

MRI based evaluation of BBB



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Contents

- Basic concept of DCE imaging
 - Pharmacokinetic parameters
 - Arterial input function (AIF)
 - T1 measurement
- Clinical application of DCE imaging

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MAGNETIC RESONANCE IN MEDICINE 17, 357-367 (1991)

Measurement of the Blood-Brain Barrier Permeability and Leakage Space Using Dynamic MR Imaging. 1. Fundamental Concepts

PAUL S. TOFTS AND ALLAN G. KERMODE

Multiple Sclerosis NMR Research Group, Institute of Neurology, Queen Square, London WC1N 3BG, United Kingdom

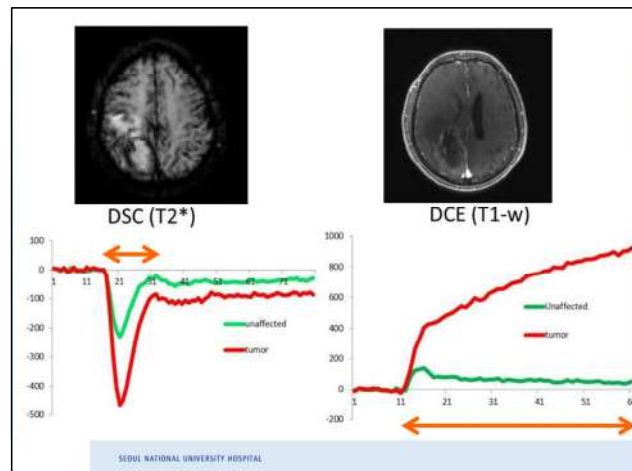
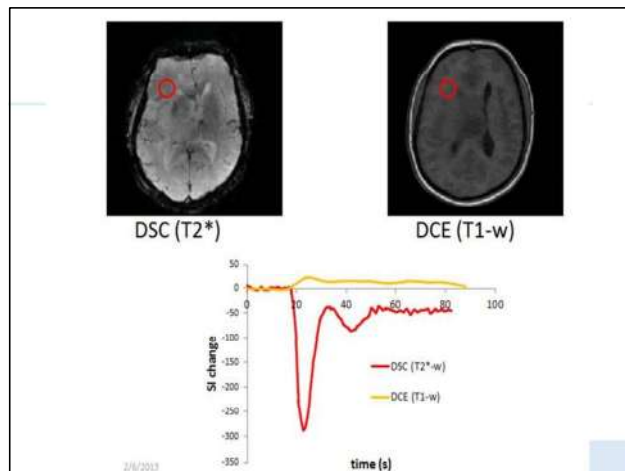
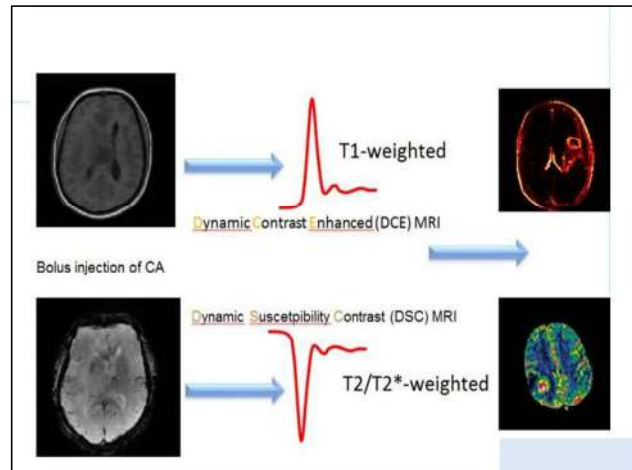
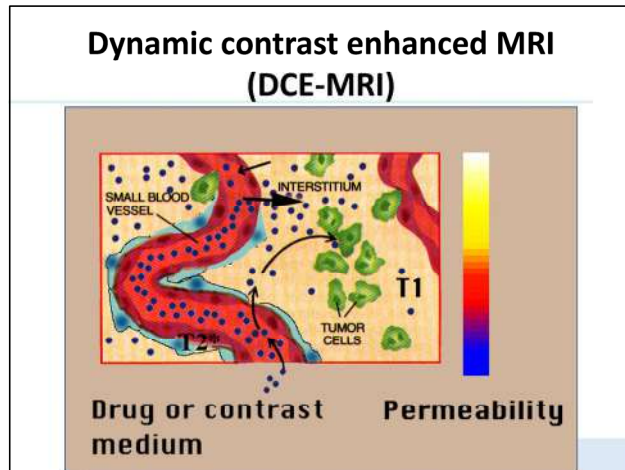
Received June 14, 1989; revised December 27, 1989

Leakage of Gd-DTPA through a defective blood-brain barrier is measured quantitatively using dynamic MRI scanning, in which repeated scans are made after a bolus injection. Image registration artifacts are minimized; a dose of 0.1 mM/kg and an IR sequence enable enhancement to be measured quantitatively. The triexponential enhancement curve is fitted to a theoretical model based on compartmental analysis. The transfer constant, or permeability surface area product per unit volume of tissue (k), and leakage space per unit volume of tissue (v_1) are measured. Estimates for a quickly enhancing multiple sclerosis lesion are $k = 0.050 \text{ min}^{-1}$, $v_1 = 21\%$; for a slow one $k = 0.013 \text{ min}^{-1}$, $v_1 = 49\%$. This implies permeability in the range $4-17 \times 10^{-6} \text{ cm s}^{-1}$, in broad agreement with other physiological methods. The method is noninvasive and can be used to make serial measurements in patients and in experimental animal models. The time course of pathological aspects of diseases with blood-brain barrier breakdowns, such as multiple sclerosis, tumors, and infections (e.g., HIV) can be studied, along with their response to therapy. The measurements are of physiological variables and are therefore independent of imaging equipment and field. © 1991 Academic Press, Inc.

Dynamic contrast enhanced MRI (DCE-MRI)

- Technique where enhancement of a tissue or organ is continuously monitored using MRI after bolus IV contrast medium
 - Low molecular weight contrast media (<1 kDa)
 - Diffuse into extravascular-extracellular space (does not cross cell membranes)
 - Experiment lasts a few minutes

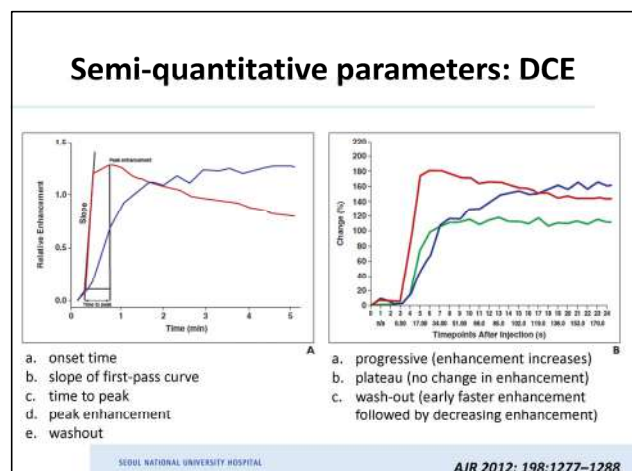
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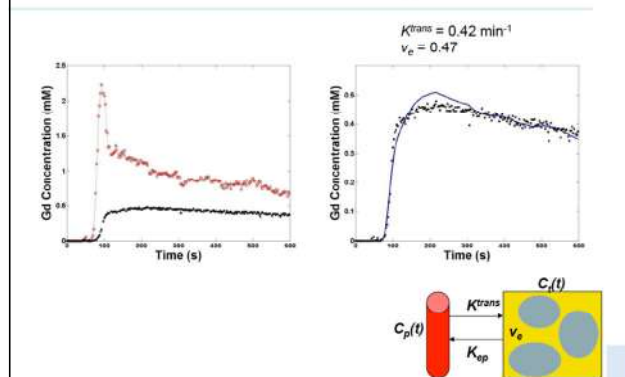
Key Perfusion Parameters: DSC

- **Cerebral Blood Flow (CBF)**
 - ✓ Delivery of blood to tissue / unit time
 - ✓ Units: ml / 100 g brain / min
- **Cerebral Blood Volume (CBV)**
 - ✓ Measure of autoregulation
 - ✓ Units: ml / 100 g brain
- **Mean Transit Time (MTT)**
 - ✓ Average time to flow thru capillaries (artery → vein)
 - ✓ Units: seconds
- **Time To Peak (TTP)**
 - ✓ Time to peak of the concentration-time curve

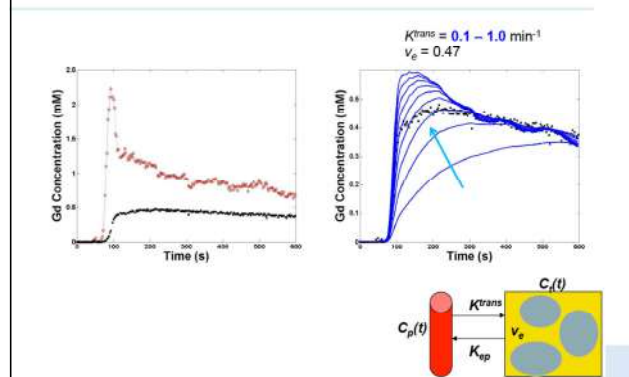
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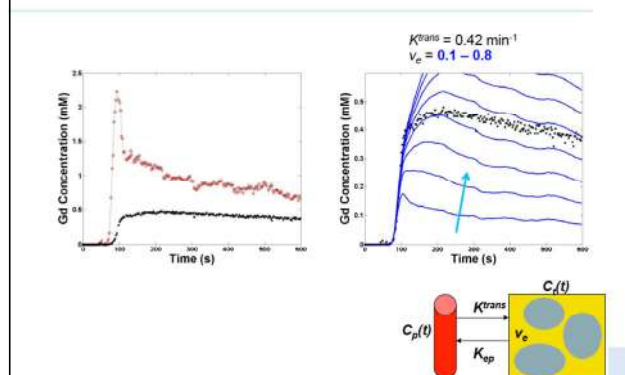
Curve fitting



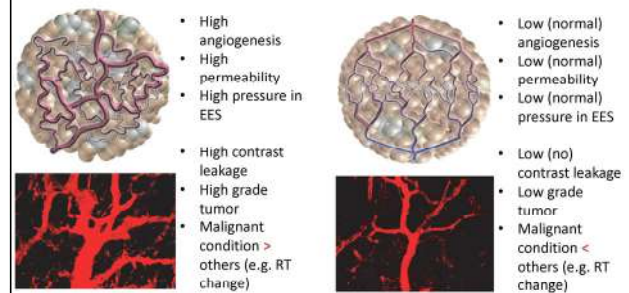
Effect of Ktrans



Effect of Ve



General concepts of DCE application



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Application of DCE imaging for pre-operative grading



Glioma: Application of Histogram Analysis of Pharmacokinetic Parameters from T1-Weighted Dynamic Contrast-Enhanced MR Imaging to Tumor Grading

S.C. Jung, J.a. Yeom, J.-H. Kim, I. Ryoo, S.C. Kim, H. Shin, A.L. Lee, T.J. Yun, C.-K. Park, C.-H. Sohn, S.-H. Park, and S.H. Choi

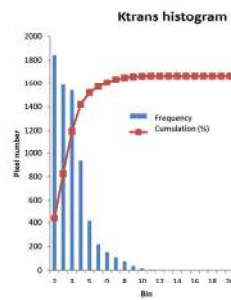
Table 1: The pharmacokinetic parameters in each grade of glioma^a

	Grade II ^b / Low-Grade ^c	Grade III ^b	Grade IV ^b	High-Grade ^c
K^{trans} ^d	0.027 ± 0.041	0.057 ± 0.091	0.158 ± 0.226	0.122 ± 0.195
v_e ^e	5.809 ± 10.381	15.469 ± 26.165	45.103 ± 63.888	35.059 ± 55.920
v_p ^e	3.858 ± 3.958	5.735 ± 5.772	10.624 ± 12.396	8.826 ± 10.723

Published January 2, 2014 as 10.3174/ajnr.A3825

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Cumulative histogram analysis



- Cumulative pixels over the range of pixels
- At each bin, all pixels (%) \leq that bin value (e.g. Bin 5: total number of pixels $\leq 5 \rightarrow 90\%$)
 - Low Ktrans pixel \uparrow : left shift
 - High Ktrans pixel \uparrow : right shift
- Reflection of high or low value (e.g. CBV, Ktrans, etc) distribution

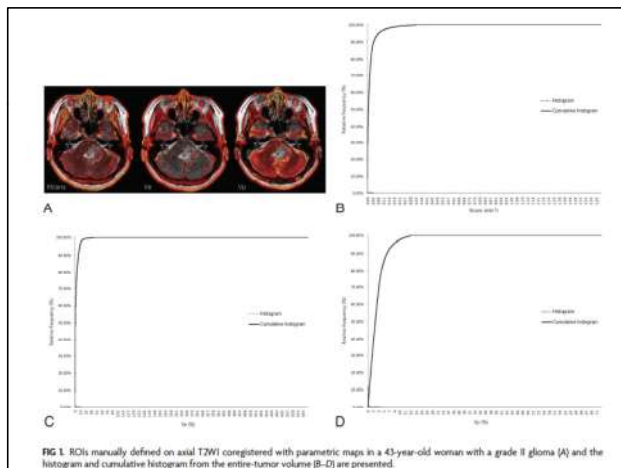
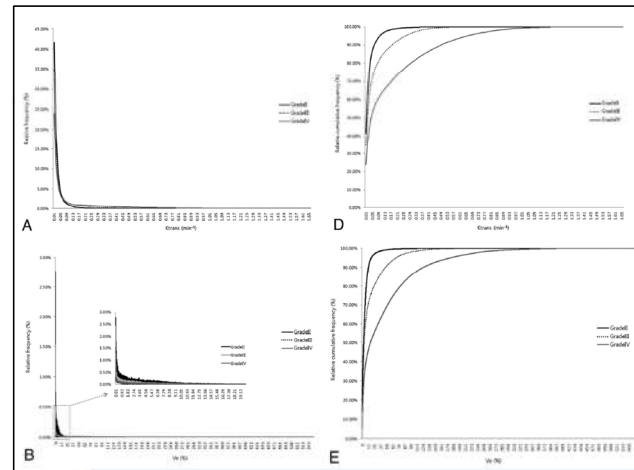


FIG 1. ROIs manually defined on axial T2WI coregistered with parametric maps in a 43-year-old woman with a grade II glioma (A) and the histogram and cumulative histogram from the entire-tumor volume (B-C) are presented.

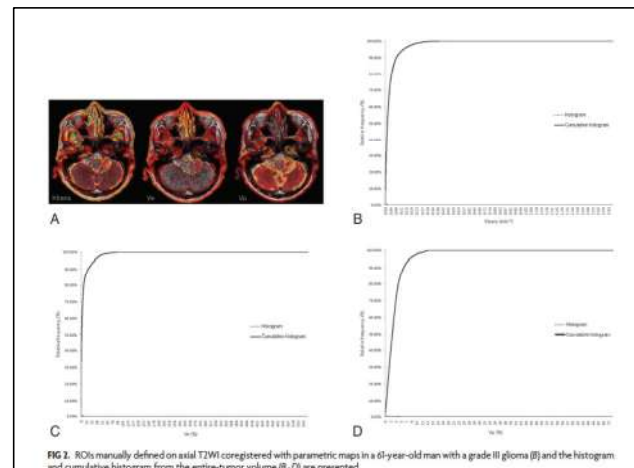


FIG 2. ROIs manually defined on axial T2WI coregistered with parametric maps in a 61-year-old man with a grade III glioma (A) and the histogram and cumulative histogram from the entire-tumor volume (B-C) are presented.

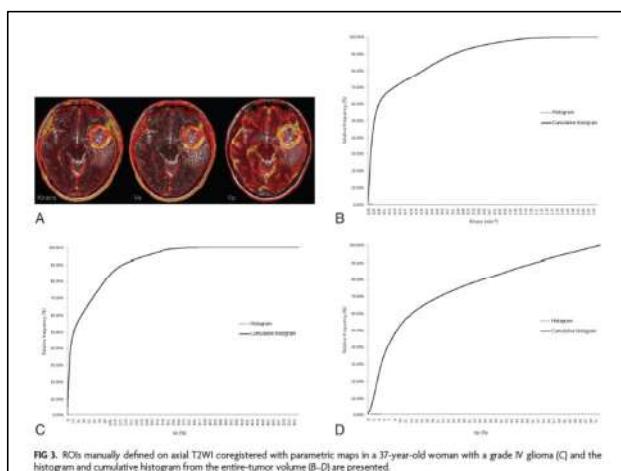
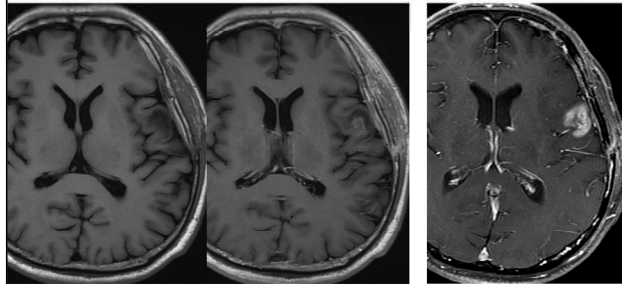


FIG 3. ROIs manually defined on axial T2WI coregistered with parametric maps in a 37-year-old woman with a grade IV glioma (A) and the histogram and cumulative histogram from the entire-tumor volume (B-C) are presented.

Application of DCE imaging for post-treatment evaluation

Question

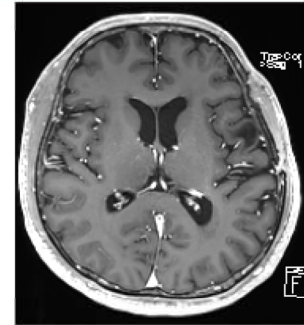


2009.1.20: immediate post-op

2010.4.17: s/p CCRT
(with Temozolomide)

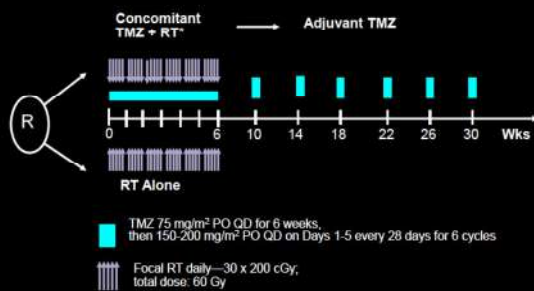
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Answer: 2011.3.20



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Phase III Study: New GBM Radiation ± Temozolomide



*PCP prophylaxis was required for patients receiving TMZ during the concomitant phase.

Stupp R, et al. *N Engl J Med* 2005;352:987-996

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma



Variable	Radiotherapy (N=286)	Radiotherapy plus Temozolomide (N=287)
Median overall survival (mo)	12.1 (11.2-13.0)	14.6 (13.2-16.8)
Overall survival (%)		
At 6 months	84.2 (80.0-88.5)	86.3 (82.3-90.3)
At 12 months	50.6 (44.7-56.4)	61.1 (55.4-66.7)
At 18 months	20.9 (16.2-26.6)	39.4 (33.8-45.1)
At 24 months	10.4 (6.8-14.1)	26.5 (21.3-31.7)
Median progression-free survival (mo)	5.0 (4.2-5.5)	6.9 (5.8-8.2)
Progression-free survival (%)		
At 6 months	36.4 (30.8-41.9)	53.9 (48.3-59.6)
At 12 months	9.1 (5.8-12.4)	26.9 (21.8-32.3)
At 18 months	3.9 (1.6-6.1)	18.4 (13.9-22.9)
At 24 months	1.5 (0.3-3.0)	10.7 (7.0-14.3)

*A total of 160 patients in the radiotherapy group and 60 patients in the radiotherapy-plus-temozolomide group received temozolomide as salvage therapy. †Denotes confidence interval.

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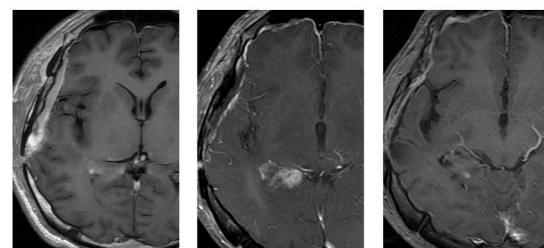
N Engl J Med 2005;352:987-996

Pseudoprogression after CCRT

- = Therapy-induced necrosis
 - Radiotherapy may enhance the efficacy of chemotherapy by maximizing drug uptake through disruption of BBB and cell membrane
 - Lead to the observation of an early radiological increase in contrast enhancement at MRI consequent to alterations in the BBB, **thus falsely suggesting tumor progression**

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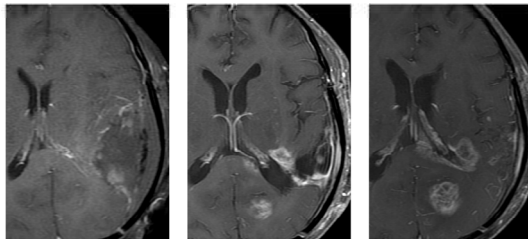
Pseudoprogression

2009.2.5:
immediate post-op2009.5.7:
s/p CCRT

2009.11.7

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True progression



2009.2.6:
immediate post-op

2009.5.18:
s/p CCRT

2009.6.16

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Hypothesis

- What are in the enhancing lesions, which are confirmed as pseudoprogression?
 - Malignant cells, but responding to CCRT with TMZ
 - Not same to primary high grade glioma cells
 - Having destination to be dead?
 - Necrotic tissues
 - Inflammatory cells
- Difference of physiologic characteristics b/w pseudoprogression and true progression
 - Lower permeability in pseudoprogression

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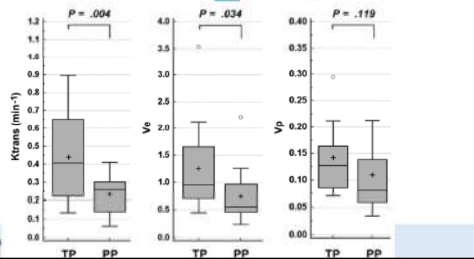
Glioblastoma Treated with Concurrent Radiation Therapy and Temozolomide Chemotherapy:

Differentiation of True Progression from Pseudoprogression with Quantitative Dynamic Contrast-enhanced MR Imaging¹

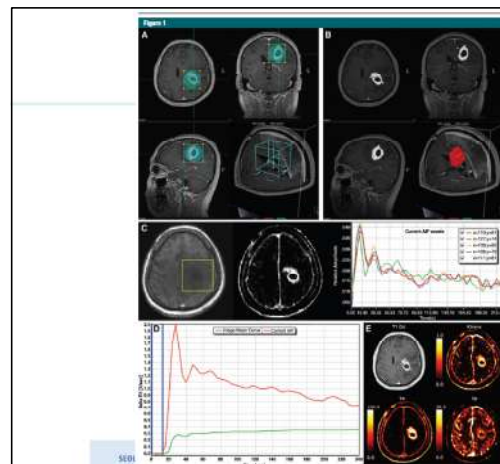
Radiology

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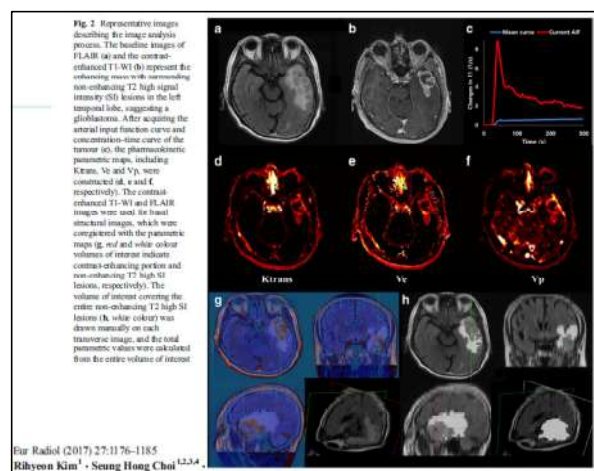
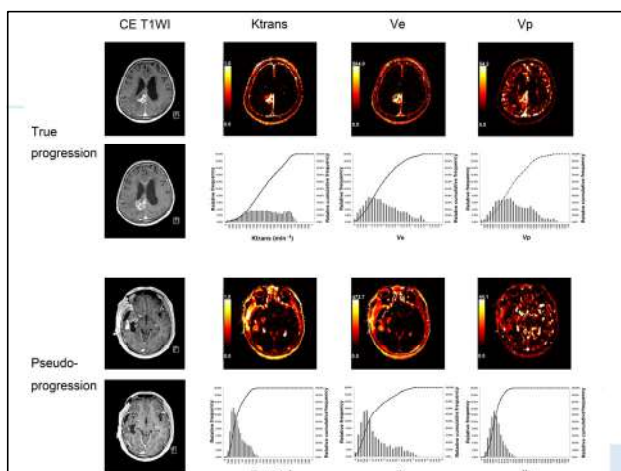
Radiology: Volume 274: Number 3—March 2015



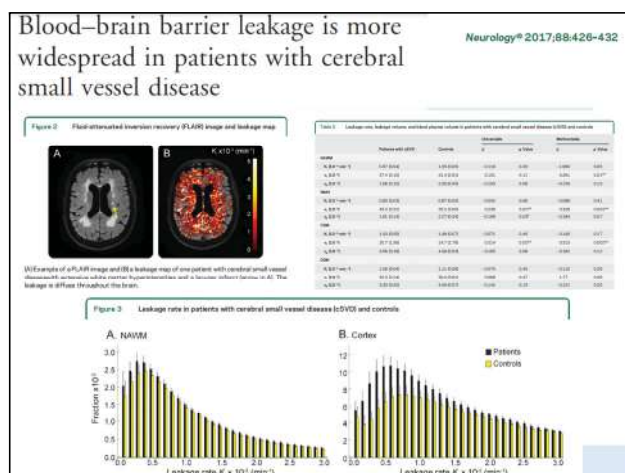
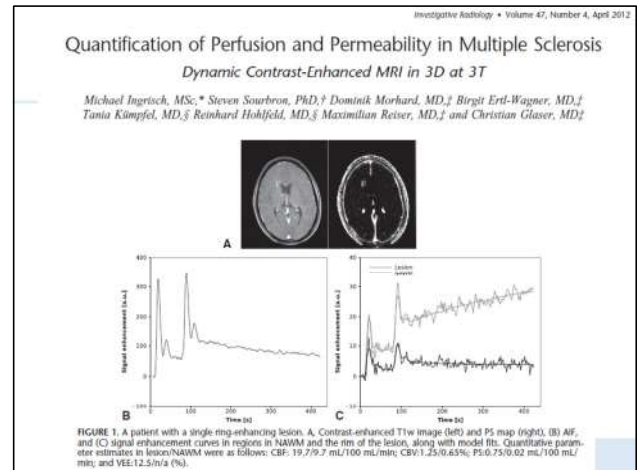
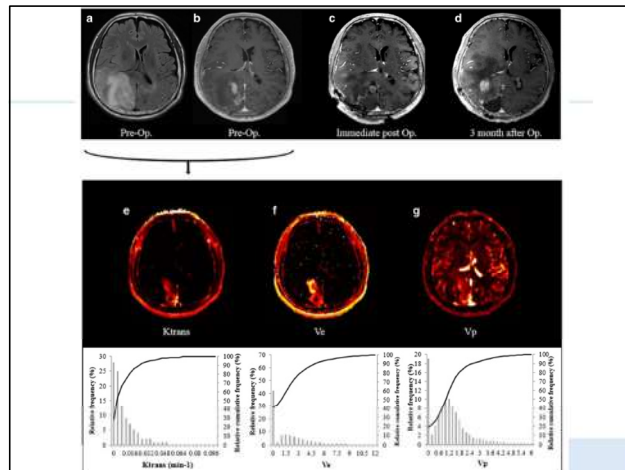
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Bar Radiol (2017) 27:1176-1185
Rihyeon Kim¹ · Seung Hong Choi^{1,2,3,4}



Thank you for your attention

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