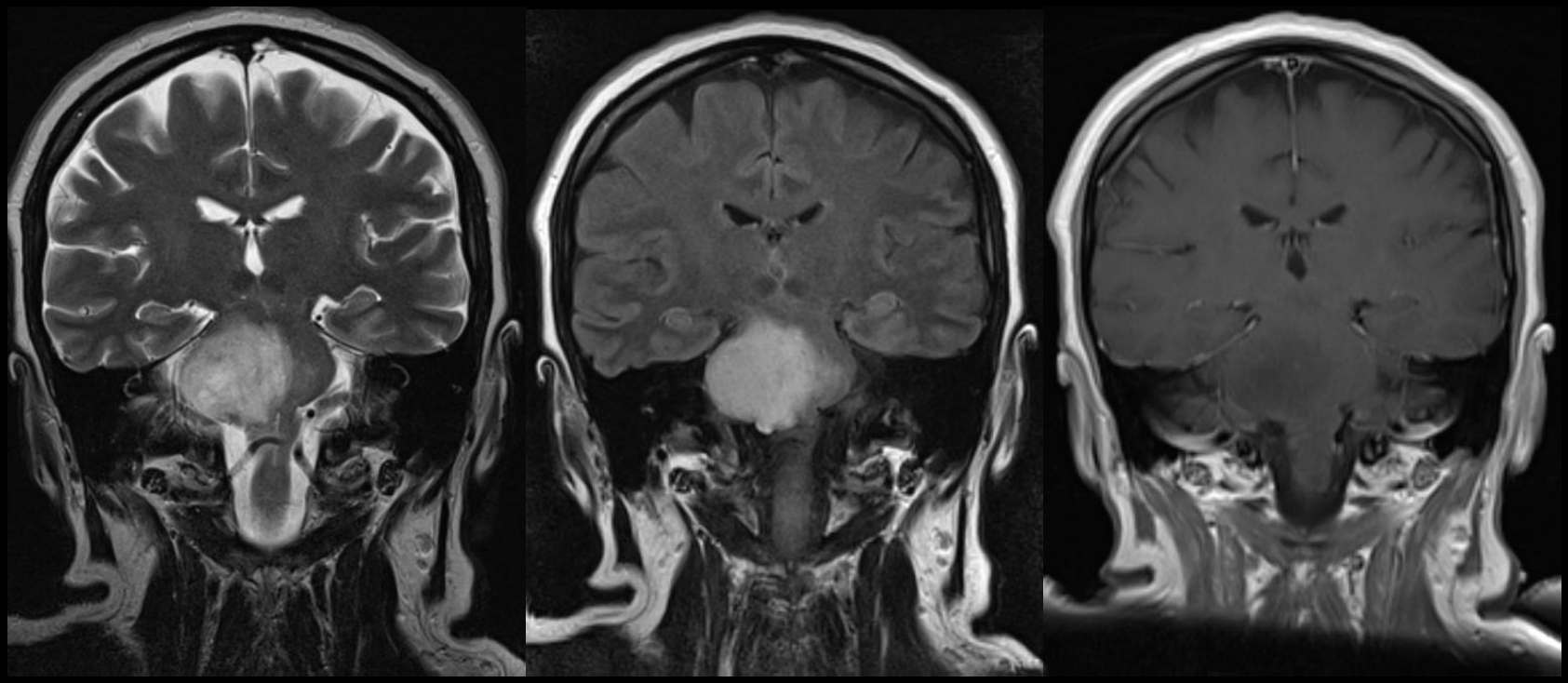
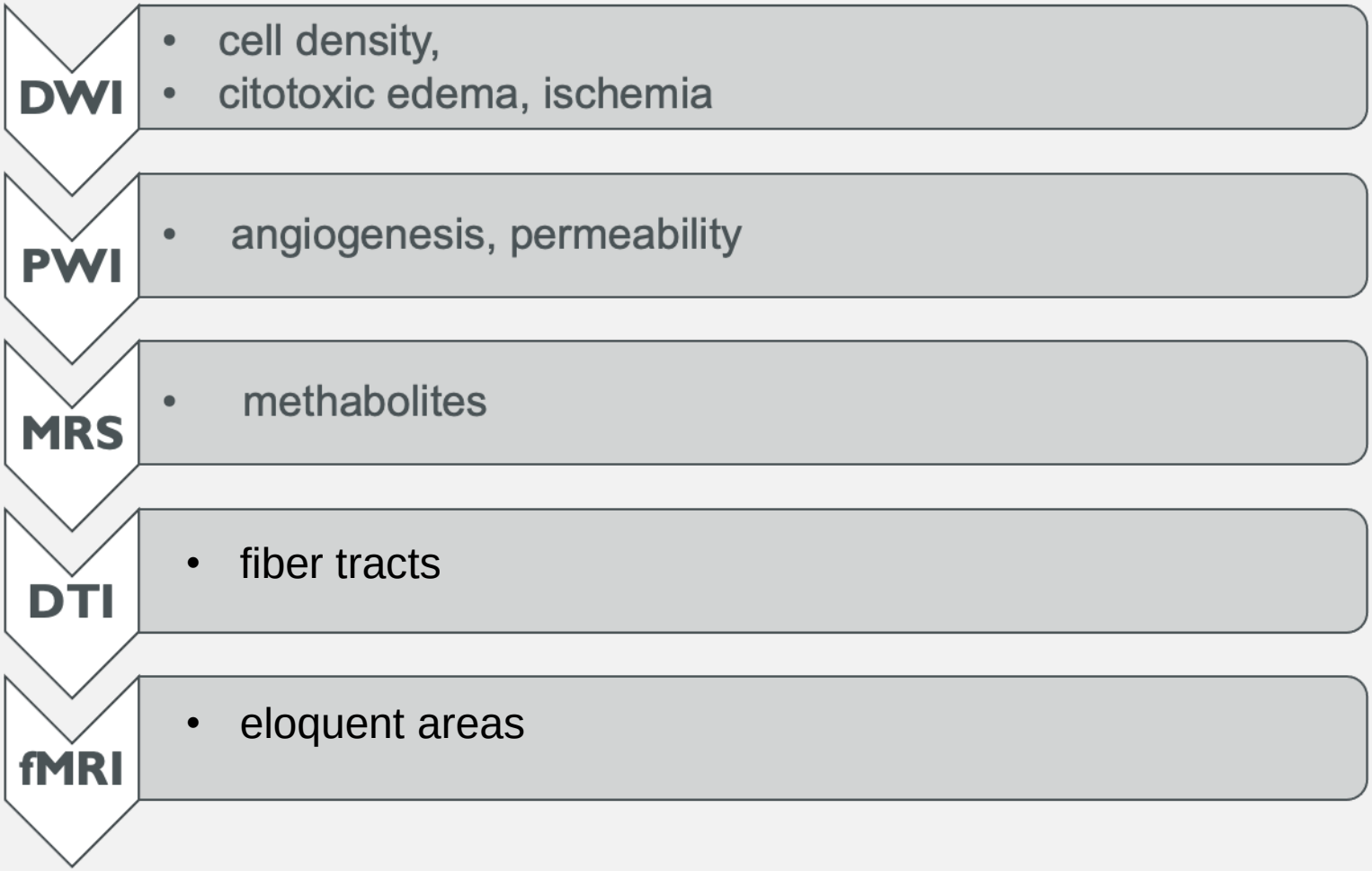
DPLG



DIAGNOSIS ADVANCED MRI



DWI OFFERS SIGNIFICANT VALUE IN THE EVALUATION OF BRAIN TUMORS.

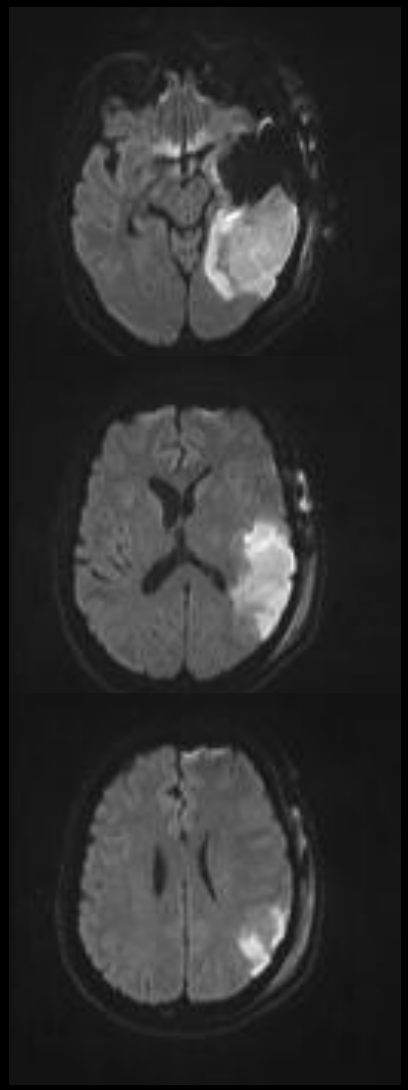
- DWI probes the random (Brownian) motion of water molecules
- Corresponding apparent diffusion coefficient (ADC) values, reflecting the magnitude of diffusivity

- Low ADC values, representing decreased water diffusivity, can be used to suggest highly cellular tumors

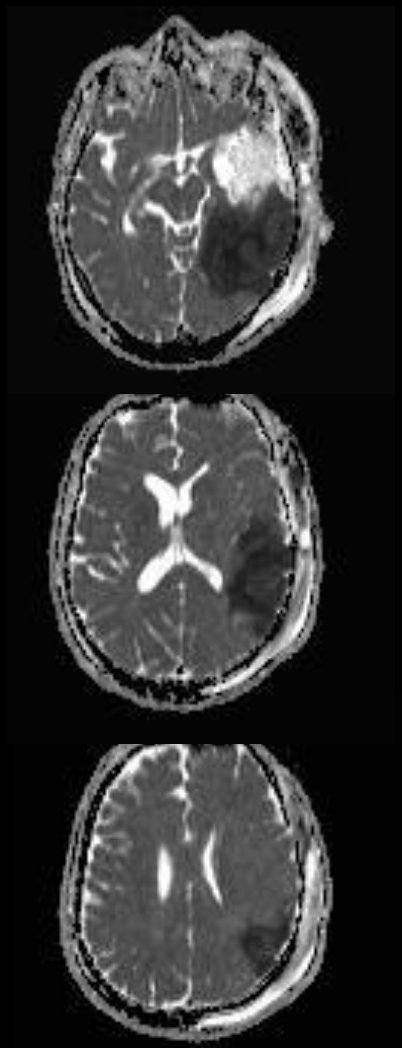
WI shows the diffusivity of the free extracellular water. When extracellular spaces are not limited (e.g., the ventricular space), there is no restriction to the diffusion of water and no signal is returned (CSF appears black).

The DWI signal appears bright (restricted) when the extracellular spaces become restricted (cellular swelling for cytotoxic edema, or increase of the cellular density, e.g., malignant tumors, embrional) and ADC usually appears dark.

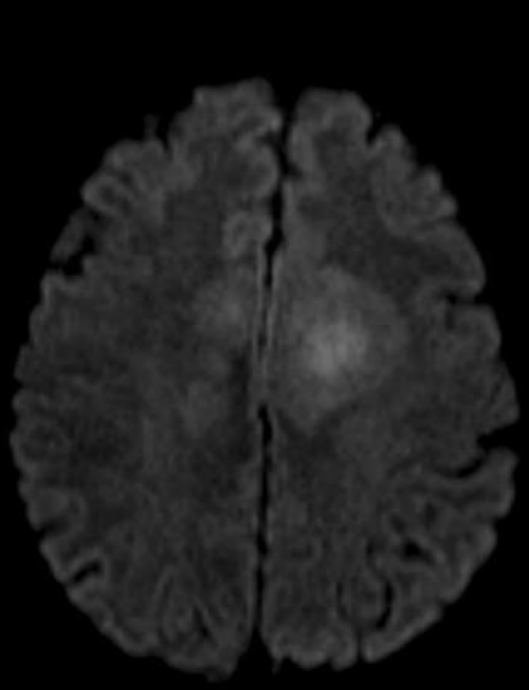
DWI



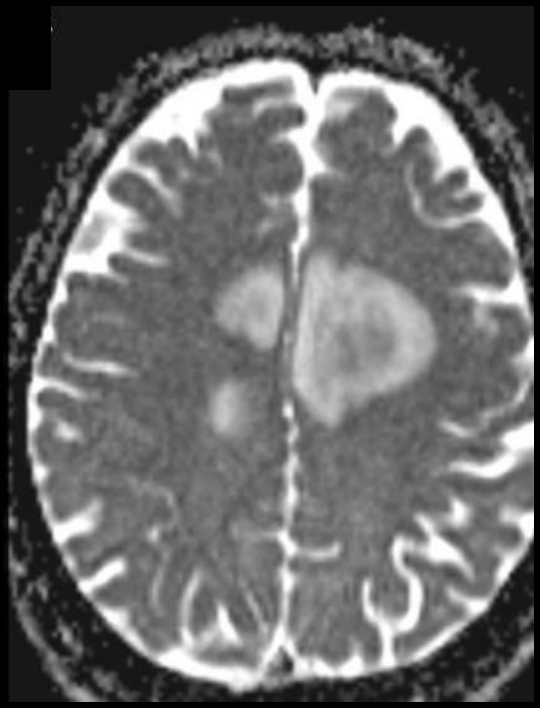
ADC



GBM DEMONSTRATING MILD RESTRICTED DIFFUSION WITH INCREASED DIFFUSION IN THE SURROUNDING EDEMA ON DWI AND ADC

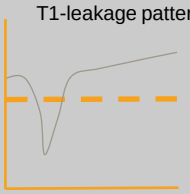


DWI



ADC

ENHANCEMENT VS PERFUSION

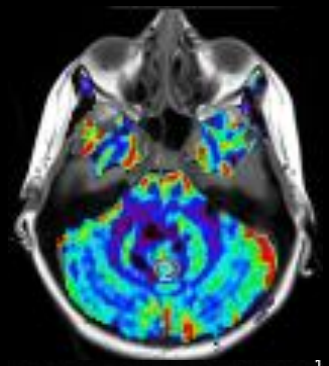
Tecnique		Informations
	● T1 with contrast medium - contrast enhancement : presence and pattern	**blood-brain barrier impairment**
Perfusion	● PWI – DSC (T2*) - CBV (and CBF): level and wash out 	**neoangiogenesis**
	● PWI – DCE (T1) - K trans: level and signal/time curve 	**vessel permeability**

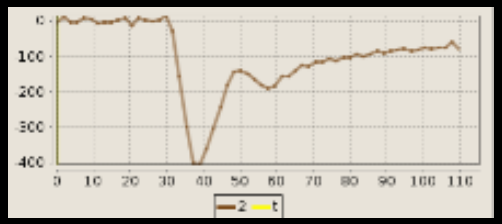
DIFFERENT PARAMETERS MEAN DIFFERENT CHARACTERISTICS

ROLE OF PWI

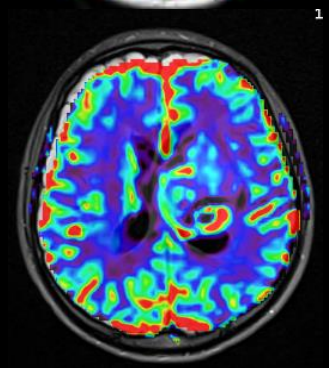
- glioma grading
- prognostic assessment
- differentiating between recurrent tumor and post-treatment changes

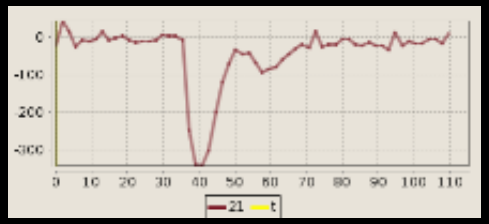
- predict IDH mutation status
- biomarker for EGFRvIII mutation in patients with GBM



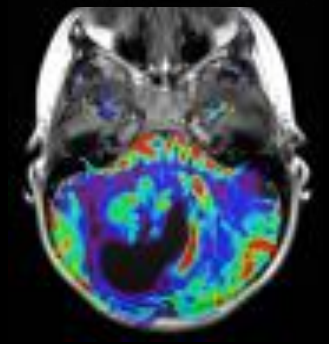


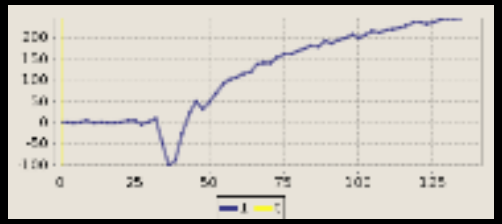
Medulloblastoma





GBM, rCBV demonstrates a return to baseline pattern





T1-dominant leakage pattern in pilocytic astrocytomas, pilomyxoid astrocytoma

AJNR Am J Neuroradiol 37:544 –51 Mar 2016

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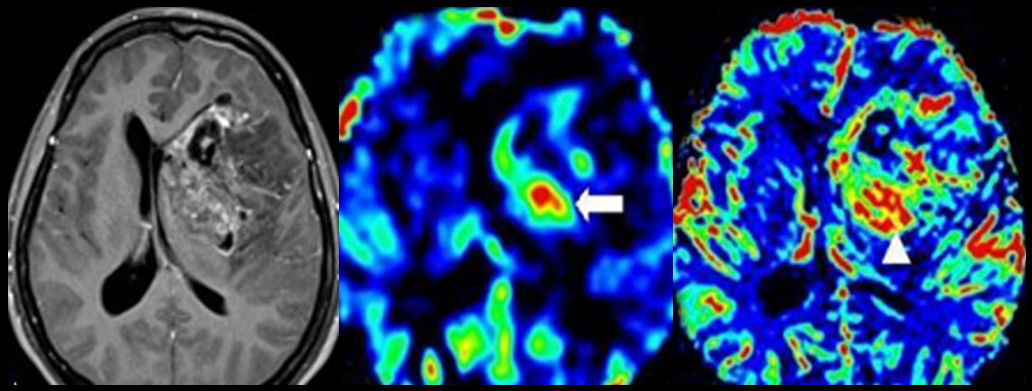
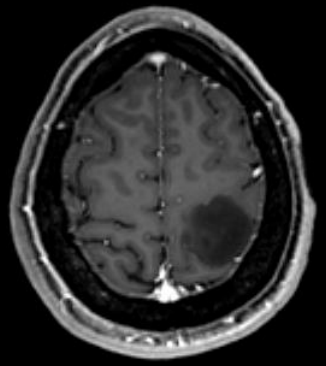
Second class

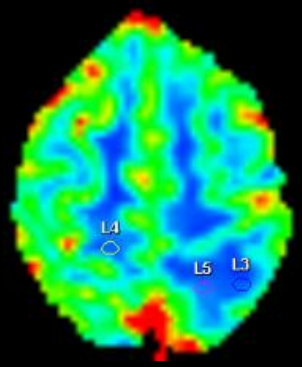
ASL (CBF arterial spin labeling)

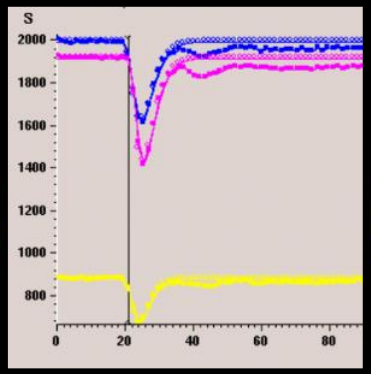


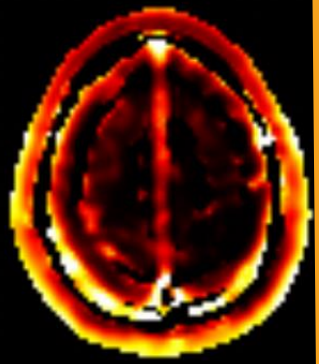
- NO GADOLINIUM (INNER contrast medium, i.e. BLOOD)
- CBF only
- Low spatial resolution

Astrocytoma (grade 2):
lack of c.e., <u>hypoperfusion</u>

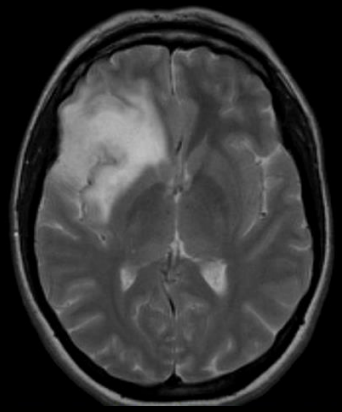


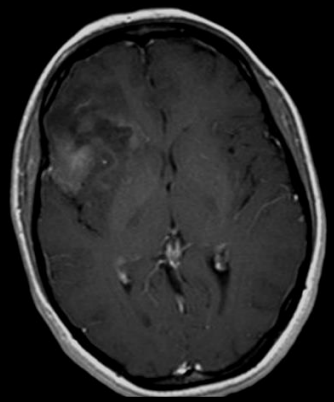


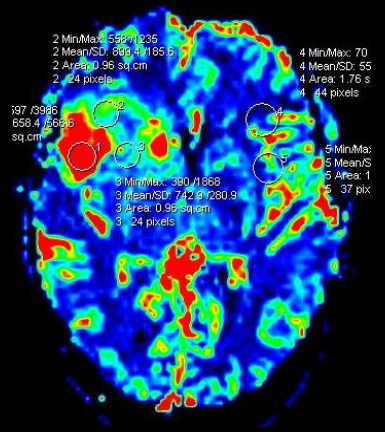


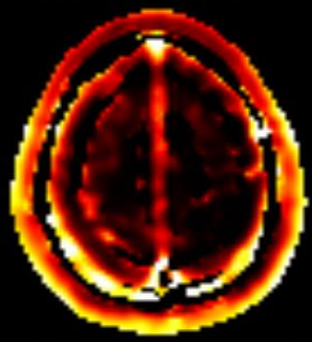


Oligodendroglioma (grade 2):
involves cortex, un-homogeneous in T2, faint c.e.,
<u>rCBV homogeneously very high, almost normal ktrans</u>









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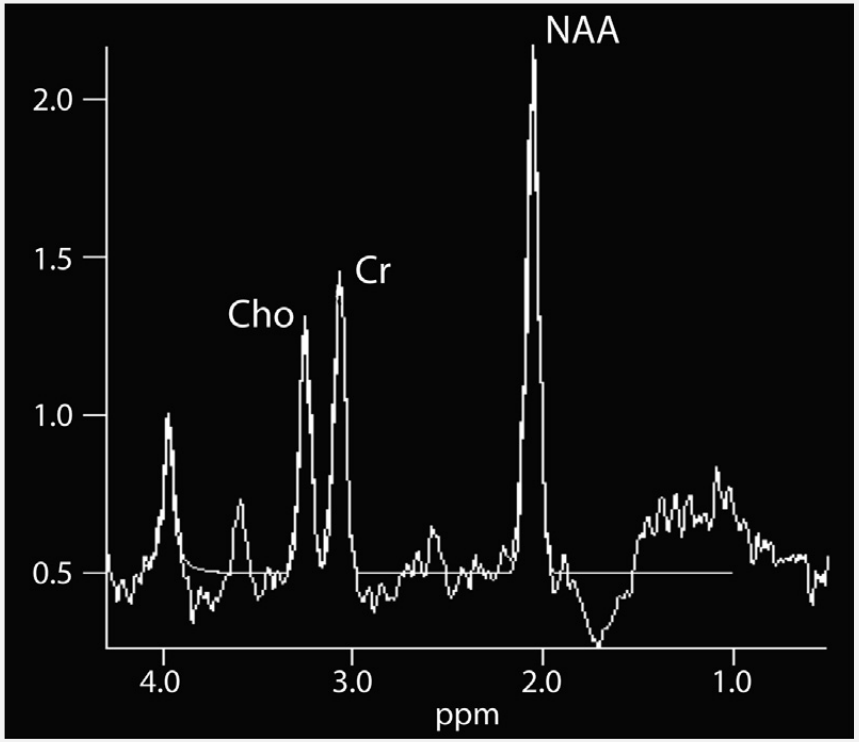
MRS: multivoxel and single voxel

Table 2
Frequently encountered metabolites and their characteristics and clinical role in evaluating brain tumors

Metabolite	ppm	Elevated in	Decreased in	Clinical Significance in Brain Tumor Imaging
Choline	3.2 ppm	Neoplasms Inflammation Gliosis	Necrosis	Grading gliomas Distinguishing glioblastomas for metastases Radiation planning in gliomas Differentiating tumor progression vs pseudoprogression/ Radionecrosis
N-acetyl aspartate	2.0 ppm		Gliomas and more so in high-grade gliomas Radiation necrosis Metastases Lymphoma	Grading of gliomas Distinguishing gliomas from metastases
Creatine	3.0 ppm		High-grade gliomas Necrosis	Grading of gliomas Distinguishing metastases from glioblastoma
Lactate	1.3 ppm	Glioblastoma Abscesses	Not present in normal spectra	Grading of gliomas
Lipids	1.3 ppm with inversion at intermediate echo time	Glioblastoma Abscess Lymphoma Metastases		Grading of gliomas
Myo-Inositol	3.5 ppm	Low-grade gliomas Progressive multifocal encephalopathy	High-grade gliomas	Grading of gliomas
2-Hydroxyglutarate	2.5 ppm	Isocitrate dehydrogenase (IDH)-1 positive tumors		Detection of IDH-1 positive tumors



MRS spectrum from an area of normal brain.
Cho, Cr, and NAA are the dominant peaks, withNAA higher than both Cho and Cr.

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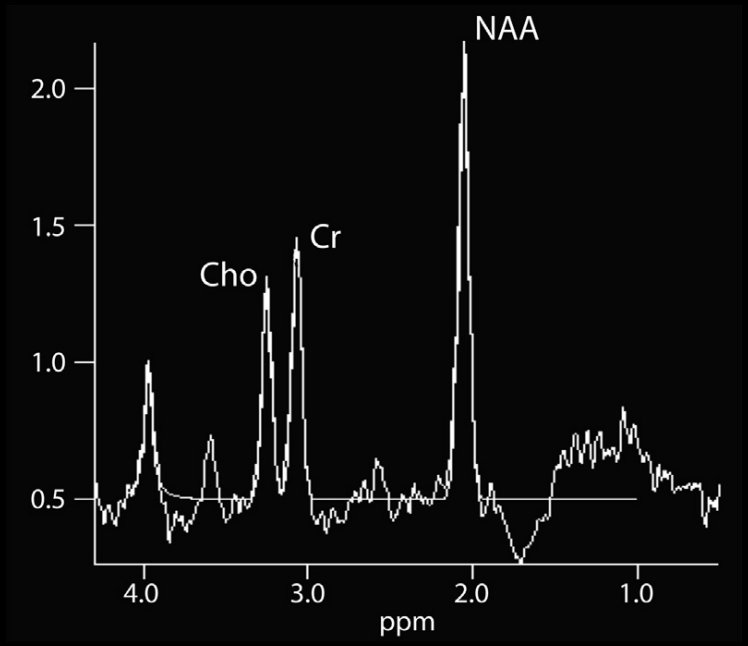
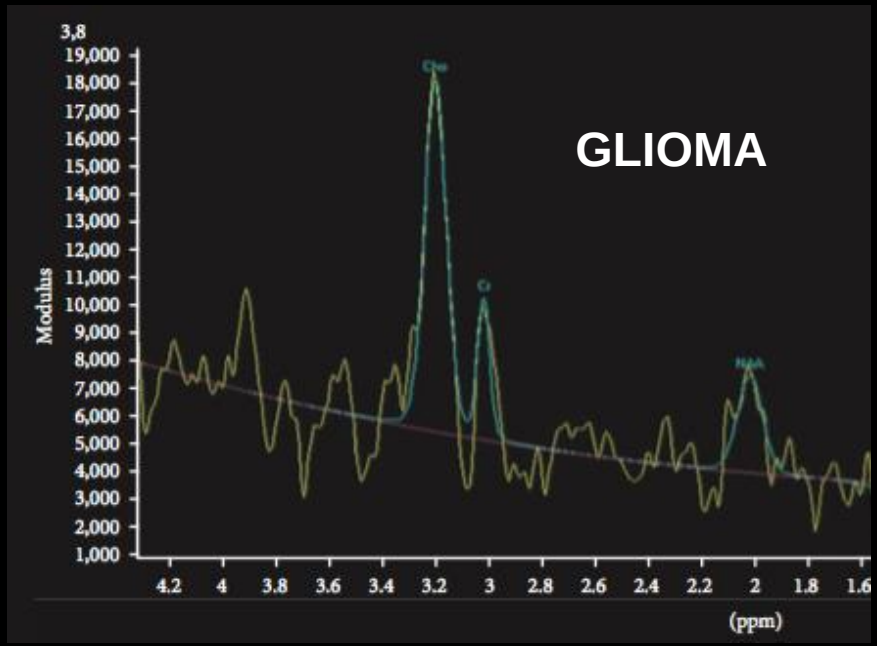
MRS: multivoxel and single voxel





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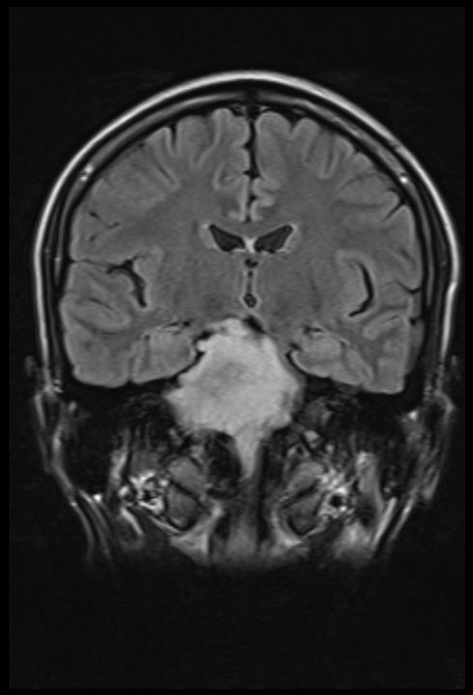
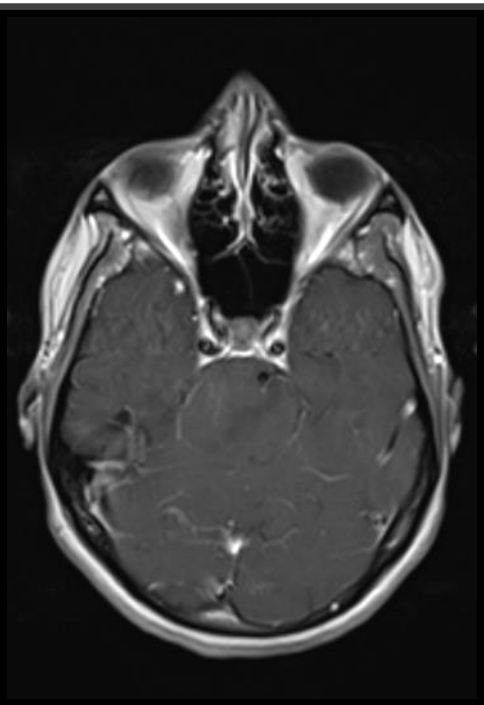
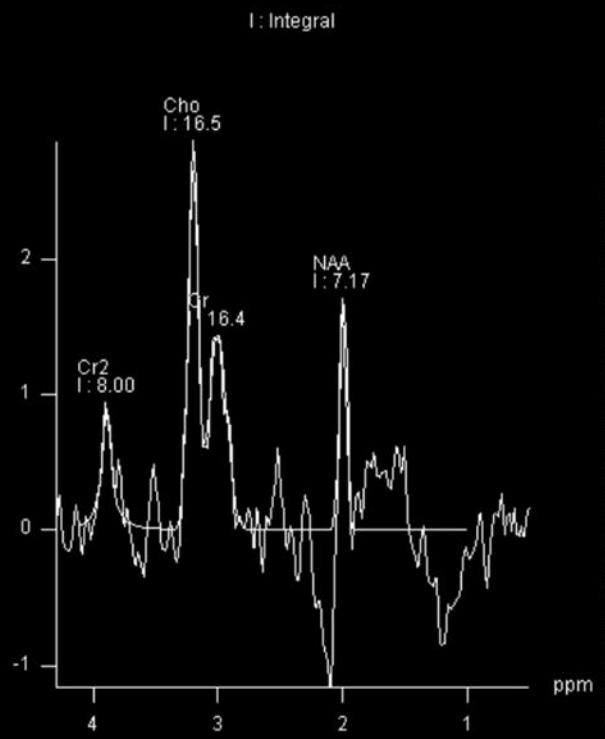
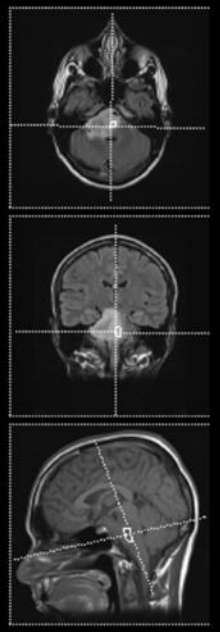
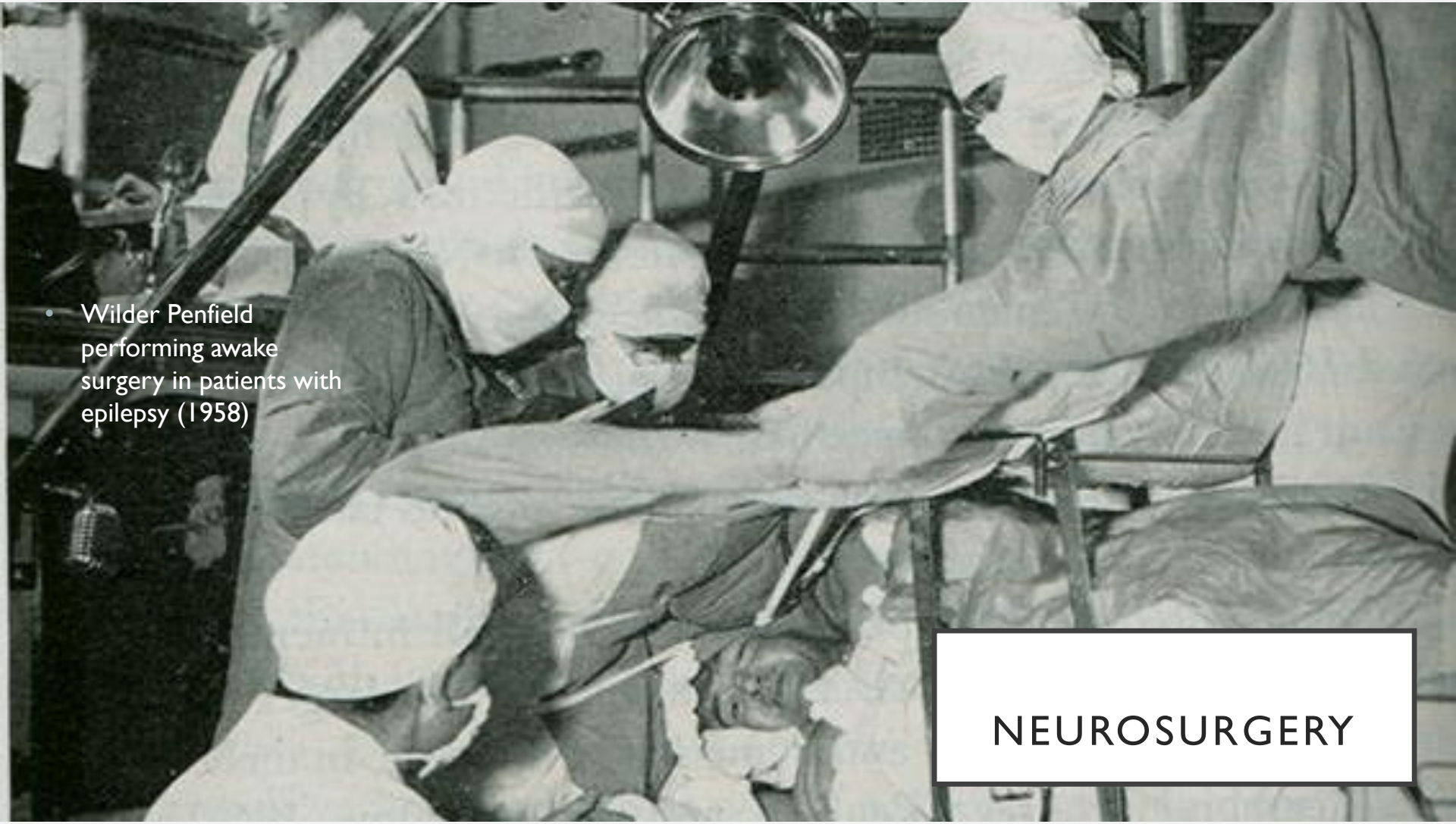
DIFFUSE INTRINSIC PONTINE GLIOMA
MRS









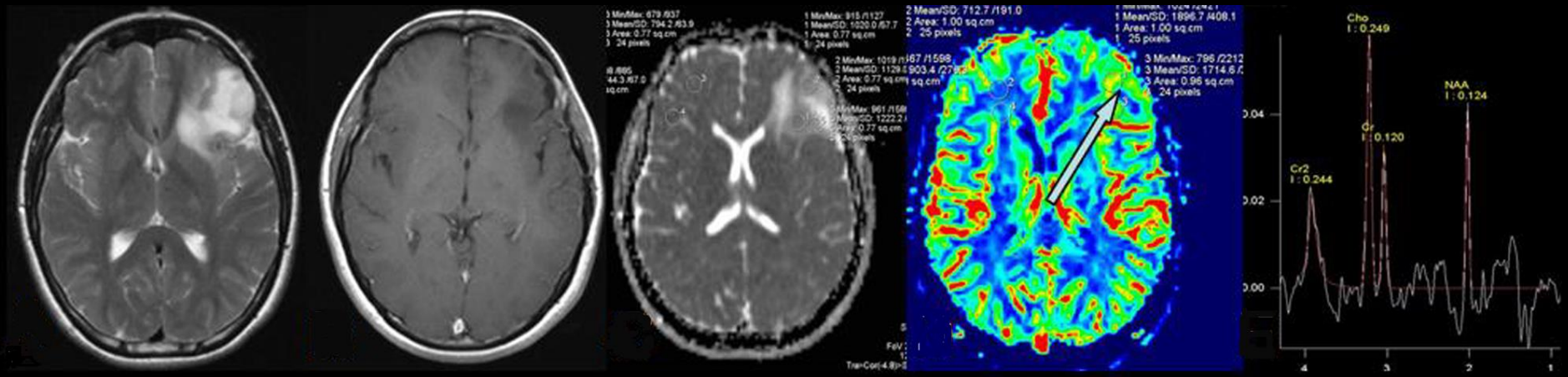


- Wilder Penfield performing awake surgery in patients with epilepsy (1958)

NEUROSURGERY

BEFORE SURGERY

GBM



MORPHOLOGIC SEQUENCES, DWI, PWI, MRS

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DIFFUSION TENSOR IMAGING (DTI)

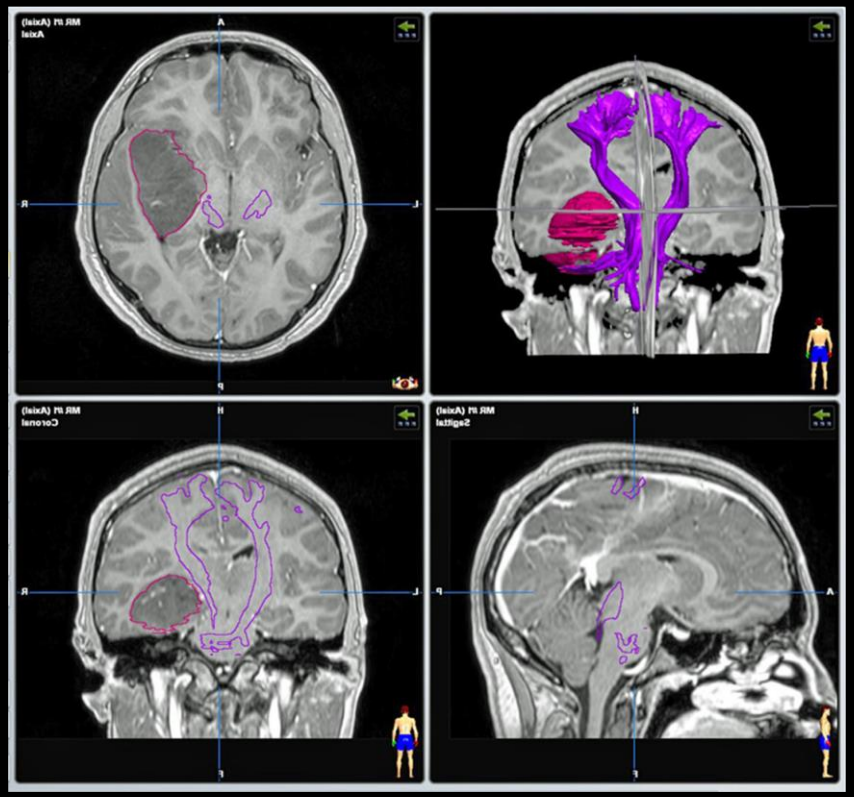
DTI with fiber tracking is increasingly requested by neurosurgeons..

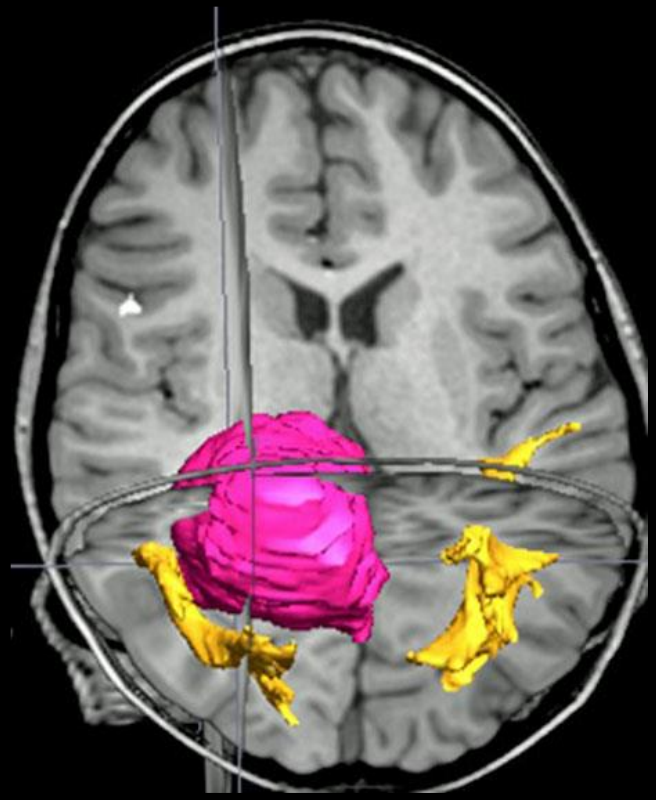
- ✧ In the motor system DTI has become very popular!
- ✧ The ventral and dorsal language pathways are nicely illustrated by MR tractography
- ✧ Determining the trajectory of the optic radiations when dislocated by a temporo-occipital mass may change the surgical approach

- Which WM fascicles should be investigated?
  - ✓Corticospinal tract (CST)
  - ✓Left arcuate fasciculus (AF, language) and inferior fronto-occipital fasciculus (IFOF)
  - ✓Optic radiation (OR), uncinate fasciculus (UF, language), inferior longitudinal fasciculus (ILF, language)

- ✧ High and low-grade gliomas may behave differently:
  - ➢ HGG have a tendency to displace or destroy fascicles
  - ➢ LGG often infiltrate fascicles that may be still functioning

DTI tractography





Childs Nerv Syst (2016) 32:1799–1811

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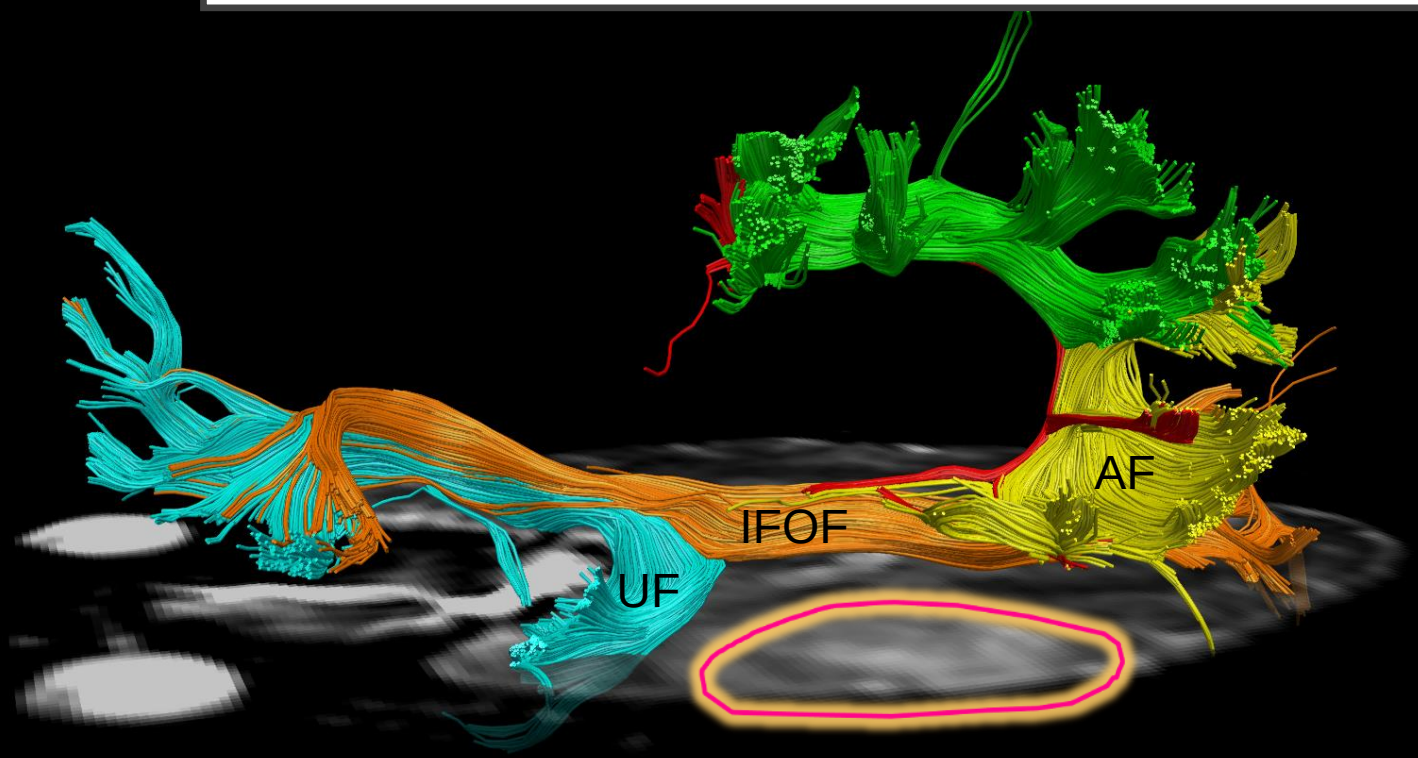
MR TRACTOGRAPHY OF DORSAL AND VENTRAL LANGUAGE PATHWAYS



- ✓inferior fronto-occipital fasciculus (IFOF)+
- ✓uncinate fasciculus (UF, language)
- ✓Left arcuate fasciculus (AF, language)

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FUNCTIONAL MAGNETIC RESONANCE IMAGING OR **FUNCTIONAL MRI (FMRI)**

- fMR imaging uses regional changes in cerebral blood flow that are induced by brain activation

- During neuronal activation, there is a change in blood oxygenation levels, which results in magnetic
- susceptibility differences.
- The blood oxygenation level–dependent (BOLD) contrast depends on the differences between
- the amount of deoxygenated and oxygenated blood present in the brain region being activated.

FUNCTIONAL MAGNETIC RESONANCE IMAGING OR **FUNCTIONAL MRI (FMRI)**

- With this technique, it is possible to identify
- **Eloquent cortex** specific brain areas that *directly control function* (

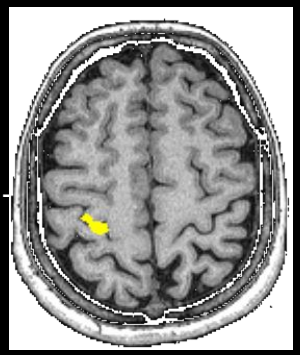
- Assisting in the decision of the best surgical approach

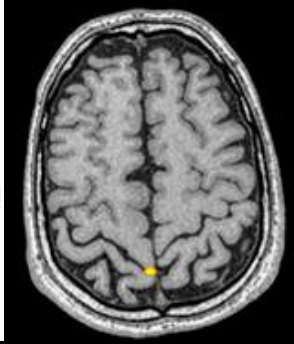
- To determine the possible extent of the resection
- To select the patients who need an intraoperative cortical stimulation procedure

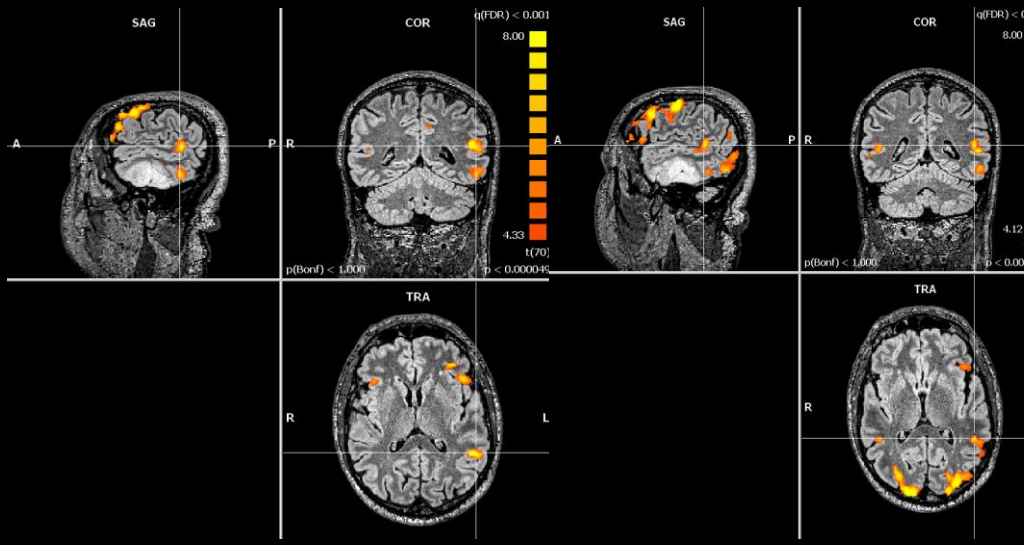
- A disadvantage is that this procedure can only be performed in *cooperative patients* (especially map language areas)

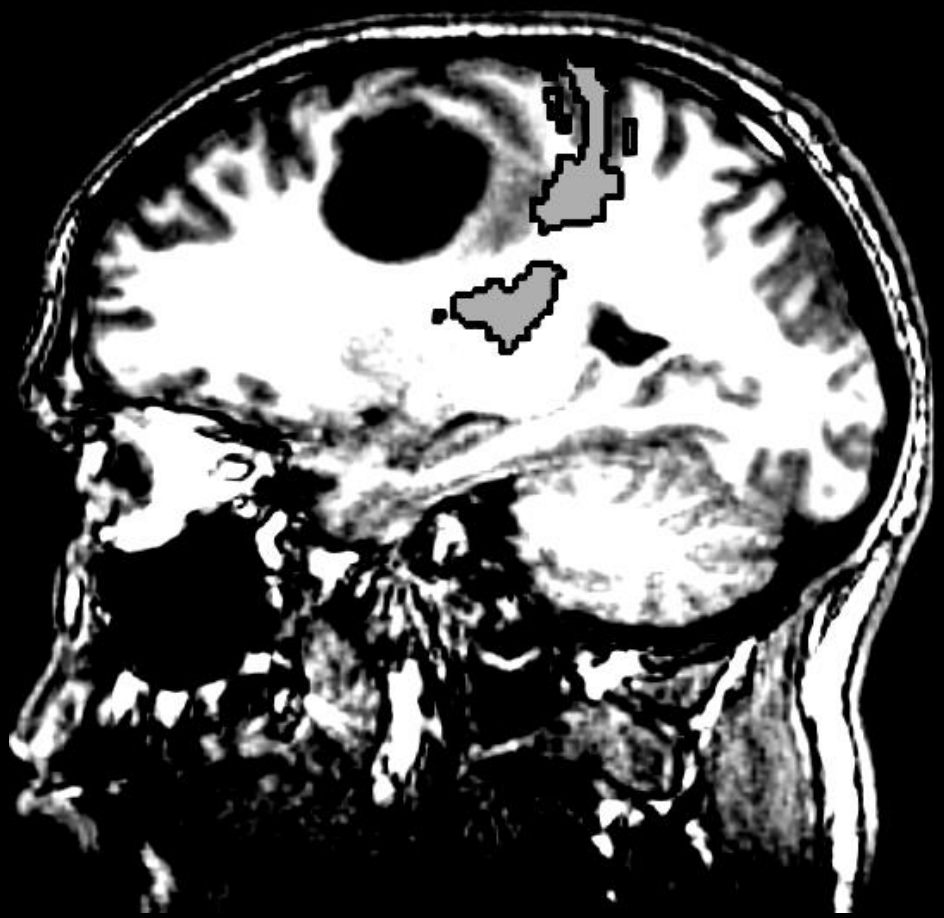
Tasks for mapping of eloquent areas

- Motor Strip
  - Simple hand movements: M1
  - Complex hand movements (finger tapping): M1+M2+S1
- Somatosensory cortex
  - Palmar or plantar surface stimulation: S1
  - Electric pulses to the median-tibial nerves: S1 + S2
- Verbal language
  - Picture naming (VLPFC, DLPFC, SMA)
  - Silent word generation (IFG and DLPFC, SMA)
  - Silent verb generation (IFG, DLPFC and STG, MTG)
  - Sentence Comprehension (STG and MTG)









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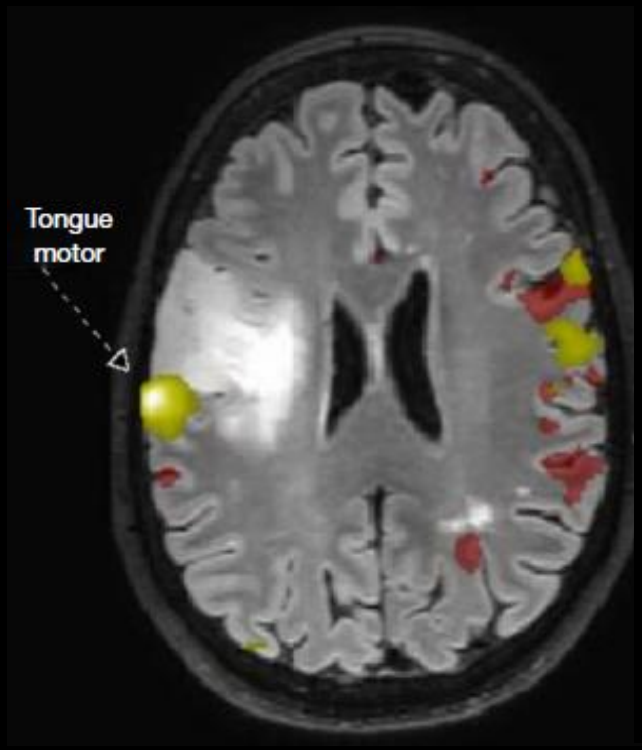
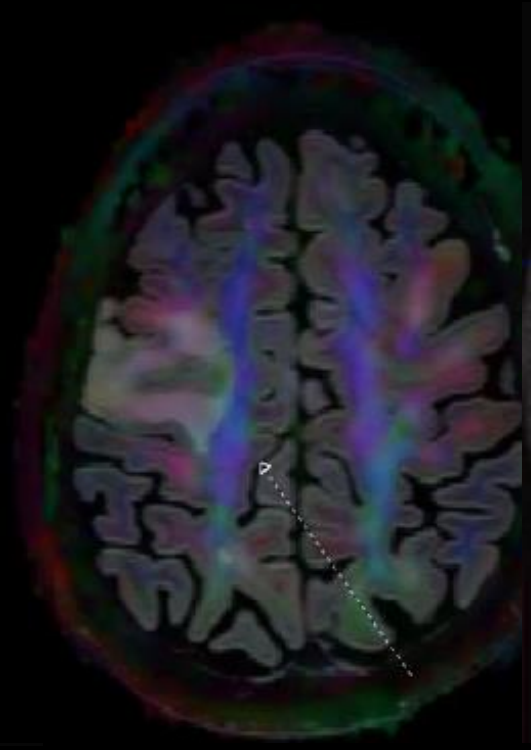
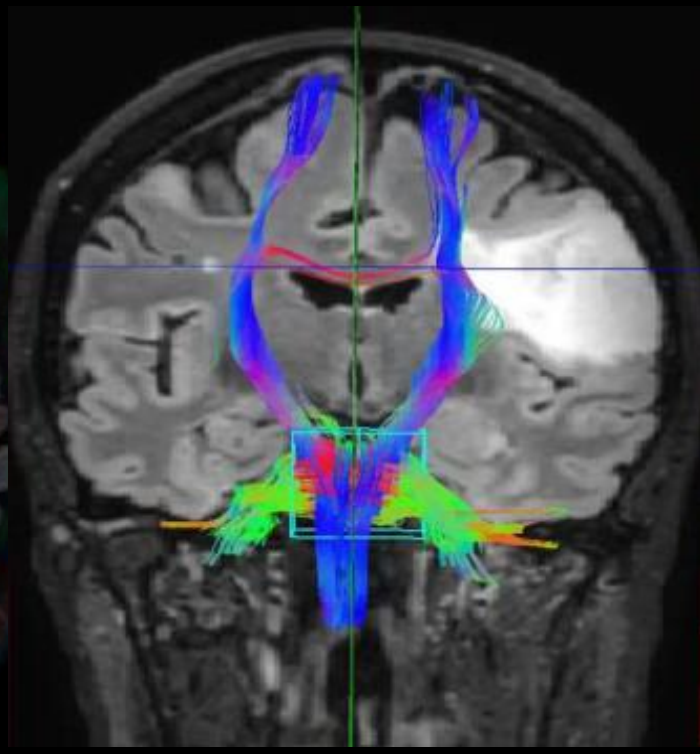
BEFORE SURGERY







3D SEQUENCES
NEURONAVIGATION - FMRI AND DTI

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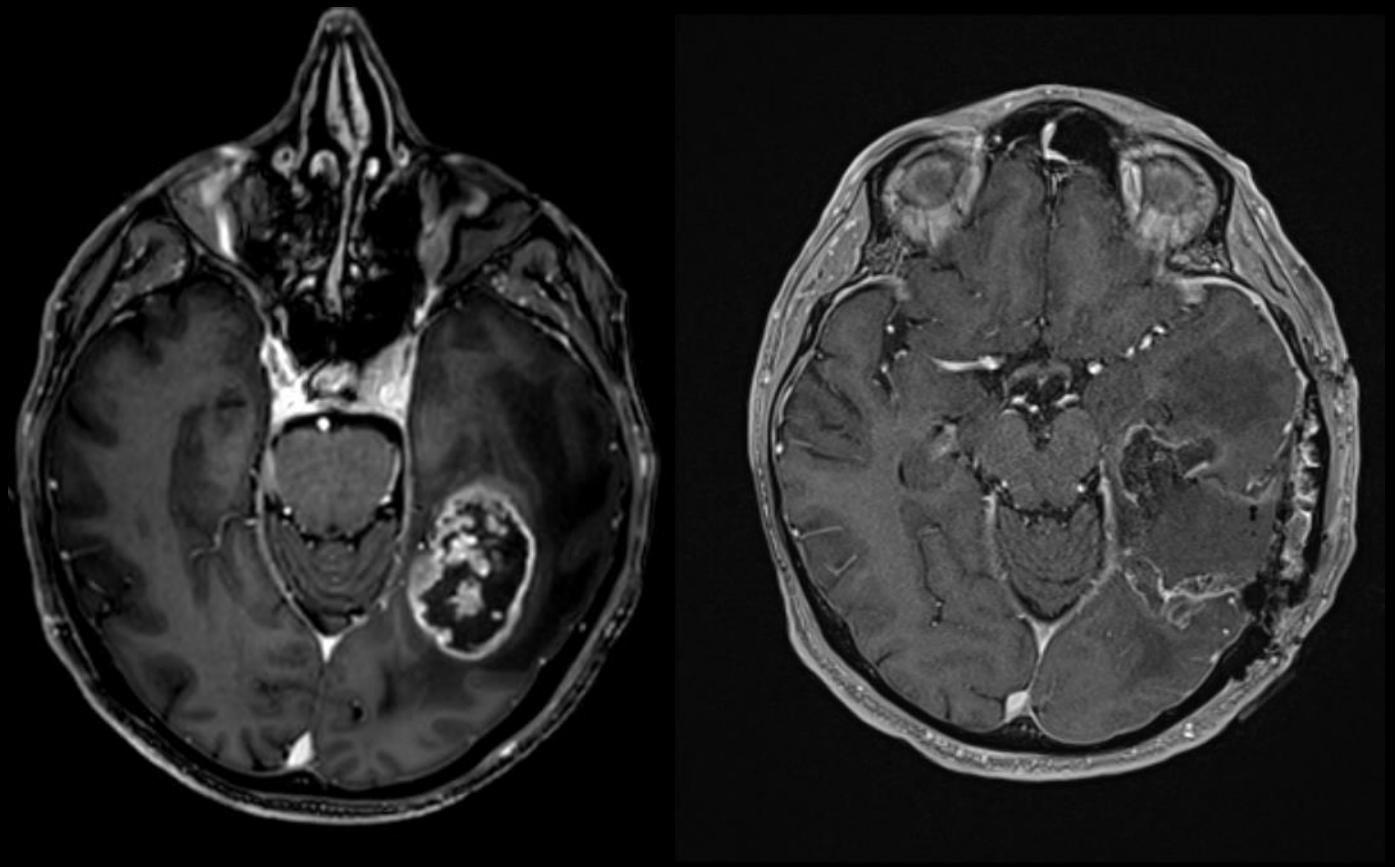
POST-SURGERY ASSESSMENT
24- 72 HOURS



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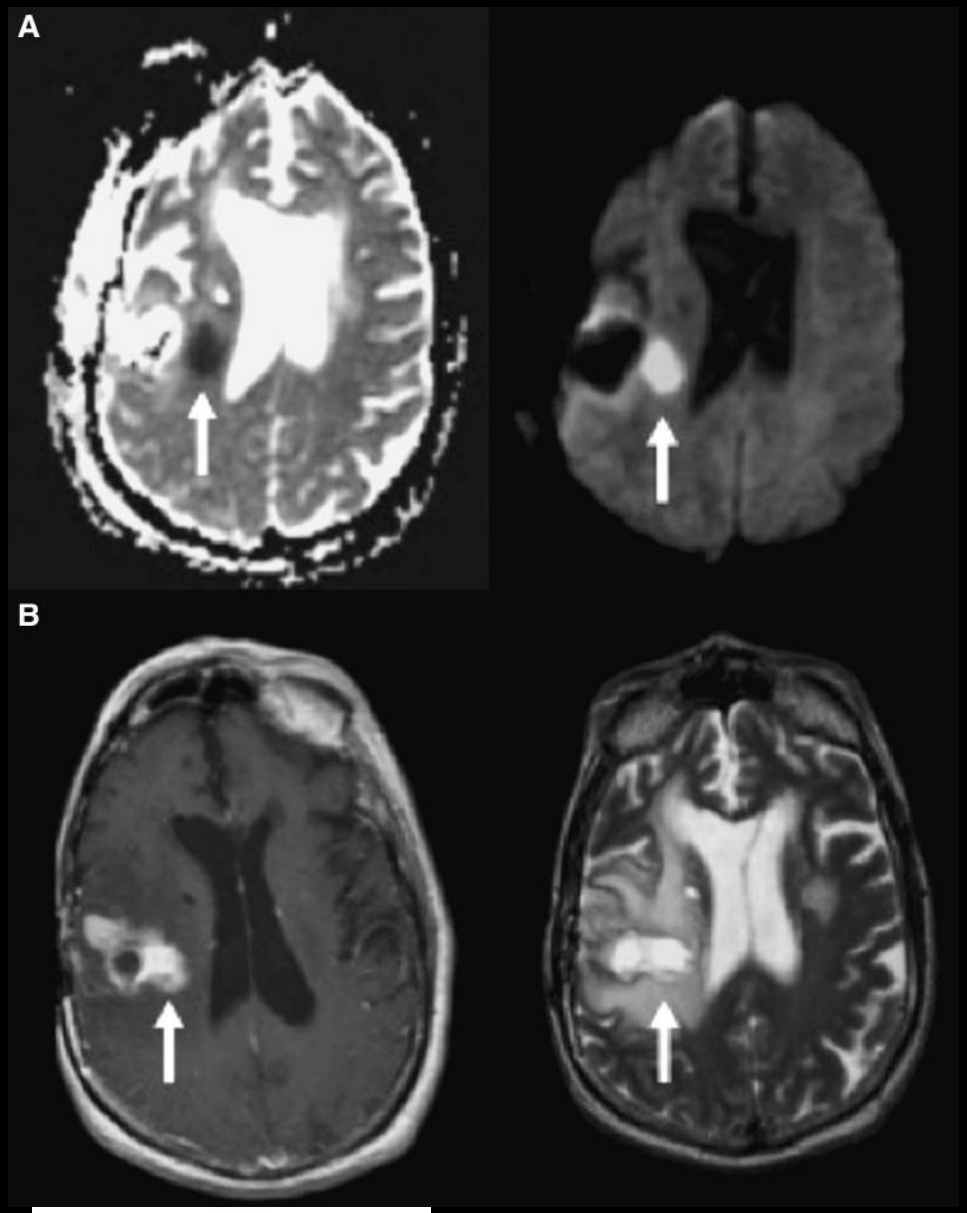
POST-SURGICAL DWI



A – peri-operative MRI:

restricted diffusion indicates an ischemic focus

B – 12 weeks after surgery:

- a focus of contrast uptake correlates with perioperative ischemia

- tumoral contrast enhancement is detectable along the anterior margin of sugical cavity

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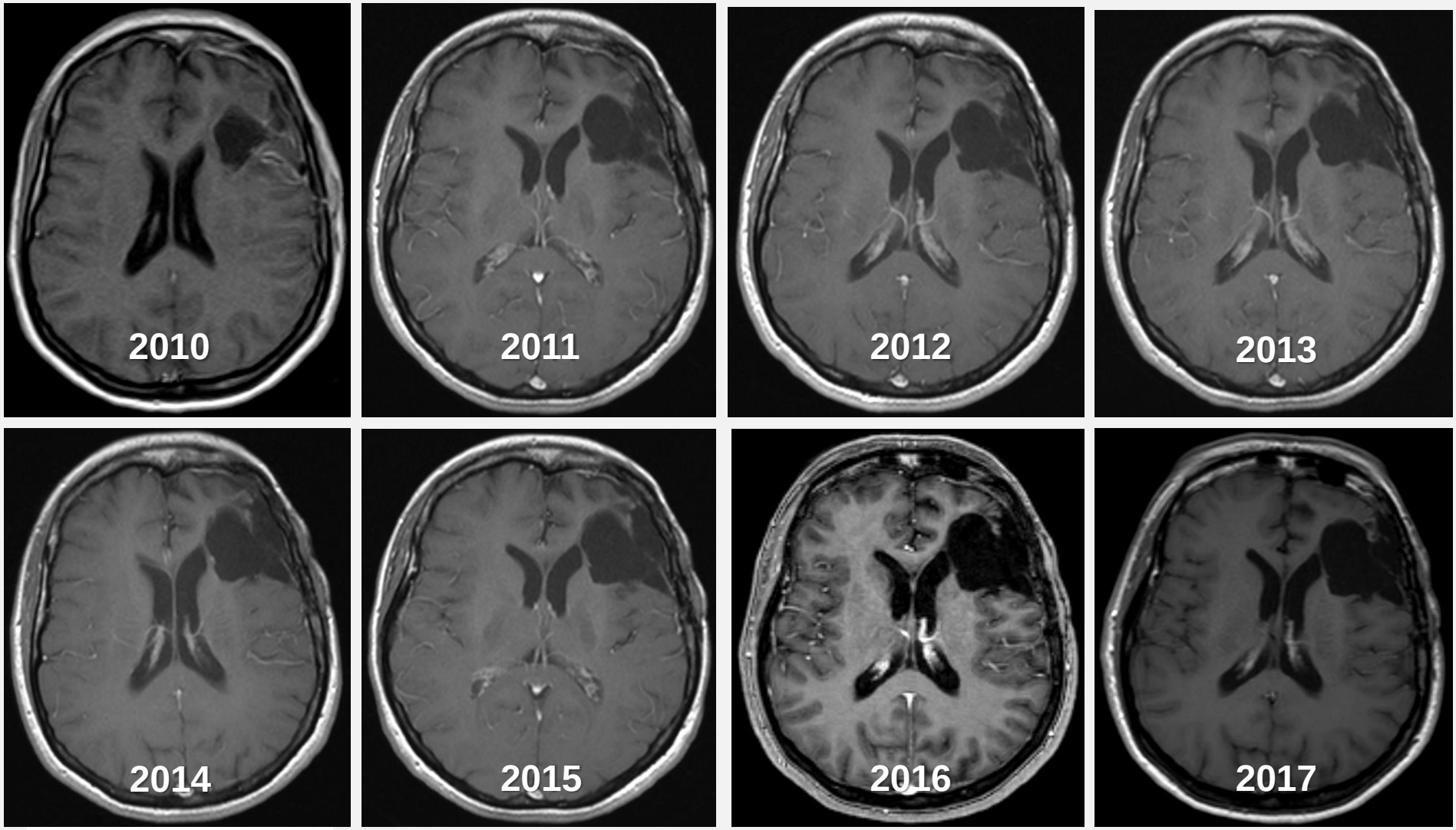
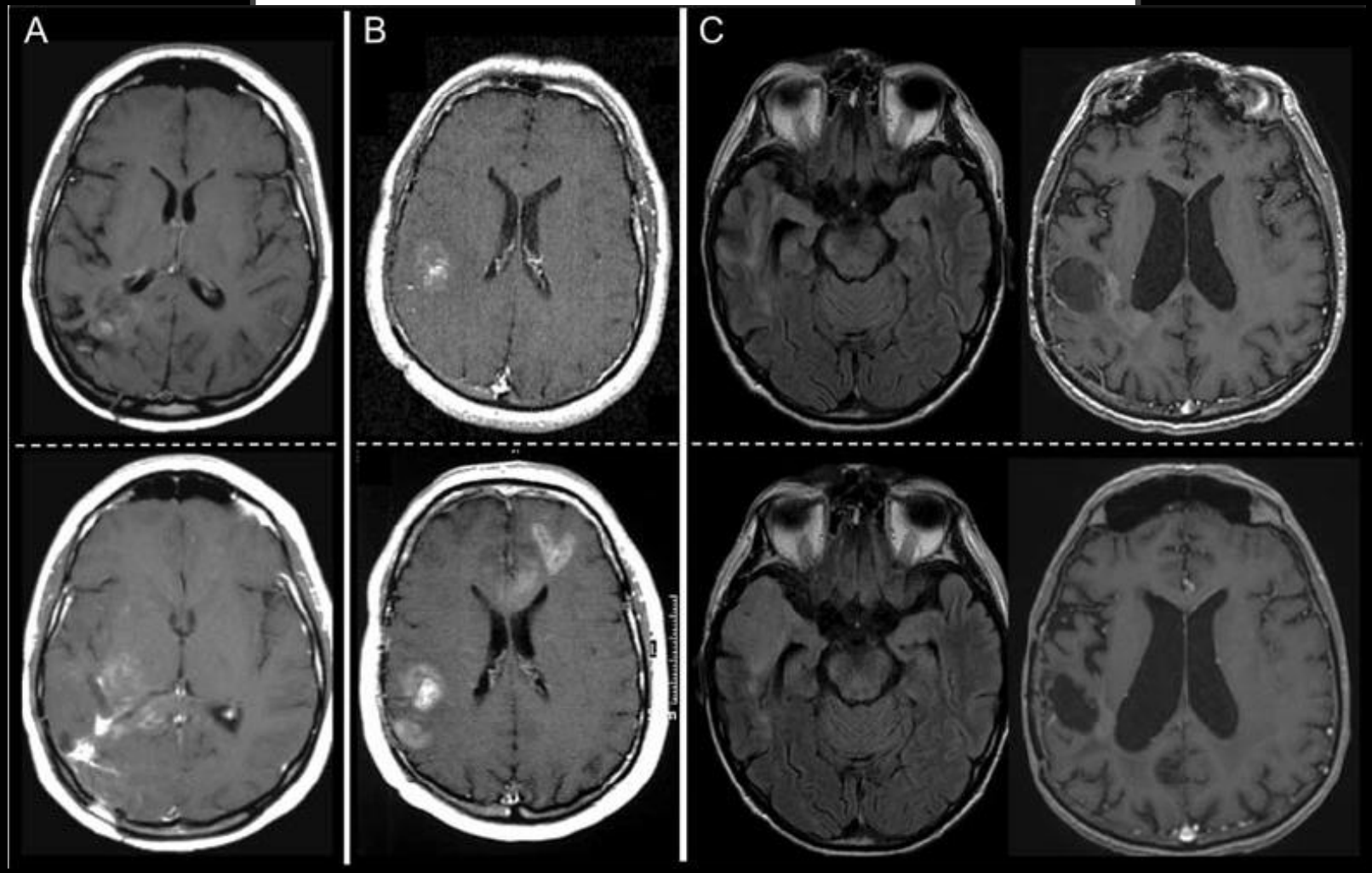
FOLLOW-UP



PATTERNS OF RECURRENCE



A – **local contrast-enhanced** recurrence

B – **distant contrast-enhanced** recurrence

C – **diffuse non enhancing** recurrence

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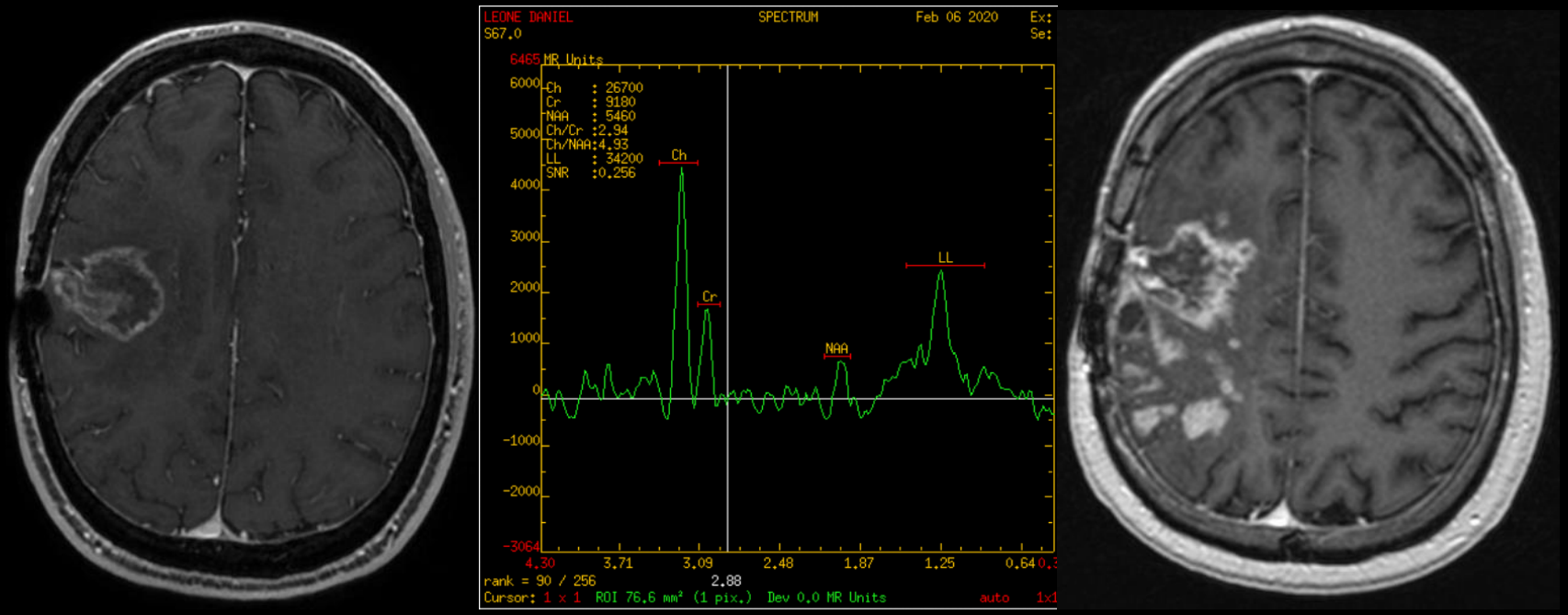
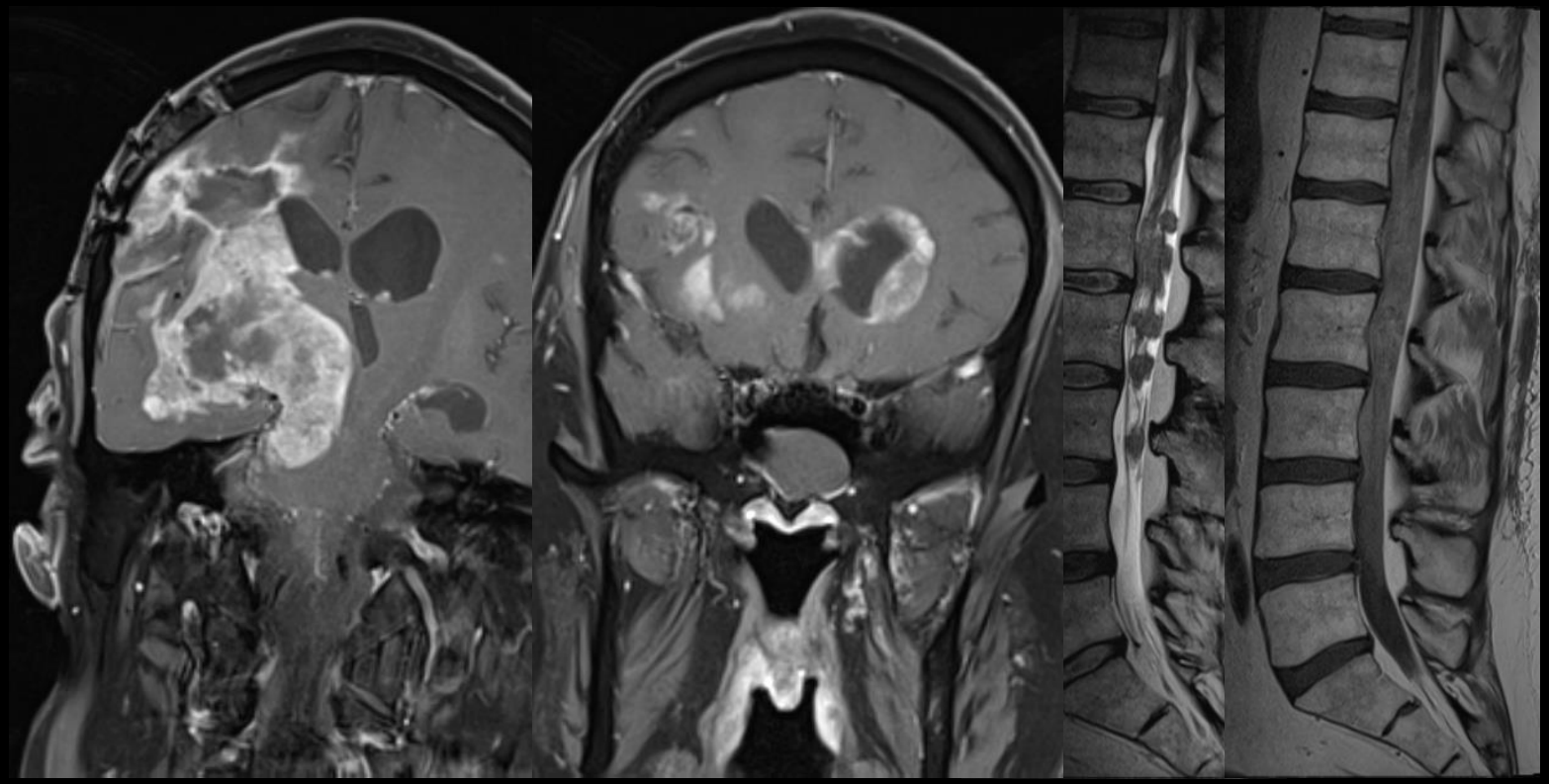


February 2020

Febbruary 2021



September 2021

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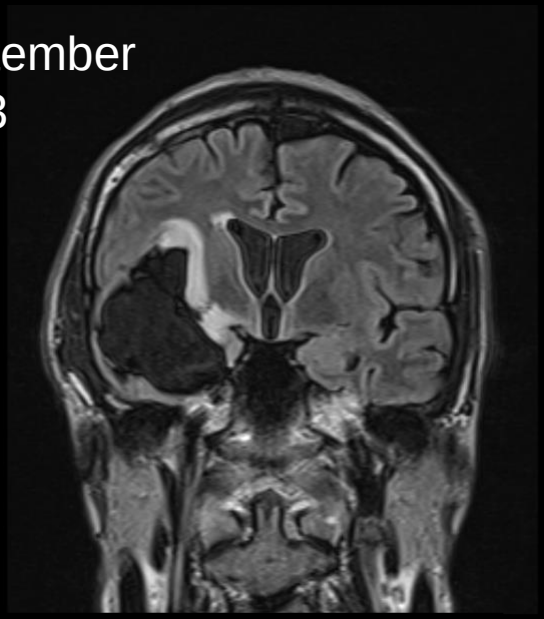
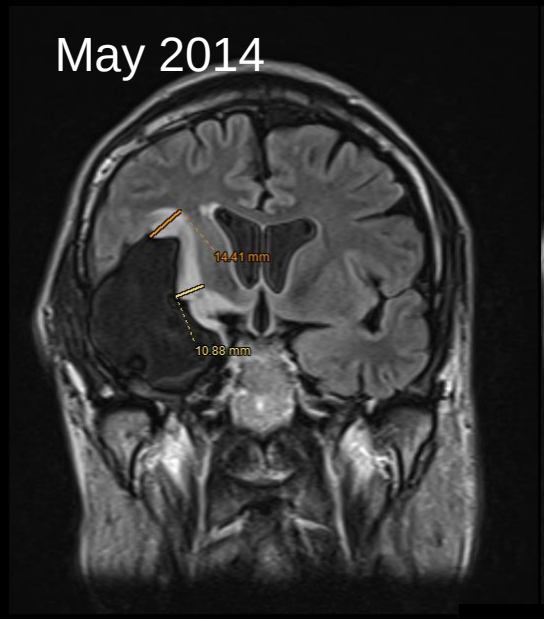
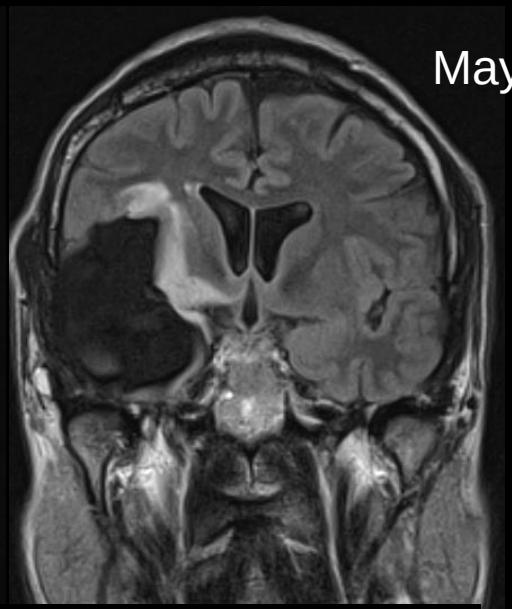
Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta



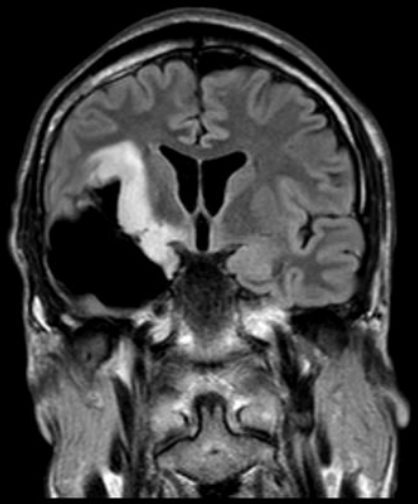
September 2013



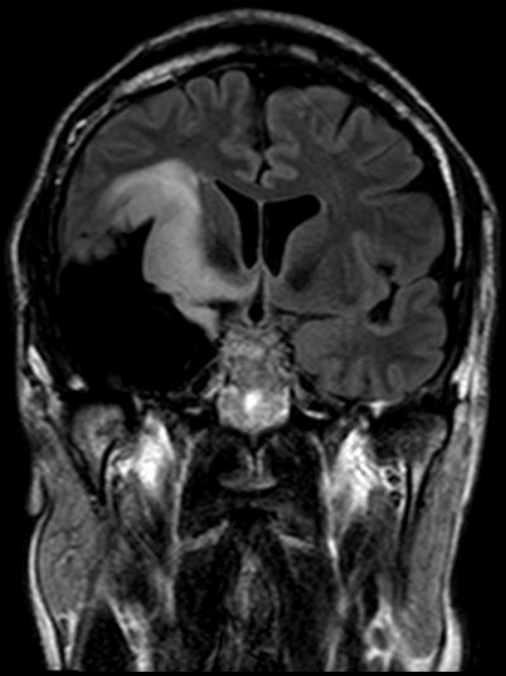
May 2014



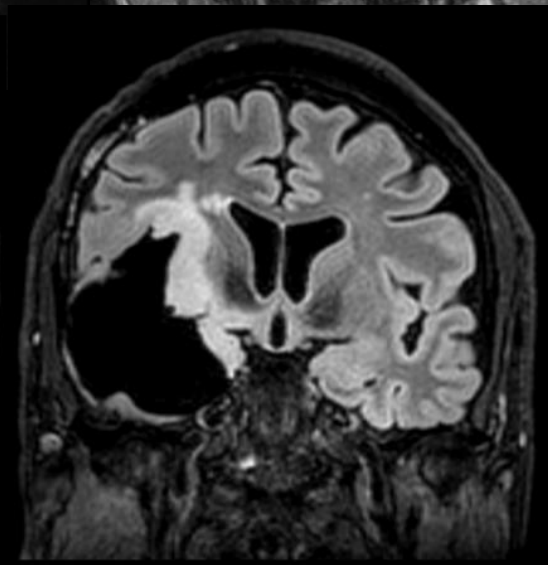
May 2015



July 2015



July 2016



July 2017
TMZ 12 mons

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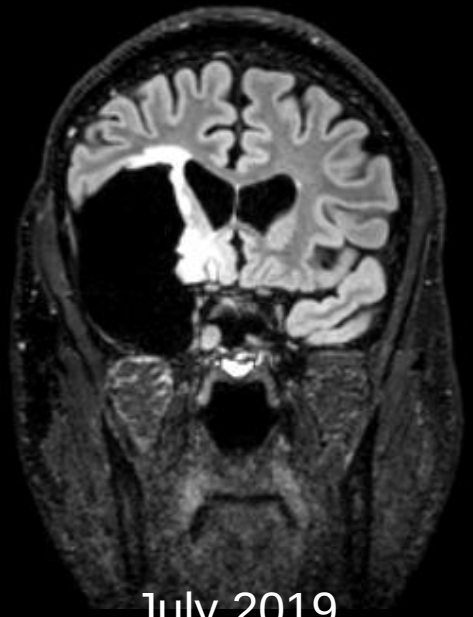

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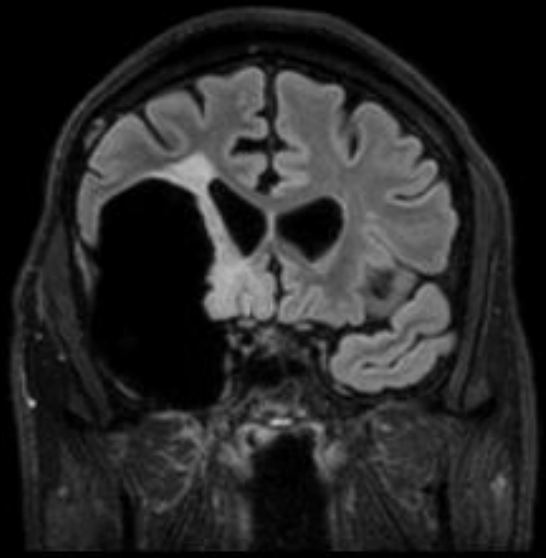
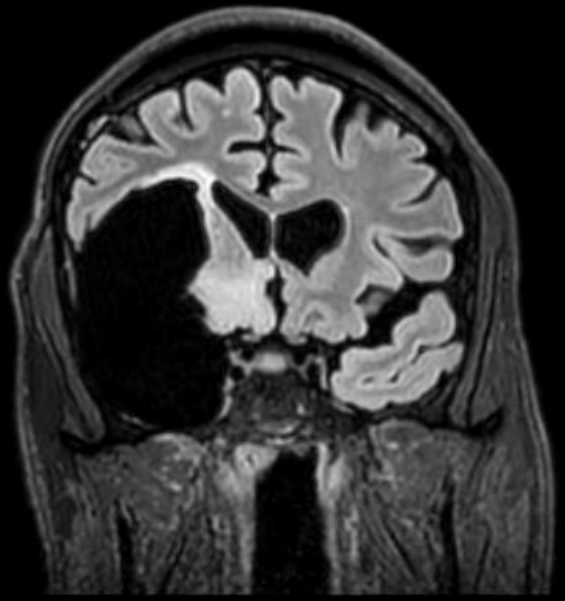
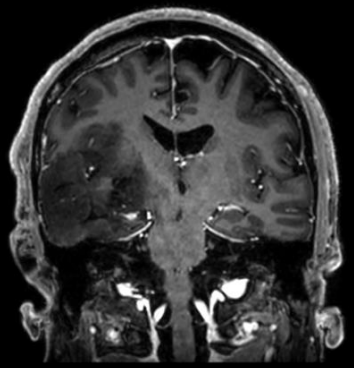
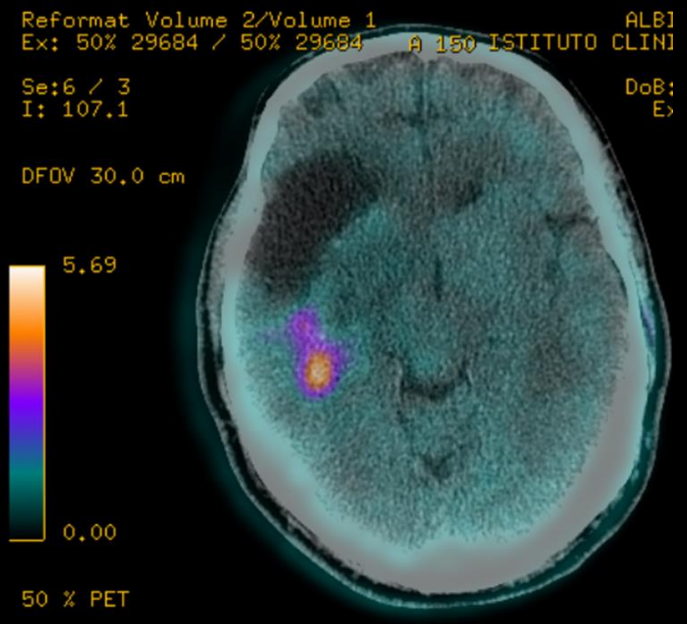


July 2020

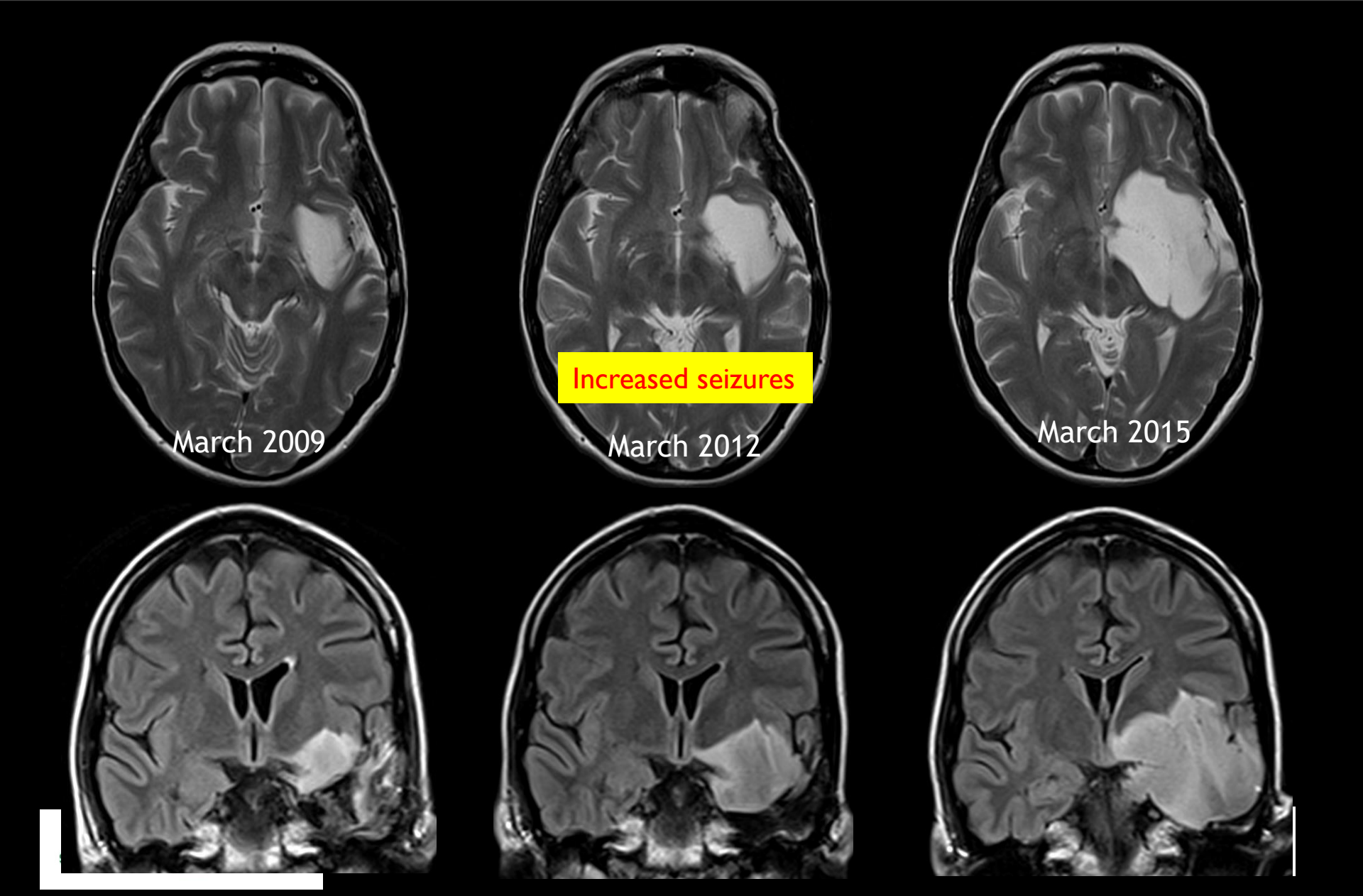




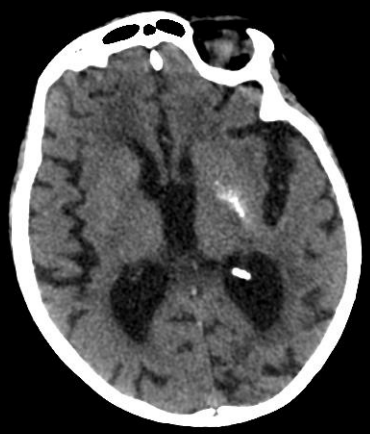


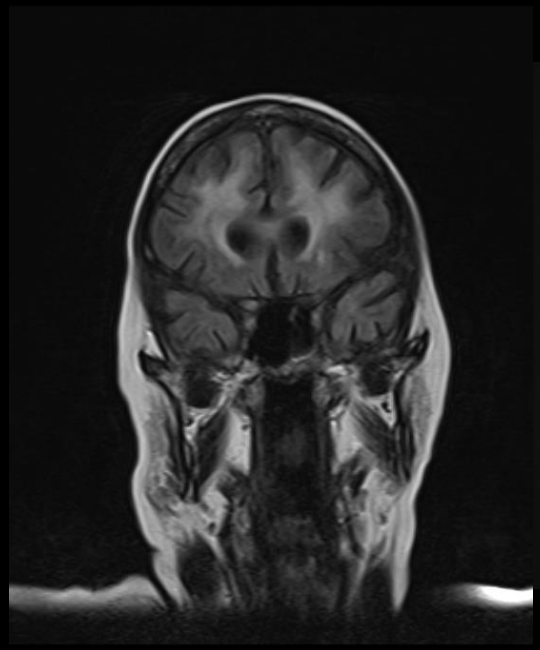
July 2021

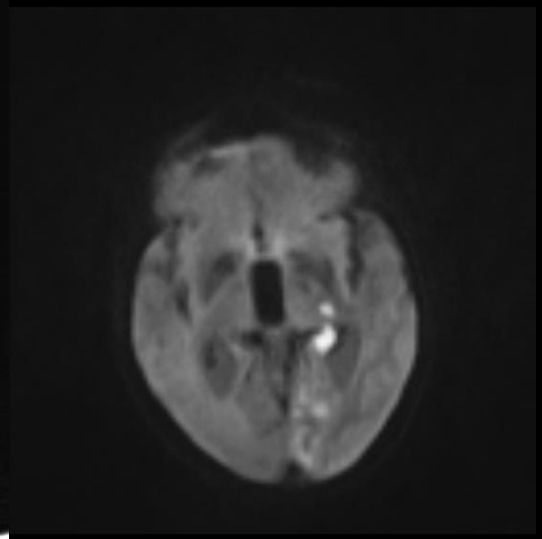
REPORTED AS "UNCHANGED SINCE PRIOR MRI" (ANNUAL CONTROLS) FOR SIX YEARS IN A ROW



VASCULAR ENCEPHALOPATHY DEVELOPED AFTER WBRT(1981) FOR MEDULLOBLASTOMA







2021

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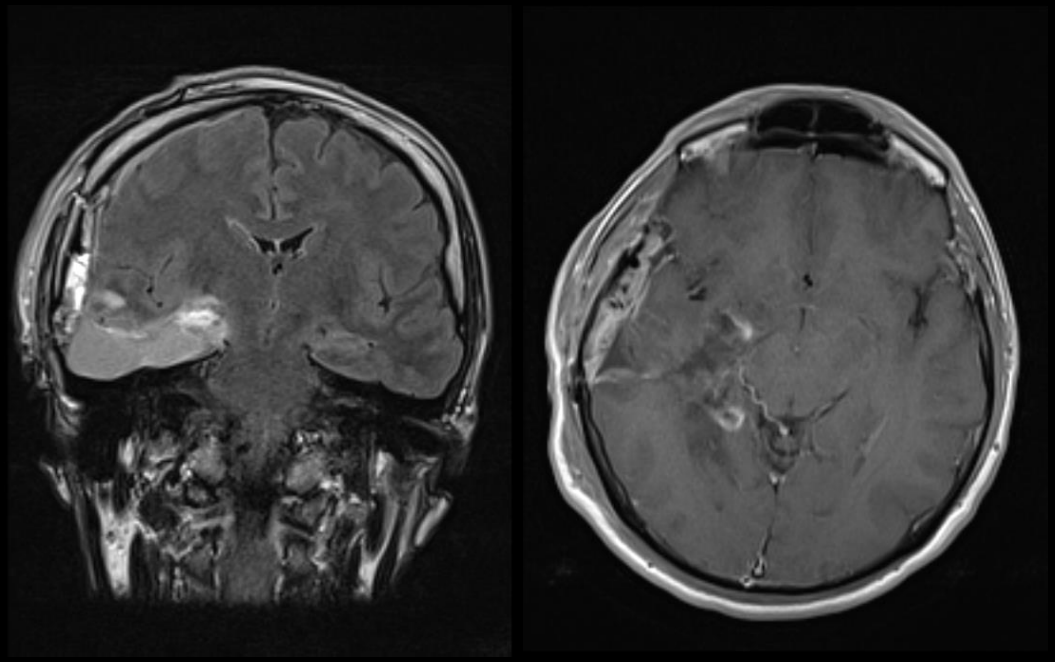

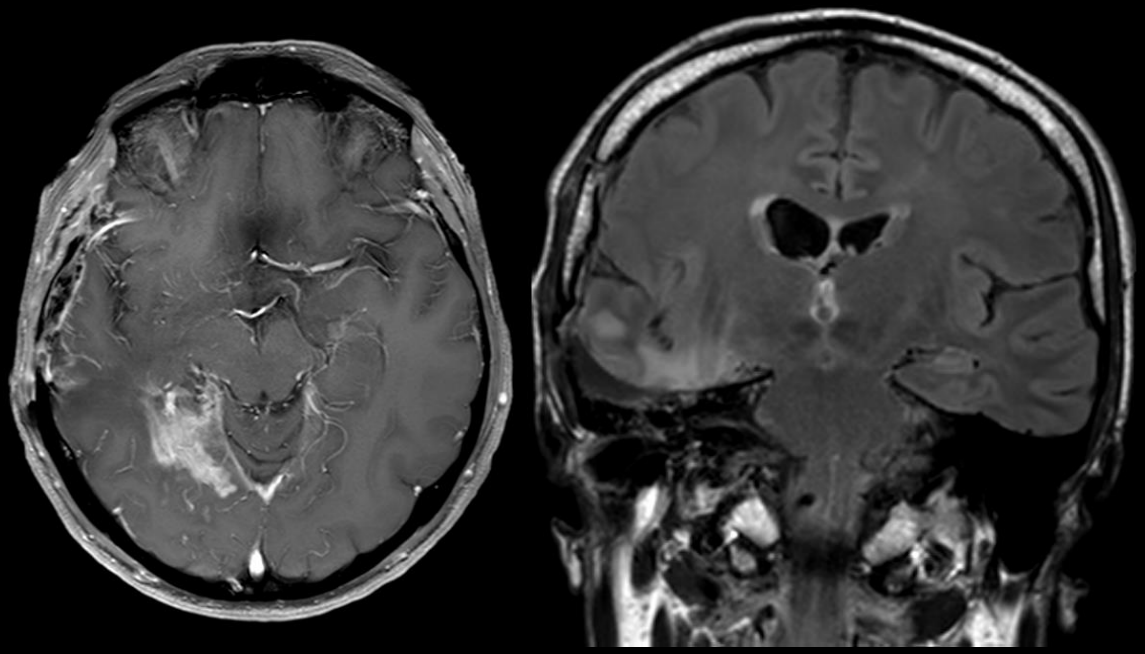

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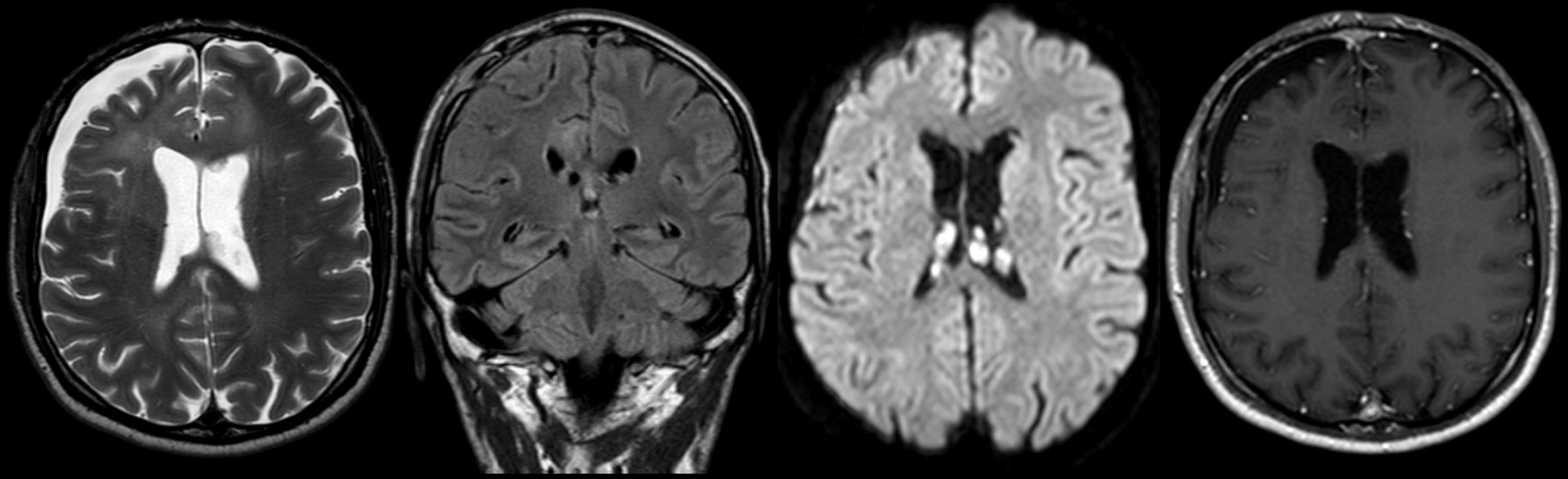
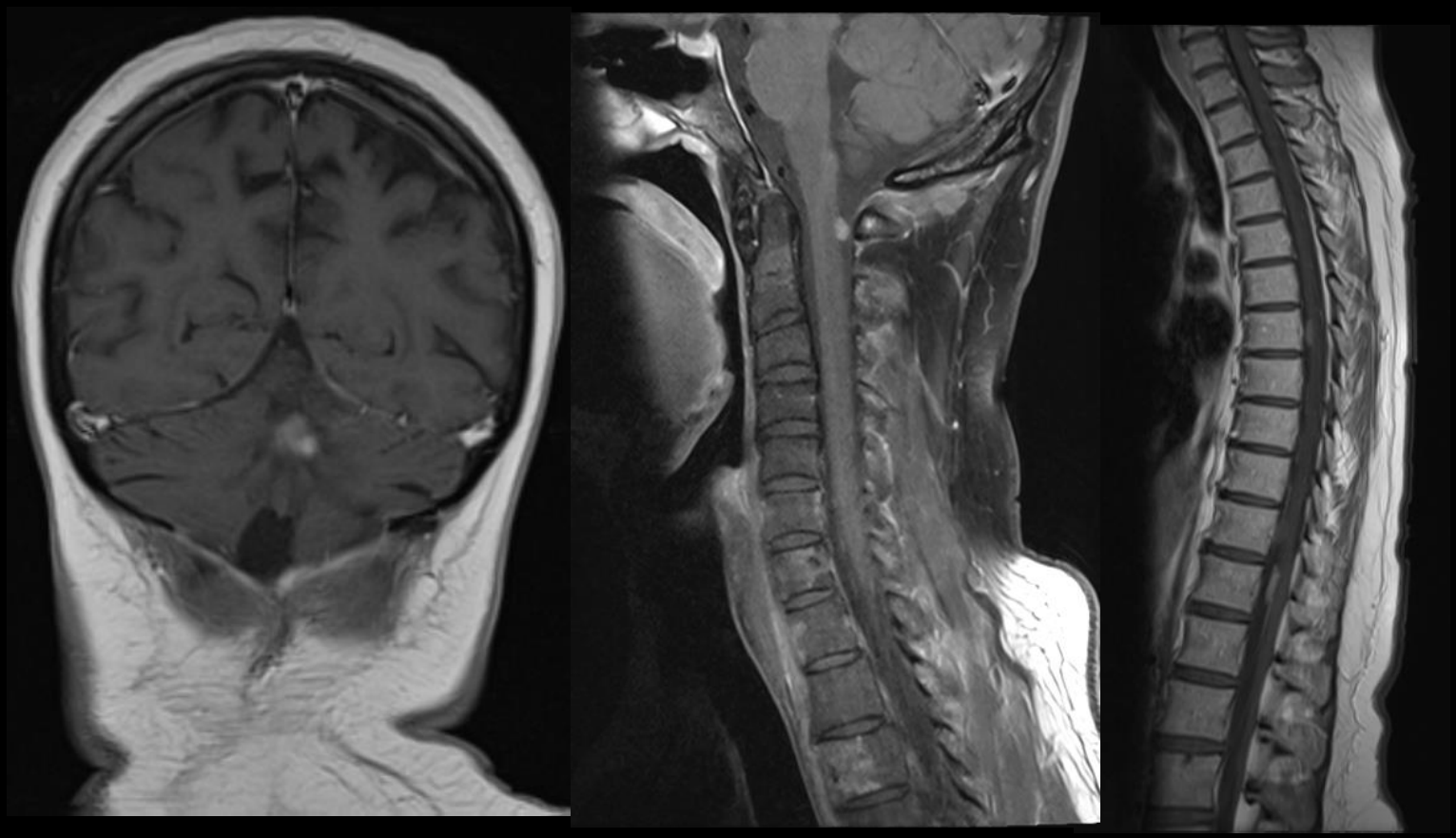
ASPERGILLUS MENINGITIS



MEDULLOBLASTOMA

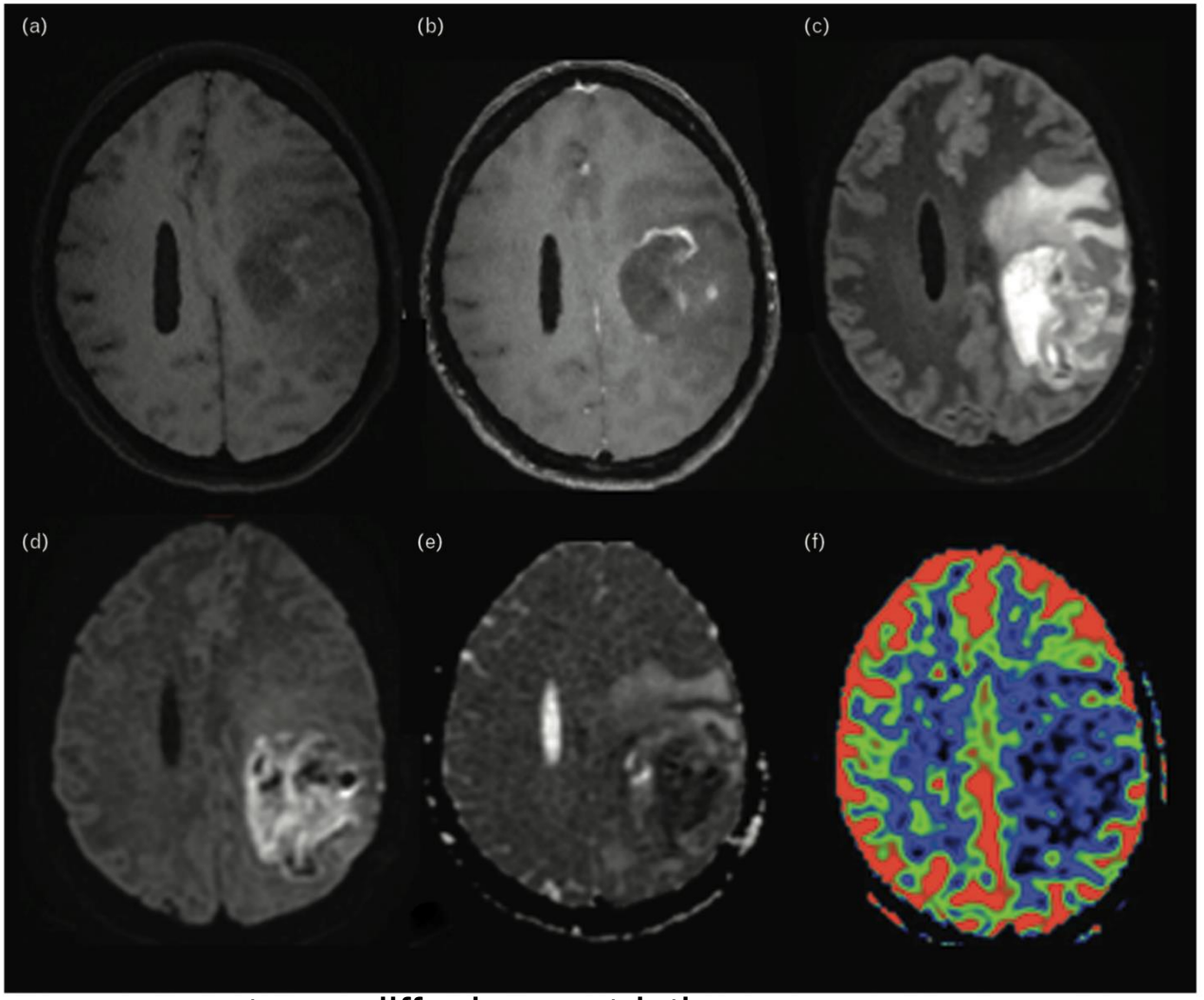


PSEUDOPROGRESSION
[RT ± CHT]

- Pseudoprogression is resulting from inflammation and upregulation of VEGF, leading on to increasing edema and vascular permeability
  - enhancement that simulates tumor growth
  - <5% CHT, 5-10% RT and up to 40% RT+CHT(temozolomide), up to 30% immunoT
  - more frequent in MGMT methylated
  - 60% within 12 weeks of radiation

If in doubt
- consider supplemental imaging
- follow to next visit?

RADIONECROSIS
ANAPLASTIC PLEOMORPHIC XANTHOASTROCYTOMA+ STUPP



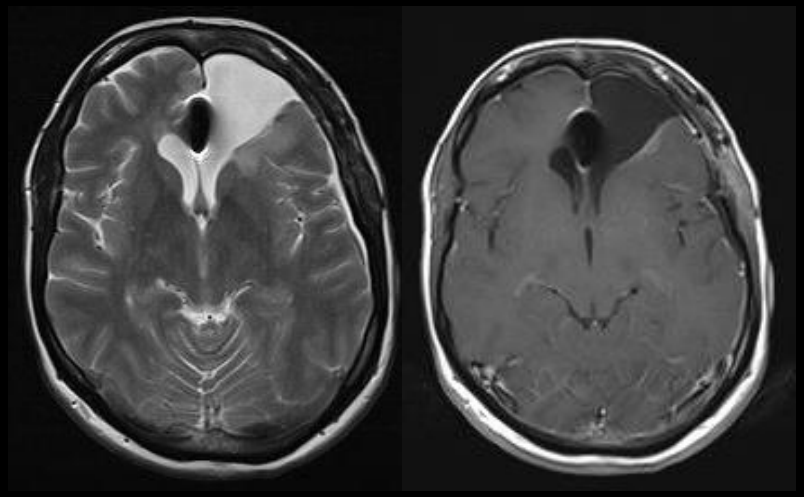
strong diffusion restriction

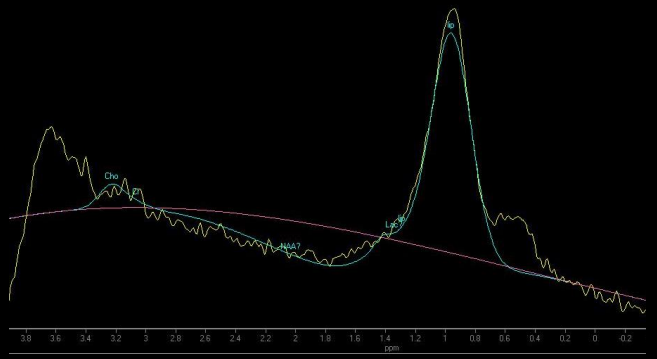
No hyperperfusion in ASL

Nichelli L 2021

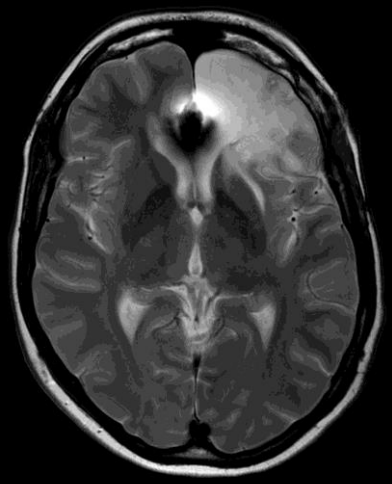
RADIONECROSIS

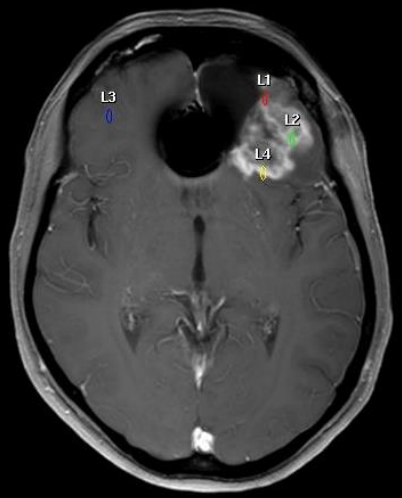
June

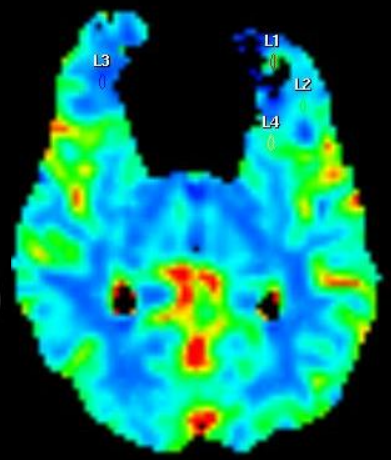


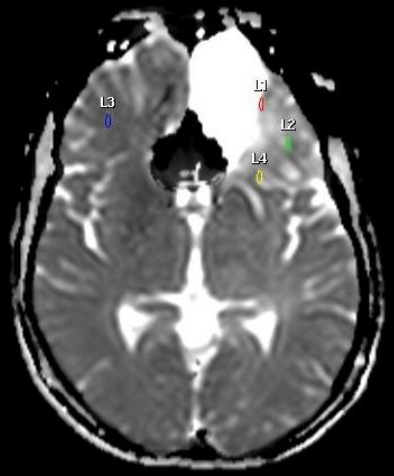


September

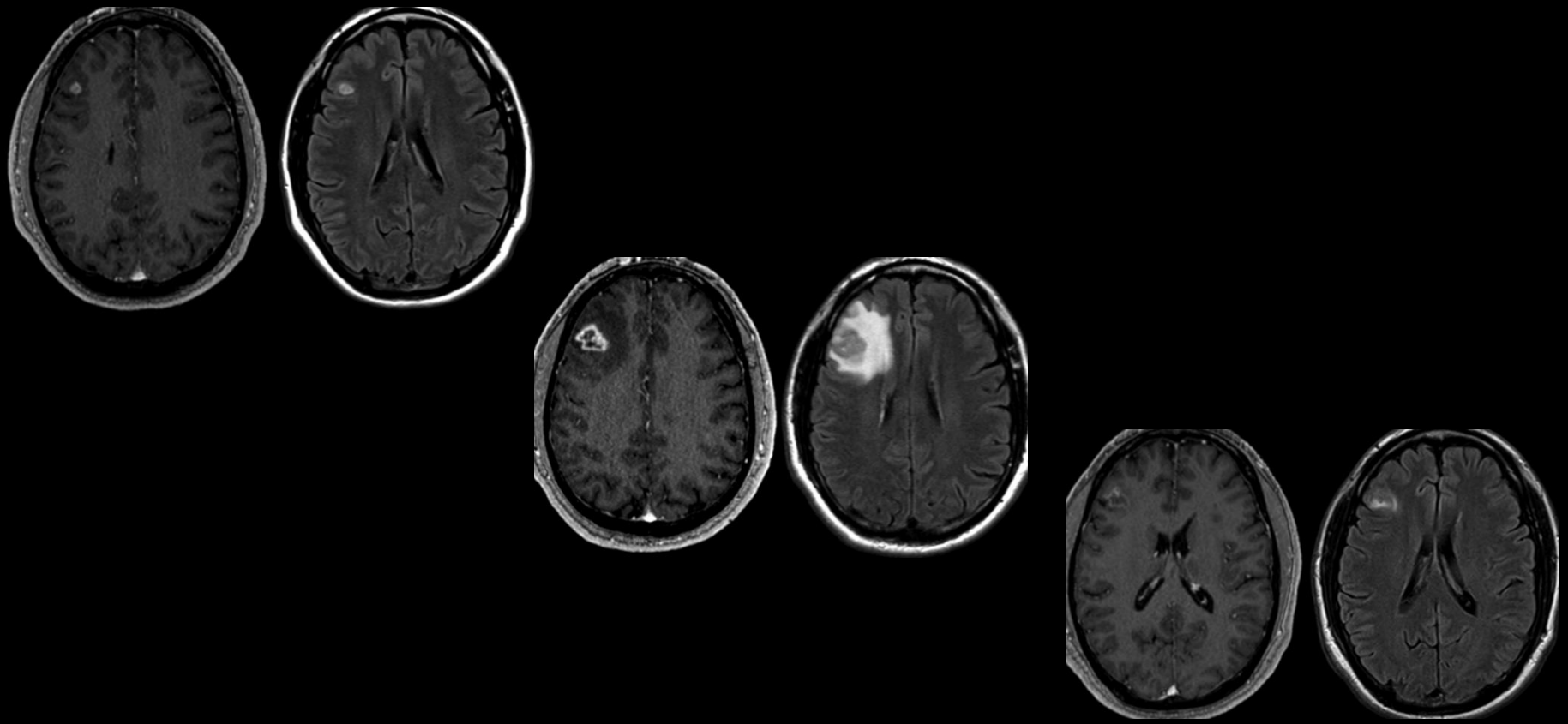


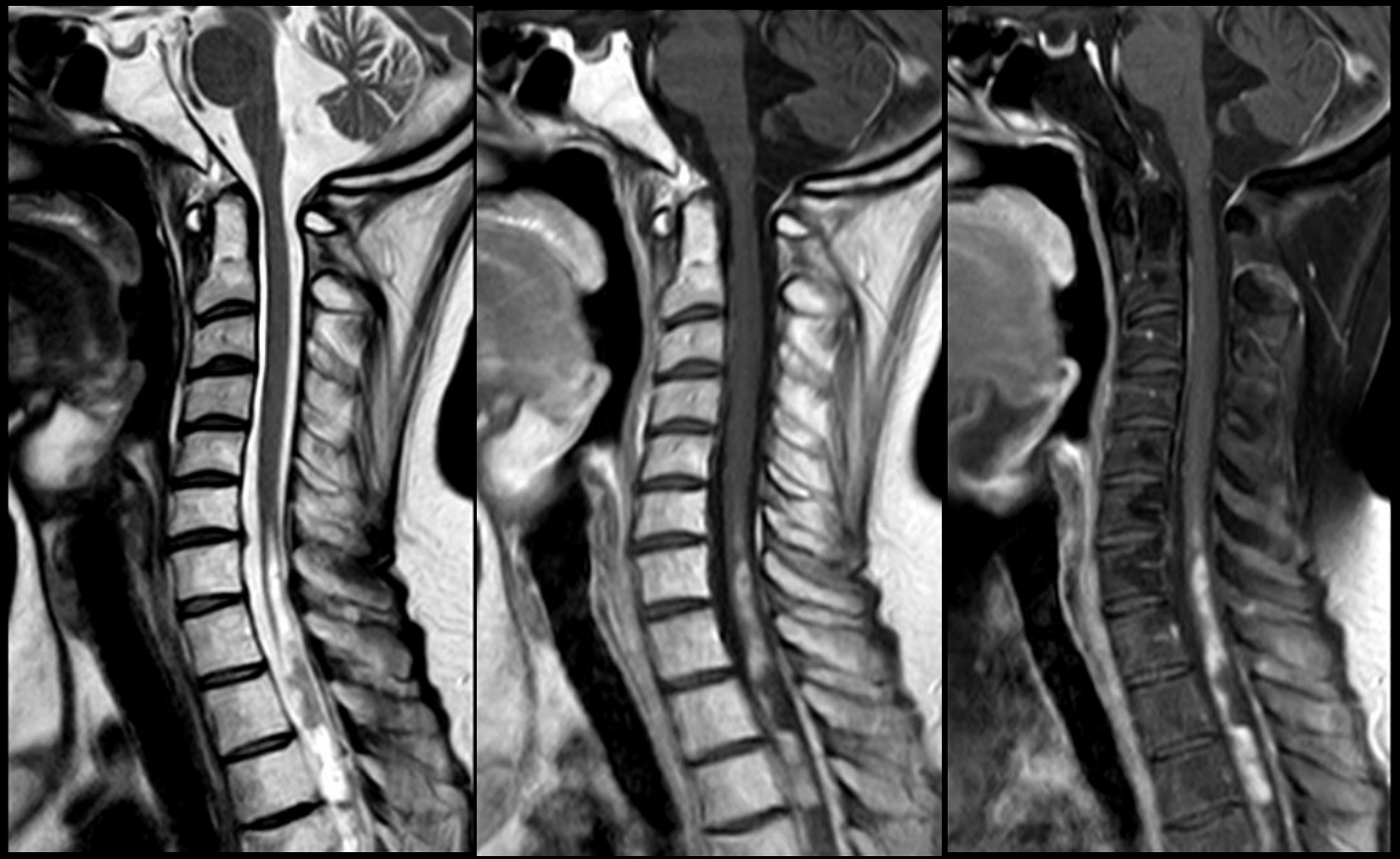






RADIONECROSIS AFTER SRT BMT



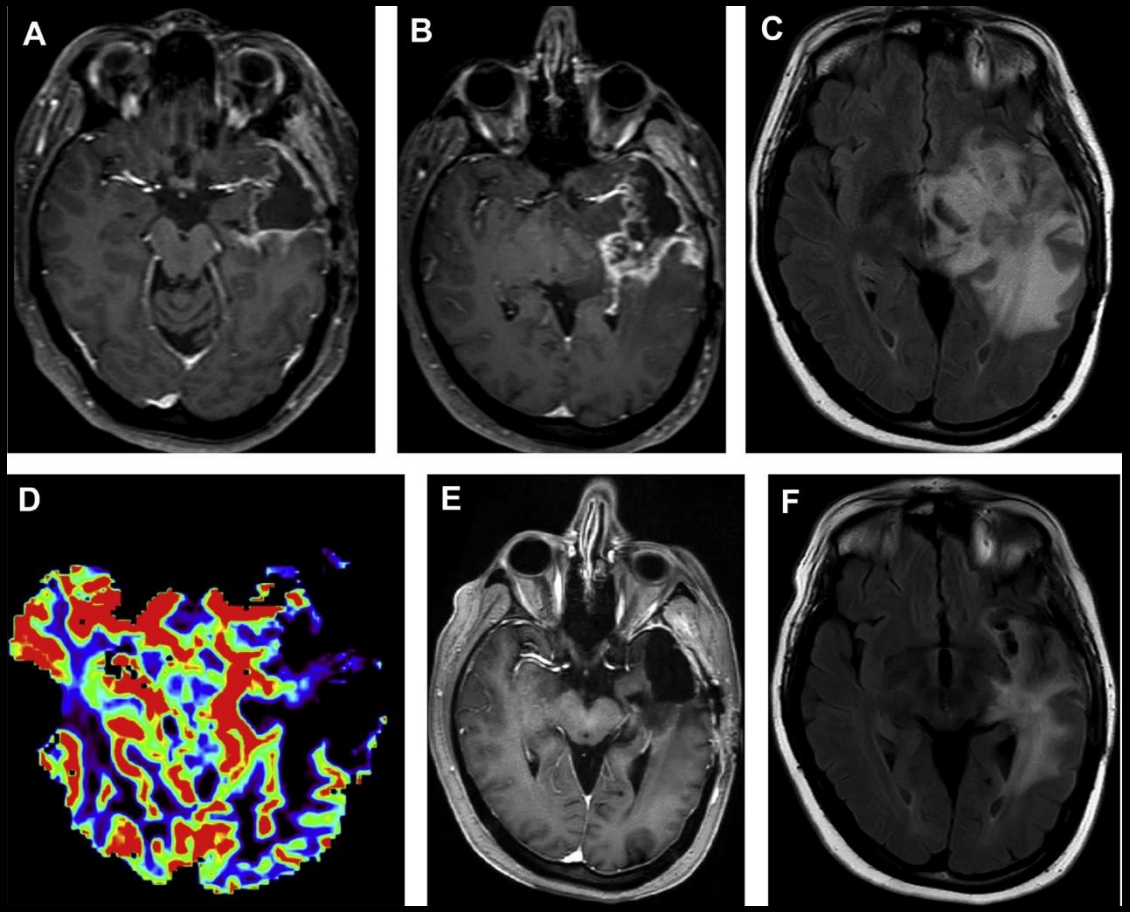


T2

T1 gad -

T1 gad +

PSEUDOPROGRESSION



Bapuraj JR Radiol Clin N Am 2021

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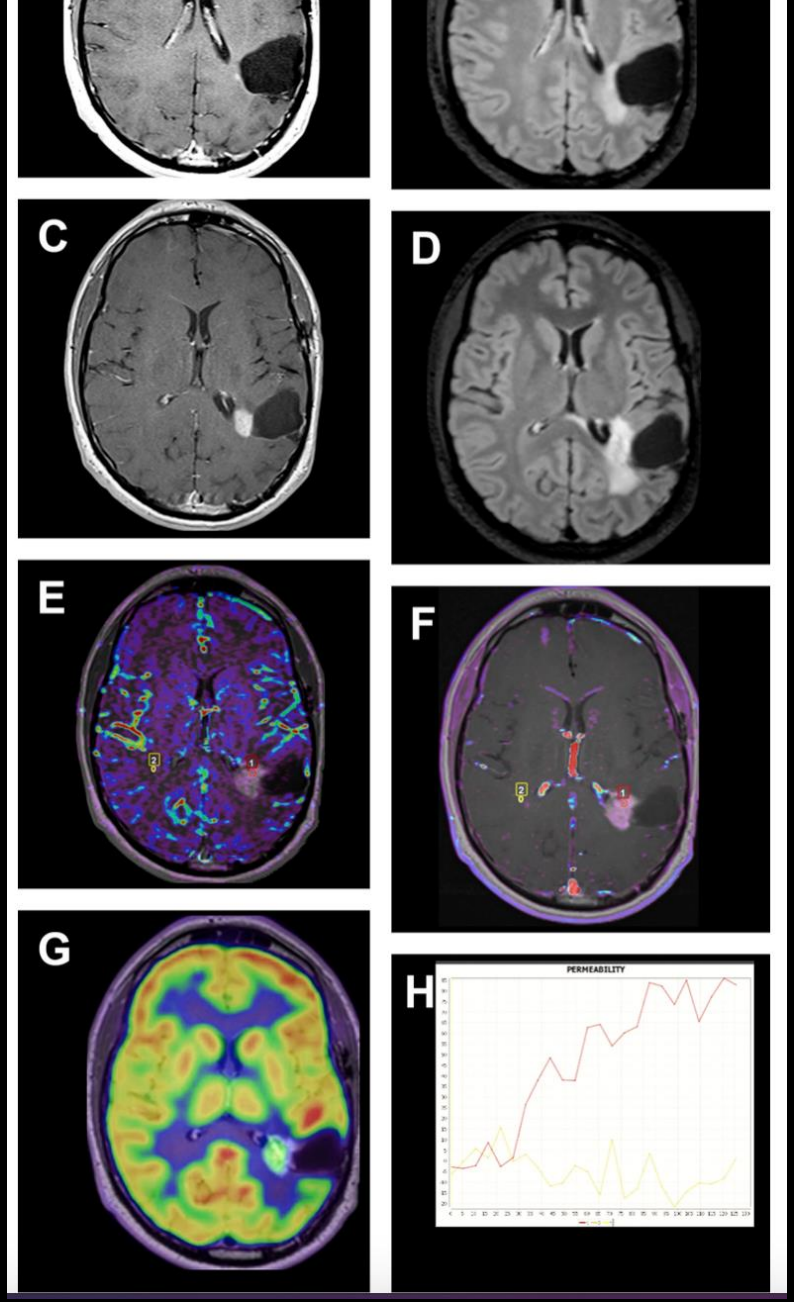
PSEUDOPROGRESSION



FDG uptake

elevated plasma volume (E)

elevated permeability (F, H)

Strauss SR Clinics of North America2021

RADIONECROSIS AND PSEUDOPROGRERSSION

- Brain radionecrosis and pseudo progression require advanced imaging.
- Perfusion holds the higher diagnostic accuracy, especially when combined with spectroscopy and susceptibility-weighted imaging.
- DWI must be interpreted with caution, as similar diffusion water molecules metric can reflect opposite phenomena (i.e. necrotic or hypercellular lesions)

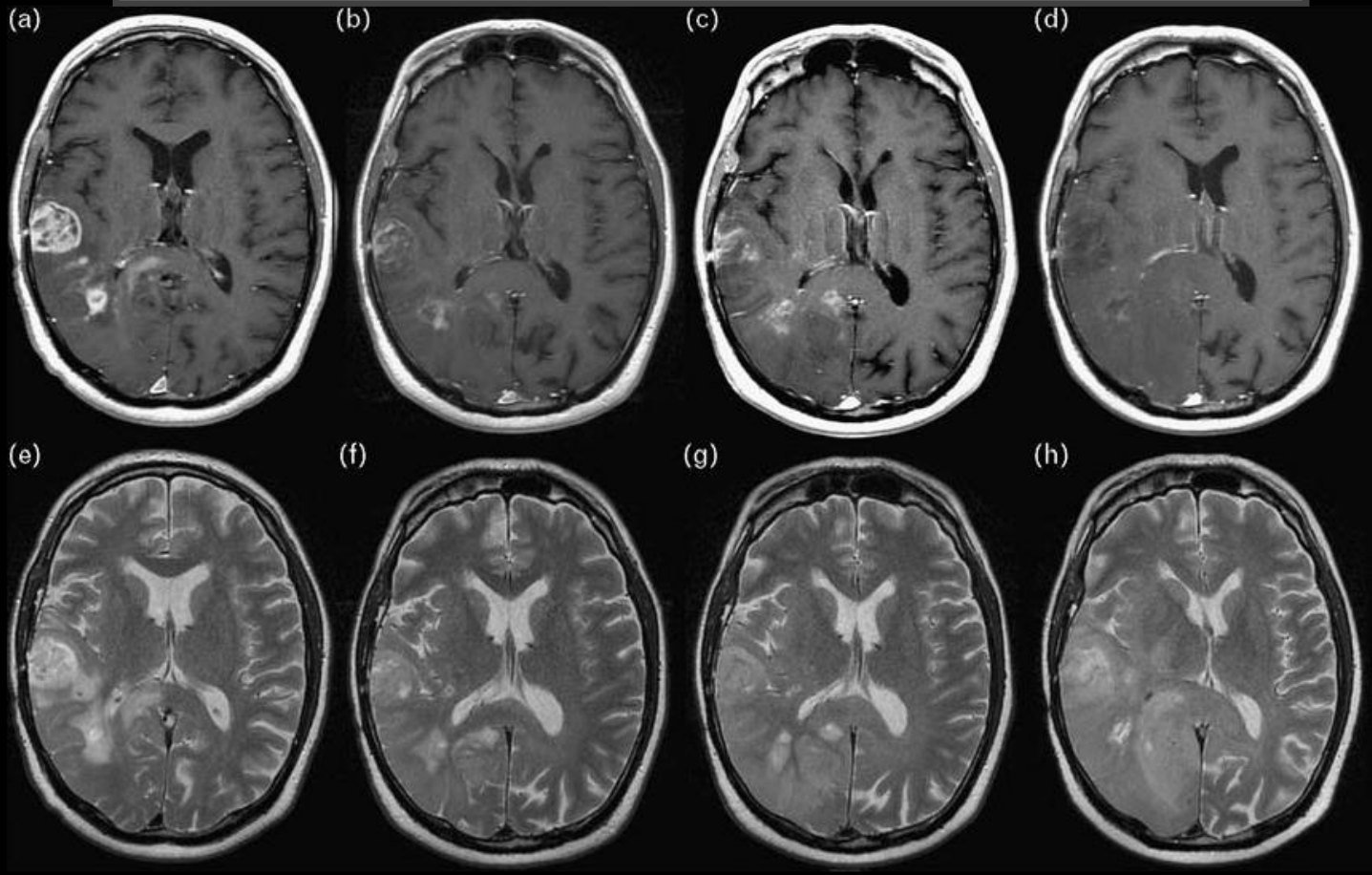
Nichelli L 2021

PSEUDORESPONSE

- Antiangiogenic drugs: anti-VEGF, anti-VEGF receptor]
  - anti-vascular effects
  - reduction of enhancement ± oedema, can look like response
  - within 4 weeks of therapy
  - [MRI+Clinical+Steroids → Overall response(OR)]

  If in doubt
  - consider supplemental imaging

PSEUDORESPONSE AND NON-ENHANCING PROGRESSION



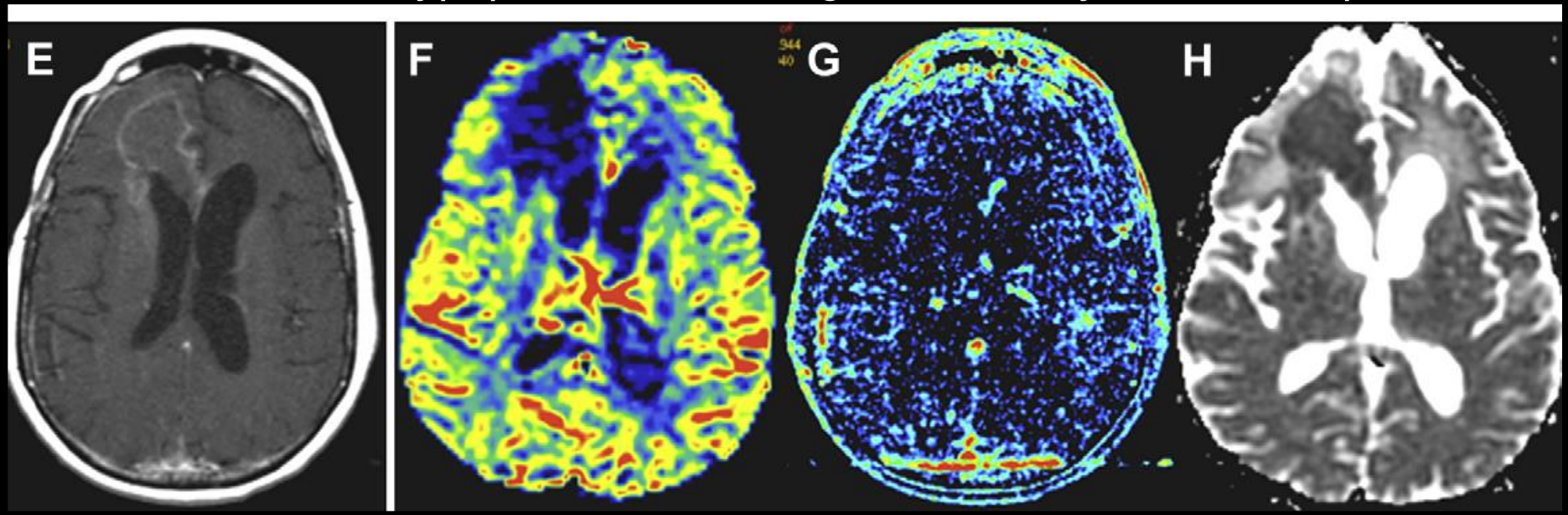
baseline (a, e), after 6 weeks (b, f), 12 weeks (c, g) and 18 weeks (d, h) of treatment with **BEVACIZUMAB**

Chinot OL Curr Neurol Neurosc Rep 2013

ANTIANGIOGENIC THERAPY

PSEUDORESPONSE

Scarce c.e., hypoperfusion, but high cell density on ADC map



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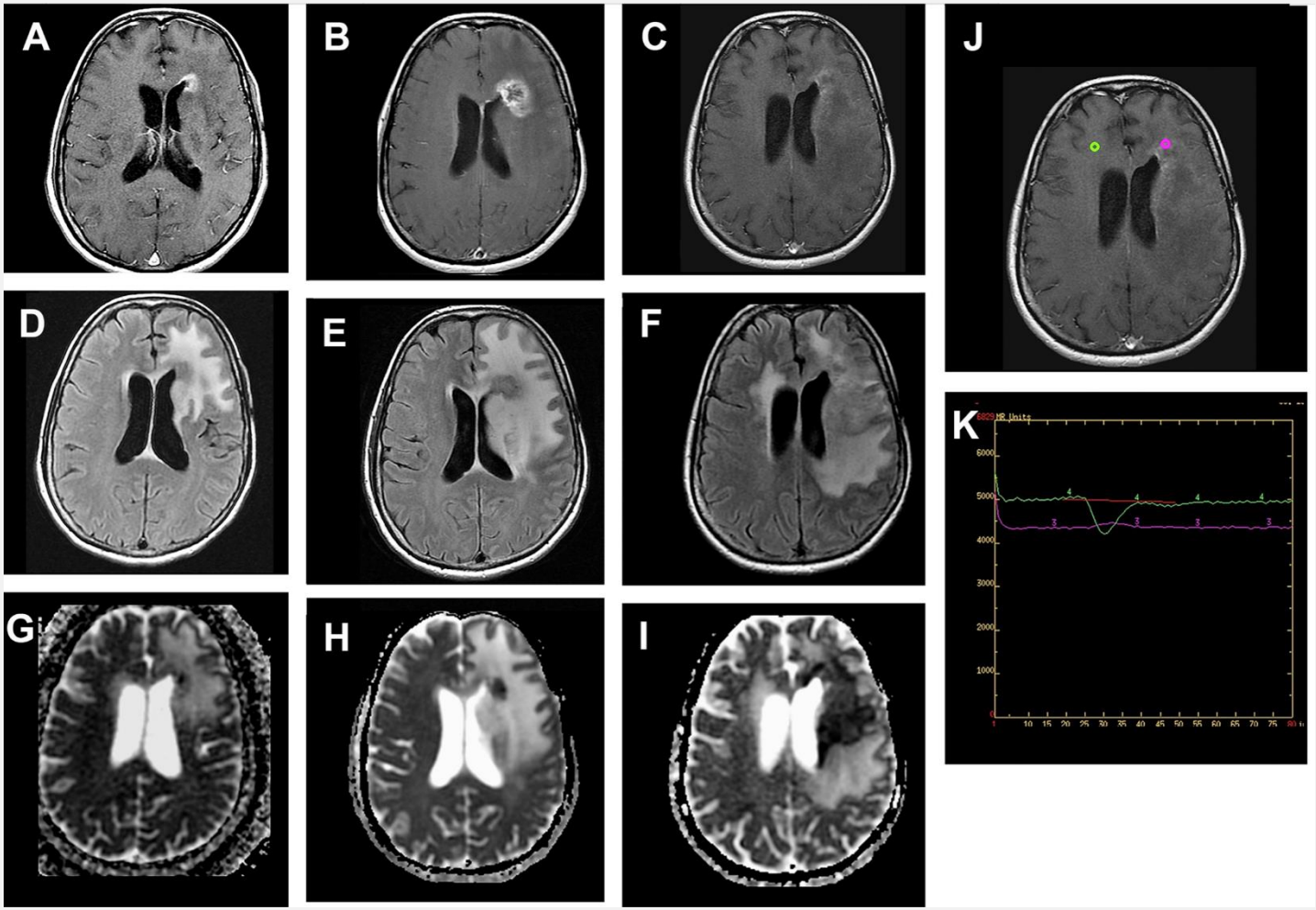
PSEUDORESPONSE



no elevated CBV

ADC hypointensity

Strauss SR Clinics of North America 2021

IMMUNOTHERAPY WITH DENDRITIC CELL VACCINE

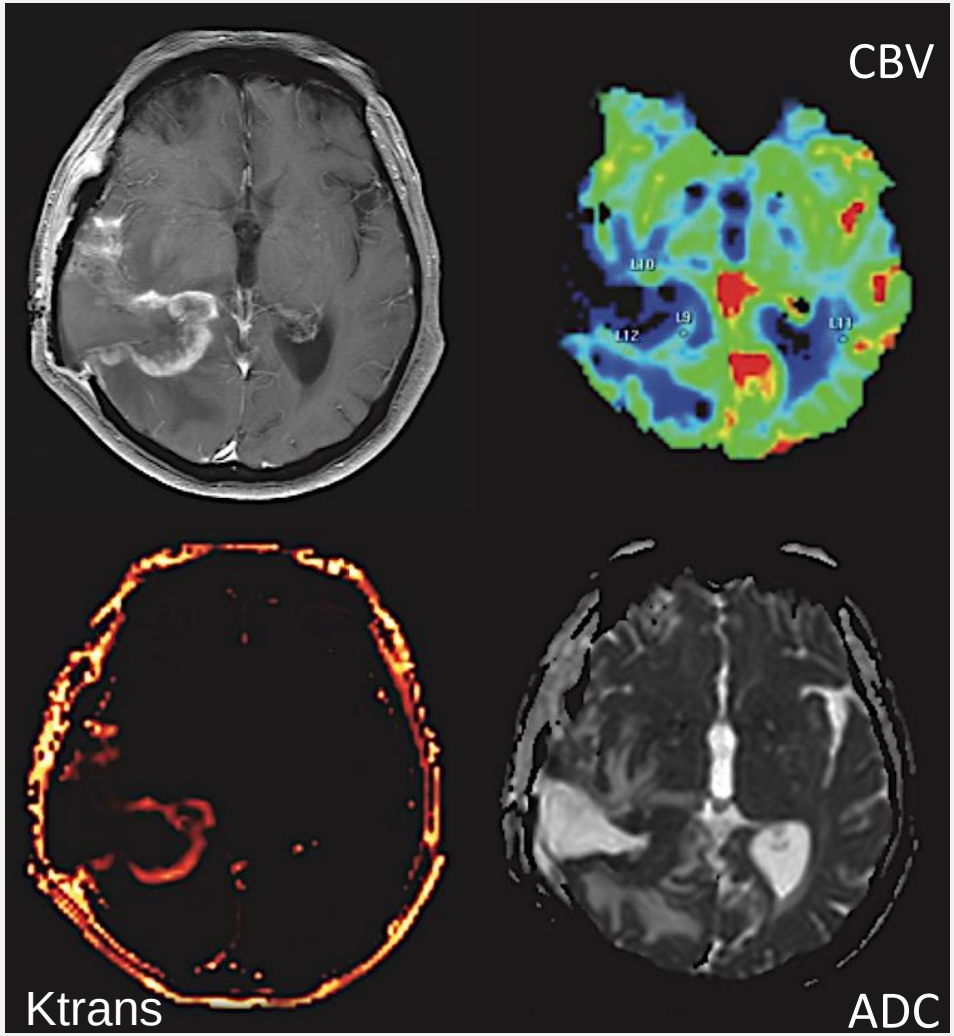
T1-enhancing lesion

"MISMATCH"

relatively low CBV
observed in PSEUDOPROGRESSION

Elevated k_{trans} and low ADC
not specific
(both in PD or PsP)

Aquino et al
J Immunology Research 2017



K_{trans} (permeability)

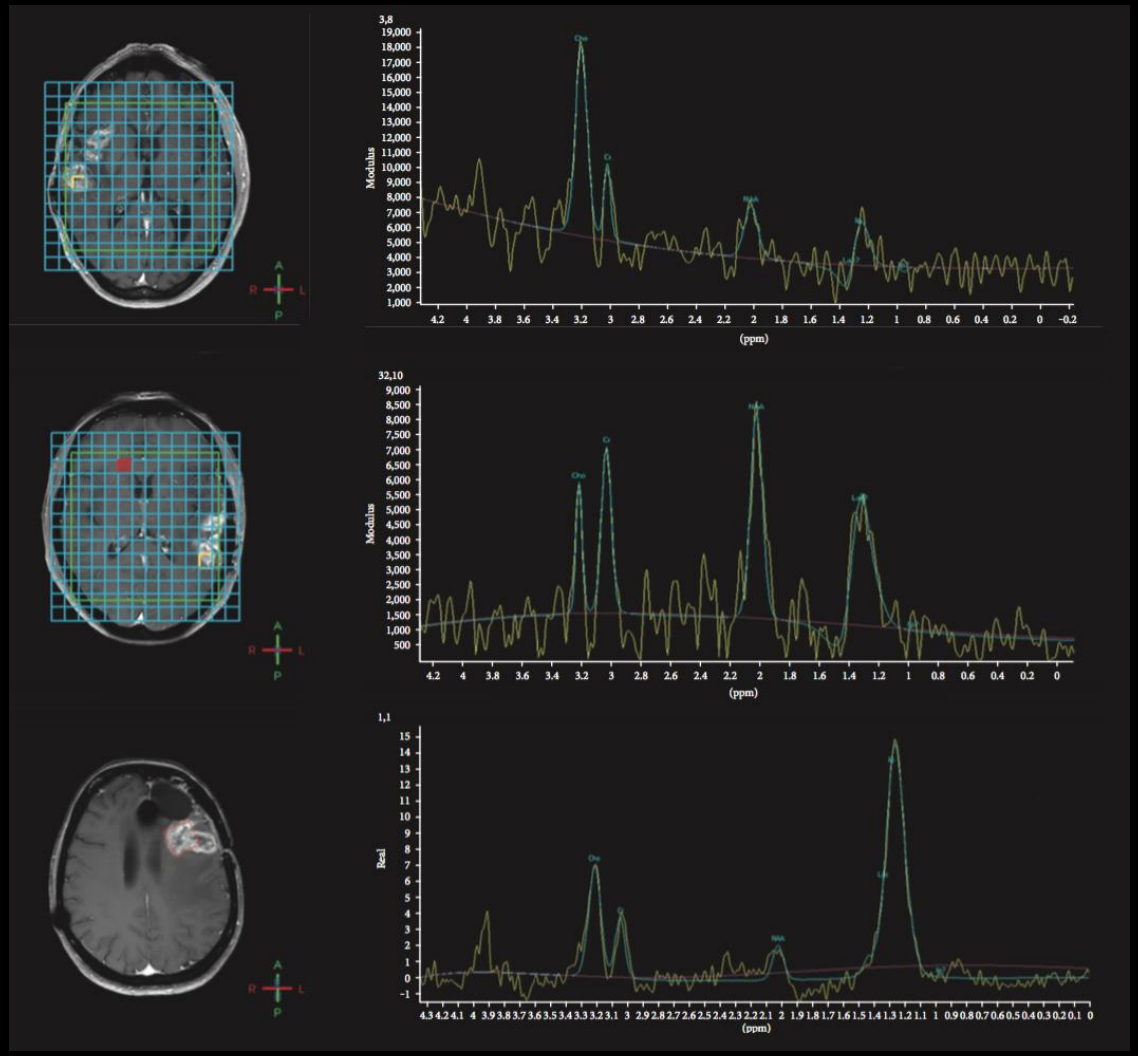
Partial discrepancy between c.e. and CBV; high Ktrans; <u>ADC restriction:</u> TUMOR and/or INFLAMMATORY EFFECTS?

MRS

True progression
after surgery and Stupp

PSEUDOPROGRESSION or
RADIONECROSIS *

MIX
GLIOMA + RADIONECROSIS



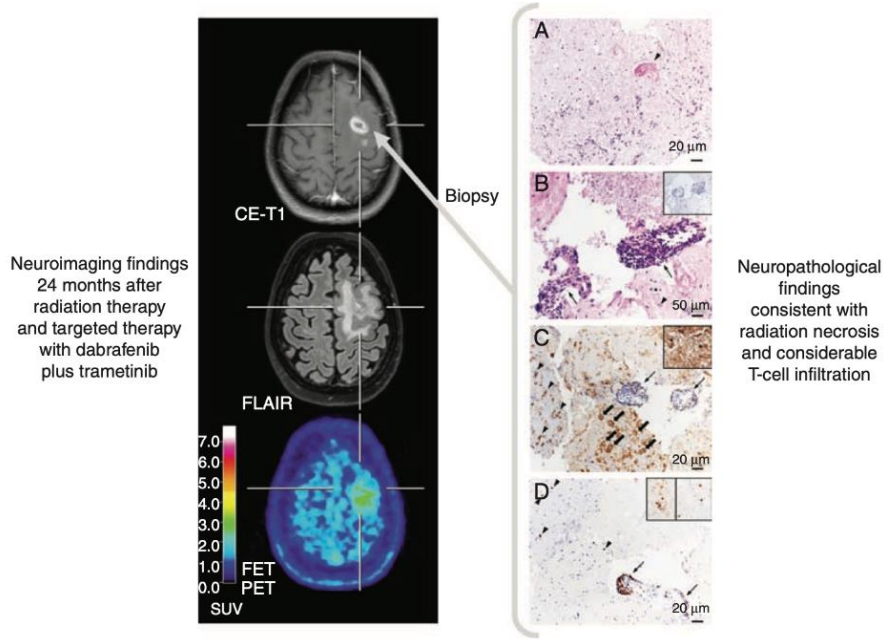
Lipids without Choline increase

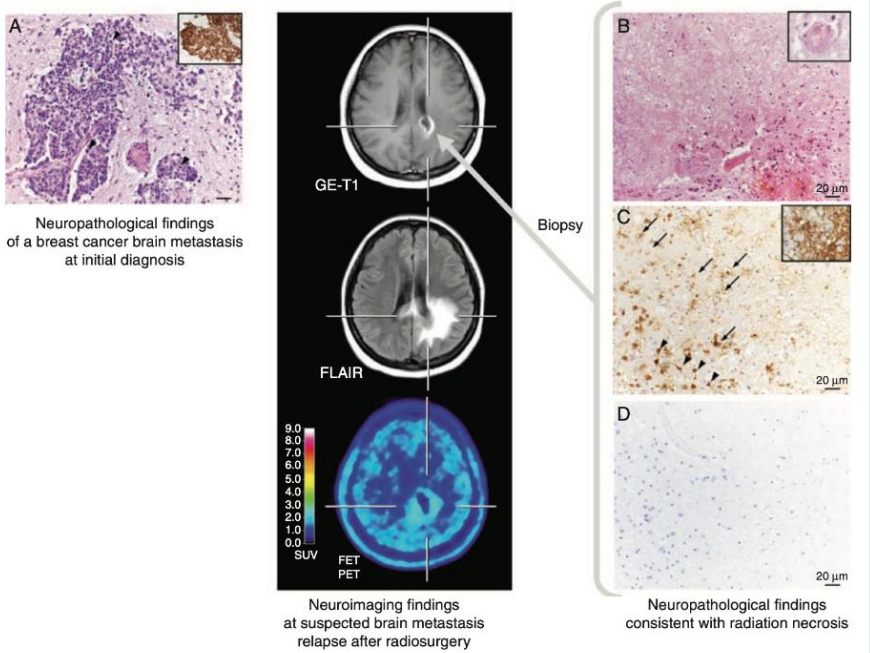
Aquino et al – J Immunology Research 2017

Neuro-Oncology
22(1), 17–30, 2020 | doi:10.1093/neuonc/noz147 | Advance Access date 22 August 2019

Imaging challenges of immunotherapy and targeted therapy in patients with brain metastases: response, progression, and pseudoprogression

Norbert Galldiks, Martin Kocher, Garry Ceccon, Jan-Michael Werner, Anna Brunn, Martina Deckert, Whitney B. Pope, Riccardo Soffietti, Emilie Le Rhun, Michael Weller, Jörg C. Tonn, Gereon R. Fink, and Karl-Josef Langen





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Fondazione I.R.C.C.S. Istituto Neurologico Carlo Besta

FOLLOW-UP IN NEURO-ONCOLOGY

- **MRI is the main imaging modality**
- Minimum sequences required:
  - Pre-contrast T1, T2-FLAIR
  - Post-contrast T1, with two orthogonal planes (or a volume acquisition) recommended
  - slice thickness ≤5 mm with no gap is recommended
- **Advanced imaging methods may be helpful to characterize microscopic tissue:**
  - TRAMs
  - Perfusion (DSC, DCE, pCASL)
  - Diffusion (DWI, ADC)
  - MR Spectroscopy (H-MRS)
- Eventual FET- and MET-Positron Emission Tomography

TAKE HOME POINTS

- Do not over-interpret the MRI findings without an accurate and complete therapy history
- **Pseudoprogression does not affect management: treatment is mantained if the patient remains clinically stable**

- Advanced MR imaging should help:
  - CBV valuable to evaluate questionable suspect pseudoprogression
  - DWI valuable in evaluating response to IT
  - MRS identifies glioma within treatment-induced alterations
  - TRAMs are user-independent and have the potential to separate tumor from radiation necrosis and/or inflammatory response
  - Evaluation of parameters' **MODIFICATIONS OVER TIME**
  - **MIXED SCENARIOS ARE CHALLENGING**
- Advice to repeat the MR after 2 months

VOLUME 28 · NUMBER 11 · APRIL 10 2010

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

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

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

Patrick Y. Wen, David R. Macdonald, David A. Reardon, Timothy F. Cloughesy, A. Gregory Sorensen, Evanthia Galanis, John DeGroot, Wolfgang Wick, Mark R. Gilbert, Andrew B. Lassman, Christina Tsien, Tom Mikkelsen, Eric T. Wong, Marc C. Chamberlain, Roger Stupp, Kathleen R. Lamborn, Michael A. Vogelbaum, Martin J. van den Bent, and Susan M. Chang

- Both enhancing and non-enhancing (T2/FLAIR) disease
- More specific about what is quantified
- Consider steroids and clinical status
- Consider "pseudo" effects
- Responses confirmation (retrospective allowed in clinical trials)

Table 1. Summary of current response criteria.

Criterion	RECIST	MacDonald	RANO
Measurement	1D contrast enhancement	2D contrast enhancement	2D contrast enhancement + T2/FLAIR
Progression	≥20% increase in sum of lesions	≥25% increase in product of perpendicular diameter	≥25% increase in product of perpendicular diameter
Response	≥30% decrease in sum of lesions	≥50% decrease in product of perpendicular diameter	≥50% decrease in product of perpendicular diameter
Durability of response	Optional	Yes (at least 4 week)	Yes (at least 4 week)
Definition of measurability	Yes	No	Yes
Number of target lesions	Up to 5	None specified	Up to 5
T2/FLAIR	Not evaluated	Not evaluated	Evaluated
Corticosteroids considered	No	Yes	Yes
Clinical status considered	No	Yes	Yes
Pseudo-progression considered	No	No	Yes

RANO: Response Assessment in Neuro-Oncology; RECIST: Response Evaluation Criteria in Solid Tumors.

CNSOncol.(2019)8(1),CNS28

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Criterion	RANO
Measurement	2D contrast enhancement + T2/FLAIR
Progression	≥25% increase in product of perpendicular diameter
Response	≥50% decrease in product of perpendicular diameter
Durability of response	Yes (at least 4 week)
Definition of measurability	Yes
Number of target lesions	Up to 5
T2/FLAIR	Evaluated
Corticosteroids considered	Yes
Clinical status considered	Yes
Pseudo-progression considered	Yes

WHAT IS QUANTIFIABLE ?

- **MEASURABLE** lesions (TARGET)
  - Contrast enhancing
  - Two perpendicular diameters ≥10mm
  - Exclude large cystic/necrotic areas & surgical cavities
  - Multiple lesions: sum of products of diameters of up to five largest lesions (SPD)

- **NON-MEASURABLE** lesions
  - Do not enhance (seen only on T2/FLAIR)
  - Too small
  - Poorly defined margin

2D measurement of T1 enhancing lesion

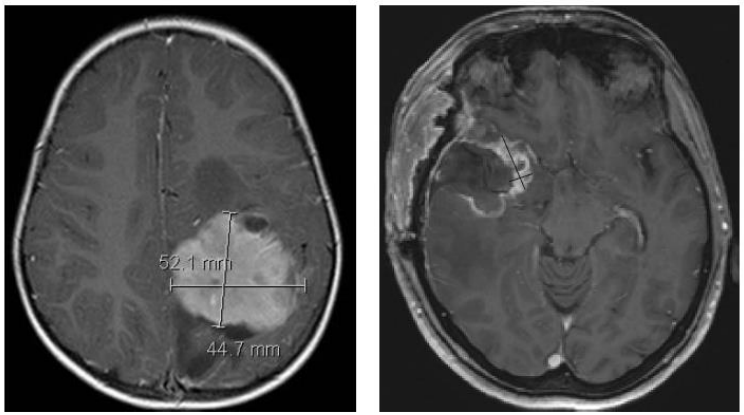


Table 2. Criteria for response assessment incorporating MRI and clinical factors.

Criterion	CR	PR	SD	PD
T1-Gd +	None	≥50% ↓	<50% ↓ to <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[‡]
Summary of HGG response criteria	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have achieved CR; the best response possible is SD	Requires all of the following: ≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically	Requires all of the following: Does not qualify for CR, PR or progression; stable nonenhancing (T2/FLAIR) lesions on the same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show SD will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose	Defined by any of the following: ≥25% increase in the sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response on stable or increasing doses of corticosteroids[†]; significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy[†] not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease

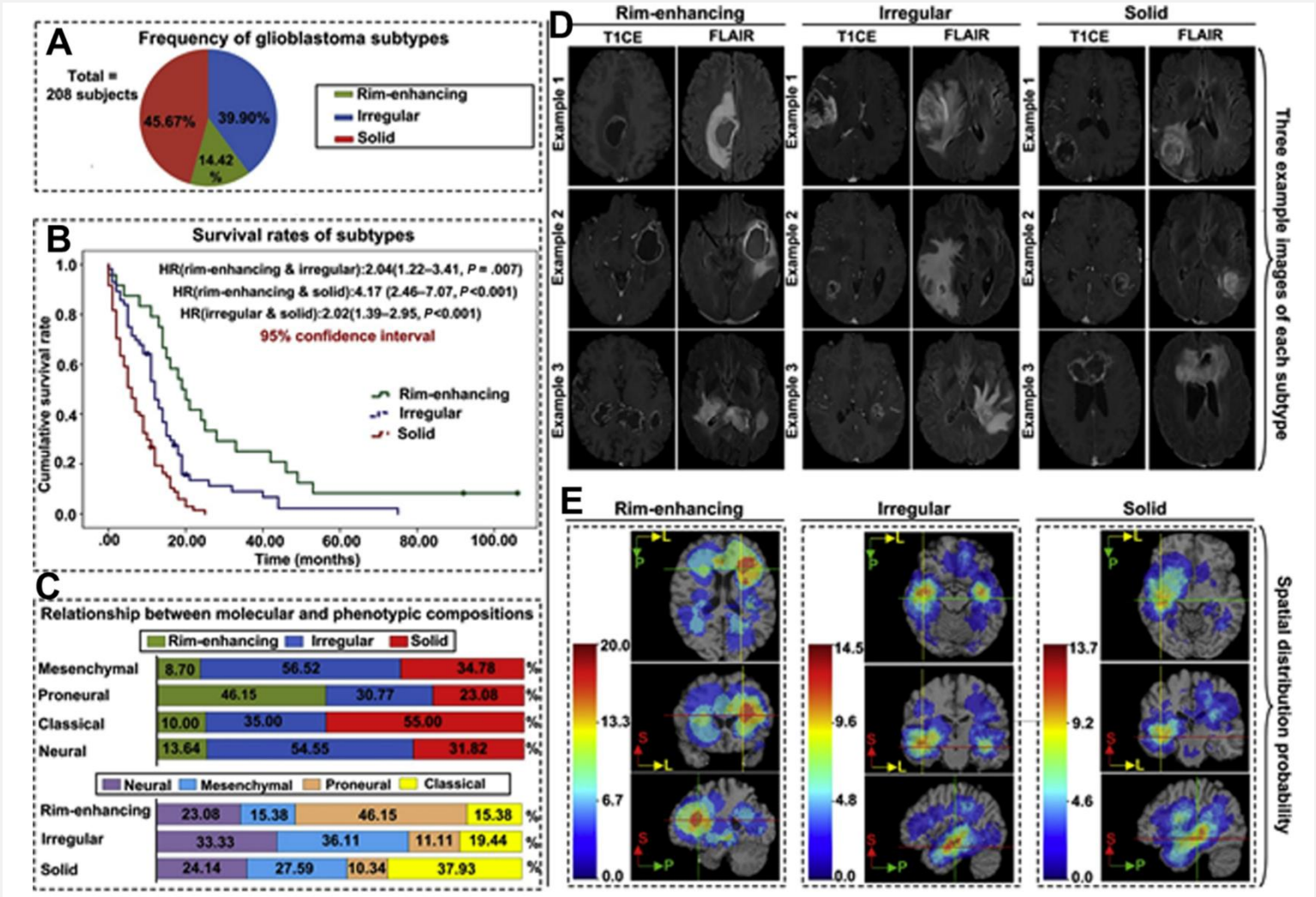
CNSOncol.(2019)8(1),CNS28

"*IMAGES ARE MORE THAN PICTURES, THEY ARE DATA*".

GILLIES RJ RADIOLOGY

Radiogenomics

RADIOGENOMICS



Badve C Radiol Clin N Am 59 (2021)

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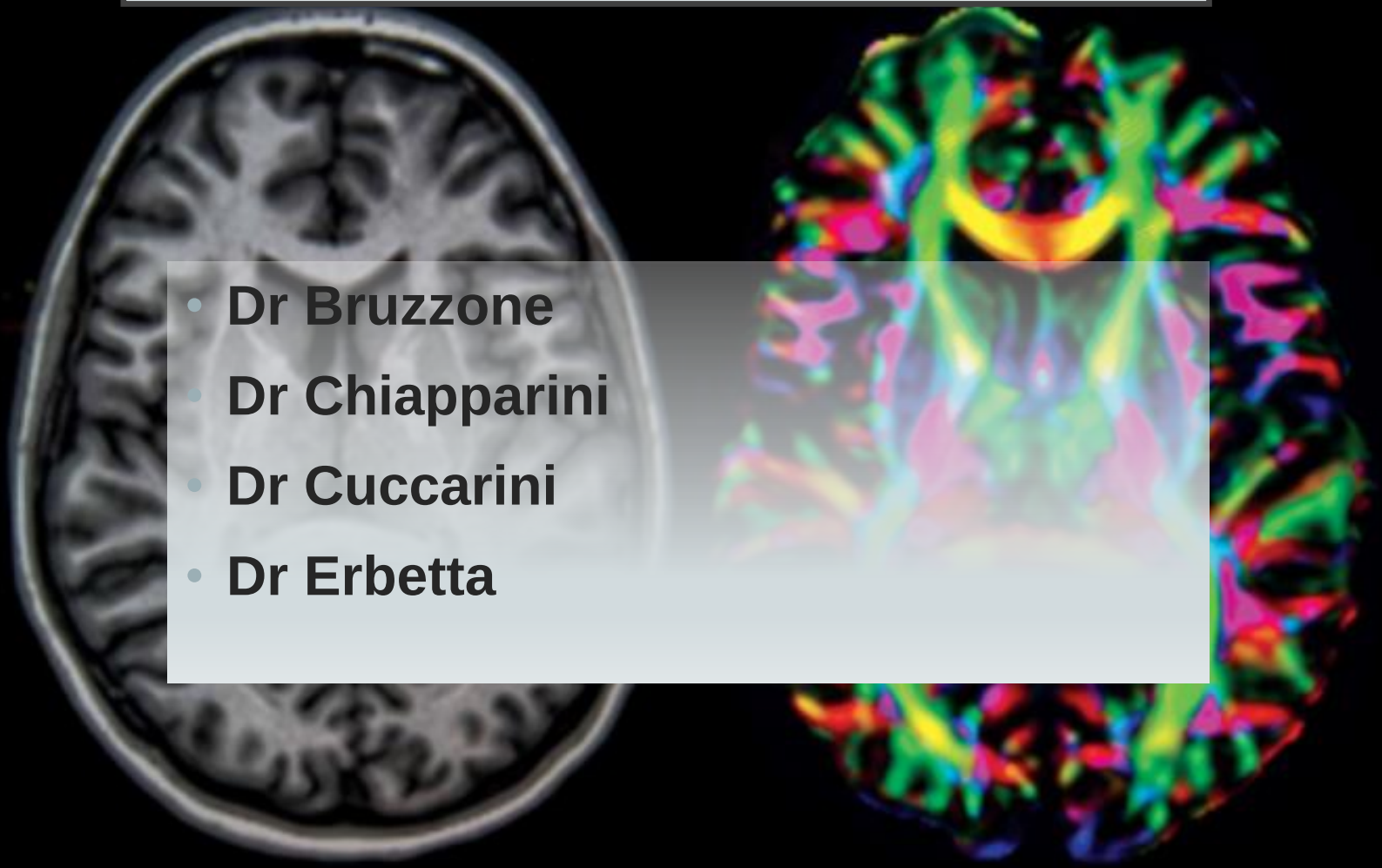

- Dr Bruzzone
- Dr Chiapparini
- Dr Cuccarini
- Dr Erbetta

Grazie per l'attenzione

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