Advance imaging and Standardization in acute stroke

Seung Chai Jung, MD, PhD

Associate Professor, Department of Radiology and Research Institute of Radiology,

University of Ulsan College of Medicine, Asan Medical Center

➢ **Funding:** The research was supported by a grant from the Ministry of Food and Drug Safety in 2018 (No. 18182MFDS402).

Overview

- Advanced techniques in acute stroke MRI

  1) Fast imaging

  2) Metabolic imaging

- Clinical trial imaging in acute ischemic stroke:

  Recommendation & Guideline with Standardization

Fast scan for MRI

Six-Minute Magnetic Resonance Imaging Protocol for Evaluation of Acute Ischemic Stroke

Pushing the Boundaries

Kambiz Nael, MD; Rihan Khan, MD; Gagandeep Choudhary, MD; Arash Meshksar, MD; Pablo Villablanca, MD; Jennifer Tay, MD; Kendra Drake, MD; Bruce M. Coull, MD; Chelsea S. Kidwell, MD

Background and Purpose—If magnetic resonance imaging (MRI) is to compete with computed tomography for evaluation of patients with acute ischemic stroke, there is a need for further improvements in acquisition speed.

Methods—Inclusion criteria for this prospective, single institutional study were symptoms of acute ischemic stroke within 24 hours onset, National Institutes of Health Stroke Scale ≥3, and absence of MRI contraindications. A combination of echo-planar imaging (EPI) and a parallel acquisition technique were used on a 3T magnetic resonance (MR) scanner to accelerate the acquisition time. Image analysis was performed independently by 2 neuroradiologists.

Results—A total of 62 patients met inclusion criteria. A repeat MRI scan was performed in 22 patients resulting in a total of 84 MRIs available for analysis. Diagnostic image quality was achieved in 100% of diffusion-weighted imaging, 100% EPI-fluid attenuation inversion recovery imaging, 98% EPI-gradient recalled echo, 90% neck MR angiography and 96% of brain MR angiography, and 94% of dynamic susceptibility contrast perfusion scans with interobserver agreements (k) ranging from 0.64 to 0.84. Fifty-nine patients (95%) had acute infarction. There was good interobserver agreement for EPI-fluid attenuation inversion recovery imaging findings (k=0.78; 95% confidence interval, 0.66–0.87) and for detection of mismatch classification using dynamic susceptibility contrast-Tmax (k=0.92; 95% confidence interval, 0.87–0.94). Thirteen acute intracranial hemorrhages were detected on EPI-gradient recalled echo by both observers. A total of 68 and 72 segmental arterial stenoses were detected on contrast-enhanced MR angiography of the neck and brain with k=0.93, 95% confidence interval, 0.84 to 0.96 and 0.87, 95% confidence interval, 0.80 to 0.90, respectively.

Conclusions—A 6-minute multimodal MR protocol with good diagnostic quality is feasible for the evaluation of patients with acute ischemic stroke and can result in significant reduction in scan time rivaling that of the multimodal computed tomographic protocol. **(*Stroke*. 2014;45:1985-1991.)**

Key Words: magnetic resonance angiography ■ magnetic resonance imaging ■ perfusion imaging ■ stroke

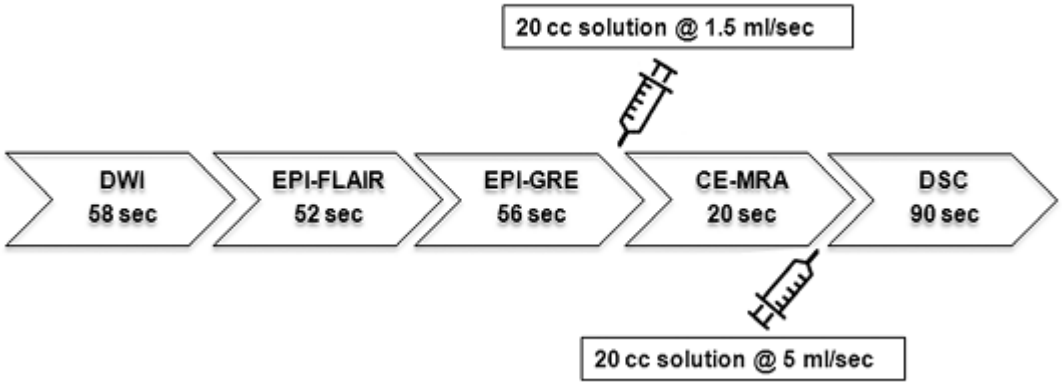
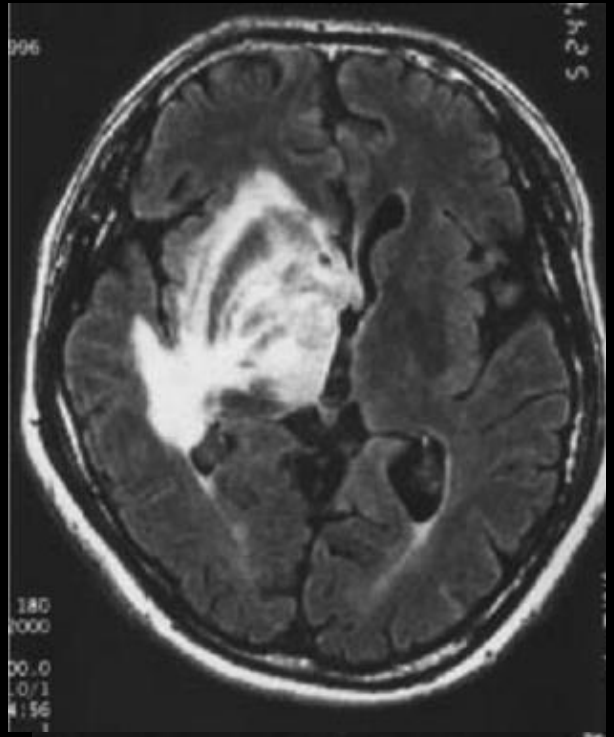
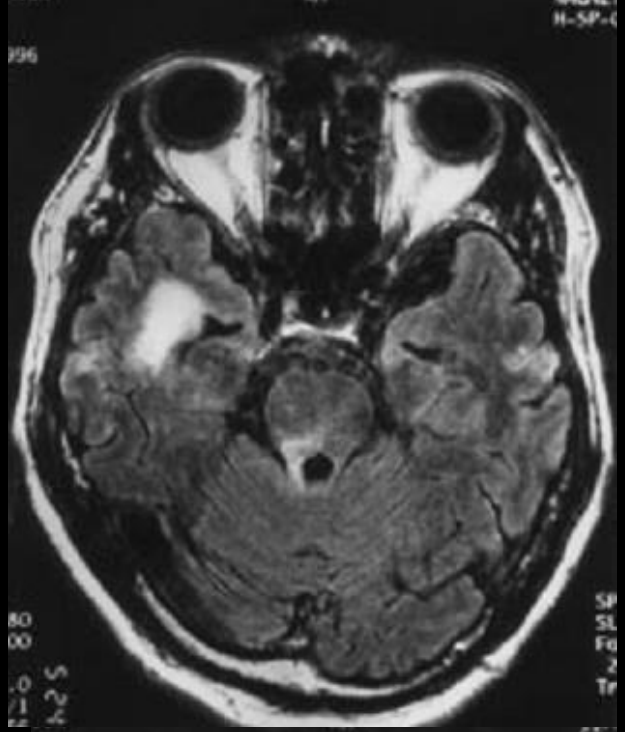
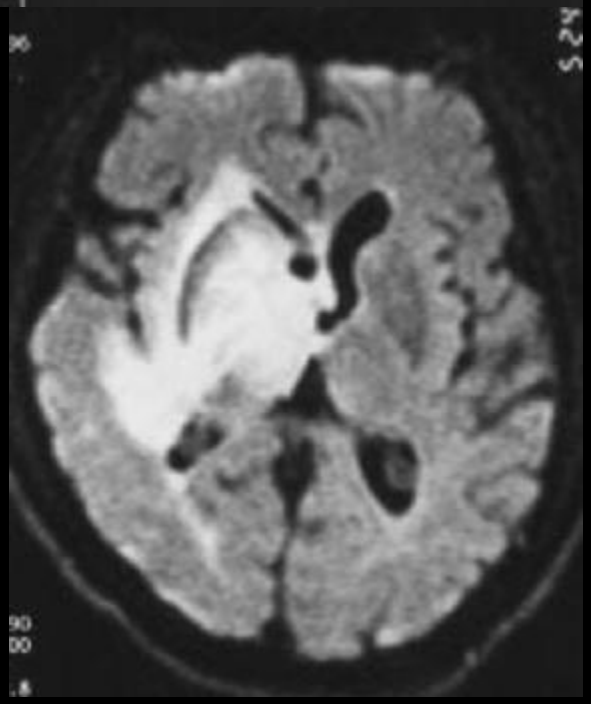


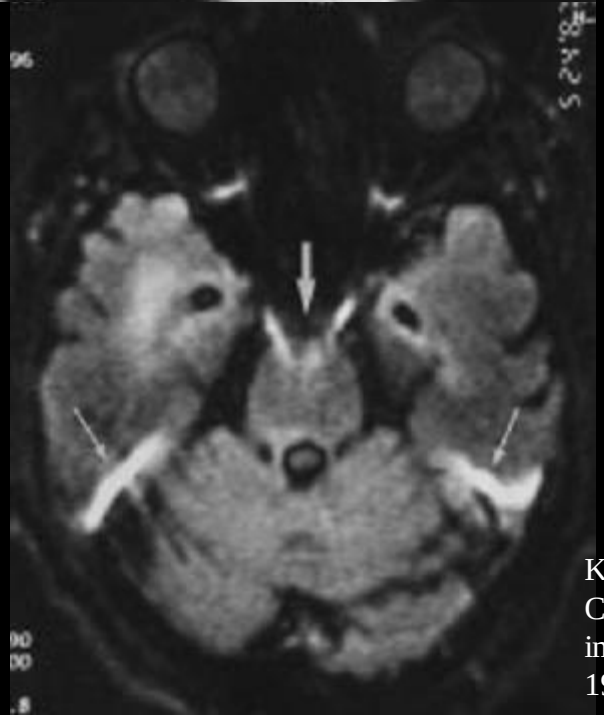
Table 1. MR Imaging Protocol and Sequence Parameters

	DWI	EPI-FLAIR	EPI-GRE	CE-MRA	DSC
TR/TE, ms	4600/65	10000/82	1860/48	3.3/1.2	1450/22
FA, °	90	90	90	25	90
Matrix, mm	160	128	192	448	128
FOV, mm	220	220	220	340	220
Slices (n×thickness), mm	30×4	30×4	40×3	120×0.8	30×4
GRAPPA	3	3	3	4	3
Acquisition time, s	58	52	56	22	90

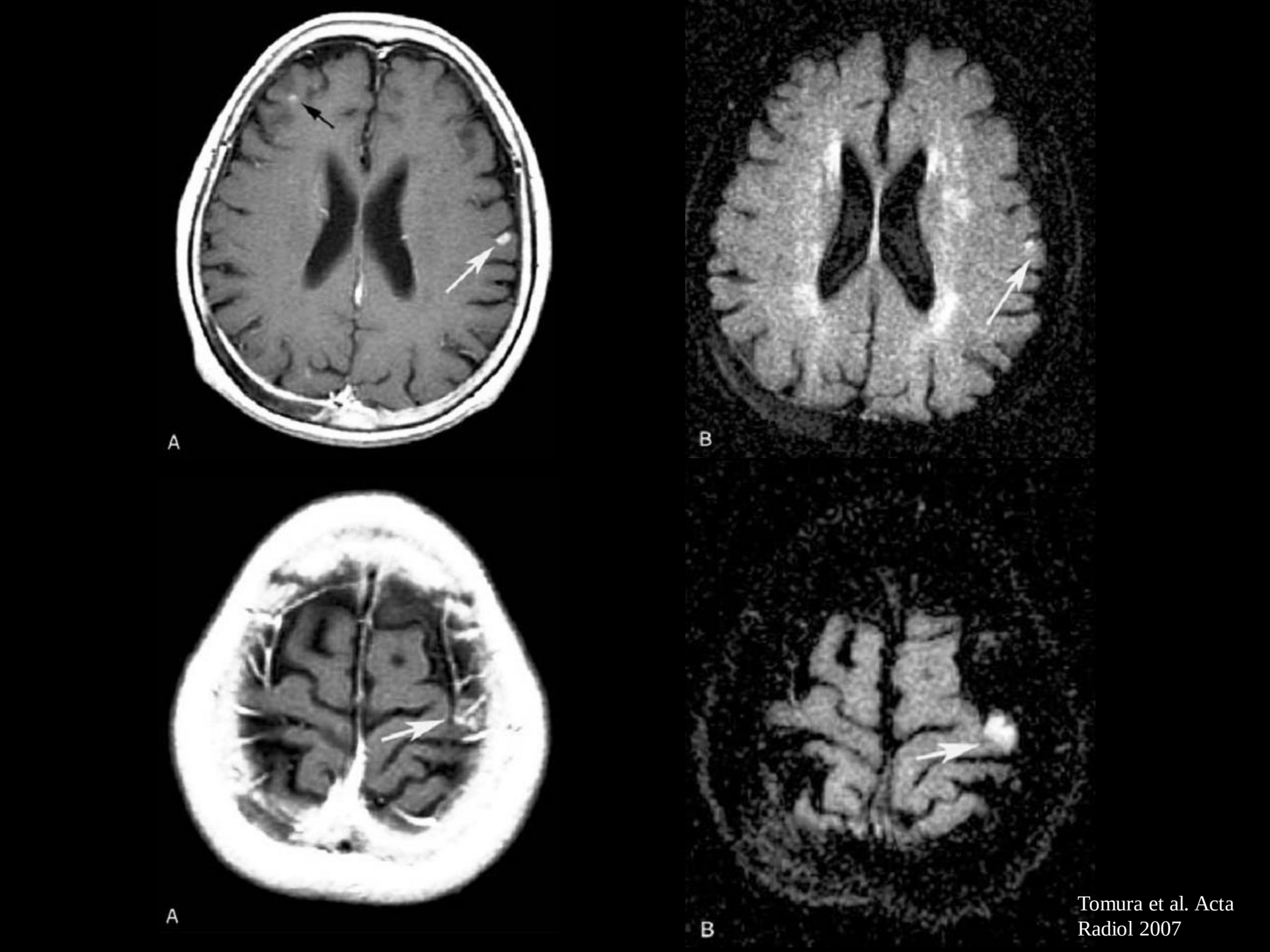




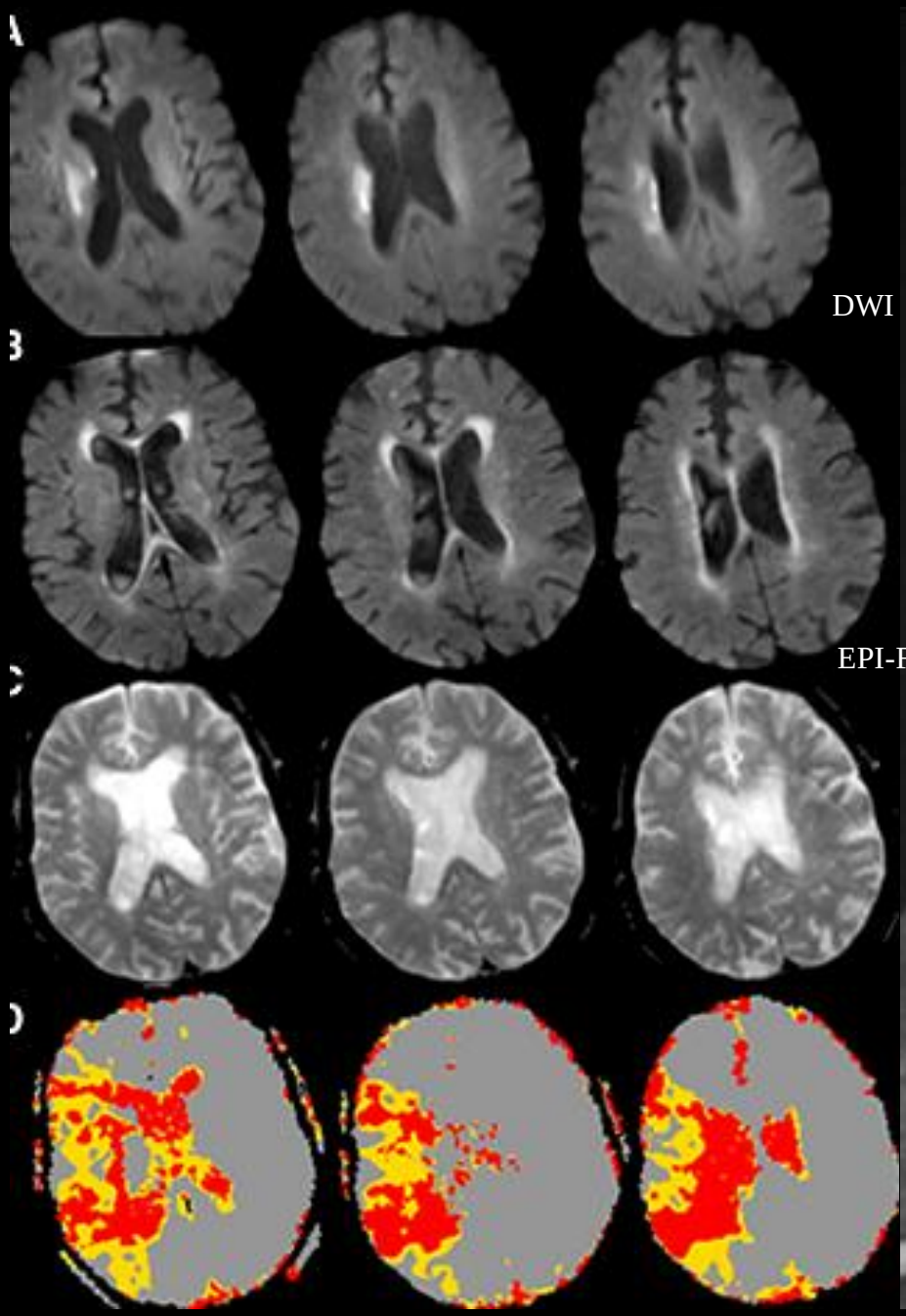


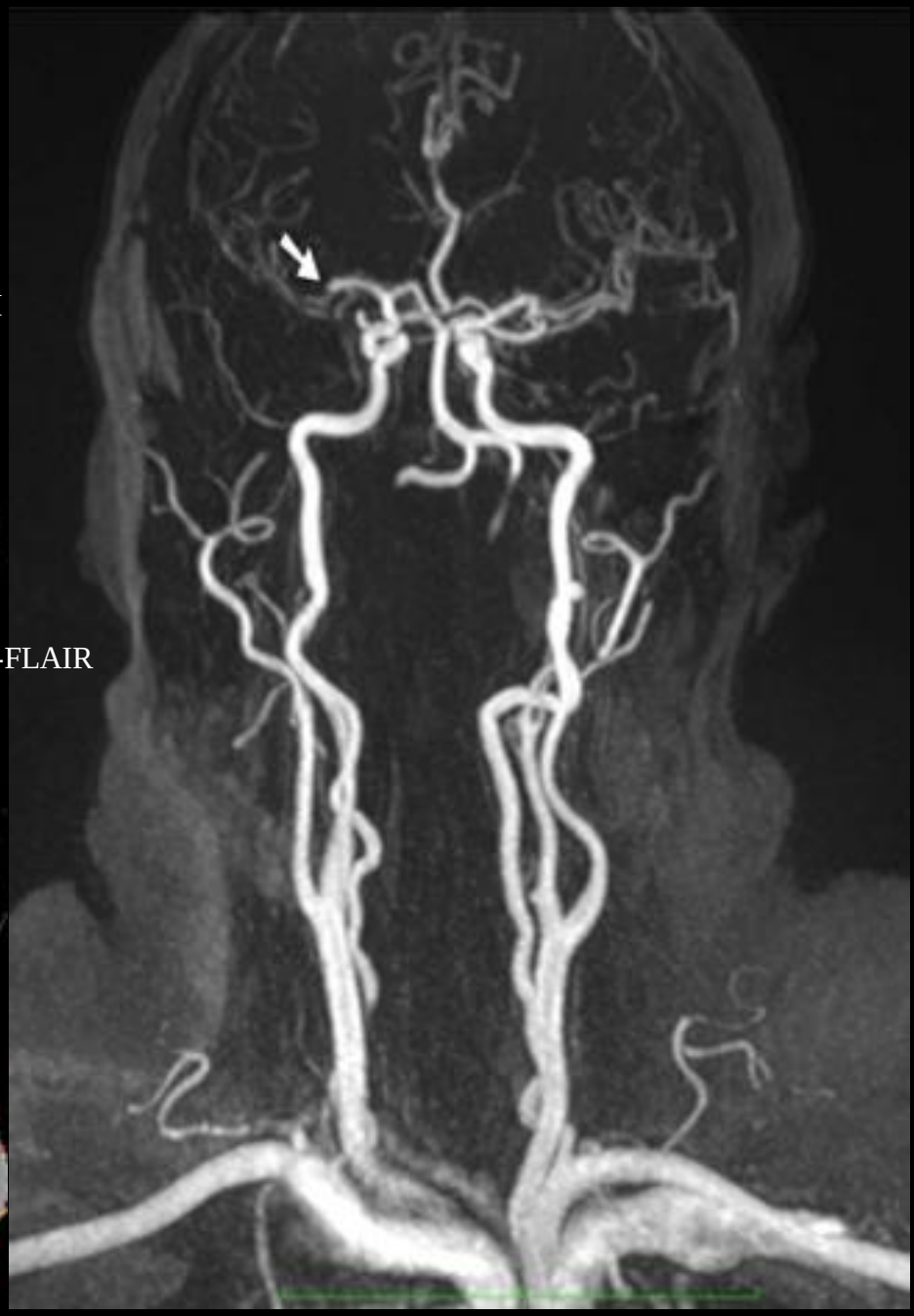


Korogi et al.
Computerized medical imaging and graphics
1999



Tomura et al. Acta Radiol 2007



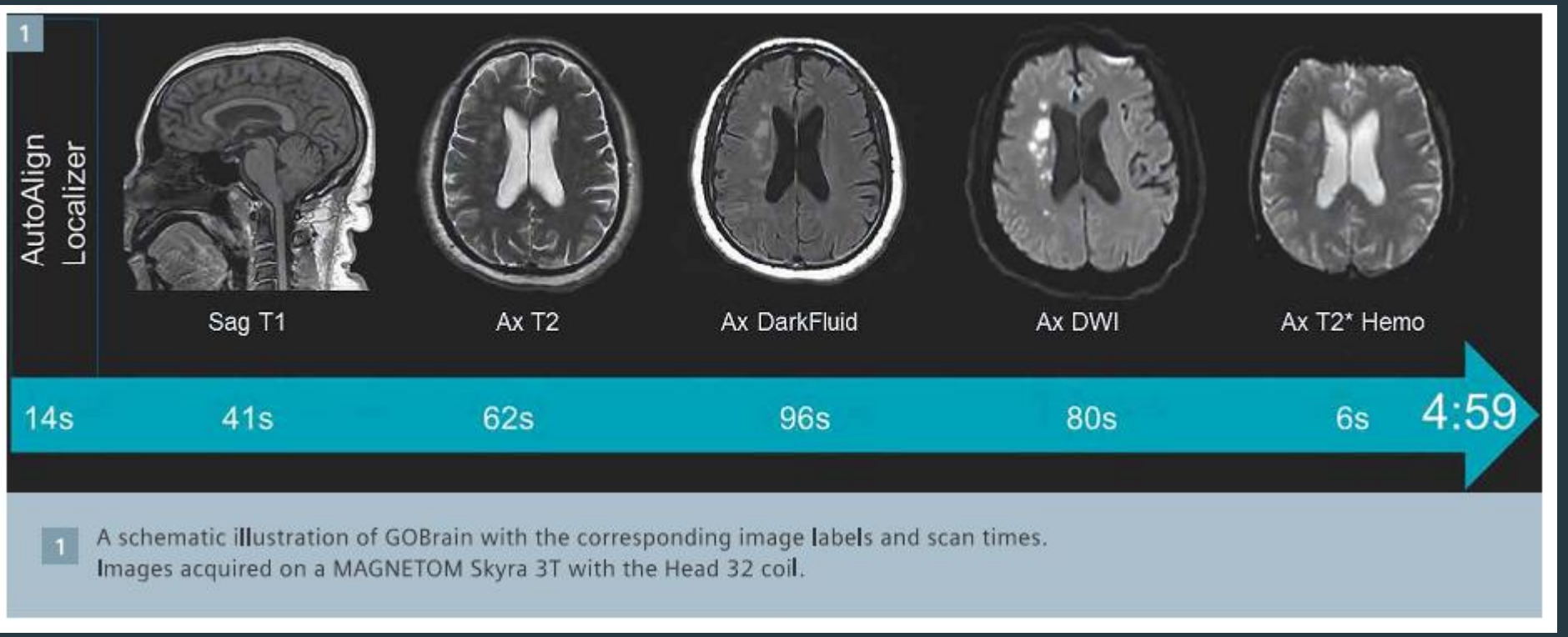


Nael et al. Stroke 2014

Ultra Fast Brain (GE Architect)

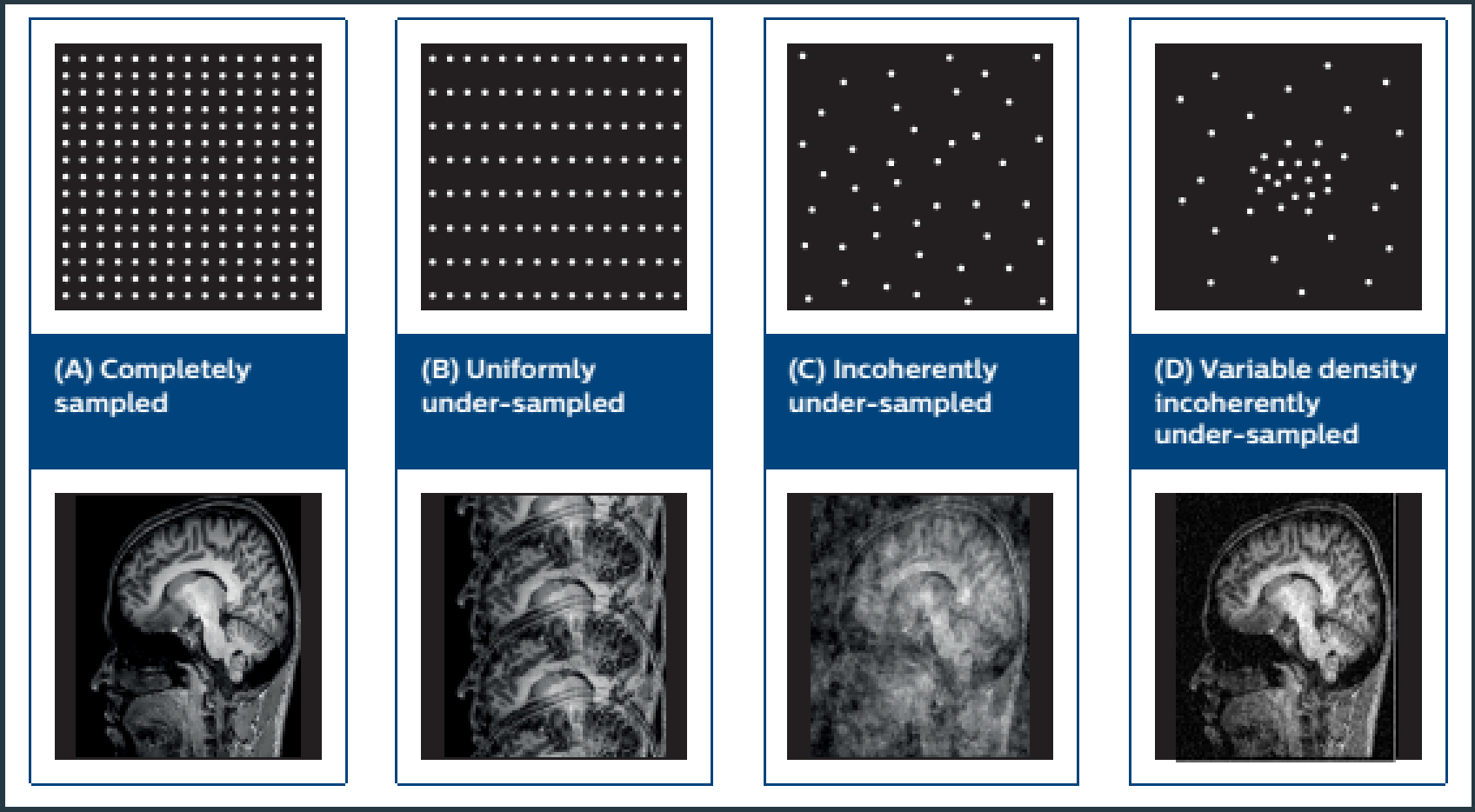
- DWI (**Hyperband**) → 00:10
- T2 SSFSE → 00:10
- T1 SPGR → 00:25
- T2 * GRE → 00:10
- 3D TOF (**Hypersense**) → 0:38

GO Brain (Siemens)

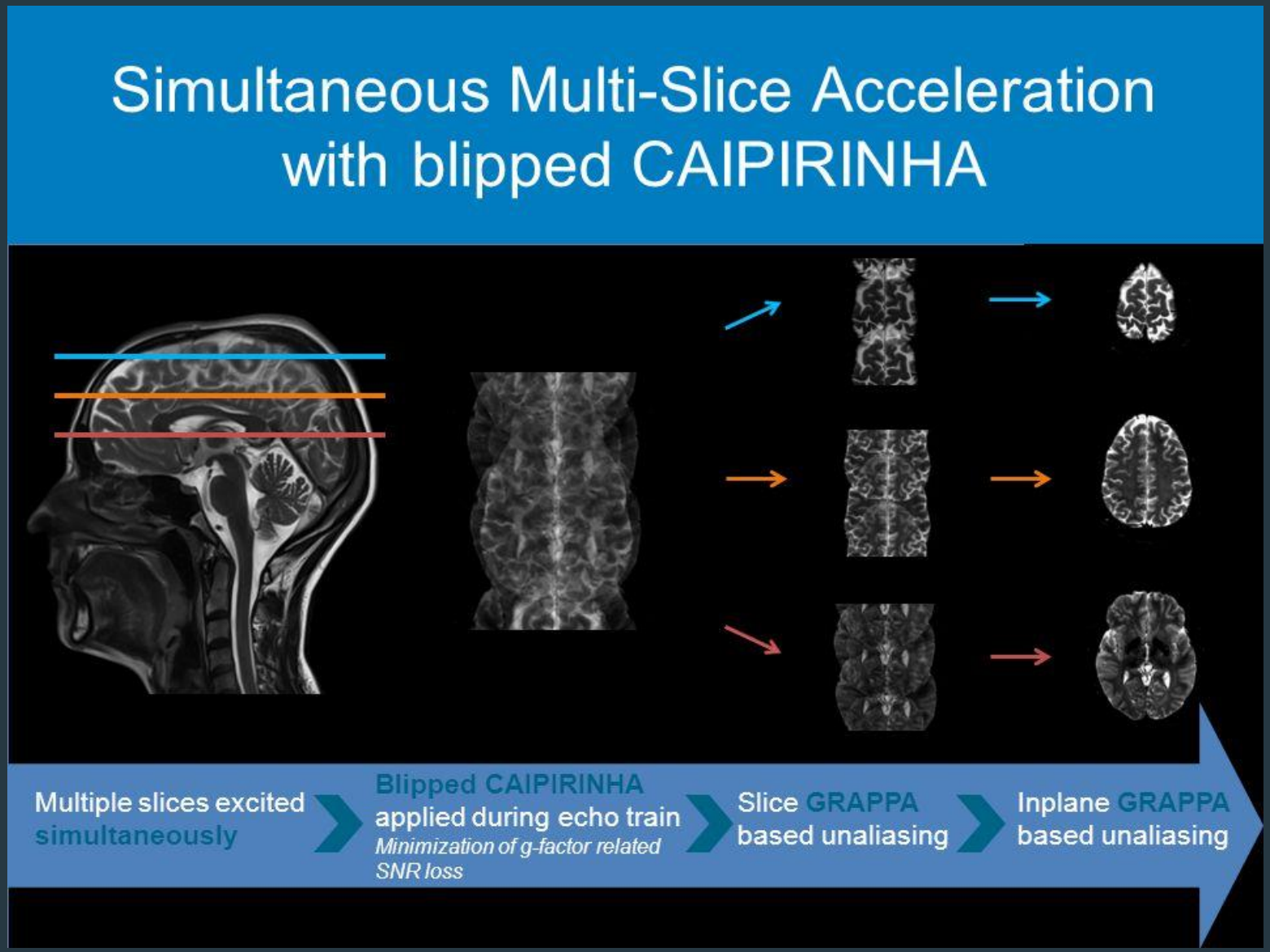


- Simultaneous multi-slice imaging = Hyperband
- Compressed sensing= Hypersense
- 3T

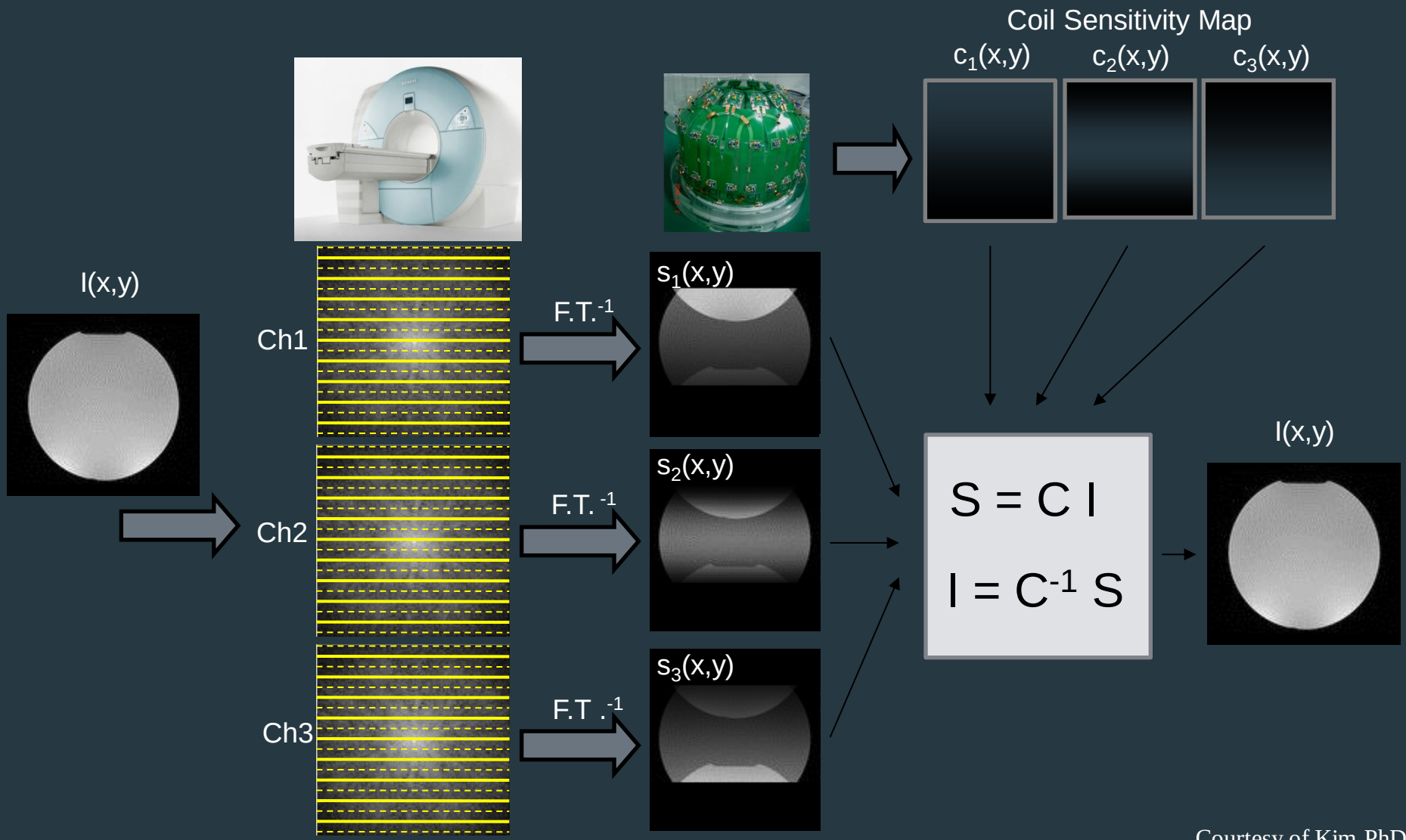
Techniques: Compressed sensing



Techniques: Multi-band



Techniques: Parallel imaging



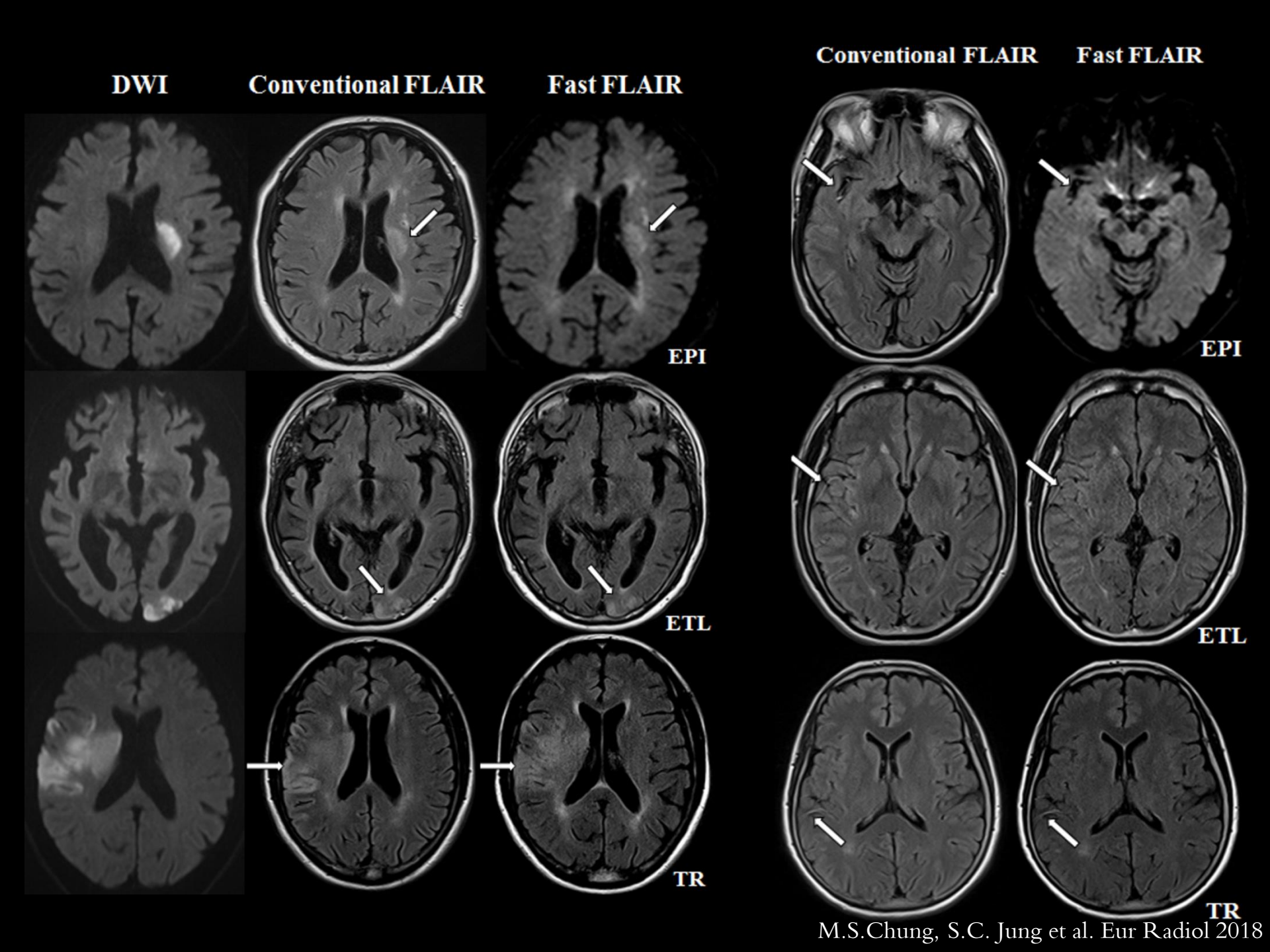
Courtesy of Kim PhD.

Fast scan for 1.5 T MRI

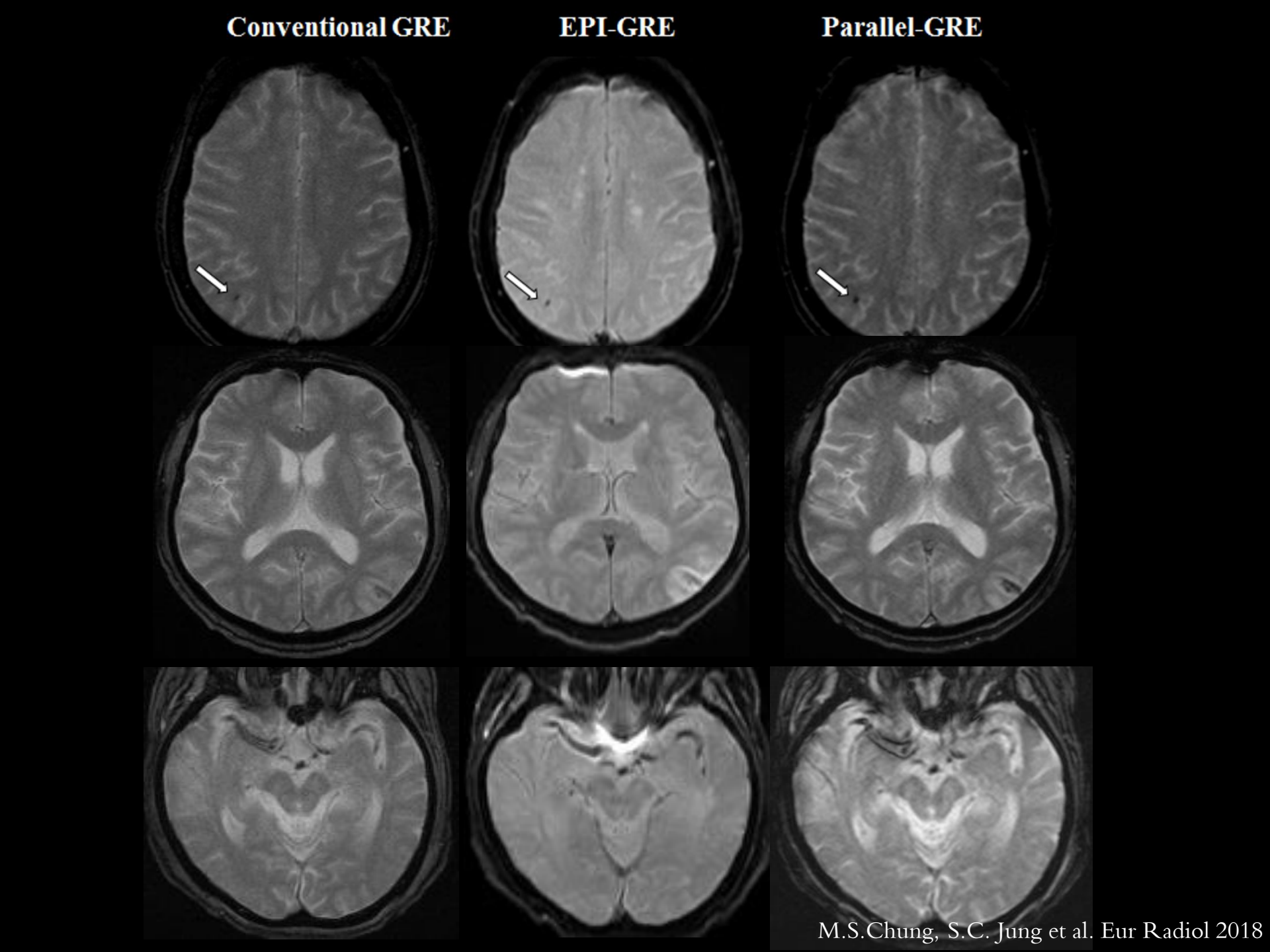
- Siemens Avanto 1.5T ER (5 min 8 s ~ 6min 43s) + 2 min (조영제)

	TR/TE/IR	FA	Matrix	FOV	Slices (nxthickness)	ETL	GRAPPA	NAV	Scan time
Localizer									10 s
Scout									10 s
FLAIR 기존	9000 / 109 / 2500	150	256 x 190	210 x 184	20 x 5	21		1	128 s
FLAIR EPI	9000/101/2000	90	**128 x 128**	230 x 230	20 x 5	**128 (EPI)**		**2**	45 s
FLAIR ETL	9000/102/2500	150	**192 x 192**	210 x 184	20 x 5	**32**	2	1	74 s
FLAIR TR	**5560**/109/1930	150	256 x 256	210 x 184	20 x 5	21	2	1	79 s
GRE 기존	690 / 16	15	256 x 205	210	20 X 5			1	141 s
GRE Parallel	765/26	20	**192 x 163**	220 x 220	20 x 5		**3**	1	54 s
GRE EPI	2260/48	90	**192 x 192**	230 x 230	20 X 5	**192 (EPI)**	**2**	10	29 s
DWI									81 s
PWI									61 s
	TR/TE/IR	FA	Slices per slab	FOV	Slices thickness	ETL	GRAPPA	NAV	Scan time
CE MRA 기존	3.67/1.31	30	240	340	0.5		2	1	74 s
CE MRA	3.37/1.2	25	**144**	340	**0.8**		**3**	1	39 s

M.S.Chung, S.C. Jung et al. Eur Radiol 2018



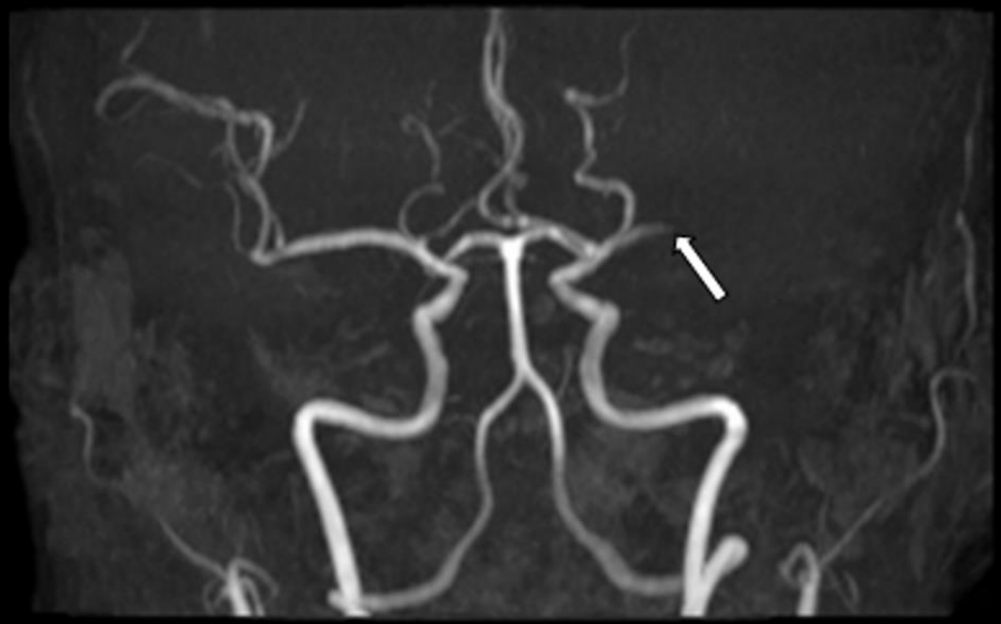
M.S.Chung, S.C. Jung et al. Eur Radiol 2018

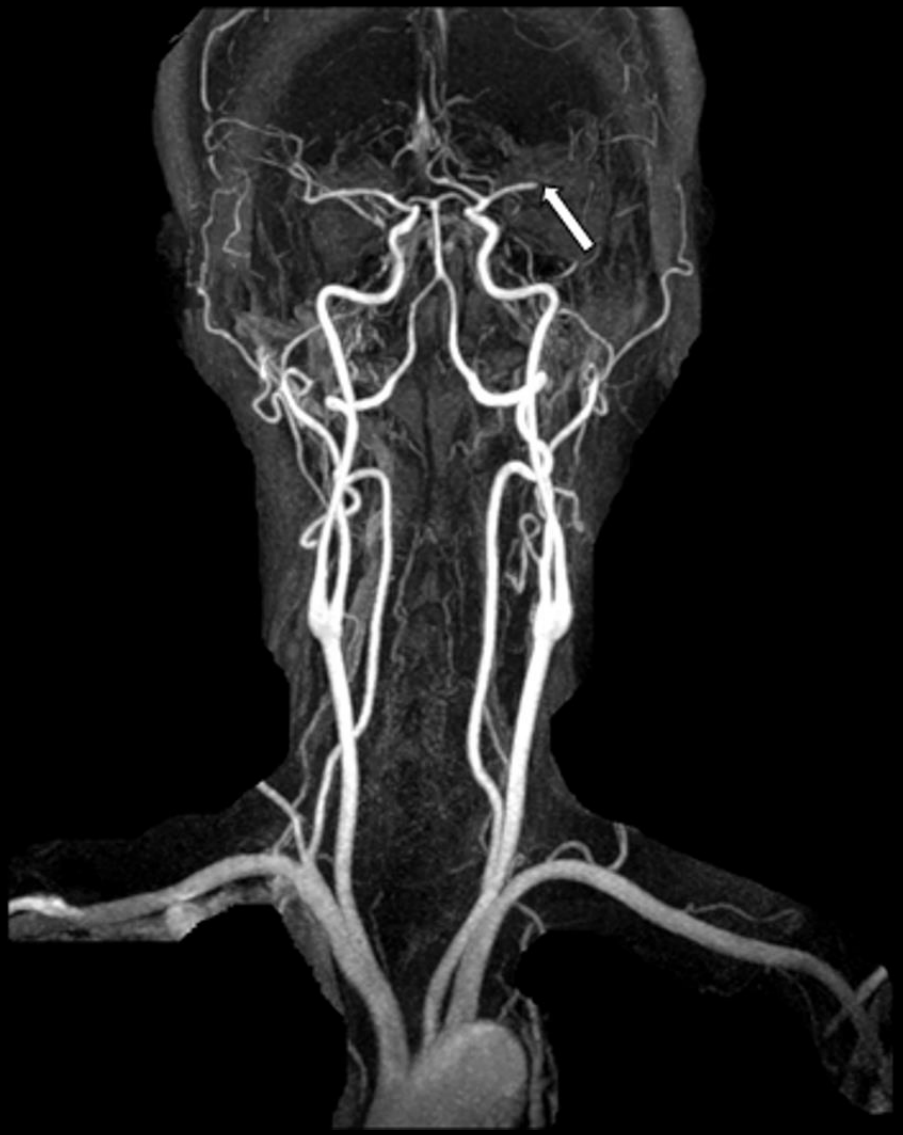


M.S.Chung, S.C. Jung et al. Eur Radiol 2018

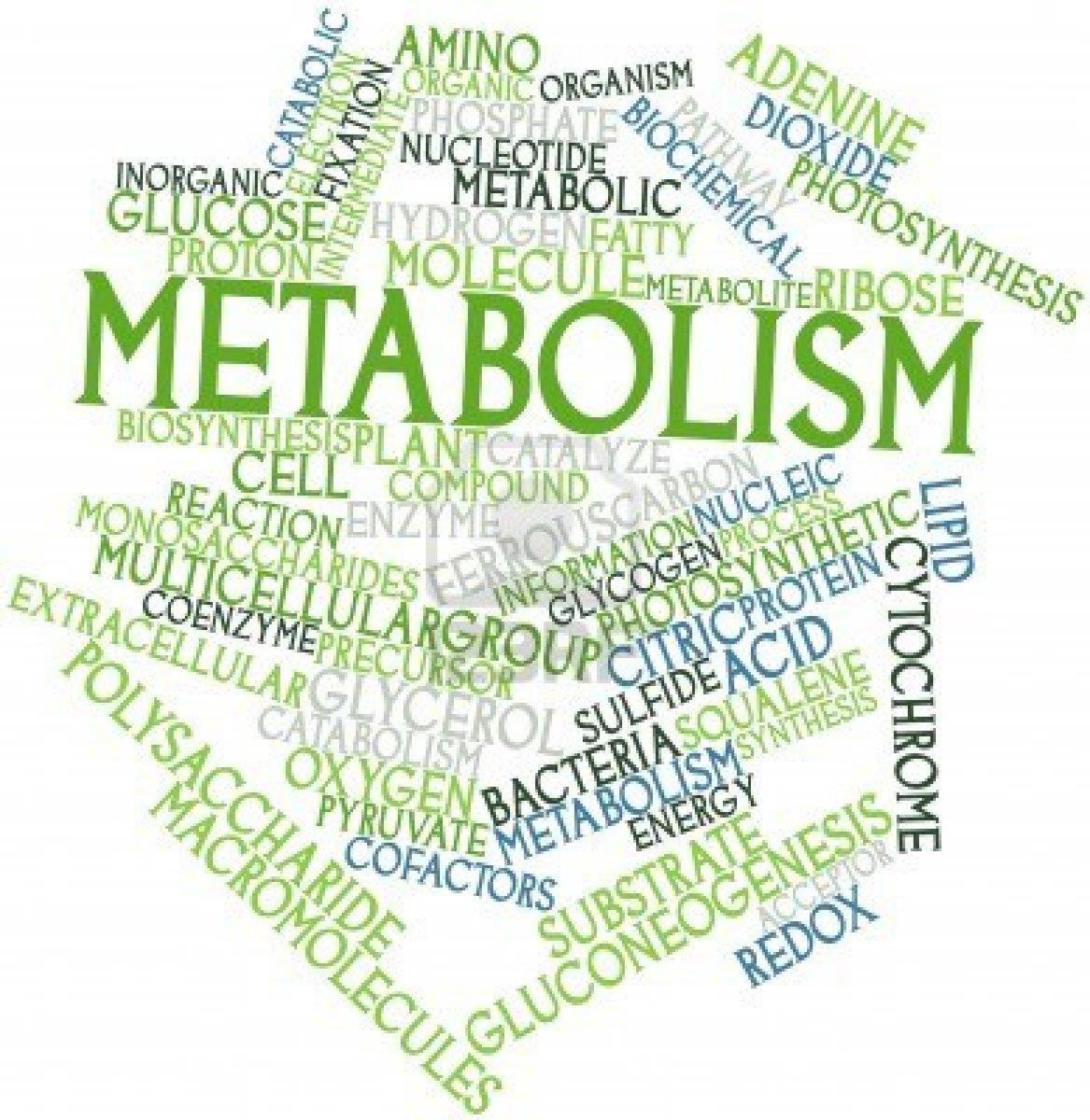
TOF-MRA

Fast CE-MRA





M.S.Chung, S.C. Jung et al. Eur Radiol 2018


METABOLISM
AMINO
ORGANISM
ADENINE
DIOXIDE
PHOTOSYNTHESIS
NUCLEOTIDE
METABOLIC
INORGANIC
GLUCOSE
HYDROGEN
FATTY
PROTON
MOLECULE
METABOLITE
RIBOSE
BIOSYNTHESIS
PLANT
CATALYZE
CELL
COMPOUND
REACTION
ENZYME
MONOSACCHARIDES
MULTICELLULAR
GROUP
COENZYME
PRECURSOR
GLYCEROL
CATABOLISM
OXYGEN
PYRUVATE
COFACTORS
BACTERIA
METABOLISM
ENERGY
SULFIDE
ACID
SQUALENE
SYNTHESIS
CITRIC
PROTEIN
PHOTOSYNTHETIC
GLYCOGEN
INFORMATION
NUCLEIC
PROCESS
LIPID
CYTOCHROME
EXTRACELLULAR
POLYSACCHARIDE
MACROMOLECULES
GLUCONEOGENESIS
SUBSTRATE
REDOX
ACCEPTOR

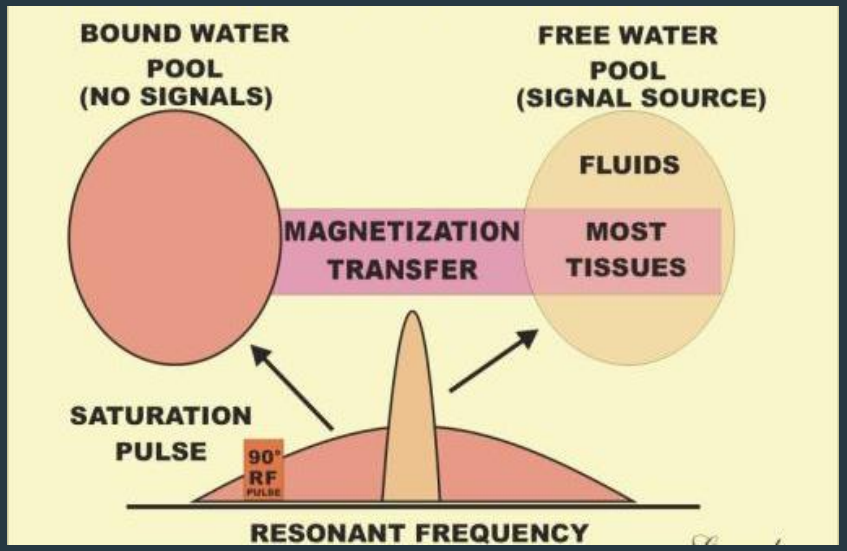
Metabolic imaging beyond perfusion

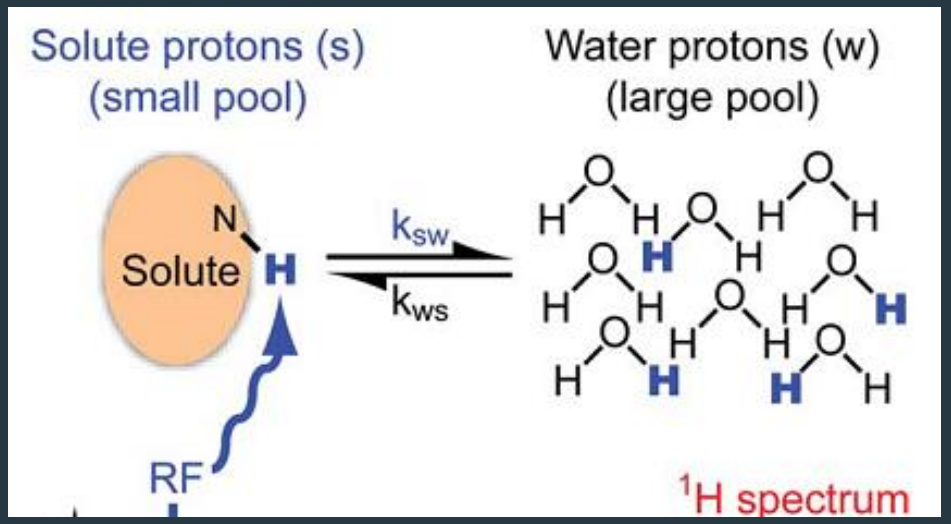
- Research >> Clinical field
- Imaging should not delay treatments

- MRS
- Oxygen extraction fraction: SWI
- Hyperpolarized C13
- .....

CEST

- CEST (Chemical exchange saturation transfer)
  - ✓ In vivo molecular imaging without exogenous contrast agents
  - ✓ Chemical exchange: proton exchange between solute and water pool
  - ✓ Signal amplification
  - ✓ Amide proton transfer (APT)

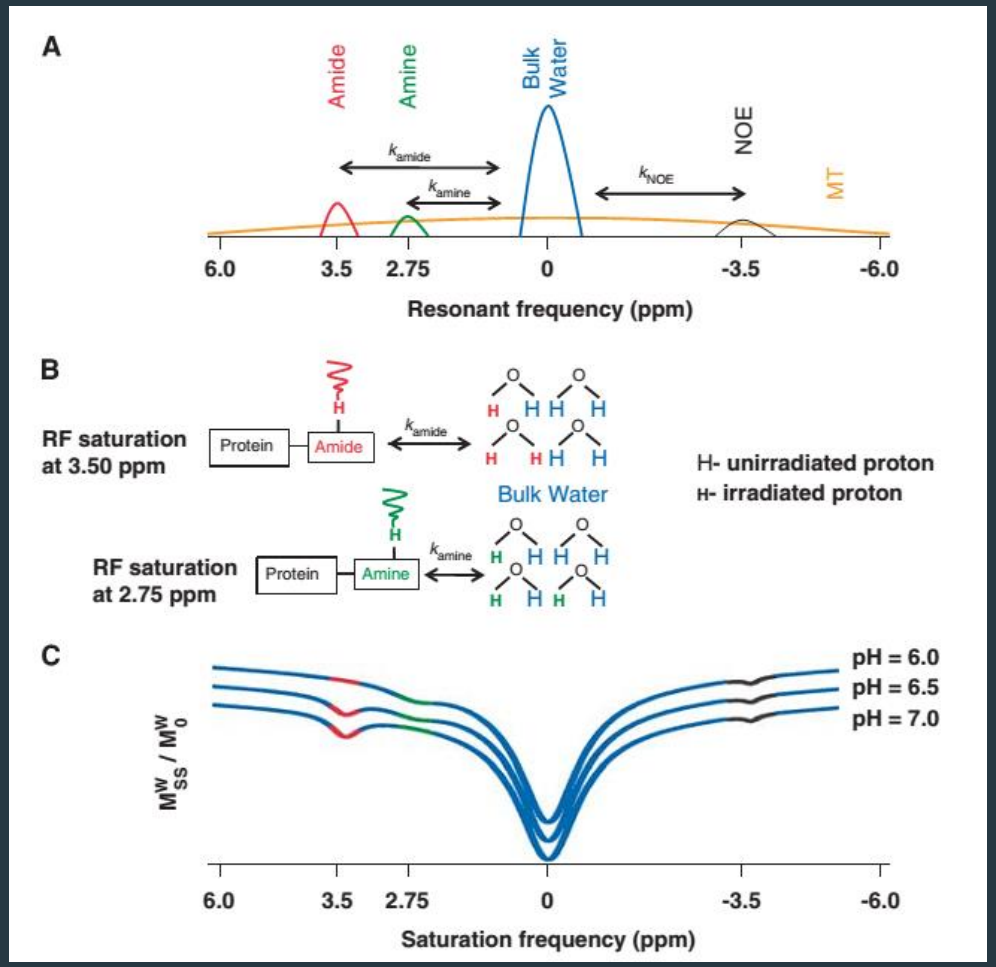




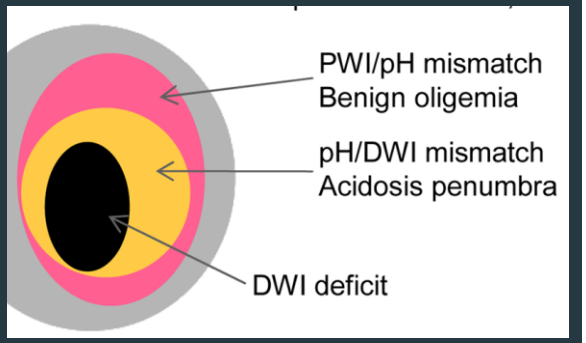
pH weighted imaging

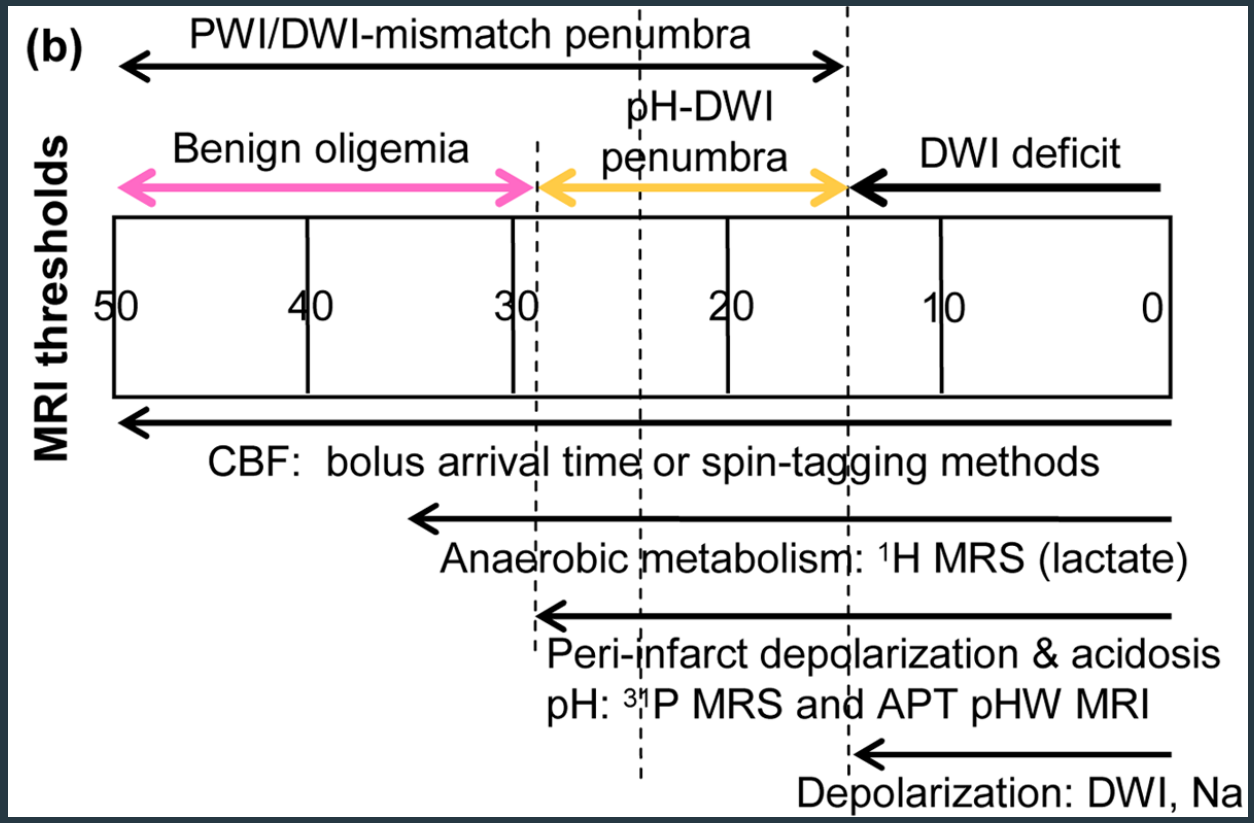
- Exchange rate (k): very pH dependent, pH↓→ k↓ (pH weighted MR imaging)

- Amide proton (APT)
- Amine proton (GluCEST)



Background : Role of pH-weighted imaging in stroke





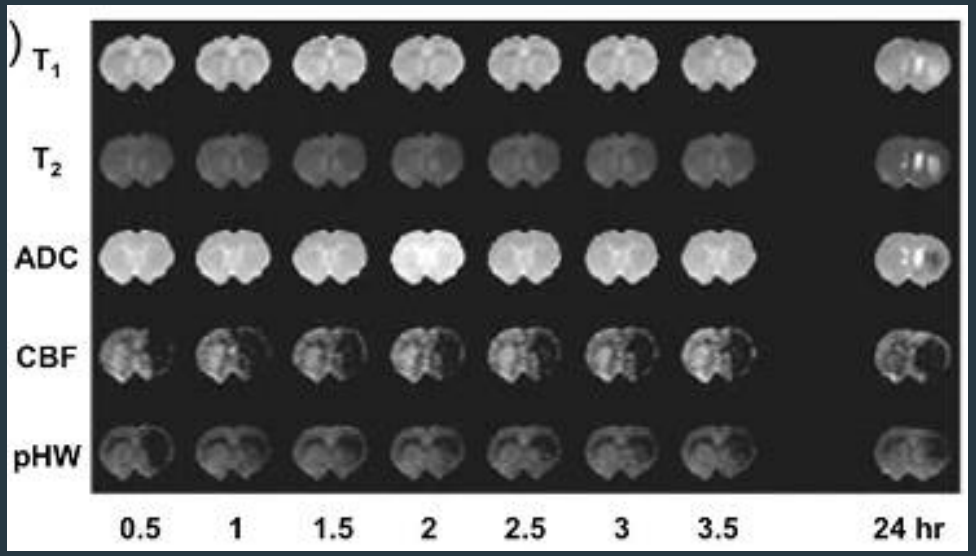
Reversal

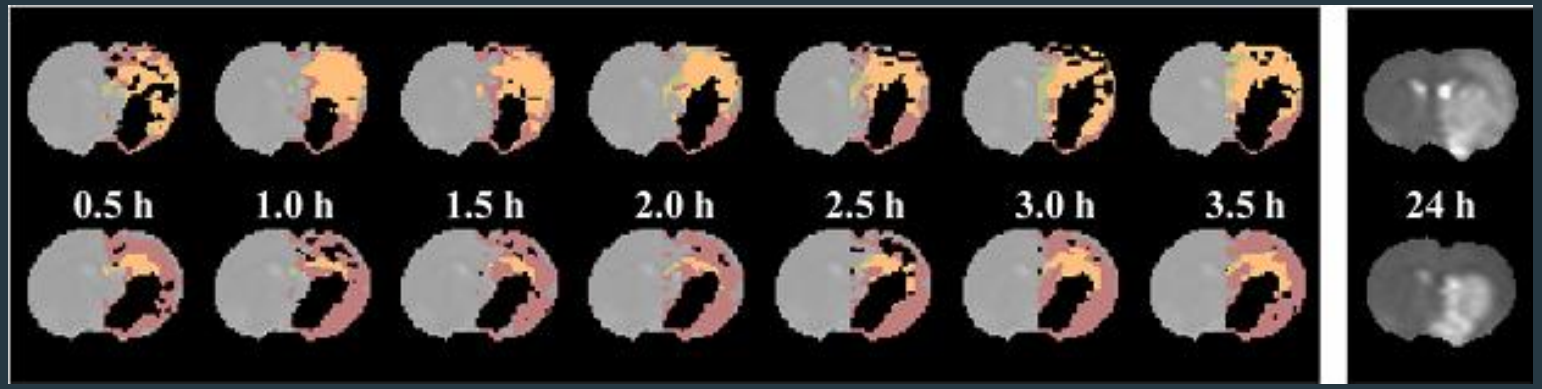
Jinyuan Zhou et al Transl Stroke Res. 2011

Amide Proton Transfer

MCAO model

pH weighte imaging



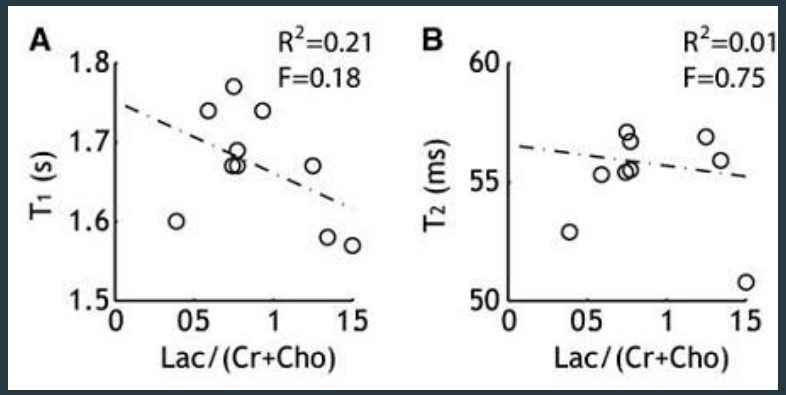


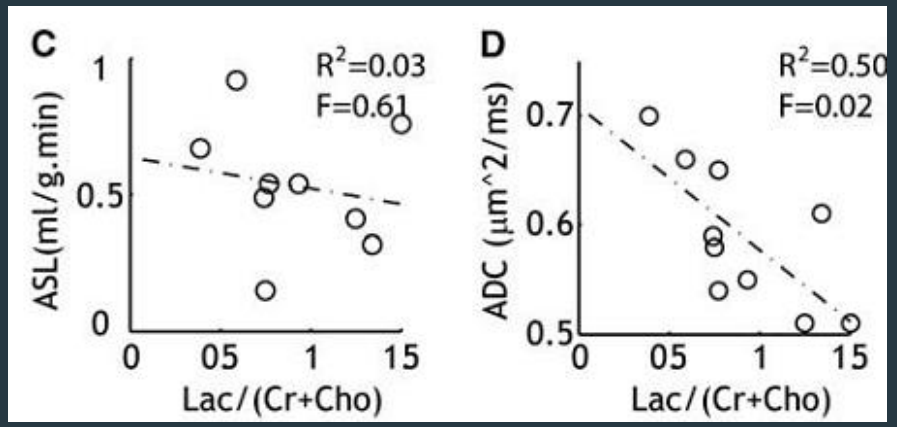
Orange: pHW deficit, Black: DWI deficit, Purple: PWI deficit

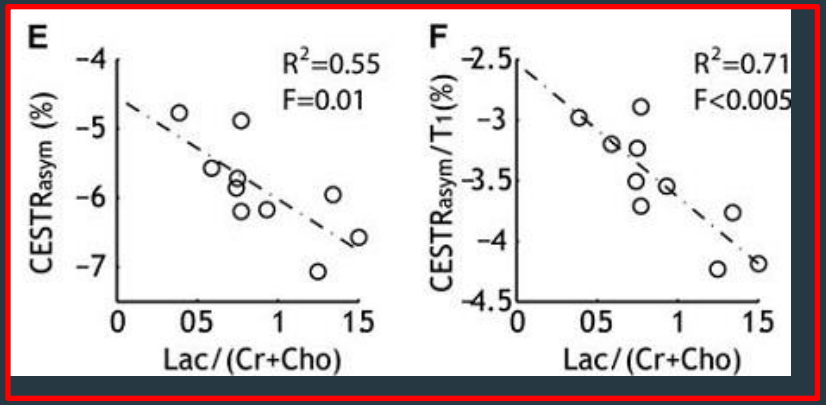
Jinyuan Zhou et al Transl Stroke Res. 2011

pH weighted imaging

- Significant correlation with lactate in linear regression: ADC, APT

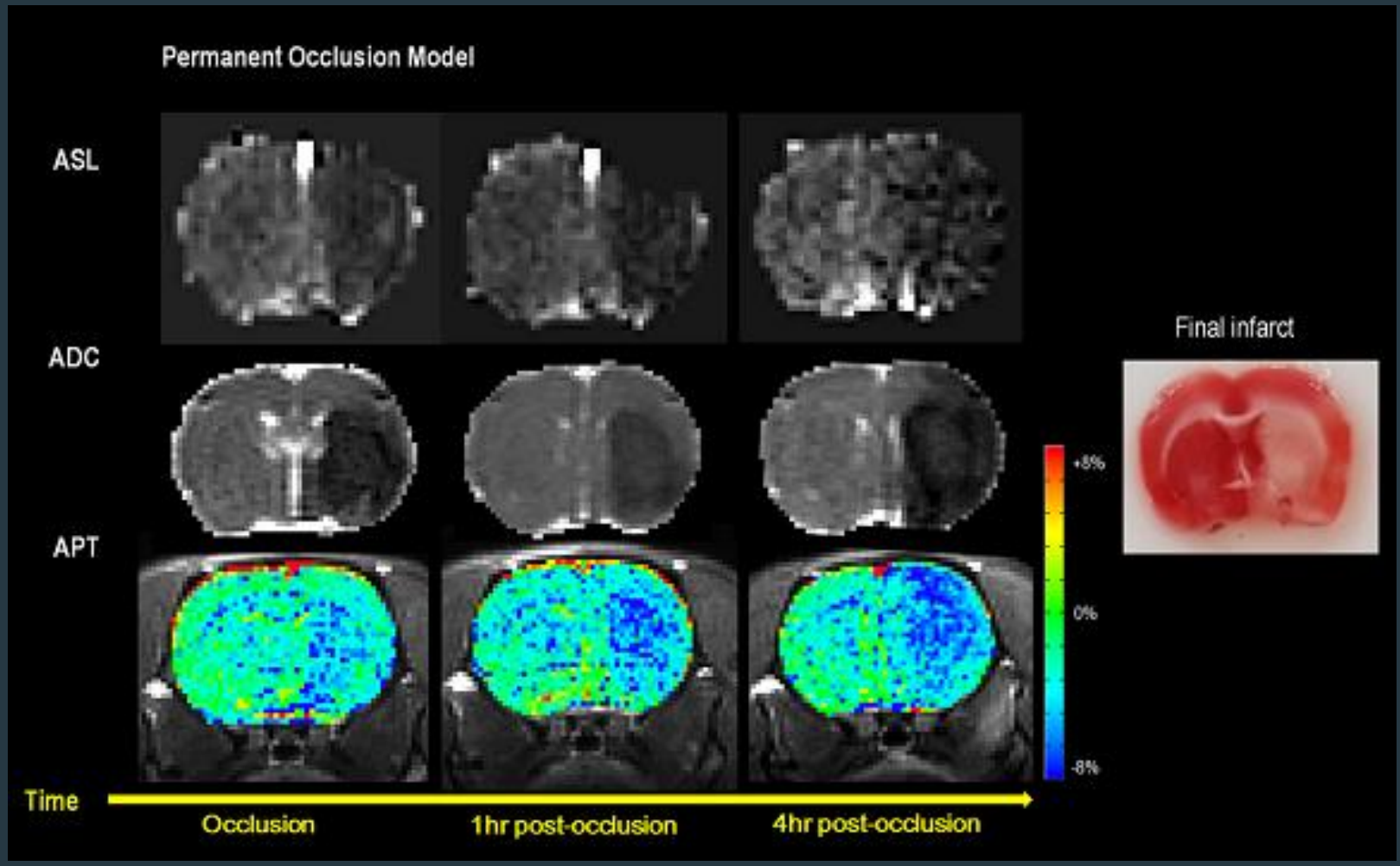






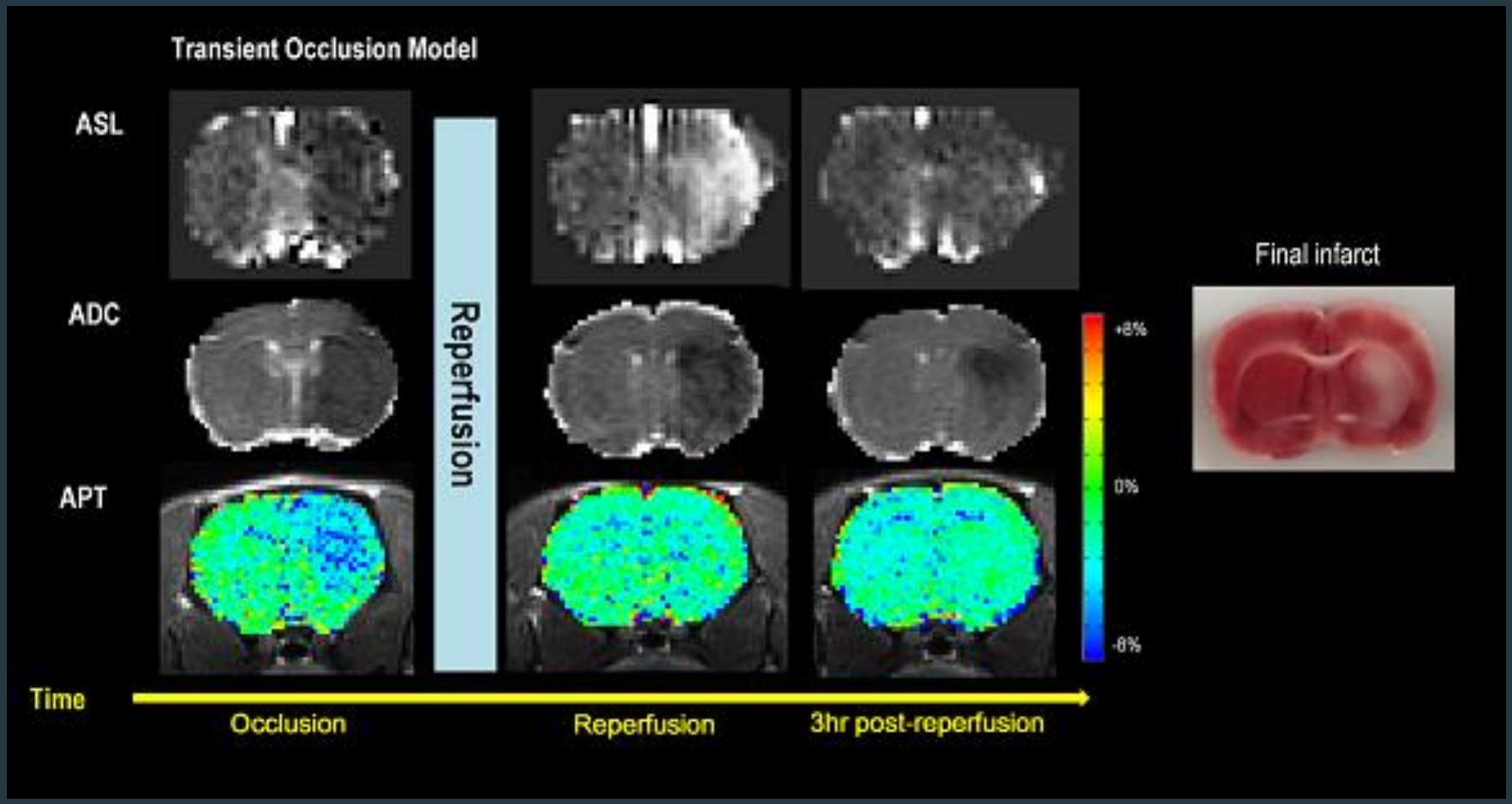
Association btw pH-weighted endogenous amide proton chemical exchange saturation transfer MRI and tissue lactic acidosis during acute ischemic stroke. Journal of Cerebral Blood Flow & Metabolism 2011.

Permanent occlusion model



JE Park, S.C. Jung et al. Eur Radiol 2019

Transient occlusion model



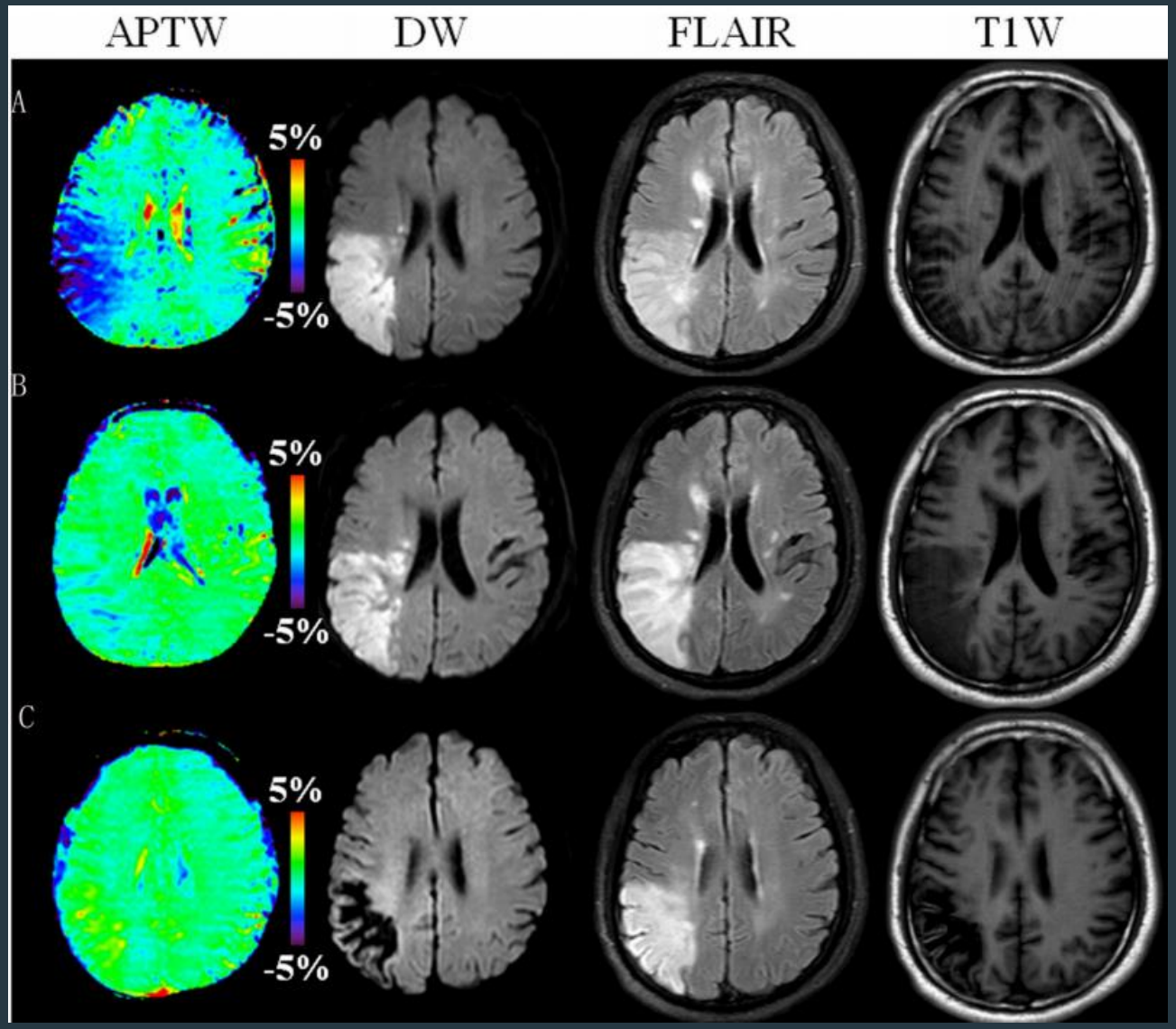
JE Park, S.C. Jung et al. Eur Radiol 2019

Human APT in acute stroke

1 day

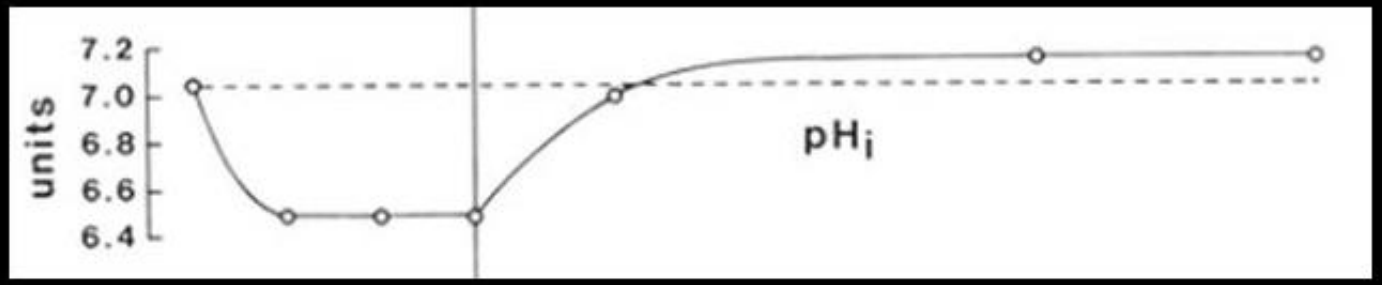
6 days

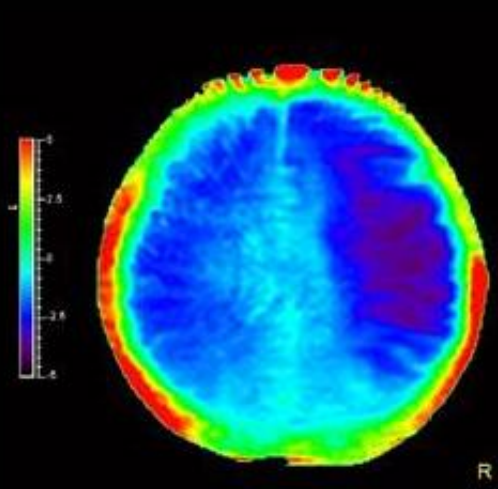
34 days



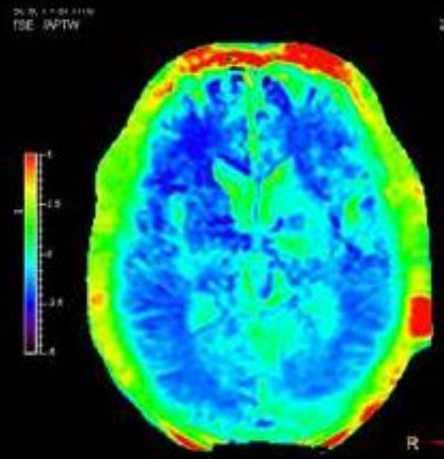
Lu Yu et al. Frontiers in Neurology 2019

Human APT in acute stroke

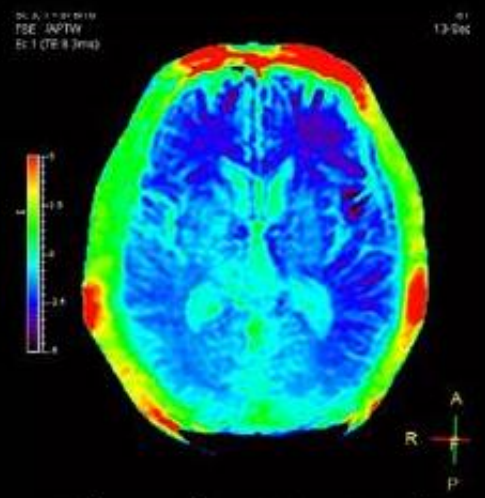




Acute: Acidosis



Subacute: Akalosis



Chronic: Neutral

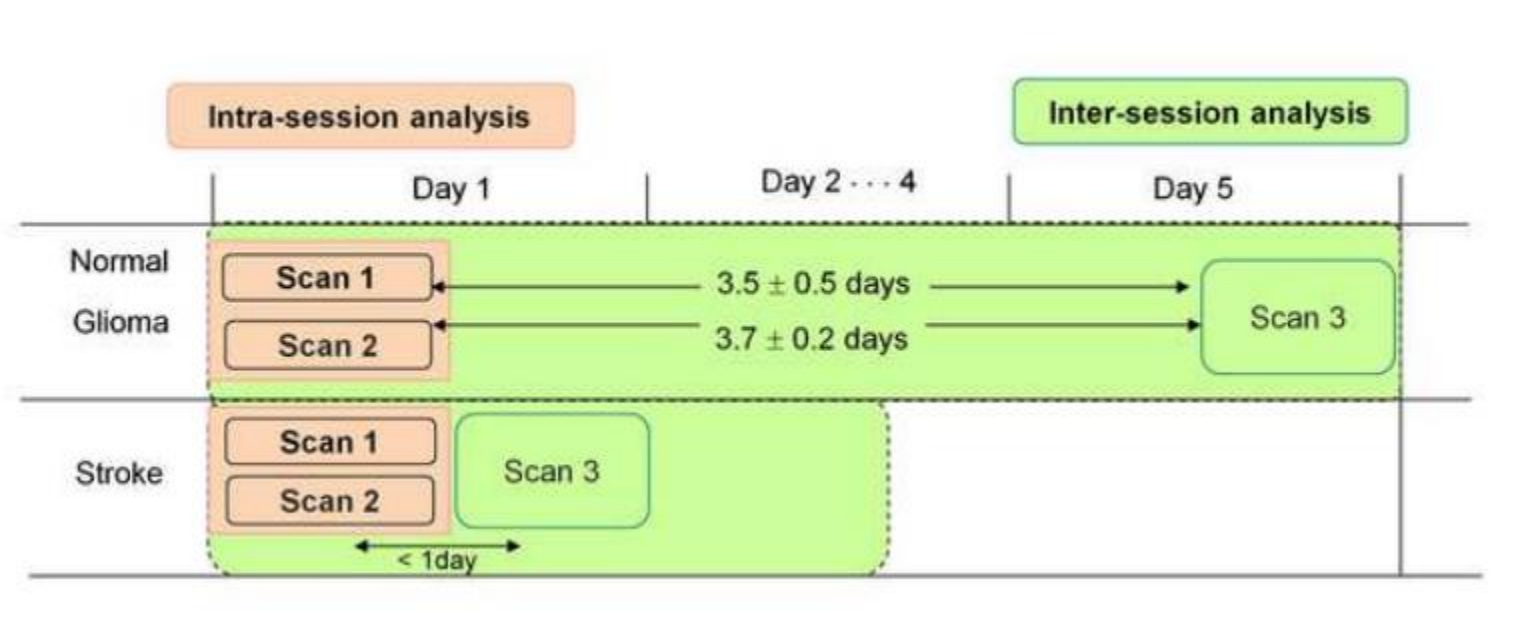
Human APT in acute stroke

Surrogate biomarker?

	Onset time ≤96 h			Onset time 4 ~ 7 days			Onset time 8 ~ 21 days	Onset time ≥22 days
	Pre-treatment ($n = 30$)	Post-treatment ($n = 12$)	*P*-value	Pre-treatment ($n = 13$)	Post-treatment ($n = 11$)	*P*-value	Post-treatment ($n = 12$)	Post-treatment ($n = 7$)
Lesion	−1.13 ± 1.05	−0.33 ± 0.61	**0.019**	−0.75 ± 0.45	−0.30 ± 0.34	**0.011**	−0.05 ± 0.69	0.82 ± 0.79
CNAWM	0.43 ± 0.50	0.46 ± 0.28	0.862	0.20 ± 0.26	0.19 ± 0.50	0.938	0.27 ± 0.57	0.21 ± 0.35
APTW contrast	−1.56 ± 1.01	−0.79 ± 0.51	**0.017**	−0.95 ± 0.46	−0.49 ± 0.32	**0.013**	−0.31 ± 0.57	0.61 ± 0.59
NIHSS	6.3 ± 4.2	3.2 ± 1.6	**0.002**	5.5 ± 3.7	3.1 ± 1.4	**0.048**	2.4 ± 0.8	1.6 ± 0.6

Lu Yu et al. Frontiers in Neurology 2019

Human APT in acute stroke: Repeatability



Euro Radiol Accepted

Human APT in acute stroke: Repeatability

	Healthy subjects	Patients with glioma	Patients with stroke
Number of subjects	19	15	12
Number of male subjects	10	5	9
Age (years)	53.8 ± 13.4	53.6 ± 10.9	68.5 ± 8.7
Imaging interval (intersession, days)	3.5 ± 0.5	3.7 ± 0.2	Less than 1 day
Supratentorial locations	19	15	12
Infratentorial locations	19	0	0
Lesionsize (mL)	-	28.7	6.6
ROI size (mL)	0.2	28.7	6.6

Euro Radiol Accepted

Human APT in acute stroke: Repeatability

		Supratentorial	Glioma	Stroke
wCV	Overall	27.4 (21.8, 35.6)	16.1 (12.6, 21.3)	15.0 (11.4, 20.6)
(%)	Intrasession	23.7 (17.3, 34.5)	12.0 (8.5, 18.1)	11.8 (8.1, 18.8)
	Intersession† (1 vs. 3)	30.4 (22.0, 45.0)	15.7 (11.1, 23.8)	16.2 (11.0, 26.0)
	Intersession* (2 vs. 3)	27.8 (20.2, 40.9)	19.8 (14.0, 30.2)	16.7 (11.4, 26.8)
ICC	Overall	0.85 (0.68, 0.94)	0.96 (0.91, 0.99)	0.93 (0.82, 0.98)
	Intrasession	0.83 (0.55, 0.93)	0.97 (0.90, 0.99)	0.95 (0.83, 0.99)
	Intersession† (1 vs. 3)	0.78 (0.43, 0.91)	0.95 (0.84, 0.98)	0.87 (0.54, 0.96)
	Intersession* (2 vs. 3)	0.77 (0.40, 0.91)	0.91 (0.74, 0.97)	0.86 (0.55, 0.96)

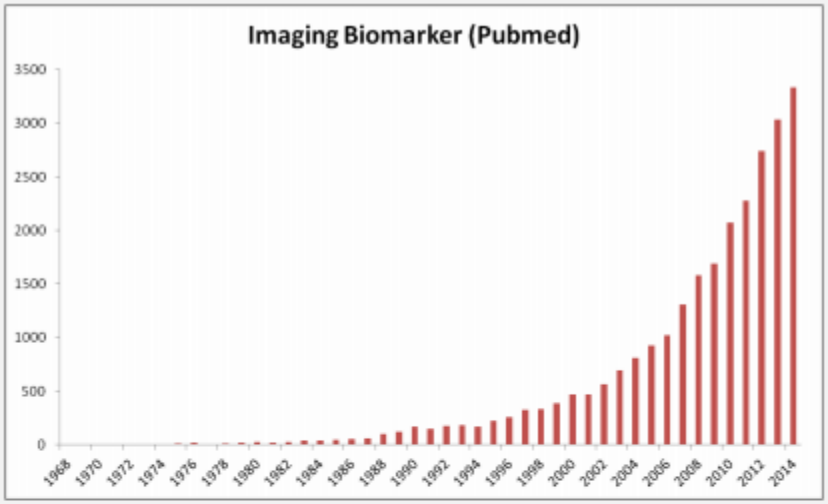
Euro Radiol Accepted

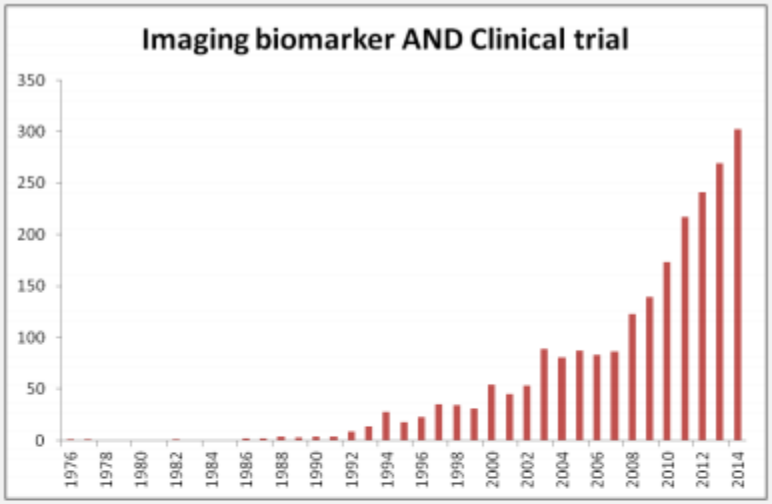
Human APT in acute stroke: Repeatability

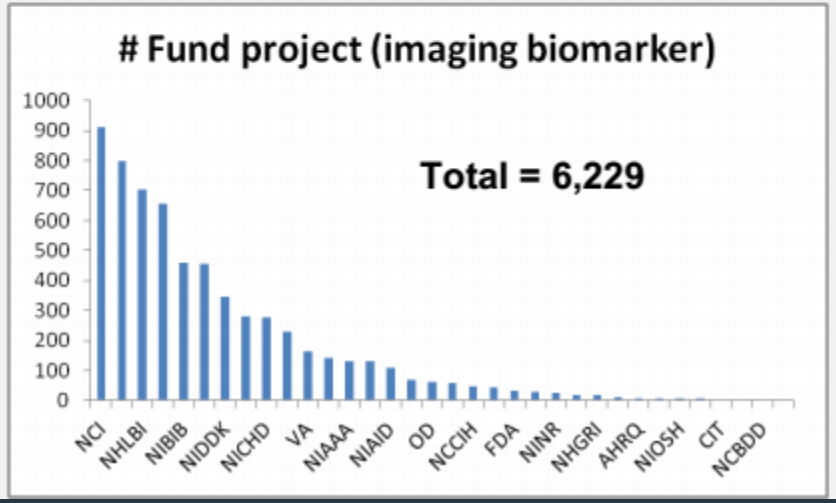
		Supratentorial	Infratentorial	Supra- + Infratentorial§
wCV (%)	Overall	27.4 (21.8, 35.6)	32.7 (25.9, 42.9)	34.0 (28.7, 41.0)
	Intrasession	23.7 (17.3, 34.5)	26.9 (19.6, 39.5)	28.3 (22.5, 36.8)
	Intersession† (1 vs. 3)	30.4 (22.0, 45.0)	33.7 (24.3, 50.4)	35.4 (27.9, 46.7)
	Intersession* (2 vs. 3)	27.8 (20.2, 40.9)	37.6 (27.0, 57.0)	38.3 (30.1, 50.8)
ICC	Overall	0.85 (0.68, 0.94)	0.44 (−0.18, 0.76)	0.84 (0.72, 0.91)
	Intrasession	0.83 (0.55, 0.93)	0.46 (−0.43, 0.80)	0.84 (0.69, 0.92)
	Intersession† (1 vs. 3)	0.78 (0.43, 0.91)	0.40 (−0.40, 0.76)	0.74 (0.49, 0.86)
	Intersession* (2 vs. 3)	0.77 (0.40, 0.91)	0.15 (−1.14, 0.67)	0.70 (0.43, 0.84)

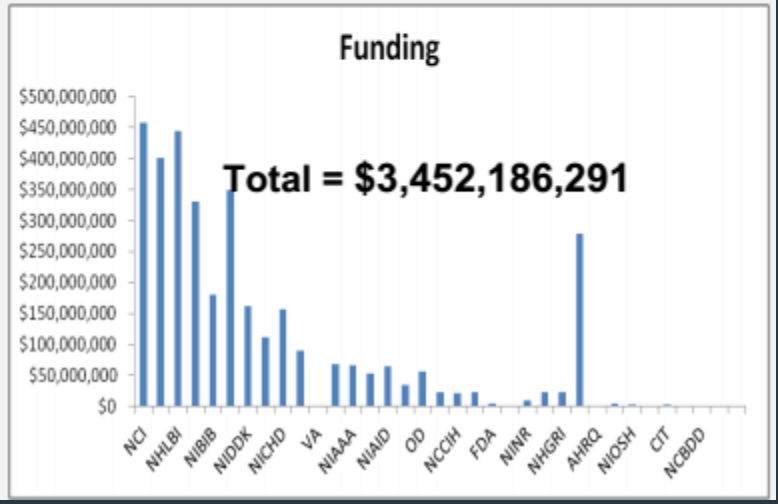
Euro Radiol Accepted

임상시험 영상활용


Imaging Biomarker (Pubmed)
3500
3000
2500
2000
1500
1000
500
0
1968 1970 1972 1974 1976 1978 1980 1982 1984 1986 1988 1990 1992 1994 1996 1998 2000 2002 2004 2006 2008 2010 2012 2014


Imaging biomarker AND Clinical trial
350
300
250
200
150
100
50
0
1976 1978 1980 1982 1984 1986 1988 1990 1992 1994 1996 1998 2000 2002 2004 2006 2008 2010 2012 2014


# Fund project (imaging biomarker)
Total = 6,229
1000
900
800
700
600
500
400
300
200
100
0
NCI NHLBI NIBIB NIDDK NICHD VA NIAAA NIAID OD NCCIH FDA NINR NHGRI AHRQ NIOSH CIT NCBDD


Funding
Total = $3,452,186,291
$500,000,000
$450,000,000
$400,000,000
$350,000,000
$300,000,000
$250,000,000
$200,000,000
$150,000,000
$100,000,000
$50,000,000
$0
NCI NHLBI NIBIB NIDDK NICHD VA NIAAA NIAID OD NCCIH FDA NINR NHGRI AHRQ NIOSH CIT NCBDD

Clinical trial imaging in Stroke

- Stroke Imaging Research (STIR) group in Stroke Treatment Academy Industry Roundtable (STAIR)의 Acute Stroke Imaging Research Roadmap II & III (2013, 2016)
- 뇌졸중 임상시험에 있어서 영상 획득과 해석에 대한 Consensus 및 권고안 제시
- 뇌졸중 임상시험의 영상 조건: Speed, Standardization, Quality control, Reproducibility, Centralization

Clinical trial imaging in Stroke

Table 1. General Requirements for Imaging in Stroke Clinical Trials

Speed: In therapeutic trials, the benefits of additional imaging should be balanced against potential treatment delay; workflow should be optimized on the basis of best practice
Standardization: Acquisition parameters and perfusion post processing should be standardized (by common software processing at centers or centralized processing) and should conform to minimum, protocol-defined, common standards
Quality control: A well-defined image quality control process should be implemented to ensure that the predefined study imaging protocol is respected and to minimize the number of protocol violations
Reproducibility: If imaging is used to define patient selection then either a system for standardized central image processing and automated analysis, or appropriate training for neuroimaging raters at participating centers, should be undertaken. Imaging methods should have demonstrated acceptable interobserver and across-center reliability
Centralization: Central analysis of imaging outcomes should be conducted as the reference standard in multicenter trials. A system for standardized central image processing and interpretation, blinded to clinical information and local investigator decision, should be implemented

→ Reliability ↑ ↑

STIR and VISTA Imaging Investigators. Stroke 2013

Standardization in Acute Ischemic Stroke

Special Report

Acute Stroke Imaging Research Roadmap III Imaging Selection and Outcomes in Acute Stroke Reperfusion Clinical Trials

Consensus Recommendations and Further Research Priorities

***Conclusions*—**Recent positive acute stroke endovascular clinical trials have demonstrated the added value of neurovascular imaging. The optimal imaging profile for endovascular treatment includes large vessel occlusion, smaller core, good collaterals, and large penumbra. However, equivalent definitions for the imaging profile parameters across modalities are needed, and a standardization effort is warranted, potentially leveraging the pooled data resulting from the recent positive endovascular trials. **(*Stroke*. 2016;47:1389-1398. DOI: 10.1161/STROKEAHA.115.012364.)**

Max Wintermark, MD, MAS; for the Stroke Imaging Research (STIR) and VISTA-Imaging Investigators*

***Background and Purpose*—**The Stroke Imaging Research (STIR) group, the Imaging Working Group of StrokeNet, the American Society of Neuroradiology, and the Foundation of the American Society of Neuroradiology sponsored an imaging session and workshop during the Stroke Treatment Academy Industry Roundtable (STAIR) IX on October 5 to 6, 2015 in Washington, DC. The purpose of this roadmap was to focus on the role of imaging in future research and clinical trials.

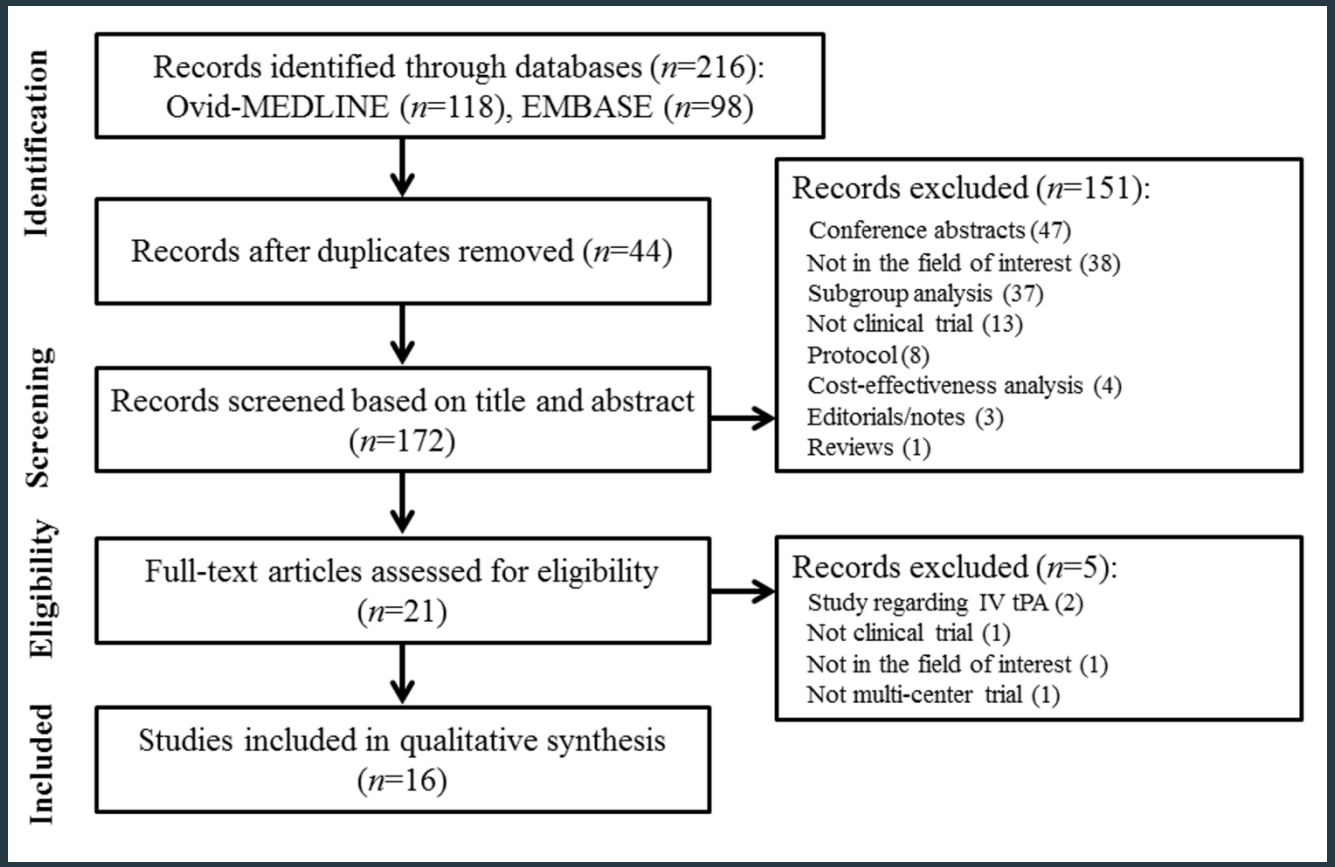
***Methods*—**This forum brought together stroke neurologists, neuroradiologists, neuroimaging research scientists, members of the National Institute of Neurological Disorders and Stroke (NINDS), industry representatives, and members of the US Food and Drug Administration to discuss STIR priorities in the light of an unprecedented series of positive acute stroke endovascular therapy clinical trials.

***Results*—**The imaging session summarized and compared the imaging components of the recent positive endovascular trials and proposed opportunities for pooled analyses. The imaging workshop developed consensus recommendations for optimal imaging methods for the acquisition and analysis of core, mismatch, and collaterals across multiple modalities, and also a standardized approach for measuring the final infarct volume in prospective clinical trials.

STIR and VISTA Imaging Investigators. Stroke 2016

Clinical trial imaging in Acute ischemic stroke

- 2012 ~ 2018
- Randomized, Multi-center clinical trials in endovascular treatment for acute cerebral ischemic stroke



IIRC, Imaging core lab, Standardization

Trial nickname	Independent image review and core laboratory	Reviewers	Standardization	[a]CT: MR
DAWN	Used		Same imaging modality is encouraged to be used during follow-up.	131: 75 (63.6: 36.4 %)
DEFUSE 3	Used		The baseline and follow-up imaging should be performed with DEFUSE 3 protocol, which is installed at all study sites.	133:49 (73.1: 26.9 %)
PISTE	Used	3 Neuroradiologists		
ASTER	Used	2 + 1		
THERAPY	Used	1 Neuroradiologist	Nonenhanced thin-section (≤ 2.5 mm) CT	
THRACE	Used	4 Neuroradiologists for CT and MR, 3 Interventional neuroradiologists for DSA		
SWIFT PRIME	Used	2+1	Sponsor will collaborate with participating centers to evaluate and optimize the quality of imaging and image transfer.	189: 15 (92.6: 7.4 %)
REVASCAT	Used			
ESCAPE	Used		NECT and CTA protocols were presented.	13: 54 (19.4: 80.6 % at 24 hours)
EXTEND-IA	Used	Neuroradiologist/Stroke neurologist	The imaging protocols will follow current international consensus guidelines. Standard CT and MR protocols were presented.	
MR CLEAN	Used	Two neuroradiologists		24: 94 (20 : 80 %)
MR RESCUE	Used		MR RESCUE protocols were presented.	
SYNTHESIS	Used			
IMS III	Used	3 CT experts (including one neuroradiologist was mandatory)		
SWIFT	Used	2 neurointerventionalists	It is preferred that whether CT or MR is taken at baseline, the same imaging modality should be obtained at follow-up.	
TREVO 2	Used			

Standardization

- The process of implementing and developing technical standards based on the consensus of different parties

1. Technical Standards: Imaging Protocols
2. Different Parties: Vendors, Scanners, Softwares
3. Consensus: Figuring out common protocols for all vendors, scanners, softwares → Standardization

Courtesy of 김인성 Ph.D.

Standardization

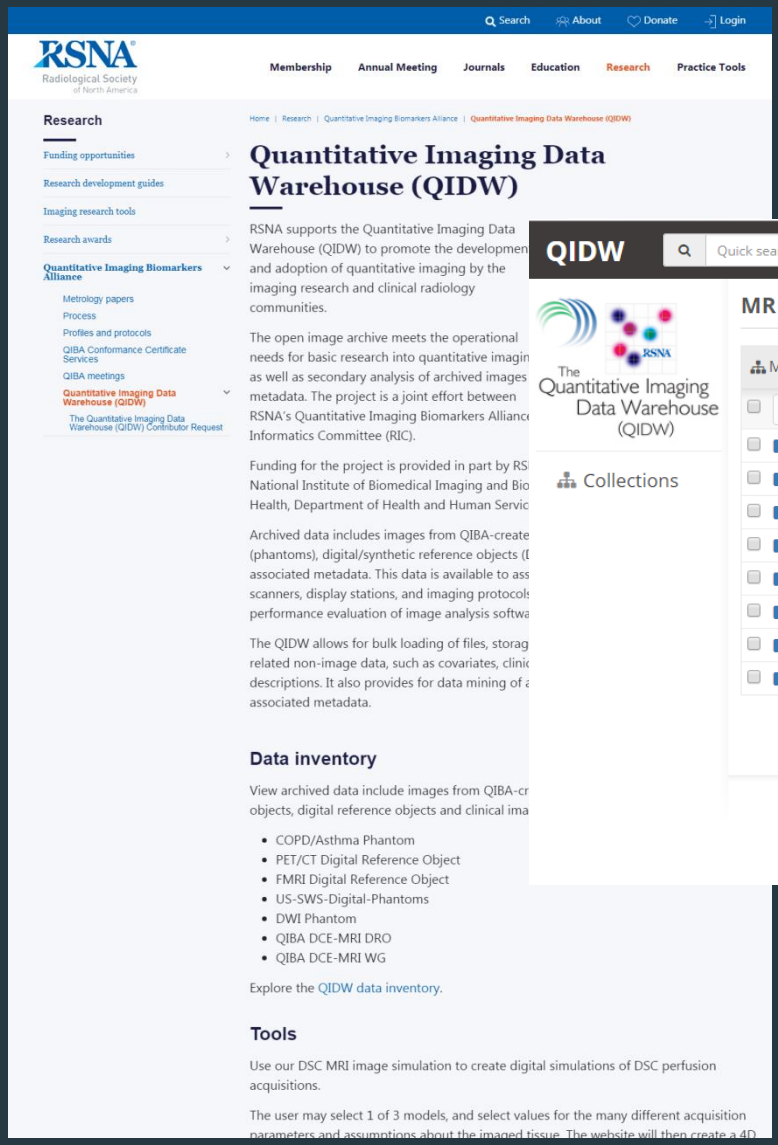
- QIBA (Quantitative Imaging Biomarkers Alliance)

  1) In 2007, RSNA organized the Quantitative Imaging Biomarkers Alliance® (QIBA) to unite researchers, healthcare professionals and industry to advance quantitative imaging and the use of imaging biomarkers in clinical trials and clinical practice.

  2) QIBA seeks to improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, sites, patients and time

- Oncology imaging

Standardization



Standardization in acute stroke imaging

- QIBA (Quantitative Imaging Biomarkers Alliance)
- Oncology imaging

- Urgent circumstance in acute ischemic stroke
- Balancing between standardization and critical pathway

Clinical trial imaging in Stroke

Table 1. General Requirements for Imaging in Stroke Clinical Trials

Speed: In therapeutic trials, the benefits of additional imaging should be balanced against potential treatment delay; workflow should be optimized on the basis of best practice
Standardization: Acquisition parameters and perfusion post processing should be standardized (by common software processing at centers or centralized processing) and should conform to minimum, protocol-defined, common standards
Quality control: A well-defined image quality control process should be implemented to ensure that the predefined study imaging protocol is respected and to minimize the number of protocol violations
Reproducibility: If imaging is used to define patient selection then either a system for standardized central image processing and automated analysis, or appropriate training for neuroimaging raters at participating centers, should be undertaken. Imaging methods should have demonstrated acceptable interobserver and across-center reliability
Centralization: Central analysis of imaging outcomes should be conducted as the reference standard in multicenter trials. A system for standardized central image processing and interpretation, blinded to clinical information and local investigator decision, should be implemented

→ Reliability ↑ ↑

STIR and VISTA Imaging Investigators. Stroke 2013

Clinical trial imaging in Stroke

Imaging support for multicenter clinical trials

- Imaging protocol / charter
- Global standards

Quantitative Imaging Biomarkers Alliance RSNA

Guidance for Industry
Standards for Clinical Trial Imaging Endpoints

- Site training
- Site monitoring

SAMSUNG 삼성의료원

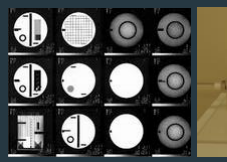
서울아산병원 Asan Medical Center

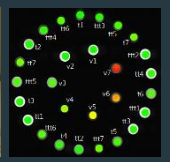
서울대학교병원 SEOUL NATIONAL UNIVERSITY HOSPITAL

- Imaging acquisition

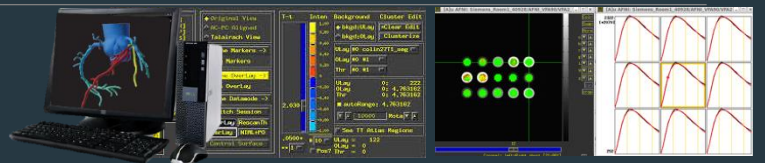


- QA/QC
- Data management





- Post-processing
- Image analysis
- Central reading



High Quality Imaging Service

Central Imaging Core Lab in clinical trials

Clinical trial imaging : Standards

Guidance for Industry
Standards for Clinical Trial Imaging Endpoints

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Dr. Rafel Rieves at 301-796-2050 or (CBER) Office of Communication, Outreach, and Development at 301-827-1800 or 800-835-4709.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

August 2011
Clinical/Medical

I:\9676dft.doc
08/08/11

Clinical Trial Imaging Endpoint Process Standards
Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2018
Clinical/Medical

Clinical trial imaging : Standards

TABLE OF CONTENTS

TABLE OF CONTENTS

Clinical trial imaging : Standardization

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in optimizing the quality of imaging data obtained in clinical trials intended to support approval of drugs and biological products.[2] This guidance focuses on imaging acquisition, display, archiving, and interpretation process standards that we regard as important when imaging is used to assess a trial's primary endpoint or a component of that endpoint.

Considerable standardization already exists in clinical imaging. There are a variety of sources, including picture archiving and communication systems and the Digital Imaging and Communications in Medicine (DICOM) formats for the handling and transmission of clinical

Standardization, while important for all clinically used measures, becomes essential for an imaging endpoint used in a clinical trial to reduce variability and to ensure interpretability of the results. The extent of trial-specific standardization may vary depending upon how standardized

within and among clinical sites, and that a verifiable record of the imaging process is created. Minimization of imaging process variability may importantly enhance a clinical trial's ability to detect drug treatment effects.

Standardization, while important for all clinically used measures, becomes essential for an imaging endpoint used in a clinical trial to reduce variability and to ensure interpretability of the results. The extent of trial-specific standardization may vary depending upon how standardized the local imaging procedures are (e.g., routine bone X-rays (relatively standardized) versus bone mineral density (more variability across sites)). This guidance does not address approaches for

Clinical Trial Imaging Endpoint Process Standards Guidance for Industry. FDA 2018

Clinical trial imaging : Standardization

F. What Procedures Should Be Standardized for an Imaging-Based Clinical Trial Primary Endpoint?

No single set of detailed imaging process standards is readily applicable to every clinical trial because the trials differ in design and objectives. When usual medical practice imaging process standards are acceptable in a trial, the plans for the use of such standards should be stated in the clinical protocol. Determinations on what to standardize beyond these expectations should be driven by consideration of the imaging processes that might introduce variability and inaccuracy to the endpoint and by consideration of the other items outlined below. When determining the

Clinical Trial Imaging Endpoint Process Standards Guidance for Industry. FDA 2018

Clinical trial imaging : Standardization

- Imaging modality availability and the modality's technical performance variation across trial sites
- Performance features of the imaging modality at the trial sites or any other locations where subjects may undergo imaging
- Qualifications of the imaging technologists and any special technological needs for the trial
- Proposed imaging measures' reliance on phantoms and/or calibration standards to ensure consistency and imaging quality control among clinical sites
- Any unique image acquisition features of the trial design, including subject positioning, anatomical coverage of imaging, use of contrast, timing of imaging, importance of subject sedation, and scanner settings for image acquisition
- Image quality control standards, including those specifying the need for repeat imaging to obtain interpretable images

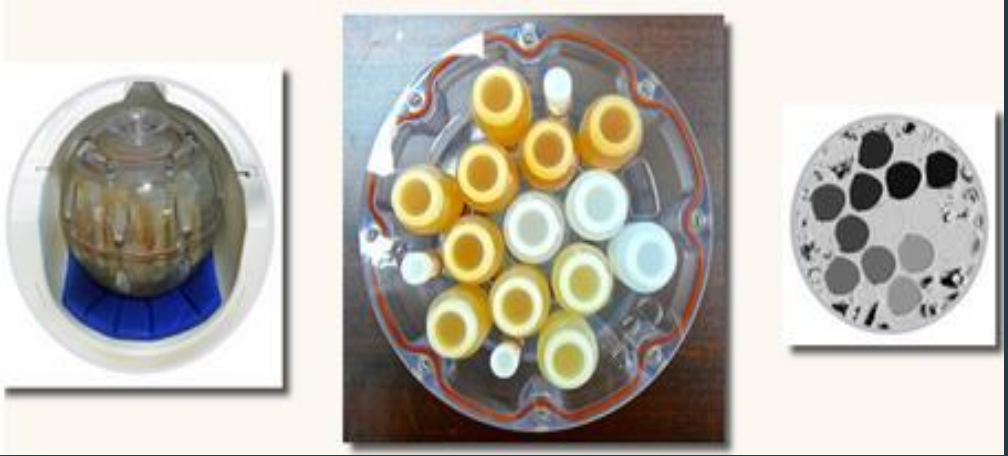
Clinical Trial Imaging Endpoint Process Standards Guidance for Industry. FDA 2018

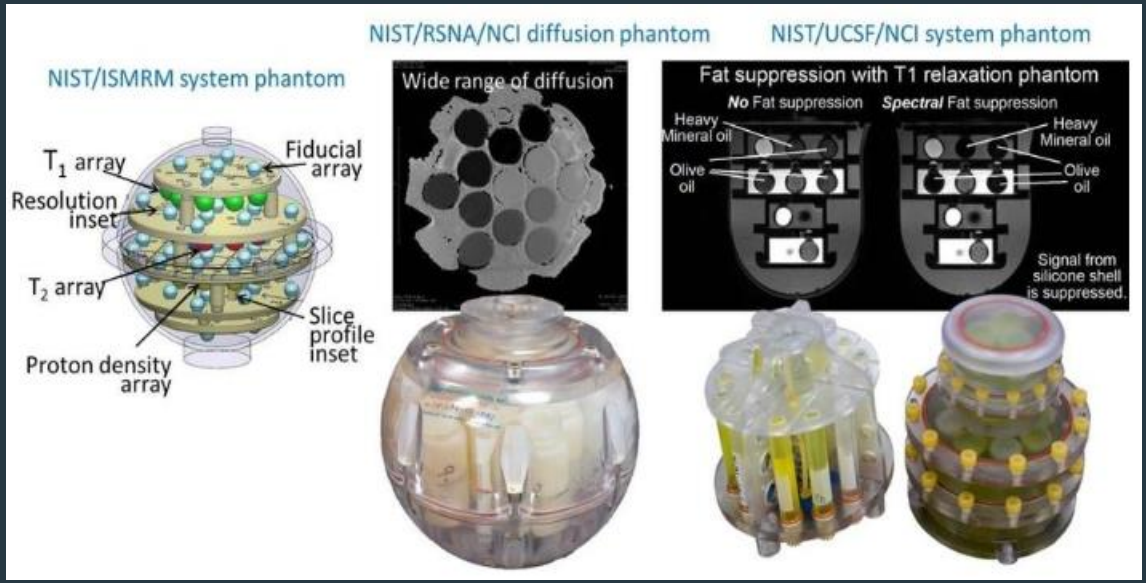
Clinical trial imaging : Standardization

- Procedures for imaging display and interpretation, including technical variations in reader display stations
- Nature of the primary endpoint image measurement, including the importance of training image readers in trial-specific quantification methods
- Extent that image archiving could be important to the trial's conduct, monitoring, and data auditing
- Potential for imaging modality upgrades or modality failures, as well as the potential variation in imaging drugs (such as contrast agents) across trial sites
- Precedent for use of the imaging-based primary endpoint measure in investigational drug development, especially previously observed imaging methodological problems

Clinical Trial Imaging Endpoint Process Standards Guidance for Industry. FDA 2018

뇌졸중 영상 적합 팬텀




NIST/RSNA/NCI diffusion phantom
NIST/UCSF/NCI system phantom
NIST/ISMRM system phantom
Wide range of diffusion
Fat suppression with T1 relaxation phantom
No Fat suppression
Spectral Fat suppression
Heavy Mineral oil
Olive oil
Signal from silicone shell is suppressed.
T1 array
Fiducial array
Resolution inset
T2 array
Slice profile inset
Proton density array

뇌졸중 영상 적합 팬텀

서울아산병원 Asan Medical Center

영상바이오마커 선정
내부 물질 협의
팬텀 디자인

KRISS 한국표준과학연구원

내부 물질 협의
팬텀 주문 제작
표준물질 공식인증

센터소개

의료융합표준센터는 2025년 세계적으로 의료측정표준 분야의 연구를 선도하는 대표적인 연구센터가 되기 위하여 기본 물리량에 소급한 의료기기 측정표준 확립, 의료영상 정량화를 통하여 재현성과 신뢰성이 확보된 영상 측정기술 개발, 정밀측정 기술을 기반으로 새로운 의료진단 및 치료기술 개발 연구를 통해 의료 빅데이터 명품화를 추구하고 있습니다.

전자 신문

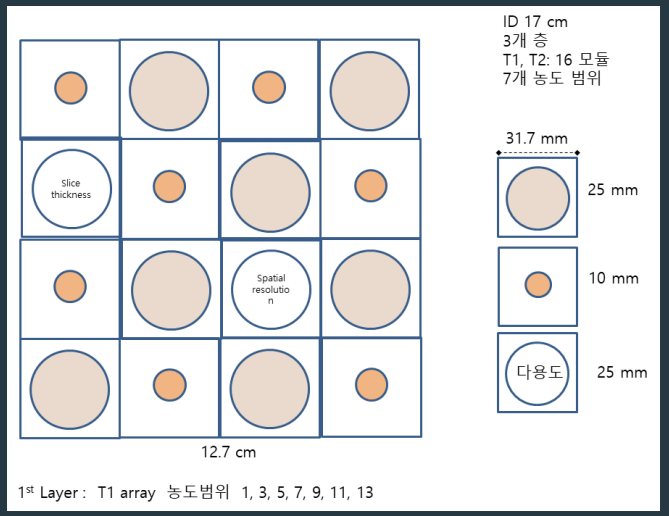
표준연, 의료기기 성능 평가하는 모듈형 팬텀 세계 첫 개발

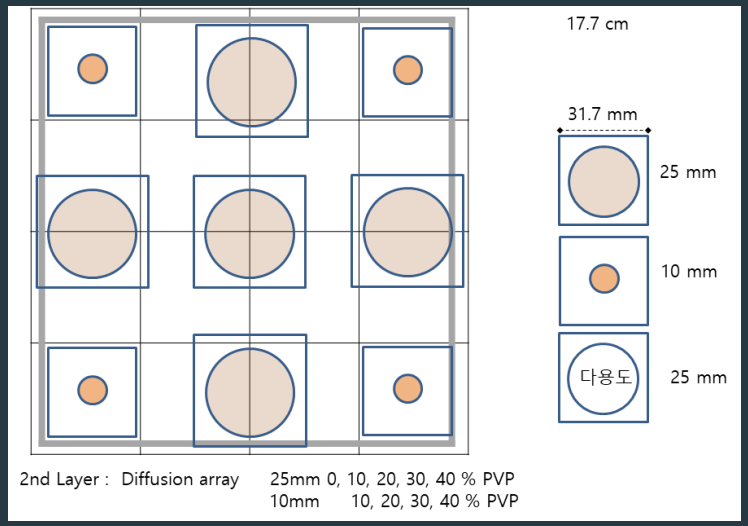
<조효민 한국표준과학연구원 의료융합측정표준센터 박사가 새로 개발한 'MOMA 팬텀' 모듈 물성을 시험하고 있다.>

뇌졸중 영상 적합 팬텀

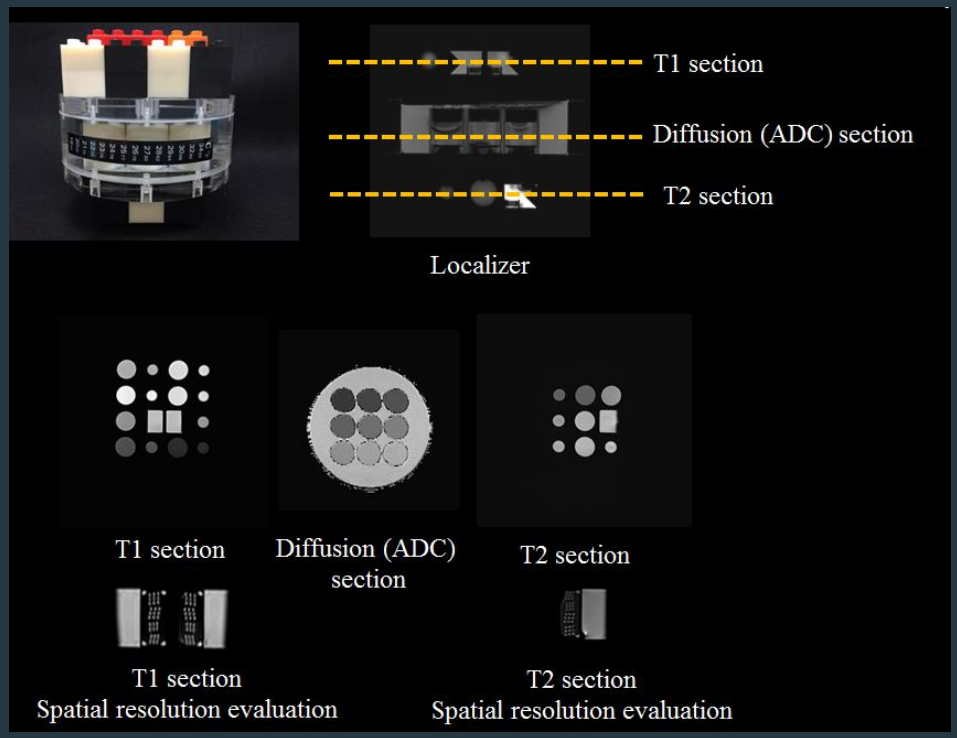
- 뇌졸중 표준화 팬텀을 위한 영상바이오마커 선정: DWI, GRE (T2*), T1
- K-Stroke-Block (KSB) 팬텀과 QIBA 및 NIST/ISMRM system 팬텀과의 차별점

1. Spatial resolution 측정 가능
2. Cost-effective 팬텀
3. GRE 동시 측정 가능 팬텀
4. 레고블럭방식의 팬텀: 다양한 영상 바이오마커 선정 및 조합 가능





뇌졸중 영상 적합 팬텀



NIST (National Institute of Standards and Technology) 공인 물질

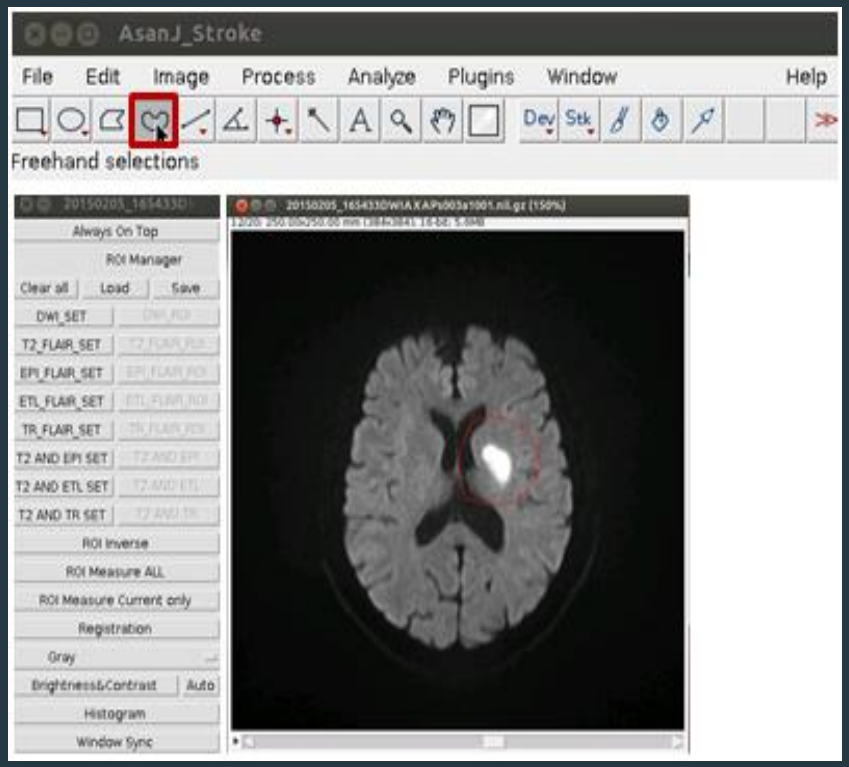
가격 경쟁력 (미국 제품의 반값)

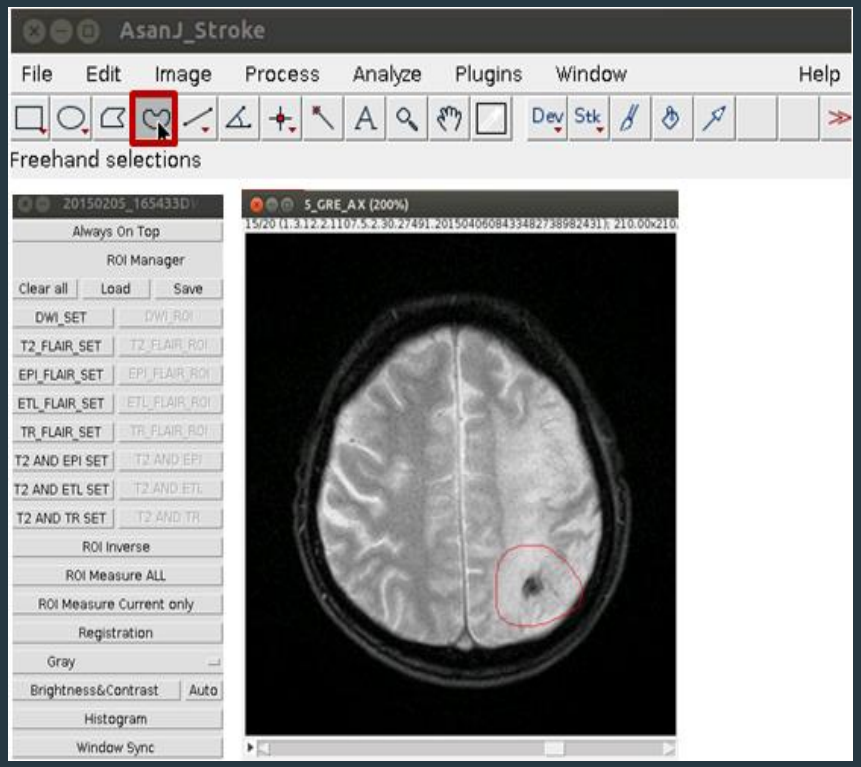
조립이 용이하고 맞춤형 디자인 가능

분석 소프트웨어

1. 국내: 소프트웨어 개발이 진행중 (자동 정량화 분석 소프트웨어가 주류, DWI-PWI mismatch 위주, 해외 소프트웨어에 비해 가격이 낮으나 개별 연구자에게는 여전히 높을 수도 있음.)
2. 해외: 다수의 글로벌 회사 및 연구자들이 다양한 분석 소프트웨어를 판매 (편리한 UI, 고가)

분석 소프트웨어





http://datasharing.aim-aicro.com/strokevolumetry?language=en

분석 소프트웨어

http://datasharing.aim-aicro.com/strokevolumetry?language=en

Clinical trial imaging in Acute ischemic stroke: Standards

- 뇌졸중 치료 약물 임상시험에서의 영상 바이오마커의 기준안을 제시한다.

1. 뇌졸중 영상 바이오마커 표준화 팬텀
2. 뇌졸중 영상 바이오마커 분석 소프트웨어
3. 뇌졸중 영상 바이오마커의 촬영, 전송, 분석 등의 기준

Clinical trial imaging in Acute ischemic stroke: Standards

급성 뇌졸중 임상시험 영상의 글로벌 동향 조사 보고서

2018. 10

제작: 서울아산병원 영상의학과/
울산대학교 의과대학/

국문표기: 본 보고서는 정부(식품의약품안전처, 18182임상평402)의 용역연구개발사업의 지원을 받아 수행된 연구임.
영문표기: This work was supported by the grant of Ministry of Food and Drug Safety (18182MFDS402).

목차

Clinical trial imaging in Acute ischemic stroke: Standards

첨부 3

급성 뇌졸중 영상촬영 프로토콜 표준화 및 팬텀 품질평가를 위한 기준안

(1차년도용)

2018.10

제작: 서울아산병원 영상의학과/
울산대학교 의과대학/

목차

Clinical trial imaging in Acute ischemic stroke: Standards

뇌졸중 영상 바이오마커 분석 프로그램 표준작업지침서

2018. 10

제작: 서울아산병원 영상의학과/
울산대학교 의과대학/

국문표기: 본 보고서는 정부(식품의약품안전처, 18182임상평402)의 용역연구개발사업의 지원을 받아 수행된 연구임.
영문표기: This work was supported by the grant of Ministry of Food and Drug Safety (18182MFDS402).

목차

Clinical trial imaging in Acute ischemic stroke: Standards

- Infarct core를 반영하는 영상: CT, MR (DWI, PWI-CTP)
- Hemorrhagic transformation/Hematoma를 반영하는 영상: CT, MR (GRE)
- Steno-occlusion을 반영하는 영상: CTA, MRA, DSA
- 영상 촬영 기준 및 팬텀 사용
- 최소한의 Standardization
- Independent centralized reading and analysis

Acknowledgement

- Asan Image Metrics
- Kyung Won Kim, M.D., PhD.

  Asan Image Metrics, Clinical Trial Center, Asan Institute for Life Sciences, Asan Medical Center
- Dong-Cheol Woo, Ph.D.

  Bioimaging Center, Biomedical Research Center, Asan Institute for Life Sciences, Asan Medical Center

경청해 주셔서 감사합니다.