Computed Tomography Perfusion Imaging of the Brain

Description

Perfusion imaging using computed tomography (CT) provides an assessment of cerebral blood flow that may assist in the identification of ischemic regions of the brain. This technology is proposed as a method to aid treatment decisions in patients being evaluated for acute ischemic stroke, subarachnoid hemorrhage, cerebral vasospasm, brain tumors, and head trauma.

Background

Stroke: The goal of acute stroke thrombolytic treatment is to rescue the ischemic penumbra, an area of brain that surrounds the infarct core and is hypoperfused but does not die quickly. Multimodal CT and magnetic resonance imaging (MRI) can be used to assess the cerebral parenchyma, vasculature, and tissue viability in the acute ischemic stroke setting and are used to detect ischemic tissue and exclude hemorrhage and other conditions that mimic acute cerebral ischemia.

- Noncontrast CT is used to rule out intracranial hemorrhage, tumor, or infection. MR diffusion-weighted imaging (DWI) demonstrates acute infarction, and a gradient-recalled echo (GRE) sequence excludes intracerebral hemorrhage.
- CT angiography (CTA) and MR angiography (MRA) are used to evaluate intra- and extra-cranial vasculature to detect the vascular occlusion and potentially guide therapy (e.g., intravenous thrombolytics, or intra-arterial or mechanical thrombolysis).

The approved therapy, intravenous tissue plasminogen activator (tPA), requires only a non-contrast CT scan to exclude the presence of hemorrhage (a contraindication to the use of the drug). Current guidelines are to administer tPA within the first 3 hours after an ischemic event, preceded by a CT scan. Many patients, however, do not present within the 3-hour window, and thrombolysis carries a risk of intracranial hemorrhage. Thus, more sophisticated imaging may be needed to select the proper use of intra-arterial thrombolysis or mechanical thrombectomy in patients who present more than 3 hours after an ischemic stroke. Perfusion imaging is also being evaluated in the management of other neurologic conditions, such as subarachnoid hemorrhage and head trauma.

The potential utility of perfusion imaging of acute stroke is described as the following:

- identification of brain regions with extremely low cerebral blood flow, which represents the core
• identification of patients with at-risk brain regions (acutely ischemic but viable penumbra) that may be salvageable with successful intra-arterial thrombolysis beyond the standard 3-hour window
• triage of patients with at-risk brain regions to other available therapies, such as induced hypertension or mechanical clot retrieval
• decisions regarding intensive monitoring of patients with large abnormally perfused brain regions
• biologically-based management of patients who awaken with a stroke for which the precise time of onset is unknown

Additional potential uses of perfusion CT in acute stroke may include the following:

• detection and differential diagnosis (e.g., excluding stroke mimics such as transient ischemic attack, complex migraine, seizure, conversion disorders, hypoglycemia, or brain tumors)
• determination of stroke subtype
• determination of stroke extent including additional vascular territories at risk
• identification of patients at high early risk for stroke following transient ischemic attack
• determining the need for blood pressure management
• establishing prognosis

Similar information can be provided by CT and MRI in terms of infarct core and penumbra. However, multimodal CT has a short protocol time (5-6 min), and because it can be performed with any modern CT equipment, is more widely available in the emergency setting. CT perfusion is performed by capturing images as an iodinated contrast agent bolus passes through the cerebral circulation and accumulates in the cerebral tissues. (Older perfusion methodologies such as single-photon emission CT [SPECT] and xenon-enhanced CT [XeCT] scanning use a diffusible tracer.) The quantitative perfusion parameters are calculated from density changes for each pixel over time with commercially available deconvolution-based software, in which cerebral blood flow (CBF) is equal to regional cerebral blood volume (CBV) divided by mean transit time (MTT). CT angiography/CT perfusion requires ionizing radiation and iodinated contrast. It is estimated that a typical perfusion CT deposits a slightly greater radiation dose than a routine unenhanced head CT (approximately 3.3 mSv).

Subarachnoid Hemorrhage and Cerebral Vasospasm: Cerebral vasospasm is one of the major causes of morbidity and mortality following aneurysmal subarachnoid hemorrhage (ASAH) in patients who survive the initial hemorrhage and can be seen in about two thirds of patients with ASAH. The typical onset of cerebral vasospasm occurs at 3 to 5 days after hemorrhage, with maximal narrowing on digital subtraction angiography at 5-14 days. Currently, the diagnosis of vasospasm and management decisions rely on clinical examination, transcranial Doppler sonography, and digital subtraction angiography. Although symptomatic vasospasm affects 20% to 30% of patients with ASAH, not all patients with angiographic vasospasm manifest clinical symptoms, and the symptoms can be nonspecific. In addition, patients do not always have both clinical and imaging findings of vasospasm.
Due to these limitations, more accurate and reliable methods to detect cerebral vasospasm are being investigated.

**Brain Tumors:** The current standard for tumor grading is histopathologic assessment of tissue. Limitations of histologic assessment include sampling error due to regional heterogeneity and interobserver variation. These limitations can result in inaccurate classification and grading of gliomas. Since malignant brain tumors are characterized by neovascularity and increased angiogenic activity, perfusion imaging has been proposed as a method to assess tumor grade and prognosis. In addition, perfusion imaging can be repeated and may help to assess the evolution of tumors and the treatment response. Traditionally, perfusion imaging of brain tumors has been performed with MRI, which can estimate tumor blood volume, blood flow, and permeability. More recently, CT perfusion has been investigated for glioma grading. Potential advantages, compared with MR perfusion, include the wider availability, faster scanning times, and lower cost. CT perfusion may also be useful in distinguishing recurrent tumor from radiation necrosis.

**Regulatory Status**

Several post-processing software packages (e.g., Siemens' syngo® Perfusion-CT, GE Healthcare's CT Perfusion 4, Philips Medical System’s Brain Perfusion Option) have received 510(k) marketing clearance from the U.S. Food and Drug Administration (FDA) for use with a CT system to perform perfusion imaging. The software is being distributed with new CT scanners. FDA product code: JAK

**Related Policies**

2.01.54 Endovascular Procedures for Intracranial Arterial Disease (Atherosclerosis and Aneurysms)

**Policy**

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

CT-based perfusion imaging may be considered **medically necessary** to select patients with anterior large-vessel stroke for mechanical embolectomy.

CT-based perfusion imaging of the brain is considered **not medically necessary** for all other indications.

**Benefit Application**

The BCBS FEP contract stipulates that FDA-approved biologics, drugs and certain devices may not be considered investigational when used for their intended purpose and thus these products may only be assessed based on medical necessity.
Policy Guidelines

Selection criteria for the EXTEND-IA trial included patients with an anterior large-vessel stroke who were receiving tPA; able to receive endovascular therapy within 6 hours of stroke onset; functionally independent prior to the stroke; and had evidence of salvageable brain tissue and an ischemic core with a volume of less than 70 mL on CT perfusion imaging.

Rationale

Acute Cerebral Ischemia

In 2009, the American Heart Association Council on Cardiovascular Radiology and Intervention, Stroke Council, and Interdisciplinary Council on Peripheral Vascular Disease published a scientific statement that included a review of the evidence on CT perfusion. (1) The scientific review determined that:

- Creation of accurate, quantitative CTP imaging has been validated in comparison with xenon computed tomography (CT), positron emission tomography (PET), and magnetic resonance perfusion imaging (MRPI). CTP imaging appears to have greater spatial resolution than MRPI, and MRPI may be more sensitive to contamination by large vascular structure, leading to the possibility that visual assessment of core/penumbra mismatch is more reliable with CTP imaging than with MRPI.
- Even relatively imprecise measures of core/penumbra mismatch may be used to select patients for treatment beyond a strict 3-hour time window for intravenous thrombolysis. Multimodal CT may also determine suitability for other therapies, such as mechanical clot retrieval and intra-arterial thrombolysis, and increase patient access to new treatments.
- CTP imaging has the potential to serve as a surrogate marker of stroke severity (final size of infarction), possibly exceeding current predictors of outcome such as the National Institutes of Health Stroke Score (NIHSS). Because of the superior quantitative capability compared with MRPI, application of specific CTP imaging thresholds to predict tissue survival or infarction appears promising; however, these thresholds must be validated in larger patient cohorts for which reperfusion status is known.

More recent literature that addresses these issues follows.

One area of active research is defining the technical CT parameters that best detect perfusion mismatches. For example, in 2011, Bivard et al reported a prospective clinical validation study of CTP imaging for acute (<6 hours) ischemic stroke in 314 consecutive patients. (2) Using a threshold of cerebral blood flow less than 40% of contralateral with a relative delay time less than 2 seconds, the correlation between the extent of CTP mismatch tissue (volume of “at-risk” tissue) salvaged from infarction and clinical improvement was a coefficient of determination (R2) of 0.59 (p=0.04) at 24 hours (National Institutes of Health Stroke Scale [NIHSS] score) and an R2 of 0.42 (p=0.02) at 90 days (Rankin Scale score). In 2016, this group of investigators reported a validation study on the threshold
settings for whole-brain 320-detector CTP imaging and compared its performance to limited-coverage CTP imaging. (3)

Evaluation for Thrombolysis

A 2015 study by Bivard et al examined the effectiveness of CTP imaging by assessing health outcomes in patients who qualified for tPA based on standard clinical/non-contrast CT criteria, who were treated or not treated based on qualitative CTP results, and later had quantitative analysis of CTP imaging data. (4) Patients selected for a tissue plasminogen activator (tPA) based on qualitative analysis of CTP imaging (n=366) had higher odds of an excellent outcome (modified Rankin Scale [mRS] score, 0-1; odds ratio [OR], 1.59, p=0.009) and lower mortality (OR=0.56, p=0.021) than historical controls (n=396) selected for tPA based on clinical/non-contrast CT information. In addition, of patients treated with tPA, those who had target mismatch by CTP imaging had significantly better outcomes than patients treated with tPA who did not (OR=13.8 for 3-month mRS score, ≤2). However, 83 (31%) of 269 untreated patients had target mismatch and 56 (15%) of 366 treated patients had a large ischemic core. This observational study suggested that CTP imaging has the potential to identify those patients with acute stroke who are likely and unlikely to respond to thrombolysis. However, questions remain about whether CTP imaging is sufficiently reliable to select individual stroke patients for treatment. (5,6)

Another area of research is whether CTP imaging can help select ischemic stroke patients for thrombolysis after the 3-hour time window. Sztriha et al studied a cohort of 254 thrombolysed patients; 174 received tPA at 0 to 3 hours using non-contrast CT, and 80 received tPA at 3 to 6 hours by using CTP imaging criteria. (7) At 3 months, there were no differences between patients thrombolysed at 0 to 3 hours or at 3 to 6 hours in symptomatic intracerebral hemorrhage (3% vs 4%), or in any intracerebral hemorrhage (7% vs 9%). There were also no differences at 3 months in mortality (16% vs 9%) or the mRS score of 0 to 2 (55% vs 54%), all respectively. The authors noted that their results could not be generalized to patients with symptoms in the posterior circulation, an area where CTP imaging is known to underperform.

In 2011, Obach et al compared outcomes for 106 patients with acute stroke assessed with multimodal CT (CT, computed tomography angiography [CTA], or CTP) to a cohort of 262 patients with acute stroke assessed without full multimodal brain imaging during a 5-year period. (8) Clinical and imaging data were collected prospectively, and all imaging studies were assessed by investigators blinded to prognostic data. Good outcome (mRS score, ≤2) at 3 months was higher in the multimodal group than in controls (adjusted OR=2.88) in models adjusted for age, sex, NIHSS score, glucose level, and treatment delay or modality. In a sensitivity analysis, multimodal-assisted thrombolysis yielded superior benefits in those patients treated after 3 hours (adjusted OR=4.48) than in patients treated within 3 hours (adjusted OR=1.31). For patients treated after 3 hours, 63% of patients assessed by multimodal CT had a Rankin Scale score of 2 or less compared with 24% of controls. Mortality (14% and 15%) and symptomatic hemorrhage (5% and 7%) were similar in the 2 groups, respectively.

In 2015, Burton et al reported a meta-analysis of 13 studies (including 3 RCTs and 6 prospective cohort studies) that used CTP imaging and gave intravenous thrombolytic treatment. (9) The objectives of the studies included comparisons of thrombolytic agents and predictions of clinical outcomes. Relatively few patients received tPA based on CTP imaging results. One study in the review prospectively
compared outcomes between 172 patients treated within 4.5 hours based on non–contrast CT criteria and 43 patients treated after 4.5 hours based on CTP mismatch criteria.10 Another 49 (54%) patients who presented beyond 4.5 hours were excluded according to CTP imaging criteria. This exploratory study found similar rates of symptomatic intracranial hemorrhagic (2.9% in the <4.5-hour group vs 2.3% in the >4.5-hour group) and good long-term outcome (64.5% vs 60.5%, respectively) in the 2 groups, supporting further study in a randomized trial.

**Section Summary: Evaluation for Thrombolysis**  
Evidence from nonrandomized comparative studies with either concurrent or historical controls has suggested that outcomes after thrombolysis are better in patients who have target mismatch on perfusion imaging than in patients without target mismatch, and that patients with target mismatch treated after a 3-hour time window have outcomes similar to those treated within 3 hours. However, randomized trials are needed to determine with greater certainty whether a strategy employing CTP imaging leads to improved health outcomes compared with traditional treatment strategies for acute stroke.

**Evaluation for Mechanical Embolectomy**  
CTP imaging was used to select patients for mechanical embolectomy in the 2015 EXTEND-IA randomized controlled trial (RCT). (11) Other comparable trials of mechanical embolectomy from the same time period (eg, ESCAPE, MR CLEAN, SWIFT PRIME) used time from stroke onset, multiphase CTA, or Alberta Stroke Program Early CT (ASPECTS) score to select patients for treatment. (12-14) The value of CTP imaging–based patient selection for intra-arterial acute ischemic stroke treatment was assessed by Borst et al in 2015 using data from the MR CLEAN trial. (15) In this trial, inclusion was not limited to CTP imaging, but investigators could perform it if it was a standard procedure at their institution. Of 500 patients in MR CLEAN, 333 (67%) underwent CTP imaging and 175 (52.6%) had adequate images. Of the 175, 102 fulfilled the CTP mismatch criteria. The primary outcome was mRS score at 90 days, which was compared between patients with and without CTP mismatch. There was no significant interaction for mismatch and treatment (mechanical embolectomy or usual care) for the mRS score at 90 days, suggesting that CTP imaging cannot reliably identify patients who will not benefit from mechanical embolectomy. In both treatment groups, there was a shift towards better outcomes in patients who had CTP mismatch compared to those who did not, suggesting a benefit for prognosis (see the Evaluation for Prognosis section).

In 2013, Sheth et al retrospectively studied the effect of multimodal CT on outcomes from endovascular therapy in 556 patients from 10 stroke centers. (16) Patients were included if they presented within 8 hours of symptom onset and were then divided into groups based on the imaging modality employed before treatment. Non–contrast CT was used in 51% of patients, CT perfusion in 34%, and MRI in 14% of patients. Patients were selected for endovascular therapy based on specific imaging criteria. Non–contrast CT patients had significantly lower median times to groin puncture (61 minutes) than with CTP imaging (114 minutes) or MRI (124 minutes) patients. There were no differences in clinical outcomes, hemorrhage rates, or final infarct volumes among the groups.

Rai et al evaluated rates of recanalization and functional outcomes in a cohort of 99 patients selected by CT perfusion for treatment with endovascular stroke therapy and results compared with historical
controls from the MERCI [Mechanical Embolus Removal in Cerebral Ischemia], Multi-MERCI, and Penumbra device trials that treated all comers. (17) Patients were included if they had anterior circulation symptoms at presentation with a baseline NIHSS score of 8 or greater and intracerebral vascular occlusion on admission CTA correlating with the neurologic deficit. There was no cutoff time for treatment, and the type of endovascular therapy was thrombolytics in 33 (33.3%), mechanical device only in 24 (24.2%), and both treatments in 42 (42.4%). Successful recanalization was achieved in 55.6%, with a good outcome in 41.4% of patients. The recanalization rate in this study did not differ significantly from the 46% for MERCI and 68% for Multi-MERCI, but was significantly lower than the 82% recanalization rate in the Penumbra trial. In patients successfully recanalized, good outcomes were obtained in 67% in this study in comparison with 46% in MERCI, 49% in Multi-MERCI, and 29% in Penumbra. The rate of futile recanalization (defined as a poor outcome despite successful recanalization) was 33% in Rai et al compared with 54% in MERCI, 51% in Multi-MERCI, and 71% for Penumbra.

Section Summary: Evaluation for Mechanical Embolectomy

contrast CT patients had significantly lower median times to groin puncture (61 minutes) than with CTP imaging is one of several approaches used in acute stroke to better define viable ischemic tissue that may benefit from mechanical endovascular intervention. One RCT showed improved outcomes with mechanical embolectomy when patients were selected based on contrast CT patients had significantly lower median times to groin puncture (61 minutes) than with CTP imaging results.

Evaluation for Prognosis

A large number of case series have assessed how contrast CT patients had significantly lower median times to groin puncture (61 minutes) than with CTP imaging at admission might facilitate clinical decision making and predict outcomes in patients with suspected acute ischemic stroke.

In 2015, Borst et al (discussed above) reported on the relationship between CTP imaging- derived parameters and functional outcomes from the MR CLEAN trial. (15) Functional outcome as measured by mRS score at 90 days was associated with the CTP imaging-derived ischemic core volume (OR=0.79 per 10 mL; 95% CI, 0.73 to 0.87 per 10 mL; p<0.001) and percentage ischemic core (OR=0.82 per 10%; 95% CI, 0.66 to 0.99 per 10%; p=0.002), but not the penumbra. This trial population had been selected for treatment using mechanical embolectomy.

A prognostic model, developed with data from the Dutch Acute Stroke Study (DUST), was reported by van Seeters et al in 2015. (18) They analyzed an unselected population of 1374 patients with suspected anterior circulation stroke who underwent multimodal CT. Images were evaluated by an observer blinded to all clinical information except for side of stroke symptoms. The analysis used 60% of patients for a prediction model and 40% for a validation cohort. Poor outcome (90 day mRS score 3-6) occurred in 501 (36.5%) patients. Included in the basic prediction model were patient characteristics (age, stroke severity, time from onset to imaging, dependency prior to stroke symptoms, glucose level, whether treatment had been given) and non–contrast CT measures. CTA and CTP imaging also were predictive of clinical outcome. However, adding CTA and CTP imaging to the basic prediction model did not improve it. For example, in the validation cohort, the area under the curve (AUC) was 0.78 (95% CI,
0.73 to 0.82) when using patient characteristics and NCCT. When CTA and CTP imaging were added to the basic prediction model, the AUC was 0.79 (95% CI, 0.75 to 0.83).

Section Summary: Evaluation for Prognosis
Retrospective analysis of data from the MR CLEAN and DUST trials found that the ischemic core detected on CTP imaging was predictive of functional outcomes. However, analysis of data from the DUST study found no improvement in a prediction model when CTP imaging was added to a basic model that used only patient characteristics and non–contrast CT.

Subarachnoid Hemorrhage and Cerebral Vasospasm
A 2010 meta-analysis on the diagnostic accuracy of CTA and CT perfusion for cerebral vasospasm identified 3 studies (64 patients) that met the inclusion criteria and contained the appropriate data for statistical analysis (19). In these studies, “vasospasm” was defined on CT perfusion as a perfusion deficit demonstrating prolonged mean transit time and decreased cerebral blood flow. However, there were no standardized thresholds of mean transit time and cerebral blood flow to determine vasospasm, contributing to the heterogeneity among these studies. For this meta-analysis, “angiographic vasospasm” was defined as evidence of arterial narrowing compared with the parent vessel or with a baseline examination, with both symptomatic and asymptomatic patients included. In comparison with digital subtraction angiography, CT perfusion pooled estimates had 74% sensitivity and 93% specificity. Given the small sample size and the heterogeneity in the CT perfusion data, these results are considered preliminary. A 2014 meta-analysis by Cremers et al included 11 studies (570 patients) on the use of CT perfusion to identify delayed cerebral ischemia. (20) CT perfusion measures at admission did not differ between patients who did and did not develop delayed cerebral ischemia. Some measures of CT perfusion (cerebral blood flow and mean transit time, but not cerebral blood volume) were found to differ between the 2 groups during the period of 4 to 14 days after subarachnoid hemorrhage, suggesting a possible role in diagnoses of delayed cerebral ischemia.

One of the studies included in the meta-analysis was a prospective 2011 study with 97 patients that evaluated the accuracy of CT perfusion to diagnose delayed cerebral ischemia following aneurysmal subarachnoid hemorrhage. (21) CT perfusion was performed between days 6 and 8 in asymptomatic patients and on the day of clinical deterioration in symptomatic patients. Perfusion maps were qualitatively evaluated by 2 neuroradiologists, who were blinded to clinical and imaging data, and compared with the reference standard. Based on a multistage hierarchical reference standard that incorporated both imaging and clinical criteria, 40 patients (41%) were diagnosed with delayed cerebral ischemia. Overall diagnostic accuracy for CT perfusion, determined from receiver operating characteristic (ROC) curves, was 93% for cerebral blood flow, 88% for mean transit time, and 72% for cerebral blood volume. The study also sought to determine a quantitative threshold for delayed cerebral ischemia with CT perfusion, although it was noted that absolute thresholds may not be generalizable due to differences in scanner equipment and post processing methods. Clinical outcomes of the delayed cerebral ischemia group included 19 patients (48%) with no permanent neurologic deficit, 16 (40%) with permanent neurologic deficit, and 5 (13%) who died during hospitalization.
Sanelli et al also reported a retrospective study of the development of vasospasm in 75 patients with aneurysmal subarachnoid hemorrhage who had an earlier CT perfusion assessment (likely overlap in subjects with the study described above). (22) Based on a multistage reference standard, 28 patients (37%) were classified as vasospasm. CT perfusion values (cerebral blood flow and mean transit time) on days 0 to 3 were significantly lower in the vasospasm group. Optimal thresholds were then determined for cerebral blood flow (50% sensitivity, 91% specificity), mean transit time (61% sensitivity, 70% specificity), and cerebral blood volume (36% sensitivity, 89% specificity). Clinical outcomes of the vasospasm group included 15 patients (54%) with no permanent neurologic deficit, 11 (39%) with permanent neurologic deficit, and 2 (7%) who died during hospitalization.

Section Summary: Subarachnoid Hemorrhage and Cerebral Vasospasm
One prospective study showed a qualitative measure of cerebral blood flow to have 93% accuracy for the detection of delayed cerebral ischemia, with lower accuracy for cerebral blood volume. RCTs are needed to evaluate whether CTP imaging in patients with aneurysmal subarachnoid hemorrhage leads to the early identification of patients at high risk for vasospasm or delayed cerebral ischemia, alters treatment decisions, and improves health outcomes.

Brain Tumors
A 2011 review by Jain indicates that most of the literature on the utility of perfusion imaging for glioma grading is based on various MR perfusion techniques. (23) One study compared CT perfusion with conventional MRI in 19 patients. (24) With a cutoff point of greater than 1.92 normalized cerebral blood volume (nCBV), there was sensitivity of 85.7% and specificity of 100% to differentiate high-grade gliomas. There were no significant differences in nCBV between grade III or IV tumors. A subsequent study by Jain and colleagues correlated CT perfusion findings with histopathologic grade in 32 patients with astroglial tumors. (25) Eight additional patients with oligodendrogliomas were excluded from analysis because of the known higher blood volume compared with astroglial tumors. Of the 32 patients included in the study, 8 had low-grade gliomas and 24 had high-grade gliomas. In this selected set of patients, CT perfusion showed significant differences in the grade III and grade IV tumors. In 2011, Xyda et al. reported a prospective study of the feasibility and efficacy of volume perfusion CT (VPCT) for the preoperative assessment of cerebral gliomas in 46 consecutive patients with suspected cerebral gliomas. (26) (Whereas typical perfusion CT covers a relatively narrow range of brain tissue, the VPCT system with multispiral acquisition covers the entire tumor.) Two blinded readers independently evaluated VPCT by drawing volumes of interest (VOIs) around the tumor according to maximum intensity projection volumes. The VOIs were mapped onto the cerebral blood volume, flow, and permeability perfusion datasets, which correspond to histopathologic microvascular density. VPCT was followed by stereotactic biopsy or surgery to evaluate the histopathology of the tumor and classified into low-grade (I and II) and high-grade (III and IV). The diagnostic power of the perfusion parameters were analyzed by receiver operating characteristic (ROC) curve analysis. Permeability demonstrated the highest diagnostic accuracy (97% sensitivity, 100% specificity), positive predictive value (100%), and negative predictive value (94%) to identify or exclude high-grade tumors. Potential uses of VPCT are to guide biopsy and to monitor low-grade gliomas.
Section Summary: Brain Tumors
For indications such brain tumors data on CTP imaging are limited. One study assessed the diagnostic accuracy of CTP imaging to differentiate high-grade from low-grade gliomas. Prospective studies in an appropriate patient population are needed to evaluate the sensitivity and specificity of CTP glioma grading, with histopathologic assessment of tumors as the independent reference standard. One prospective study performed ROC analysis to evaluate the diagnostic accuracy of VPCT. This is the first report using VPCT to differentiate gliomas; therefore, replication of these findings in an independent sample is needed. Consistency in the thresholds used is also needed. Studies are also needed to show an improvement in health outcomes with CTP imaging. No recent reports on the use of CTP imaging for the evaluation of brain tumors were identified.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

<table>
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<tr>
<th>NCT No.</th>
<th>Trial Name</th>
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<th>Completion Date</th>
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<td>NCT02360670</td>
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<td>NCT02586415</td>
<td>Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (Defuse 3)</td>
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<td>Jun 2020</td>
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NCT: national clinical trial.

Practice Guidelines and Position Statements

American Heart Association and American Stroke Association
American Heart Association (AHA) and American Stroke Association (ASA) 2012 guidelines for the management of aneurysmal subarachnoid hemorrhage recommend that perfusion imaging with CT or MR can be useful to identify regions of potential brain ischemia (Class IIa; Level of Evidence B). (27)
The guidelines state that there are emerging data that perfusion imaging, demonstrating regions of hypoperfusion, may be more accurate for identification of delayed cerebral ischemia than anatomic imaging of arterial narrowing or changes in blood flow velocity by transcranial Doppler. The guidelines concluded that CT perfusion is a promising technology, although repeat measurements are limited by the risks of dye load and radiation exposure.

AHA/ASA 2013 guidelines for the early management of adults with ischemic stroke recommend that CT perfusion and MRI perfusion and diffusion imaging, including measures of infarct core and penumbra, may be considered for selecting patient for acute reperfusion therapy beyond IV fibrinolytic time windows. (28) The guidelines state that these techniques provide additional information that may improve diagnosis, mechanism, and severity of ischemic stroke and allow more informed clinical decision making. (Class llb, Level of Evidence B)

American Society of Neuroradiology, etal.
In 2013, the American Society of Neuroradiology, the American College of Radiology, and the Society of NeuroInterventional Surgery issued a joint statement on imaging recommendations for acute stroke and transient ischemic attack patients. (29) The following statements were made regarding perfusion imaging:

- “In acute stroke patients who are candidates for endovascular therapy, vascular imaging (CTA, MRA, DSA) is strongly recommended during the initial imaging evaluation. Perfusion imaging may be considered to assess the target tissue “at risk” for reperfusion therapy. However, the accuracy and usefulness of perfusion imaging to identify and differentiate viable tissue have not been well-established.”

- “Determination of tissue viability based on imaging has the potential to individualize thrombolytic therapy and extend the therapeutic time window for some acute stroke patients. Although perfusion imaging has been incorporated into acute stroke imaging algorithms at some institutions, its clinical utility has not been proved.”

- “It is important to note that perfusion imaging has many applications beyond characterization of the penumbra and triage of patients to acute revascularization therapy. …These applications include, but are not limited to, the following: 1) improving the sensitivity and accuracy of stroke diagnosis (in some cases, a lesion on PCT [perfusion CT] leads to more careful scrutiny and identification of a vascular occlusion that was not evident prospectively, particularly in the M2 and more distal MCA branches); 2) excluding stroke mimics; 3) better assessment of the ischemic core and collateral flow; and 4) prediction of hemorrhagic transformation and malignant edema.”

In 2014, ACR, ASNR, and the Society for Pediatric Radiology published a practice parameter on the performance of computed tomography perfusion in neuroradiologic imaging. (30) The primary indications for CTP imaging of the brain were described as acute neurologic change suspicious for stroke, suspected vasospasm following subarachnoid hemorrhage, and cerebral hemorrhage with secondary local ischemia. Secondary indications included follow-up of acute cerebral ischemia or infarction, to assist in planning and evaluating the effectiveness of therapy, in patients with a
contraindication to MRI, in the setting of acute traumatic brain injury, and intracranial tumors. There were no data to support a role of brain CTP imaging in pediatric stroke.

**American College of Radiology**

American College of Radiology (ACR) Appropriateness Criteria® updated in 2016 provides the following ratings for CT head perfusion with contrast: (31)

- Rating of 5 (may be appropriate) for asymptomatic individuals with structural lesion on physical examination (cervical bruit) and/or risk factors.
- Rating of 5 (may be appropriate) if directly employed in decision making and planning treatment for carotid territory or vertebrobasilar transient ischemic attack; initial screening survey.
- Rating of 6 (may be appropriate) for a new focal neurologic defect, fixed or worsening; less than 3 hours, if CT is used for planning treatment such as thrombectomy.
- Rating of 6 (may be appropriate) for a new focal neurologic defect, fixed or worsening; less than 6 hours. Rating of 5 (may be appropriate) for evaluation for cerebral vasospasm after aneurysmal subarachnoid hemorrhage.
- The ACR also notes that CT stroke protocols combining a brain non-contrast CT, CT angiography, and CT perfusion may produce a relative radiation level of 1-10 mSv, and repeated use of this protocol in an individual patient may result in high radiation exposure to the scalp and eyes.

**Agency for Healthcare Research and Quality**

The Agency for Healthcare Research and Quality (AHRQ) published a report on acute stroke in 2005. (32) This report addressed multiple issues regarding CT perfusion and also angiography in terms of how these modalities affect the use of thrombolytic therapy for acute ischemic stroke. This report indicated that studies with prospective use of CT perfusion and angiography techniques in patient selection for thrombolysis were not identified.

**U.S. Preventive Services Task Force Recommendations**

Perfusion CT imaging is not a preventive service.

**Summary of Evidence**

For individuals with acute stroke who are being evaluated for thrombolysis who receive CT perfusion imaging, the evidence includes non-randomized comparative studies. Relevant outcomes are overall survival, test accuracy, symptoms, morbid events, and functional outcomes. One potential area of benefit is greater individualization of therapy for acute stroke by better defining ischemic areas at risk that may benefit from thrombolysis. Evidence from non-randomized comparative studies suggests that outcomes after thrombolysis are better in patients who have target mismatch on perfusion imaging than in patients without target mismatch, and that patients with target mismatch treated after a 3-hour time window have outcomes similar to patients treated within 3 hours. However, randomized controlled trials (RCTs) are needed to determine whether a strategy employing CT perfusion imaging leads to an
improvement in health outcomes compared with traditional strategies for the treatment of acute stroke. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with acute anterior large-vessel stroke who are being evaluated for mechanical embolectomy who receive CT perfusion imaging, the evidence includes a randomized controlled trial. Relevant outcomes are overall survival, test accuracy, symptoms, morbid events, and functional outcomes. CT perfusion is one of several approaches that have been used in acute stroke to better define viable ischemic tissue and therefore may benefit from mechanical endovascular intervention. Alternative methods of patient selection for mechanical embolectomy have included time from stroke onset, multiphase computed tomography angiography, or ASPECTS score. One RCT showed improved outcomes with mechanical embolectomy when patients were selected based on CT perfusion results. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals with acute stroke who are being evaluated for prognosis who receive CT perfusion imaging, the evidence includes retrospective analysis of data from large prospective studies. Relevant outcomes are overall survival, test accuracy, symptoms, morbid events, and functional outcomes. Retrospective analysis of data from the MR CLEAN and DUST studies found that the ischemic core found on CT perfusion was predictive of functional outcomes. However, analysis of data from the DUST study found no improvement in a prediction model when CT perfusion was added to a basic model that used only patient characteristics and NCCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have suspected subarachnoid hemorrhage and cerebral vasospasm who receive CT perfusion, the evidence includes a prospective study. Relevant outcomes are overall survival, test accuracy, symptoms, morbid events, and functional outcomes. CT perfusion is being evaluated for the diagnosis of vasospasm and delayed cerebral ischemia following aneurysmal subarachnoid hemorrhage. One prospective study showed a qualitative measure of cerebral blood flow to have 93% accuracy for the detection of delayed cerebral ischemia, with lower accuracy for cerebral blood volume. Prospective trials are needed to evaluate whether CT perfusion in patients with aneurysmal subarachnoid hemorrhage leads to the early identification of patients at high risk for vasospasm/delayed cerebral ischemia, alters treatment decisions, and improves health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have brain tumors who receive CT perfusion imaging, the evidence includes a few studies on diagnostic accuracy. Relevant outcomes are test accuracy, symptoms, morbid events, and functional outcomes. For indications such brain tumors, the data on CT perfusion are limited. One study assessed the diagnostic accuracy of CT perfusion to differentiate high grade from low grade gliomas. Prospective studies in an appropriate population of patients are needed to evaluate the sensitivity and specificity of CT perfusion glioma grading, with histopathologic assessment of tumors as the independent reference standard. One prospective study performed ROC analysis to evaluate the diagnostic accuracy of VPCT. This is the first report using VPCT to differentiate gliomas; therefore, replication of these findings in an independent sample of patients is needed. Consistency in the thresholds used is needed. Studies are also needed to show an improvement in health outcomes with
CT perfusion. No recent reports on the use of CT perfusion for the evaluation of brain tumors have been identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**References**


### Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>June 2012</td>
<td>New Policy</td>
<td></td>
</tr>
<tr>
<td>March 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature search, references added and reordered, policy statement unchanged</td>
</tr>
<tr>
<td>December 2013</td>
<td>Update Policy</td>
<td>Policy updated with literature search through July 17, 2013; reference 16 added; “of the Brain” added to title and policy statement for clarification.</td>
</tr>
<tr>
<td>December 2014</td>
<td>Update Policy</td>
<td>Policy updated with literature review adding references 18, 25, 27, and 28. The policy statement is unchanged.</td>
</tr>
<tr>
<td>December 2015</td>
<td>Updated Policy</td>
<td>Policy updated with TEC Assessment (reference 1). CT perfusion considered medically necessary in patients with anterior large-vessel stroke being evaluated for mechanical embolectomy. CT perfusion in other situations remains not medically necessary.</td>
</tr>
<tr>
<td>December 2016</td>
<td>Updated Policy</td>
<td>Policy updated with literature review; references 3, 6, 15, 18, and 30 added; reference 31 updated. The TEC Assessment was not published and has been removed from the reference list. Policy statements unchanged.</td>
</tr>
</tbody>
</table>

### Keywords

Cerebral Perfusion, CT  
Computed Tomography, Cerebral Perfusion

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 2, 2016 and is effective January 15, 2017.

Signature on File

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