

Perfusion computed tomography to assist decision making for stroke thrombolysis

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The use of perfusion imaging to guide selection of patients for stroke thrombolysis remains controversial because of lack of supportive phase three clinical trial evidence. We aimed to measure the outcomes for patients treated with intravenous recombinant tissue plasminogen activator (rtPA) at a comprehensive stroke care facility where perfusion computed tomography was routinely used for thrombolysis eligibility decision assistance. Our overall hypothesis was that patients with ‘target’ mismatch on perfusion computed tomography would have improved outcomes with rtPA. This was a prospective cohort study of consecutive ischaemic stroke patients who fulfilled standard clinical/non-contrast computed tomography eligibility criteria for treatment with intravenous rtPA, but for whom perfusion computed tomography was used to guide the final treatment decision. The ‘real-time’ perfusion computed tomography assessments were qualitative; a large perfusion computed tomography ischaemic core, or lack of significant perfusion lesion-core mismatch were considered relative exclusion criteria for thrombolysis. Specific volumetric perfusion computed tomography criteria were not used for the treatment decision. The primary analysis compared 3-month modified Rankin Scale in treated versus untreated patients after ‘off-line’ (post-treatment) quantitative volumetric perfusion computed tomography eligibility assessment based on presence or absence of ‘target’ perfusion lesion-core mismatch (mismatch ratio >1.8 and volume >15 ml, core <70 ml). In a second analysis, we compared outcomes of the perfusion computed tomography-selected rtPA-treated patients to an Australian historical cohort of non-contrast computed tomography-selected rtPA-treated patients. Of 635 patients with acute ischaemic stroke eligible for rtPA by standard criteria, thrombolysis was given to 366 patients, with 269 excluded based on visual real-time perfusion computed tomography assessment. After off-line quantitative perfusion computed tomography classification: 253 treated patients and 83 untreated patients had ‘target’ mismatch, 56 treated and 31 untreated patients had a large ischaemic core, and 57 treated and 155 untreated patients had no target mismatch. In the primary analysis, only in the target mismatch subgroup did rtPA-treated patients have significantly better outcomes (odds ratio for 3-month, modified Rankin Scale 0–2 = 13.8, $P < 0.001$). With respect to the perfusion computed tomography selected rtPA-treated patients ($n = 366$) versus the clinical/non-contrast computed tomography selected rtPA-treated patients ($n = 396$), the perfusion computed tomography selected group had higher adjusted odds of excellent outcome (modified Rankin Scale 0–1 odds ratio 1.59, $P = 0.009$) and lower mortality (odds ratio 0.56, $P = 0.021$). Although based on observational data sets, our analyses provide support for the hypothesis that perfusion computed tomography improves the identification of patients likely to respond to thrombolysis, and also those in whom natural history may be difficult to modify with treatment.

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Abbreviations: JHH = John Hunter Hospital; NIHSS = National Institutes of Health Stroke Scale; rtPA = recombinant tissue plasminogen activator; SITS = Safe Implementation of Thrombolysis Registry

Introduction

The use of perfusion imaging to assist in selection of ischaemic stroke patients for acute reperfusion therapy remains controversial. It seems obvious that an imaging technique able to demonstrate areas of potentially salvageable brain would be preferable both in trials and clinical practice to the standard approach, which relies purely on clinical assessment and exclusion of intracranial haemorrhage on non-contrast CT. However, clinical trials of perfusion imaging have so far led to mixed results. The EPITHET study (Davis *et al.*, 2008) examined the hypothesis that patients with a perfusion-diffusion magnetic resonance ‘mismatch’ would have less infarct growth from intravenous recombinant tissue plasminogen activator (rtPA), compared to placebo, in the 3–6-h window. Although virtually all secondary imaging and clinical outcomes favoured the rtPA mismatch group, the primary outcome (log transformed infarct growth) did not reach clinical significance. The two DEFUSE trials (Albers *et al.*, 2006; Lansberg *et al.*, 2012) were not randomized, but both showed that patients with perfusion-diffusion magnetic resonance mismatch that had successful reperfusion following either intravenous rtPA or endovascular therapy had better clinical outcomes than those without reperfusion. Patients without target mismatch did not benefit from reperfusion therapy. With the development of multi-slice CT technology a number of studies have shown that perfusion CT, a generally more accessible acute imaging modality, can provide similar information to perfusion/diffusion MRI, and identify both the ischaemic core and the penumbra (Campbell *et al.*, 2010; Bivard *et al.*, 2013). Perfusion CT more reliably identifies the extent of irreversibly damaged tissue (ischaemic core) than non-contrast CT (Murphy *et al.*, 2006; Muir *et al.*, 2007; Wintermark *et al.*, 2013), and demonstrates that reperfusion therapy may be futile or even potentially harmful (Campbell *et al.*, 2010) when the ischaemic core is large, or the perfusion lesion is particularly severe (Yassi *et al.*, 2013). A phase III trial of a newer thrombolytic agent, desmoteplase, failed to show superior clinical outcomes to placebo in patients selected >3 h after stroke onset using either MRI or perfusion CT to identify mismatch tissue using a visual approach (Hacke *et al.*, 2009). However, a phase II study showed that patients selected by perfusion CT <6 h after stroke onset with a small ischaemic core and significant mismatch had substantially better clinical outcomes when treated with a more effective reperfusion agent, tenecteplase (Parsons *et al.*, 2012).

Given the increasing data on the reliability of perfusion CT to identify ischaemic core and penumbra, some centres do routinely perform perfusion CT before making a therapeutic decision on acute reperfusion therapy. However, this is by no means considered standard practice as the level 1 evidence for the benefit of this approach is still lacking. The widespread promotion of ultra-fast door to needle time has also been a factor and means that many stroke centres eschew imaging of tissue pathophysiology and use only non-contrast CT before thrombolytic treatment.

To date there are limited data on the outcomes of patients where perfusion CT is used to guide thrombolytic treatment decisions, and none comparing outcomes to those treated with the standard clinical and non-contrast CT criteria. Our centre has considerable experience with multimodal CT imaging, and perfusion CT is used routinely in all patients before treatment to assist in the final treatment decision. We thus present data from a ‘real world’ consecutive cohort of patients presenting to a tertiary referral university hospital stroke centre, who fulfilled standard rtPA clinical and non-contrast CT treatment eligibility criteria, but in whom the final treatment decision was made following an assessment of qualitative perfusion CT criteria. These criteria were a large perfusion CT ischaemic core, or lack of significant perfusion lesion-core mismatch, and were considered relative exclusion criteria for thrombolysis (see ‘Materials and methods’ section), and dependent on full informed consent with the patient and family, thrombolytic therapy was not administered in patients with these perfusion CT relative contraindications. This cohort of patients was used for two main analyses. The first analysis was of all patients who were eligible for rtPA based on standard clinical/non-contrast CT criteria, but who were either treated or not treated taking into account the additional perfusion CT criteria. The ‘real-time’ perfusion CT assessments were qualitative, and also not absolute contraindications to treatment. Thus, we hypothesized that ‘off-line’ (post-treatment) classification of patients based on specific perfusion CT volumetric criteria for ischaemic core and penumbra would identify: (i) a favourable perfusion CT profile for treatment response (i.e. ‘target’ mismatch) whereby treated patients with this profile would have better clinical outcomes than untreated patients with the same profile; and, conversely (ii) outcomes of treated patients not fulfilling quantitative perfusion CT target mismatch criteria would not be better than the untreated patients who did not fulfil perfusion CT target mismatch criteria.

The second analysis compared outcomes of the perfusion CT selected rtPA-treated patients from our centre to outcomes in a historical cohort of rtPA-treated patients selected by standard/non-contrast CT criteria from the Australian Safe Implementation of Thrombolysis (SITS) registry (Marion *et al.*, 2010; Meretoja *et al.*, 2014). The main hypothesis of this analysis was that perfusion CT selected patients would have better outcomes than non-contrast CT selected cases.

Materials and methods

Patients with baseline, 24 h, and Day 90 clinical and imaging data from the John Hunter Hospital (JHH) were prospectively collected over a 5-year period (2009–13). All patients presenting within 4.5 h of symptom onset were rapidly screened on arrival in the Emergency Department by a Stroke Neurologist or Stroke Fellow. If they had an acute neurological deficit deemed significant enough to warrant consideration for thrombolysis [National Institutes of Health Stroke Scale (NIHSS) cut-off not used] they routinely underwent perfusion CT and CT angiography after exclusion of intracranial haemorrhage on non-contrast CT. Intra-arterial techniques were not available during the study period. During the study period there were no changes to the institutional clinical eligibility criteria of patients for thrombolysis, which included no upper age limit and <4.5-h time window. The treating clinicians involved in this study were either stroke neurologists or neurology fellows who all had treated at least 20 patients with thrombolysis (with use of perfusion CT as part of the pre-treatment work-up) before their involvement in the study. Follow-up imaging with MRI at 24 h post-stroke was also routine unless the patient was magnetic resonance-incompatible, in which case repeat multimodal CT was performed. Clinical stroke severity was assessed immediately prior to acute and 24 h imaging using the NIHSS. At 90 days after stroke onset, patient disability was assessed by the modified Rankin Scale by an observer not involved in the patient's acute care and blind to treatment. The blinded observer only asked the patient specific questions pertaining to the scale scoring. All patients gave written informed consent during hospital admission (typically between Days 2 and 7) to have their clinical and imaging data used along with permission to have a 3-month Rankin assessment. The study protocol was reviewed and approved by the Hunter New England Area Health Service Human Research Ethics Committee.

Multimodal 'decision-assistance' for thrombolysis

Perfusion CT was routinely used as part of the decision-making process in addition to standard clinical and non-contrast CT criteria. The non-contrast CT criteria for treatment were no intracranial haemorrhage and absence of extensive early ischaemic change (depending on symptomatic territory affected, >1/3 middle cerebral artery or >1/2 anterior/posterior cerebral artery). As we did not have automated, immediately available, on-line volumetric analysis at the CT console during the recruitment time period, the following

perfusion CT criteria were based on visual assessment using vendor software perfusion maps. These were considered relative exclusion criteria for treatment, even if patients fulfilled standard clinical and non-contrast CT criteria for treatment:

- (i) A large ischaemic core on perfusion CT. This determined visually by low regional cerebral blood volume and cerebral blood flow, which were deemed to be larger than 1/3 middle cerebral artery territory (or >1/2 anterior or posterior cerebral artery territory if relevant).
- (ii) Lack of significant visual perfusion lesion-core 'mismatch'. This was determined visually by comparing the transit time lesion (perfusion lesion) and the cerebral blood volume and cerebral blood flow lesions (core). Similar sized perfusion lesion and core were considered to indicate a lack of potentially salvageable tissue.

Our institutional practice was in accordance with the Australian National Guidelines for Stroke Management (2012), which indicate that advanced imaging may provide improved selection for thrombolytic therapy, provided expertise in interpretation of such imaging is immediately available (Wright *et al.*, 2012). All patients (and their family/persons responsible) were fully informed of the risks and benefits of thrombolysis, and provided informed consent before treatment. This informed consent process included a discussion of the risk-benefit ratio of thrombolysis informed by the imaging (including perfusion CT) results. Patients/family were informed if there was a less favourable risk-benefit ratio for thrombolysis such as a large ischaemic core (increased risk), or minimal potentially salvageable brain tissue (reduced benefit). In such cases, the decision to give or withhold thrombolysis was made as a joint decision between the treating clinician and patient/family. This procedure was part of the standard clinical consent process for giving thrombolysis, which is also part of our institutional protocol

Multimodal CT protocol

Acute CT imaging included whole brain non-contrast CT, perfusion CT and CT angiography using 64 or 320 slice scanners (Philips Brilliance, Toshiba Aquilion One). For the 64 slice scanner, non-contrast CT was followed by perfusion CT, comprising two 60-s series with 40 ml contrast agent (Ultravist 370; Bayer HealthCare) injected at 6 ml/s followed by 30 ml of saline at 6 ml/s. CT angiography was performed after perfusion CT with acquisition from the aortic arch to the top of the lateral ventricles (Parsons *et al.*, 2007) with a second contrast injection of 40 ml contrast (Ultravist 370; Bayer HealthCare) injected at 6 ml/s followed by 30 ml of saline at 6 ml/s. For 320-slice scanning a whole brain non contrast CT was performed in one rotation (detector width 16 cm). Next, a 4D time-resolved whole-brain CT angiography and whole-brain perfusion were acquired simultaneously. For the CT angiography-perfusion CT, 40 ml of contrast agent (ultravist 370; Bayer HealthCare) was injected at 6 ml/s followed by 30 ml of saline (Parsons *et al.*, 2009). A continuous scan with a total scan time of 65 s was used. Total radiation dose for multimodal CT examination with either scanner was 7–8 mSv.

Treatment discussions with patient and family occurred immediately after review of non-contrast CT and the on-console perfusion CT maps. The perfusion CT maps were available and reviewed within 5 min of completion of acquisition of

perfusion CT. CT angiography data were not used in treatment decision-making as reconstructions were still occurring after the patient was returned to the Emergency Department. Treatment was initiated in the Emergency Department after the above informed consent process.

Twenty-four hour imaging protocol

As close as possible to 24 h after acute imaging, all patients, regardless of treatment, underwent a stroke MRI protocol on a 1.5 T or 3 T scanner (Siemens Avanto or Verio). The magnetic resonance protocol included: diffusion weighted imaging (DWI), perfusion weighted imaging (PWI), magnetic resonance time of flight angiography (MRA) and fluid attenuated inversion recovery (FLAIR) imaging. For those with a contraindication to MRI, repeat non-contrast CT and perfusion CT was performed using the above protocols.

Post-treatment quantitative ‘off-line’ perfusion CT analysis and classification of patients

All perfusion CT data were analysed with the same commercial software (MiStar). Perfusion data were processed using a single value deconvolution algorithm with delay and dispersion correction with cerebral blood flow and cerebral blood volume being determined by the peak height and area under the curve of the input residue function, respectively, with mean transit time calculated as the ratio of cerebral blood volume to cerebral blood flow (Bivard and Parsons, 2012). Arterial input function and venous outflow function were automatically selected by the software from the non-stroke middle cerebral artery/anterior cerebral artery and superior sagittal sinus, respectively. Previously validated thresholds were applied to measure the volume of the acute perfusion lesion (relative delay time, delay time >3 s) and acute ischaemic core (relative cerebral blood flow <40 and relative delay time >3 s). Major reperfusion was defined as a reduction in the acute 24-h perfusion lesion volume of $>80\%$ (Wintermark *et al.*, 2006). Penumbra volume was calculated from the volume of the perfusion lesion (delay time threshold >3 s) minus the volume of the ischaemic core (relative cerebral blood flow threshold $<40\%$ within the delay time >3 -s lesion).

Using the above post-processing, patients were classified based on quantitative perfusion CT lesion volumes as either: (i) ‘target’ mismatch (perfusion lesion-core mismatch ratio >1.8 and perfusion lesion volume >15 ml, core <70 ml); (ii) large perfusion CT ischaemic core (>70 ml); or (iii) no ‘target’ mismatch (perfusion lesion-core mismatch ratio <1.8 or volume <15 ml, core <70 ml, Lansberg *et al.*, 2012). Symptomatic intracranial haemorrhage was defined as the presence of parenchymal haematoma type 2 and deterioration on NIHSS of ≥ 4 within the first 36 h.

SITS registry data collection

The historical control group consisted of de-identified individual patient data from the SITS registry between December 2002 and December 2008 from 13 Australian academic stroke centres, (Marion *et al.*, 2010; Meretoja *et al.*, 2014) excluding our own centre. Patients in the Australian arm of

the SITS registry were treated according to standard eligibility criteria according to national guidelines (Wright *et al.*, 2012). These guidelines require only a non-contrast CT to rule out potential haemorrhage patients as well as clinical guidelines to exclude patients with fluctuating symptoms or thrombolysis contraindications such as raised INR (international normalized ratio).

Statistical analysis

For Analysis 1 (outcomes in clinically/non-contrast CT eligible patients for treatment with intravenous rtPA, but who were treated or not based on on-line perfusion CT assessment) we compared baseline variables of rtPA-treated versus untreated patients using non-parametric statistics. Outcomes examined were dichotomous modified Rankin Scale 0–1 (excellent outcome), 0–2 (good outcome), 5–6 (poor outcome), death, and spontaneous intracranial haemorrhage. We used logistic regression analyses to determine the odds of achieving each of the above outcomes for treated versus untreated patients in each of the three quantitative perfusion CT categories (target mismatch, large core, and no target mismatch). Each analysis was adjusted for baseline variables that were significant predictors of the outcome. These baseline variables were age, sex, NIHSS, onset to CT time, diabetes, blood glucose, presence and site of vessel occlusion, core and perfusion lesion volumes (significance level for inclusion in models, 0.1). We also examined inter-rater reliability from four of the clinicians involved in the study on 50 patients—half with Philips perfusion maps and half with Toshiba perfusion maps. Multi-rater kappa statistics were used to test inter-rater reliability for simply scoring whether the patient had visually obvious perfusion lesion-core ‘mismatch’. This was determined visually by comparing the transit time lesion (perfusion lesion) and the cerebral blood volume and cerebral blood flow lesions as described above.

For Analysis 2 (clinical/non-contrast CT/perfusion CT selected rtPA treated cases versus the SITS clinical/non-contrast CT selected rtPA treated historical controls) we used multi-level logistic regression models to determine the odds of achieving the above outcomes for perfusion CT selected versus clinical/non-contrast CT selected patients, with adjustment for baseline variables that also may have potentially influenced outcomes (Table 4). These were age, sex, NIHSS, onset to treatment time, diabetes, and blood glucose (note that advanced imaging variables were not available for the SITS data set). We then repeated the same analyses, but this time comparing outcomes of only the treated patients with target mismatch by the off-line quantitative criteria to the SITS clinical/non-contrast CT selected rtPA treated historical controls.

Results

Clinically rtPA-eligible patients: perfusion CT selected versus perfusion CT excluded

Over the study period, 1271 patients presenting within 4.5 h of onset of stroke-like symptoms were assessed. On initial neurological triage 391 patients were excluded as being

ineligible for thrombolysis based on standard clinical criteria, such as resolving or clinically ‘minor’ deficit, stroke mimic, anticoagulation/elevated international normalized ratio, significant premorbid disability and/or multiple co-morbidities.

Thus, 880 patients were potentially eligible for thrombolytic treatment and underwent multimodal CT examination. Ninety patients had intracranial haemorrhage on non-contrast CT. Fifteen patients did not have perfusion CT due to contraindications (severe known renal failure or contrast allergy). Twelve patients had severe motion artefact and uninterpretable perfusion CT data, and two had contrast injection failure with no perfusion maps calculated. A further 41 patients who underwent multimodal CT were excluded from treatment solely based on clinical contradictions that became apparent by the end of the imaging examination. These contraindications were often obtained by corroborative history (e.g. from family, or primary care physician). There were also 31 patients with vertebrobasilar thrombosis on CT angiography who did not have perfusion CT used in their treatment decision. A further 43 patients were excluded from treatment due to extensive early ischaemic change on non-contrast CT alone and so did not have perfusion CT used in their treatment decision. Eleven patients refused consent or were lost to follow-up after hospital discharge (six received rtPA).

Thus, there were 635 patients with hemispheric ischaemic stroke with complete 3-month follow-up deemed eligible for rtPA based on standard clinical/non-contrast CT criteria who had perfusion CT used in their treatment decision-making. Subsequent analyses refer to these 635 patients (Table 1). Ultimately, 366 (58%) of the 635 patients were treated with thrombolysis, based on combined clinical, non-contrast CT and perfusion CT criteria (Table 1). The median stroke onset to treatment time was 173 min (95th centiles 75–225 min), with a median door to needle time of 51 min (95th centiles 39–70 min).

There were 269 (42%) patients potentially eligible for rtPA based on standard clinical and non-contrast CT grounds who did not receive thrombolysis when the additional visual on-line perfusion CT criteria were taken into consideration. Fifty-four patients with a visually large ischaemic core did not receive rtPA treatment, and 215 patients considered to lack significant mismatch visually did not receive rtPA treatment. The clinico-radiological features and 3 month outcomes of these subgroups of patients is shown in Table 1. With respect to the inter-rater assessment of the four clinicians, we found substantial agreement for the presence of visual mismatch (multi-rater kappa = 0.70, $P < 0.001$). There was no significant difference in kappa scores between the two vendor software maps.

Quantitative off-line imaging classification

Of the 366 patients treated with rtPA based on combined clinical, non-contrast CT and qualitative on-line perfusion

Table 1 Comparison of acute and 24 h imaging, and 3 month outcomes of all clinical/non-contrast CT rtPA-eligible patients who received treatment (or not) based on perfusion CT criteria

	<i>n</i>	Age	Median acute NIHSS	Median time to acute CT, mins	Median acute core, ml	Median acute perfusion lesion, ml	Presence of vessel occlusion	Median 24 h NIHSS	Median 24 h infarct, ml	Modified Rankin Scale 0–1 (%)	Modified Rankin Scale 5–6 (%)
All patients	635 ^a	74 (45–88)	13 (6–20)	154 (65–220)	12 (0–105)	60 (0–218)	431/628 (69%)	7 (1–24)	20 (1–191)	279 (44)	146 (23)
rtPA treated	366 ^a	73 (46–87)	14 (6–22)	150 (75–225)	14 (0–106)	91 (2–224)	292/360 (81%)	8 (1–24)	22 (1–195)	146 (40)	91 (25)
rtPA excluded on-line no mismatch	215	69 (40–90)	9 (5–18)	170 (55–240)	9 (0–30)	25 (0–74)	86/214 (40%)	4 (1–16)	9 (0–63)	107 (50)	41 (19)
rtPA excluded on-line large core	54	73 (49–91)	17 (13–23)	150 (60–205)	73 (45–193)	165 (109–332)	53/54 (98%)	18 (10–28)	157 (53–302)	6 (12)	39 (73)

Numbers in brackets refer to 5th and 95th centiles unless otherwise specified. Decimals rounded to nearest integer. Note that vessel occlusion status was not available in seven patients who did not have baseline CT angiography. ^aNumber of patients per year/number treated: 2009 = 114/65; 2010 = 118/69; 2011 = 127/73; 2012 = 136/79; 2013 = 140/80.

CT criteria, 253 (69%) met the quantitative 'target mismatch' criteria. Eighty-three patients (31%) of the 269 patients excluded from rtPA treatment based on qualitative perfusion CT grounds also fulfilled quantitative target mismatch criteria. Sixty of these patients were excluded on-line from treatment because of visual assessment suggesting lack of significant mismatch, and 23 were excluded on-line because of what was deemed visually to be a large ischaemic core (Fig. 1).

Patients with target mismatch had considerably better outcomes with rtPA treatment than those without (Table 2 and Fig. 2). Baseline characteristics were not significantly different between the treated and untreated target mismatch patients, apart from smaller baseline perfusion lesions ($P = 0.003$) and less occlusions on CT angiography in the untreated group ($P = 0.039$). However, proximal occlusions were not significantly higher in the treated group (70% versus 63% in untreated, $P = 0.299$). Despite larger baseline perfusion lesions and more occlusions, the treated target mismatch group had substantially greater rates of major reperfusion (62% versus 19%, $P < 0.001$). This greater reperfusion of target mismatch tissue translated into smaller volumes of infarction at 24 h, and substantially better unadjusted clinical outcomes (Tables 2 and 3). Adjusted odds of good (3-month modified Rankin Scale 0–2) and excellent outcomes (3-month modified Rankin Scale 0–1) were also dramatically higher in rtPA-treated target mismatch patients. The adjusted odds of poor outcomes (3-month modified Rankin Scale 5–6 and death) were also substantially lower in the tPA treated patients (Table 3). Importantly, the rate of spontaneous intracranial haemorrhage was only 1.9% (5/253) in the rtPA treated target mismatch patients and not significantly different to that in the untreated target mismatch group ($P = 0.684$, Table 3). This low spontaneous intracranial haemorrhage rate compared with the 13.2% rate of spontaneous intracranial haemorrhage (15/113) seen in the combined group of treated patients with either large cores or without target mismatch on quantitative 'off-line' perfusion CT analysis ($P < 0.001$).

Of note, the 83 patients excluded from treatment based on lack of visual mismatch but who fulfilled quantitative mismatch criteria fell into two somewhat disparate groups: (i) 60 patients with smaller perfusion lesions (but large enough to fulfil absolute volumetric mismatch criteria); and (ii) those thought to have large cores on visual analysis but on quantitative assessment had core volumes < 70 ml, these patients generally had larger perfusion lesions (Supplementary Table 1). With respect to the former group of 60 patients, most of the patients had proximal occlusions, with a minority having perfusion lesions in a pattern suggesting a distal middle cerebral artery embolus, where an occlusion is difficult to detect on CT angiography. Despite most patients in this group still having an occlusion detectable on CT angiography, the perfusion lesion and core volumes were smaller than in the treated target mismatch group. This group did not do as well

clinically as the treated target mismatch patients despite more favourable baseline imaging (Supplementary Table 1). The latter group of untreated 23 patients fulfilled target mismatch criteria but their baseline core volumes were larger than the treated target mismatch group.

Thirty-one of 54 patients excluded from rtPA treatment based on a visually large perfusion CT ischaemic core had a quantitative perfusion CT ischaemic core > 70 ml (the remaining 23 fulfilled off-line target mismatch criteria, as detailed above). There were also 56 rtPA treated patients, where, on quantitative analysis, baseline perfusion CT ischaemic core volume exceeded 70 ml. Baseline characteristics of treated and untreated patients with core volumes > 70 ml were similar (Table 2). Treated and untreated groups both had very poor outcomes (3-month modified Rankin Scale 5–6 90% untreated versus 88% treated, death rate 71% untreated versus 67% treated), with no patients reaching a good 3-month functional outcome (modified Rankin Scale < 2). After adjusting for baseline variables there was still no discernible benefit from treatment in this subgroup of patients (Table 3). Indeed, the rate of spontaneous intracranial haemorrhage was very high (9/56, 16%) in the treated group with large cores, with none in the untreated group ($P = 0.02$).

Of the 215 patients excluded from rtPA treatment based on a lack of a perfusion lesion-core mismatch at the on-line visual assessment, 155 also did not fulfil quantitative target mismatch criteria. The remaining 60 did fulfil target mismatch criteria as detailed above. A further 57 patients were treated as on-line evaluation of perfusion maps suggested visual perfusion CT mismatch; however, quantitative off-line analysis showed that they did not achieve target mismatch criteria. Apart from younger age in the treated group ($P = 0.023$, a factor which, ordinarily, might be expected to favour this group), baseline characteristics were similar between the treated and untreated patients not fulfilling quantitative target mismatch criteria (Table 2). Our data suggested that patients with absence of a quantitative target mismatch did not benefit from treatment. In fact, in this subgroup, the untreated patients had significantly higher rates of good and excellent outcomes (Table 3), and much lower rates of poor outcomes. This, in part, was underpinned by a 6/57 spontaneous intracranial haemorrhage rate (versus none in the untreated group, Fisher's exact $P < 0.001$).

Perfusion CT selected rtPA cases (JHH) versus historical rtPA-treated non-perfusion CT selected patients (SITS)

Baseline characteristics

There were 396 patients in the Australian SITS database with complete follow-up from 13 hospitals where perfusion CT was not used for treatment decision assistance. Median

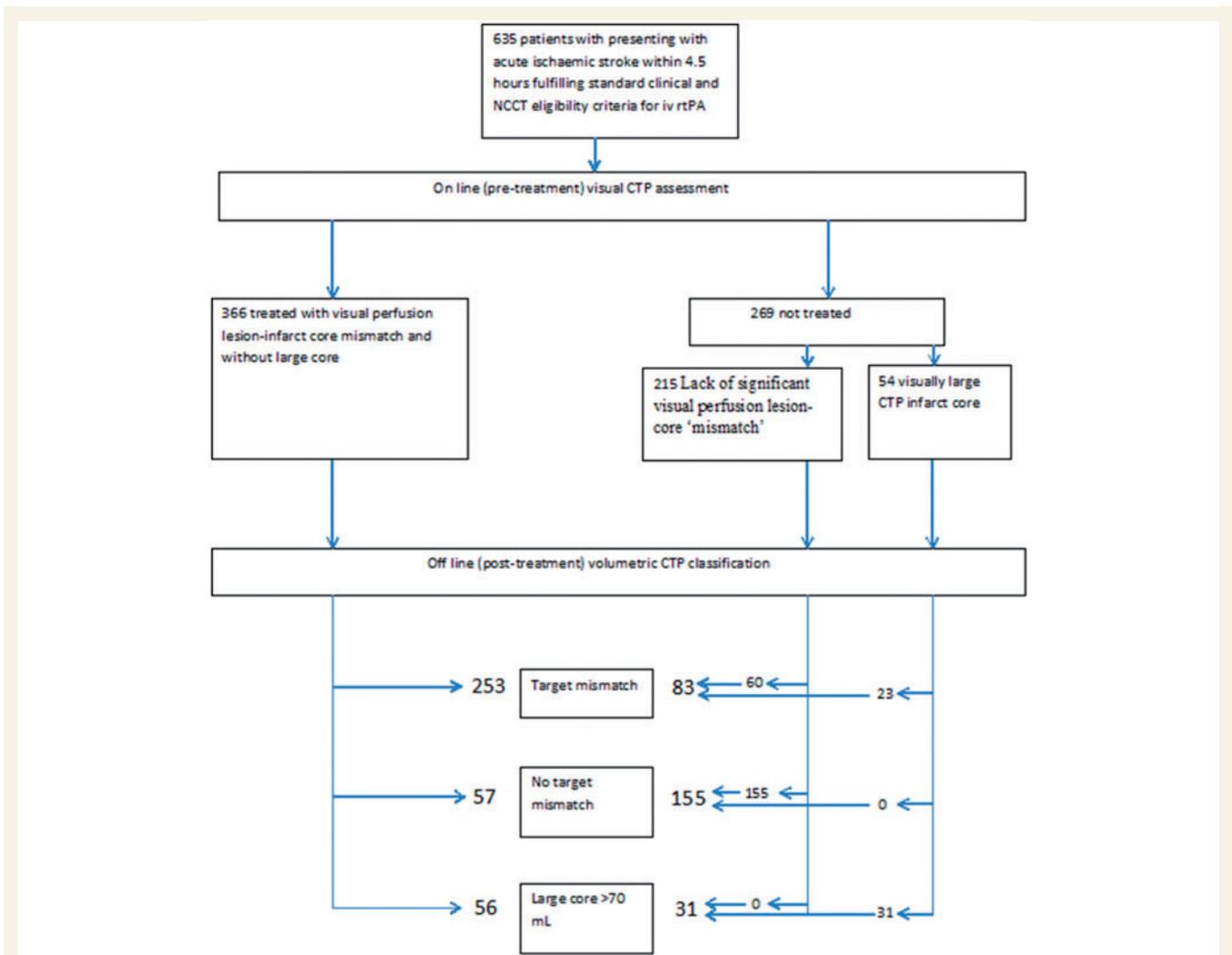


Figure 1 Flow chart showing patients treated according to visual on-line perfusion CT assessment and subsequent classification of patients based on volumetric perfusion CT analysis. CTP = perfusion CT; iv = intravenous.

Table 2 Patient characteristics following quantitative perfusion CT lesion classification into target mismatch, large acute core (> 70 ml), or lack of target mismatch

	<i>n</i>	Age	Median Acute NIHSS	Median time to CT, mins	Median acute core, ml	Median acute perfusion lesion, ml	Presence of vessel occlusion (%)	Median 24 h NIHSS	Median 24 h infarct, ml
Target, mismatch									
Treated	253	74 (49–86)	14 (7–21)	144 (75–221)	12 (2–52)	88 (23–191)	219/250 (88)	7 (1–20)	19 (2–138)
Untreated	83	76 (51–92)	14 (6–19)	150 (60–204)	14 (2–57)	61** (29–179)	65/83* (78%)	12*** (4–21)	48*** (16–145)
No target mismatch									
Treated	57	67 (38–86)	9 (6–17)	140 (84–220)	9 (0–35)	15 (0–48)	17/55 (31)	6 (0–22)	19 (0–90)
Untreated	155	72* (37–89)	9 (5–16)	165 (55–215)	8 (0–32)	14 (0–43)	43/154 (28)	3*** (0–9)	9* (0–30)
Large core									
Treated	56	76 (49–90)	18 (13–24)	178 (74–250)	83 (71–157)	173 (111–277)	56/56 (100)	20 (12–30)	163 (75–255)
Untreated	31	75 (42–89)	18 (14–24)	148** (60–208)	95 (71–198)	188 (121–330)	31/31 (100)	20 (14–28)	180* (92–303)

Note that vessel occlusion status was not available in seven patients who did not have baseline CT angiography. There were 37 patients with confirmed lacunar infarction on 24 h magnetic resonance—all in the no target mismatch group (26 untreated and 11 treated). The significance of any imbalances in the baseline or outcome variables are illustrated as such: * $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$. If no annotation any differences are not significant at the $P = 0.05$ level.

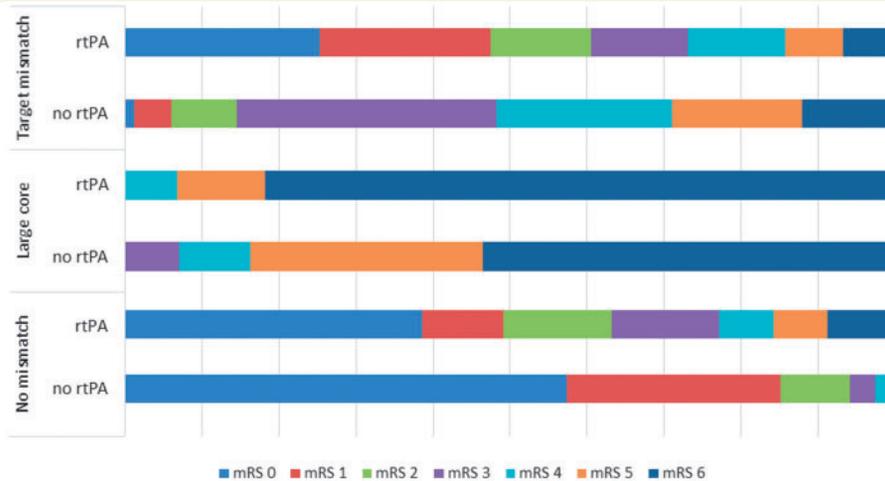


Figure 2 Modified Rankin Scale distribution of patients following off-line volumetric perfusion CT classification into one of three groups (target mismatch, large core, or no target mismatch). Only the target mismatch group showed a clear benefit from thrombolytic therapy.

age in the JHH case and SITS control groups was similar, JHH median 73 years (95th centiles 46–87) versus SITS 74 years (95th centiles 46–88). However, baseline stroke severity was higher ($P < 0.001$) in the JHH group with median NIHSS 14 (95th centiles 4–24) versus SITS median 12 (95th centiles 4–22). The median onset to hospital arrival time was longer ($P < 0.001$) in the JHH group (121 mins, 95th centiles 50–203 mins) compared to median 60 mins in SITS (95th centiles 0–145 mins). However, despite the additional multimodal CT imaging, door to needle time in the JHH group was notably shorter ($P < 0.001$), median 51 mins (95th centiles 39–70 mins), SITS median 74 mins (95th centiles 31–135 mins). Nevertheless, the onset to treatment time was shorter ($P < 0.001$) in the SITS group (median 145 mins, 95th centiles 85–184 mins) versus JHH median 174 mins (95th centiles 102–249 mins).

Outcomes

The unadjusted rates of favourable or unfavourable outcomes in the on-line perfusion CT selected rtPA cases (JHH) were similar to those of historical rtPA-treated non-perfusion CT selected controls (SITS). However, after adjustment for significant baseline predictors (age, NIHSS, and onset to treatment time), the on-line perfusion CT selected rtPA cases had significantly better odds of excellent and good 3-month outcome, with lower odds of poor 3-month outcome and death (Table 4 and Fig. 2). Rates of spontaneous intracranial haemorrhage were similar.

Similar findings were seen in the comparison of the rtPA patients with confirmed off-line quantitative target mismatch and the historical rtPA-treated non-perfusion CT selected controls (Table 4 and Fig. 3). However, the odds of good and excellent outcomes appeared even more in favour of the target mismatch rtPA patients than the SITS controls,

as did the lower odds of poor outcomes seen with the target mismatch rtPA patients.

Discussion

Our data provide support for our two main hypotheses and suggest that quantitative perfusion CT-based selection within the current standard thrombolysis time window can identify patients most likely to benefit and less likely to be harmed by intravenous rtPA. Perfusion CT can identify a subgroup of patients with ‘target mismatch’, who cannot be identified on clinical/non-contrast CT criteria alone. Our data suggest that these patients gain considerable treatment benefit from rtPA-enhanced reperfusion compared to patients with a similar target mismatch profile and similar clinical characteristics who are not treated with rtPA. Conversely, quantitative perfusion CT also identifies subgroups of patients who cannot be identified on clinical/non-contrast CT criteria alone, with an ischaemic core of >70 ml, or with lack of target mismatch, who appear to gain little benefit from rtPA therapy and have an increased risk of spontaneous intracranial haemorrhage.

The standard approach to patient selection for stroke thrombolysis uses clinical assessment to diagnose stroke and gauge severity, non-contrast CT to exclude intracranial haemorrhage and extensive early infarction, and time (<4.5 h currently in most countries) as a surrogate for salvageable tissue. Our study, whilst not a randomized comparison of the standard selection approach versus additional perfusion CT decision assistance, produces the strongest evidence yet available that quantitative perfusion CT selection may lead to better outcomes with intravenous rtPA than selection using clinical and non-contrast CT alone (Parsons *et al.*, 2005). Our data also suggest that

Table 3 Logistic regression analysis of the effect of treatment on the various outcomes for patients in the quantitative perfusion CT classifications groups (target mismatch, small perfusion lesion, large acute core or lack of target mismatch)

n	Modified Rankin Scale 0–1 n (%)	Adjusted OR modified Rankin Scale 0–1 (95% CI)	Modified Rankin Scale 0–2 n (%)	Adjusted OR modified Rankin Scale 0–2 (95% CI)	Modified Rankin Scale 5–6 n (%)	Adjusted OR modified Rankin Scale 5–6 (95% CI)	Death n (%)	Adjusted OR death (95% CI)	Spontaneous intracranial haemorrhage n (%)	Adjusted OR spontaneous intracranial haemorrhage (95% CI)
Target mismatch										
Treated	120 (47)	23.1*** (7.6–70.4)	153 (60)	13.8*** (6.1–31.6)	36 (14)	0.40*** (0.2–0.8)	17 (7)	0.23*** (0.1–0.5)	5 (2)	1.1 (0.2–6.2)
Untreated	83 (5)		12 (14)		24 (29)		15 (18)		2 (2)	
Large core										
Treated	56 (0)		0 (0)		49 (88)	0.67 (0.1–3.2)	36 (64)	0.52 (0.2–1.5)	9 (25)	
Untreated	31 (0)		0 (0)		28 (90)		23 (74)		0 (0)	
No mismatch										
Treated	57 (28)	0.07*** (0.02–0.2)	36 (63)	0.08*** (0.02–0.3)	9 (16)	16.5*** (1.8–155)	5 (9)		6 (11)	
Untreated	155 (85)		146 (94)	2.1 (2–52)	1 (1)		0 (0)		0 (0)	

Baseline variables ($P < 0.1$) included in logistic regression outcome models for target mismatch: core volume (modified Rankin Scale 0–1, 0–2, 5–6), time to CT (0–1, 0–2, 5–6, death), presence of baseline occlusion (modified Rankin Scale 0–1, 0–2), baseline NIHSS (modified Rankin Scale 5–6, death), and age (spontaneous intracranial haemorrhage, death).
 Baseline variables ($P < 0.1$) included in logistic regression outcome models for large core group—age (modified Rankin Scale 5–6, death), baseline NIHSS (modified Rankin Scale 5–6).
 Baseline variables ($P < 0.1$) included in logistic regression outcome models for no mismatch group—age (modified Rankin Scale 0–1, 0–2), perfusion lesion volume (modified Rankin Scale 0–1, 0–2), core volume (modified Rankin Scale 5–6).
 No odds ratio (OR) was available when there was no outcome in one or both of the treated and untreated groups.
 * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Table 4 Outcomes of JHH real-time perfusion CT selected treated patients and JHH off-line quantitative target mismatch treated patients versus SITS patients

Outcome	On-line perfusion CT selected JHH 366 patients n (%)	SITS 396 patients n (%)	JHH on-line perfusion CT selected versus SITS Odds ratio (95% CI)	Off-line target MM treated JHH, 253 patients n (%)	Off-line target mismatch treated JHH versus SITS Odds ratio (95% CI)
3 month modified Rankin Scale 0–1	147 (40)	154 (39)	1.59 (1.12–2.23)***	120 (47)	2.11 (1.45–3.06)***
3 month modified Rankin Scale 0–2	187 (51)	207 (52)	1.49 (1.05–2.09)*	153 (60)	2.12 (1.45–3.10)***
3 month modified Rankin Scale 5–6	95 (26)	120 (30)	0.45 (0.30–0.69)***	36 (14)	0.22 (0.13–0.37)***
Dead	58 (16)	70 (18)	0.56 (0.35–0.92)*	17 (7)	0.26 (0.14–0.49)***
Spontaneous intracranial haemorrhage	20 (5)	17 (5)	1.38 (0.65–2.92)	5 (2)	0.56 (0.19–1.66)

Odds ratios (OR) for outcomes apart from spontaneous intracranial haemorrhage all adjusted for age, baseline NIHSS and onset to treatment time (all $P < 0.1$). For spontaneous intracranial haemorrhage, baseline NIHSS was the only significant predictor.

* $P < 0.05$; *** $P < 0.001$.

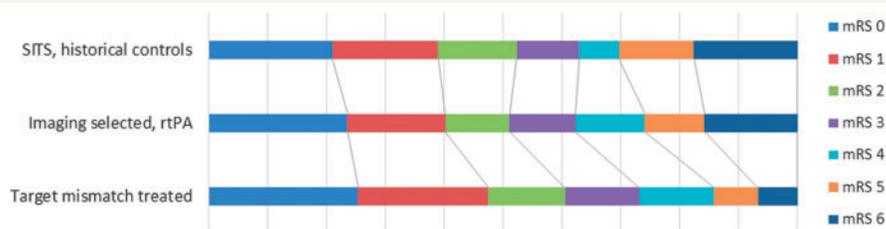


Figure 3 Patient outcome distribution comparing JHH perfusion CT selected rtPA-treated patients to the historical controls from the National registry treated based on standard clinical/non-contrast CT criteria. The JHH patients had worse baseline stroke severity and later onset to treatment time yet had equivalent unadjusted, and better adjusted outcomes. The 253 JHH rtPA treated target mismatch patients had better unadjusted and adjusted outcomes.

around half of all patients eligible for rtPA on clinical and non-contrast CT grounds (i.e. those with target mismatch) gain substantial benefit when treated. We found no significant benefit of intravenous rtPA in those patients without target mismatch or with large ischaemic cores. Interestingly, this combined group of patients had significantly more spontaneous intracranial haemorrhage with rtPA than in the target mismatch group. These findings also highlight that comparing outcomes of thrombolysis (or placebo) treated patients between centres, between countries, or between trials, without knowledge of pre-therapy tissue pathophysiology is likely to be just as potentially inaccurate as making such comparisons without knowledge of baseline clinical factors such as stroke severity and time to treatment. That is, differences in baseline advanced imaging measures such as (i) ischaemic core volume (which is not accurately measurable on early non-contrast CT); (ii) total perfusion lesion volume; and (iii) extent of penumbra, might largely explain any variance in outcomes between centres and/or treatment groups.

Despite the positive results of the quantitative perfusion CT analysis, the substantial misclassification of patients using visual analysis of perfusion CT represents a major caution in the applicability of these findings to routine practice. Visual perfusion CT assessment could result in failure to treat patients suitable for intravenous lysis based on both current trial-derived non-contrast CT/clinical criteria, and also our proposed tissue-based quantitative criteria. This is likely to be exacerbated in less experienced centres or potentially in situations where the perfusion CT coverage is restricted to smaller brain volumes. A number of studies have shown that visual interpretation of perfusion CT mismatch, and even quantitative assessment using vendor-specific thresholded maps, has significant variability (Agarwal *et al.*, 2011). This highlights the need for standardized post-processing using validated algorithms and perfusion thresholds (Ogata *et al.*, 2013). Notably, we had substantial agreement between observers for the presence of visual mismatch. So we cannot fully explain the differences seen between visual assessment and the quantitative analysis due to inter-observer variability. Indeed, it is

probably unrealistic to expect that visual assessment can closely approximate automated measures of penumbra and ischaemic core, particularly where the criteria are based on volumetric cut-offs. Given the marked differences in outcomes we identified between treated patients and untreated patients with quantitatively determined target mismatch, automated on-line (i.e. immediately available) quantitative volumetric criteria would appear to be the preferred option if perfusion CT selection for acute reperfusion therapy is used in clinical trials or in clinical practice.

Eighty-three patients were felt not to have significant mismatch on visual perfusion CT assessment yet did fulfil quantitative mismatch criteria. It is quite likely where non-contrast CT is the only imaging modality used these patients would have been treated. These excluded fell into two groups (Fig. 1 and Supplementary Table 1): (i) 60 patients with smaller perfusion lesions (but large enough to fulfil absolute volumetric mismatch criteria); and (ii) 23 patients thought to have large cores on visual analysis but on quantitative assessment had core volumes <70 ml. We cannot make definitive assumptions regarding possible outcomes with treatment, particularly the 23 in the larger visual core group (as their baseline core volumes were still much higher than the treated target mismatch group). However, the 60 patients without visually large cores had more favourable baseline imaging characteristics than treated target mismatch (smaller cores and smaller perfusion lesions), yet still had a worse outcome than the treated target mismatch group. This implies they might have benefited from treatment and strongly supports the concept that automated (and validated) volumetric assessment is superior to visual perfusion CT assessment. Our data also strongly favour the concept that quantitative perfusion CT can better identify treatment responders compared to standard clinical/non-contrast CT selection and also those who have little to gain (i.e. no mismatch, or large core). With respect to visual perfusion CT analysis, it does appear that the 60 patients with target mismatch without relatively large cores may have benefited from treatment, and this is the major drawback to this approach compared to quantitative perfusion CT. Visual assessment also ‘missed’ 56 patients with quantitatively large cores who were probably treated with little chance of benefit, even though they still had considerable mismatch. So, should visual perfusion CT assessment be used as an adjunct to the standard non-contrast CT/clinical assessment alone? We do not think our data support this. This includes the SITS comparison with our visual perfusion CT selected cohort. The SITS patients were only treated based on non-contrast CT/clinical selection, and in all likelihood includes the treated and untreated sub-populations we have described above with quantitative perfusion CT in our JHH cohort. The results of the entire JHH cohort selected based on visual perfusion CT assessment are much less compelling than the quantitative target mismatch group comparison.

Our study again highlights the lack of sensitivity of non-contrast CT for assessing ischaemic core in hyperacute

ischaemia (Bivard and Parsons, 2012), with 87/636 (14%) patients deemed to have no major infarction on non-contrast CT actually having an ischaemic core on perfusion CT >70 ml. Our data suggest that this group, who would generally receive rtPA if non-contrast CT alone is used to guide imaging eligibility, have a very poor prognosis either with or without therapy. This finding has major implications for clinical trials and clinical practice, although some still debate the accuracy of perfusion CT in measuring ischaemic core volume compared to diffusion weighted imaging. We concede that there probably is a margin of error in the measurement of ischaemic core volume with perfusion CT (as the technique measures very low flow as a surrogate for core). However, substantial validation work has been done to identify consistent ischaemic core thresholds that are now being used in clinical trials (Bivard *et al.*, 2011a, b; Campbell *et al.*, 2011; LinglongTin *et al.*, 2013; Qiao *et al.*, 2014). We do not propose that all patients with perfusion CT core >70 ml should be excluded from reperfusion therapy in clinical practice, as it still is possible that therapy might ‘shift’ a patient from severe to moderate disability, for example. Nonetheless, it would seem that the odds of this occurring are low. In essence, expectations of a good recovery with any form of reperfusion therapy when the quantitative perfusion CT core is >70 ml are unrealistic.

The main limitation of our study is its observational nature where comparisons are not between randomized groups. Despite this limitation, for the treated versus untreated group comparisons based on volumetric perfusion CT, we only found minor baseline imbalances between groups. The treated ‘no target mismatch’ group were younger, however, despite this potentially unfavourable imbalance, the untreated no mismatch group had better outcomes. This finding strongly implies that the no target mismatch group identified on quantitative perfusion CT have little to gain from rtPA treatment. Furthermore, adjustment for other baseline variables known to influence response to treatment, including ischaemic core volume, and site of occlusion did not affect the apparent benefit seen with tPA-treatment in target mismatch patients (nor affect the lack of benefit in the other groups). With respect to the comparison of perfusion CT selected rtPA treated patients versus the standard non-contrast CT selected historical cohort, the perfusion CT selected group had higher baseline stroke severity and a later onset to treatment time because the time window for treatment was extended to 4.5 h in our centre after ECASS III (Hacke *et al.*, 2008). Despite these differences, which clearly should favour better outcomes in the SITS group, there was no difference in unadjusted good or poor outcomes between the two groups. Further, when we corrected for baseline stroke severity and onset to treatment time, the perfusion CT selected group had better outcomes. In addition, when the comparison to SITS controls was limited to the treated target mismatch patients only, even unadjusted outcomes were superior. However, our centre during the study

period did treat more patients per year than any of the hospitals in the SITS Australian historical data set. This is because we had to limit the time period of the SITS data to before there was use of perfusion CT in the treatment selection process at some of the Australian centres. This is a potential bias of the comparison as there are data to suggest that outcomes at centres with higher thrombolytic rates are better than ‘lower volume’ centres (Morris *et al.*, 2014). Of course, we cannot exclude more subtle differences between the treated and untreated patients in the different perfusion CT-defined groups, nor between the perfusion CT selected versus non-contrast CT selected rtPA groups, that may have influenced outcomes. The retrospective nature of the study may have meant that the clinical and non-contrast CT criteria applied for selection within our centre may also have subtly changed over time as a result of non-random shifts in clinical practice, or influence of accumulating (open) data on perfusion CT. This is difficult to identify, however it is notable that the proportion of patients eligible by clinical/non-contrast CT criteria, but treated with additional perfusion CT criteria taken into account, did not change over the study period (Table 1). Thus, our study does not provide level 1 evidence that perfusion CT selection leads to better outcomes with rtPA treatment than non-contrast CT selection.

There are also many questions raised by our data that are beyond the scope of the current paper to explore, such as the influence of collateral status, and the effect of ‘malignant mismatch’ on treatment outcomes. We do not include these data as CT angiography was not used in the treatment decision (see ‘Materials and methods’ section), nor was it possible to assess malignant mismatch by visual analysis. It is possible that these factors may be able to add value to the quantitative perfusion CT target mismatch criteria applied in the current study. Further, our current target mismatch is based on past studies and may possibly be refined further (Churilov *et al.*, 2013). It is by no means clear that an absolute volume of mismatch of >15 ml or ratio >1.8 is the ‘ideal’ (Wintermark *et al.*, 2013).

Finally, the ‘time is brain’ mantra, while clearly relevant and important, has tended to inhibit research into the use of advanced imaging in patient selection, particularly within the early thrombolytic time window. Although the Australian SITS control group is from an earlier time period (2002–08) it is interesting to note that we were able to achieve door to needle time that was substantially shorter than the historical group. Our experience demonstrates that with good organization and inter-departmental collaboration it is feasible to use this approach in routine practice without unnecessarily delaying treatment. To further explore the generalizability of these findings from a single expert centre with a large experience and research interest in the techniques we strongly recommend the evaluation of quantitative imaging-based selection in a randomized controlled trial.

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Supplementary material

Supplementary material is available at *Brain* online.

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