Imaging and treatment response after ischaemic stroke

Use of brain imaging to predict treatment response after ischaemic stroke, a test of which is reported by Maarten Lansberg and colleagues1 in this issue of The Lancet Neurology, has a long history. In 1993, Gilles Marchal and colleagues2 used information about both blood flow and metabolic activity obtained with PET to predict differential clinical outcomes. They identified three outcome groups: first, when perfusion was normal or increased and metabolism was normal, clinical outcome was uniformly favourable, and spontaneous recanalisation was assumed to have occurred; second, when blood flow was severely reduced and brain metabolism in the ischaemic region was very low, clinical outcomes were uniformly poor: irreversible damage had already occurred; and third, when perfusion was reduced but oxygen consumption was reduced although still present, clinical outcomes were variable. Patients in the last group had a substantial volume of tissue with features consistent with ischaemic penumbra,3 a state of critical hypoperfusion associated with impaired neuronal activity that is amenable to salvage by restoration of perfusion, but which is otherwise likely to progress to infarction. A penumbral pattern on brain imaging might be used to define the subset of patients for whom intervention might affect clinical outcome, and who therefore could be the best target for clinical trials.4 Investigation of penumbral imaging with the clinically practical approaches of CT and MRI has been a focus of acute stroke imaging.

The MRI signature of irreversible tissue injury is a lesion on diffusion-weighted imaging.5 When combined with information about tissue perfusion from dynamic susceptibility weighted contrast MRI (perfusion-weighted imaging), the region of mismatch on the MRI scans can be used to define the penumbra.6 However, optimum parameters for image processing and patient selection have emerged from small datasets.6 The combined data from two well-conducted small studies, Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE),7 in which all participants received intravenous alteplase, and the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET),8 a randomised controlled trial of intravenous alteplase compared with placebo, have yielded tissue viability thresholds—ie, values of brain perfusion that discriminate viable from non-viable tissue, and viable tissue that is at risk of infarction if hypoperfusion persists from tissue that will survive despite being hypoperfused—and pragmatic clinical trial selection criteria that also incorporate lesion volume. To minimise observer variability, these criteria have been included in a scanner-independent software package (RAPID9) that forms the basis for ongoing trials of late intravenous alteplase (Extending the Time for Thrombolysis in Emergency Neurological Deficits [EXTEND] and European Cooperative Acute Stroke Study [ECASS] 4) and the DEFUSE 2 study.10

The DEFUSE 2 investigators postulated that different treatment responses would occur depending on pretreatment MRI characteristics in patients undergoing an intra-arterial revascularisation procedure within 12 h after onset of stroke. Selection of such population enabled the investigators to accurately characterise early recanalisation and reperfusion status, the major determinants of both radiological and clinical outcomes, in 99 patients. The study confirmed a differential response to successful reperfusion: patients with target mismatch had a more favourable clinical outcome (increase in National Institutes of Health Stroke Scale score of 8 points or more) than those who did not have target mismatch (odds ratio 8.8, 95% CI 2.7–29.0 vs 0.2, 0.0–1.6; p=0.003).

DEFUSE 2 adds support for the use of MRI mismatch as an entry criterion for phase 2 clinical trials—it could minimise harm among those unlikely to benefit, and also substantially reduce sample sizes needed10—and more specifically for adoption of the RAPID definitions in multicentre trials, as opposed to several alternative approaches to mismatch definition and patient selection that are in use. Limitations of use of MRI target mismatch approaches for large trials include restriction to sites with access to imaging equipment and exclusion of up to 20% of patients, for example because of ferromagnetic implants or acute illness, evident in very slow recruitment rates in previous studies.11 The additional time needed for mismatch imaging, including acquisition, processing, and interpretation of images is a consideration when the benefit of treatment decreases rapidly with time—for example, with intravenous alteplase, which has a 4.5 h window. In such situations, non-contrast CT remains the standard of care. CT perfusion imaging—potentially more widely available than MRI—has yet to be standardised sufficiently for investigators to be wholly confident in

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its application in multicentre trials, although it has been used successfully in small trials and could provide an alternative to MRI.

The DEFUSE 2 investigators took advantage of widespread regulatory approval of intra-arterial thrombectomy devices, despite the absence of evidence of clinical benefit from randomised controlled trials. Data from several ongoing trials (Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke [THRACE, NCT01062698], MR CLEAN: Endovascular treatment for acute ischemic stroke in the Netherlands [ISRCTN10888758], Intra-arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke [SYNTHESIS EXP, NCT00640367]), which are based predominantly on structural and angiographic CT imaging, are expected to establish the risk-to-benefit ratio of this resource-intensive intervention. DEFUSE 2 was not designed to test the efficacy of late revascularisation, and does not support its adoption. If the ongoing trials of intra-arterial treatment do not report a benefit, the pneumoencephalographic selection hypothesis investigated in DEFUSE 2 could offer an insight into why this might be the case. Data from the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE, NCT00389467) trial, which randomises patients between standard care (including intravenous alteplase, if indicated) and thrombectomy, with preintervention MRI mismatch scanning, will be an additional test of the validity of mismatch selection but sample size is modest (120 patients planned) and only older thrombectomy devices are included. If a trial of late intervention based on MRI target mismatch reports significantly greater benefit than any reported in randomised controlled trials that use only conventional imaging selection, then a randomised comparison of imaging selection criteria might be needed. Individualised treatment selection based on brain imaging is not yet clearly supported, but is a step closer.

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Clinical stratification of subtypes of Alzheimer’s disease

In the past few decades neuropathology has shown that the presence of extracellular plaques consisting of amyloid β (Aβ) and intracellular neurofibrillary tangles composed of tau protein, both of which were detected with classic staining techniques before the molecular pathology era, are the most frequent pathological findings in the brains of individuals with dementia. These changes are defined as the unifying hallmark of Alzheimer’s disease, although both clinicians and neuropathologists have noted that clinical presentations and anatomical predominance of lesions vary between patients. Whether the various morphological and molecular subtypes of neurodegenerative diseases identified by neuropathologists have any relevance for daily clinical practice is under debate. But, certainly in the case of Alzheimer’s disease, by considering this disease as a single entity, rather than as...