

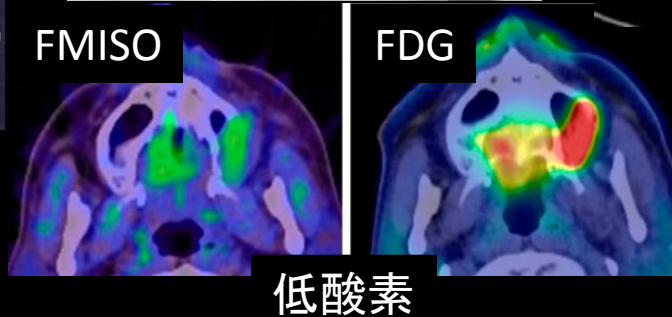
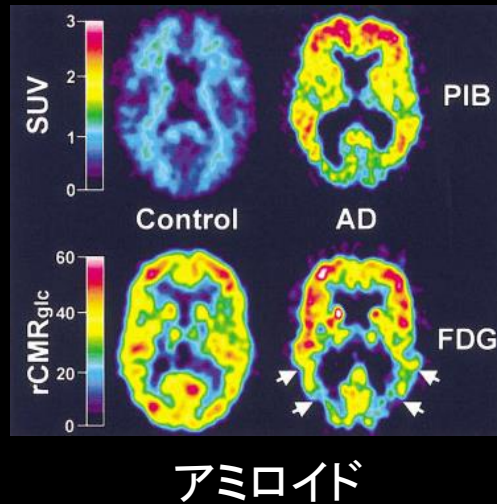
知っておきたい 新しいMR分子画像法

鹿児島大学大学院医歯学総合研究科
放射線診断治療学分野

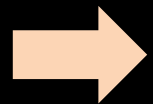
吉浦 敬

分子イメージング

生体分子の検出、機能の画像化 がん、認知症



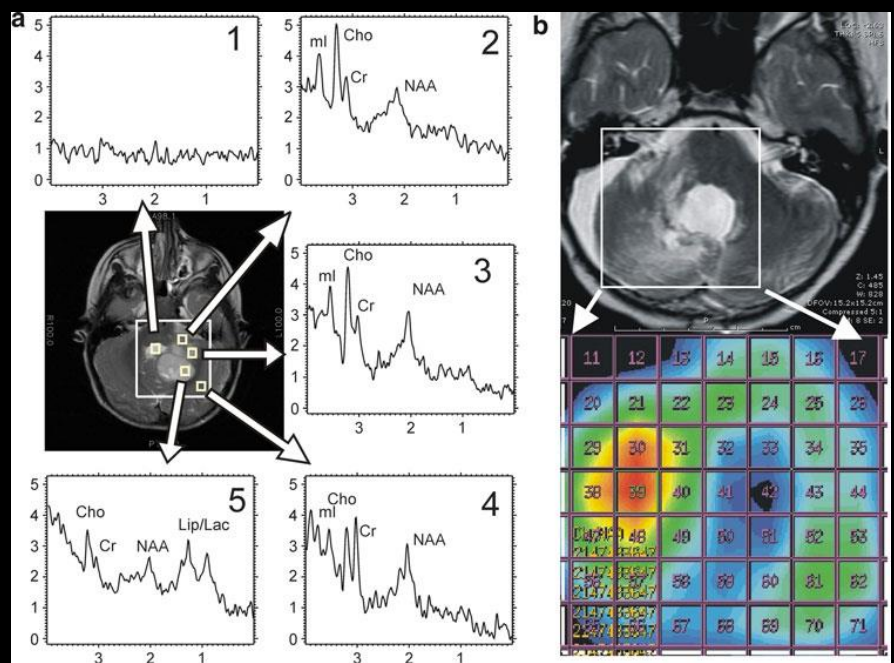
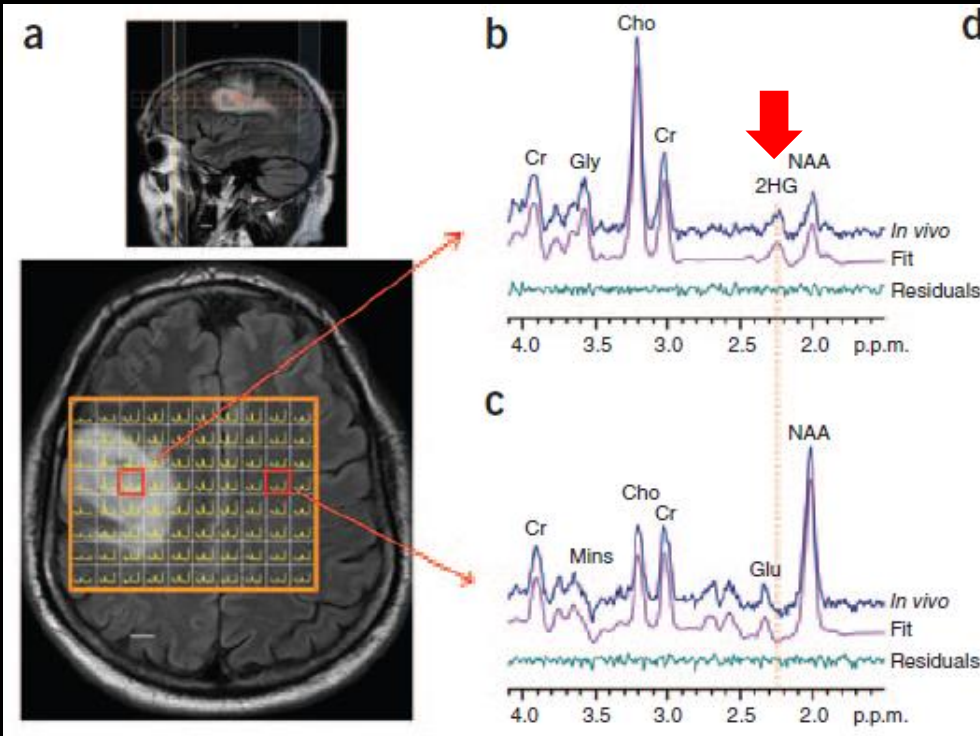
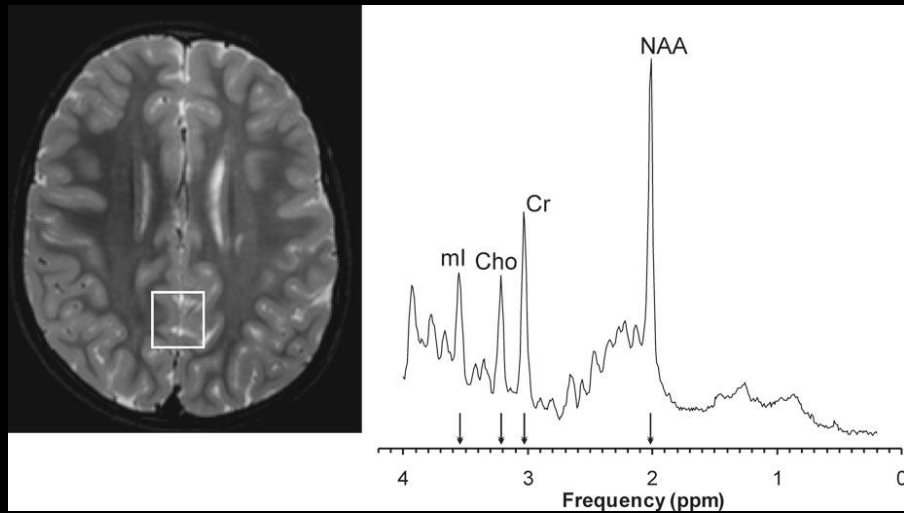
これまでPETが中心



高分解能、被ばくがなく、普及しやすいMRIによる
分子イメージングへの期待

感度が低いことが問題点

MRIによる分子イメージング



Choi C, et al. Nat Med 2012

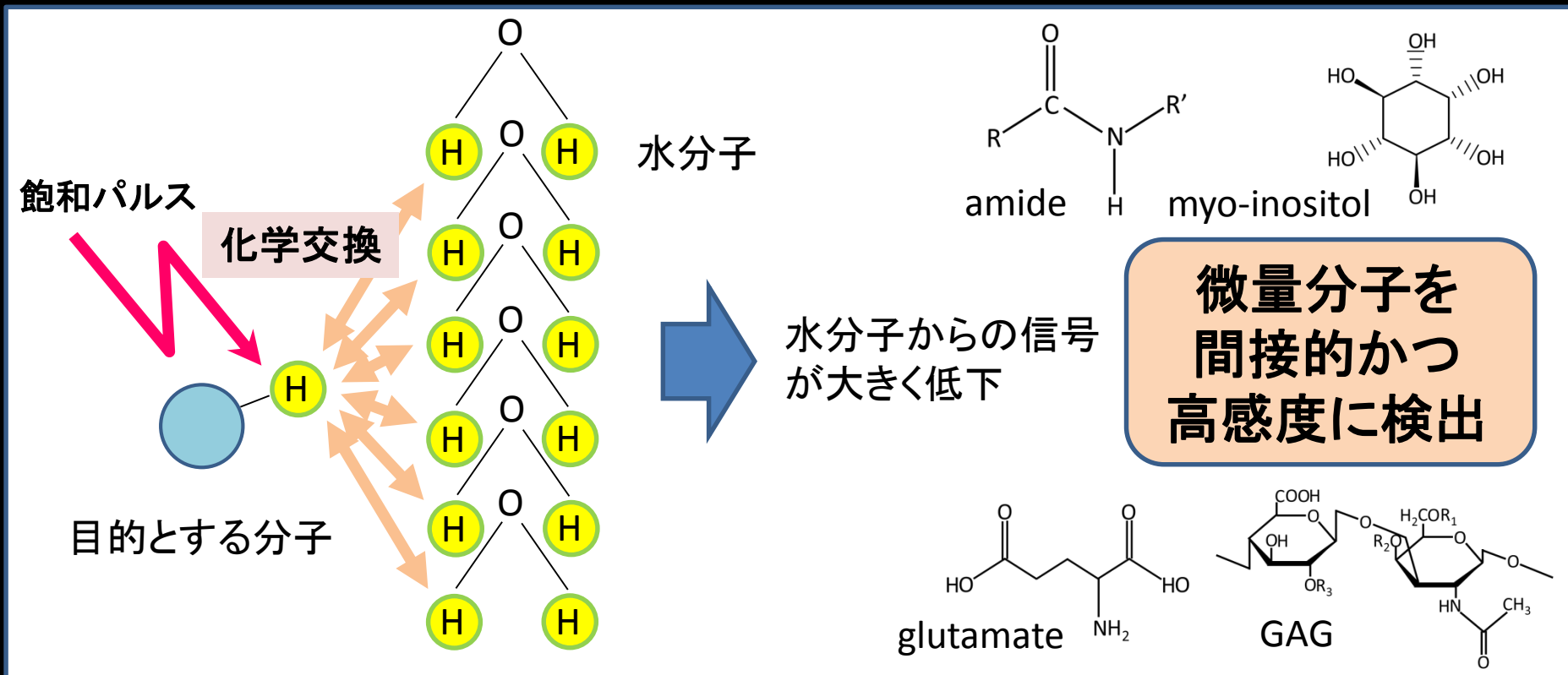
Blüml S, et al. MR spectroscopy of Pediatric Brain disorders

Chemical Exchange Saturation Transfer (CEST)

- 新規MR画像コントラスト
(Ward and Balaban 2000)
- 溶質と水分子のプロトン交換に基づく
-NH(アミド), -OH(ヒドロキシル)
- 低濃度分子の検出

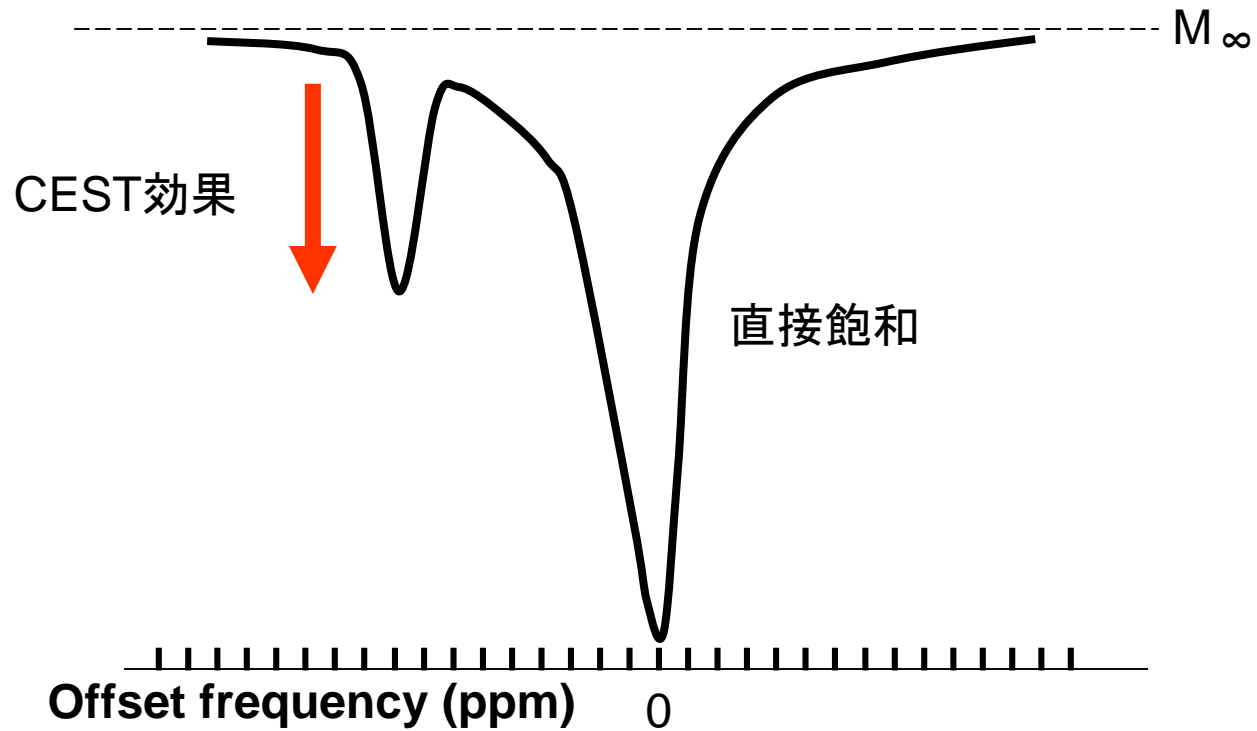
CESTイメージング

Chemical Exchange Saturation Transfer



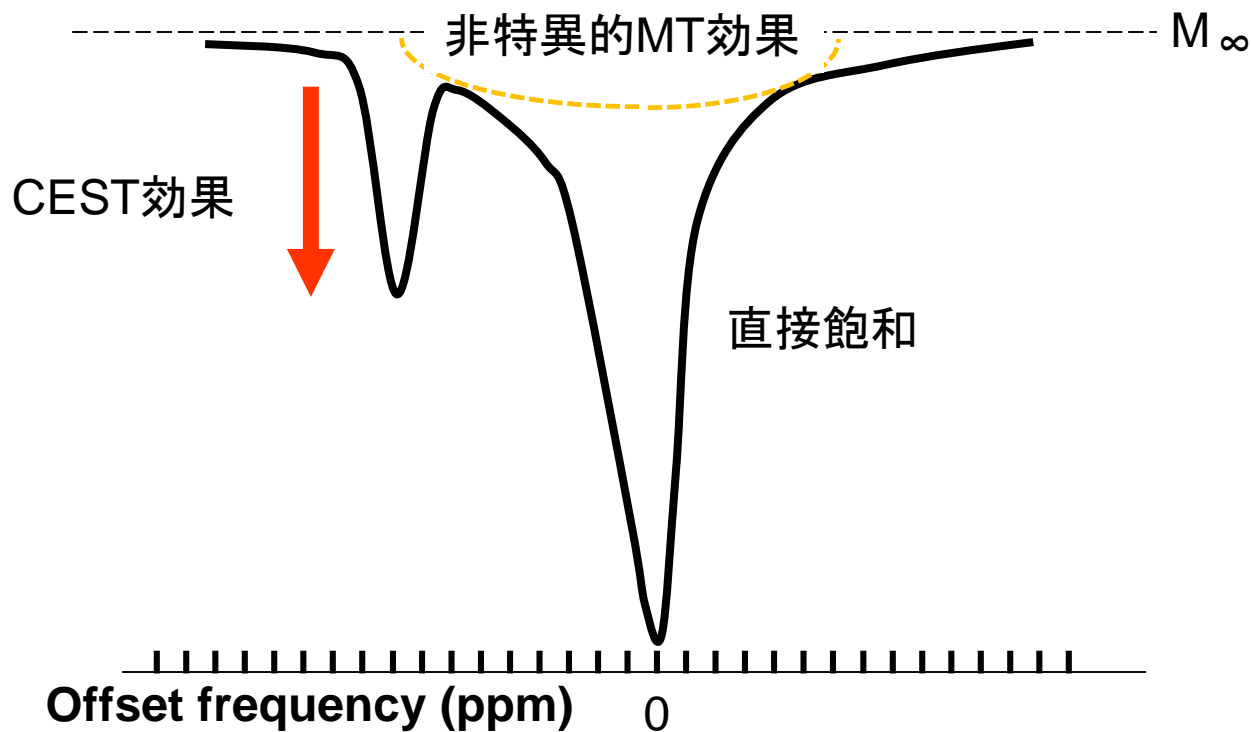
CESTイメージング

Z-spectrum



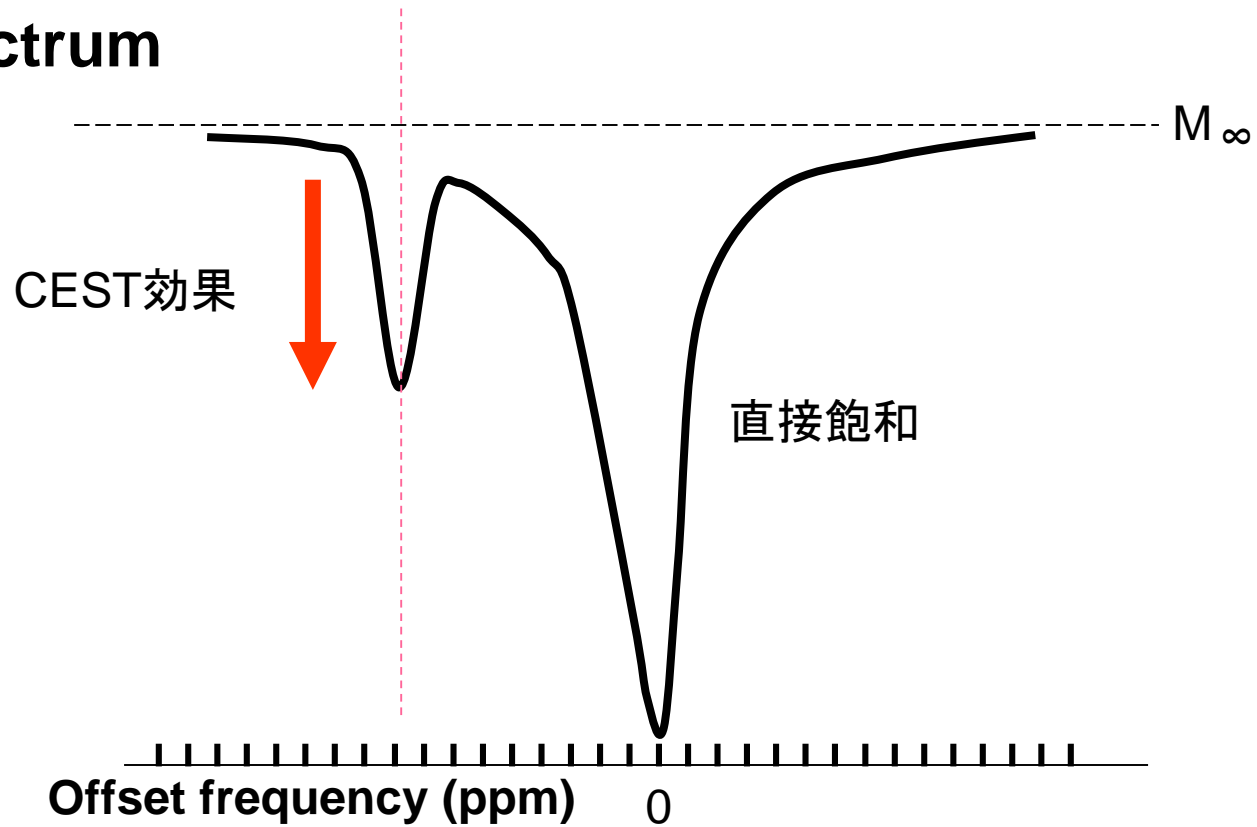
CESTイメージング

Z-spectrum



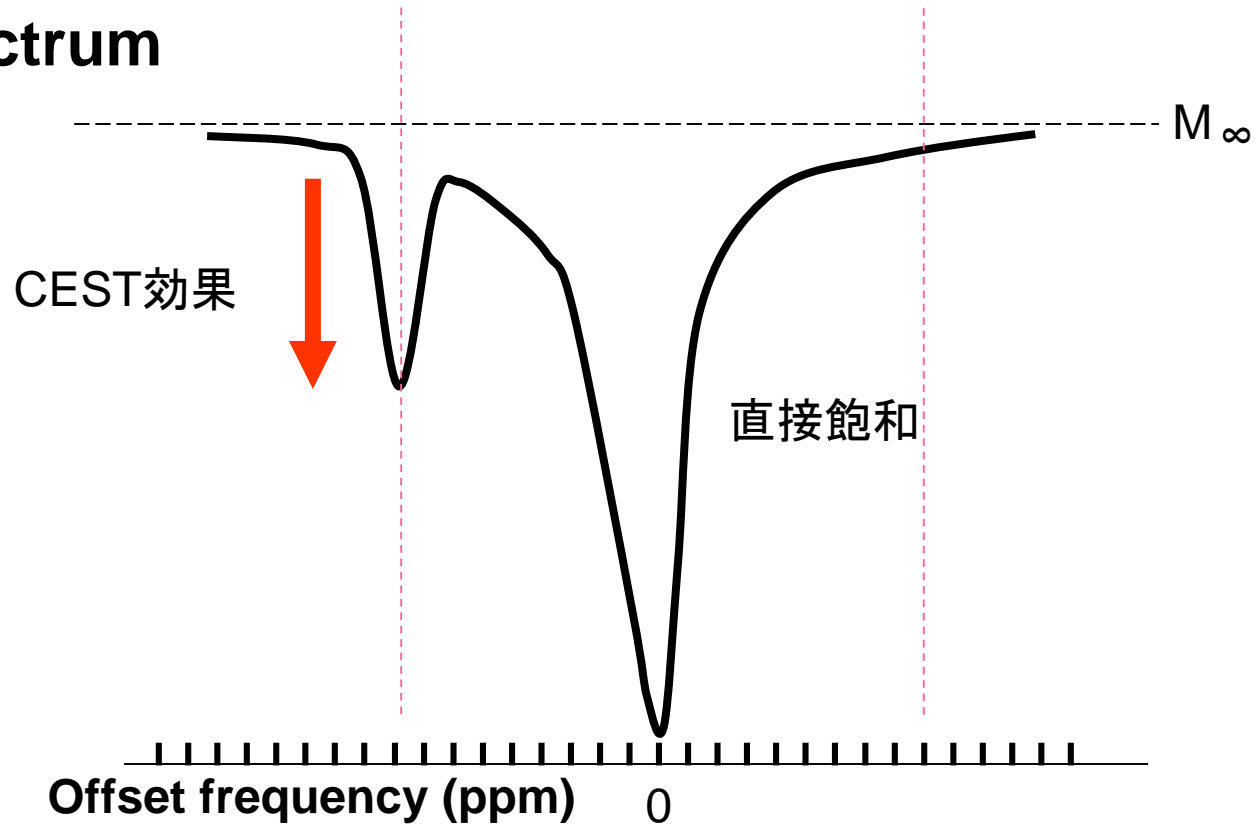
CESTイメージング

Z-spectrum



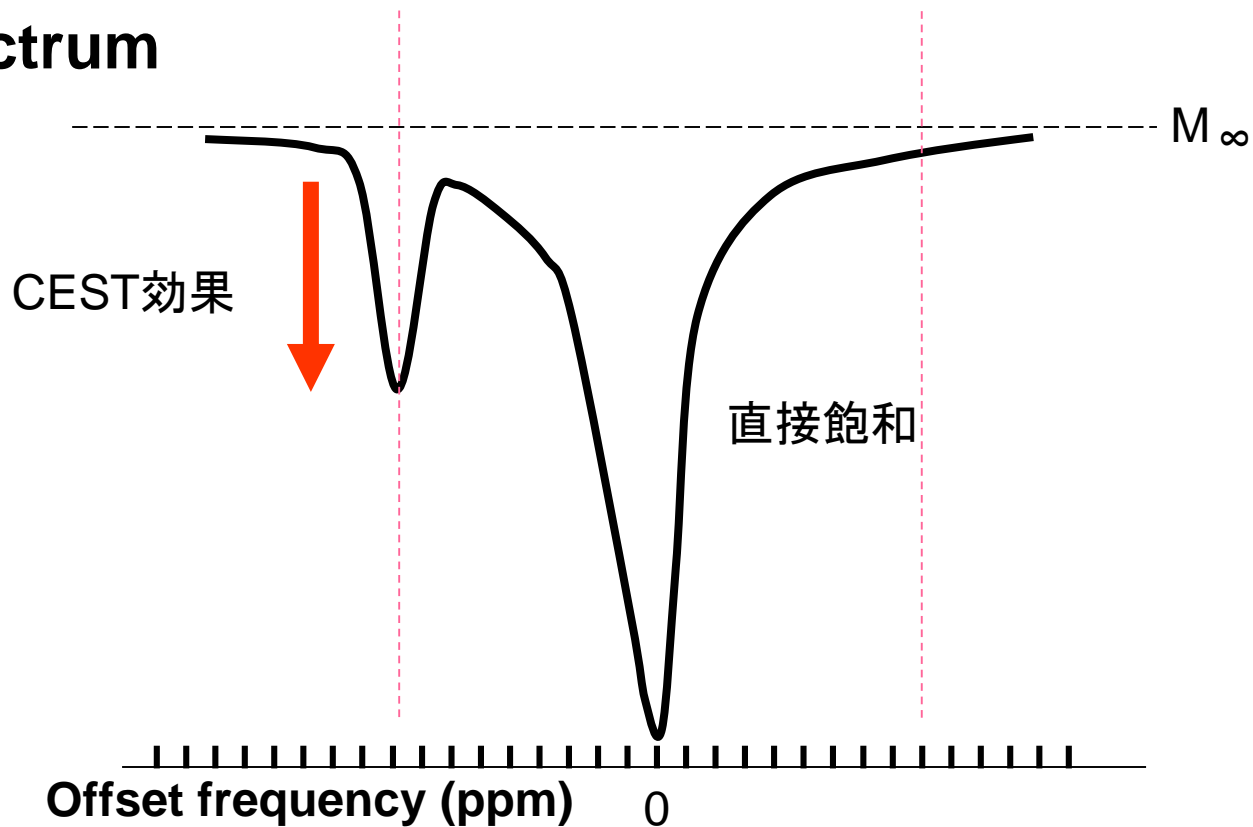
CESTイメージング

Z-spectrum



CESTイメージング

Z-spectrum



$$\text{MTR}_{\text{asym}} = (M_{-s} - M_s) / M_\infty \times 100 (\%)$$

$$= \text{MTR}'_{\text{asym}} + \text{PTR}$$

CESTとMT

どちらも”saturation transfer”

CEST

Chemical exchange

Mobile molecules with long T2

Specific in frequency

MT

Cross relaxation, chemical exchange, etc

Semisolid macromolecules with short T2

Non-specific in frequency

CESTとMT

どちらも”saturation transfer”

CEST

Chemical exchange

Mobile molecules with long T2

Specific in frequency

MT

Cross relaxation, chemical exchange, etc

Semisolid macromolecules with short T2

Non-specific in frequency

CESTとMT

どちらも”saturation transfer”

CEST

Chemical exchange Proteins, peptides, glucose...

Mobile molecules with long T2

Specific in frequency

MT

Cross relaxation, chemical exchange Myelin

Semisolid macromolecules with short T2

Non-specific in frequency

CESTとMT

どちらも”saturation transfer”

CEST

Chemical exchange

Mobile molecules with long T2

Specific in frequency

MT

Cross relaxation, chemical exchange, etc

Semisolid macromolecules with short T2

Non-specific in frequency

CESTイメージング

Endogenous (内因性)

生体に内在する分子のイメージング

Exogenous (外因性)

CEST効果を示す物質を投与 造影剤

外因性CESTイメージング

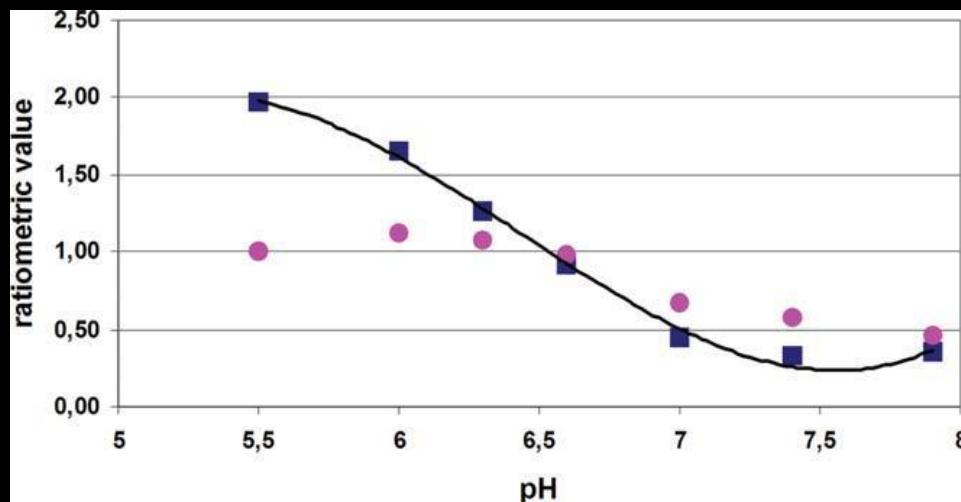
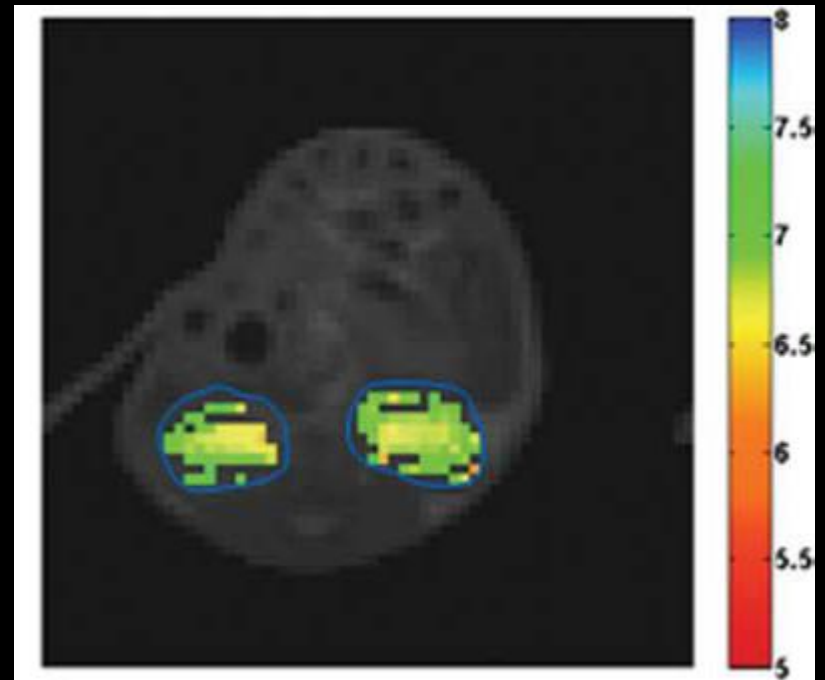
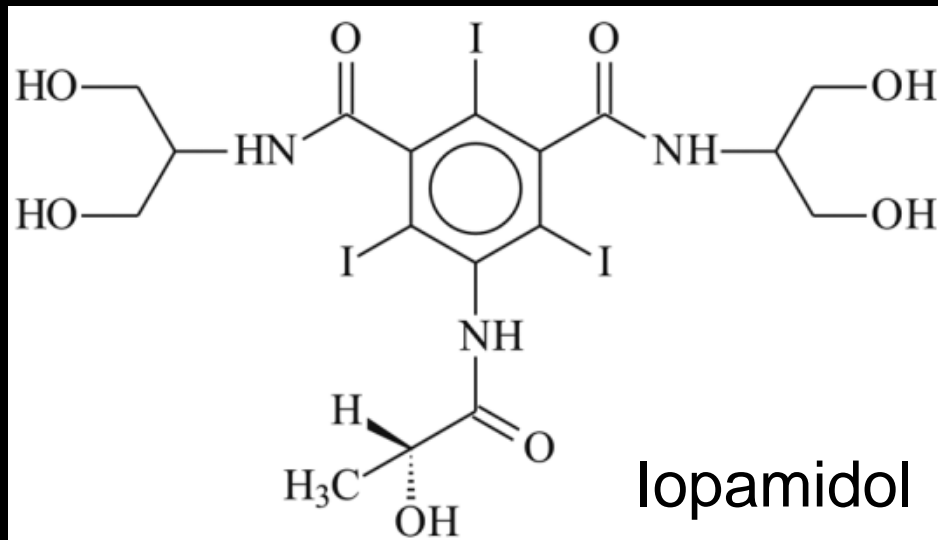
Diamagnetic CEST (DiaCEST)

Iopamidol, glucoseなど

Paramagnetic CEST (ParaCEST)

Eu, Tb, Yb などを持つ造影剤

DiaCEST contrast agent

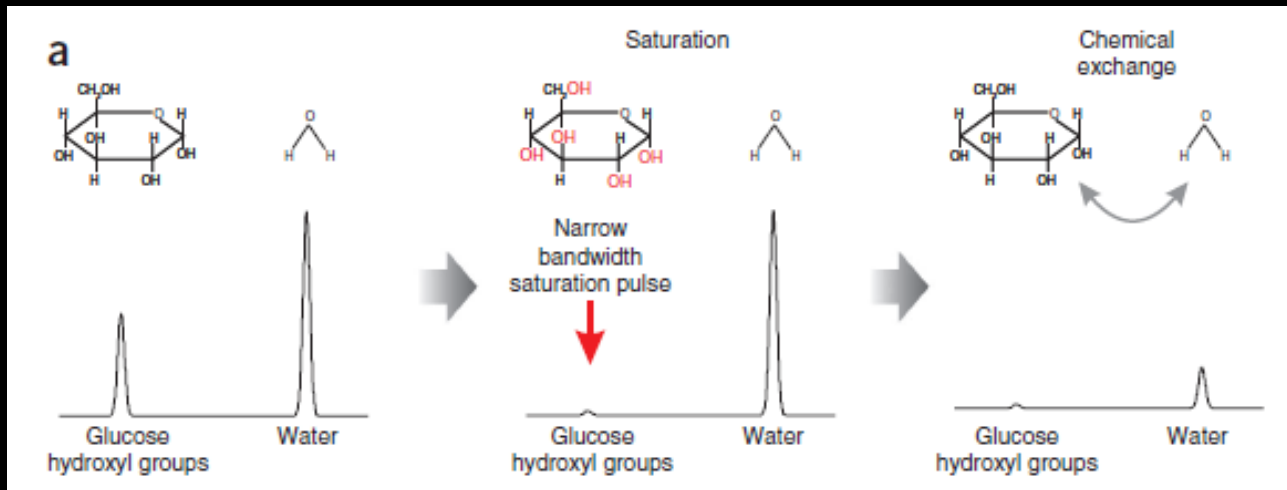


腎のpHモニタリング@7T

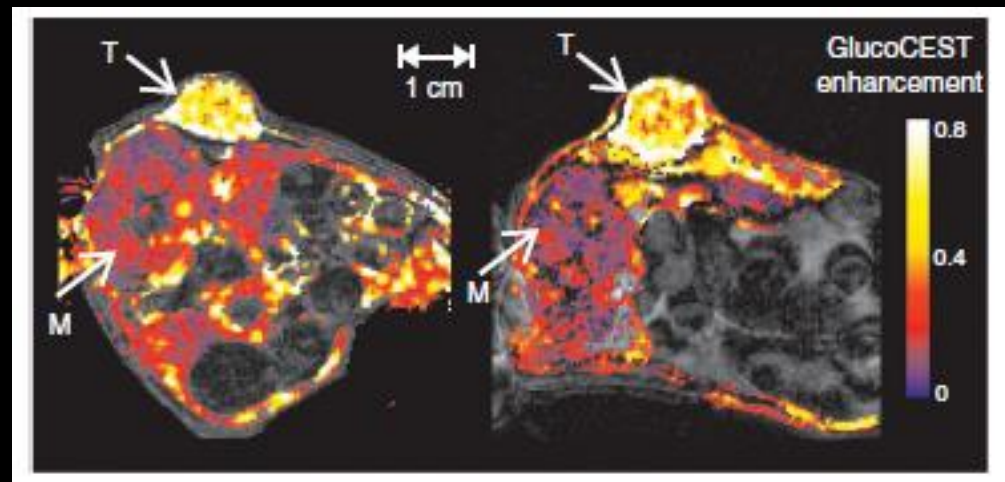
Longo DL, et al. MRM 2011

GlucoCEST

CESTイメージングによるglucose代謝の画像化

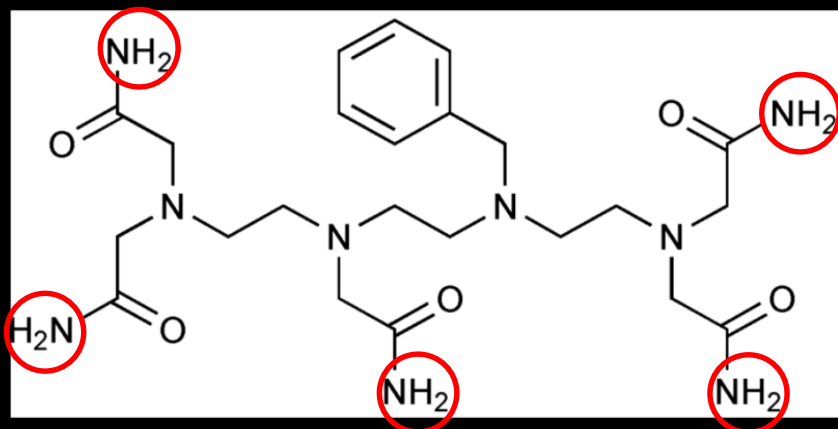


Glucose腹腔内投与 60分後

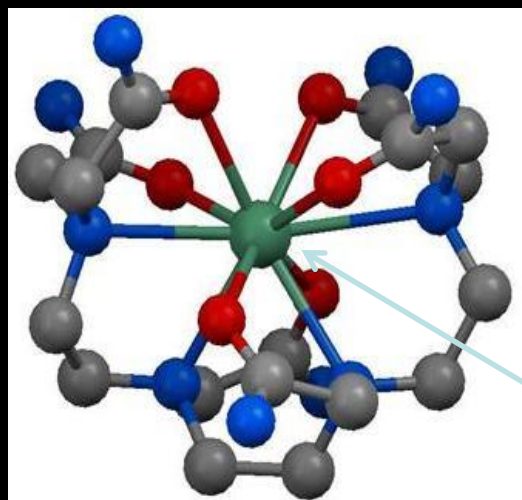


Walker-Samuel et al. Nat Med 2013

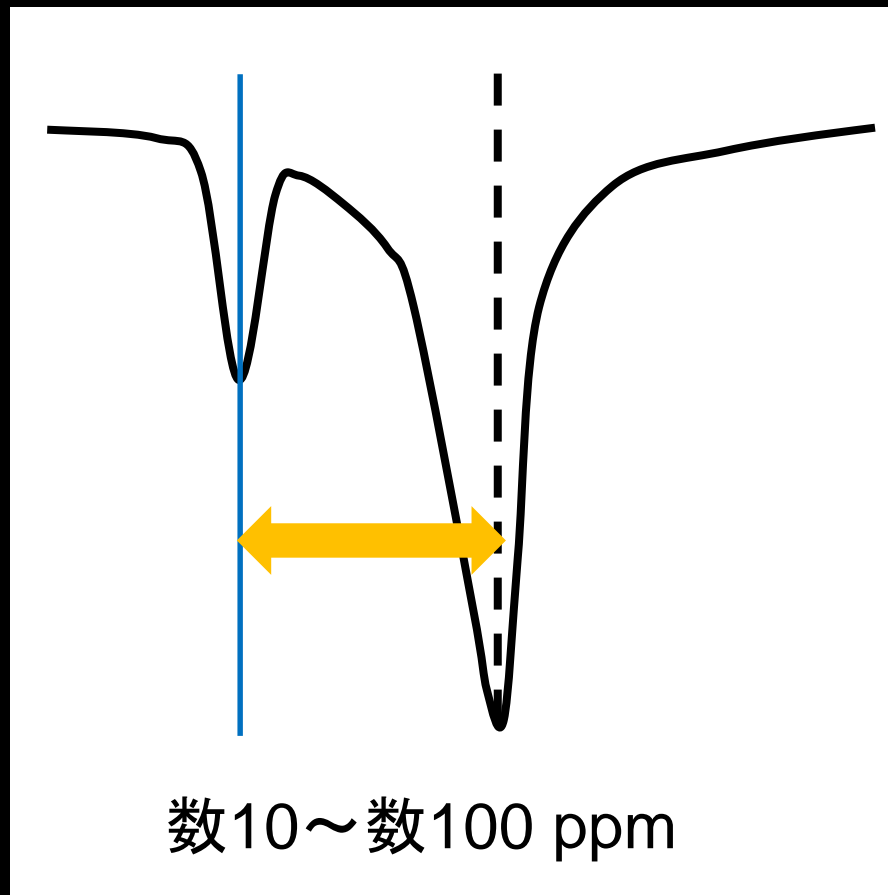
ParaCEST contrast agent



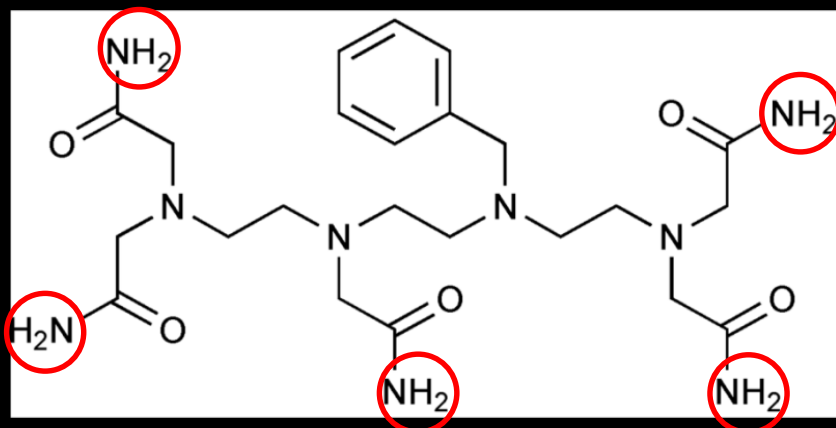
4bttpam



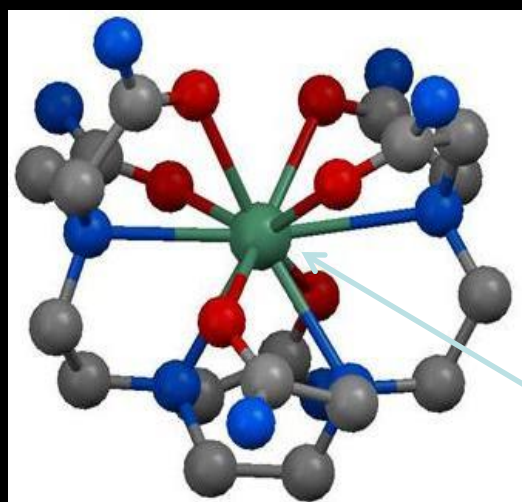
Yb



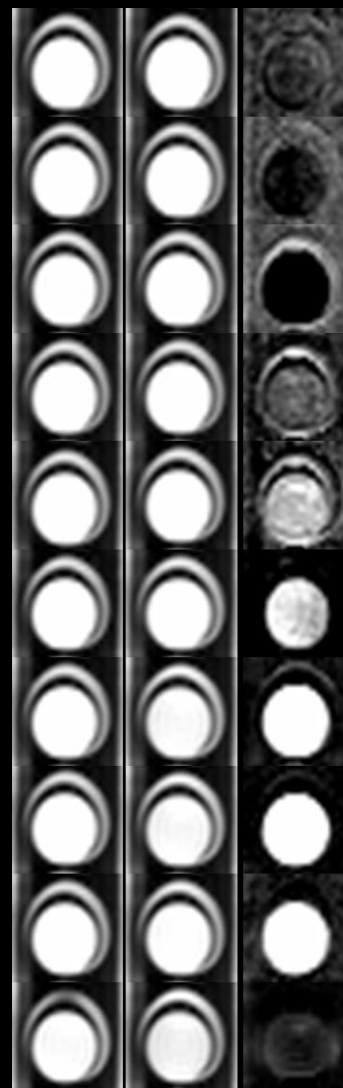
ParaCEST contrast agent



4bttpam



Yb



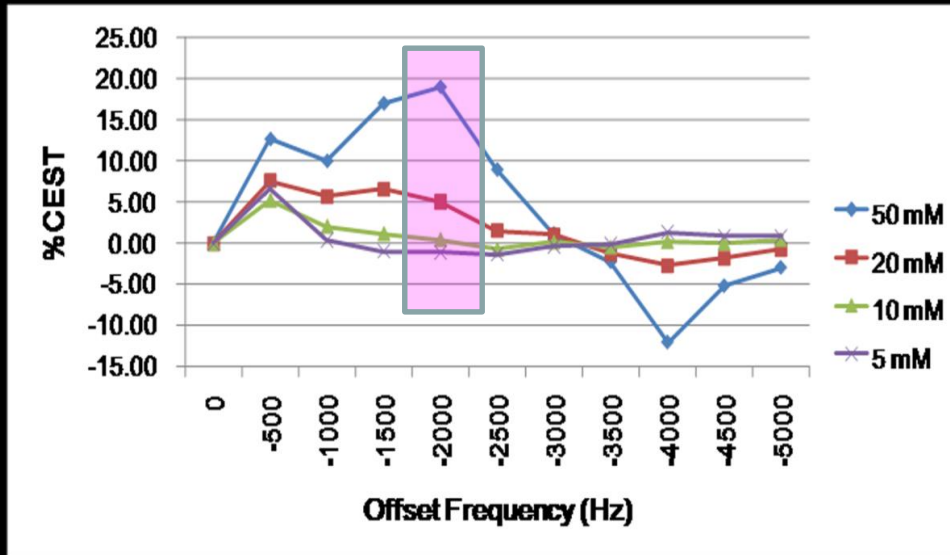
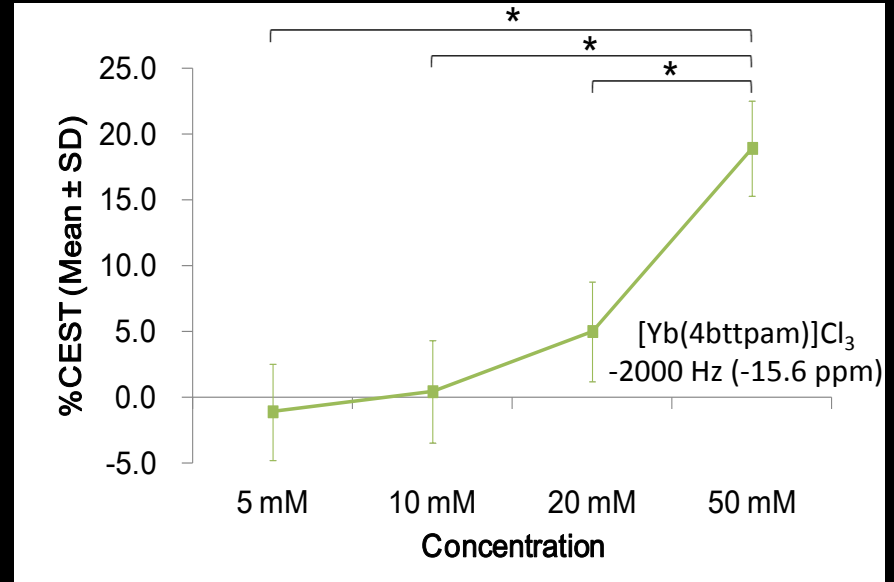
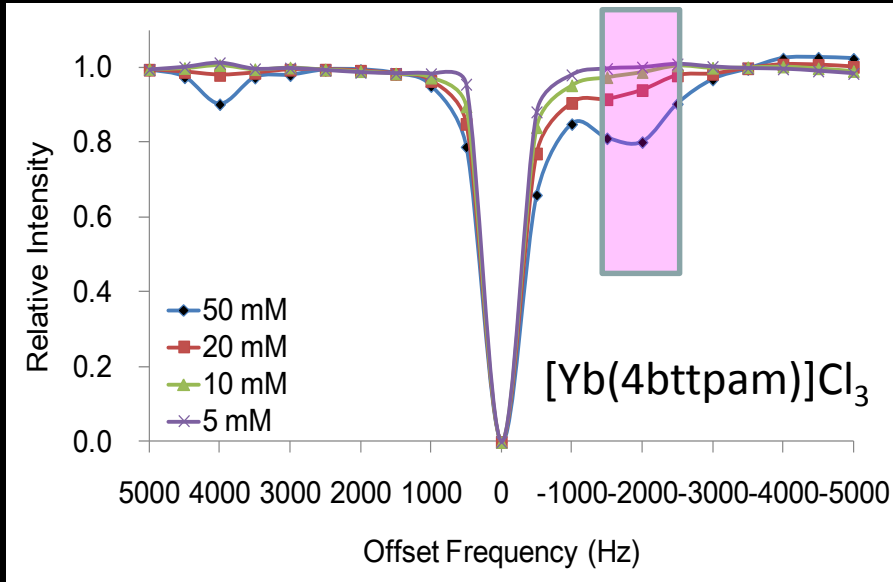
臨床用3T

5000 Hz	-5000 Hz	
4500 Hz	-4500 Hz	
4000 Hz	-4000 Hz	
3500 Hz	-3500 Hz	
3000 Hz	-3000 Hz	差
2500 Hz	-2500 Hz	分
2000 Hz	-2000 Hz	画
1500 Hz	-1500 Hz	像
1000 Hz	-1000 Hz	
500 Hz	-500 Hz	

濃度 50 mM

pH 7.4

ParaCEST contrast agent



Takayama Y, et al. Magn Reson Med Sci 2012

人体に利用できるparaCEST
造影剤は、まだ存在しない

CESTイメージング

内因性

Amide proton transfer (APT)	3.5 ppm
Glycogen (glyco CEST)	0.5-1.5 ppm
Glycosaminoglycan (gag CEST)	0.9-1.9 ppm
Glutamate (gluCEST)	3.0 ppm
Myo-inositol (MI CEST)	0.6 ppm

CESTイメージング

内因性

Amide (amide proton transfer) 3.5 ppm

APTイメージング

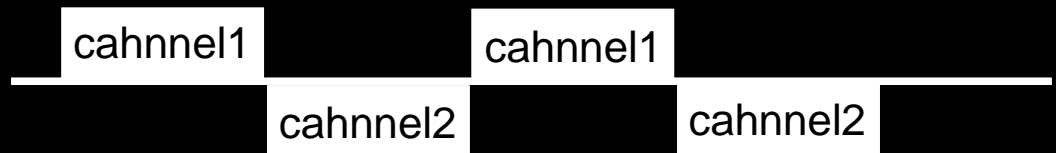
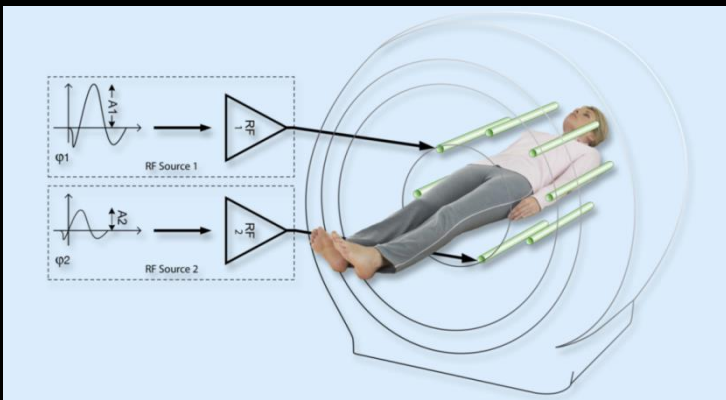
タンパク、ペプチド

最も臨床に近いCESTイメージング

技術的問題点 - 1

低いSNR 3Tでも $MTR_{asym} < 5\%$

限られた静磁場強度 (3Tは必ずしも十分でない)
飽和パルスの制限 (SAR、duty cycle)



Keupp J et al. ISMRM 2011

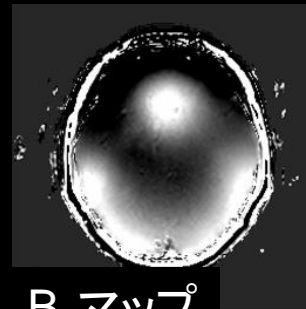
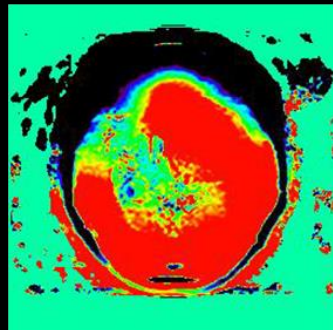
技術的問題点 - 2

B_0 および B_1 不均一への高感受性

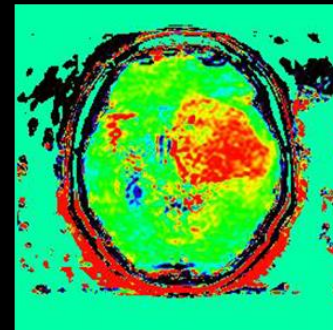
δB_0 補正は必須

B_1 均一化のためのRF送信技術

δB_0 -uncorrected



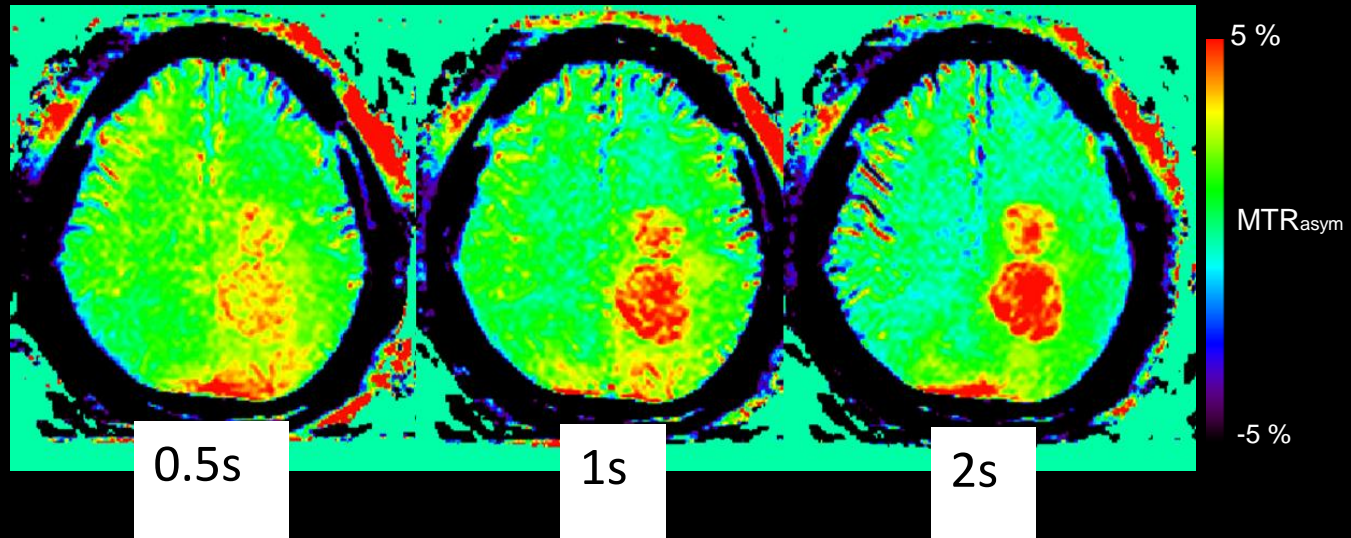
δB_0 -corrected



技術的問題点 - 3

シーケンスの最適化 特に飽和パルス
強度、長さ(飽和時間)

飽和時間の影響



APTイメージング 撮影プロトコル

3T clinical scanner with parallel transmission

8-channel coil

Pulse strength = 2 μ T, length = 0.5, 1, 2 sec

25 offset frequencies (-6 .. 6 ppm)

Turbo spin-echo with driven equilibrium

TR/TE = 5000/6 ms, FOV = 230x230 mm, Matrix = 128x128

Resolution = 1.8x1.8x5 mm³

Imaging time = 2 min 10 s

臨床応用 - Oncology

脳腫瘍

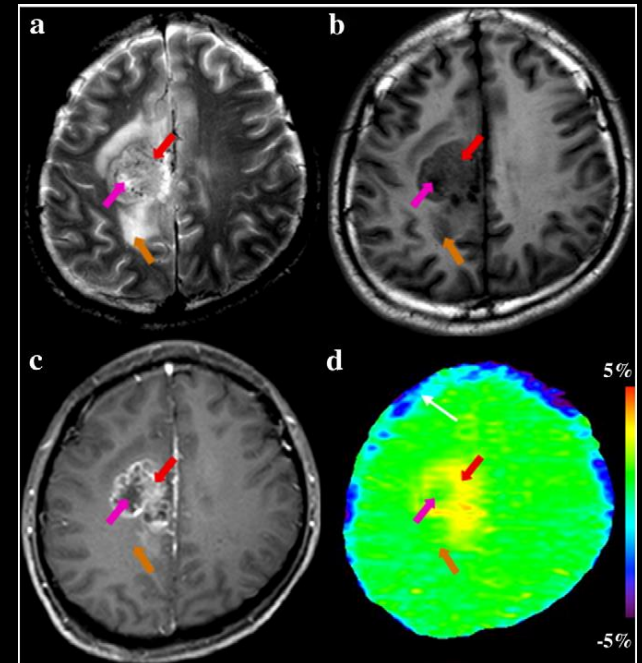
Glioma : 悪性度との相関

Zhou J et al. MRM 2008

高い増殖能



高いタンパク濃度

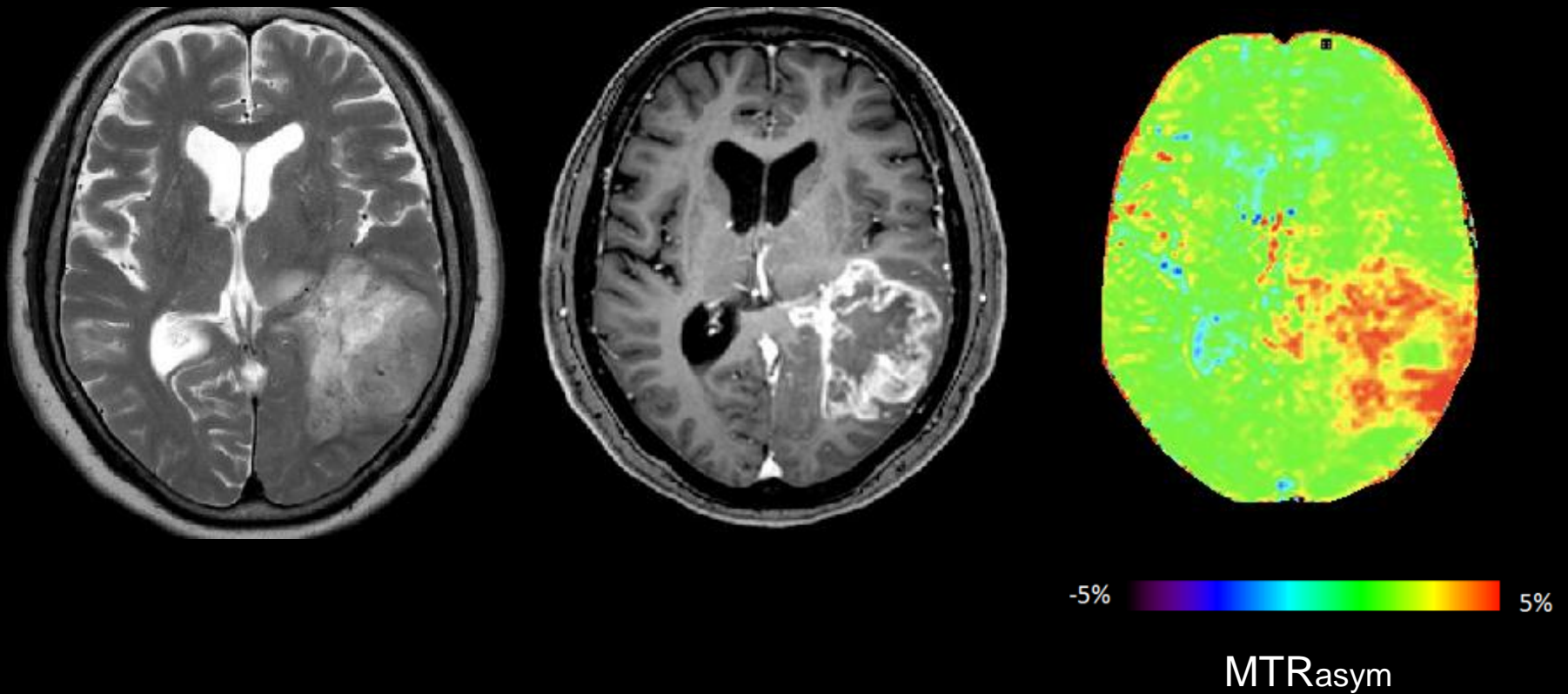


放射線壊死と腫瘍再発の鑑別

Zhou J et al. Nat Med 2010

APT Imaging of Gliomas

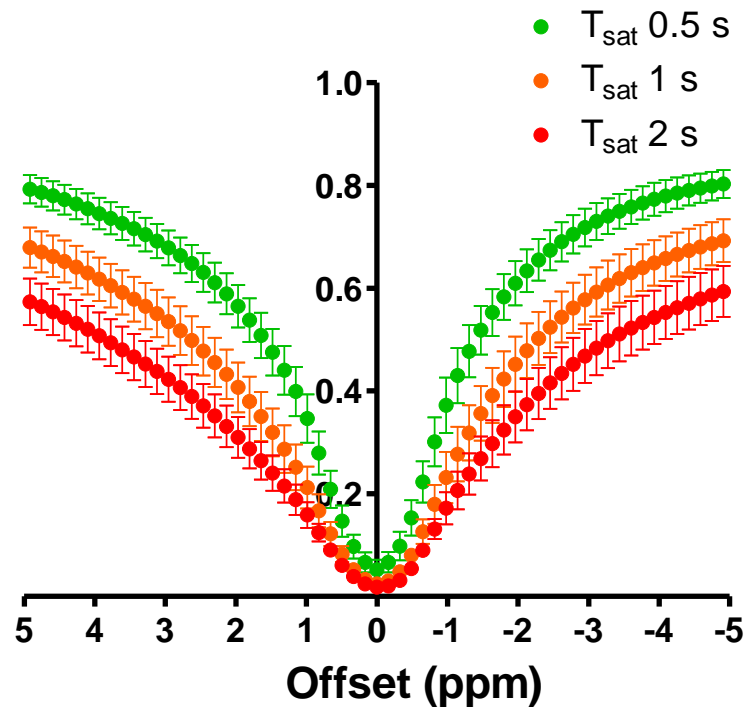
Glioblastoma (Grade IV)



APT Imaging of Gliomas

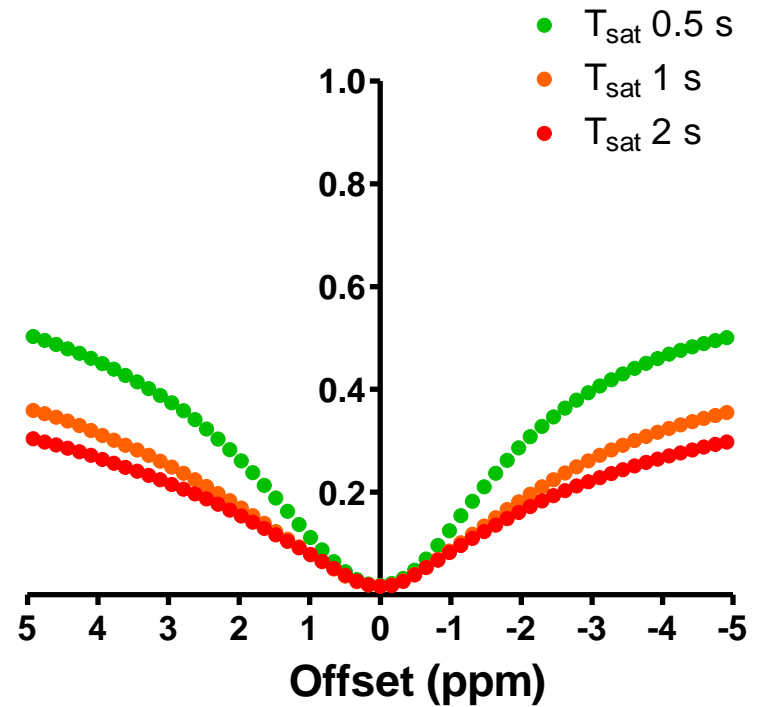
Z-spectra

High Grade Glioma



(n = 7)

Normal White Matter

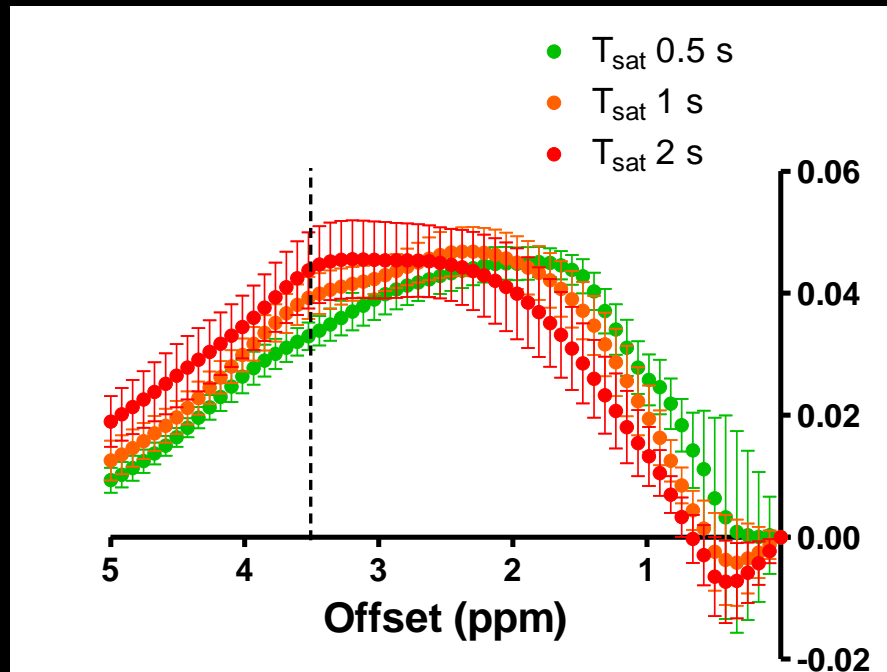


(n = 7)

APT Imaging of Gliomas

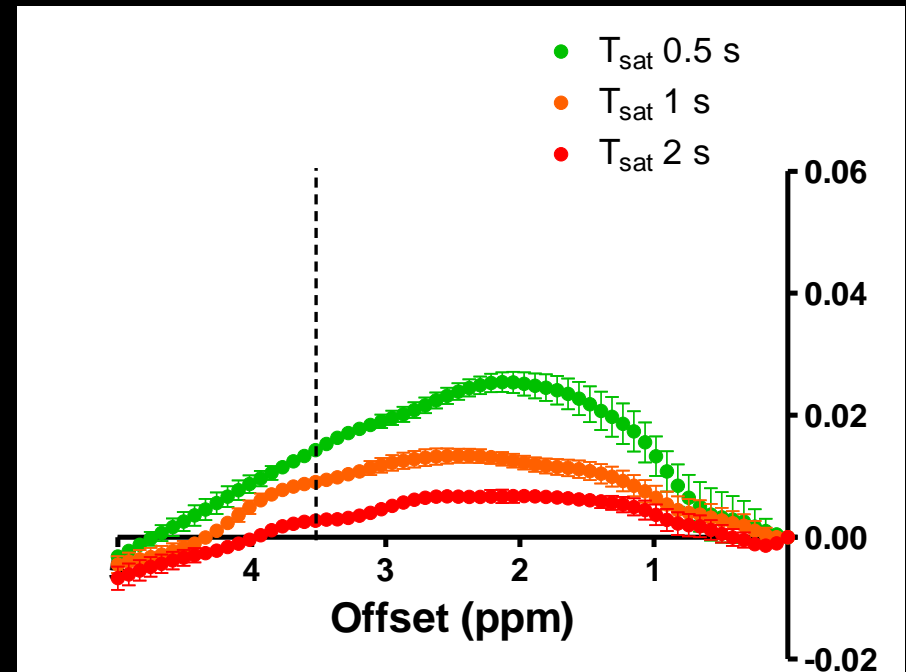
MTR_{asym}

High Grade Glioma



(n = 7)

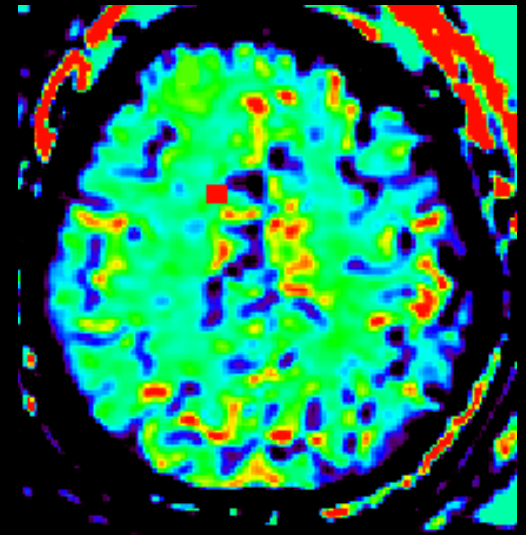
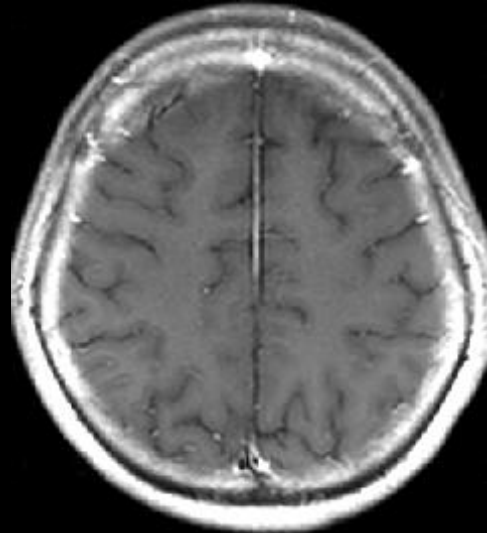
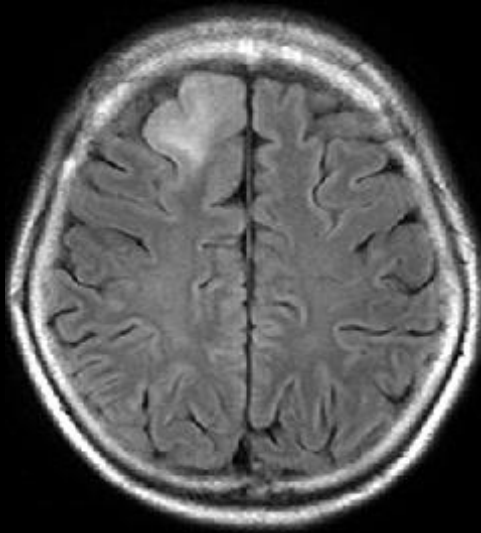
Normal White Matter



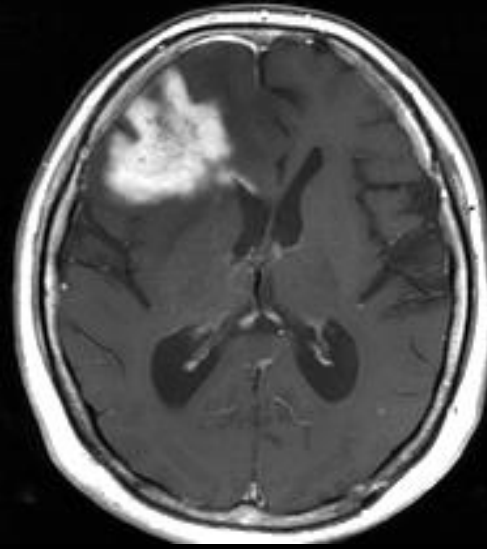
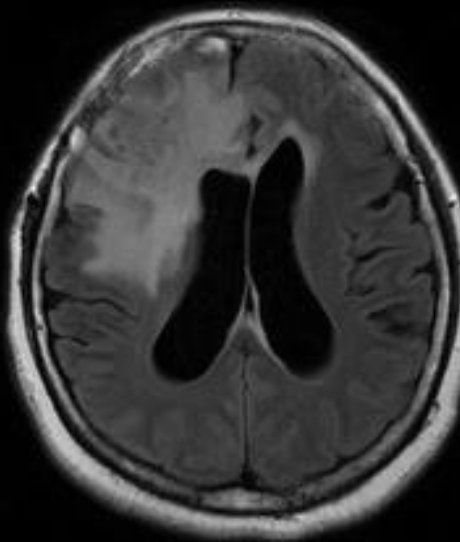
(n = 7)

APT Imaging of Gliomas

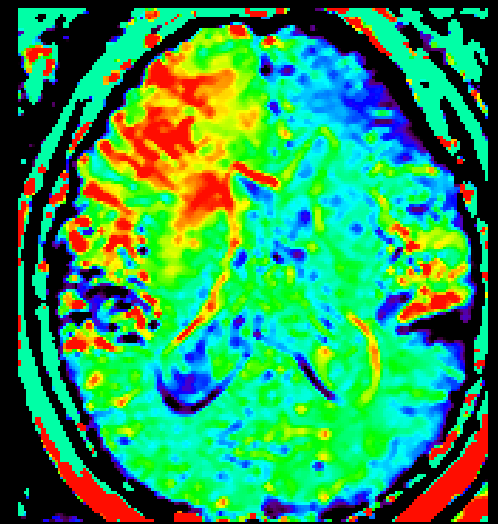
Grade2
Oligo



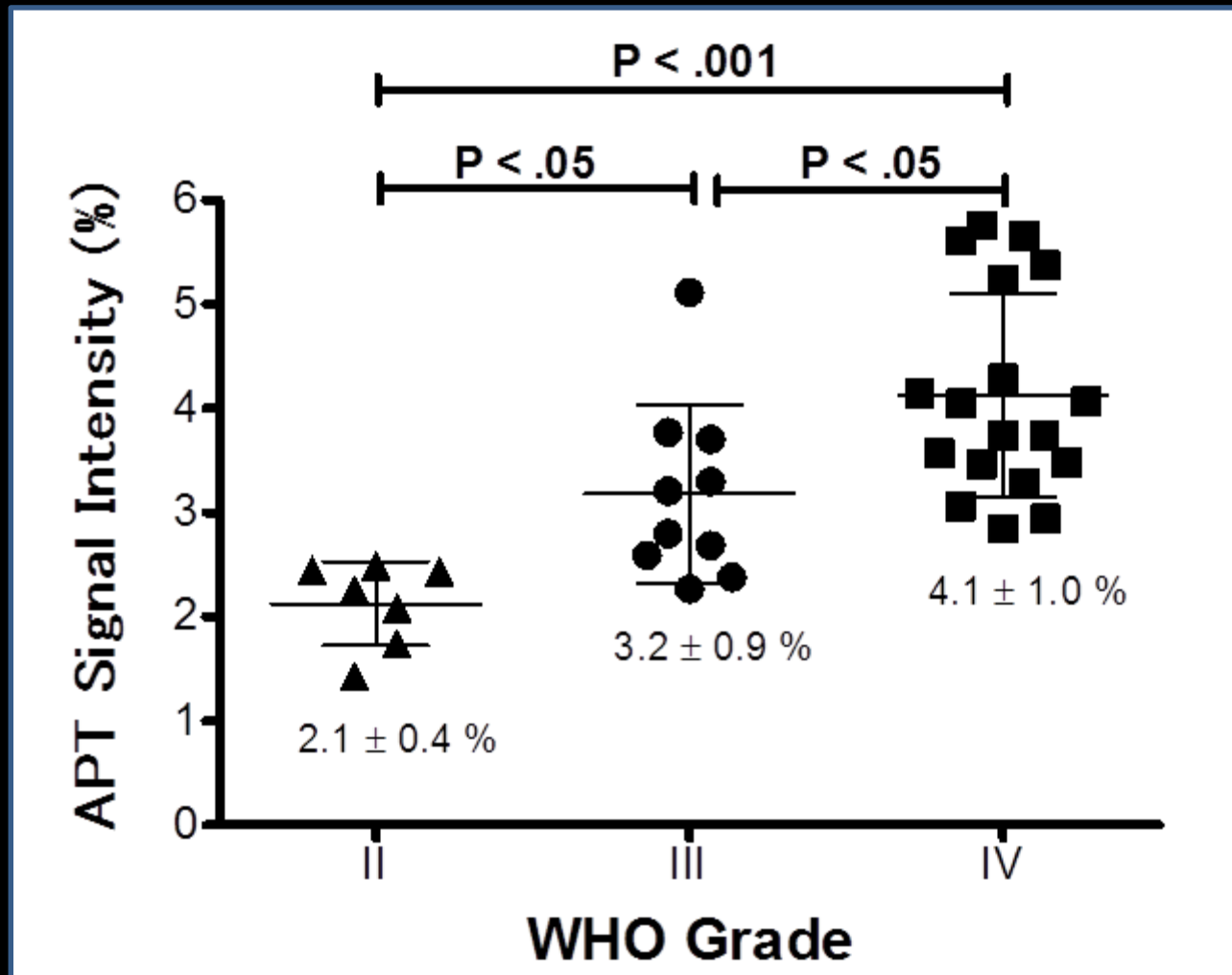
Grade4
GBM



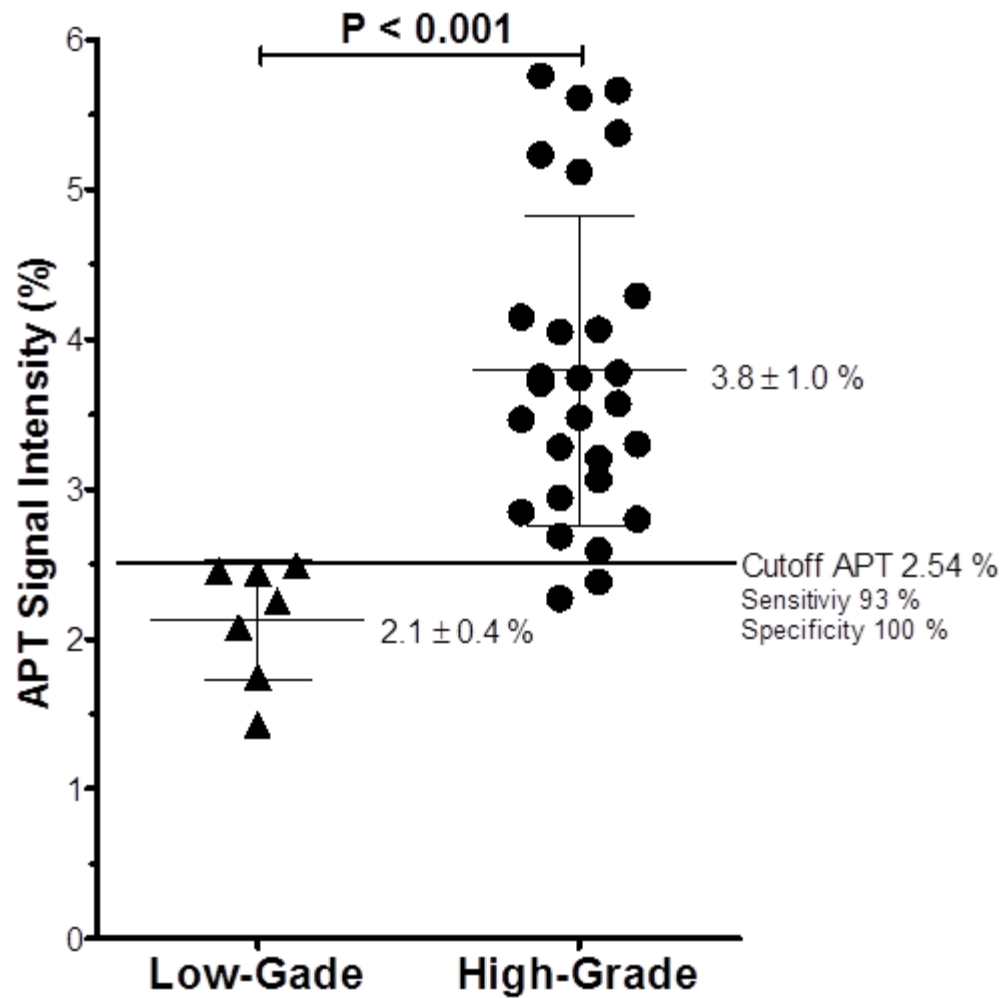
-5%  5%



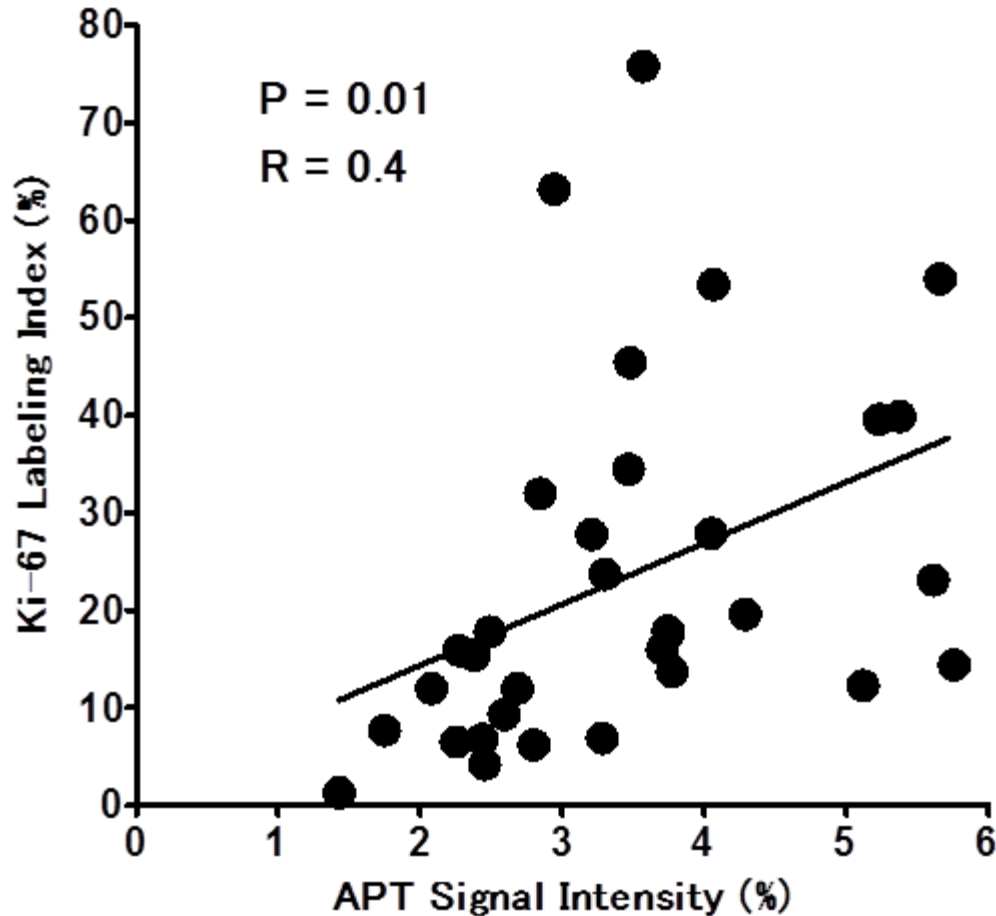
APT vs. Histological Grade



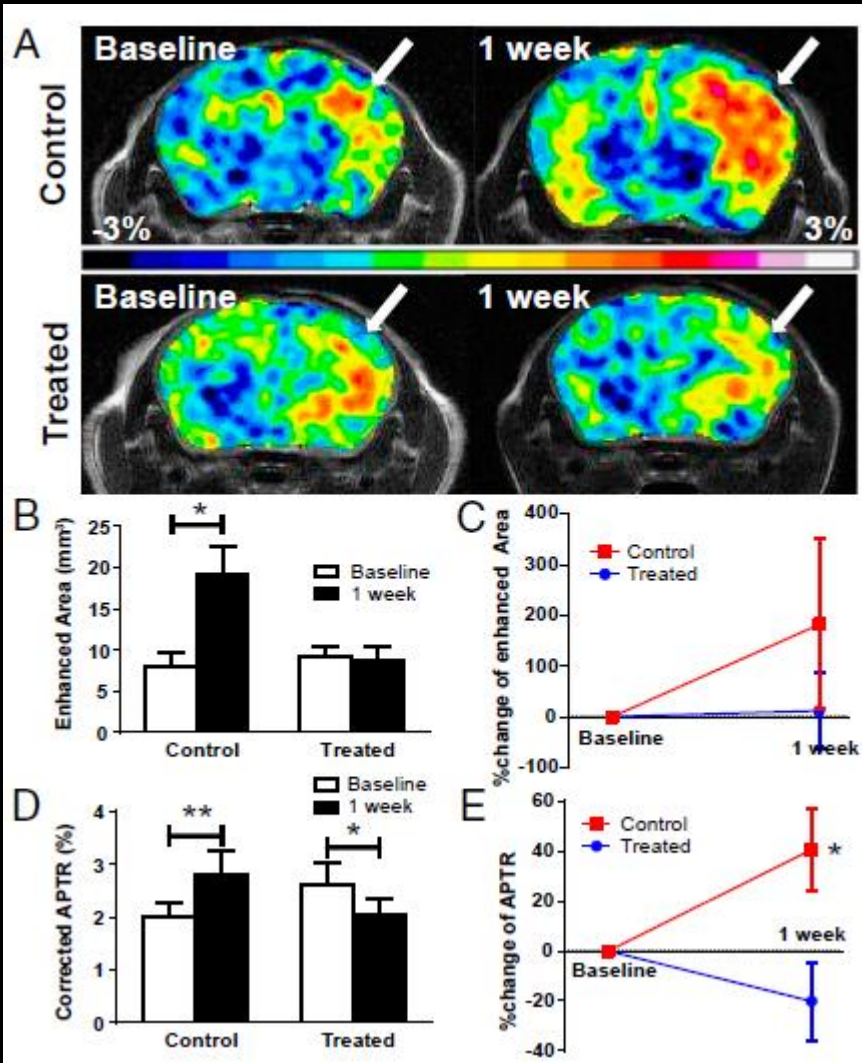
APT vs. Histological Grade



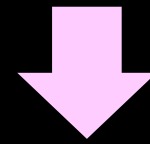
APT vs. Ki-67 Labeling Index



Early response to chemotherapy



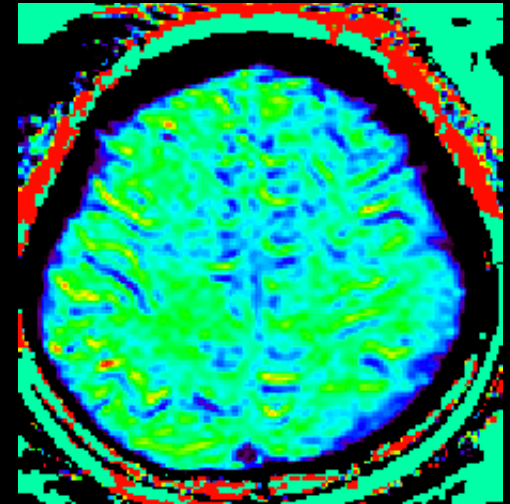
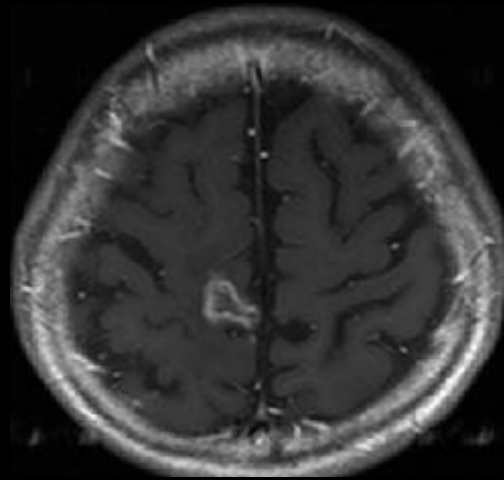
TMZ治療後1週間で、APT
コントラストが有意に低下



治療効果の早期指標として
の有用性

Tumor recurrence vs. Radiation necrosis

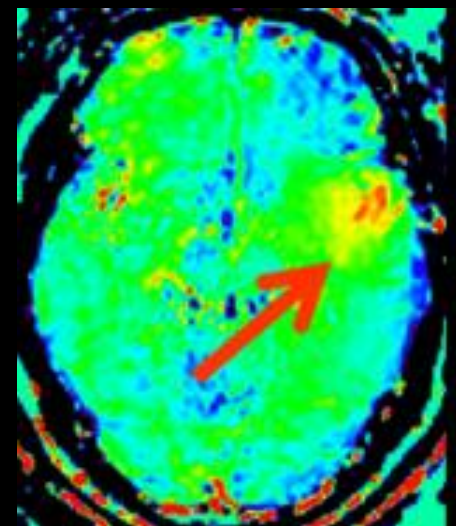
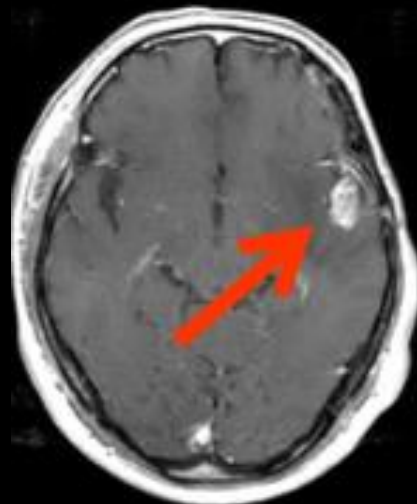
Post Cyber-knife therapy
for metastasis



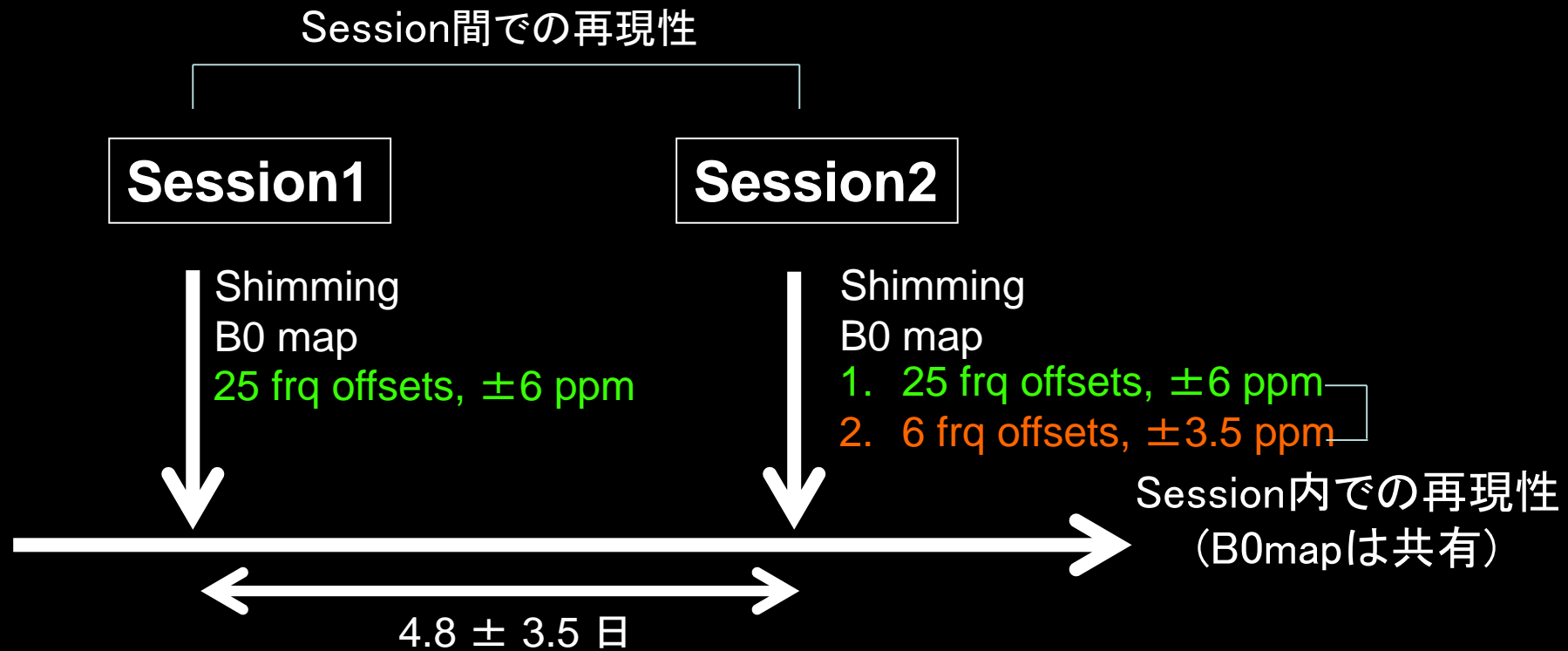
-5%

5%

Recurrent GBM

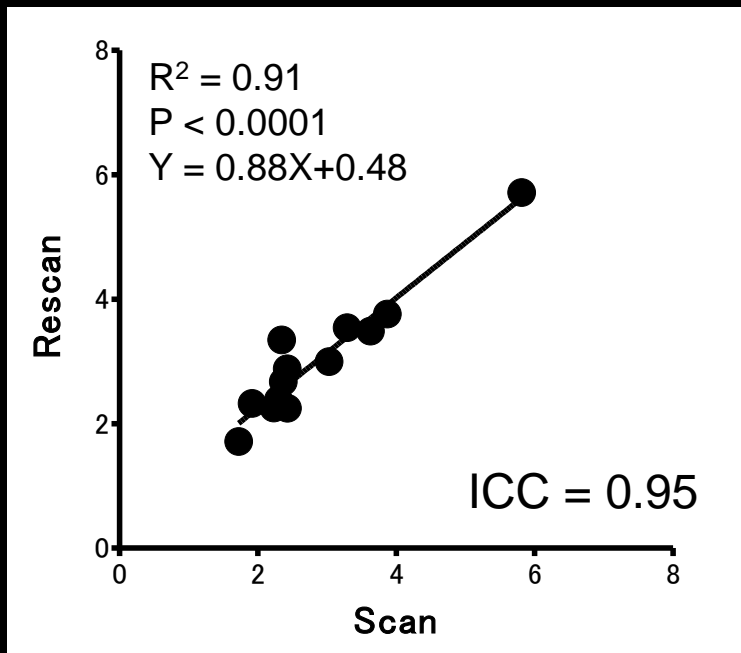


APTイメージングの再現性

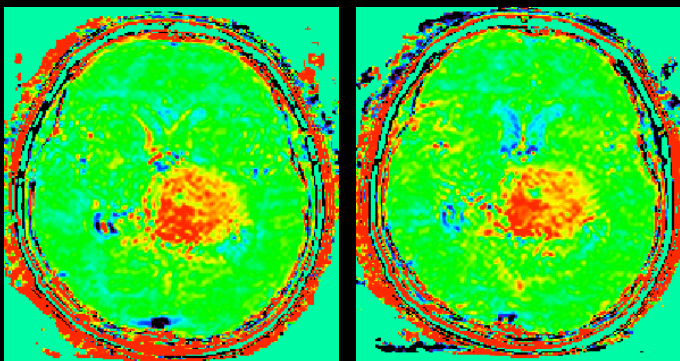
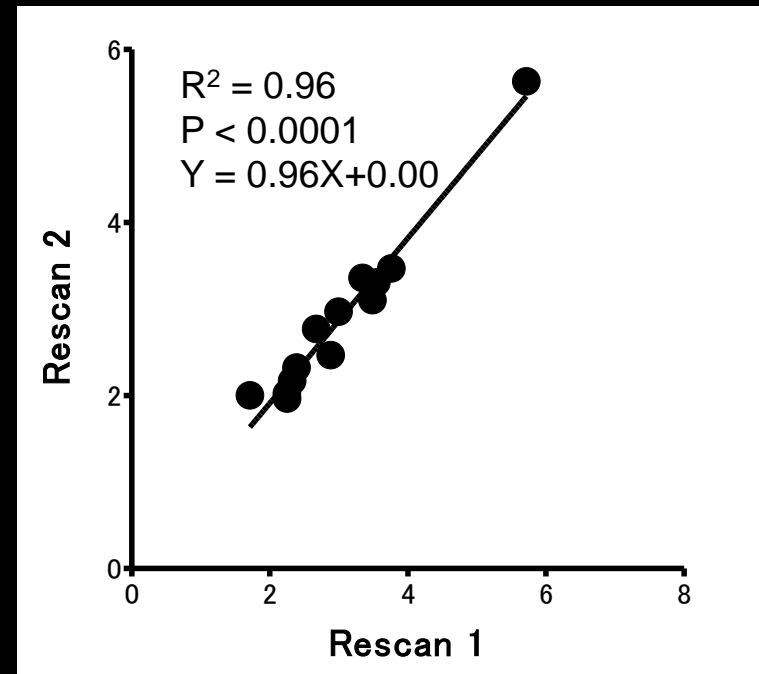


APTイメージングの再現性

セッション間

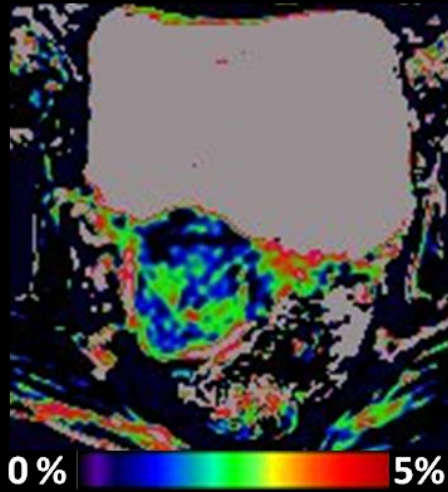
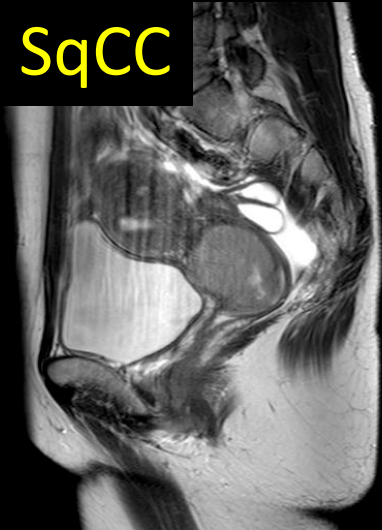


セッション内



Uterine tumors: SqCC vs. EMCA

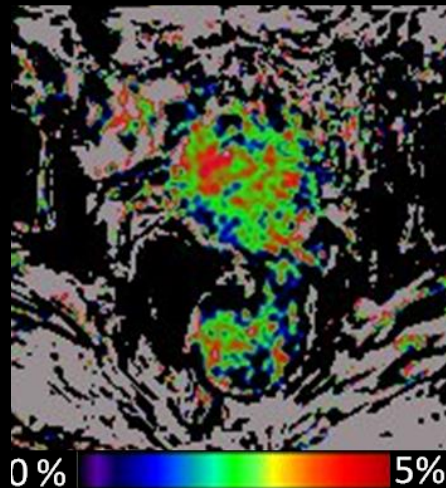
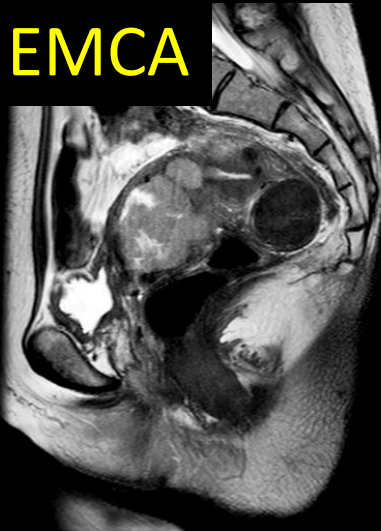
SqCC



0% 5%

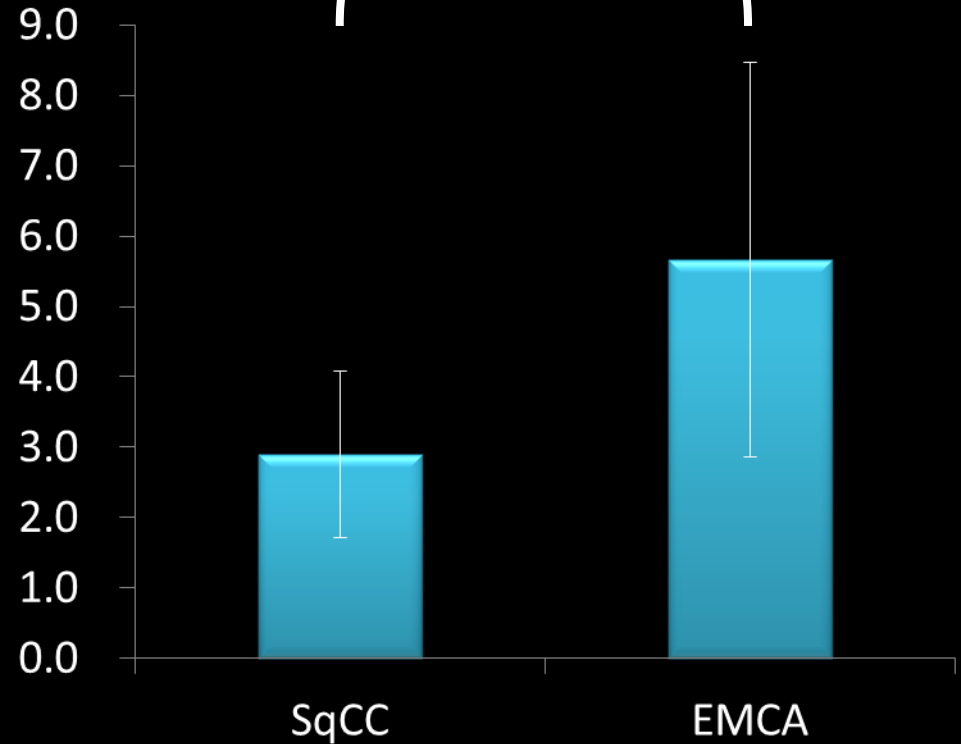
Takayama Y, et al. ISMRM2013

EMCA



0% 5%

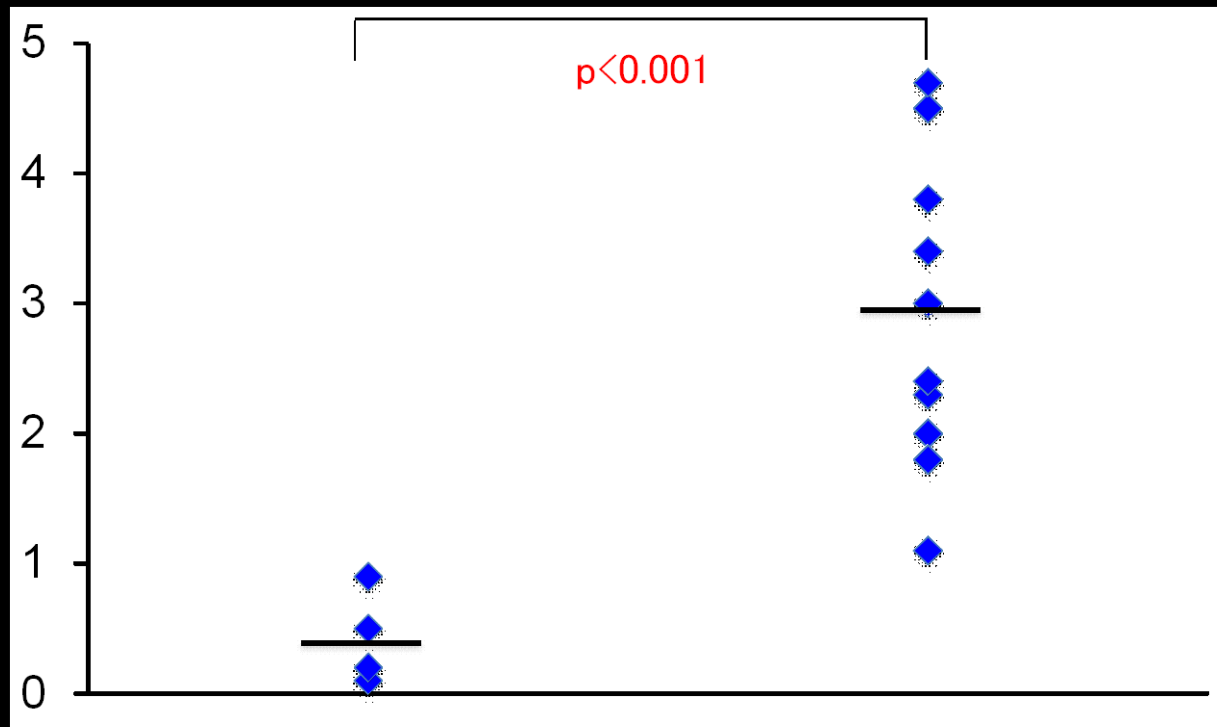
APT signal [%]



SqCC

EMCA

Rectal cancer: 分化度による違い

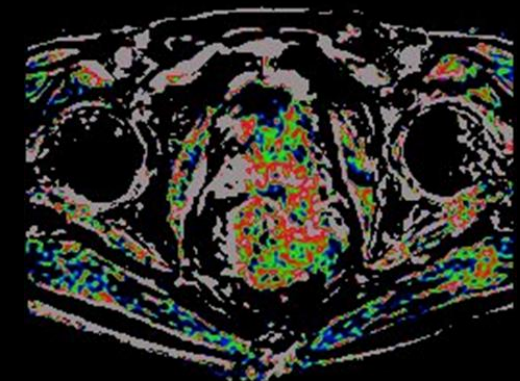


高分化優位 (n=4)
0.43 ± 0.36

中分化優位 (n=11)
2.95 ± 1.14



T2WI



0%  5%
APT

臨床応用 – pHイメージング

CEST (APT) 効果はpHに依存する



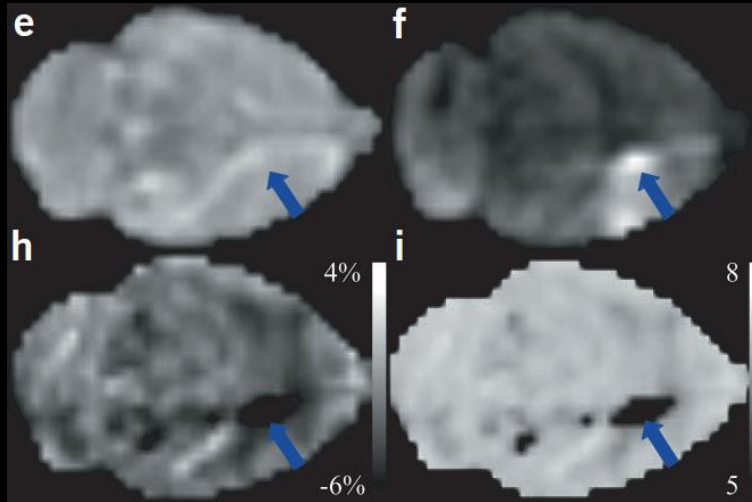
$$\text{APTR} = \frac{k [\text{amide proton}]}{2 \cdot [\text{H}_2\text{O}] \cdot R_{1w}} [1 - e^{-R_{1w}T_{\text{sat}}}]$$

$$k = k_{\text{base}} \cdot 10^{\text{pH} - \text{pK}_w}$$

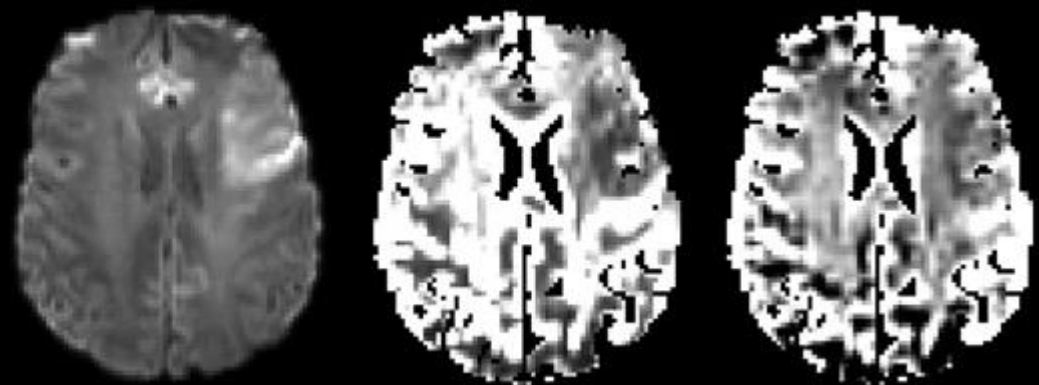
$$\approx 5.57 \times 10^{\text{pH} - 6.4}$$

k : proton exchange rate
[amide proton]: concentration of amide proton
 R_{1w} : R_1 of water
[H_2O]: concentration of water
 T_{sat} : saturation time

臨床応用 – pHイメージング



Zhou J, et al. Nat Med 2003



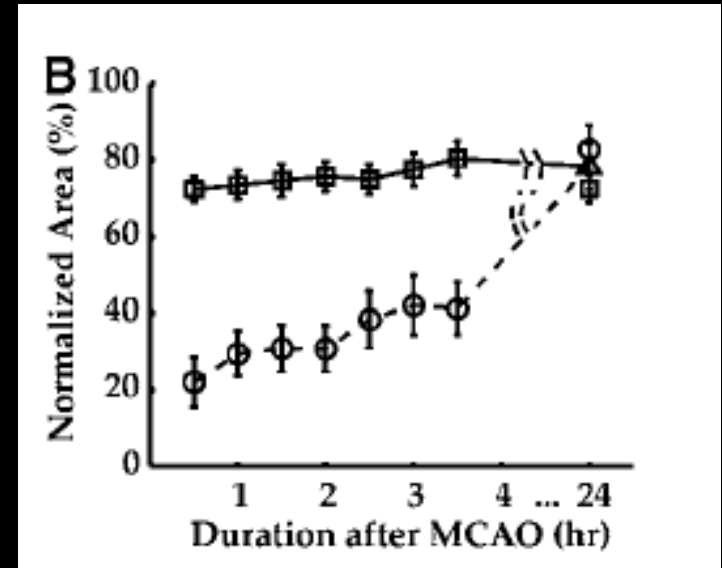
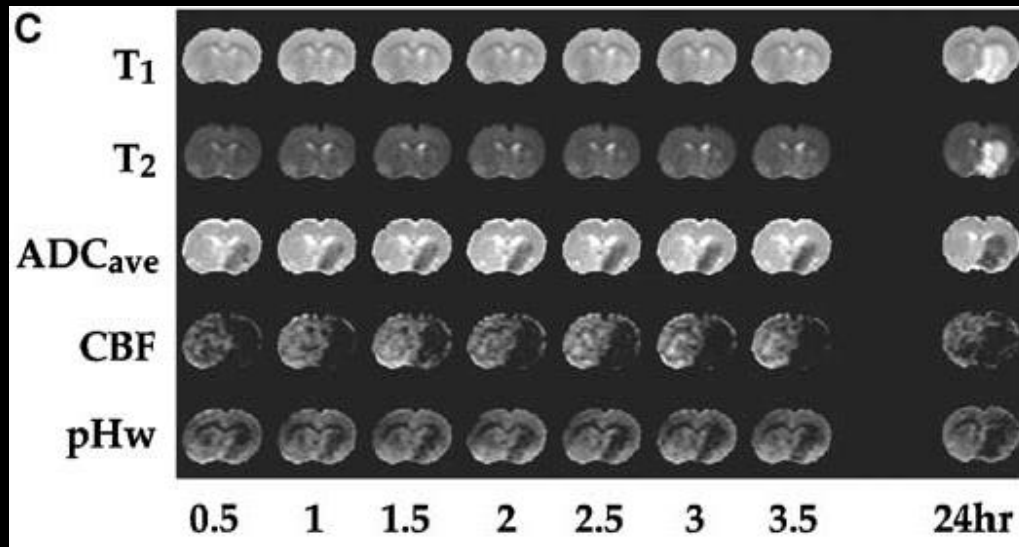
DWI

APTR*

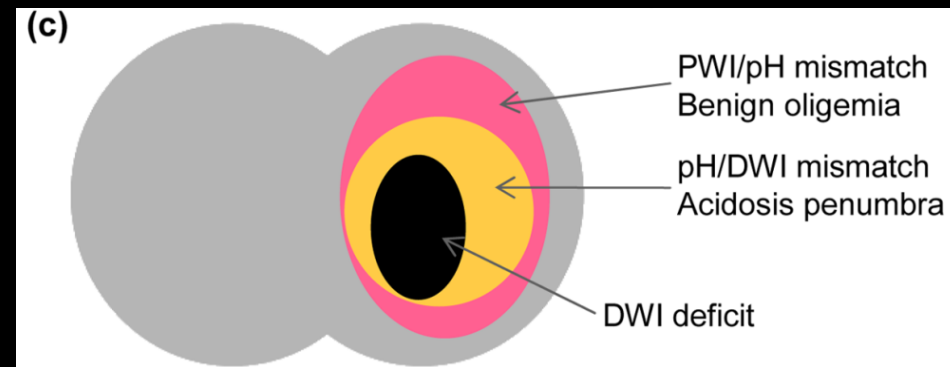
MTR_{asymp}

Tee YK, et al. NMR Biomed 2014

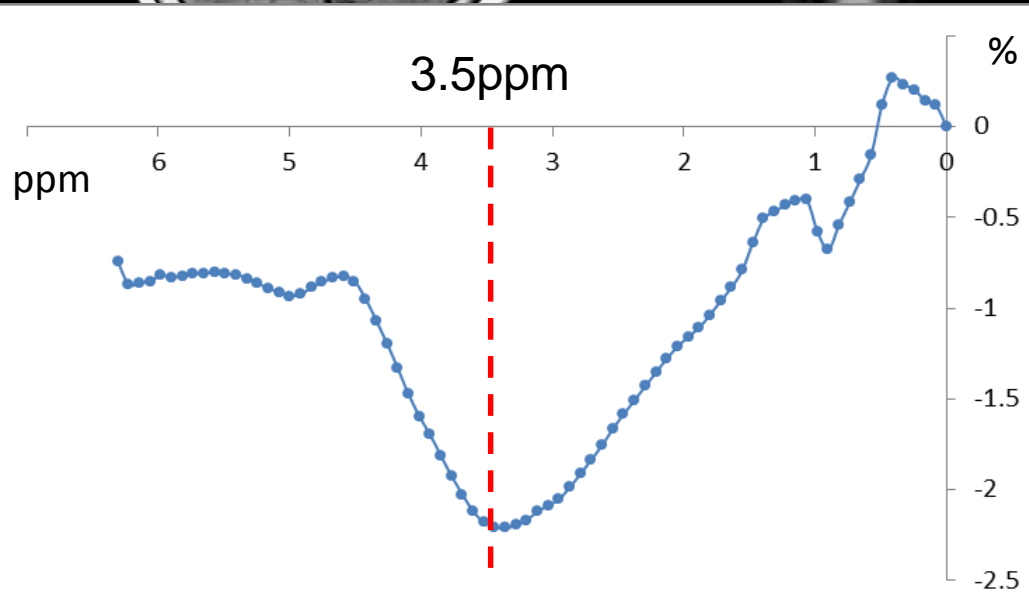
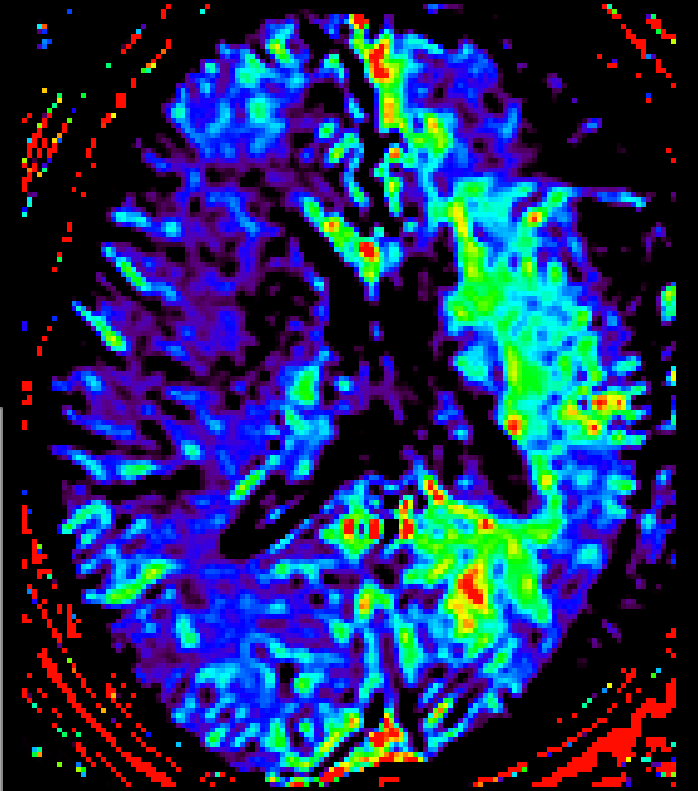
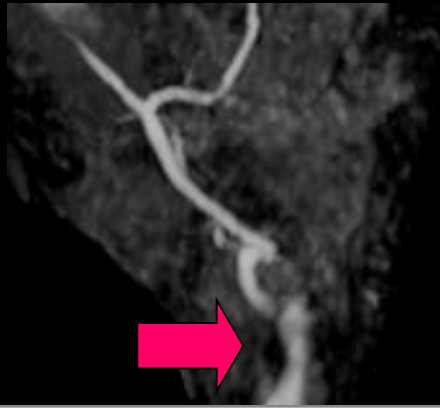
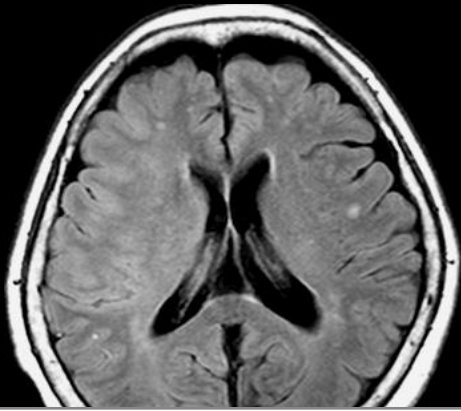
脳梗塞モデルにおけるpHイメージング



pH-weighted imaging predicts the extent of final infarction better than DWI or PWI.



67yo F Right MCA, 10 hrs after onset



0 5 %
MTR_{asym}

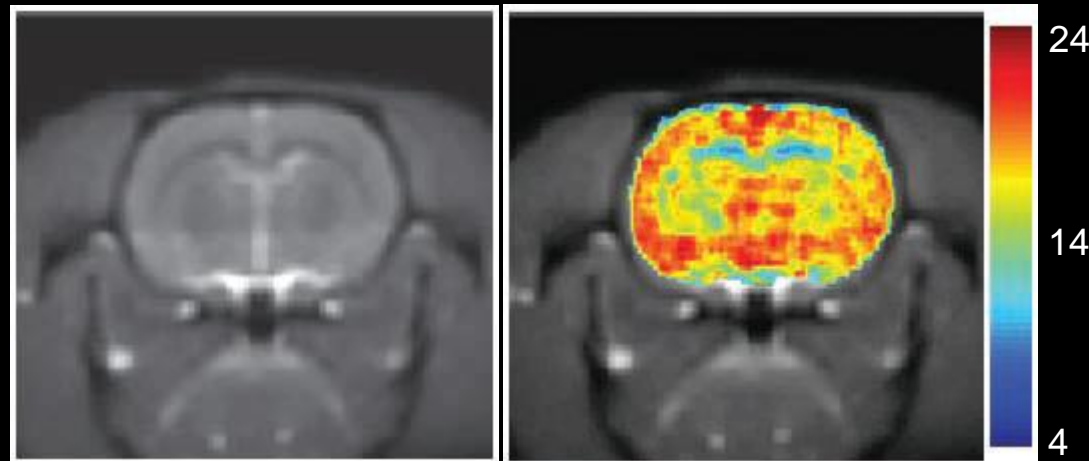
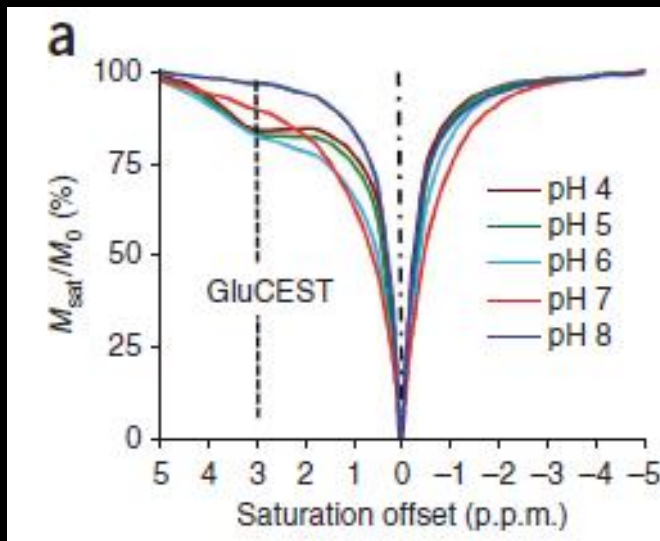
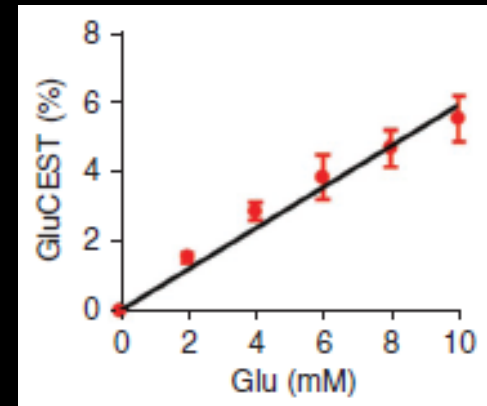
今後の可能性

Glutamate (GluCEST)

神経伝達物質 (-NH₂)

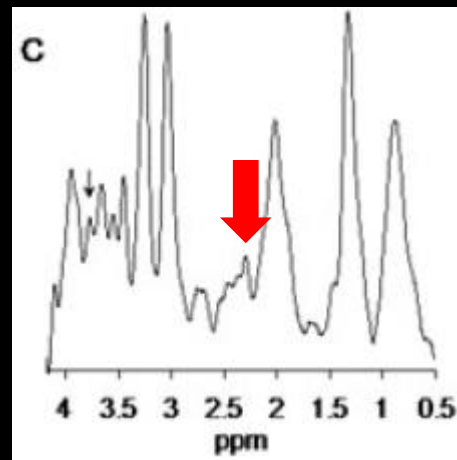
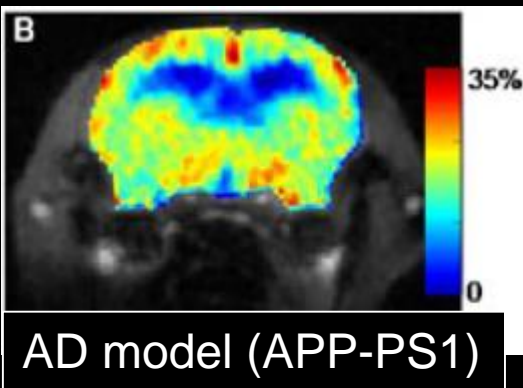
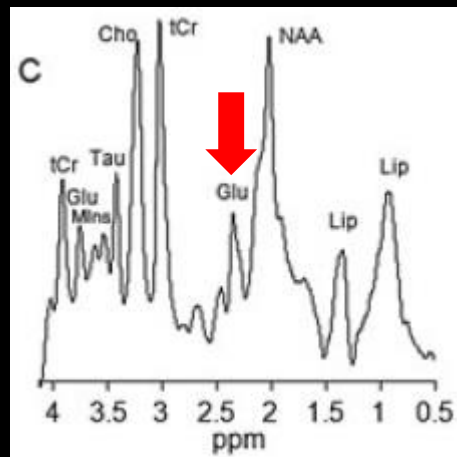
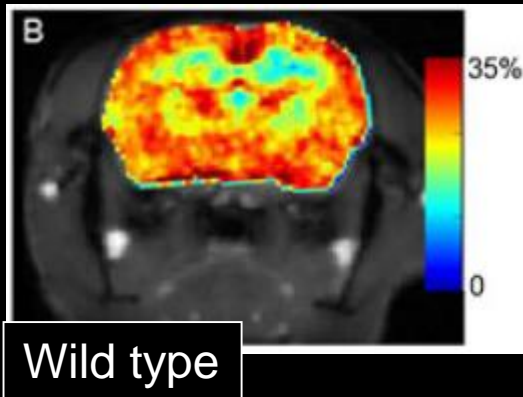
3.0 ppm

9.4T (animal)、7T (human)での報告

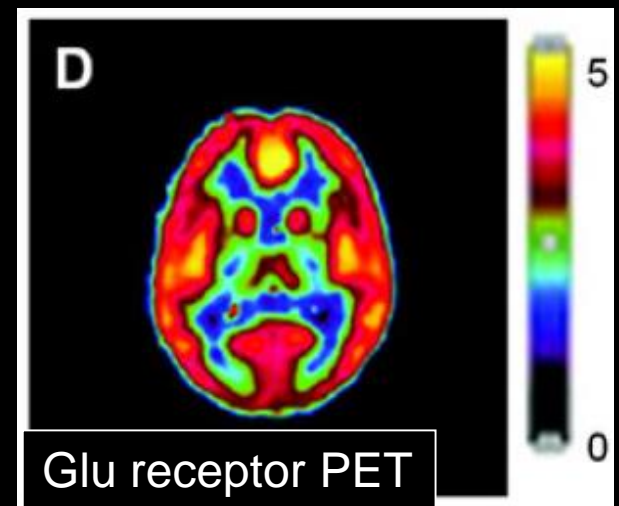
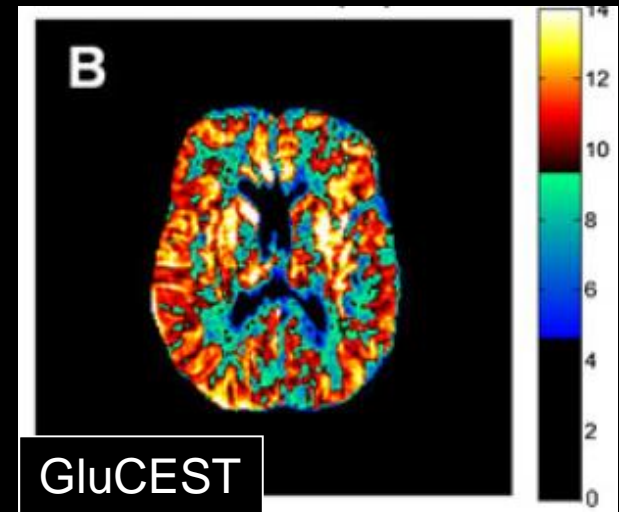


GluCEST

ADモデルへの応用



健常者の脳(7T)

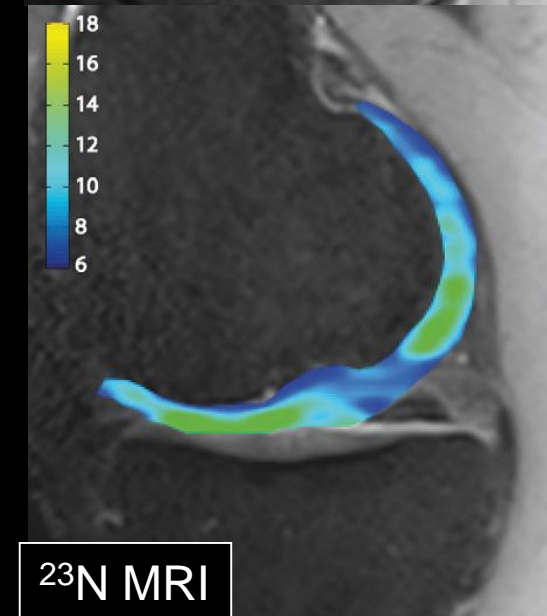
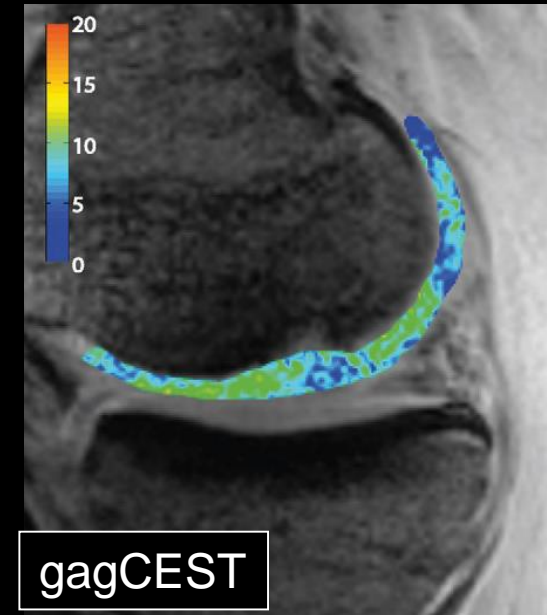
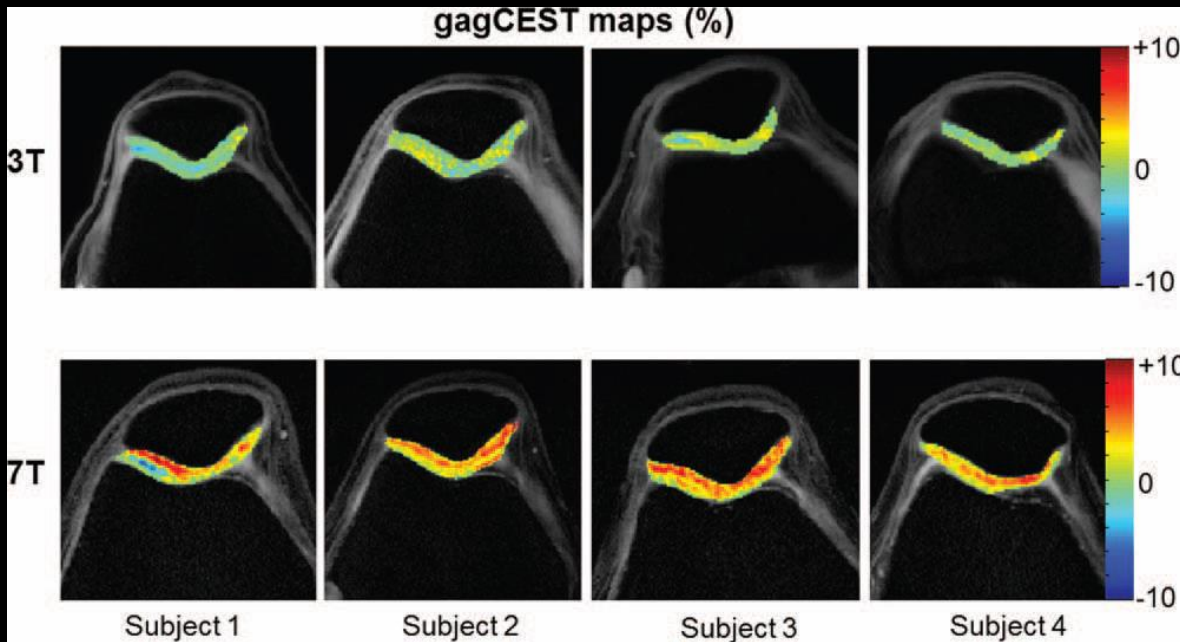


Glycosaminoglycans (gagCEST)

コンドロイチン硫酸など 関節軟骨 (-OH)

0.9-1.9 ppm

3T << 7T (human)との報告

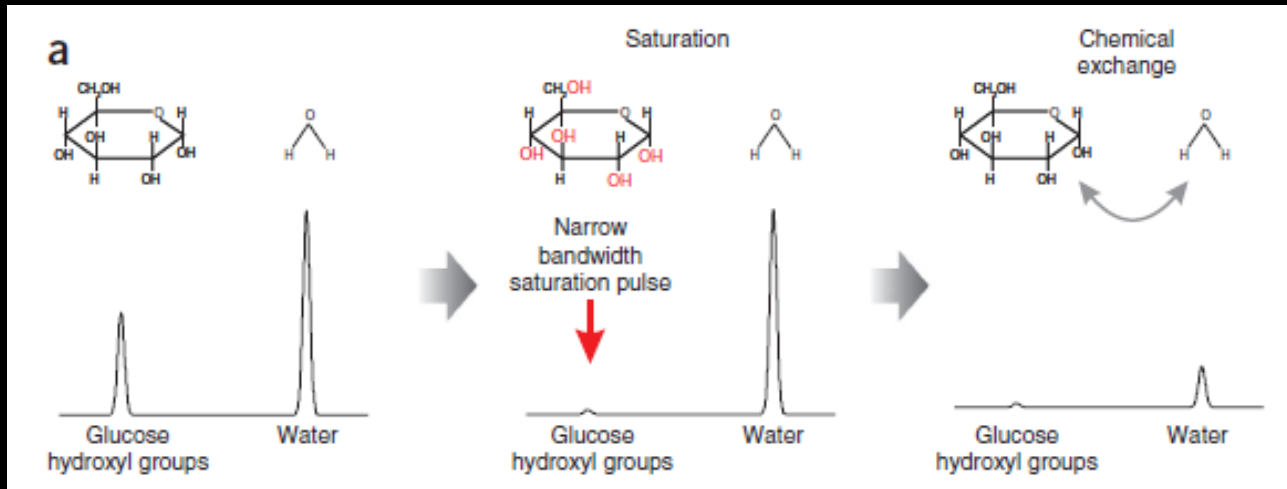


Singh A, et al. MRM 2012

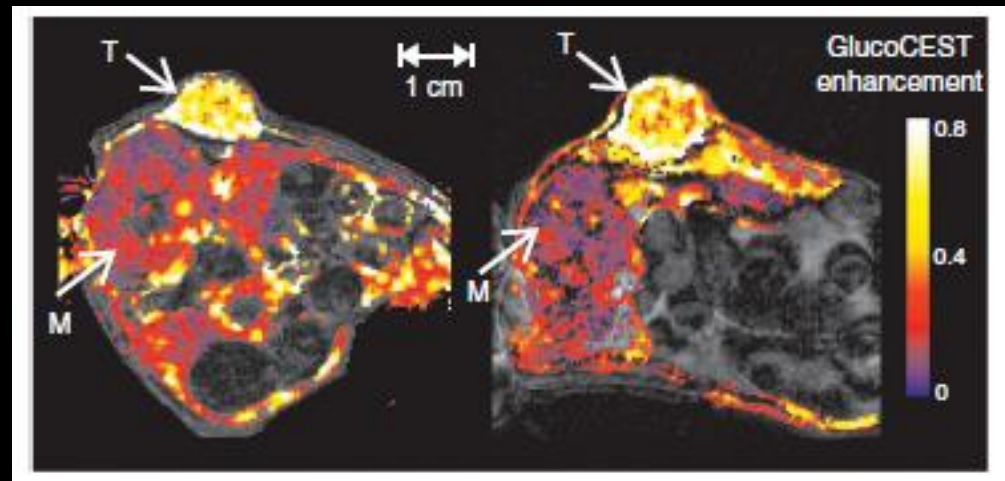
Schmitt B, et al. Radiology 2012

GlucoCEST

CESTイメージングによるglucose代謝の画像化



Glucose腹腔内投与 60分後



Walker-Samuel et al. Nat Med 2013

CESTイメージング まとめ

微量な溶質を検出するMR分子イメージング法

APTイメージングの脳腫瘍における有用性が明らかになりつつある

pHイメージング、Glutamate、Glucose代謝などが現在研究中

早朝からお疲れ様でした