Edinburgh 2012

20th Advance Course

"Multimodality imaging of brain tumours: High Grade Brain Tumours"

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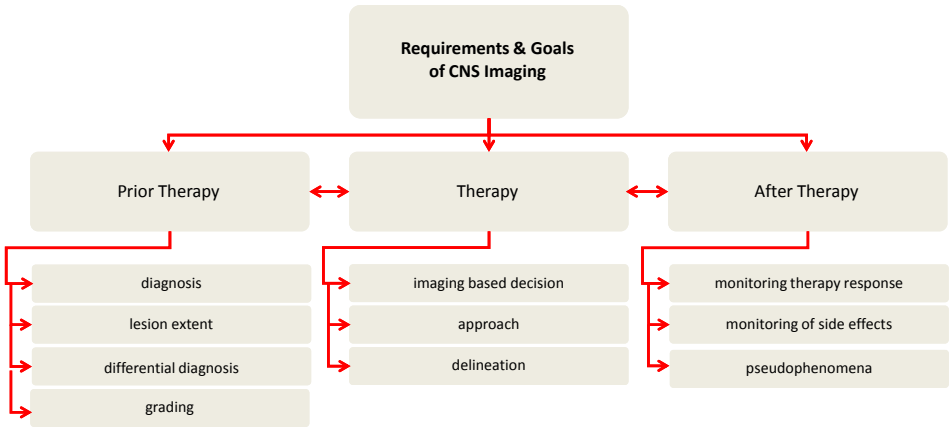
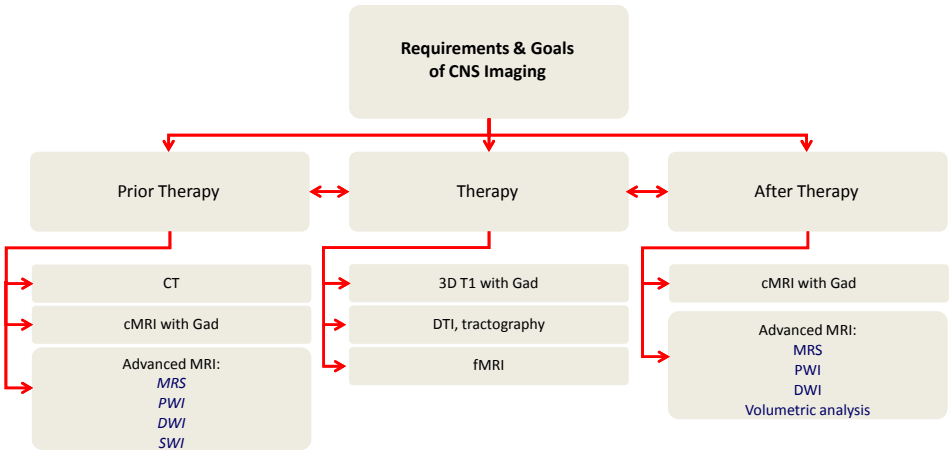
Requirements & Goals of CNS Imaging
Tumor *imaging in clinical practice*

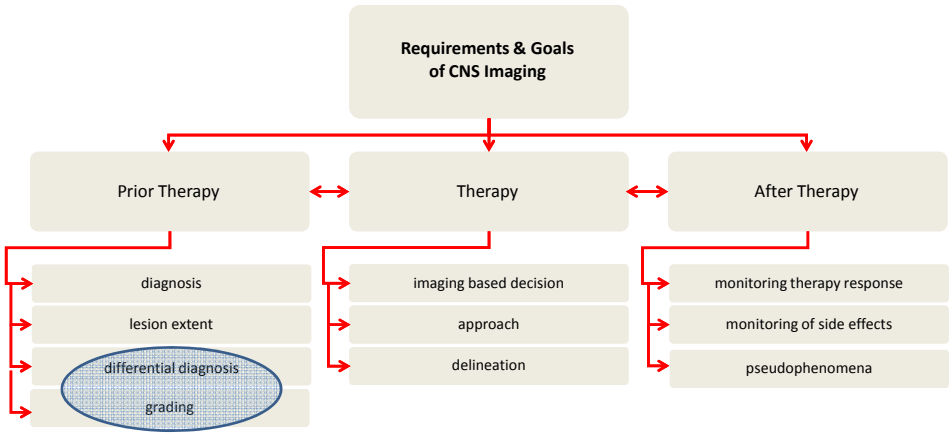


Modified from M. Essig

Requirements & Goals of CNS Imaging
Tumor imaging in clinical practice



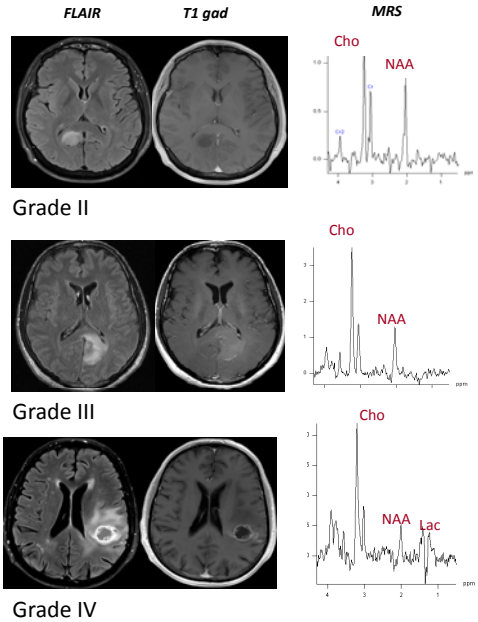
Requirements & Goals of CNS Imaging
Tumor imaging in clinical practice



Modified from M. Essig

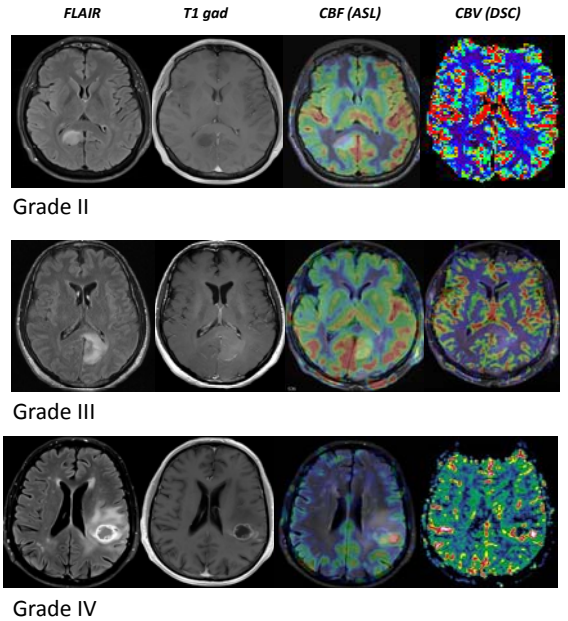
Proton MR spectroscopy

Astrocytomas grade II, III and IV

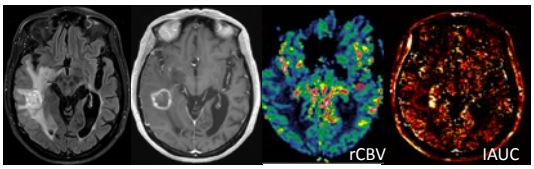


Perfusion-weighted MR imaging

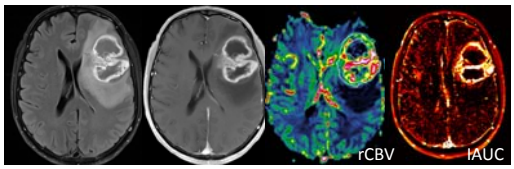
Astrocytomas grade II, III and IV



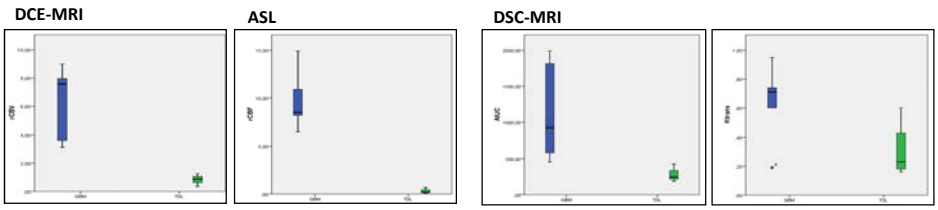
TDLs



HGG



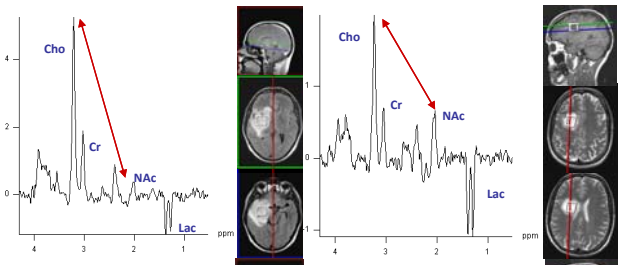
	Mean (sd) rCBF	Mean (sd) rCBV	Mean (sd) IAUC	Mean (sd) Ktrans
TDLs	0.32 (0.31)	0.83 (0.45)	276.7 (104)	0.3050 (0.200)
HGG	9.80 (3.24)	6.25 (2.68)	1155.6 (707)	0.638 (0.280)



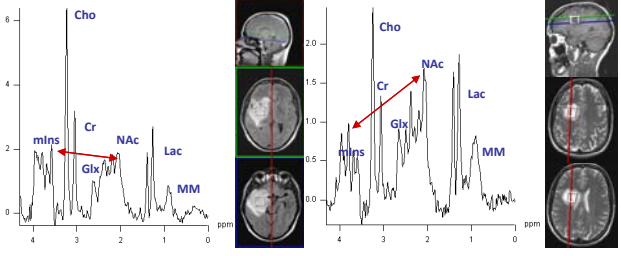
rCBV rCBF IAUC Ktrans

Grade III MS

Long TE

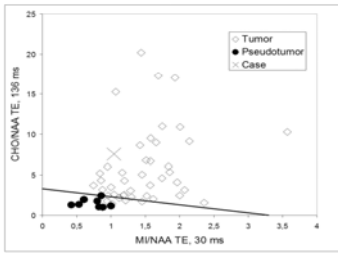


Short TE



NAc / Cho pseudotumoral > tumors (long TE)

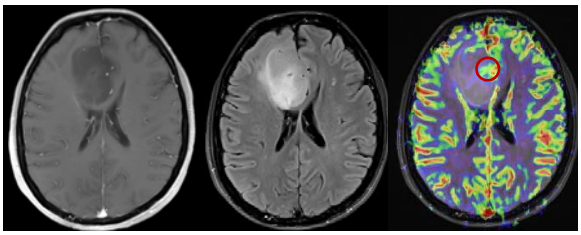
mIns / NAc tumors > pseudotumoral (short TE)

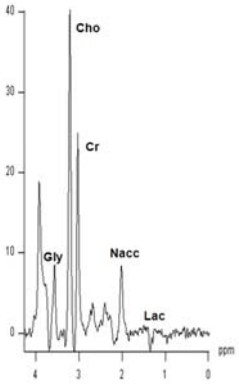


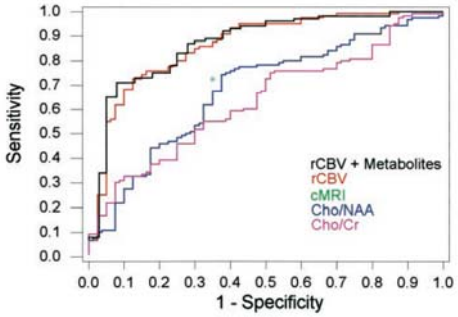
Majós et al. *Am J Neuroradiol 2009*

Glioma grading

Combined rCBV and MRS





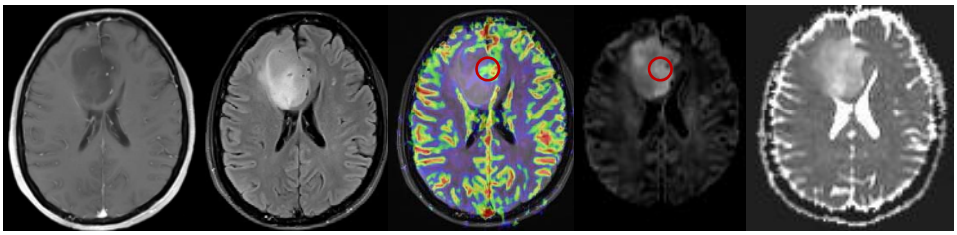


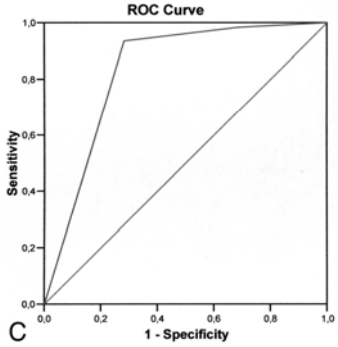
rCBV threshold values: 1.75

Law et al. Am J Neuroradiol 2003

Glioma grading

Combined rCBV and ADC





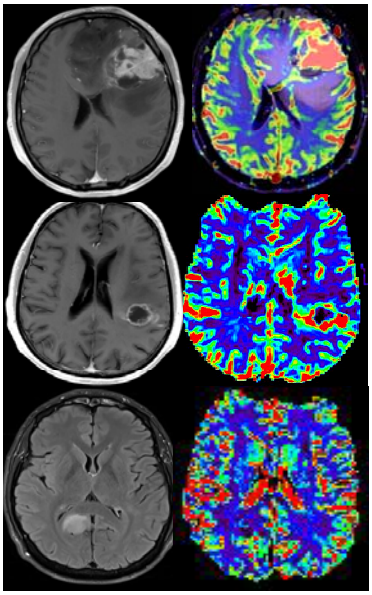
differentiation of high-grade from low grade gliomas

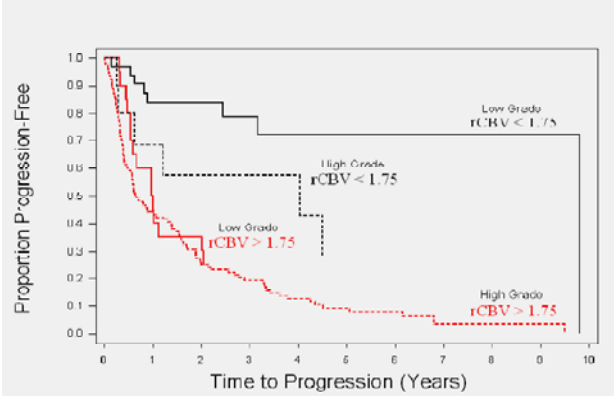
	Sensitivity	Specificity	PPV	NPV
Max rCBV ≥ 1.74	94.4%	50.0%	88%	69.6%
Min ADC ≤ 1.185	97.6%	53.1%	89%	85%
Max rCBV ≥ 1.74 OR Min ADC ≤ 1.185	98.4%	31.3%	84.7%	83.3%
Max rCBV ≥ 1.74 AND Min ADC ≤ 1.185	93.5%	71.9%	92.8%	74.2%

Hilario et al. Am J Neuroradiol 2012

Perfusion-weighted imaging (DSC)

Prognostic value

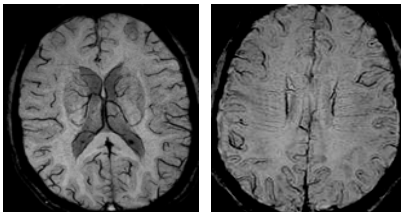




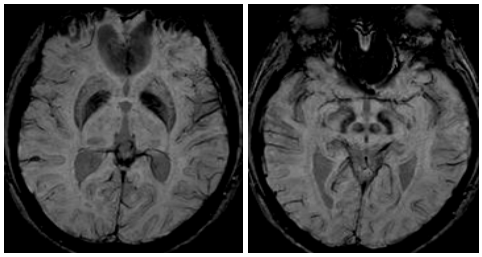
Law et al. Radiology 2008

Susceptibility-weighted images (SWI)

- Source of contrast: mostly deoxygenated blood (veins) and iron



[deOxihemoglobin]



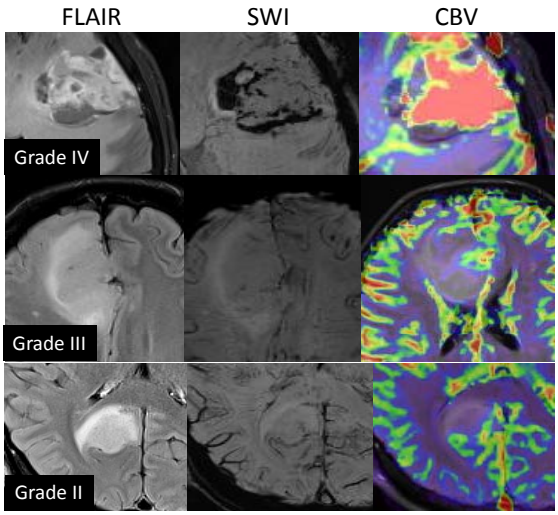
[iron]

SWI in astrocytoma
Intratumoral susceptibility signal (ITSS)

ITSSs prevalence

- 100% of GBM
- 43% of anaplastic astrocytoma
- 0% of low grade glioma

Park et al. AJNR 2009

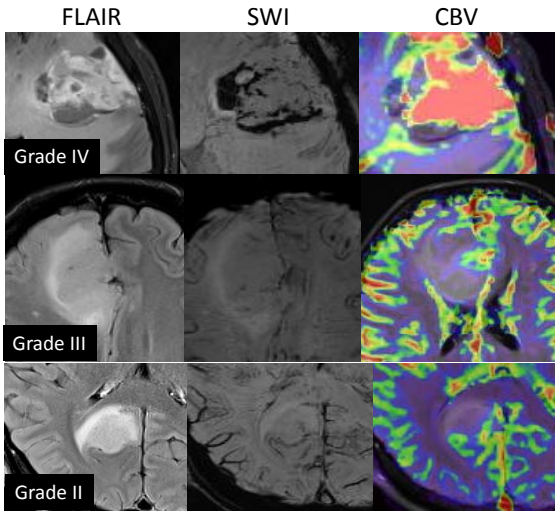


SWI in astrocytoma
Intratumoral susceptibility signal (ITSS)

ITSSs type

- •GBM: Conglomerated, mixed (linear and dotlike)
- •Grade III: fine linear

Park et al. AJNR 2009

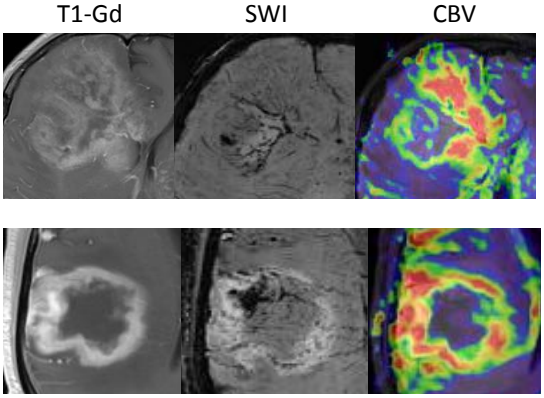


SWI in astrocytoma

Intratumoral susceptibility signal (ITSS)

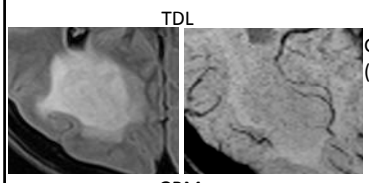
Pattern of ITSS in GBMs (inner portion of CE rim)

- Fine, linear
  - Related to ↑CBV
  - Tumor vascularity (angiogenesis)
- Densely packed
  - Not related to ↑CBV
  - Macro-micronecrosis

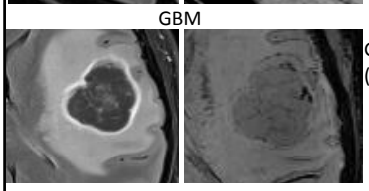


SWI in solitary enhancing lesions

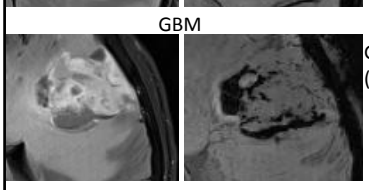
Intratumoral susceptibility signal (ITSS)



Grade I
(no ITSS)



Grade II
(1-10 dotlike, fine linear)



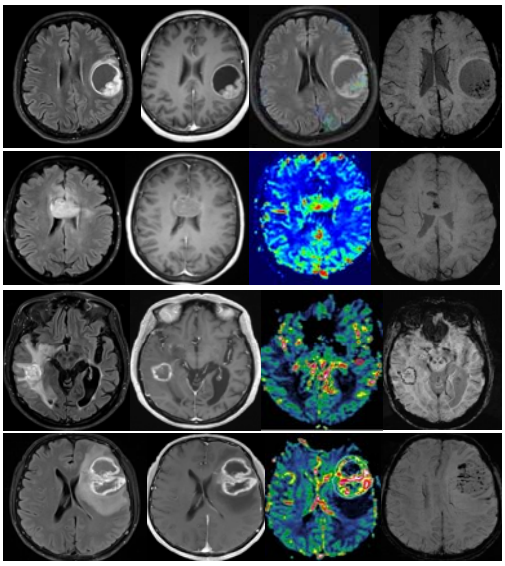
Grade III
(>10 dotlike, packed)

Pathologic Diagnosis	ITSS Degree		
	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
GBM	0/25 (0)	4/25 (16)	21/25 (84)
AA	3/5 (60)	2/5 (40)	0/5 (0)
Metastasis	4/15 (27)	5/15 (33)	6/15 (40)
Lymphoma	7/7 (100)	0/7 (0)	0/7 (0)
MS	3/3 (100)	0/3 (0)	0/3 (0)
Granuloma	9/9 (100)	0/9 (0)	0/9 (0)

Kim et al. AJNR 2009

SWI in solitary enhancing lesions

Intralesional signals

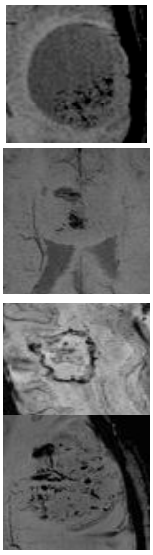


Grade III metastasis

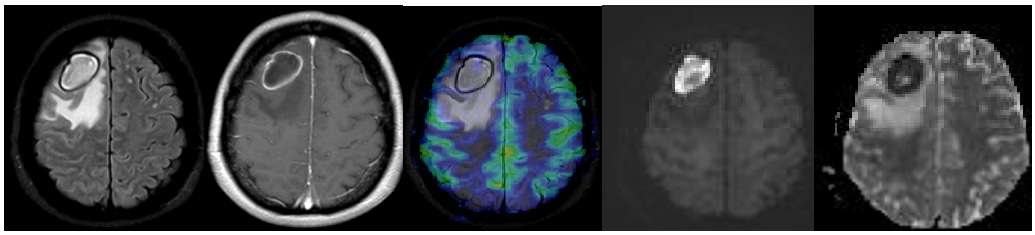
Grade II Lymphoma

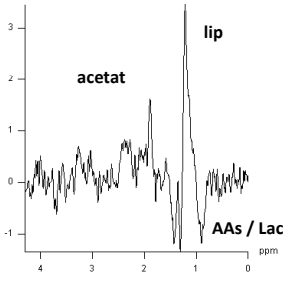
Grade II TDL

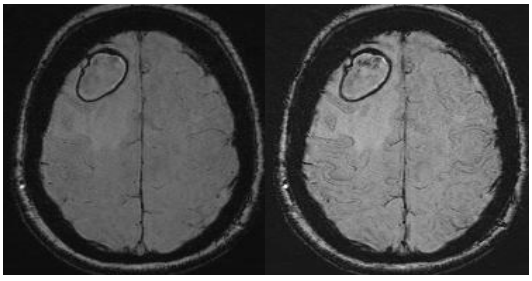
Grade III GBM



SWI in brain abscess

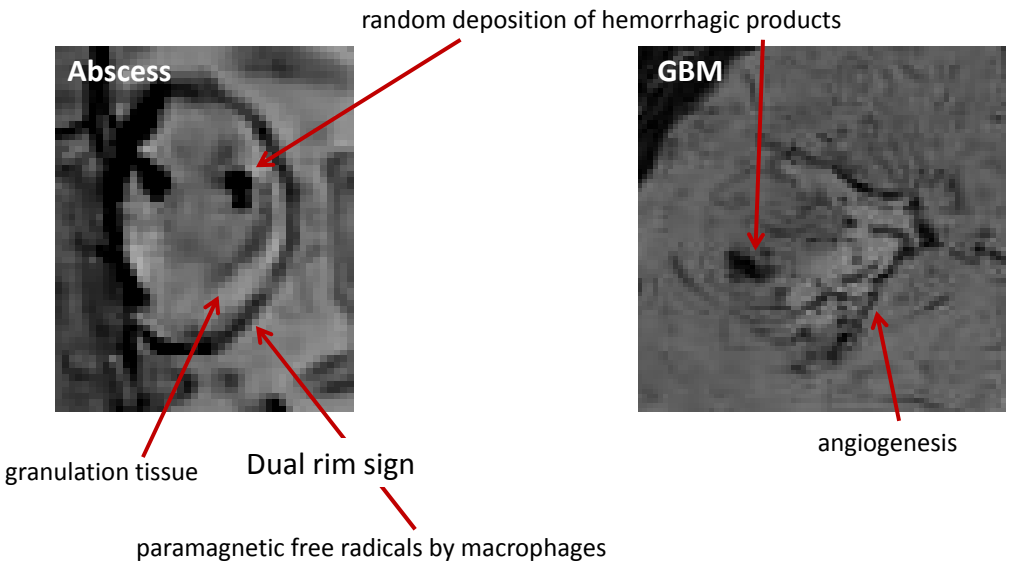






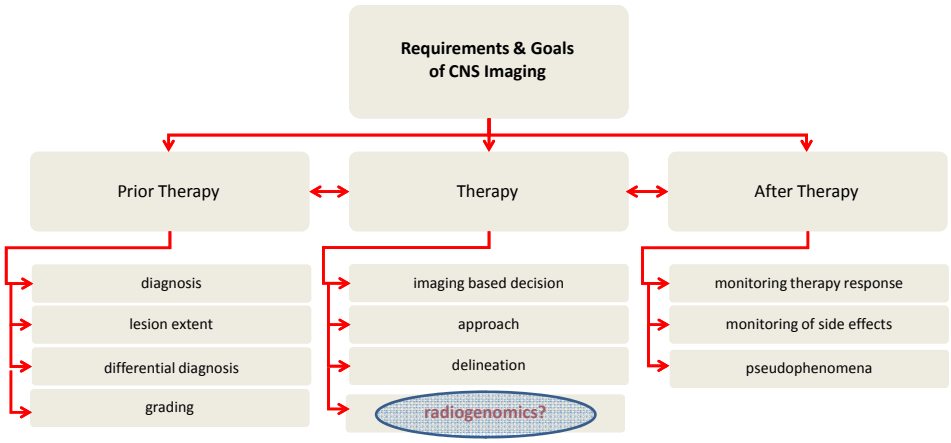
Dual rim sign in pyogenic abscess *(Toh et al. AJNR 2012)*

SWI in brain abscess and GBM Interpretation



Requirements & Goals of CNS Imaging

Tumor *imaging: future?*



Modified from M. Essig

Gliomas

Diagnosis

- Conventional diagnosis: morphological and architectural features
- Significant interobserver variability
- Heterogeneity in prognosis and in therapeutic response

- Additional markers are required (genomics, imaging)!!!

•Refined and objective classification
•Predictor of prognosis
•Tailored therapeuthic decision-making

Glioblastoma multiforme

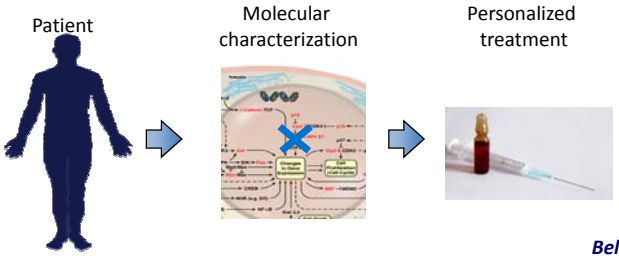
Genetics

- Genetic alterations
  - *Mutations*
  - *Amplifications*
  - *Deletions*
- Gen expression

Influence in tumor biology

↕

Influence in imaging features

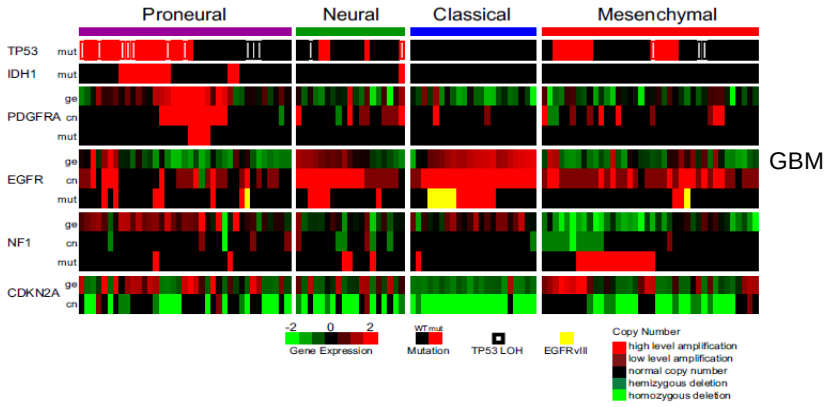


Belden et al. Radiographics 2011
Riemenschneider et al. Acta Neuropathol 2010
Verhaak et al. Cancer Cell 2010

Glioblastomas

Classification based on gene expression profile

signaling pathways: RTK/P13K/PTEN; P53; RB1



Verhaak et al. Cancer Cell 2010

Associations Between MR Imaging and Genomic Features of Glioblastomas

Purpose

- To advance the understanding of the molecular basis of cancer through the application of genome analysis technologies, histopathology, and imaging.
- To identify imaging features of primary glioblastomas that may predict genomic features, including mutation status and gene expression.

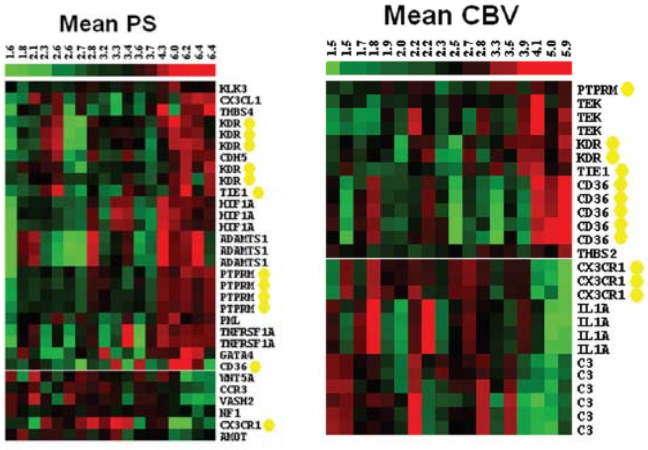
•Predic prognosis and treatment response
•Personalized treatment

Glioblastoma
Tumor biology and imaging

- **Angiogenesis**
  Leaky and inefficient vessels: Gd+ and edema; rCBV
  (partially vs complete enhancing tumors)
- **Cell proliferation**
  Mass effect, Cho, diffusivity
- **Cell invasion** (adhesion, EC matrix remodeling, migration, immune modulation)
  Extensive infiltrating T2 changes beyond Gd (not edema)
  (infiltrating pattern of glioblastoma)
- **Cell survival and antiapoptosis**
  Necrosis

Belden et al. RadioGraphics 2011

Radiogenomics in High grade gliomas
Perfusion parameters and angiogenic gene expression

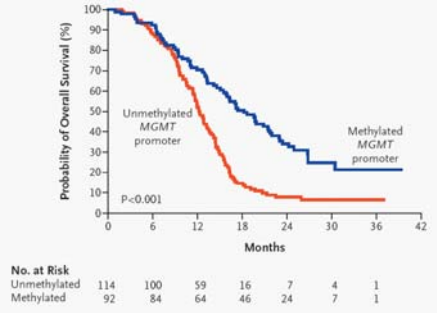


Proangiogenic genes show a positive correlation with tumor perfusion parameters
Perfusion MRI as a biomarker of angiogenic gene expresion?

Jain et al. AJNR 2012

Radiogenomics in High grade gliomas
MGMT repair enzyme

- MGMT repair enzyme of tumor cells (increase tumor cell survival)
- Methylated MGMT inactivates its repair function in cancer cells (50% of GBMs)
- M-MGMT better disease-free survival, better response to TMZ, increase incidence of PsP

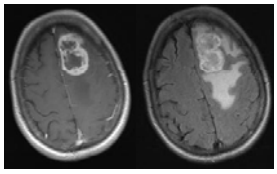


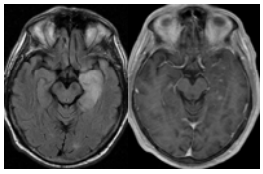
Hegi et al. N Engl J Med 2005

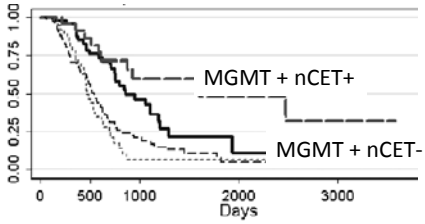
Radiogenomics in High grade gliomas
MGMT repair enzyme

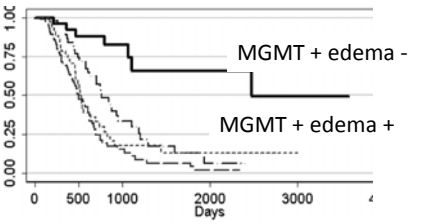
Imaging features have a weak correlation with MGMT promoter

- *Ring enhancement associated with u-MGMT*
  - *M-MGMT without edema better survival*
  - *M-MGMT with nCET better survival*



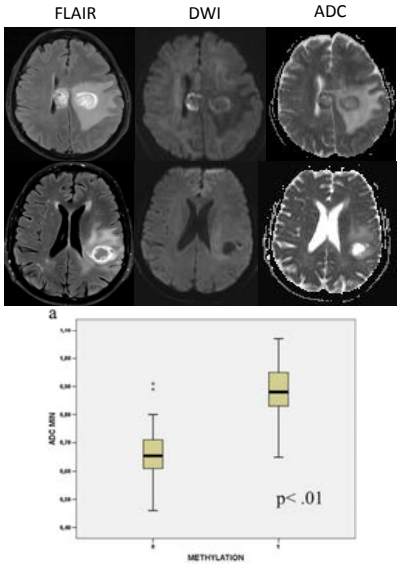




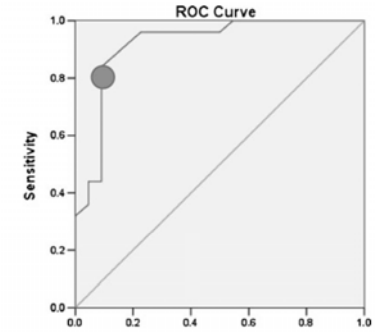


Drabycz et al. Neuroimage 2010
Carrillo et al. AJNR 2012

Radiogenomics in High grade gliomas
ADC and MGMT repair enzyme



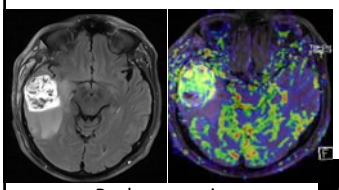
differentiation of methylated from unmethylated gliomas



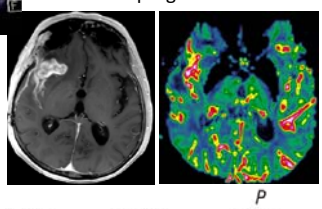
minimum ADC value: 0.80×10-3 mm2/s, sensitivity (84 %) and specificity (91 %)

Romano et al. Eur Radiol 2012

True early Progression vs Pseudoprogression
Diagnostic value of PWI (rCBV)

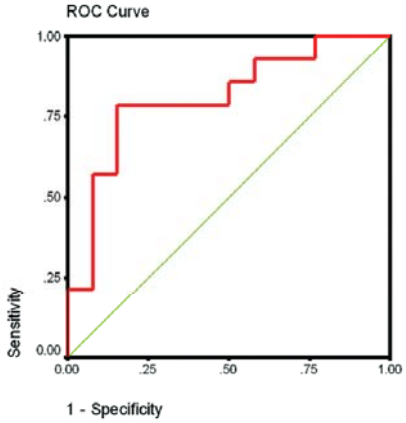


Real progression



Pseudoprogression

	No.	rCBV	95% CI	*P* Value
Unmethylated group	22			.009
Pseudoprogression	4	0.87	0.10–1.63	
Real progression	12	3.25	1.46–5.04	
Methylated group	26			.258
Pseudoprogression	9	1.56	0.57–2.55	
Real progression	7	2.34	1.05–3.61	



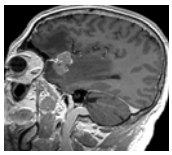
rCBV ratio of 1.49 has an 81.5% sensitivity and 77.8% specificity

Kong et al. Am J Neuroradiol 2011

True early Progression vs Pseudoprogression

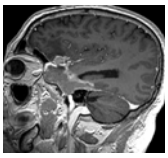
Diagnostic Strategy after concurrent RT/Chemotherapy

Diagnosis & treatment planning

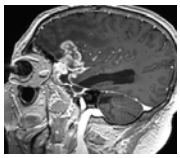


Surgery

Before concurrent RT/TMZ



Before Adjuvant TMZ



Lesion growth

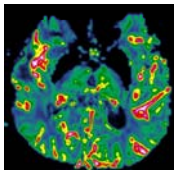
Consider methylation status of the *MGMT promoter gene*

methylated

Consider pseudoprogression

continued TMZ is recommended

unmethylated



Assess rCBV

If the rCBV is >1.47, then the second-line treatment technique should be considered.

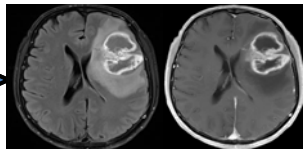
Standardize terminology to describe radiological features

VASARI (Visually AccesSAble Rembrandt Images)

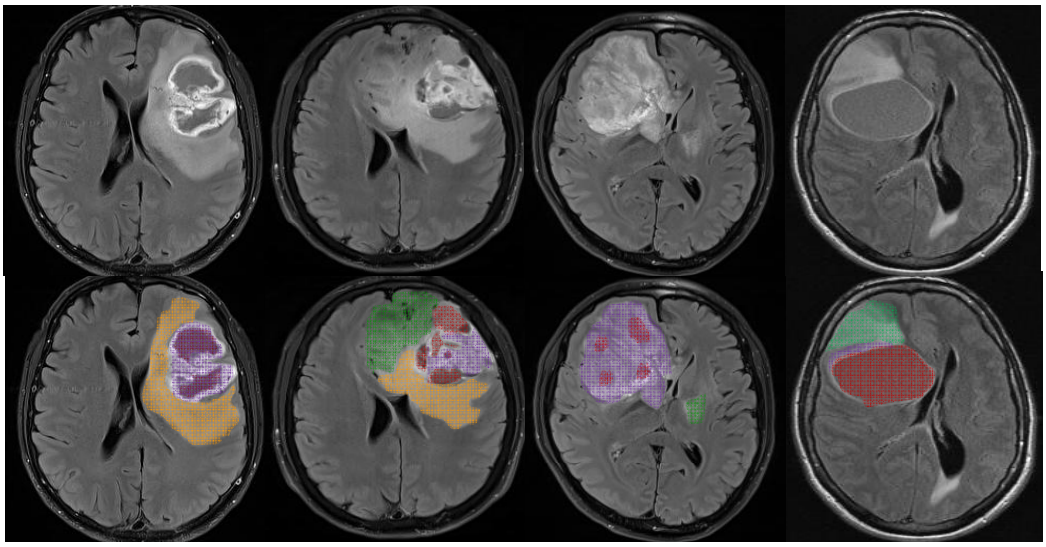
Purpose:

- **Classify the different MR imaging patterns**
- **Establish radiogenomic correlations**

Most common features used to describe primary cerebral neoplasia on standard contrast enhanced MR



- Location
- Size
- Edema
- Mass effect
- CE pattern (enhancing and non-enhancing)
- Margins (circumscribed, infiltrative)
- Necrosis
- Cysts
- Pial/cortical invasion



Non-enhancing tumor → Cell invasion and migration

Edema

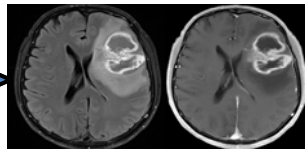
Necrosis / cyst → Cell survival and antiapoptosis

Contrast-enhancement → Angiogenesis

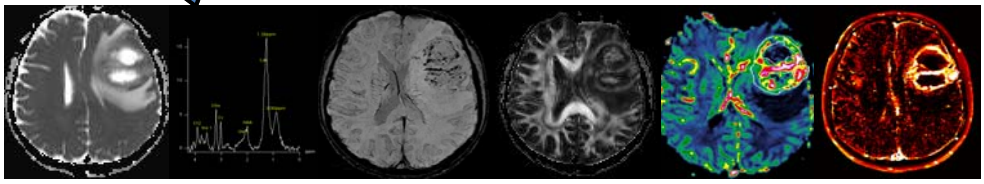
Standardize terminology to describe radiological features

VASARI (**V**isually **A**cces**SA**ble **R**embrandt **I**mages)

Most common features used to describe primary cerebral neoplasia on standard contrast enhanced MR

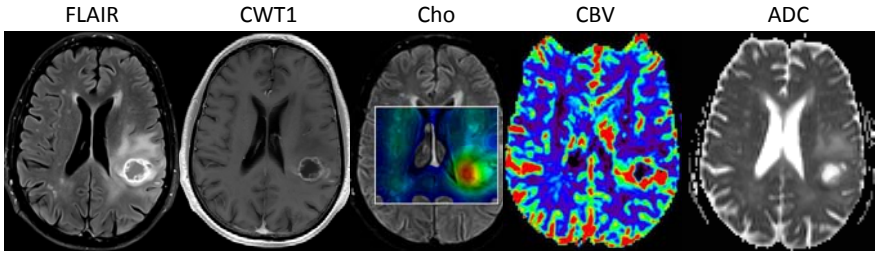


Features based on advanced MR techniques



ADC
MRS
SWI
FA
CBV
PS

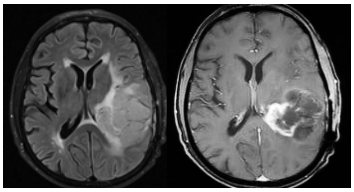
Modern neuroradiological assessment of HGG



MR imaging features
- Infiltrative type
- Mass effect
- Ring-enhancement
- Necrosis
- High Cho
- High rCBV
- Low ADC

Interpretation
- High cell proliferation
- High cell invasion
- Antiapoptosis
- High angiogenesis
- Un-methylated MGMT

Outcome
- Low risk of PsP
- Poor response to RT/Ch
- High risk of early progression



Conclusions

Conventional and advanced MR techniques useful for initial diagnosis and follow-up of focal mass brain lesions

- ❖*Diagnosis*
- ❖*Tumoral vs. non tumoral*
- ❖*Grading*
- ❖*Treatment planning*
- ❖*Response-progression*
- ❖*Pseudophenomena: pseudoprogression / radiation necrosis / pseudoresponse*
- ❖***Radiogenomics?***