Experience in Imaging Core Lab and Independent Central Review

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

Overview

- **Imaging CRO (contract research organization) and Imaging core laboratory, and Independent Image Review Committee (IIRC)**

- **Experience in Acute ischemic stroke**

- **Summary & Recommendation**

CRO

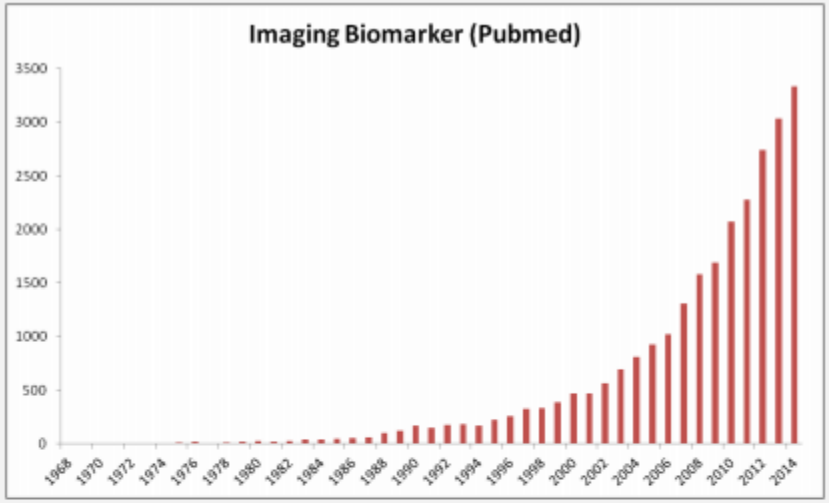
- Company that provides **support** to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis.

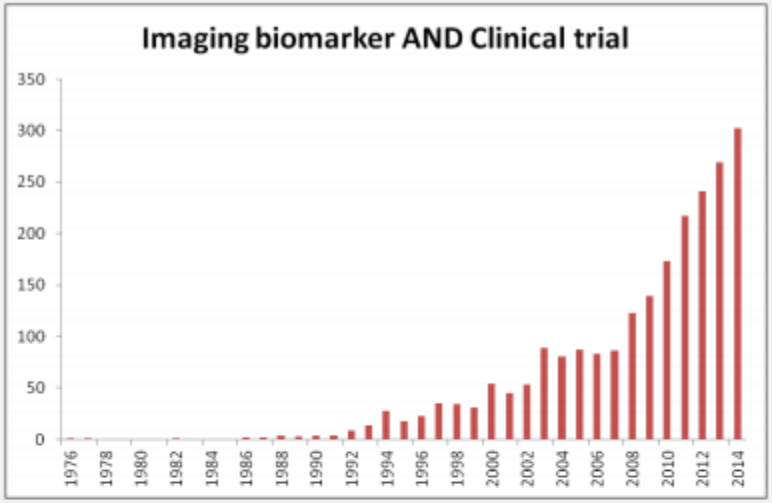
- **Imaging CRO: CRO for Imaging service in Research**

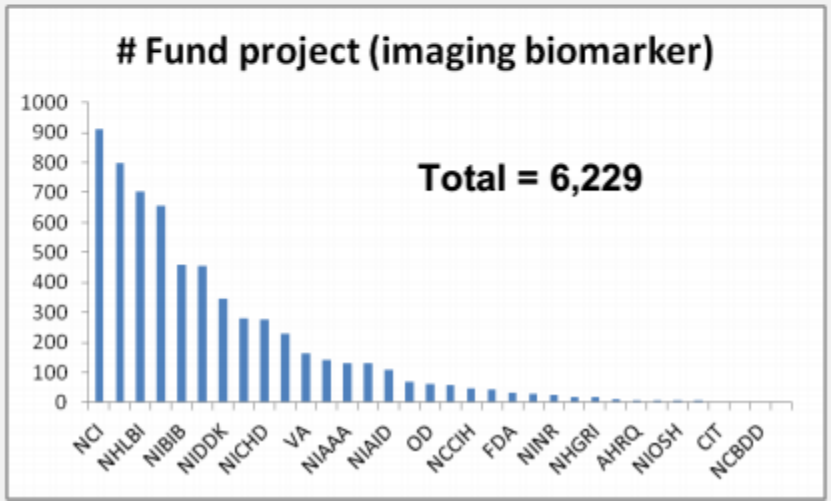
- **Imaging core laboratory for Centralized imaging analysis**

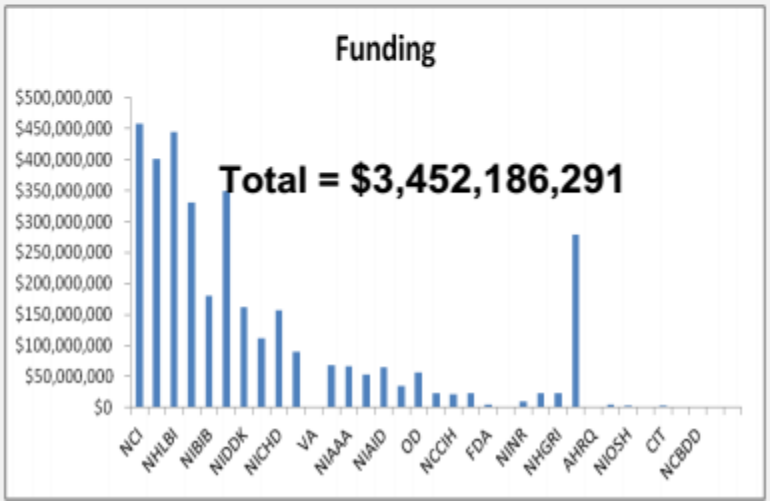
- **Independent Image Review Committee (IIRC) for Centralized reading**

Imaging biomarker









Imaging biomarker

역할

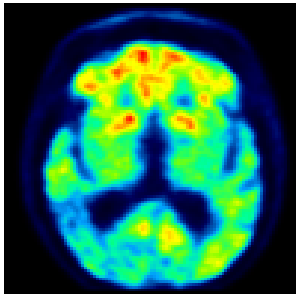
- Predictive biomarker
- 약력학/약동학 평가
- 약리 메커니즘
- 유효성/독성 평가

장점

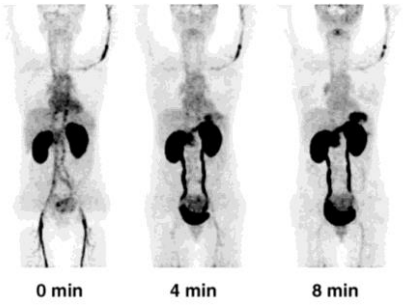
- 비침습적, 생체 내 현상
- 시간에 따라 반복적 관찰
- 개체수/피험자수 최소화
- 전임상–임상 연계

효과

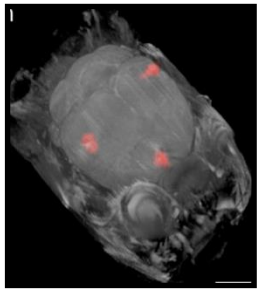
피험자수 ↓
시험기간 ↓
개발비용 ↓



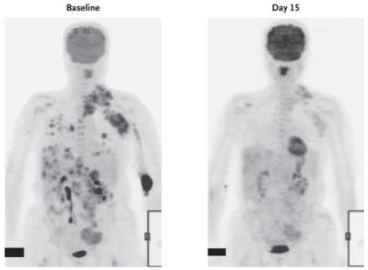
환자선별
:아밀로이드 PET으로
알츠하이머병 선별



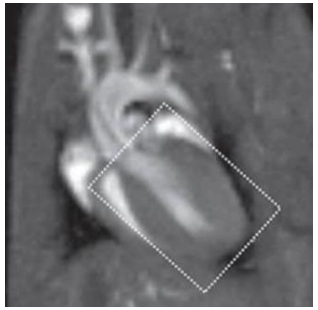
약물 약동학 평가
: Dynamic PET



약리작용 평가
(수용체 영상화)



유효성 평가
(CT, MR, PET)



독성 평가
(심장 MRI 로 심근독성)

Imaging CRO

Imaging support for multicenter clinical trials

- Imaging protocol / charter
- Global standards

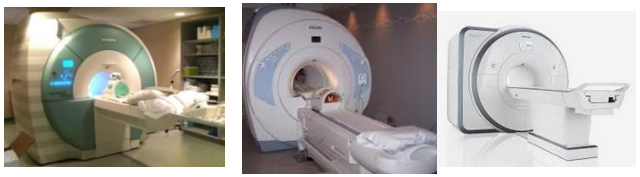
Quantitative Imaging Biomarkers Alliance (RSNA)

Guidance for Industry
Standards for Clinical Trial Imaging Endpoints

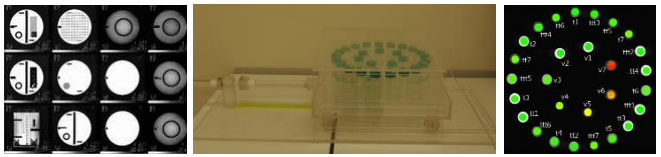
- Site training
- Site monitoring

SAMSUNG 삼성의료원
서울아산병원 Asan Medical Center
서울대학교병원 SEOUL NATIONAL UNIVERSITY HOSPITAL

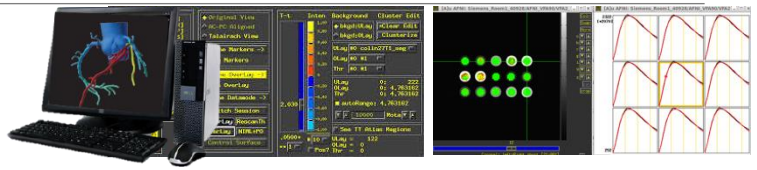
- Imaging acquisition



- QA/QC
- Data management



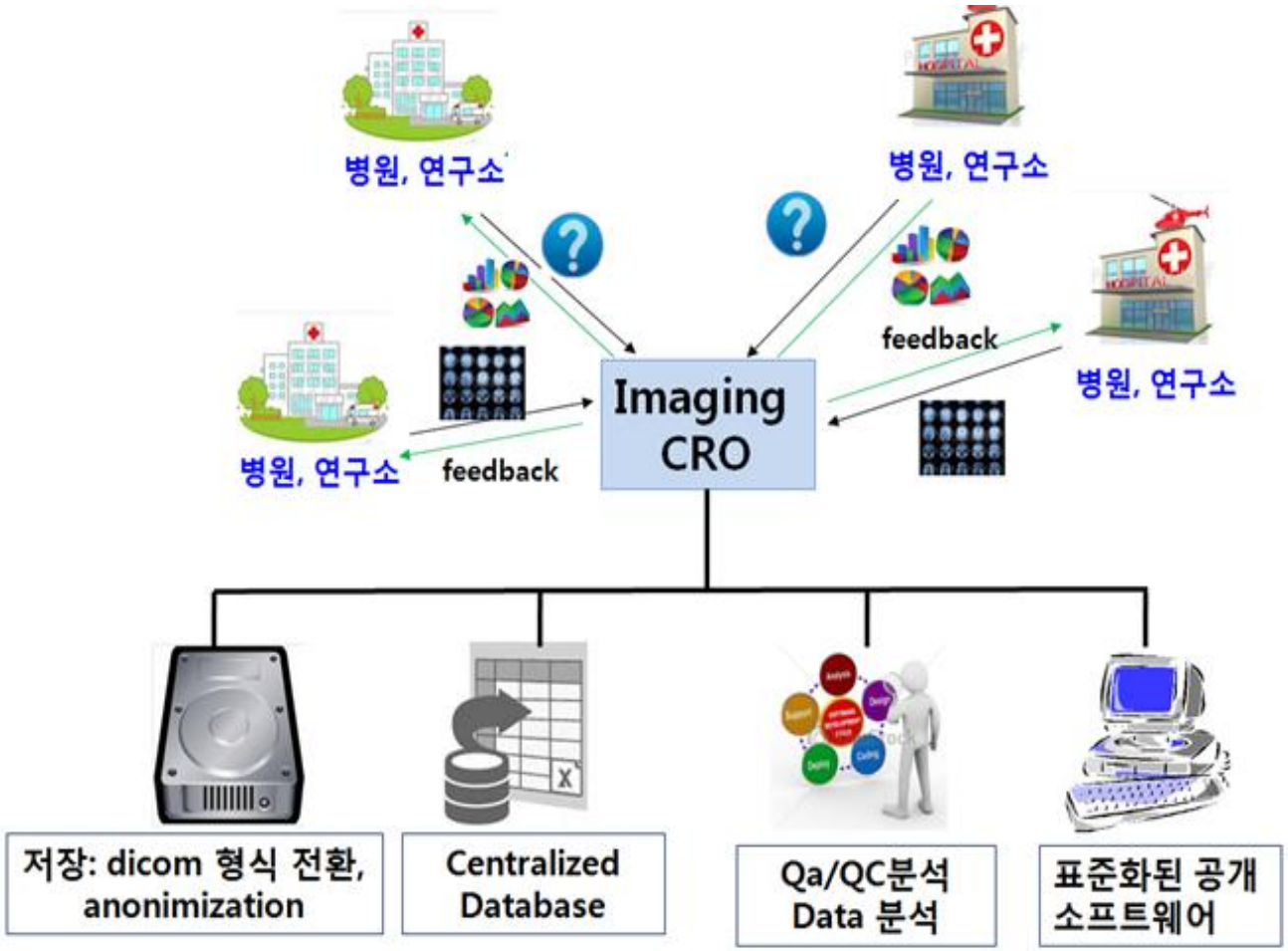
- Post-processing
- Image analysis
- Central reading



High Quality Imaging Service

Central Imaging Core Lab in clinical trials

CRO Team for multicenter trial



- Project Manager
- Imaging CRA
- Imaging QC
- IT manager
- Radiologists
- Regulation medicine

Site core lab service

Investigator (Clinician)

Imaging CRC

- Coordinate imaging device & protocol
- Image acquisition
- Data anonymization & transfer
- Pre-study validation
- Local reading

Radiology Department

Radiologist

Central core lab service

Image Analyst Central Reader

- Image protocol
- Site training/monitoring
- Imaging data management
- Image quality control
- Central reading
- Regulation/SOP

Image CRA

IT system Manager

Imaging physicist (PhD)

ASAN Image Metrics Medical Center

About AIM | Imaging Core Lab Service | IT System | Share Resou

AIM : Asan Image Metrics

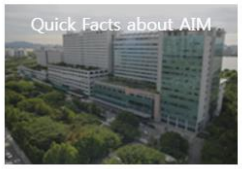
It is the first Central Imaging Core Lab in Korea that was establ
Asan Medical Center to support all aspects of imaging use in c

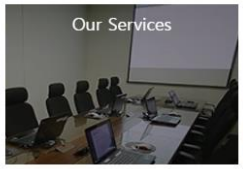
In clinical trials, we support to continue efficient, quick and accurate clinical trials t
consultantion and imaging support services from imaging protocol plan to

Reliable Results
Reliable results by medical imaging professionals

Rapid Results
Rapid results by web-based process

High Quality
High quality with expertise in the latest imaging technique





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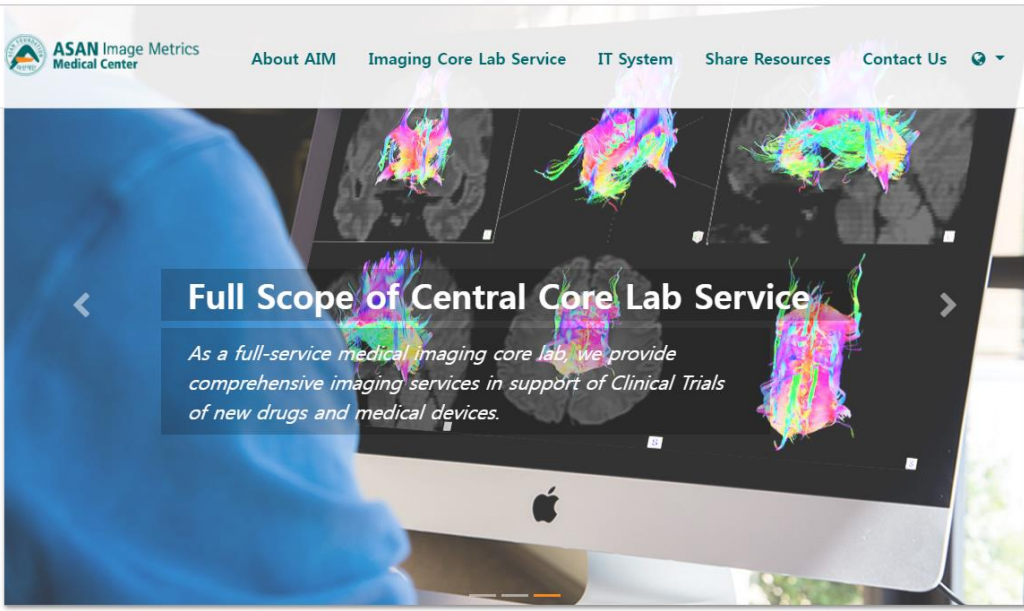
Contact Information +82-2-3010-4392

FAMILY

ASAN Image Metrics Medical Center

About AIM | Imaging Core Lab Service | IT System | Share Resources | Contact Us



Full Scope of Central Core Lab Service

As a full-service medical imaging core lab, we provide comprehensive imaging services in support of Clinical Trials of new drugs and medical devices.

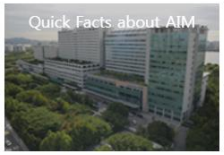
In clinical trials, we support to continue efficient, quick and accurate clinical trials through integrated consultantion and imaging support services from imaging protocol plan to analysis.

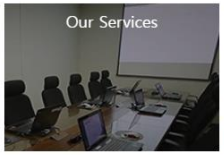
Reliable Results
Reliable results by medical imaging professionals

Rapid Results
Rapid results by web-based process

High Quality
High quality with expertise in the latest imaging technique

Standard Process
Global standardized process for FDA





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FAMILY SITE

Imaging core lab

1. European Cooperative Acute Stroke Study (ECASS, JAMA 1995), The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (NINDS, NEJM 1995): 급성 뇌경색 환자에서의 IV alteplase의 약물 유효성 평가를 위한 Randomized multicenter clinical trial로서 noncontrast CT를 약물 적용 환자군 선정과 alteplase의 주요한 합병증인 뇌출혈의 검출 및 분류를 위하여 이용함. Primary·Secondary outcome은 임상지표였으며 noncontrast CT는 Safety parameters로서 사용됨.
2. The European Atrial Fibrillation Trial Study Group (NEJM 1995): Nonrheumatic atrial fibrillation환자에서 뇌졸중의 리스크를 줄이기 위한 항응고제의 약물 유효성 평가를 위한 Randomized multicenter clinical trial로서 항응고제의 주요한 합병증인 뇌출혈의 검출 및 분류를 위하여 이용함. Primary·Secondary outcome은 임상지표였으며 Safety parameters로서 noncontrast CT를 이용함.
3. Low-molecular-weight Heparin for the treatment of acute ischemic stroke (NEJM 1995): 뇌졸중 환자에서 low-molecular-weight Heparin의 유효성 평가를 위한 연구로서 Primary outcome은 임상지표를 사용하였고 Secondary outcome으로서 low-molecular-weight Heparin의 합병증 (예: 뇌경색 후 뇌출혈)을 밝히고자 하였으며 noncontrast CT를 이용하여 뇌경색 후 뇌출혈을 객관적으로 평가하고자 하였고 independent image review system을 도입하였음.
4. The Multicenter Acute Stroke Trial-Europe Study Group (MAST-E, NEJM 1996): 중대뇌동맥의 중등도 이상의 뇌졸중 환자에서 IV streptokinase의 유효성 평가를 위한 연구로서 Primary·Secondary outcome은 임상지표였으며 noncontrast CT를 Safety parameters와 환자 배제 기준으로서 사용함. Independent image review system을 도입하여 noncontrast CT상 뇌경색과 뇌출혈을 평가하였음.

Imaging core lab

5. **ECASS II (Lancet 1998):** 급성 뇌졸중 환자에서 IV alteplase의 6시간까지의 연장 사용에 관한 유용성 평가를 위한 연구로서 noncontrast CT를 약물 적용 환자군 선정과 alteplase의 주요한 합병증인 뇌출혈의 검출 및 분류를 위하여 이용함. Primary·Secondary outcome은 임상지표였으며 noncontrast CT는 Safety parameters로서 사용됨.
   Noncontrast CT가 환자 선정의 전면에 나온 연구이며 뇌경색, 뇌출혈의 검출 뿐 아니라 뇌경색의 부피를 **정량**적으로 분석하였음.
6. **Phenylpropanolamine and the Risk of Hemorrhagic stroke (NEJM 2000):** Phenylpropanolamine (식욕 억제 및 감기 치료제)의 hemorrhagic stroke 발생에 미치는 영향을 평가한 연구로서 subarachnoid hemorrhage와 intracerebral hemorrhage 검출에 **noncontrast CT**를 이용하였음.
7. **Pravastatin therapy and the Risk of Stroke (NEJM 2000):** Prevastatin의 stroke risk 감소에 대한 유효성 평가를 위한 연구로서 **CT, MR, Angiography**를 Ischemic stroke, Hemorrhagic stroke의 진단과 분류에 이용하였음.
8. **The Desmoteplase in Acute Ischemic Stroke Trial (DIAS, Stroke 2005):** 급성 뇌졸중 환자에서 Desmoteplase의 9시간까지의 연장 사용에 대한 유효성 평가를 위한 연구로서 **DWI, TOF-MRA, FLAIR, PWI**의 MR 영상 검사가 환자 선정 및 outcome에서 주요한 역할을 수행함. Primary outcome으로서 PWI의 **정량**적 감소와 MRA의 재개통 소견을 사용하였고 유효성 평가의 다른 outcome으로서 DWI의 뇌경색 범위의 변화를 이용하였음. DWI은 뇌경색의 진단 및 부피 측정을 위해 사용되었고 FLAIR는 만성적 허혈성 병변 검출에 사용하였음.

Imaging core lab

9. **Recombinant Activated Factor VII for Acute Intracerebral hemorrhage (NEJM 2005)**: 급성 뇌출혈 환자에서의 Recombinant Activated Factor VII의 유효성 평가를 위한 연구로서 Noncontrast CT상 뇌출혈 부피의 변화를 Primary outcome으로 사용하였음. **Digital CT 정보를 imaging core lab으로 전송**하여 Neuroradiologist에 의한 **Independent image review system**을 이용하여 Primary outcome을 분석하였음.
10. **The Dose Escalation of Desmoteplase in Acute Stroke (DEDAS, Stroke 2006)**: 급성 뇌졸중 환자에서 Desmoteplase의 9시간 연장 사용에 대한 유효성 평가를 위한 연구로서 MRI를 Primary efficacy endpoint로 사용하였고 Safety endpoint로서 noncontrast CT를 이용하였음. DWI을 이용한 **정성적·정량적 뇌경색 부피 분석**, MRA를 이용한 혈관의 재개통 분석, 관류 MR을 이용한 **정량적 관류 분석**, Noncontrast CT를 이용한 뇌출혈 발생률을 연구의 주요 결과로서 보고하였음. **Imaging core lab과 Independent image review system**을 통한 정성적·정량적 분석을 시행하였음.
11. **The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE, Ann Neurol 2006)**: 급성 뇌졸중 환자에서 MRI profile과 임상지표를 직접적으로 비교하는 연구로서 **DWI, DSC PWI, FLAIR, GRE, MRA, T1-weighted imaging**을 이용하여 정성적·**정량적 분석을** 시행하였음.
12. **The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET, Lancet 2008)**: Alteplase의 6시간 연장 사용의 유효성 평가를 위한 연구로서 임상지표를 우선하여 영상바이오마커 지표가 Primary endpoint로서 사용되었음. Primary endpoint로서 DWI (baseline) 과 T2-weighted imaging (=FLAIR, 90 days after)사이의 뇌경색 부피 변화를 사용하였음. **정량적 영상 분석 소프트웨어를** 이용하여 뇌경색 부피 변화를 측정하였음. PWI, MRA를 이용하여 관류 변화와 재개통 여부를 판정하였음.

Imaging core lab

13. The Factor Seven for Acute Hemorrhagic Stroke (FAST, NEJM 2008): 급성 뇌출혈 환자에서 Recombinant activated factor VII의 유효성 평가를 위한 연구로서 Primary endpoint로서 Noncontrast CT를 이용한 뇌출혈 부피 변화를 이용하였음. **정량적 영상 분석 소프트웨어**를 이용하여 뇌출혈 부피 변화 결과를 산출하였음.
14. DIAS II (Lancet Neurol 2009): 급성 뇌졸중 환자에서 Desmoteplase의 9시간 연장 사용에 대한 유효성 평가를 위한 연구로서 환자 선정과 Secondary outcome을 위하여 CT와 MR을 사용하였음. 환자 선정을 위해 DWI과 PWI을 이용한 회생가능한 반음영의 **정량적 분석을** 시행하였고 Secondary outcome을 위하여 DWI과 noncontrast CT를 이용한 뇌경색 부피 분석을 하였음. 치료에 의한 혈관의 재개통여부를 위해 MR 혹은 CT angiography를 이용하였으며 Safety outcome으로서 Noncontrast상의 뇌출혈 발생을 사용하였음. Imaging core lab과 함께 정량적 영상분석이 이용되었음.
15. A Randomized Trial of Tenecteplase versus Alteplase for Acute Ischemic Stroke (NEJM 2012): 급성 뇌졸중 환자에서 IV Tenecteplase의 유효성 평가를 위한 연구로서 환자 선정을 위해 CT angiography를 이용하여 혈관의 폐색 정도와 여부를 평가하였고 CT perfusion을 이용하여 뇌경색 병변 범위와 관류상태를 평가하였음. Primary outcome으로서 관류 영상을 통한 관류 상태 변화를 측정하였고 Secondary outcome으로서 뇌경색 부피 변화와 혈관 재개통 분석을 하였으며 Secondary imaging safety outcome으로서 뇌출혈 양 변화를 영상 검사를 통하여 분석하였음. MR 검사로서는 GRE, FLAIR, DWI, PWI, MRA가 사용되었음. Imaging core lab과 Independent image review system을 통한 정성적·정량적 분석을 시행하였으며 정량적 영상 분석을 위해서 Commercial software를 사용하였음.

Imaging core lab & IIRC

2012 – 2018 Clinical trials for endovascular treatment in acute ischemic stroke

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			

Guidance

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

Guidance

A. Choice of Imaging Modality

If an imaging-based primary endpoint is chosen for a phase 3 trial, the choice of the imaging modality (such as echocardiography versus single photon emission computerized tomography) may prove to be an especially important consideration. Imaging modality upgrades and malfunctions are sometimes unpredictable. Clinical sites may also experience unforeseen limitations on the use of the modality or modality-specific imaging drugs and processes, such as the interchange of certain contrast agents that may not affect typical diagnostic imaging but may alter trial-specific quantitative imaging measures.

- **Protocol setting: Survey, Site training, Site monitoring**

Guidance

B. Is Centralized Image Interpretation Important for an Imaging-Based Primary Endpoint?

In clinical trials, images are interpreted either at the clinical site or at a centralized facility that

As compared to site-based image interpretations in multicenter clinical trials, a centralized image interpretation process may provide more verifiable and uniform reader training as well as ongoing management of reader performance, helping to ensure quality control of the images and the interpretations and to decrease variability in image interpretations, leading to a more precise estimate of treatment effect. Nevertheless, the overarching trial design features and the other previously described features may justify the use of site-based imaging interpretations even in large phase 3 multicenter clinical trials, so long as blinding of image interpretation to treatment can be assured or bias is otherwise controlled.

medicine, little imaging acquisition or interpretation variability is anticipated, and potential

- **Independent image review committee (IIRC)**

Guidance

C. Should Image Interpretation Be Blinded to Clinical Data?

To determine whether image readers should be blinded to clinical information, sponsors should have knowledge of the underlying clinical condition, an understanding of the precedent for the use of imaging as a trial's primary endpoint, and detailed insight into the trial's unique image interpretation procedures (such as a plan for sequential *locked-read* image interpretation where an assessment cannot be altered versus an option for modification of prior image interpretations). In certain disease conditions, readers also should be blinded to the image acquisition date and/or knowledge of prior imaging observations. Again, we note that even if the image reader is aware of individual-level clinical information, blinding to treatment assignment is almost always critical.

- **Independent image review committee (IIRC)**

Guidance

D. How Often Should Imaging Evaluations Be Performed?

When a medical image serves as a trial's primary endpoint, its timing and frequency of ascertainment depends upon the underlying condition being studied, the feasibility of the imaging schedule, and the overarching trial design features. For a trial using time point-based imaging measures as a primary endpoint, the frequency of imaging evaluations should be the same in all trial arms. Asymmetric imaging evaluation time points can introduce bias in the treatment effect assessment. For a primary endpoint that uses a time-to-event analytical approach, imaging evaluations should be performed at baseline and at sufficient frequency to provide a reasonably precise measure of the time to the expected clinical event.

- **Imaging core lab / IIRC**

Guidance

E. How Soon After Acquisition Should Images Be Interpreted?

In diagnostic medical imaging practice, images typically are interpreted on site within several hours following acquisition. In contrast, in clinical trials using centralized imaging interpretation, the interpretation may require a longer time frame. Therefore, image interpretation timing typically is more of a consideration when clinical trials use centralized imaging interpretation. When planning a clinical trial that uses an imaging primary endpoint, the *turnaround time* by a central image interpretation facility should be appropriate for the anticipated trial design. For example, prompt image interpretation may be an important consideration for trials that use centralized image interpretations as components of interim analyses, which may occur when imaging-based analyses are important to accommodate prespecified sample size adjustment plans. Similarly, image interpretation expediency may prove critical when centralized imaging interpretation is used to help control imaging quality; in this situation, the centralized imaging readers or an appropriately prespecified centralized imaging quality control process should promptly identify technical flaws that necessitate repeat imaging of a subject. In other circumstances, interpretation of batches of randomized images at specified intervals during a trial may be appropriate. Sponsors should consider the timeliness of centralized image interpretation when developing a clinical trial protocol that uses an imaging-based primary endpoint.

- **Imaging core lab / IIRC, Quality assurance/Quality control**

Guidance

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

- **Standardization**

Guidance: 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

Guidance: 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

Imaging core lab

1. **Protocol setting: Survey, Site training, Site monitoring**

   Standardization

   Acquistion and transfering imaging data

   Quality assurance/Quality control

2. **Post-processing**

   Imaging analysis

3. **Central reading**

Independent image review committee (IIRC)

1. **Reader 1 – Independent reader**
2. **Reader 2 – Independent reader**
3. **Moderator – Independent reader or Adjudicator**

1. **Outside Reader 3 – Consult or Evaluation**
2. **Image review committe (IRC)**
3. **Data & Safety monitoring board (DSMB)**

Experience 1

Neuroprotective agent

1. **Prospective, Randomized, Double-blinded, Phase IIa**
2. **80 participants**
3. **Primary endpoint: CT**
4. **Secondary endpoint: SAE, mRS, sICH, NIHSS, Barthel index, Death rate, major systemic bleeding rate**
5. **Exploratory endpoint: DWI, GRE**
6. **Imaging CRO & Imaging core lab & IIRC**

Primary outcome

- **Safety and Efficacy of Novel Neuroprotective agent**

- **rtPA** 표준 치료 시 **NA**주 투여 후 **24**시간 시점에 촬영한 뇌 **CT** 영상에서 유럽급성뇌졸중협력연구 **(ECASS) I** 과 **II** 기준에 따른 실질혈종 **(Parenchymal hematoma)**의 발생 비율

→ **Consultant for appropriate imaging protocol and analysis for evaluation of drug safety and efficacy**

Secondary outcome

- 5일 이내에 발생한 모든 두개내 출혈의 발생 비율
- 5일 이내에 **DWI** 영상에 확인된 뇌경색 크기의 증가 비율
- 5일 이내에 **DWI** 영상에 확인된 뇌경색의 재발 비율
- 5일 이내에 **GRE** 영상에 확인된 출혈의 발생 건수 및 크기
- **GRE**와 **DWI** 영상을 통해 확인된 뇌출혈과 뇌경색의 변화 비율

Consultant

1. Hemorrhagic transformation: BBB stabilizer → Prevent HT

1) Definition and classification → ECASS (4 classification)

2) Imaging modality: CT & MR

3) MR: GRE (SWI vs GRE)

→ The same imaging machine after Phantom

4) Measurement

→ Quantitative In-house Software

Hemorrhagic transformation

- The most critical risk of tPA
- HT
  - ✓ Autopsy: 38 – 71 %
  - ✓ CT: 13 – 43 %
  - ✓ Symptomatic: 0.6 – 20 %
  - ✓ HI vs PH: 9 % vs 3 % (in large cohort)
- European Cooperative Acute Stroke Study (ECASS) in 1990s
- Parenchymal hematoma $\propto$ poor clinical outcome

Zhang et al. Ann Transl Med 2014
Neeb et al. Cerebrovasc Dis Extra 2013
ECASS I, II
Berger C et al. Stroke 2001

Hemorrhagic transformation

- **Predictors**
  - ✓ Massive infarction
  - ✓ Gray matter (abundant collateral → reperfusion injury)
  - ✓ Afib & Embolism
  - ✓ NIHSS ↑
  - ✓ Hyperglycemia
  - ✓ TC & LDLC ↓
  - ✓ Platelet ↓
  - ✓ Collateral ↓
  - ✓ Medication (tPA, warfarin)
  - ✓ Globulin ↑
  - ✓ Early CT signs
  - ✓ Albuminuria

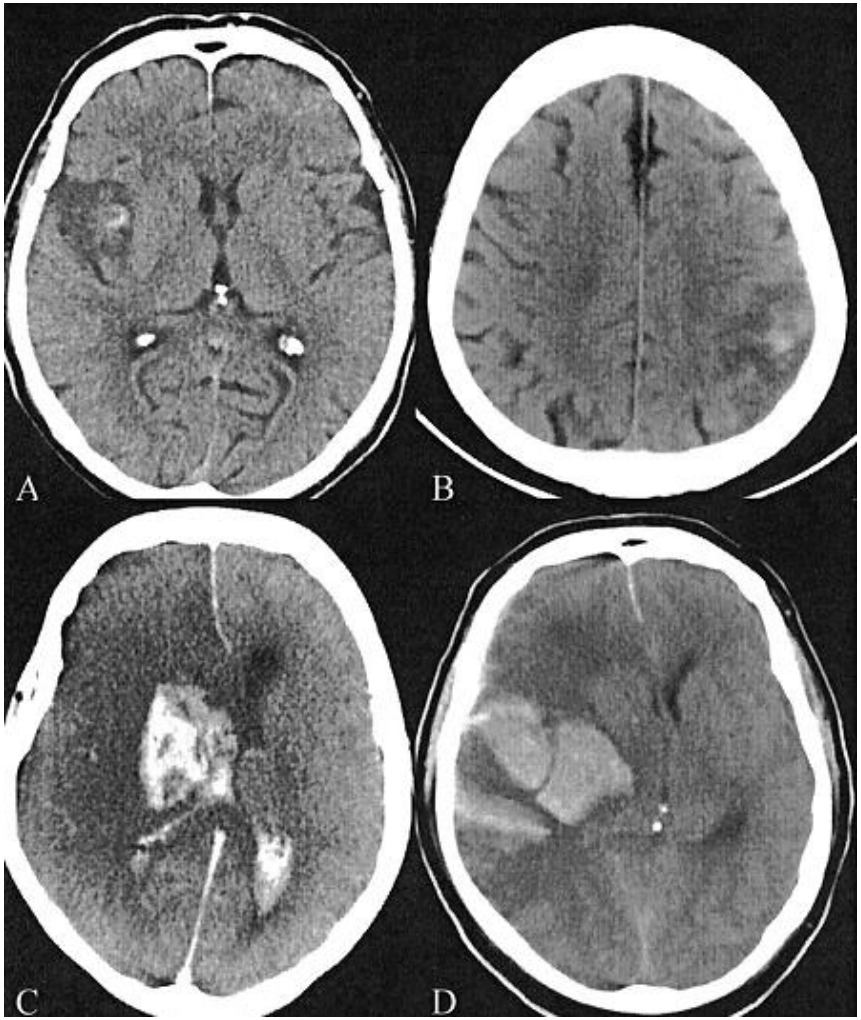
Zhang et al. Ann Transl Med 2014

Hemorrhagic transformation

- **Pathophysiology**
  - ✓ Unclear
  - ✓ Ischemia → ATP ↓ → Na-K ATPase alteration → cellular/metabolic imbalance → **BBB disruption**
  - ✓ Ischemia → strong inflammation → distorting normal cerebrovascular anatomy and physiology → **impairment of autoregulatory capacity**
  - ✓ **Recanalization** predispose to blood extravasation
  - ✓ **tPA** (neurotoxic?): degrade extracellular matrix integrity, BBB leakage...

Zhang et al. Ann Transl Med 2014

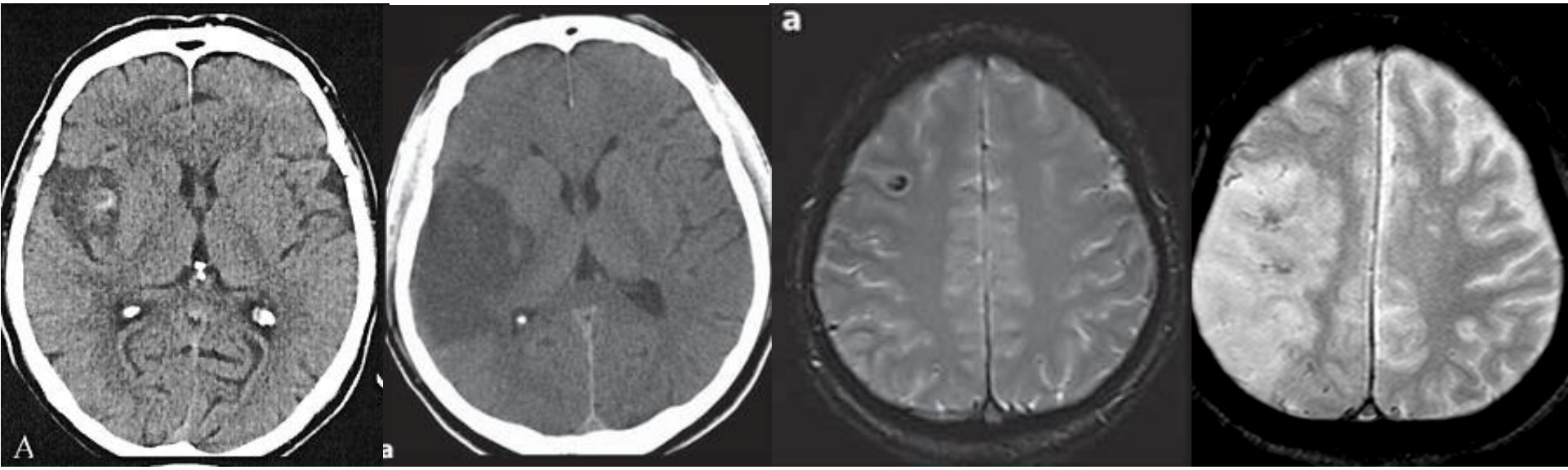
Hemorrhagic transformation Classification



ECASS I, II
Berger C et al. Stroke 2001

Hemorrhagic infarct type 1 (HI-1)

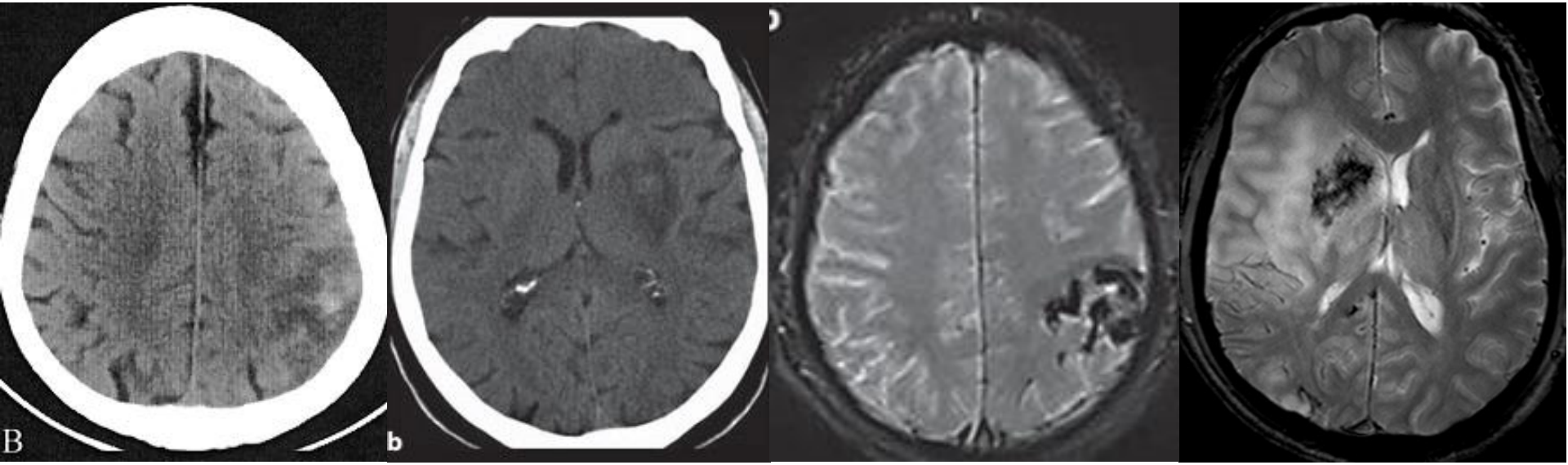
- ✓ ***Small petechiae along the margins of the infarct***
- ✓ ***Smaller than 10 mm***



Berger C et al. Stroke 2001
Renou et al. Cerebrovasc Dis 2010
Neeb et al. Cerebrovasc Dis Extra 2013

Hemorrhagic infarct type 2 (HI-2)

- ✓ ***More confluent petechiae within the infarcted area but without space-occupying effect***
- ✓ ***> 10 mm***



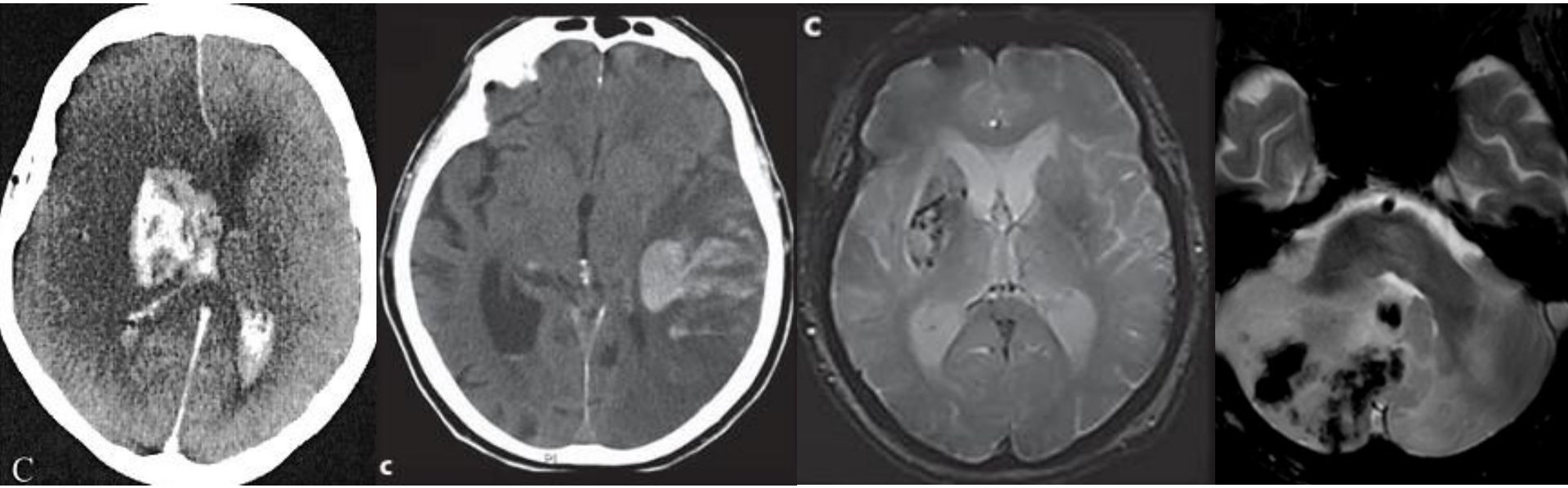
Berger C et al. Stroke 2001
Renou et al. Cerebrovasc Dis 2010
Neeb et al. Cerebrovasc Dis Extra 2013

Parenchymal hematoma type 1 (PH-1)

✓ *Hematoma in ≤ 30 % of the infarcted area*

with some slight space-occupying effect

✓ *Round-shaped hypointensity (sometimes central hyperintensity)*



Berger C et al. Stroke 2001
Renou et al. Cerebrovasc Dis 2010
Neeb et al. Cerebrovasc Dis Extra 2013

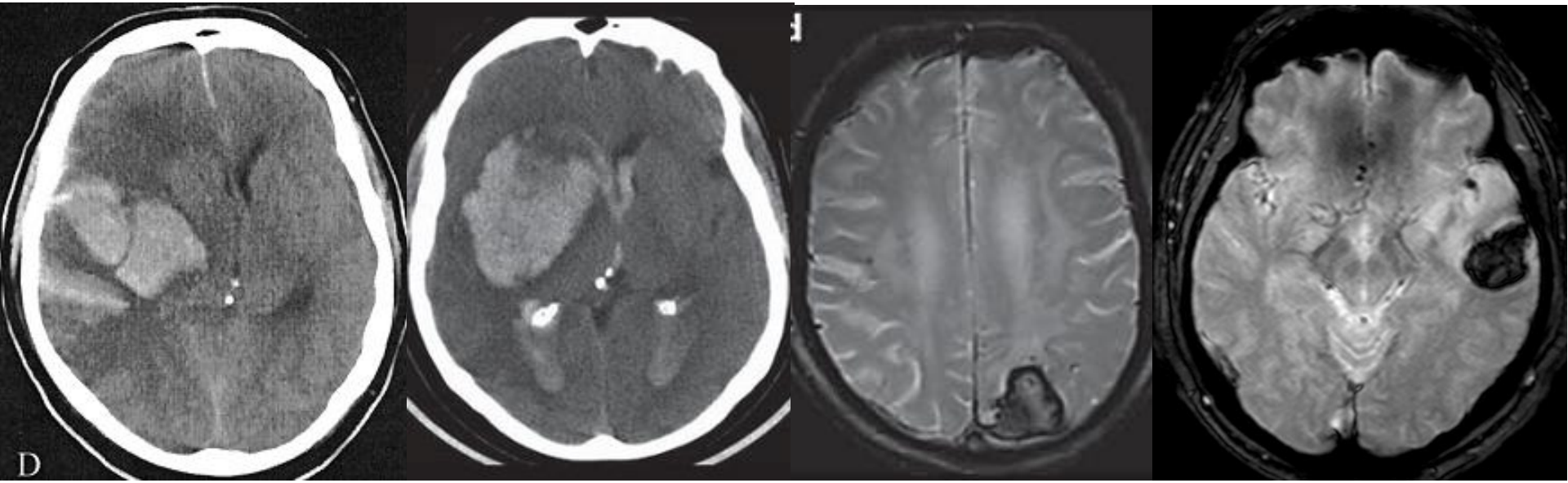
Parenchymal hematoma type 2 (PH-2)

- ✓ *Dense hematoma > 30 % of the infarcted area*

  with substantial space-occupying effect

  or as any hemorrhagic lesion outside the infarted area

- ✓ *Round-shaped hypointensity (possible central hyperintensity)*



Berger C et al. Stroke 2001
Renou et al. Cerebrovasc Dis 2010
Neeb et al. Cerebrovasc Dis Extra 2013

CT vs MR

1. **Upward shift**
2. **Overestimation of PH**
3. **Variability**

   (Inter- & Intra-)

Comparison of CT and Three MR Sequences for Detecting and Categorizing Early (48 Hours) Hemorrhagic Transformation in Hyperacute Ischemic Stroke

Marie-Cécile Arnould, Cécile B. Grandin, André Peeters, Guy Cosnard, and Thierry P. Duprez

BACKGROUND AND PURPOSE: Our goal was to compare the sensitivity of CT and three MR sequences in detecting and categorizing early (48 hours) hemorrhagic transformation (HT) in hyperacute ischemic stroke.

METHODS: Twenty-five consecutive patients with hyperacute ischemic stroke (<6 hours) without MR signs of cerebral bleeding at admission were included. Twenty-one underwent thrombolytic therapy. A standardized follow-up protocol, performed 48 hours after admission, combined brain CT scan and MR examination (1.5 T) including fast spin-echo–fluid-attenuated inversion recovery (FSE-FLAIR), echo-planar spin-echo (EPI-SE) T2-weighted, and EPI-gradient-recalled echo (GRE) T2*-weighted sequences. Both CT scans and MR images were obtained within as short a time span as possible between techniques (mean delay, 64 minutes). CT scans and MR images were independently rated as negative or positive for bleeding and categorized for bleeding severity (five classes) by two blinded observers. Prevalence of positive cases, intra- and interobserver agreement, and shifts in bleeding categorization between respective modalities and sequences were assessed.

RESULTS: Twelve patients (48%) were rated positive for HT on the basis of findings of at least one technique or sequence. From this subset of bleeding patients, seven (58%) had positive CT findings, nine (75%) had positive FSE-FLAIR and EPI-SE T2-weighted findings, and 12 (100%) had positive EPI-GRE T2*-weighted findings. CT had lower intra- and interobserver agreement for positivity than did MR imaging. Among the seven patients with positive CT and MR findings, only two had convergent ratings for bleeding category based on findings of two modalities. The five remaining had upward grading from CT to MR, which varied according to pulse sequence.

CONCLUSION: MR imaging depicted more hemorrhages and had higher intra- and interobserver agreement than did CT. The EPI-GRE T2*-weighted sequence demonstrated highest sensitivity. Equivocal upward shifts in bleeding categorization were observed from CT to MR imaging and between MR images.

Arnould et al. AJNR 2004

Intra- and inter observer agreement

	CT	FSE-FLAIR	EPI-SE T2	EPI-GRE T2*
Observer 1:				
First session	6	9	9	12
Second session	6	9	11	12
Consensus	8	9	9	12
Intraobserver 1 *kappa*	*0.780702*	*1*	*0.834437*	*1*
Observer 2:				
First session	6	9	8	12
Second session	4	9	9	12
Consensus	4	9	8	12
Intraobserver 2 *kappa*	*0.752475*	*1*	*0.911032*	*1*
Interobserver consensus	7	9	9	12
Interobserver *kappa*	*0.576271*	*1*	*0.911032*	*1*

Arnould et al. AJNR 2004

	Kendall's coefficient of concordance *(W)*		
	overall (n = 6)	residents (n = 3)	experts (n = 3)
Bleeding categorization (HI-1, HI-2, PH-1, PH-2)	0.79	0.87	0.81
Distinction between HI and PH	0.82	0.91	0.82

Kendall's coefficient of concordance *(W)* was determined for the bleeding categorization and the distinction between HI and PH for all observers and for each group (3 residents and 3 experts). *W* values of 0.6–0.8 indicated a substantial and of 0.81–1 an almost perfect degree of agreement.

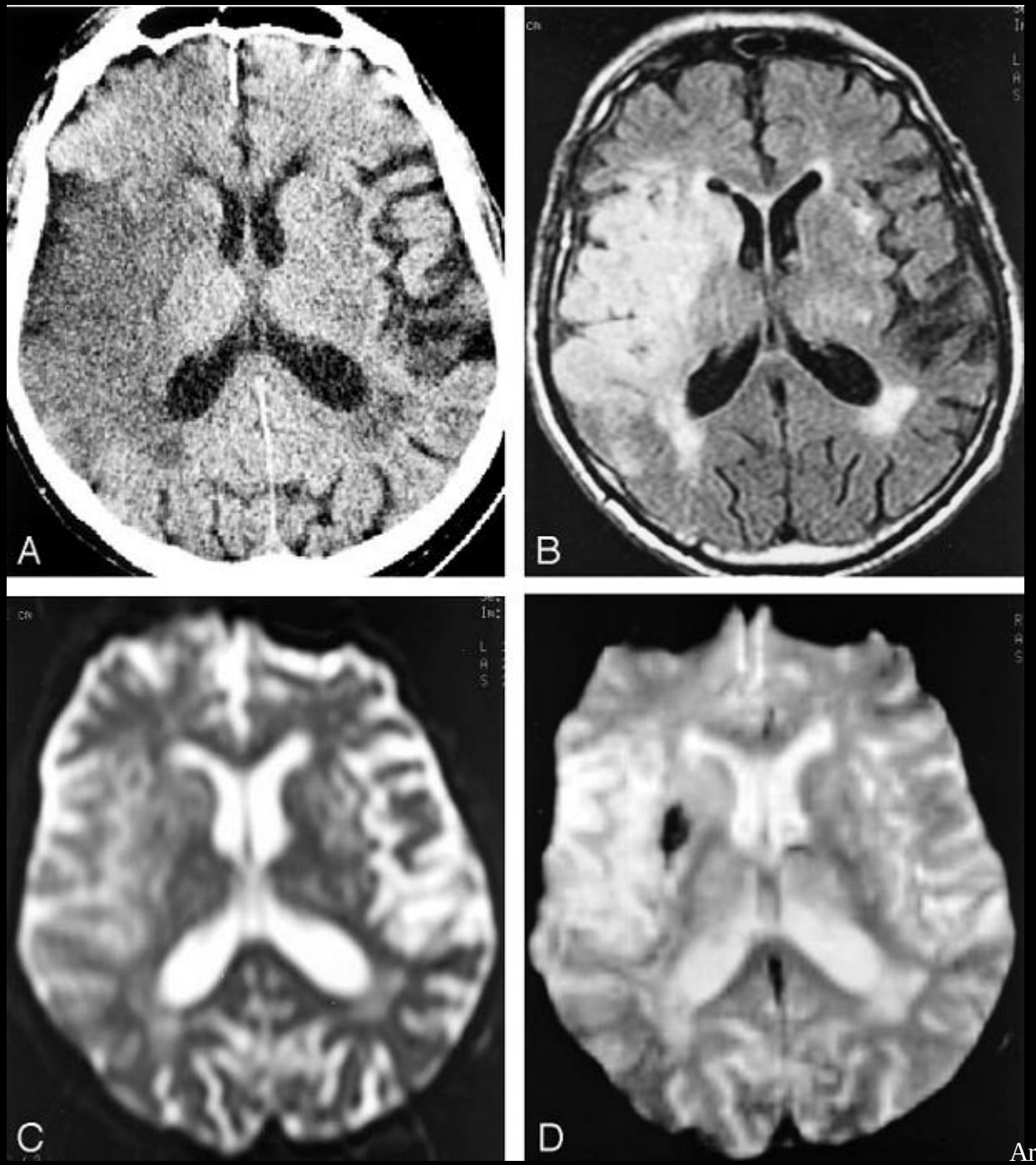
Neeb et al. Cerebrovasc Dis Extra 2013

Intra- and inter observer agreement

	Interobserver Fleiss' κ								
	CT		T2*GRE		DWI		FLAIR		FLAIR DWI T2*GRE
	group 1	group 2	group 1	group 2	group 1	group 2	group 1	group 2	group 1
Bleeding detection	0.66 (0.43–0.82)	0.59 (0.39–0.77)	0.80 (0.61–0.94)	0.75 (0.57–0.90)	0.50 (0.30–0.66)	0.58 (0.39–0.74)	0.51 (0.32–0.67)	0.19 (0.02–0.37)	0.87 (0.72–0.97)
Overall concordance									
Simple κ	0.54 (0.42–0.64)	0.48 (0.34–0.59)	0.63 (0.50–0.76)	0.58 (0.45–0.69)	0.39 (0.26–0.52)	0.47 (0.36–0.58)	0.35 (0.22–0.47)	0.22 (0.10–0.33)	0.53 (0.41–0.63)
Weighted κ	0.70 (0.63–0.77)	0.68 (0.61–0.75)	0.74 (0.66–0.82)	0.75 (0.69–0.82)	0.54 (0.45–0.62)	0.66 (0.59–0.73)	0.55 (0.47–0.64)	0.42 (0.33–0.51)	0.74 (0.68–0.80)
Bleeding categorization									
HI1	0.60 (0.40–0.77)	0.42 (0.20–0.60)	0.34 (0.21–0.45)	0.42 (0.19–0.62)	0.25 (0.08–0.40)	0.34 (0.17–0.50)	−0.11 (−0.17 to 0.06)	0.03 (−0.10 to 0.15)	0.29 (0.02–0.52)
HI2	0.50 (0.31–0.68)	0.44 (0.24–0.61)	0.56 (0.38–0.73)	0.47 (0.22–0.66)	0.31 (0.12–0.49)	0.38 (0.18–0.57)	0.32 (0.14–0.49)	0.31 (0.12–0.48)	0.33 (0.17–0.49)
PH1	0.43 (0.23–0.62)	0.34 (0.10–0.54)	0.61 (0.21–0.86)	0.54 (0.30–0.73)	0.43 (0.08–0.67)	0.52 (0.25–0.75)	0.34 (0.08–0.57)	0.10 (−0.11 to 0.33)	0.49 (0.26–0.69)
PH2	0.41 (−0.03 to 0.78)	0.87 (0.49–1.00)	0.82 (0.38–1.00)	0.77 (0.54–0.94)	0.85 (−0.01 to 1.00)	0.58 (0.18–0.87)	0.55 (−0.02 to 0.86)	0.64 (0.23–0.89)	0.66 (0.33–0.88)
Distinction PH/HI	0.66 (0.46–0.83)	0.51 (0.26–0.71)	0.83 (0.62–0.96)	0.78 (0.65–0.91)	0.53 (0.26–0.73)	0.75 (0.57–0.89)	0.55 (0.34–0.74)	0.34 (0.11–0.55)	0.78 (0.63–0.92)

Renou et al. Cerebrovasc Dis 2010

0



HI 2

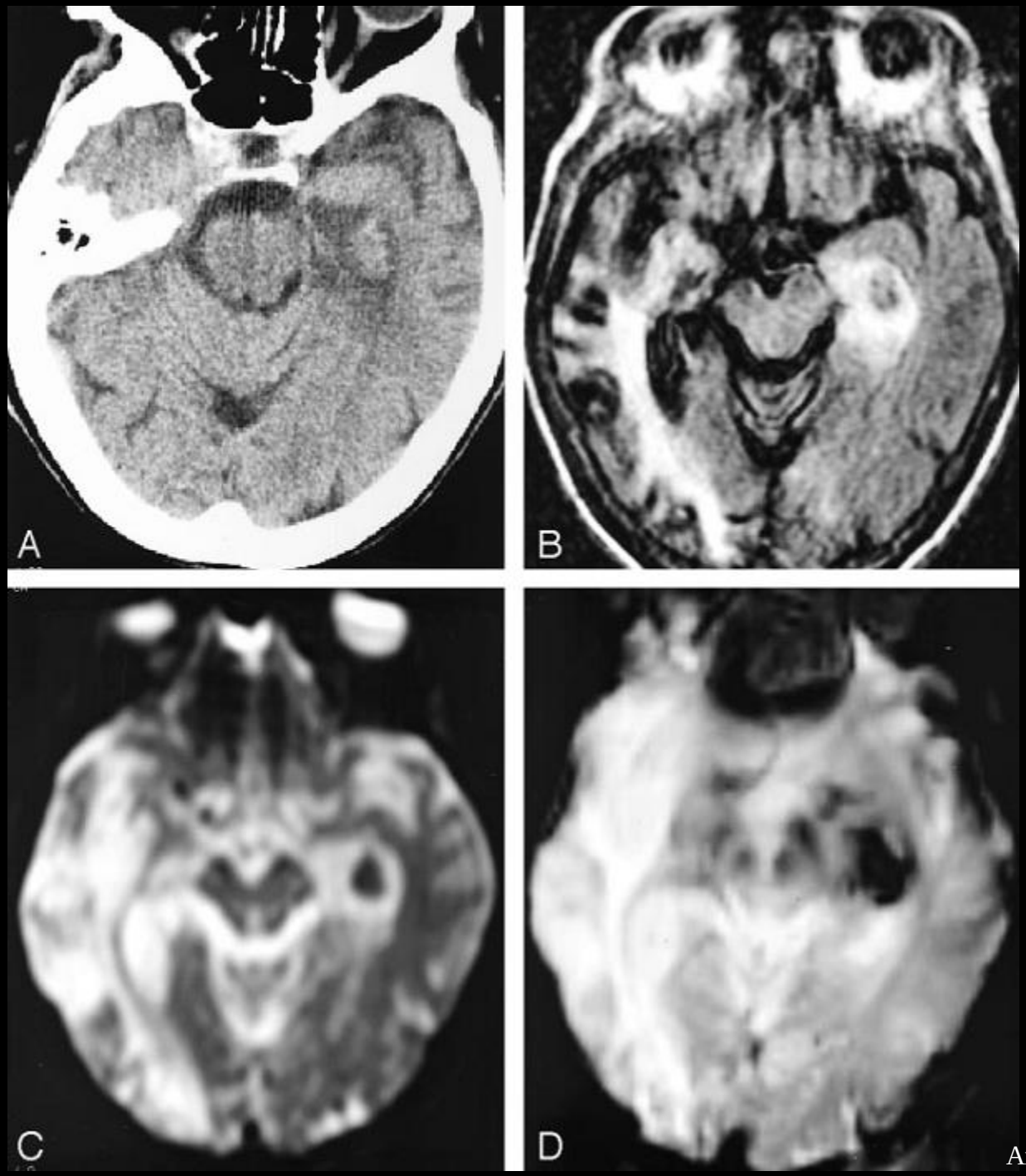
Confluent petechiae

Arnould et al. AJNR 2004

HI 1

Extended debate

Spared tissue vs petechial HT



PH 2

>30 %

Arnould et al. AJNR 2004

Consultant

2. Acute infarct

1) Definition : DWI restricted lesion

2) Presence or Absence

3) Anatomic location

4) Measurement: DWI (b1000 with ADC)

5) Semi- automated In-house software

Consultant

3. New infarct or recurred infarct

1) Definition

→ **New DWI restricted lesions** on follow-up outside the region of the acutely symptomatic lesion and which is not detected on initial DWI.

→ Although new DWI restriction occurs on follow-up image after no DWI restriction on initial images, the lesion is defined as **No New infarction** in case of occurrence in the perfusion territory which is the same with initial perfusion deficit.

Consultant

3. New infarct or recurred infarct

2) Imaging modality: DWI

3) Measurement: The entire infarct core volume on F/U using In-house analysis software

Consultant

4. Steno-occlusion

1) Definition: Revascularization

2) Imaging modality: CTA, MRA

3) Scoring: mTICI

mTICI

Table 2: Varying definitions of TICI grades in the literature

Category	Definition
Grade 0	No flow
	No canalization
	Complete occlusion
	No recanalization/reperfusion
Grade 1	Minimal recanalization (<20%)
	Minimal flow (very slow) without significant flow distal to the occlusion site
	Limited or no reperfusion
	Distal movement of thrombus without reperfusion
	Perfusion past initial occlusion, but limited distal branch
	Filling
Grade 2	Partial recanalization—recanalization of some but not all of the occluded arteries
	Incomplete recanalization/reperfusion
	Near-normal flow, with flow distal to the occlusion but not filling the distal branches normally
Grade 2a	Perfusion of <50% of the MCA distribution
	Partial filling of the entire vascular territory
	Partial perfusion with incomplete distal filling of <50% of expected territory
	Partial filling of the entire vascular territory
Grade 2b	Partial perfusion with incomplete distal branch filling of ≥50–99% of the expected territory
	Complete filling, but the filling is slower than normal
	Perfusion of half or greater of the vascular distribution of the occluded artery
Grade 2c	Near-complete perfusion without clearly visible thrombus but with delay in contrast run-off
Grade 3	Full perfusion with filling of all distal branches, including M3, M4
	Normal flow
	Partial recanalization with >50% reperfusion
	Full perfusion with normal filling of distal branches in a normal hemodynamic fashion
Grade 4	Complete recanalization/reperfusion

J.E.Fugate et al. AJNR 2013

Table 2. Modified Treatment in Cerebral Ischemia Scale

mTICI Grades	Definitions
Grade 0	No perfusion
Grade 1	Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
Grade 2a	Antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (eg, in 1 major division of the MCA and its territory)
Grade 2b	Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (eg, in 2 major divisions of the MCA and their territories)
Grade 3	Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

MCA indicates middle cerebral artery; and mTICI, Modified Treatment in Cerebral Ischemia Scale.

Osama O. Zaidat et al. Stroke 2013

Imaging CRO

1. Protocol setting: Survey & Site evaluation

- CT 프로토콜의 최소 충족 요건 (Full protocol 별첨 첨부)

Protocol	Standard	CT 1 장비(서관5번방)	CT2 장비(서관 6번방)	CT 3 장비(응급실 CT)
제조업체 및 장비모델 명	-	SIEMENS SOMATOM Definition Edge	SIEMENS SOMATOM Definition Edge	SIEMENS SOMATOM Definition AS
Channel				
Slice thickness				
Display FOV (DFOV)				
Matrix				
Resolution				
Table pitch				
Kernal, Reconstruction				
kVp, mAs, AEC				

Imaging CRO

1. Protocol setting: Survey & Site evaluation

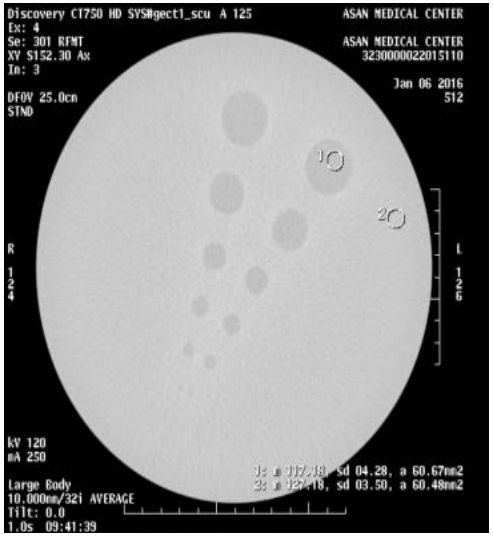
- MR DWI 프로토콜의 최소 충족 요건 (Full protocol 별첨 첨부)

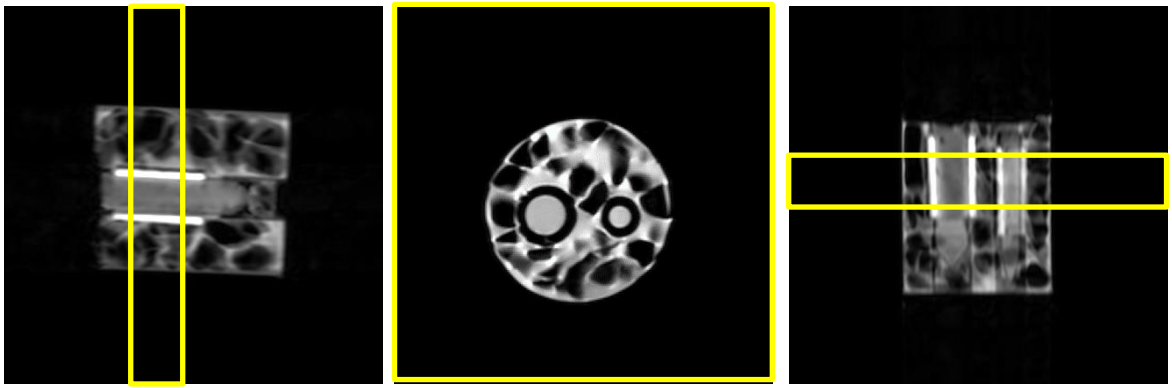
Protocol	Standard	MRI 1 장비(동관 3번방)	MRI 2 장비(응급실 MR)
제조업체 및 장비모델 명	-	Siemens Magnetom Avanto	Siemens Magnetom Avanto
Tesla			
Coil			
FOV			
Matrix			
Resolution			
TR			
TE			
Slice thickness			
Gap thickness			
B-value 수			

Imaging CRO

1. Protocol setting: Imaging protocol standard

2. Standardization: Phantom (CT, DWI, GRE) with 3-month interval





Imaging CRO

1. Protocol setting: Imaging protocol standard
2. Standardization
3. **Site training: Imaging acquistion & transfer**
4. **Site monitoring: QC/QA**

Brain CT

➢ 최소 요구 사항

Channel	4 channel 이상
Slice thickness	5 mm 또는 그 이하
Display FOV (DFOV)	20 – 25 cm
Matrix	512 × 5120이상
Resolution	10 line pairs / cm 이상
Table pitch	2 이하 (Helical scanning일 경우) 대부분 1 (Sequential scanning)
Kernal	Manufacturer's recommendation
KvP, mAS, AEC	Manufacture's setting (60mGy 선량 이하에서 기기에 적합한 KvP, mAS, Automatic exposure control 기법 활용)

DWI

➢ 최소 요구 사항

Coil	8 ch 이상의 Head coil 혹은 NV coil
FOV	200 – 250 mm
Matrix	128 x 128 이상
Resolution	2.0x 2.0mm^2
TR	2000 ms 이상
TE	110 ms 이하
Slice thickness	4-6 mm
Gap thickness	0-2 mm
Number of b-value	2 이상
High b-value strength	700 – 1200 s mm^{-2}

T2* GRE

➢ 최소 요구 사항

Coil	8CH 이상의 Head coil 혹은 NV coil
FOV	200-250mm
Matrix	128×128 이상
Resolution	2.0×2.0 mm^2
TR	500-1000 ms
TE	16-32ms
Slice thickness	4.0-6.0mm
Gap thickness	0-2.0mm
Average수	1 이상

Imaging CRO

서울아산병원 Asan Medical Center

C-BiND 신약개발 바이오이미징

C-BiND Protocol Number :

Phantom scanning guide v1.0

C-BiND, 신약 개발 바이오 이미징 센터

의 효능시험을 위한 팬텀 스캐닝 안내서

- 팬텀 테스트를 통과한 장비와 Coil 만을 사용하여 신뢰도 높은 데이터 획득을 가능하게 한다.
- 테스트를 통과한 장비와 Coil 을 대상으로 3 개월에 1 회 이상 팬텀 영상을 획득하여 지속적인 품질관리를 진행한다.

Document File Nam	L_ Phantom_Scanning_Guide
Version: 1.0	
Version Date: 01-Apr-16	

서울아산병원 Asan Medical Center

C-BiND 신약개발 바이오이미징

4. 팬텀 종류 (총 3개)

- CT 팬텀: 1개
- MR 팬텀(DWI 팬텀, GRE 팬텀): 2개

사진 1. 1)DWI 팬텀, 2)GRE 팬텀, 3)CT 팬텀

5. 로컬 라이저 획득 방법.

- 팬텀이 위를 향하도록 하여 해당 Coil 혹은 장비 테이블 중앙에 위치 시킴.
- 팬텀 번호(음각으로 각인된 일련번호)가 테이블 다리 방향으로 향하게 위치시킴.
- 팬텀 상면에 각인된 십자선에 레이저 포인터를 일치시킴.
- 로컬라이저 획득 파라메터는 각 기관의 protocol을 따른다.

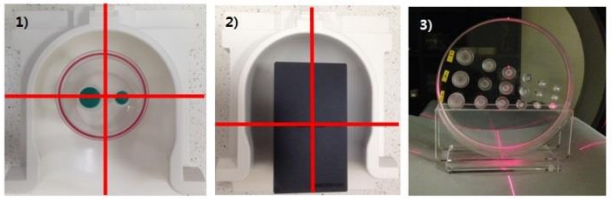


사진 2. 1)DWI 팬텀, 2)GRE 팬텀, 3)CT 팬텀

Quality assurance/Quality control

기관번호	대상자번호	Initial CT(DAY-0)	Follow-up CT(DAY-1)	Initial MRI(DAY-0)	Follow-up MRI(DAY-5)
05	S2-05-S01	2016-10-17	2016-10-18	2016-10-18	2016-10-22
07	S2-07-S01	ND	2016-11-04	2016-11-03	2016-11-08
07	S2-07-S02	NA	NA	2016-11-04	NA
05	S2-05-S02	2016-11-21	2016-11-22	2016-11-22	2016-11-26
01	S2-01-S01	2016-11-25	2016-11-26	2016-11-25	2016-11-30
01	S2-01-S02	2016-11-26	2016-11-27	2016-11-26	2016-12-01
05	S2-05-S03	2016-11-28	2016-11-29	2016-11-28	2016-12-03
05	S2-05-S04	2016-11-28	2016-11-29	2016-11-28	2016-12-03
03	S2-03-S01	2016-12-01	2016-12-02	2016-12-01	2016-12-06
06	S2-06-S01	2016-12-06	2016-12-07	2016-12-06	2016-12-11
01	S2-01-S03	2016-12-09	2016-12-10	2016-12-09	2016-12-14
03	S2-03-S02	2016-12-09	2016-12-10	2016-12-09	2016-12-14
01	S2-01-S04	2016-12-10	2016-12-11	2016-12-11	2016-12-16
04	S2-04-S01	2016-12-11	2016-12-12	2016-12-11	ND
					대상자사망(중도탈락)
07	S2-07-S03	2016-12-17	2016-12-18	2016-12-17	2016-12-23
06	S2-06-S02	2016-12-21 / 26	2016-12-21 / 2017-01-11	2016-12-29	2016-12-27 / 2017-01-11

02	S2-02-S01	2016-12-23	2016-12-23	2016-12-23	2016-12-27
	(QC보류)	Image_기관명생성	Image_기관명생성	Image_기관명생성	Image_기관명생성
07	S2-07-S04	2016-12-27	2016-12-27 / 2017-01-06	2016-12-27	2017-01-02 / 2017-01-06 / 2017-01-18
		QC	QC	GRE 영상 없음(01월31일 업로드 하였으나, GRE영상이 없어 다시 영상 확인 요청 함.)_0206 다시 메일 보냄!	QC
06	S2-06-S03	2016-12-26	2016-12-26	2016-12-27	2017-01-03
03	S2-03-S03	2016-12-28	2016-12-28	2016-12-28	2017-01-04
	(CT QC만 가능)	QC	QC	Image_기관명생성 (17.02.06_CRC 선생님께 이와 관련하여 다시 메일 전달!)	Image_기관명생성
05	S2-05-S05	2016-12-29	2016-12-30 / 2017-01-10	2016-12-30 / 2017-02-06	2017-01-04
		QC	QC	QC MRA 영상_기관명이 나타나 삭제 후, 재업로드!	QC

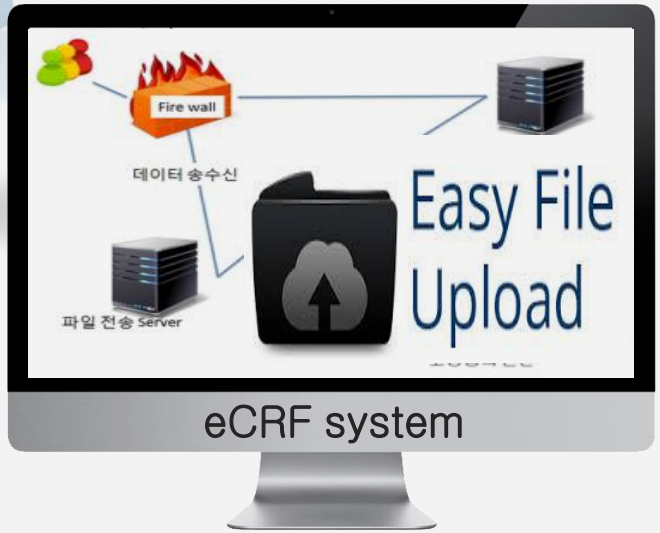
Quality assurance/Quality control

02	S2-02-S02 (QC보류)	2017-01-11	2017-01-11	2017-01-11	2017-01-12
		Image_기관명생성	Image_기관명생성	Image_기관명생성	Image_기관명생성
04	S2-04-S02	2017-01-02	2017-01-02	2017-01-02	2017-01-12 / 2017-01-19
		QC	QC	B-value 0 영상 누락	QC
01	S2-01-S05	2017-01-03	2017-01-03	2017-01-04	ND
		QC	QC	QC	맥박이 급격히 낮아짐 Drop out
04	S2-04-S03	2017-01-09	2017-01-09	2017-01-09	2017-01-12
		QC	QC	QC	QC
05	S2-05-S06	2017-01-12	2017-01-16	2017-01-12	2017-01-16
				MRA 영상 파일 재업로드 17.02.06 CRC에게 재업로드 요청함.	
03	S2-03-S04	2017-01-17	2017-01-17	2017-01-17	-
		QC	QC	Image_기관명생성 (17.02.06_CRC 선생님께 이와 관련하여 다시 메일 전달!)	Image, DTF 없음
07	S2-07-S05	2017-01-23	2017-01-23	2017-01-23	2017-02-01
		QC	QC	QC	QC
06	S2-06-S04	2017-02-02	2017-02-02	2017-02-02	2017-02-02
		QC	QC	QC	QC
03	S2-03-S05	2017-02-01	2017-02-02	2017-02-01	2017-02-02
		QC	QC	Image_기관명생성 (17.02.06_CRC 선생님께 이와 관련하여 다시 메일 전달!)	Image_기관명생성, (17.02.06_업로드 요청함)
04	S2-04-S04	2017-01-31	2017-01-31	-	-
		QC	QC	Image, DTF 없음	Image, DTF 없음
02	S2-02-S03	-	-	-	-
		Image, DTF 없음	Image, DTF 없음	Image, DTF 없음	-
01	S2-01-S06	2017-02-01	2017-02-06	2017-02-01	2017-02-06
		QC	QC	QC	QC
04	S2-04-S05	2017-02-06	2017-02-06	2017-02-06	-
		QC	QC	QC	-
04	S2-04-S06	2017-02-06	2017-02-06	2017-02-06	
		QC	QC	QC	
03	S2-03-S06				

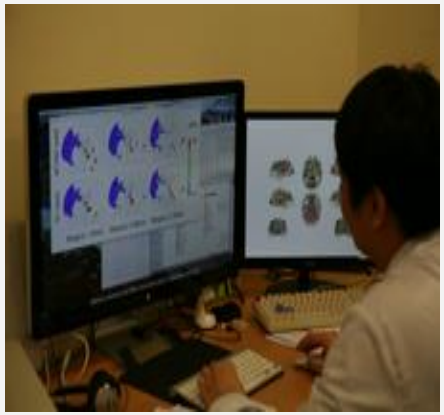
Image Transfer

- Anonymized imaging data and Transfer

영상 촬영 완료 후 2일(근무일기준) 이내에 e-CRF로 전송

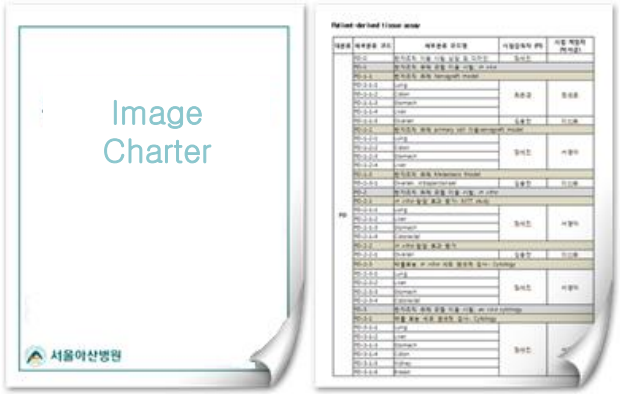


eCRF system



Quality Check

Charter Documentation



- 시험설계와 시험에서 영상의 역할에 대한 요약
- 표준화된 영상 획득 프로토콜
- 시험에 사용할 장비 및 소프트웨어의 표준화
- 영상 품질 및 장비 평가에 있어 각 기관의 방사선사의 역할
- 기관 적격성 평가 및 영상 품질 모니터링을 위한 절차 및 팬텀 영상 획득 방법
- 피험자 전 처치 및 촬영 자세 기준
- 영상 평가 일정
- 데이터 전송 및 보관, 관리 방법
- 표준화된 영상 획득용 의약품
- 영상 전송 및 수신된 내역에 대한 문서화 및 품질평가법
- 영상 디스플레이 및 판독 방법과 품질관리 절차
- 영상 데이터 보안화 절차
- 영상 증례 기록서

Imaging core lab

1. Protocol setting: Imaging protocol standard
2. Standardization
3. Site training: Imaging acquistion & transfer
4. Site monitoring: QC/QA
5. **Image analysis considering endpoints**

Quantitative imaging analysis

1. Infarct core volume measurement

2. Hemorrhagic transformation volume measurement

Infarct core volume segmentation

- ECASS I, II (JAMA 1995, Lancet 1998), ATLANTIS (JAMA 1999)
  - **CT (infarction≒hypodensity, hemorrhage or not)**
  - IV tPA beneficial? within 6 hrs of the onset of stroke
  - Try a time window of upto 6 hrs → Fail

- DIAS (Desmoteplase In Acute ischemic Stroke phase II, Stroke 2005)
  - **MR (infarct lesion volume ≒ DWI abnormality)**
  - IV Desmoteplase within 3 to 9 hrs improves outcome

- DEDAS (Dose Escalation study of Desmoteplase in Acute ischemic Stroke, Stroke 2006)
  - **MR (infarct lesion volume ≒ DWI lesion)**
  - **CT (hemorrhage for exclusion)**
  - IV Desmoteplase within 3 to 9 hrs improves outcome

Infarct core volume segmentation

- DIAS-2 (Desmoteplase In Acute ischemic Stroke phase III, Lancet Neurol 2009)

  ➢**MR (infarct lesion volume ≒ DWI abnormality), CT**

- DEFUSE (Diffuseion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study, Ann Neurol 2006)

  ➢**MR (infarct lesion volume ≒ DWI high SI + ADC confirm)**

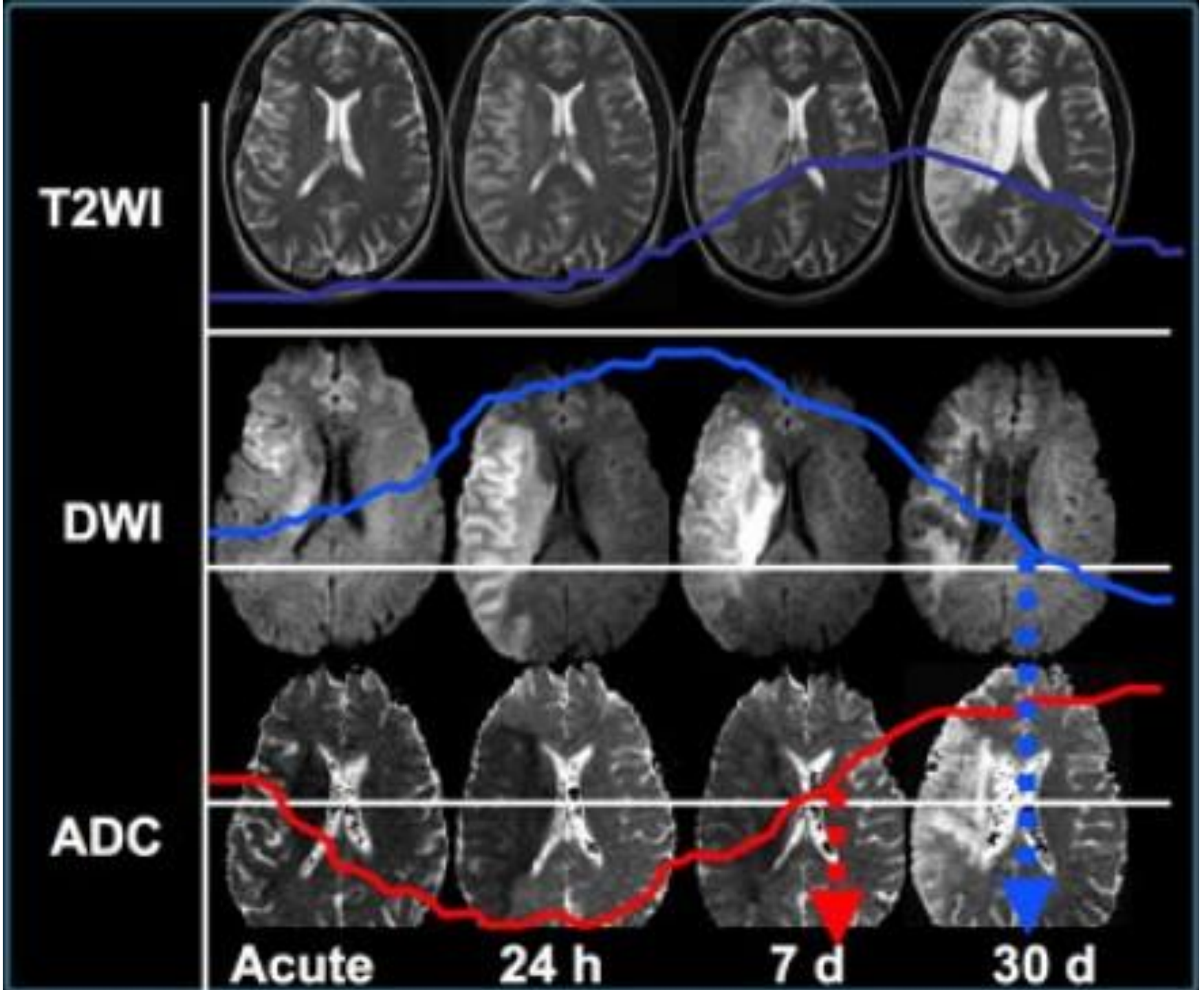
- EPITHET (Echoplanar Imaging Thrombolytic Evaluation Trial, Lancet Neurol 2008)

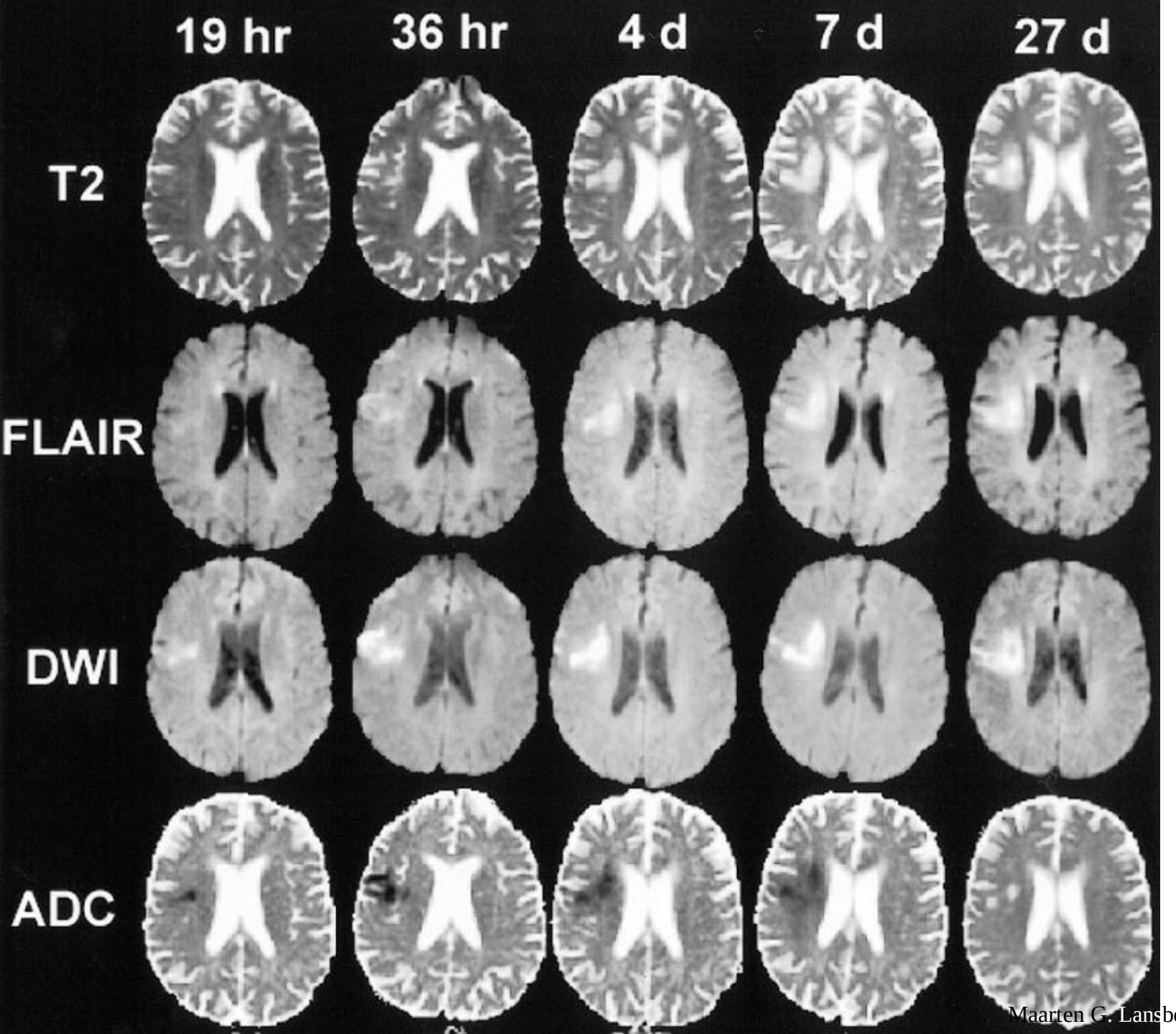
  ➢**MR (infarct lesion volume ≒ DWI volume, no comment about ADC)**

- DEFUSE 2 (Lancet Neurol 2012)- MRI can identify

  ➢**RAPID software**

  ➢**MR (infarct lesion volume ≒ less than ADC 600x100^{-6} mm^2/s)**


T2WI
DWI
ADC
Acute
24 h
7 d
30 d



Maarten G. Lansberg et al. AJNR 2001

Infarct core volume

- DWI high SI
- ADC low SI
- FLAIR high SI
- ADC pseudonormalization

(B.C.) who was not blinded to treatment. Regions of interest were manually drawn using careful windowing to outline the maximal visual extent of the acute DWI (B1000 trace-weighted) lesion with reference to the apparent diffusion coefficient image to avoid regions of T2 shine-through. The B1000 image was used as the primary template because quantitative apparent diffusion coefficient thresholds tend not to accurately outline the visually evident lesion and have been shown to vary with time after stroke onset and perfusion status.

→ **Infarction volume is measured based on DWI high SI with reference to ADC**

Toshiyasu Ogata et al. Stroke 2013

Infarct core/Hemorrhage volume

Datasharing.aim-aicro.com/strokevolumetry

Independent image review committee (IIRC)

1. Protocol setting: Imaging protocol standard
2. Standardization
3. Site training: Imaging acquistion & transfer
4. Site monitoring: QC/QA
5. Image analysis considering endpoints
6. **Central reading**

Independent image review committee (IIRC)

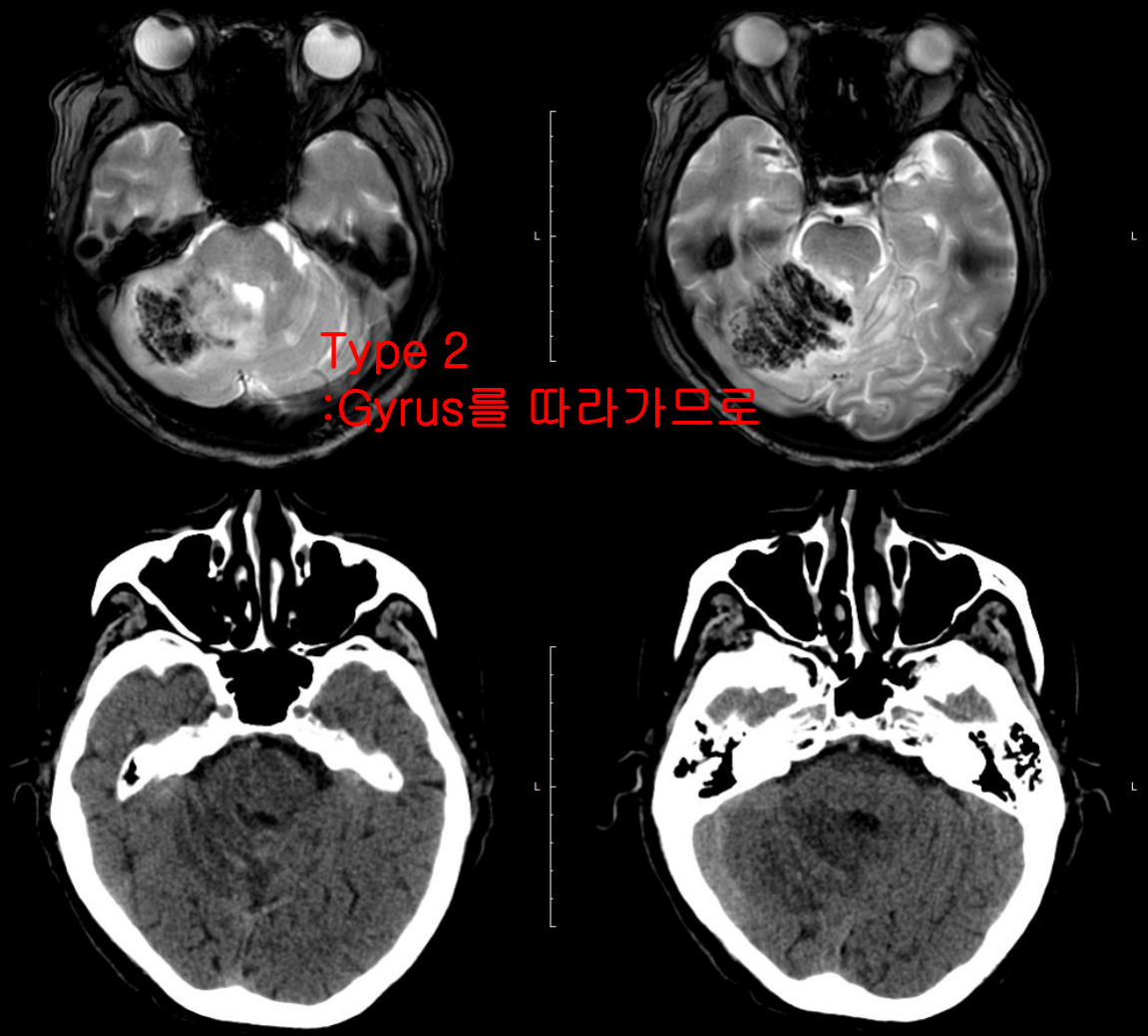
1. Mock training (모의고사) : around 20 ~ 30 cases

1) Inter-observer agreement

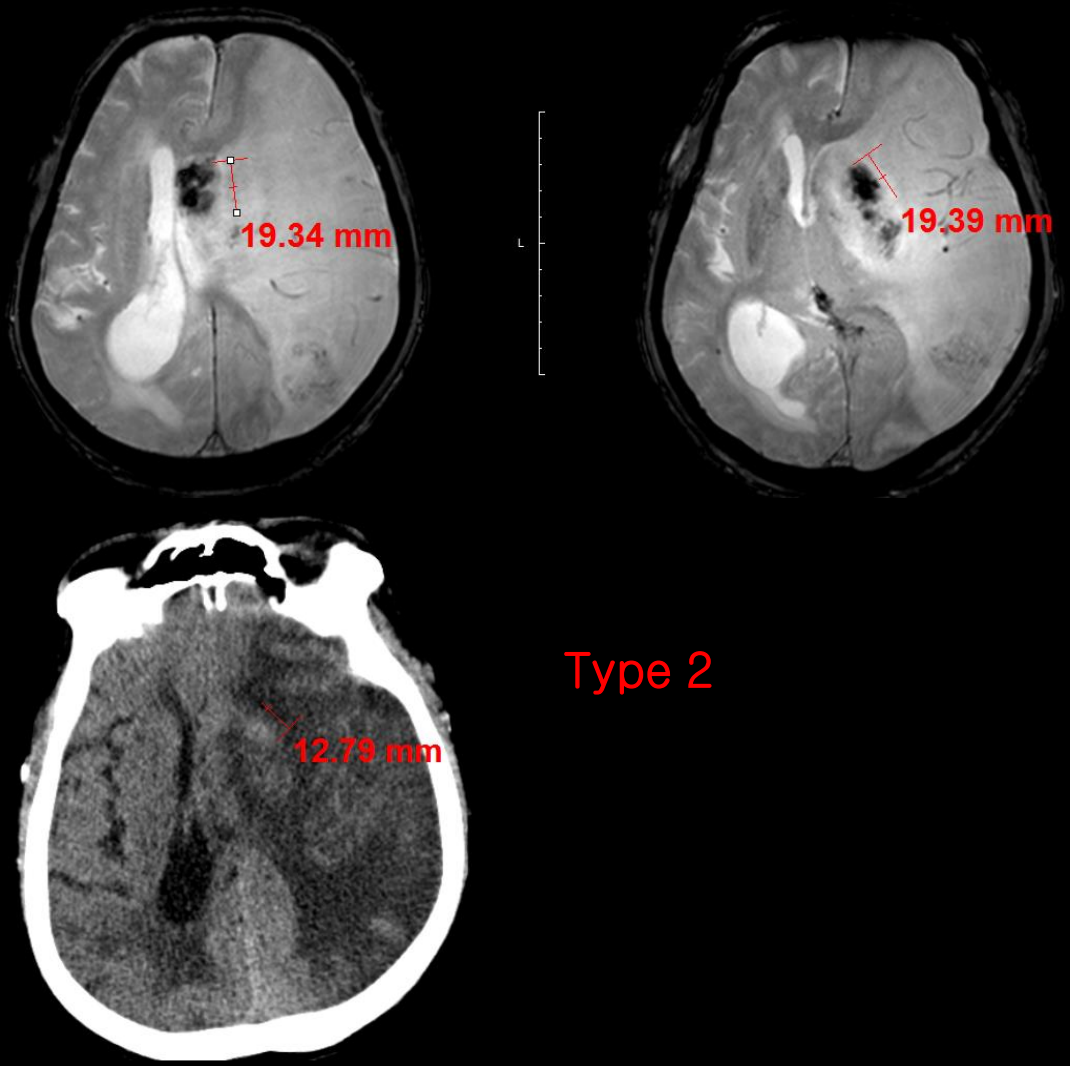
2) Reliability

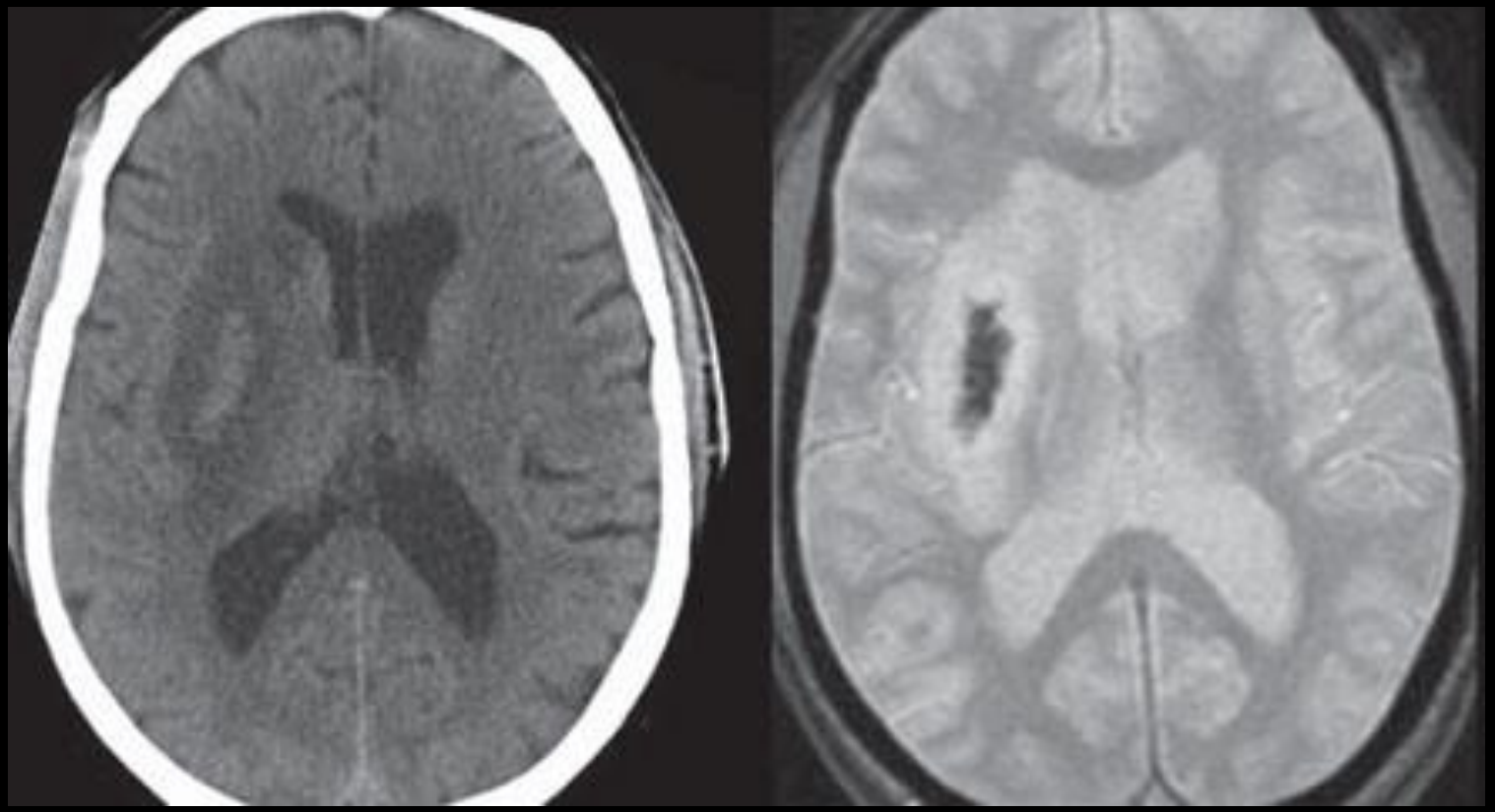
2. Reading (수능)→ Actually, Independent

Independent image review committee (IIRC)



Independent image review committee (IIRC)



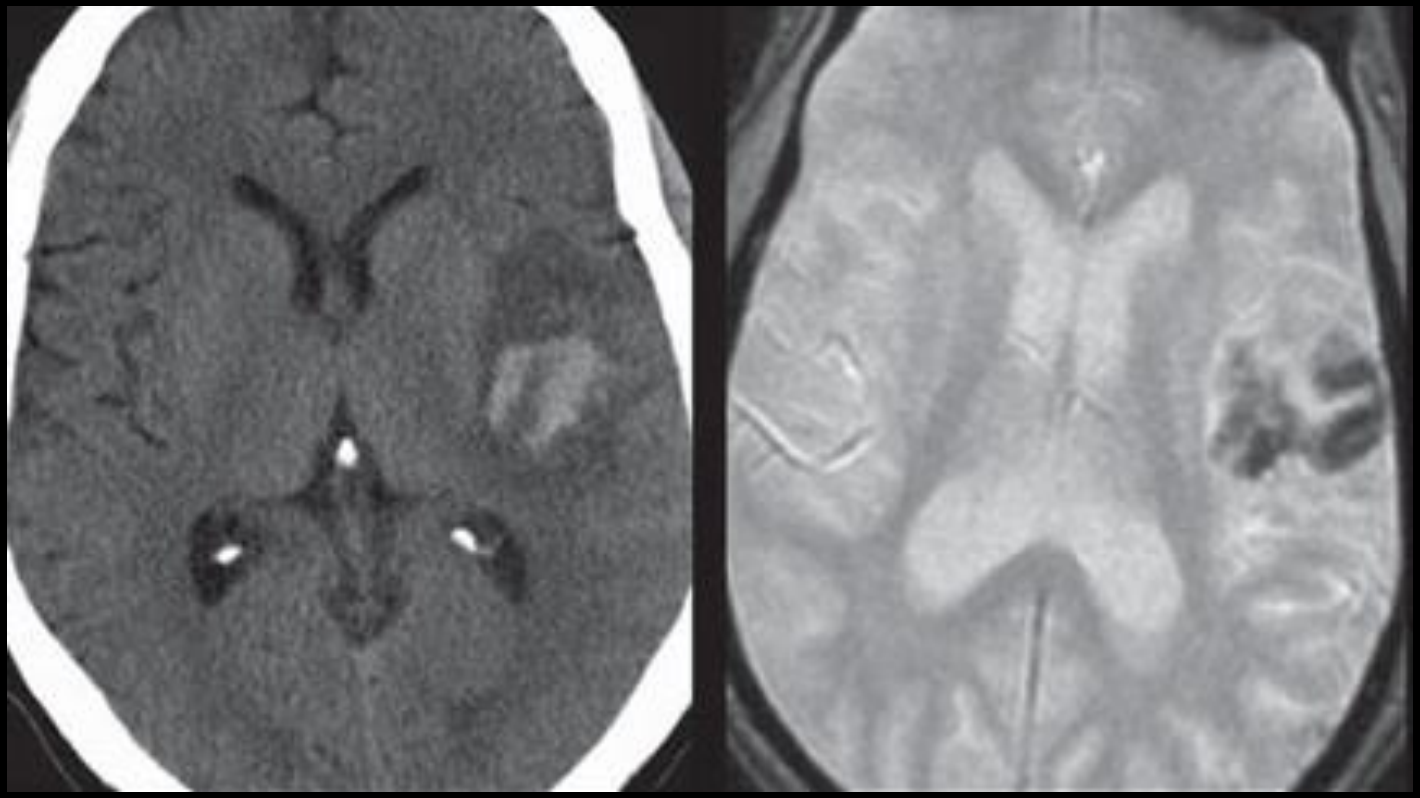


HI 2

PH 1

→ HI 2?

Renou et al. Cerebrovascular Dis 2010



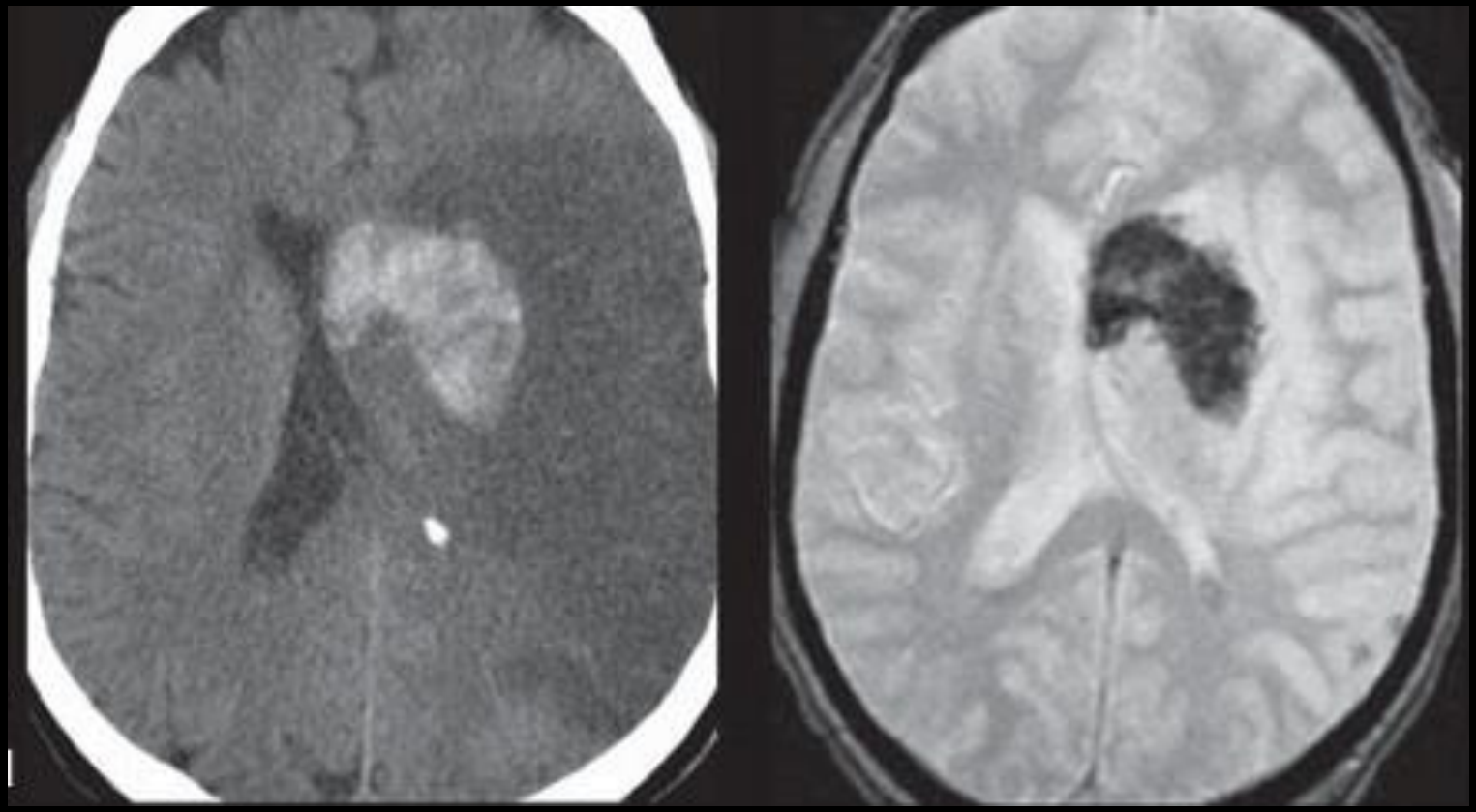
PH 1

→ PH1/HI 2?

HI 2

HI 2?

Renou et al. Cerebrovascular Dis 2010

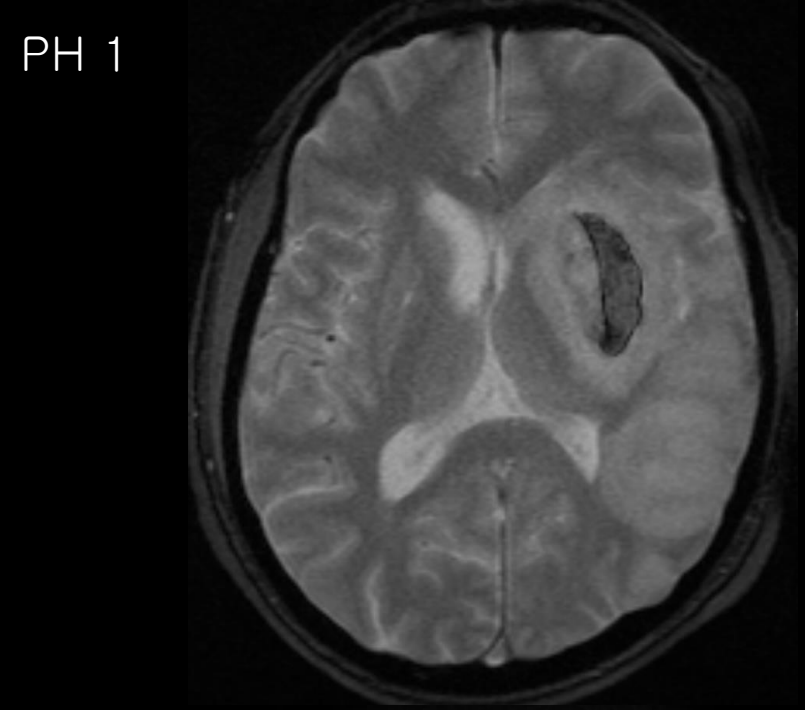


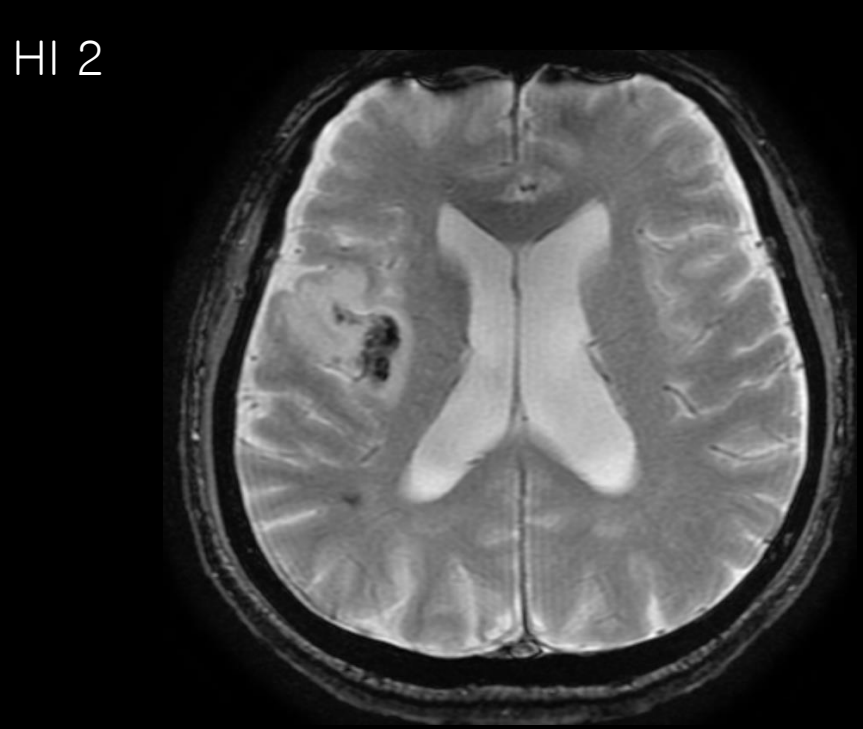
PH 1

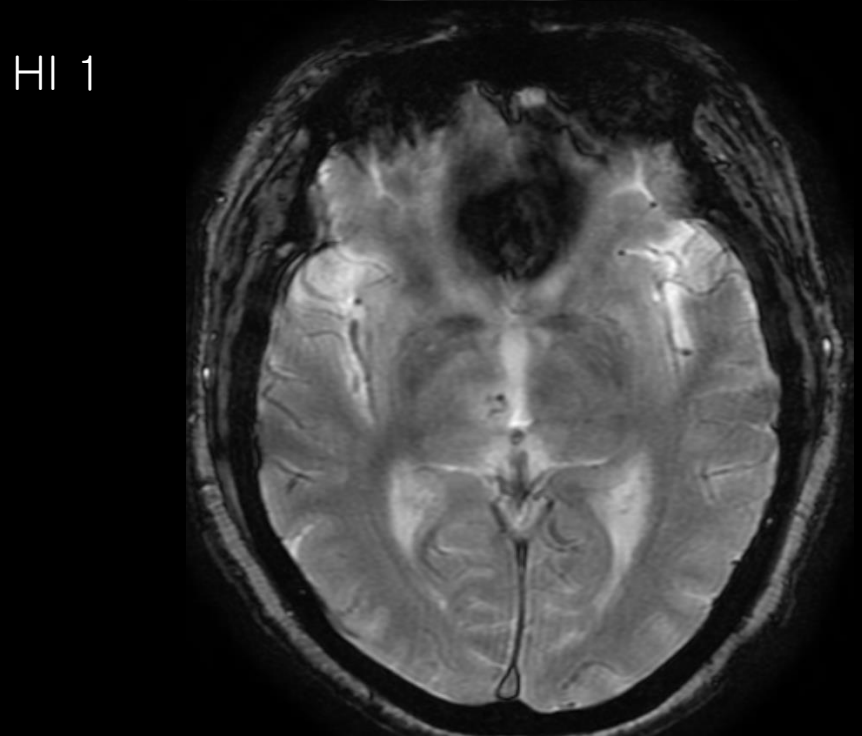
PH 2

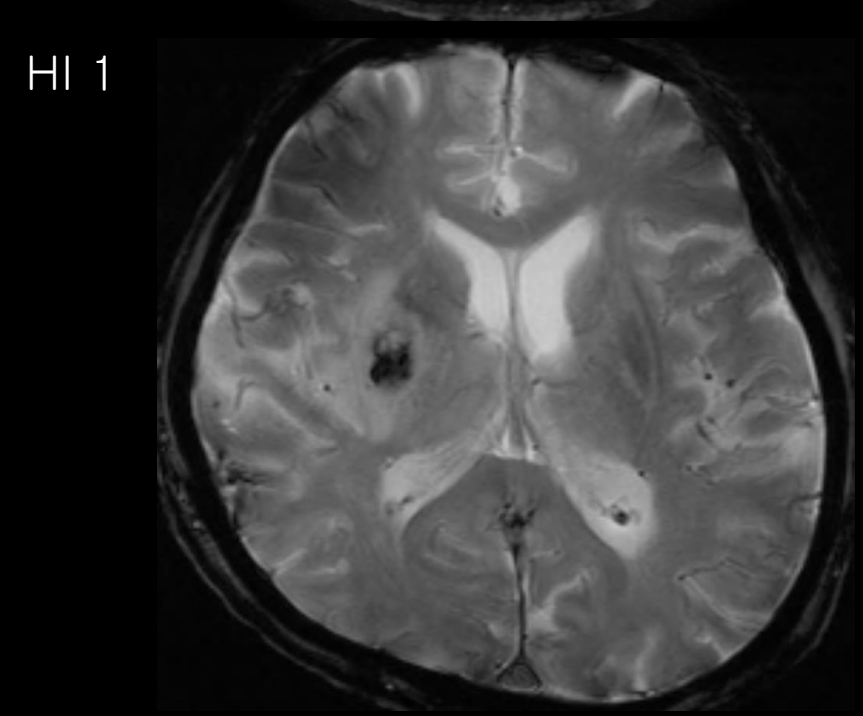
→ PH1?

Renou et al. Cerebrovascular Dis 2010


PH 1

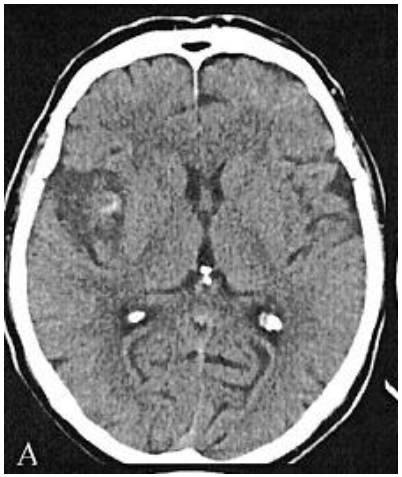

HI 2


HI 1


HI 1

Hemorrhagic infarct type 1 (HI-1)

✓ ***Def.: Small petechiae along the margins of the infarct***

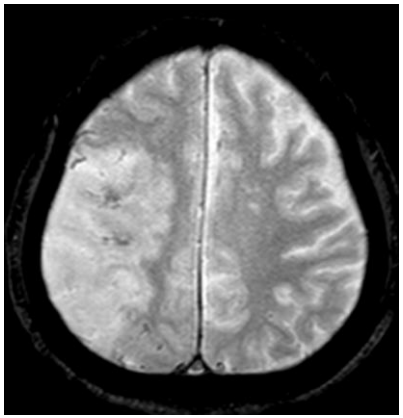


✓ < 1 cm (largest dimension)

✓ petechial hemorrhage:

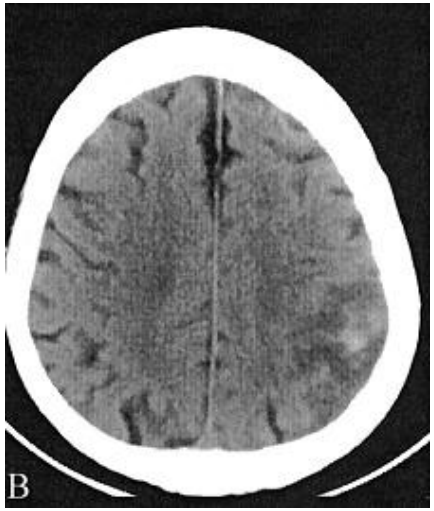
→ gyral, dot-to-dot hemorrhage, cleft 有

✓ crowding (not confluent)

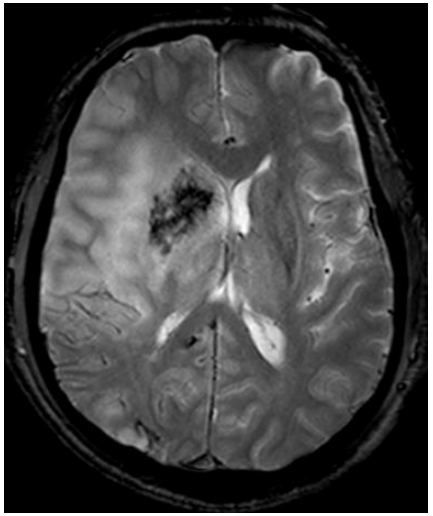


Hemorrhagic infarct type 2 (HI-2)

- ✓ ***Def.: More confluent petechiae within the infarcted area but without space-occupying effect***

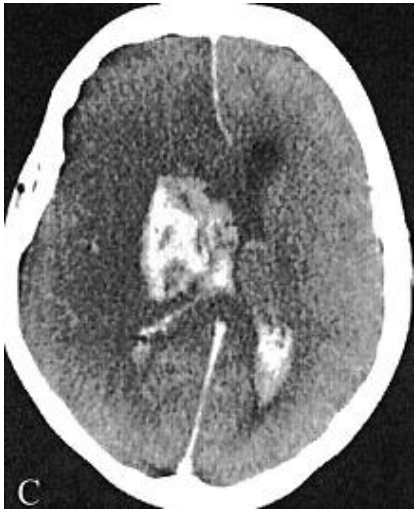


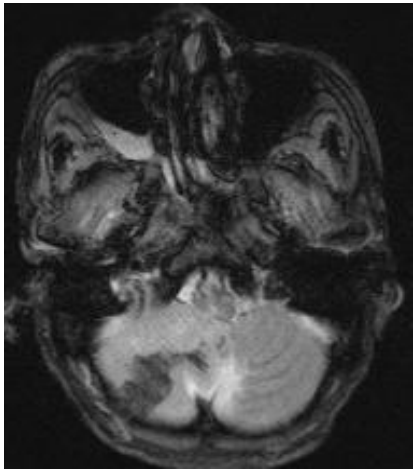
- ✓ ≥ 1cm (largest dimension)
- ✓ petechial hemorrhage:
  - → gyral, dot-to-dot hemorrhage, cleft 有
- ✓ confluent (not crowding)



Parenchymal hematoma type 1 (PH-1)

✓ ***Def.: Hematoma in ≤ 30 % of the infarcted area with some slight space-occupying effect***



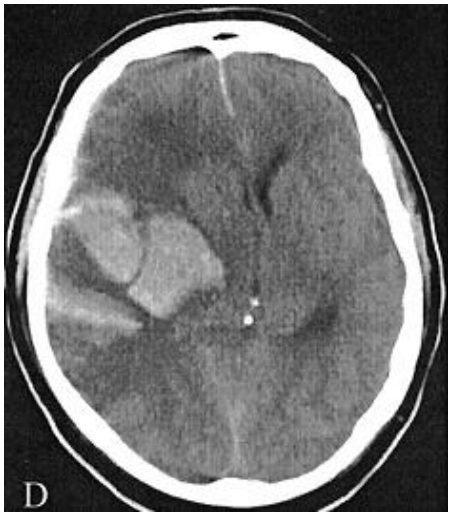


- ✓ Hematoma (not gyral, not cleft, mass effect 有, ≥ 1cm)
- ✓ HI type 2와 헷갈릴때, hematoma는 3cm이상
- ✓ Midline shifting/Ventricular deformity (+) – 최우선 순위 아님.
- ✓ < 0.6 (largest dimension ratio)

  → based on each plane with largest area of hemorrhage/infarction

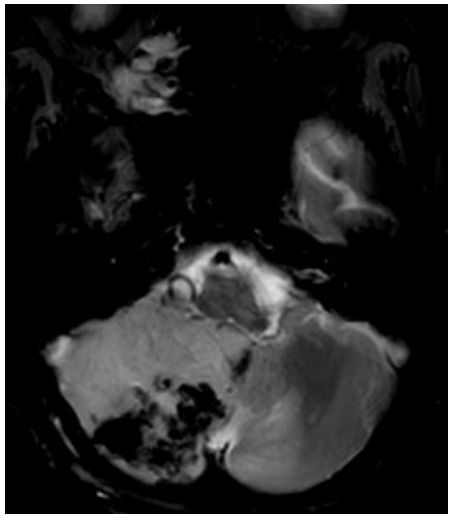
Parenchymal hematoma type 2 (PH-2)

✓ ***Def.: Dense hematoma > 30 % of the infarcted area with substantial space-occupying effect or as any hemorrhagic lesion outside the infarted area***



✓ ≥ 0.6 (largest dimension ratio)

→ based on each plane with largest area of hemorrhage/infarction



Independent image review committee (IIRC)

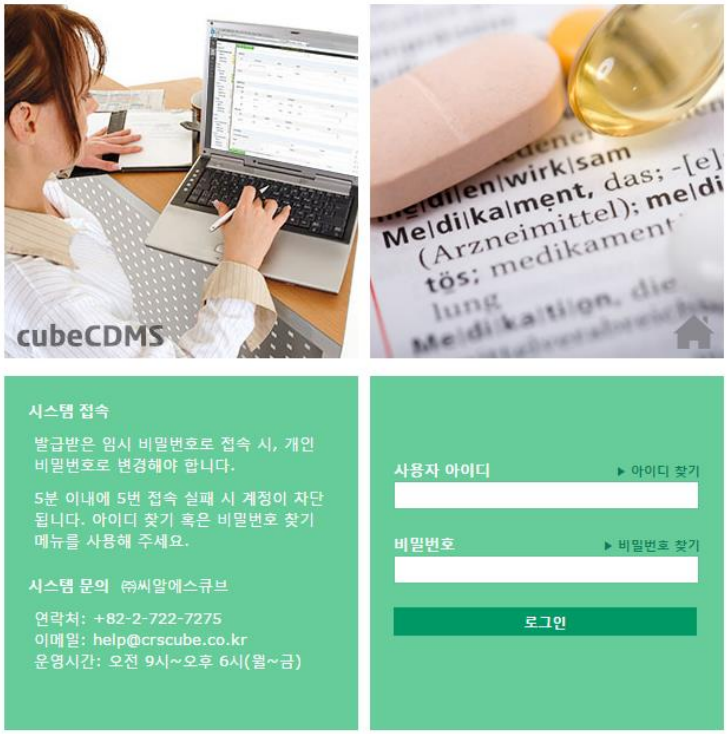
	A	B	C	D	E	F	G	H
1		Jung	Jung	Leo	Leo	Yoo	Yoo	
2		Baseline to F/U	Overall	Baseline to F/U	Overall	Baseline to F/U	Overall	
3	AMC 1	NC	PD	CR -> CR -> CR -> PD	PD	CR, CR, CR, PD	PD	
4	AMC 2	Pseudoprogression	PD	CR -> PD -> CR? -> PD	PD	NC, PsP, CR, PD	PD	CR 처럼
5	AMC 3	Pseudoprogression	PsP	PsPD -> PsPD	PD	PsP, PsP	PsP	
6	AMC 4	NC	PD	NC -> NC -> PD	PD	NC, NC, PD	PD	
7	AMC 5	NC	NC	CR -> CR -> CR	CR	CR, CR, CR	CR	
8	AMC 6	PD	PD	PsPD -> PsPD -> NC -> NC	NC	PsP, PsP, NC, NC	NC	
9	AMC 7	NC or PD	PD	PD	PD	PD	PD	
10	SNUBH 1	PD	PD	PsPD -> PsPD vs PD?	PD	PsP, PD	PD	첫 번째 F
11	SNUBH 2	Pseudoprogression	PsP	PsPD -> PD	PD	PsP, PsP	PsP	
12	SNUBH 3	Pseudoprogression	PsP	PD -> PD -> CR	CR	PsP, PsP, PD, CR	CR	첫 번째 F
13	SNUBH 4		PR	PsPD -> NC	NC? (Baseline 불분명 ㅠ	PsP, PD	PD	첫 번째 F
14	SNUBH 5	Pseudoprogression	PD	PsPD -> PsPD -> PSPD	PsP	PsP, PsP, PD	PD	첫 번째 F
15	SNUBH 6	Pseudoprogression	PD	PsPD -> PsPD -> PD	PD	PsP, PsP, PD	PD	첫 번째 F
16	SNUBH 7	PR	PR	PR -> PR -> PR	PR	PR, PR, PR	PR	
17	SNUH 1	Pseudoprogression	PD	PSPD -> PsPD -> PsPD -> PD	PD	PsP, PsP, PsP, PD	PD	첫 번째 F
18	SNUH 2	Pseudoprogression	PD	PsPD -> PsPD -> PD	PD	PsP, PsP, PsP	PsP	첫 번째 F
19	SNUH 3	Pseudoprogression	PD	PsPD -> PsPD -> PsPD -> PD	PD	PsP, PsP, PD, PD	PD	첫 번째 F
20	SNUH 4	Pseudoprogression	CR	PsPD -> CR -> CR	CR	PsP, CR, CR	CR	Measural
21	SNUH 5	PD	PD	PsPD -> PsPD -> PD?	PD	PsP, PsP, PsP	PsP	첫 번째 F
22	SNUH 6	PR (Baseline을 preCCRT	NC	PsPD -> PsPD -> PD	PD	PsP, PsP, PsP, PD	PD	첫 번째 F
23	SNUH 7	Pseudoprogression-NC	NC	PsPD -> PsPD -> PsPD -> PsPI	PsP	PsP, PsP, PsP, PsP	PsP	궁극적으
24								
25	AMC 1	CR > NC	Postop. marginal enhancement는 CR					
26	AMC 2	PsP > PD						
27		CR > NC						
28	AMC 3	PsP > PD ? compared to	연속 PsP					
29	AMC 5	CR > NC	Postop. marginal enhancement는 CR					
30								
31	SNUBH 1	PsP-PD > PsP-PsP						
32	SNUBH 2	psp-psp >PsP-PD						
33	SNUBH 3	PsP-PsP-CR >						
34	SNUBH 4	No baseline	PsP-NC or PR > PD					
35	SNUBH 5	Two lesion, PsP-PsP-PD						
36								
37	SNUH 2	3연속 PsP < PsP-PsP-PD						
38	SNUH 3	PsP-PsP-PD > PsP-PsP-PsP						
39	SNUH 5	PreCCRT가 Baseline, NC-NC-PD						
40		기존 Baseline, 연속 PsP						
41	SNUH 6	PreCCRT가 Baseline, NC-NC-NC						
42		Postop.가 Baseline, 연속 PsP						
43	SNUH 7	PsP-PsP-PsP-NC						

Independent image review committee (IIRC)

1. Pseudoprogression interval은 정확히 6 months로 계산한다. (제공된 CCRT termination기준)
   Example: 2010-03-10 → 2010-09-10부터 progression, 2010-09-09는 pseudoprogression
2. Target lesion (1 cm이상)은 nontarget (1 cm미만)이 되어도 target에 기록
   Nontarget lesion은 target이 되어도 nontarget에 기록
   Target과 nontarget이 합쳐지는 경우, Target과 Nontarget을 동일하게 기록 및 판정.
3. RT field의 정의: RT field는surgical cavity, nonenhancing T2W high signal intensity를 아우르면서 그 보다 조금 더 넓은 것으로 본다.
4. New lesion: CR후에 같은 부위의 recurrence도 new lesion 으로 본다.
5. Seeding (1cm이상의 nodular lesion이 없는이상)은 nontarget 으로 한다.
6. CR후에 baseline과 동일부위 비슷한 크기의 lesion이 생겼다면 PD이다.

eCRF (clinical report form)

- Outcomes
  - ✓ Hemorrhagic transformation
  - ✓ Infarction

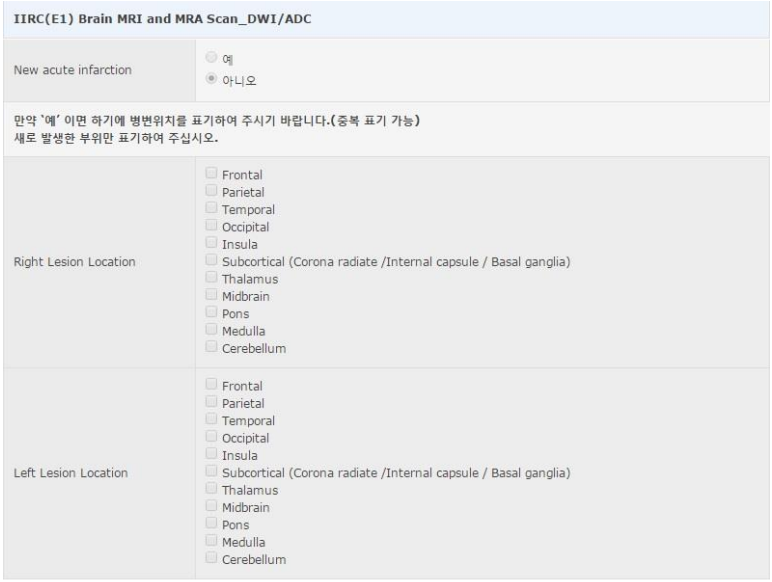


Primary outcome

- **rtPA 표준 치료 시 NA주 투여 후 24시간 시점에 촬영한 Brain noncontrast CT 영상에서 유럽급성뇌졸중협력연구 (ECASS) I 과 II 기준에 따른 실질혈종 (Parenchymal hematoma)의 발생 비율**

CT

1. **Hemorrhagic transformation (yes/no)**
2. **Hemorrhagic transformation grade**
   - ✓ HI type I
   - ✓ HI type II
   - ✓ PH type I
   - ✓ PH type II



IIRC(E1) Brain MRI and MRA Scan_DWI/ADC

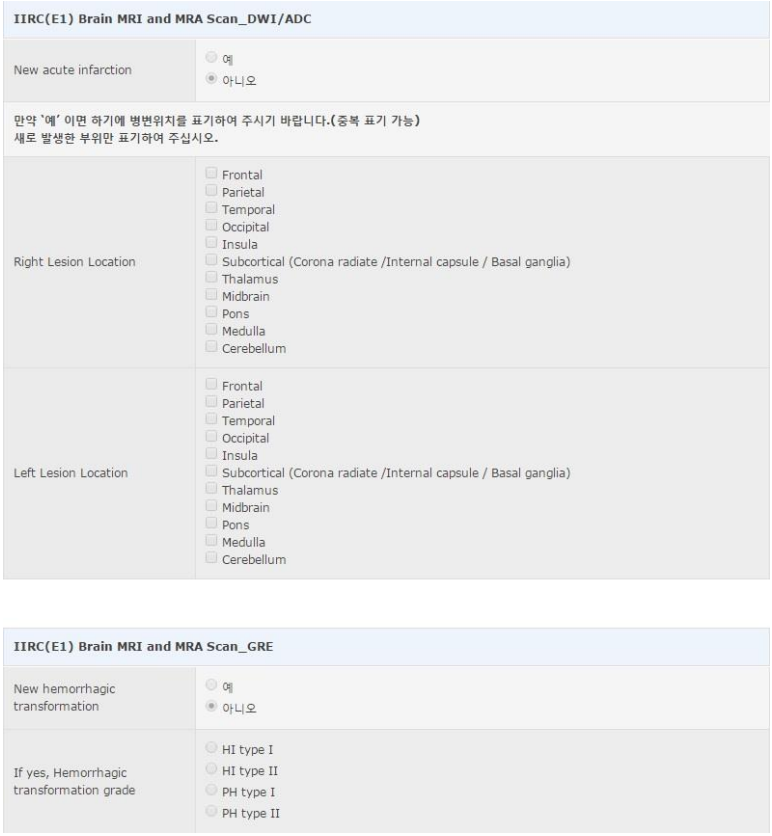
New acute infarction	○ 예 ◉ 아니오
만약 '예' 이면 하기에 병변위치를 표기하여 주시기 바랍니다.(중복 표기 가능) 새로 발생한 부위만 표기하여 주십시오.	
Right Lesion Location	☐ Frontal ☐ Parietal ☐ Temporal ☐ Occipital ☐ Insula ☐ Subcortical (Corona radiate /Internal capsule / Basal ganglia) ☐ Thalamus ☐ Midbrain ☐ Pons ☐ Medulla ☐ Cerebellum
Left Lesion Location	☐ Frontal ☐ Parietal ☐ Temporal ☐ Occipital ☐ Insula ☐ Subcortical (Corona radiate /Internal capsule / Basal ganglia) ☐ Thalamus ☐ Midbrain ☐ Pons ☐ Medulla ☐ Cerebellum

IIRC(E1) Brain MRI and MRA Scan_GRE

New hemorrhagic transformation	○ 예 ◉ 아니오
If yes, Hemorrhagic transformation grade	○ HI type I ○ HI type II ○ PH type I ○ PH type II

CT F/U

1. **Hemorrhagic transformation (yes/no)**
2. **Hemorrhagic transformation grade**
   - ✓ HI type I
   - ✓ HI type II
   - ✓ PH type I
   - ✓ PH type II



IIRC(E1) Brain MRI and MRA Scan_DWI/ADC

New acute infarction	○ 예 ◉ 아니오
만약 '예' 이면 하기에 병변위치를 표기하여 주시기 바랍니다.(중복 표기 가능) 새로 발생한 부위만 표기하여 주십시오.	
Right Lesion Location	☐ Frontal ☐ Parietal ☐ Temporal ☐ Occipital ☐ Insula ☐ Subcortical (Corona radiate /Internal capsule / Basal ganglia) ☐ Thalamus ☐ Midbrain ☐ Pons ☐ Medulla ☐ Cerebellum
Left Lesion Location	☐ Frontal ☐ Parietal ☐ Temporal ☐ Occipital ☐ Insula ☐ Subcortical (Corona radiate /Internal capsule / Basal ganglia) ☐ Thalamus ☐ Midbrain ☐ Pons ☐ Medulla ☐ Cerebellum

IIRC(E1) Brain MRI and MRA Scan_GRE

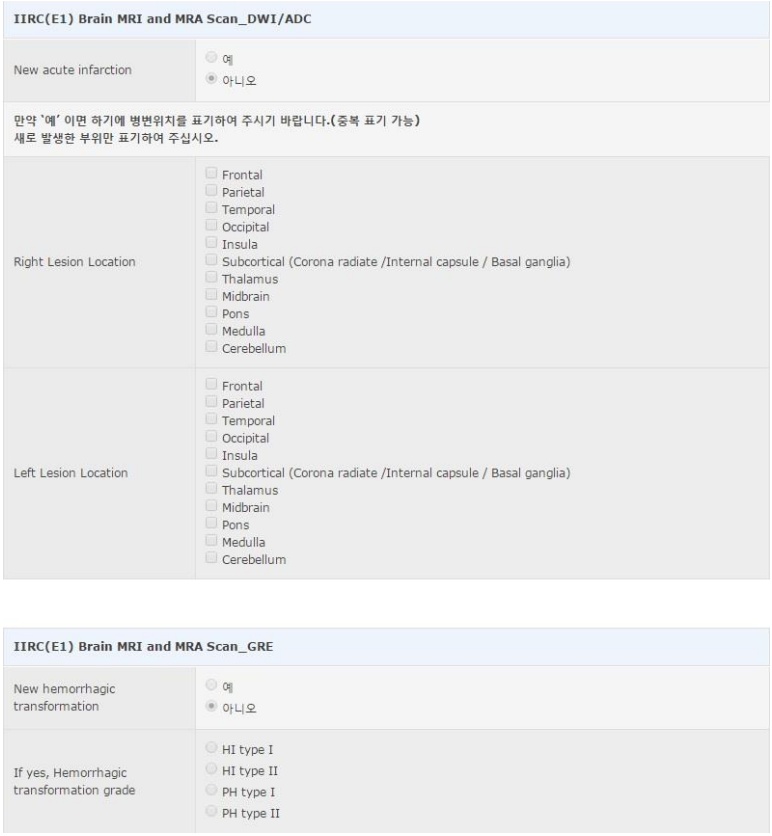
New hemorrhagic transformation	○ 예 ◉ 아니오
If yes, Hemorrhagic transformation grade	○ HI type I ○ HI type II ○ PH type I ○ PH type II

Secondary outcome

- 5일 이내에 발생한 모든 두개내 출혈의 발생 비율
- 5일 이내에 **DWI** 영상에 확인된 뇌경색 크기의 증가 비율
- 5일 이내에 **DWI** 영상에 확인된 뇌경색의 재발 비율
- 5일 이내에 **GRE** 영상에 확인된 출혈의 발생 건수 및 크기
- **GRE**와 **DWI** 영상을 통해 확인된 뇌출혈의 변화 비율

MR (DWI-baseline)

1. **Acute infarction (yes/no)**
2. Acute infarction volume (Software)



IIRC(E1) Brain MRI and MRA Scan_DWI/ADC

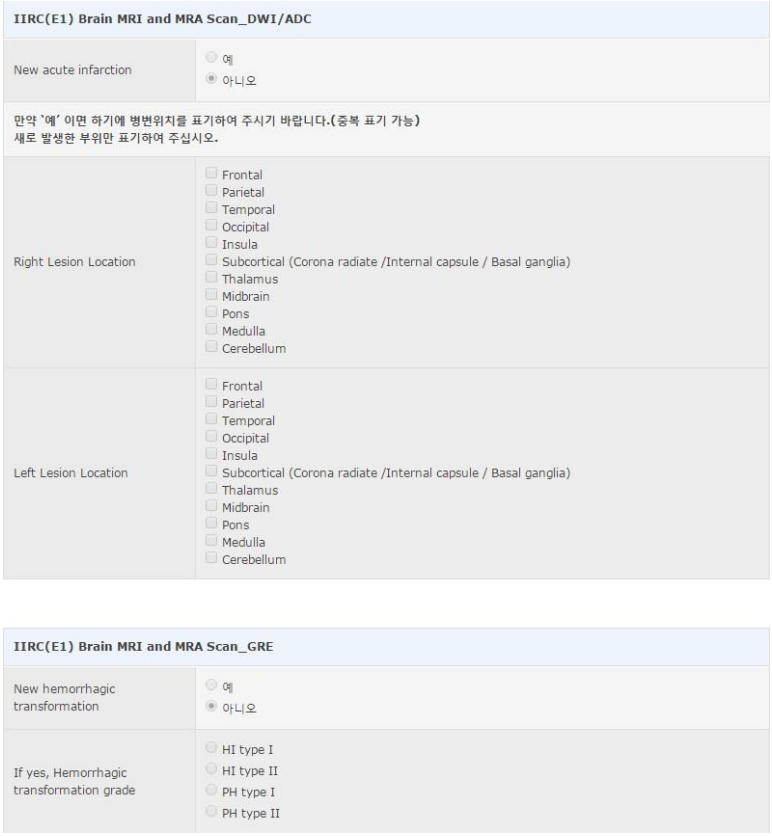
New acute infarction	○ 예 ◉ 아니오
만약 '예' 이면 하기에 병변위치를 표기하여 주시기 바랍니다.(중복 표기 가능) 새로 발생한 부위만 표기하여 주십시오.	
Right Lesion Location	☐ Frontal ☐ Parietal ☐ Temporal ☐ Occipital ☐ Insula ☐ Subcortical (Corona radiate /Internal capsule / Basal ganglia) ☐ Thalamus ☐ Midbrain ☐ Pons ☐ Medulla ☐ Cerebellum
Left Lesion Location	☐ Frontal ☐ Parietal ☐ Temporal ☐ Occipital ☐ Insula ☐ Subcortical (Corona radiate /Internal capsule / Basal ganglia) ☐ Thalamus ☐ Midbrain ☐ Pons ☐ Medulla ☐ Cerebellum

IIRC(E1) Brain MRI and MRA Scan_GRE

New hemorrhagic transformation	○ 예 ◉ 아니오
If yes, Hemorrhagic transformation grade	○ HI type I ○ HI type II ○ PH type I ○ PH type II

MR (DWI-F/U)

1. **New acute infarction (yes/no)**
2. Acute infarction volume (Software)



IIRC(E1) Brain MRI and MRA Scan_DWI/ADC

New acute infarction	○ 예 ◉ 아니오
만약 '예' 이면 하기에 병변위치를 표기하여 주시기 바랍니다.(중복 표기 가능) 새로 발생한 부위만 표기하여 주십시오.	
Right Lesion Location	☐ Frontal ☐ Parietal ☐ Temporal ☐ Occipital ☐ Insula ☐ Subcortical (Corona radiate /Internal capsule / Basal ganglia) ☐ Thalamus ☐ Midbrain ☐ Pons ☐ Medulla ☐ Cerebellum
Left Lesion Location	☐ Frontal ☐ Parietal ☐ Temporal ☐ Occipital ☐ Insula ☐ Subcortical (Corona radiate /Internal capsule / Basal ganglia) ☐ Thalamus ☐ Midbrain ☐ Pons ☐ Medulla ☐ Cerebellum

IIRC(E1) Brain MRI and MRA Scan_GRE

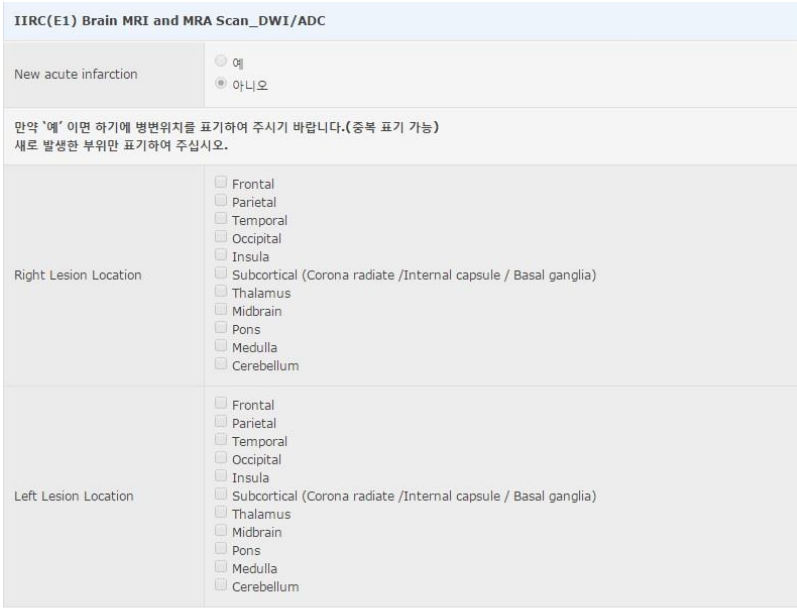
New hemorrhagic transformation	○ 예 ◉ 아니오
If yes, Hemorrhagic transformation grade	○ HI type I ○ HI type II ○ PH type I ○ PH type II

Secondary outcome

- 5일 이내에 발생한 모든 두개내 출혈의 발생 비율
- 5일 이내에 **DWI** 영상에 확인된 뇌경색 크기의 증가 비율
- 5일 이내에 **DWI** 영상에 확인된 뇌경색의 재발 비율
- 5일 이내에 **GRE** 영상에 확인된 출혈의 발생 건수 및 크기
- **GRE**와 **DWI** 영상을 통해 확인된 뇌출혈의 변화 비율

MR (GRE-baseline)

1. **Hemorrhagic transformation (yes/no)**
2. **Hemorrhagic transformation grade**
   - ✓ HI type I
   - ✓ HI type II
   - ✓ PH type I
   - ✓ PH type II
3. Hemorrhage volume (Software)



IIRC(E1) Brain MRI and MRA Scan_DWI/ADC	
New acute infarction	○ 예 ◉ 아니오
만약 '예' 이면 하기에 병변위치를 표기하여 주시기 바랍니다.(중복 표기 가능) 새로 발생한 부위만 표기하여 주십시오.	
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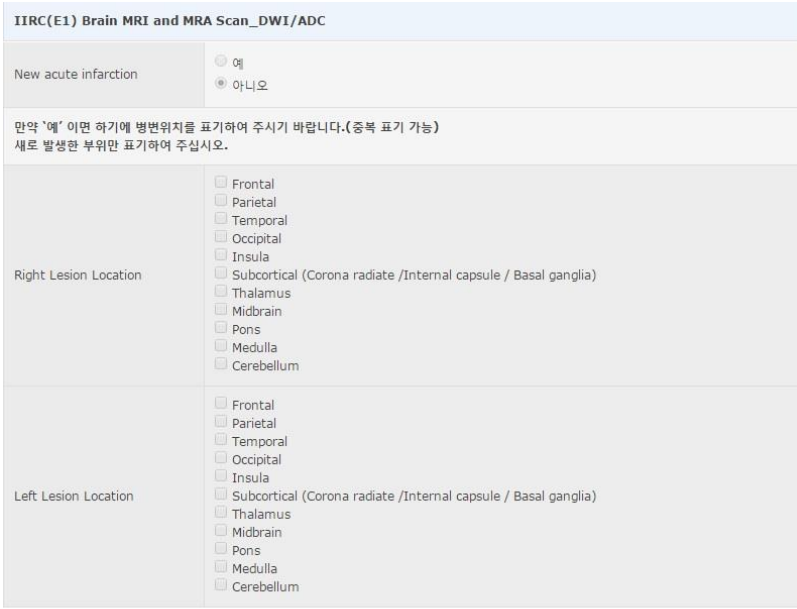
Left Lesion Location	☐ Frontal ☐ Parietal ☐ Temporal ☐ Occipital ☐ Insula ☐ Subcortical (Corona radiate /Internal capsule / Basal ganglia) ☐ Thalamus ☐ Midbrain ☐ Pons ☐ Medulla ☐ Cerebellum

IIRC(E1) Brain MRI and MRA Scan_GRE	
New hemorrhagic transformation	○ 예 ◉ 아니오
If yes, Hemorrhagic transformation grade	○ HI type I ○ HI type II ○ PH type I ○ PH type II

MR (GRE-F/U)

1. **New hemorrhagic transformation (yes/no)**
2. **Hemorrhagic transformation grade**
   - ✓ HI type I
   - ✓ HI type II
   - ✓ PH type I
   - ✓ PH type II
3. Hemorrhage volume (Software)



IIRC(E1) Brain MRI and MRA Scan_DWI/ADC	
New acute infarction	○ 예 ◉ 아니오
만약 '예' 이면 하기에 병변위치를 표기하여 주시기 바랍니다.(중복 표기 가능) 새로 발생한 부위만 표기하여 주십시오.	
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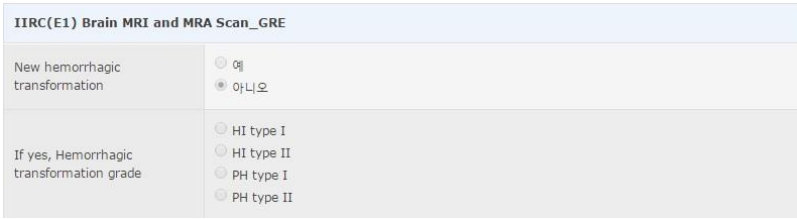
Left Lesion Location	☐ Frontal ☐ Parietal ☐ Temporal ☐ Occipital ☐ Insula ☐ Subcortical (Corona radiate /Internal capsule / Basal ganglia) ☐ Thalamus ☐ Midbrain ☐ Pons ☐ Medulla ☐ Cerebellum



IIRC(E1) Brain MRI and MRA Scan_GRE	
New hemorrhagic transformation	○ 예 ◉ 아니오
If yes, Hemorrhagic transformation grade	○ HI type I ○ HI type II ○ PH type I ○ PH type II

Independent image review committee (IIRC)

1. **Reader 1 – Independent reader**
2. **Reader 2 – Independent reader**
3. **Moderator – Independent reader or Adjudicator**

1. **Outside Reader 3 – Consult or Evaluation**
2. **Image review committe (IRC)**
3. **Data & Safety monitoring board (DSMB)**

Independent image review committee (IIRC)

1. Reader 1 – Independent reader

2. Reader 2 – Independent reader

3. **Moderator – Independent reader** or Adjudicator

1. Outside Reader 3 – Consult or Evaluation

2. Image review committe (IRC)

3. Data & Safety monitoring board (DSMB)

Independent image review committee (IIRC)

1. Reader 1 – Independent reader
2. Reader 2 – Independent reader
3. Moderator – Independent reader or Adjudicator

1. Outside Reader 3 – External validation (German Radiologist)
2. Image review committe (IRC)
3. Data & Safety monitoring board (DSMB)

Image Review Flow

Site : Uploading subject's images on eCRF:

Initial & follow-up Brain CT / MRI & MRA

When images are uploaded on eCRF, alarm email will be sent to Imaging core lab

Imaging core lab : Quality check within 48 hours from uploading images

- As to adequate images according to the Imaging protocol
- As to adequate full series images

➔ Result : Pass or Recheck

If Pass, alarm email will be sent to IIRC members.

1st & 2nd reviewers of IIRC will review the passed images within 48 hours.

- Brain CT : for primary endpoint
- Brain MRI : for exploratory endpoint

If the result of two reviewers is the same, alarm email will be sent to Imaging core lab for calculating lesion volume.

Imaging core lab : Lesion volume calculation by automatic program

Imaging CRO/Imaging core lab & IIRC

1. Protocol setting: Imaging protocol standard

2. Standardization

3. Site training: Imaging acquistion & transfer

4. Site monitoring: QC/QA

5. Image analysis considering endpoints

6. Central reading

7. Report results

→ Phase IIb

Imaging CRO/Imaging core lab & IIRC

1. Protocol setting: Imaging protocol standard

2. Standardization

3. Site training: Imaging acquistion & transfer

4. Site monitoring: QC/QA

5. Image analysis considering endpoints

6. Central reading

7. Report results

→ Phase IIb

Experience 2

Anti-coagulation

1. **Prospective, Randomized, Phase II**
2. **68 participants**
3. **Primary endpoint: Recurred infarct on DWI**
4. **Secondary endpoint: Hemorrhagic transformation on GRE, Recanalization on TOF-MRA**
5. **Imaging CRO & Imaging core lab & IIRC with imaging consult**

Experience 2

Anti-coagulation

1. 에독사반(edoxaban)은 factor Xa를 선택적으로 저해하는 약물로서, 심방세동을 가진 환자에서 뇌경색 위험을 낮추는 데 있어 와파린과 비슷한 정도의 효능을 가지면서도, 출혈의 위험은 유의하게 낮은 새로운 경구용 항응고제(Novel oral anticoagulants, NOAC)이다. 에독사반은 factor Xa 저해 기능을 가지는 다른 NOAC들과 비교해서도 출혈 위험이 적은 것으로 알려져 있다.
2. 비판독성 심방세동에 의한 급성 허혈성 뇌졸중 환자에서 조기 에독사반 투여의 효과 및 안전성 평가를 위한 무작위배정, 평행대조, 다기관 예비 임상시험 (Early adminstration of edoxaban after acute ischemic stroke in patients with non-valvular atrial fibrillation: a randomized, multi-center, parallel-group trial (PILOT)
3. 가설: 비판막성 심방세동을 가진 급성 뇌경색 환자에서 에독사반의 조기 투여가 고식적 항응고제 투여에 비해 뇌경색의 이른 재발을 줄일 수 있다.
4. Phase II

Anti-coagulation

5. 다기관 뇌졸중 치료제 임상시험: 국내 3개 기관
6. 68 Participants
7. Primary endpoint: DWI (Recurred infarct 10-14 days after the onset)
8. Secondary endpoints
   1) Imaging indexes: GRE (Hemorrhagic transformation), TOF-MRA (Recanalization)
   2) Clinical indexes: NIHSS deterioration, mRS
9. Safety endpoints
   1) Symptomatic ICH
   2) Hemorrhage
10. Imaging CRO/Imaging core lab/IIRC

Experience 2

Consultant

1. New infarct or recurred infarct

1) Definition: New separate restricted lesions on follow-up diffusion-weighted imaging (DWI) outside the region of the acutely symptomatic lesion and which is not detected on initial DWI.

2) **Classification**: **Local** recurrent infarcts are defined as new lesions within the territory of the initial perfusion deficit based on angiography and/or perfusion-weighted imaging. **Distant** recurrent infarcts are defined as new lesions outside the territory of the initial perfusion deficit based on angiography and/or perfusion-weighted imaging.The initial perfusion is assessed primarily on angiography followed by perfusion-weighted imaging.

Experience 2

Consultant

1. New infarct or recurred infarct

2) Primary outcome → eCRF (Anatomic and Vascular territory)

3) DWI → Standardization (Phantom), Presence or absence, local or distant, numbers

4) Measurement → Semi automated analysis in-house software

Experience 2

Consultant

2. Hemorrhagic transformation

1) Definition and classification → ECASS

2) Secondary outcome

3) CT and MR → Discrepancy

4) MR: Standardization (SWI vs GRE) → Same imaging modality between initial and F/U

5) Measurement → Semi automated analysis in-house software

Consultant

3. Infarct core

1) Definition or Criteria: b1000 after ADC correction

2) Secondary outcome

3) MR (DWI), ASPECT (X)

4) Measurement: DWI, Δ Infarc core volume

5) Semi automated analysis in-house software

Consultant

4. Steno-occlusion

1) Definition: Recanalization

2) Secondary outcomes

3) MRA > CTA

4) Scoring: mAOL (MR RESCUE, ESCAPE)

Experience 2

Table S3. Arterial Occlusive Lesion (AOL) Rating Scale[8]

Score	Definition
0	No recanalization of the primary occlusion lesion
I	Incomplete or partial recanalization of the primary occlusion lesion with no distal flow
II	Incomplete or partial recanalization of the primary occlusion lesion with any distal flow
III	Complete recanalization of the primary occlusion with any distal flow

Table S4. Thrombolysis in Cerebral Infarction (TICI) Rating Scale[3]

Score	Definition
0	No perfusion
1	Perfusion past the initial obstruction but limited distal branch filling with little or slow distal perfusion
2a	Perfusion of less than 2/3 of the vascular distribution of the occluded artery
2b	Perfusion of 2/3 or greater of the vascular distribution of the occluded artery
3	Full perfusion with filling of all distal branches

Table S5. Thrombolysis in Myocardial Ischemia (TIMI) Rating Scale[7]

Score	Definition
0	No perfusion: absence of any antegrade flow beyond a coronary occlusion
1	Penetration without perfusion: faint antegrade coronary flow beyond the occlusion, with incomplete filling of the distal coronary bed
2	Partial reperfusion: delayed or sluggish antegrade flow with complete filling of the distal territory
3	Complete perfusion: normal flow which fills the distal coronary bed completely

Experience 3

Anti-coagulation

1. **Prospective, Randomized, Open-label, Phase IV**
2. **220 participants**
3. **Primary endpoint: Leaflet thrombosis on Cardiac CT**
4. **Secondary endpoint: New infarct lesions on DWI**
5. **Imaging CRO & Imaging core lab & IIRC with imaging consult**

Guidance

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

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

Guidance

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 imaging information that describe the standards generally employed by clinical practitioners. This guidance recommends additional imaging endpoint process standards that are more specific to clinical trials. Imaging process standards help sponsors ensure that imaging data are obtained in a manner that complies with a trial's protocol, that the quality of imaging data is maintained 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 in Acute Ischemic 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

STIR and VISTA Imaging Investigators. Stroke 2013

Clinical Trial Imaging in Acute Ischemic Stroke

1. Protocol setting: Imaging protocol standard

2. Standardization

3. Site training: Imaging acquistion & transfer

4. Site monitoring: QC/QA

5. Image analysis considering endpoints

6. Central reading

7. Report results

→ 뇌졸중 임상시험 영상 기준 권고안 (with 식약처)

Summary & Recommendation

1. **Role: Imaging CRO/core lab, IIRC**
2. **Standardization & Consultant: Characteristics of Imaging modalities**
3. **IIRC: Mock training/detailed reading point, Independent**
4. **Evidence and Documentation**
5. **Recommendation and Guidelines for clinical trial imaging in acute ischemic stroke is necessary.**

경청해 주셔서 감사합니다.