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Patients With the Malignant Profile Within 3 Hours of Symptom Onset Have Very Poor Outcomes After Intravenous Tissue-Type Plasminogen Activator Therapy

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Abstract

Background and Purpose—The malignant profile has been associated with poor outcomes after reperfusion in the 3- to 6-hour time window. The aim of this study was to estimate the incidence and prognostic implications of the malignant profile, as identified by CT perfusion, in intravenous tissue-type plasminogen activator-treated patients who were imaged <3 hours from stroke onset.

Methods—The incidence of the malignant profile, based on the previously published optimal perfusion-weighted imaging definition, was assessed in consecutive patients using a fully automated software program (RAPid processing of Perfusion and Diffusion [RAPID]). A receiver operating characteristic curve analysis was done to identify time to maximum and core volume thresholds that optimally identify patients with poor outcome (modified Rankin Scale 5–6).

Results—Forty-two patients had an interpretable CT perfusion performed within 3 hours of symptom onset. Mean age was 74±14 years and median (interquartile range) National Institutes of Stroke Scale score was 13 (6–19). Four patients (9.5%) met the prespecified criteria for the malignant profile and all 4 had poor outcome. Receiver operating characteristic analysis determined that the best CT perfusion measure to identify patients with poor outcome was a cerebral blood flow based infarct core >53 mL (100% specificity and 67% sensitivity). This criterion identified 5 patients as malignant (12%). The poor outcome rate in these patients was 100% versus 7.1% in the 37 nonmalignant patients ($P<0.001$).

Conclusion—The incidence of the malignant profile on CT perfusion is approximately 10% in tissue-type plasminogen activator-eligible patients imaged within 3 hours of symptom onset. The clinical outcome of these patients is very poor despite intravenous tissue-type plasminogen activator therapy.

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Keywords

acute stroke; CT perfusion; MRI; PWI; tPA

The malignant profile describes patients who are at high risk for parenchymal hemorrhage and poor outcomes by following reperfusion. The malignant profile was originally characterized by the Diffusion and Perfusion Imaging Evaluation For Understanding Stroke Evolution (DEFUSE) group¹ as a baseline diffusion-weighted imaging lesion ≥ 100 mL and/or a severe perfusion-weighted MRI lesion (time to maximum of the residue function obtained by deconvolution [Tmax] delay >8 seconds) ≥ 100 mL in patients treated with intravenous thrombolytic therapy 3 to 6 hours after symptom onset. Optimized criteria for this profile were generated from a pooled analysis of the DEFUSE and Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET)² studies and found to be a perfusion-weighted MRI lesion of >85 mL (Tmax >8 seconds).³ No data are available regarding the incidence or prognosis of the malignant profile within 3 hours of stroke onset or the ability of CT perfusion (CTP) to identify this profile.

Methods

Consecutive patients with acute stroke treated with intravenous tissue-type plasminogen activator (tPA) at the Stanford Stroke Center from May 2009 to May 2011 who had CTP performed before tPA therapy, and within 3 hours of symptom onset, were retrospectively studied. National Institutes of Health Stroke Scale scores before therapy were verified by National Institutes of Health Stroke Scale-certified vascular neurologists. Outcome data were obtained from the Stanford Stroke registry and chart review. Poor outcome was defined as a modified Rankin Scale of 5 to 6 at 30 days. Parenchymal hematoma was assessed on follow-up scans (CT or MRI) performed within 36 hours after tPA therapy by a blinded neuroradiologist (G.Z.) using the European Cooperative Acute Stroke Study criteria.⁴ CTP imaging was performed on multidetector helical CT scanners (Lightspeed 16 and 64 rowed-Lightspeed VCT scanners; GE Healthcare, Waukesha, WI) in cine mode (80 kV, 100 mAs, 50 frames at 1.0-second resolution). Two separate scans (each with injection of 35 mL of Omnipaque 350 followed by 20 mL saline chaser at 4 mL/s) were done in each patient to yield total brain coverage of either 40 mm or 80 mm. Anatomic coverage was located parallel to the orbital roof and higher. On the 16-slice scanner, 20 mm of coverage per scan was obtained with 2 slices of 10 mm thickness. On the 64-slice scanner, 40-mm coverage per scan was obtained using 8 slices of 5 mm thickness. Perfusion parameters (regional cerebral blood flow and Tmax) were automatically computed with RAPid processing of Perfusion and Diffusion (RAPID) software⁵ using a delay-independent deconvolution approach. Based on recent data suggesting cerebral blood flow is more accurate than cerebral blood volume for defining ischemic core,⁶ stroke core was prespecified as regional cerebral blood flow $<30\%$ of contralateral hemisphere median.

The incidence and prognosis of the malignant profile was first determined using the previously defined optimal perfusion-weighted MRI criterion (>85 mL with a Tmax delay of >8 seconds). Subsequently, receiver operating characteristic analysis was done to determine

optimal criteria of the malignant profile using CTP. Optimal lesion volume thresholds were determined for 3 Tmax parameters (>6, >8, and >10 seconds) and for one regional cerebral blood flow parameter (<30% of contralateral). The optimal threshold was defined as the threshold that provided maximal sensitivity for predicting poor outcome at 30 days with a required specificity of >95%. Statistical analysis was performed with SPSS Statistics 19, IBM.

Results

Of 73 consecutive patients treated with intravenous tPA, 43 had CTP performed within 3 hours of symptom onset but one scan was technically inadequate. Therefore, 42 patients were included in this study and their clinical characteristics are summarized in the Table. The median (interquartile range) baseline National Institutes of Health Stroke Scale and mean age for patients who did not receive CTP was 15 (12.5–18) and 70±16 years compared with 13 (6–19) and 74±14 for the CTP patients, respectively (no significant difference for National Institutes of Health Stroke Scale or age). Anatomic coverage was 8 cm in 32 patients and 4 cm in the other 10 patients. Four patients (9.5%) met the prespecified criterion for the malignant profile (Tmax >8 seconds lesion >85 mL). Three of 4 died from the stroke during the acute hospitalization and the other patient had a modified Rankin Scale of 5 at 30 days.

The prespecified criterion of Tmax (>8 seconds) >85 mL was 56% sensitive and 100% specific for identifying patients with poor outcome (modified Rankin Scale 5–6). CTP coverage was 8 cm in all of the malignant profile patients identified with the prespecified criteria. The optimal Tmax thresholds in the receiver operating characteristic analyses were 103 mL for Tmax >6, 86 mL for Tmax >8, and 78 mL for Tmax >10 seconds; all 3 of these thresholds had 56% sensitivity and 100% specificity. The receiver operating characteristic analysis identified a regional cerebral blood flow core lesion of >53 mL as the optimal infarct core threshold for the malignant profile. This optimal threshold identified one additional patient (also with 8 cm of CTP coverage) as “malignant” for an overall rate of 12%, 67% sensitivity and 100% specificity for predicting poor outcome. This additional patient died during the acute hospitalization from stroke. The poor outcome rate (modified Rankin Scale 5–6) in the 37 nonmalignant patients was 7.1% compared with 100% in the 5 malignant profile patients ($P<0.001$). All but one patient had a follow-up CT or MRI scan within 36 hours to assess intracerebral hemorrhage. The rate of intracranial hemorrhage (either parenchymal hemorrhage Type 1 or parenchymal hemorrhage Type 2) on follow-up imaging was 40% (2 of 5) in malignant profile patients versus 5.6% (2 of 36) in patients with nonmalignant CTP patterns ($P=0.066$; OR, 11.3; 95% CI, 1.2–112).

Discussion

The results of this study suggest that CTP can identify patients with the malignant profile within 3 hours of symptom onset and the clinical outcome of these patients is very poor. The incidence of the malignant profile appears to be approximately 10% of tPA-eligible patients imaged within 3 hours. The high rate of parenchymal hematoma we observed in malignant patients after early tPA treatment has also been reported in malignant profile patients who

were treated with tPA 3 to 6 hours after symptom onset² and may be a result of reperfusion of a large volume of severely ischemic brain tissue.

Despite the limited brain coverage (4–8 cm), the optimal Tmax thresholds (86 mL for Tmax >8 and 78 mL for Tmax >10) for identification of the malignant profile in this study were very similar to those found with full brain coverage perfusion-weighted MRI in patients treated with tPA 3 to 6 hours after symptom onset (85 and 65 mL, respectively). In addition, a core lesion volume >53 mL also performed well and identified one additional patient (for an overall incidence rate of 12%).

There are several limitations to this preliminary retrospective analysis. The small sample size limits the statistical conclusions and the variable CTP coverage precludes translating the observed thresholds to scanners with more extensive brain coverage. The CIs for assessing the risk of brain hemorrhage in patients with the malignant profile are wide. Larger prospective studies are warranted to clarify the incidence of the malignant profile within 3 hours of symptom onset and randomized studies would be required to verify if CTP findings can identify a subgroup of patients who do not benefit from intravenous tPA. Additional studies are also needed to explore optimal definitions of poor outcome including alternative modified Rankin Scale thresholds (such as 4–6) or scales that assess quality of life.

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Table

Clinical Characteristics (N=42)

	No. (%)	Mean (SD)	Median (IQR)
Age, y		74 (14)	
Sex, female	24 (57)		
Hypertension	26 (62)		
Diabetes	5 (12)		
Hyperlipidemia	15 (36)		
Smoking	3 (7)		
Atrial fibrillation	15 (36)		
SBP baseline, mm Hg		158 (33)	
DBP baseline, mm Hg		84 (19)	
NIHSS baseline			13 (6–19)
mRS at 30 d			3 (2–4)
Time to baseline CT, min		88 (35)	

IQR indicates interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.