EXPERT REVIEWS

Modern imaging of the infarct core and the ischemic penumbra in acute stroke patients: CT versus MRI

Expert Rev. Cardiovasc. Ther. 7(4), 395–403 (2009)

Carlos J Ledezma, Jochen B Fiebach and Max Wintermark†

†Author for correspondence University of California, San Francisco, Department of Radiology, Neuroradiology Section, 505 Parnassus Avenue, L-358, Box 0628, San Francisco, CA 94143-0628, USA max.wintermark@radiology.ucsf.edu

Thrombolysis has become an approved therapy for acute stroke. However, many stroke patients do not benefit from such treatment, since the presently used criteria are very restrictive, notably with respect to the accepted time window. Even so, a significant rate of intracranial hemorrhage still occurs. Conventional cerebral computed tomography (CT) without contrast has been proposed as a selection tool for acute stroke patients. However, more-modern MRI and CT techniques, referred to as diffusion- and perfusion-weighted imaging and perfusion-CT, have been introduced, which afford a comprehensive noninvasive survey of acute stroke patients as soon as their emergency admission, with accurate demonstration of the site of arterial occlusion and its hemodynamic and pathophysiological repercussions for the brain parenchyma. The objective of this article is to present the advantages and drawbacks of CT and MRI in the evaluation of acute stroke patients.

Keywords: computed tomography • MRI • perfusion imaging • stroke • thrombolysis

The central premise of acute stroke thrombolytic treatment is to rescue the ischemic penumbra. When a cerebral artery is occluded, a core of brain tissue dies rapidly. Surrounding this infarct core is an area of brain that is hypoperfused but does not die quickly. This area is called the ischemic penumbra [1–3]. In the case of early recanalization, either spontaneous or resulting from thrombolysis or mechanical clot disruption, the penumbra will be salvaged from infarction [4].

The presence and extent of the ischemic penumbra is time dependent but more especially patient dependent. Indeed, from patient to patient, survival of the penumbra can vary from less than 3 h to well beyond 48 h. In total, 90–100% of patients with supratentorial arterial occlusion show ischemic penumbra in the first 3 h of a stroke, but, interestingly enough, 75–80% of patients still have penumbral tissue at 6 h after stroke onset [5]. The relatively negative results to date of thrombolysis trials beyond the conventional 3-h time window, recently extended to 4.5 h [6], in spite of the high percentage of patients with penumbra within this time allocation, relates to the fact that these trials did not use any method of penumbral imaging to select patients for therapy, despite penumbra being the target for treatment [7].

Thus, a tissue clock, where the extents of both the infarct and penumbra are determined, would seem an ideal guide to patient selection for thrombolysis, rather than a rigid time window, as in the current thrombolysis guidelines [8–10]. Extension of the therapeutic window beyond 4.5 h could substantially increase the number of patients able to receive thrombolysis. However, for this to occur with improved outcomes, a rapid and accessible neuroimaging technique able to assess the ischemic penumbra is required [11].

Multimodal computed tomography stroke imaging

Multimodal computed tomography (CT) allows for the assessment of the four Ps: parenchyma, pipes, perfusion and penumbra [12]. Noncontrast CT enables one to rule out hemorrhage, while CT angiography (CTA) identifies the site of intra-arterial occlusion and perfusion CT (PCT) may

 10.1586/ERC.09.7 ISSN 1477-9072

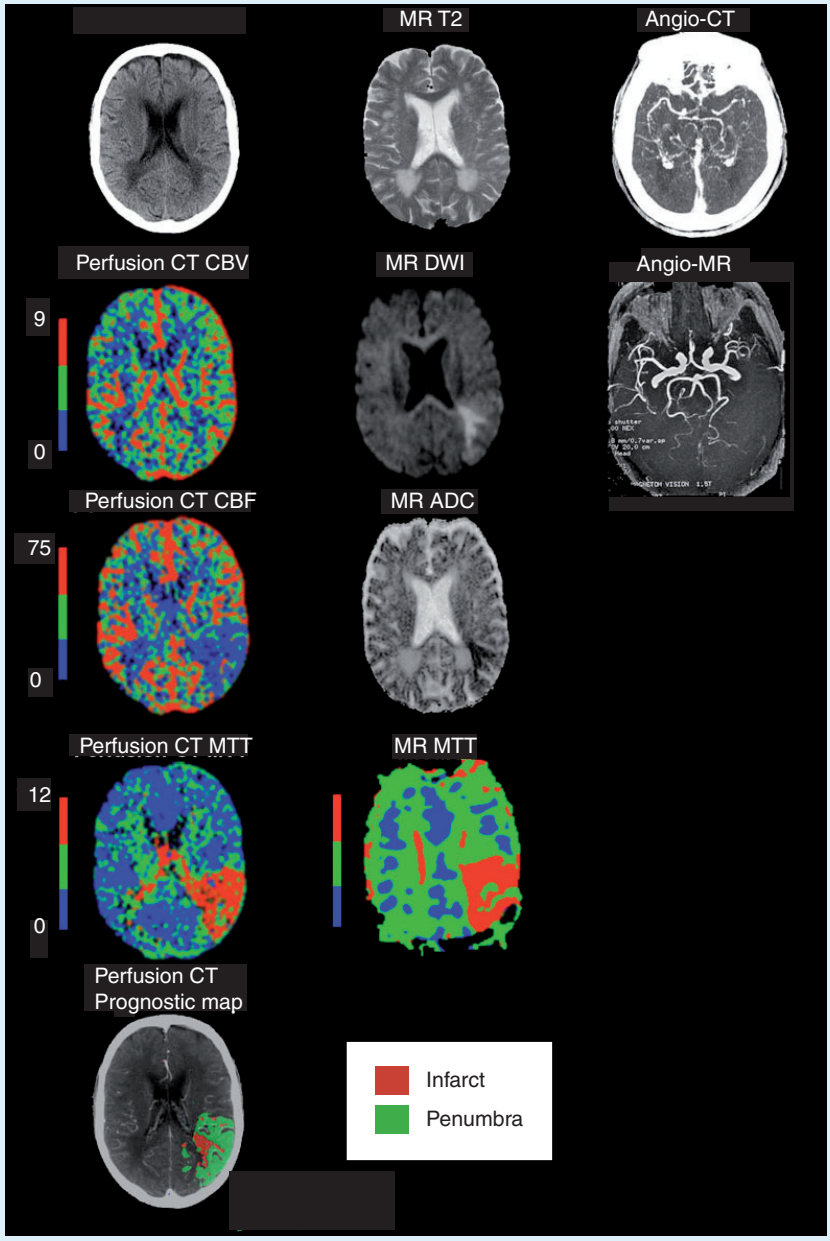

Figure 1. 71-year-old male patient with sudden onset of a right face–arm–leg motor hemisyndrome, associated with fluent aphasia, 1.5 h before admission.
Noncontrast cerebral CT and perfusion CT were obtained 1.75 h after symptomatology onset, whereas DWI/PWI was performed 20 min after CT. Noncontrast cerebral CT shows left insula ribbon sign. The sizes of cerebral infarct and of CBV abnormality on perfusion CT (cc × 100g^{-1}) are similar to that of DWI MR abnormality. The sizes of cerebral ischemic lesion and of CBF (cc × 100 g^{-1} × min^{-1})/MTT(s) abnormality on perfusion CT correlate with that of MR MTT abnormality, located on the left temporo–parietal region. Computed tomography angiography and MRA demonstrate occlusion of the left M1–M2 junction. This patient underwent successful thrombolysis,with significant regression of the symptoms.
ADC: Apparent diffusion coefficient; CBF: Cerebral blood flow; CBV: Cerebral blood volume; CT: Computed tomography; DWI: Diffusion-weighted imaging; MR: Magnetic resonance; MTT: Mean transit time; PWI: Perfusion-weighted imaging.

differentiate between 'at-risk' (the so-called penumbra) and irreversibly damaged brain tissue (Figure 1) [13,14]. Multimodal CT offers rapid data acquisition and can be performed with any modern CT equipment.

The advantages of multimodal CT include short protocol time (5–6 min), and the availability in the emergency setting. The new generation of portable multislice CT scanners may bring PCT to the patient's bedside in the emergency room or the intensive-care unit. The principle disadvantages of this CT-based stroke protocol would be ionizing radiation exposure (recent technological CT advancements, such as dose modulation, have effectively reduced the amount of radiation exposure) and its limited ability to assess ischemia in areas that have a propensity to create so-called 'beam-hardening' artifacts (e.g., posterior fossa ischemia).

Noncontrast CT

With its widespread availability, short scan time, noninvasiveness and safety, CT has been the traditional first-line imaging modality for the evaluation of acute ischemic stroke. In the acute ischemic stroke setting, noncontrast CT is typically used to rule out intracranial hemorrhage (a contraindication to thrombolysis), or other stroke mimics (e.g., tumor and infection), which preclude the use of thrombolytic therapy, and to detect early CT signs [15–17]. Although these early ischemic changes can be helpful in stroke detection, they are subtle and difficult to detect. They also have limited sensitivity for the hyperacute stage of ischemic stroke, particularly within the first 3 h after onset of symptoms, a critical window for therapeutic interventions. When compared to MR diffusion-weighted imaging (DWI), these signs have a sensitivity of 25% [18]. Finally, the relationship between early ischemic changes on CT and adverse outcomes after recombinant tissue plasminogen activator (rtPA) treatment is not straightforward [19,20].

In contrast to these early ischemic changes, frank hypoattenuation is highly specific for irreversible tissue damage [21] and its extent is predictive of the risk of hemorrhagic transformation [22]. Nevertheless, it is critical to determine the tissue at risk before irreversible tissue

damage occurs and frank hypoattenuation appears, as this is essential to prevent hemorrhagic transformation. In the European Cooperative Acute Stroke Study (ECASS) I and II trials, involvement of more than a third of the major cerebral artery (MCA) territory on noncontrast CT was utilized as the criterion for patient exclusion for reperfusion therapy due to the potential increased risk for hemorrhagic transformation [23]. However, subsequent studies using the 'a third MCA rule' showed limited interobserver correlation [19,24,25], leading to the development of grading scores, such as the Alberta Stroke Program Early CT Score (ASPECTS) method, to facilitate the assessment of the extent of the hypodensity [26]. This outcome emphasizes the need for more-reliable imaging techniques that can help determine the extent of both irreversibly damaged brain tissue and tissue at risk to avoid unnecessary thrombolytic therapy. In an attempt to provide a more quantitative approach, some clinicians have attempted to design algorithmic methods to quantitatively assess the extent of cerebral acute ischemia on conventional CT by using the 10-point topographic scoring system (ASPECTS) [27].

CT angiography

Although conventional cerebral angiography is considered to be the gold standard for the evaluation of cerebrovascular disease, the advances in multidetector-row CT (MDCT) technology have made CTA an alternative to conventional catheter-based cerebral angiography [28,29]. CTA is widely available, with fast, thin-section, volumetric spiral CT images acquired during the injection of a time-optimized bolus of contrast material for vessel opacification [30]. With modern multisection CT scanners, the entire region from the aortic arch to the circle of Willis can be covered in a single data acquisition, with isotropic spatial resolution and an acquisition time of less than 5 s. Multiplanar reformatted images, maximum intensity projection images (MIPs) and 3D reconstructions of axial CTA source images provide figures comparable to those obtained with conventional angiography [31–33].

A detailed evaluation of the intra- and extra-cranial vasculature can be achieved with CTA [32,34]. Its utility in acute stroke not only lies in its ability to detect large-vessel thrombi within intracranial vessels and to evaluate the carotid and vertebral arteries in the neck [35–37], but also in its potential in guiding therapy. In particular, the exact location (i.e., proximal vs peripheral occlusions) and the extent of vascular occlusion have been shown to have prognostic value in the response to thrombolytics and determination of collateral circulation and possible risk of subsequent recanalization [38]. For example, 'top of carotid' occlusions, proximal MCA branch occlusions, or significant thrombus burden might be poor candidates for intravenous thrombolytics and, possibly, may be better candidates for intra-arterial or mechanical thrombolysis [39]. This is a hypothesis presently tested in the Interventional Management of Stroke Trial (IMS) III [101].

Perfusion CT

Within the last few years, PCT has become the third component in the multimodal CT assessment of acute ischemic stroke. There is considerable literature on the measurement and assessment of cerebral perfusion [40] and a brief review is necessary to understand the parameters and quantitative data that PCT technique provides. In 1981, the landmark study by Jones *et al.* used a primate model to elucidate thresholds for MCA ischemia by restricting blood flow in an awake primate model with pathological correlation [41]. Their findings form the basis of contemporary human perfusion studies:

- 15–30 min of complete ischemia produced only microscopic infarcts
- 2–3 h of ischemia produced moderate-to-severe infarcts
- Cerebral blood flow (CBF) between 10–12 and 23 ml/100 g/min caused reversible paralysis
- CBF under 10–12 ml/100 g/min for 2–3 h, or CBF below 17–18 ml/100 g/min permanently resulted in irreversible paralysis

Subsequent PET findings [42–44] in humans have corroborated these earlier findings in primates (in particular, CBF < 15 ml 100 g^{-1} min^{-1}, has strongly correlated with infarction) [42].

Recently, PCT has been introduced as a simple imaging technique [45,46]. The concepts behind this imaging technique were developed approximately two decades ago, but its widespread clinical use has been facilitated by the advent of fast, multidetector CT technology.

Perfusion CT involves dynamic acquisition of sequential CT slices on a cine mode during rapid intravenous administration of nonionic iodinated contrast material. PCT allows rapid, noninvasive, quantitative evaluation of cerebral perfusion. Based on the multicompartmental tracer kinetic model, dynamic PCT imaging is performed by monitoring the first pass of an iodinated contrast agent bolus through the cerebral circulation. As the change in CT enhancement (in Hounsfield units [HU]) is proportional to the concentration of contrast, perfusion parameters are calculated by deconvolution from the changes in the density–time curve for each pixel using mathematical algorithms based around the central volume principle [40,47].

- Mean transit time (MTT) indicates the time difference between the arterial inflow and parenchymal venous outflow
- Cerebral blood volume (CBV) indicates the volume of blood per unit of brain mass (normal range in gray matter: 4–6 ml/100 g)
- CBF indicates the volume of blood flowing per unit of brain mass per min (normal range in gray matter: 50–60 ml/100 g/min)
- The relationship between CBF and CBV is expressed by the equation CBF = CBV/MTT.

Deconvolution softwares allow much lower injection rates – 5 ml/s as reported previously – compared with other softwares that use different approaches, such as the maximal slope model [47]. These lower injection rates are more practical and tolerable for patients. They do not impair accuracy, since the deconvolution analysis controls for bolus dispersion by comparing the arterial input time-attenuation curve with that of the tissue [47].

Perfusion CT maps can be generated in a short time at an appropriate workstation [48]. Post-image-collection processing involves semiautomated definition of an input artery and a 'vein'. In acute stroke patients, selection of different arterial inputs has been demonstrated to have no significant effect on PCT results for an individual patient [49]. As a result, the anterior cerebral artery as the arterial input function is rountinely used to provide standardization and facilitate intersubject comparison. In patients with chronic cerebral vascular disease, situation is different and, for each vascular territory, its own specific arterial input function. The reference 'vein' actually needs to be the pixel with the largest contrast–enhancement AUC. As such, it must be selected at the center of the largest vascular structure perpendicular to the PCT slices. These requirements are usually met by pixels at the center of the superior sagittal sinus. However, in some instances, other venous structures, or even the supraclinoid internal carotid arteries, can be appropriate 'veins' for PCT processing purposes.

Mean transit time maps are more sensitive, while CBF and CBV maps are more specific for distinguishing ischemia from infarction [50,51]. PCT distinction of the infarct core from the penumbra is based on the concept of cerebral vascular autoregulation. In the penumbra, autoregulation is preserved, MTT is prolonged but CBV is preserved because of vasodilatation and collateral recruitment as part of the autoregulation process. In the infarct core, autoregulation is lost, MTT is prolonged and CBV is decreased [46]. Thus, using appropriate MTT and CBV thresholds, infarct core and penumbra can be distinguished on PCT maps [14]. Direct assessment of an individual patient's ischemic penumbra ('penumbra is brain') may allow more-personalized appropriate selection of candidates for intervention than generalized time criteria ('time is brain'), since individuals may have different timelines for evolution of penumbra into infarct.

Perfusion CT provides equivalent results to diffusion/perfusion MRI in terms of characterizing the infarct and penumbra [14,45,46], and also in terms of selection of patients for acute reperfusion therapies [52]. PCT requires a shorter scan time and is usually more widely available in the emergency setting compared with MRI. As such, it represents a very appealing imaging technique to assess acute stroke patients [11,53]. However, there are some specific situations (e.g., lacunar infarcts, posterior fossa strokes and young patients) in which MRI is warranted instead of PCT.

The main advantage of PCT is its wide availability and quantitative accuracy [54]. Its main limitation is its inability to image the whole brain as it is limited to a 2–4-cm section of brain tissue per bolus. Introduction of 256- and 320-slice CT scanners, offering whole-brain coverage, is likely to overcome this limitation in the near future [53].

Multimodal magnetic resonance stroke imaging

Diffusion-weighted imaging

The advent of new MRI techniques, such as DWI and perfusion MRI (perfusion-weighted imaging [PWI]) in the early 1990s, added a new dimension to diagnostic imaging in stroke [55]. In the late 1990s, improved gradient hardware that was needed for echo planar imaging was implemented in clinical MRI scanners. Brain ischemia leads to a shortage of metabolites. This causes a Na^+/K^+ channel failure in each ischemic cell. This membrane channel failure causes a subsequent cytotoxic edema. Without any net water uptake in the affected brain the tissue, water content remains unchanged and, therefore, x-ray attenuation does not change. During this early stage, native CT does not show any changes in tissue contrast. Cytotoxic edema leads to a narrowing of the extracellular matrix and, thus, to a reduction of Brownian molecular motion in the extracellular space. This phenomenon can be measured with DWI. It was first described 1965 and it can be measured quantitatively in the form of the apparent diffusion coefficient (ADC) [56].

Kucinski and coworkers presented clinical data from ischemic stroke patients who were imaged with CT and DWI. They measured ADC and x-ray attenuation changes in infarcted tissue [57]. In a cohort of 25 patients, they observed mean ADC changes of 170×10^{-6} mm^2/s in the infarcted tissue 1.3–5.4 h after symptom onset. This ADC decrease caused a strong contrast between infarcted and unaffected brain tissue (ADC 803×10^{-6} mm^2/s) on DWI. In contrast to the ADC changes, Kucinski *et al*. observed a time-dependent x-ray attenuation decrease of 0.4 HU/h. Based on these data, CT appears to be less sensitive for early brain infarction compared with DWI.

A stroke MRI protocol consists of T2-, T2*-, DWI and PWI images and MR angiography (MRA). On T2-weighted and fluid-attenuated inversion recovery images ischemic infarction appears as a hyperintense lesion seen, at the earliest, 6–8 h after stroke onset in humans [58].

Ischemic tissue changes can be seen within minutes using DWI after vessel occlusion with a reduction of the ADC [58]. A net shift of extracellular water into the intracellular compartment (cytotoxic edema) with a consecutive reduction of free-water diffusion is the main underlying mechanism for the ADC decrease [59]. DWI leads to a significantly improved detection of early infarction compared with CT (up to 91%) [60,61].

Perfusion-weighted imaging

The measurement of capillary perfusion of the brain can be achieved with PWI [62]. The contrast bolus passage causes a nonlinear signal decrease in proportion to the perfused CBV. It is not yet clear which PWI parameter gives the optimum approximation to critical hypoperfusion and allows differentiation of infarct from penumbra and penumbra from oligemia [62]. Calculation of the quantitative CBF requires knowledge of the arterial input function, which, in clinical practice, is estimated from a major artery, such as the MCA or internal carotid artery (ICA). Thijs *et al.* evaluated the impact of different arterial input functions (AIFs) measured at four different locations in 13 ischemic stroke patients [63]. The curves of AIF were measured near both middle cerebral arteries, in MCA branches adjacent to the largest DWI abnormality and in the contralateral tissue to the DWI lesion. The largest PWI lesion was measured based on the AIF of the unaffected MCA. The other three AIF led to an underestimation of the infarct size on follow-up images.

The attempt to differentiate infarction from penumbra by imaging techniques was made by introducing DWI and PWI into the clinical setting. In a simplified approach, it has been hypothesized that DWI more or less reflects the irreversibly damaged infarct and PWI the complete area of hypoperfusion [64]. The volume difference between these two is also termed the PWI/DWI mismatch (i.e., PWI volume minus DWI volume) would, therefore, be the stroke MRI correlate of the ischemic penumbra. On the other hand, if there is no difference in PWI and DWI volumes or even a negative difference (PWI < DWI) this is termed a PWI/DWI match and, according to the model, is equivalent to a patient who does not have penumbral tissue because of normalization of prior hypoperfusion or completion of infarction and total loss of penumbra [65,66]. This model may be criticized as it does not take into account that the PWI lesion also assesses areas of oligemia that are not in danger and that DWI abnormalities do not necessarily become infarction [67].

Fiehler and coworkers analyzed the frequency of ADC normalization in 68 acute stroke patients. In total, 19.7% of their cohort had ADC normalization in more than 5 ml of brain tissue. In patients imaged within 3 h after symptom onset, ADC normalization was seen in 35.5%, while in patients imaged between 3 and 6 h, it was 7.5%. ADC normalization was predominantly seen in the basal ganglia and white matter in patients with distally located vessel occlusions, and it was associated with a trend toward a better clinical outcome [68].

Thus, patients presenting with a PWI/DWI match within 3 h after symptom onset might have salvageable tissue at risk and benefit from fibrinolysis. However, it is still not known whether the absence of hyperintensities on follow-up T2-weighted images indicates neuronal integrity in humans. DeLaPaz and coworkers and Li and coworkers observed neuronal damage in histological examinations of tissue showing ADC normalization after reperfusion in a rat stroke model [69,70].

Stroke MRI was investigated in a routine clinical setting. Based on an open, nonrandomized patient cohort of 139 patients treated at six different academic hospitals, Röther *et al.* compared the results of 76 rtPA-treated patients with 63 control subjects. Presenting with a slightly more severe stroke score similar DWI lesions and larger mismatch ratios, the treated patients showed early vessel recanalization more frequently and had better clinical outcome after 90 days [71].

The recently published Desmoteplase In Acute Stroke (DIAS) and Dose Escalation Desmoteplase In Acute Stroke (DEDAS) trials used a new fibrinolytic drug similar to a peptide from the salivaria of *Desmodus rotundus,* a vampire bat. Patient screening was based on clinical examination, medical history and guided by stroke MRI. Only patients presenting a clear DWI/PWI mismatch were randomized. Patients who received placebo or ineffective dosage showed a low recanalization rate and an unfavorable outcome. In patients who achieved an early vessel recanalization and reperfusion of penumbra tissue, a significant clinical benefit was observed and 60% of the patients from the most effective dose tier had an excellent clinical outcome [72]. In the DIAS2 study, patients were enrolled based on a mismatch diagnosed either by MRI (PWI/DWI) or PCT. Intention-to-treat analysis found no significant difference between the groups in clinical response rates, with numbers that contrasted sharply with their previous findings with this agent in the DIAS and DEDAS trials. Clinical response rate was 46.0% in the placebo group, 47.4% in the 90-µg/kg group and 36.4% in the 125-µg/kg group.

Hemorrhage imaging

Hyperacute stroke imaging demands the differentiation between ischemic stroke and intracranial hemorrhage (ICH), which is impossible by clinical means only. The diagnosis of ICH is still a domain of CT. The need to perform both CT for exclusion of ICH and stroke MRI to guide therapeutic efforts, is time consuming and medicoeconomically questionable [73]. The appearance of ICH at MRI depends primarily on the age of the hematoma and the type of MR contrast. The key substrate for early MRI visualization of hemorrhage is deoxyhemoglobin, a blood degradation product with paramagnetic properties due to unpaired electrons. The typical appearance of ICH on MRI images is a heterogeneous focal lesion. With increasing susceptibility weight, the central area of hypointensity becomes more pronounced. On T2*-weighted images no or few areas of hyperintensity are visible in the lesions core surrounded by a hypointense rim. There is a surrounding hyperintensity on T2- and T2*-weighted images, but T1-weighted images are hypointensive, representing perifocal vasogenic edema. One randomized, blinded prospective multicenter trial recently investigated the role of stroke MRI in ICH [74]. Images from 62 ICH patients and 62 nonhemorrhagic stroke patients all imaged within the first 6 h after symptom onset (mean: 3 h 18 min) were analyzed after randomization for the order of presentation. The size of ICH ranged from 1–101.5 ml (mean: 17.3 ml). Three readers experienced in-stroke imaging and three final-year medical students each separately evaluated sets of DWI, T2- and T2*-weighted images unaware of clinical details. The experienced readers identified ICH with a 100% sensitivity (confidence interval: 97.1–100%) and a 100% overall accuracy. The medical students achieved a mean sensitivity of 95.16% (90.32–98.39%). Thus, hyperacute ICH is detectable with excellent accuracy, even if the raters have only limited experience.

PCT/CTA or MRI: which one to choose?

Similar information is provided by CT and MRI in terms of infarct core and penumbra. As a reminder, the DWI lesion corresponds to the infarct core, whereas the DWI/PWI mismatch is representative of the ischemic penumbra. The infarct core and the ischemic penumbra, as demonstrated by DWI/PWI and by PCT, respectively, are comparable [45,46]. Similarly, CTA and MRA results are very much alike.

Besides the similarity of their results, both CT and MRI techniques show respective advantages and drawbacks to be considered in the special settings of acute stroke.

Stroke MRI is still available only in a limited number of hospitals. Despite the advantages of stroke MRI there are still doubts as to whether it is a safe approach in severely affected patients and depending on each individual setting it is hard to conduct stroke MRI without losing too much time before treatment onset.

The main advantages are, first, direct visualization of the full extent of infarction on DWI and, second, whole-brain coverage can be achieved with PWI at a time resolution of 1.4 s/frame and, thus, even small but clinically relevant hypoperfusion can be visualized. Visualization of the circle of Willis can be performed within 3 min with a time-of-flight MRA. If a patient moves the head during image acquisition, a sequence can be easily repeated. No additional x-ray dosage or iodinated contrast agent is needed and, therefore, no nephrotoxicity or relevant allergic reactions are expected. In contrast to iodinated contrast media, MRI perfusion measurement does not cause a feeling of heat and, therefore, movement artifacts are less likely during perfusion imaging.

However, the control of vital signs and the access to the patient during the 10-min scan procedure is limited by the magnet. In addition, it takes some efforts to train technicians to conduct stroke MRI in a short period of time to establish an adequate work flow during the hyperacute phase of ischemic stroke.

Computed tomography is often objected to without reason for its use of x-rays and iodinated contrast material. However, the radiation dose involved in PCT imaging is less than a conventional cerebral CT examination [75], and no renal failure has yet been reported following a PCT examination [76].

Owing to its limited spatial resolution, PCT cannot detect small lacunas, whereas noncontract CT is not as sensitive to microbleeds as gradient–echo MRI. PCT has a limited spatial coverage (20–48-mm thickness). However, the issue of spatial coverage will be addressed in the near future through the development of larger multidetector CT scanners with greater arrays of elements and, even at present, PCT has demonstrated 95% accuracy in the delineation of the extent of supratentorial strokes, despite its limited spatial coverage [51]. PCT has also been demonstrated as useful in the evaluation of vertebrobasilar ischemia [77].

The low requirements for performing PCT/CTA technology and its wide availability are key to its taking over MRI in the imaging of acute stroke patients. Indeed, due to their relatively low cost and utility in other areas of medicine, particularly emergency medicine and trauma, CT scanners are becoming very widely available and, as opposed to MRI, it is foreseeable that every major emergency center will eventually be able to complete this form of imaging within minutes of the patient presenting to the emergency department.

Another major advantage of PCT over MRI relates to its quantitative accuracy, whereas perfusion MRI affords only semiquantitative comparison of one hemisphere with the other. Quantitative accuracy of PCT makes it a potential surrogate marker to monitor the efficiency of acute reperfusion therapy, which is a decisive element when it comes to finding and validating new individualized therapeutical strategies for acute stroke patients.

Conclusion

Both CT and MRI fulfill all the requirements for hyperacute stroke imaging. CTA and MRA can define the occlusion site, depict arterial dissection, grade collateral blood flow and characterize atherosclerotic disease. PCT and DWI/PWI accurately delineate the infarct core and the ischemic penumbra. CT and MRI both have their own advantages and drawbacks. The selection of one technique over another depends upon the intrinsic characteristics pertaining to each imaging technique, but also upon the settings and on the knowledge and experience of the institution's staff.

Controversies regarding the superiority of either CT or MRI technique for acute stroke imaging should not obscure the ultimate goal, which is to increase the availability and improve the efficiency of thrombolytic therapy. From that standpoint, CT and MRI must be considered as equivalent tools. Hopefully, using CT and/or MRI to define new individualized strategies for acute reperfusion will allow the number of acute stroke patients benefiting from thrombolytic therapy to be significantly increased.

Expert commentary

Standardization of acute stroke CT and MRI will facilitate their widespread use. This, combined with clinical trials of acute stroke treatments (including, but not limited to, treatment of stroke patients in an extended time window, treatment of patients with wake-up stroke and with strategies to change patient/population behavior to promote earliest possible admission to hospital) should result in more acute stroke patients being appropriately treated and in an overall improvement of their outcome, as well as in reduced societal costs from economic disability.

Five-year view

Stroke imaging experts need to pool large datasets in order to standardize and identify the imaging variables that allow the optimal selection of acute stroke patients who will benefit from reperfusion therapy. Other parameters of interest include aspects that will improve our understanding of collateral perfusion, including determinants of tissue fate and clinical outcome, and predictors of hemorrhagic transformation. A consensus on the definition of clinically meaningful hemorrhagic transformation will be developed.

At this point in time, the stage will be set for one or more clinical trials. Stroke centers will all apply standardized imaging acquisition protocols and use standardized processing algorithms to process images and apply the same optimized criteria to interpret these processed images. This process will significantly minimize any source of variation other than the specific intervention (i.e., drug or device) that will be tested in the clinical trial. Initially, the identified imaging biomarkers will need to be validated in clinical trials with conventional clinical primary end points. Subsequently, it is anticipated that sample sizes will be reduced by the increased power afforded by the use of imaging biomarkers. In addition, if validated, the shorter follow-up periods that will be tested as part of the pilot projects will reduce loss to follow-up and minimize variation in clinical outcome due to unrelated events. This will greatly increase the feasibility and decrease the duration and cost of stroke treatment clinical trials.

Among the future stroke treatment clinical trials considered, particular interest has focused upon two that have the potential to increase the proportion of acute stroke patients that are treated. The first trial is one of image-guided recanalization therapy in an extended time window (3–6 or 9 h); the second would assess image-guided recanalization therapy in wake-up stroke patients. Preliminary analysis indicates that increasing the time window for acute reperfusion therapy from 3 to 6 h could result in a 10-year societal benefit of US$60 million. Neuroprotective agents and collateral enhancement could also be tested, and future analyses should include attention to tissue repair, neurogenesis from stem cells, neurovascular remodeling and stroke recovery.

Financial & competing interests disclosure

Max Wintermark receives funding from the National Center for Research Resources, Grant KL2 RR024130, GE Healthcare and Philips Healthcare. The content of the article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Neurological Disorders and Stroke, the National Center for Research Resources, the National Institutes of Health or other sponsors. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- A tissue clock ('penumbra is brain') is the ideal guide to patient selection for thrombolysis, rather than a rigid time window ('time is brain'), as in the current thrombolysis guidelines.
- Extension of the therapeutic window beyond 4.5 h could substantially increase the number of patients able to receive thrombolysis. However, for this to occur with improved outcomes, a rapid and accessible neuroimaging technique able to assess the ischemic penumbra is required.
- Both computed tomography (CT) and MRI fulfill all the requirements for hyperacute stroke imaging. CT angiography and MR angiography can define the occlusion site, depict arterial dissection, grade collateral blood flow and characterize atherosclerotic disease. Perfusion CT and diffusion- and perfusion-weighted imaging accurately delineate the infarct core and the ischemic penumbra.
- Controversies regarding the superiority of either CT or MRI for acute stroke imaging should not obscure the ultimate goal, which is to increase the availability and improve the efficiency of thrombolytic therapy. From that standpoint, CT and MRI must be considered as equivalent tools.

References

1 Astrup J, Siesjo BK and Symon L. Thresholds in cerebral ischemia – the ischemic penumbra. *Stroke* 12(6), 723–725 (1981).

2 Hossmann KA. Neuronal survival and revival during and after cerebral ischemia. *Am. J. Emerg. Med.* 1(2), 191–197 (1983).

3 Hossmann KA. Viability thresholds and the penumbra of focal ischemia. *Ann. Neurol.* 36(4), 557–565 (1994).

4 Read SJ, Hirano T, Abbott DF *et al.* The fate of hypoxic tissue on ^{18}F-fluoromisonidazole positron emission tomography after ischemic stroke. *Ann. Neurol.* 48(2), 228–235 (2000).

5 Ebinger M, De Silva DA, Christensen S *et al.* Imaging the penumbra – strategies to detect tissue at risk after ischemic stroke. *J. Clin. Neurosci.* 16(2), 178–187 (2009).

6 Hacke W, Kaste M, Bluhmki E *et al.* Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N. Engl. J. Med.* 359(13), 1317–1329 (2008).

7 Hacke W, Donnan G, Fieschi C *et al.* Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA Stroke trials. *Lancet* 363(9411), 768–774 (2004).

8 Albers GW, Thijs VN, Wechsler L *et al.* Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. *Ann. Neurol.* 60(5), 508–517 (2006).

9 Davis SM, Donnan GA, Parsons MW *et al.* Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. *Lancet Neurol.* 7(4), 299–309 (2008).

10 Donnan GA, Davis SM. Neuroimaging, the ischaemic penumbra, and selection of patients for acute stroke therapy. *Lancet Neurol.* 1(7), 417–425 (2002).

11 Kaste M. Reborn workhorse, CT, pulls the wagon toward thrombolysis beyond 3 hours. *Stroke* 35(2), 357–359 (2004).

12 Rowley HA. The four Ps of acute stroke imaging: parenchyma, pipes, perfusion, and penumbra. *AJNR Am. J. Neuroradiol.* 22(4), 599–601 (2001).

13 Kloska SP, Nabavi DG, Gaus C *et al.* Acute stroke assessment with CT: do we need multimodal evaluation? *Radiology* 233(1), 79–86 (2004).

14 Wintermark M, Flanders AE, Velthuis B *et al.* Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. *Stroke* 37(4), 979–985 (2006).

15 Schuierer G, Huk W. The unilateral hyperdense middle cerebral artery: an early CT-sign of embolism or thrombosis. *Neuroradiology* 30(2), 120–122 (1988).

16 Schuknecht B, Ratzka M, Hofmann E. The "dense artery sign" – major cerebral artery thromboembolism demonstrated by computed tomography. *Neuroradiology* 32(2), 98–103 (1990).

17 Tomsick TA, Brott TG, Chambers AA *et al.* Hyperdense middle cerebral artery sign on CT: efficacy in detecting middle cerebral artery thrombosis. *AJNR Am. J. Neuroradiol.* 11(3), 473–477 (1990).

18 Lansberg MG, Albers GW, Beaulieu C, Marks MP. Comparison of diffusion-weighted MRI and CT in acute stroke. *Neurology* 54(8), 1557–1561 (2000).

19 Patel SC, Levine SR, Tilley BC *et al.* Lack of clinical significance of early ischemic changes on computed tomography in acute stroke. *JAMA* 286(22), 2830–2838 (2001).

20 Roberts HC, Dillon WP, Furlan AJ *et al.* Computed tomographic findings in patients undergoing intra-arterial thrombolysis for acute ischemic stroke due

to middle cerebral artery occlusion: results from the PROACT II trial. *Stroke* 33(6), 1557–1565 (2002).

21 von Kummer R, Bourquain H, Bastianello S *et al.* Early prediction of irreversible brain damage after ischemic stroke at CT. *Radiology* 219(1), 95–100 (2001).

22 Larrue V, von Kummer RR, Muller A, Bluhmki E. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European–Australasian Acute Stroke Study (ECASS II). *Stroke* 32(2), 438–441 (2001).

23 Hacke W, Kaste M, Fieschi C *et al.* Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA* 274(13), 1017–1025 (1995).

24 Lyden P. Early major ischemic changes on computed tomography should not preclude use of tissue plasminogen activator. *Stroke* 34(3), 821–822 (2003).

25 Wardlaw JM, Mielke O. Early signs of brain infarction at CT: observer reliability and outcome after thrombolytic treatment – systematic review. *Radiology* 235(2), 444–453 (2005).

26 Mak HK, Yau KK, Khong PL *et al.* Hypodensity of >1/3 middle cerebral artery territory versus Alberta Stroke Programme Early CT Score (ASPECTS): comparison of two methods of quantitative evaluation of early CT changes in hyperacute ischemic stroke in the community setting. *Stroke* 34(5), 1194–1196 (2003).

27 Pexman JH, Barber PA, Hill MD *et al.* Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. *AJNR Am. J. Neuroradiol.* 22(8), 1534–1542 (2001).

28 Prestigiacomo CJ. Surgical endovascular neuroradiology in the 21st century: what lies ahead? *Neurosurgery* 59(5 Suppl. 3), S48–S55; discussion S43–S13 (2006).

29 Wang H, Fraser K, Wang D, Lanzino G. The evolution of endovascular therapy for neurosurgical disease. *Neurosurg. Clin. N. Am.* 16(2), 223–229, vii (2005).

30 Vieco PT. CT angiography of the intracranial circulation. *Neuroimaging Clin. N. Am.* 8(3), 577–592 (1998).

31 Lell MM, Anders K, Uder M *et al.* New techniques in CT angiography. *Radiographics* 26 (Suppl. 1), S45–S62 (2006).

32 Prokop M. Multislice CT angiography. *Eur. J. Radiol.* 36(2), 86–96 (2000).

33 Prokop M, Shin HO, Schanz A, Schaefer-Prokop CM. Use of maximum intensity projections in CT angiography: a basic review. *Radiographics* 17(2), 433–451 (1997).

34 Lev MH, Farkas J, Rodriguez VR *et al.* CT angiography in the rapid triage of patients with hyperacute stroke to intraarterial thrombolysis: accuracy in the detection of large vessel thrombus. *J. Comput. Assist. Tomogr.* 25(4), 520–528 (2001).

35 Cumming M and Morrow I. Carotid artery stenosis: a prospective comparison of CT angiography and conventional angiography. *Am. J. Roentgenol.* 163(3), 517–523 (1994).

36 Katz DA, Marks MP, Napel SA, Bracci PM and Roberts SL. Circle of Willis: evaluation with spiral CT angiography, MR angiography, and conventional angiography. *Radiology* 195(2), 445–449 (1995).

37 Shrier DA, Tanaka H, Numaguchi Y *et al.* CT angiography in the evaluation of acute stroke. *AJNR Am. J. Neuroradiol.* 18(6), 1011–1020 (1997).

38 Tan JC, Dillon WP, Liu S *et al.* Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. *Ann. Neurol.* 61(6), 533–543 (2007).

39 Zaidat OO, Suarez JI, Santillan C *et al.* Response to intra-arterial and combined intravenous and intra-arterial thrombolytic therapy in patients with distal internal carotid artery occlusion. *Stroke* 33(7), 1821–1826 (2002).

40 Latchaw RE, Yonas H, Hunter GJ *et al.* Guidelines and recommendations for perfusion imaging in cerebral ischemia: a scientific statement for healthcare professionals by the Writing Group on Perfusion Imaging, from the Council on Cardiovascular Radiology of the American Heart Association. *Stroke* 34(4), 1084–1104 (2003).

41 Jones TH, Morawetz RB, Crowell RM *et al.* Thresholds of focal cerebral ischemia in awake monkeys. *J. Neurosurg.* 54(6), 773–782 (1981).

42 Eastwood JD, Lev MH, Azhari T *et al.* CT perfusion scanning with deconvolution analysis: pilot study in patients with acute middle cerebral artery stroke. *Radiology* 222(1), 227–236 (2002).

43 Mayer TE, Hamann GF, Baranczyk J *et al.* Dynamic CT perfusion imaging of acute stroke. *AJNR Am. J. Neuroradiol.* 21(8), 1441–1449 (2000).

44 Powers WJ, Grubb RL Jr, Darriet D, Raichle ME. Cerebral blood flow and cerebral metabolic rate of oxygen requirements for cerebral function and viability in humans. *J. Cereb. Blood Flow Metab.* 5(4), 600–608 (1985).

45 Wintermark M, Reichhart M, Cuisenaire O *et al.* Comparison of admission perfusion computed tomography and qualitative diffusion- and perfusion-weighted magnetic resonance imaging in acute stroke patients. *Stroke* 33(8), 2025–2031 (2002).

46 Wintermark M, Reichhart M, Thiran JP *et al.* Prognostic accuracy of cerebral blood flow measurement by perfusion computed tomography, at the time of emergency room admission, in acute stroke patients. *Ann. Neurol.* 51(4), 417–432 (2002).

47 Wintermark M, Maeder P, Thiran JP, Schnyder P, Meuli R. Quantitative assessment of regional cerebral blood flows by perfusion CT studies at low injection rates: a critical review of the underlying theoretical models. *Eur. Radiol.* 11(7), 1220–1230 (2001).

48 Wintermark M, Sesay M, Barbier E *et al.* Comparative overview of brain perfusion imaging techniques. *J. Neuroradiol.* 32(5), 294–314 (2005).

49 Wintermark M, Lau BC, Chien J and Arora S. The anterior cerebral artery is an appropriate arterial input function for perfusion-CT processing in patients with acute stroke. *Neuroradiology* 50(3), 227–236 (2008).

50 Sparacia G, Iaia A, Assadi B and Lagalla R. Perfusion CT in acute stroke: predictive value of perfusion parameters in assessing tissue viability versus infarction. *Radiol. Med. (Torino)* 112(1), 113–122 (2007).

51 Wintermark M, Fischbein NJ, Smith WS *et al.* Accuracy of dynamic perfusion CT with deconvolution in detecting acute hemispheric stroke. *AJNR Am. J. Neuroradiol.* 26(1), 104–112 (2005).

52 Wintermark M, Meuli R, Browaeys P *et al.* Comparison of CT perfusion and angiography and MRI in selecting stroke patients for acute treatment. *Neurology* 68(9), 694–697 (2007).

53 Wintermark M, Bogousslavsky J. Imaging of acute ischemic brain injury: the return of computed tomography. *Curr. Opin. Neurol.* 16(1), 59–63 (2003).

54 Wintermark M, Thiran JP, Maeder P, Schnyder P, Meuli R. Simultaneous measurement of regional cerebral blood flow by perfusion CT and stable xenon CT: a validation study. *AJNR Am. J. Neuroradiol.* 22(5), 905–914 (2001).

55 Moseley ME, Kucharczyk J, Mintorovitch J *et al.* Diffusion-weighted MR imaging of acute stroke: correlation with T2-weighted and magnetic susceptibility-enhanced MR imaging in cats. *AJNR Am. J. Neuroradiol.* 11(3), 423–429 (1990).

56 Stejskal E, Tanner J. Spin diffusion measurements: spin echoes in the presence of a time-dependent field gradient. *J. Chem. Phys.* 42, 288–292 (1965).

57 Kucinski T, Vaterlein O, Glauche V *et al.* Correlation of apparent diffusion coefficient and computed tomography density in acute ischemic stroke. *Stroke* 33(7), 1786–1791 (2002).

58 Mohr JP, Biller J, Hilal SK *et al.* Magnetic resonance versus computed tomographic imaging in acute stroke. *Stroke* 26(5), 807–812 (1995).

59 Röther J, Gass A, Busch E. Diffusion- and perfusion-weighted MRI in cerebral ischaemia – part 1: results of animal experiments. *Akt Neurol.* 26, 300–308 (1999).

60 Fiebach JB, Schellinger PD, Jansen O *et al.* CT and diffusion-weighted MR imaging in randomized order: diffusion-weighted imaging results in higher accuracy and lower interrater variability in the diagnosis of hyperacute ischemic stroke. *Stroke* 33(9), 2206–2210 (2002).

61 Saur D, Kucinski T, Grzyska U *et al.* Sensitivity and interrater agreement of CT and diffusion-weighted MR imaging in hyperacute stroke. *AJNR Am. J. Neuroradiol.* 24(5), 878–885 (2003).

62 Rosen BR, Belliveau JW, Vevea JM, Brady TJ. Perfusion imaging with NMR contrast agents. *Magn. Reson. Med.* 14(2), 249–265 (1990).

63 Thijs VN, Somford DM, Bammer R *et al.* Influence of arterial input function on hypoperfusion volumes measured with perfusion-weighted imaging. *Stroke* 35(1), 94–98 (2004).

64 Jansen O, Schellinger P, Fiebach J, Hacke W, Sartor K. Early recanalization in acute ischemic stroke saves tissue at risk defined by MRI. *Lancet* 353, 2036–2037 (1999).

65 Parsons MW, Barber PA, Chalk J *et al.* Diffusion- and perfusion-weighted MRI response to thrombolysis in stroke. *Ann. Neurol.* 51(1), 28–37 (2002).

66 Schellinger PD, Fiebach JB, Hacke W. Imaging-based decision making in thrombolytic therapy for ischemic stroke: present status. *Stroke* 34(2), 575–583 (2003).

67 Kidwell CS, Alger JR, Saver JL. Beyond mismatch: evolving paradigms in imaging the ischemic penumbra with multimodal magnetic resonance imaging. *Stroke* 34(11), 2729–2735 (2003).

68 Fiehler J, Foth M, Kucinski T *et al.* Severe ADC decreases do not predict irreversible tissue damage in humans. *Stroke* 33(1), 79–86 (2002).

69 DeLaPaz RL, Shibata D, Steinberg GK, Zarnegar R, George C. Acute cerebral ischemia in rabbits: correlation between MR and histopathology. *AJNR Am. J. Neuroradiol.* 12(1), 89–95 (1991).

70 Li F, Liu KF, Silva MD *et al.* Transient and permanent resolution of ischemic lesions on diffusion-weighted imaging after brief periods of focal ischemia in rats : correlation with histopathology. *Stroke* 31(4), 946–954 (2000).

71 Rother J, Schellinger PD, Gass A *et al.* Effect of intravenous thrombolysis on MRI parameters and functional outcome in acute stroke <6 hours. *Stroke* 33(10), 2438–2445 (2002).

72 Hacke W, Albers G, Al-Rawi Y *et al.* The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a Phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke* 36(1), 66–73 (2005).

73 Powers WJ, Zivin J. Magnetic resonance imaging in acute stroke: not ready for prime time. *Neurology* 50(4), 842–843 (1998).

74 Fiebach JB, Schellinger PD, Gass A *et al.* Stroke magnetic resonance imaging is accurate in hyperacute intracerebral hemorrhage: a multicenter study on the validity of stroke imaging. *Stroke* 35(2), 502–506 (2004).

75 Wintermark M, Maeder P, Verdun FR *et al.* Using 80 kVp versus 120 kVp in perfusion CT measurement of regional cerebral blood flow. *AJNR Am. J. Neuroradiol.* 21(10), 1881–1884 (2000).

76 Smith WS, Roberts HC, Chuang NA *et al.* Safety and feasibility of a CT protocol for acute stroke: combined CT, CT angiography, and CT perfusion imaging in 53 consecutive patients. *AJNR Am. J. Neuroradiol.* 24(4), 688–690 (2003).

77 Nagahori T, Hirashima Y, Umemura K *et al.* Supratentorial dynamic computed tomography for the diagnosis of vertebrobasilar ischemic stroke. *Neurol. Med. Chir. (Tokyo)* 44(3), 105–110; discussion: 110–111 (2004).

Website

101 Interventional Management of Stroke Trial III
www.ims3.org

Affiliations

- Carlos J Ledezma, MD
Morristown Memorial Hospital, Department of Radiology, Morristown, NJ, USA
- Jochen B Fiebach, MD
Center for Stroke Research Berlin (CSB), Charité – Universitätsmedizin Berlin, Germany
- Max Wintermark, MD
University of California, San Francisco, Department of Radiology, Neuroradiology Section, 505 Parnassus Avenue, L-358, Box 0628, San Francisco, CA 94143-0628, USA
max.wintermark@radiology.ucsf.edu