Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 11/1/12**
(See policy history boxes for previous effective dates)

Title: CT (Computed Tomography) Perfusion Imaging

Description/Background

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

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). CT perfusion covers limited areas of the brain. Commonly used 16- to 64-slice CT scanners can detect an area of 2- to 4-cm of brain tissue.

On October 8, 2009, the U.S. Food and Drug Administration (FDA) issued an Initial Communication about excess radiation during perfusion CT imaging to aid in the diagnosis and treatment of stroke from one facility. Together with state and local health authorities, the FDA has identified at least 250 patients who were exposed to excess radiation during CT perfusion scans. The FDA has received reports of possible excess exposures at facilities in other states, involving more than one manufacturer of CT scanners. In response, the FDA has provided recommendations for facilities and practitioners and is continuing to work with manufacturers, professional organizations, and state and local public health authorities to investigate the scope and causes of these excess exposures and their potential public health impact. A December 8, 2009 update of this issue is available online at:
http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm185898.htm.

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. Two methods being evaluated are CTA and CT perfusion.

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 FDA for use with a CT system to perform perfusion imaging. The software is being distributed with new CT scanners.

Medical Policy Statement

Cerebral perfusion analysis using computed tomography is experimental/investigational. It has not been scientifically demonstrated to be as effective as conventional testing for the diagnosis of stroke.

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

N/A

CPT / HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

0042T

Rationale

Acute Cerebral Ischemia

At the time this policy was created, the literature focused on technical capabilities and feasibility. A number of retrospective studies indicated that blood flow values obtained using a diffusible gas indicator are accurate and that the flow rates correlate with physiologic changes such as the onset of neurologic deficits. (1) The limited availability of medical-grade Xe gas was another issue with this approach to computed tomography (CT) perfusion imaging. Because of more widespread availability, studies were also being done using non-diffusible tracers, i.e., contrast agents. (2,3) As of 2008, studies were identified that reported on the use of CT perfusion imaging to identify infarcted tissue versus viable tissue (penumbra). (4-7) However, many studies evaluating use of thrombolytic therapy in acute stroke beyond 3 hours of symptom onset were based on magnetic resonance (MR) imaging with perfusion-diffusion mismatching. (8) As Lev commented in an editorial, although many investigators have advocated CT perfusion imaging as a reliable method for detecting both infarct core and penumbra, almost all the major clinical trials aimed at extending the time window for thrombolysis used advanced MR rather than CT imaging for triage. (9) Prospective controlled studies had not been reported that demonstrated that use of perfusion imaging (CT or MR) improved outcomes in patients with acute stroke.

In 2009, the American Heart Association (AHA) Council on Cardiovascular Radiology and Intervention, Stroke Council, and the Interdisciplinary Council on Peripheral Vascular Disease published a scientific statement that included a review of the evidence on CT perfusion. (10) The scientific review determined that:

- Creation of accurate, quantitative CT perfusion has been validated in comparison with xenon-CT, PET [positron emission tomography], and MR perfusion. CT perfusion appears to have greater spatial resolution than MR perfusion, and MR perfusion 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 CT perfusion than with MR perfusion.
- Studies are evaluating various thresholds to predict the upper and lower limits of final infarct size, and outcome prediction studies suggest that CT perfusion 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 to MR perfusion imaging, application of specific CT perfusion thresholds to predict tissue survival or infarction appears promising; however, it is essential that these thresholds be validated in larger patient cohorts for which reperfusion status is known.
- There is increasing but as yet indirect evidence that 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.

A 2011 report compared outcomes of 106 patients with acute stroke who were assessed with multimodal CT (CT/CT angiography[CTA]/CT perfusion) versus a cohort of 262 patients with acute stroke who were assisted without full multimodal brain imaging during a 5-year period. (11) Clinical and imaging data were collected prospectively, and all imaging studies were

assessed by investigators blinded to prognostic data. The two groups were comparable at baseline, with the exception of a greater percentage of patients with a time-to-treatment of greater than 3 hours (28% vs. 16%) and a greater percentage treated with endovascular therapy (26% vs. 11%, both respectively) in the multimodal CT group. Good outcome (modified Rankin scale score $\leq$ 2) at 3 months was increased in the multimodal group compared with controls (adjusted odds ratio [OR] of 2.88) in models adjusted for age, gender, NIHSS, glucose, and treatment delay or modality. Fifty-six percent of patients assessed by multimodal CT had a Rankin score equal to or less than 2 in comparison with 41% of controls (p=0.008). In a sensitivity analysis, multimodal-assisted thrombolysis yielded superior benefits in those patients treated after 3 hours (adjusted OR, 4.48) than for 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 score equal to or less than 2 in comparison with 24% of controls. Mortality (14% and 15%) and symptomatic hemorrhage (5% and 7%m both respectively) were similar in the 2 groups. Randomized trials are needed to establish the value of multimodal CT to assist thrombolytic therapy in acute stroke.

Cerebral Vasospasm

An updated search of the MEDLINE database in 2011 identified a meta-analysis on the diagnostic accuracy of CTA and CT perfusion for cerebral vasospasm. (12) Three studies with a total of 64 patients met the inclusion criteria and contained the appropriate data for statistical analysis. 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.

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. (13) One study compared CT perfusion with conventional MRI in 19 patients. (14) 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. (15) 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. 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.

Ongoing Clinical Trials

A search of ClinicalTrials.gov in April 2011 found one ongoing large observational trial, the "Dutch acute stroke trial (DUST): Prediction of outcome with computed tomography (CT) – perfusion and CT-angiography” to assess whether combined CT perfusion and CT

angiography parameters can predict patient outcome in acute ischemic stroke (NCT00880113). The study will include patients with acute stroke symptoms who present in the hospital within 9 hours of onset of symptoms. Patients who awaken with stroke symptoms can only be included if they went to sleep without any stroke symptoms, and the time from going to sleep until imaging is less than 9 hours. Estimated enrollment is 1,500 patients with completion in December 2011.

Also posted on online at: ClinicalTrials.gov in January 2010 is a study titled "The effect of implementing hyper-acute stroke guidelines on decision-making for or against thrombolytic therapy for stroke in the emergency department" (NCT01050049). The objective of this completed study is to determine if use of multi-modal CT alters the time to decision making for or against use of tissue plasminogen activator (tPA), the time to therapy, and time to transfer from the department. A secondary objective is to determine whether using CT perfusion/CT angiography acute stroke guidelines improves safety by decreasing symptomatic intracerebral hemorrhage and mortality in patients who receive tPA. This study has been completed as of April 2011.

Summary

While CT perfusion appears to hold promise for improving care of patients with various neurologic conditions, including the potential individualization of therapy for acute stroke, randomized clinical trials are needed. In addition, data on CT perfusion for cerebral vasospasm and brain tumors is limited. Because the impact of CT perfusion imaging on clinical outcomes is not known, this technique is considered investigational.

Practice Guidelines and Position Statements

In 2009, the American Heart Association (AHA) issued a scientific statement on imaging of acute ischemic stroke. (10) The statement included the following recommendations regarding perfusion imaging:

Perfusion-Derived Values

Quantitative thresholds of tissue that is dead or destined to die versus tissue that is still living and may be salvageable are the goal of all perfusion techniques. Although the performance of such studies may be considered to identify and differentiate the ischemic penumbra and infarct core, their accuracy and usefulness have not been well established (Class IIb, Level of Evidence B).

Clinical Role of Perfusion Imaging

- The admission volumes of infarct core and ischemic penumbra may be significant predictors of clinical outcome, possibly exceeding the prognostic value of admission NIHSS score [National Institutes of Health Stroke Score] (Class IIb, Level of Evidence B).
- There is increasing but as yet indirect evidence that 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. Together with vascular imaging, these approaches may determine suitability for other therapies such as mechanical clot retrieval and intra-arterial thrombolysis, as well as provide a surrogate marker for treatment efficacy (Class IIb, Level of Evidence B).

The Agency for Healthcare Research and Quality (AHRQ) published a report on acute stroke in 2005. (16) 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.

Government Regulations

National/Local:

There is no national or local coverage determination.

Michigan Department of Community Health:

According to the MDCH Outpatient Prospective Payment System fee schedule, procedure code 0042T is a non covered service.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

PET/CT Fusion

References

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4. Wintermark M, Flanders AE, Velthuis B et al. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. Stroke 2006; 37(4):979-85.
5. Tan JC, Dillon WP, Liu S et al. Systematic comparison of perfusion-CT and CT-angiography in acute stroke patients. Ann Neurol 2007; 61(6):533-43.
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13. Jain R. Perfusion CT imaging of brain tumors: an overview. AJNR Am J Neuroradiol 2010 [Epub ahead of print].
14. Ellika SK, Jain R, Patel SC et al. Role of perfusion CT in glioma grading and comparison with conventional MR imaging features. AJNR Am J Neuroradiol 2007; 28(10):1981-7.
15. Jain R, Ellika SK, Scarpace L et al. Quantitative estimation of permeability surface-area product in astroglial brain tumors using perfusion CT and correlation with histopathologic grade. AJNR Am J Neuroradiol 2008; 29(4):694-700.
16. Agency for Healthcare Research and Quality. Acute stroke: evaluation and treatment. *Evidence Report/Technology Assessment: Number 127* 2005. Available online at: http://www.ahrq.gov/clinic/epcsums/acstrokesum.htm. Last accessed April 2011.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through June 28, 2012, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/09	7/15/09	6/16/09	Joint policy established
7/1/11	4/19/11	5/3/11	Policy reformatted; additional references added.
11/1/12	8/21/12	8/21/12	Routine maintenance; title changed from “Cerebral Perfusion Analysis Using Computed Tomography” to “CT (Computed Tomography) Perfusion Imaging.”

Next Review Date: 3rd Qtr, 2013

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: CT (COMPUTED TOMOGRAPHY) PERFUSION IMAGING

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	Not covered.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.
Blue Cross Complete of Michigan	Not covered.

II. Administrative Guidelines:

N/A