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Is CT Perfusion Ready for Prime Time?

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Detection of Perineural Spread: Fat Suppression versus No Fat Suppression

One could easily argue that, when imaging head and neck malignancy, evaluation of possible perineural spread is more important than identifying the primary tumor or finding metastatic nodes. In almost every case, the clinician has already identified the primary lesion and has made a good estimate of the margins. The location and size of the primary tumor determine the treatment of lymph nodes at least as much as does the imaging assessment. Perineural spread, on the other hand, can be unsuspected and can carry a tumor beyond the region that is to be treated by either surgery or radiation. If the extent of perineural spread is not correctly identified, the patient will likely undergo significant morbidity without hope of cure. Assessment of perineural spread is therefore a key concept in head and neck imaging. The radiologist absolutely must understand the concept and be comfortable with its assessment.

The article by Chang et al in this issue of the *AJNR* presents a series of patients with malignant melanoma exhibiting perineural spread. More specifically, they write that a particular subtype, the desmoplastic melanoma, has a particular propensity for following nerves. Presentation of this material affords an opportunity to examine several points, some controversial, related to perineural spread. By far the most important issue to an imager is how to look for perineural spread and that is the main point of this editorial. At our institution, we avoid fat suppression at the skull base. Before discussing imaging, however, a comment regarding the basic concept and a word about terminology is appropriate as an introduction.

Perineural spread refers to extension of tumor along a nerve. The nerve acts as a conduit carrying tumor a significant distance from the original lesion. As indicated in the article by Chang et al, one must distinguish between perineural tumor and perineural spread. Pathology reports frequently refer to perineural tumor or invasion when describing a primary lesion. The pathologist is identifying tumor in and around nerves at the primary site. Perineural tumor or neural invasion has a significant negative effect on prognosis, correlating with recurrence, but this finding does not necessarily imply tumor leaving the original location of the primary lesion. Emphasizing the term "spread" is important in avoiding this ambiguity.

The term "perineural" leads to confusion regarding the exact location of tumor traveling along the nerve. Each nerve is organized into compartments by several connective tissues. In a medium to large nerve, the fibers are grouped into fascicles or bundles. The perineurium is a condensed fascia surrounding each bundle of nerve fibers. The endoneurial space is the compartment contained within the perineurium. The endoneurium itself is the wispy, looser connective tissue within that space and surrounding individual fibers. A relatively loose fascia called the epineurium surrounds the multiple bundles making up the final nerve. The most peripheral layer may be more compact or condensed, separating the nerve bundles from the surrounding adipose tissue. This more condensed layer has been referred to as a sheath.

There are examples of tumor invading all of the compartments and bordering all of the fascial layers: endoneurium, perineurium, and epineurium. There are examples of the tumor extending along the space between the nerve bundles and the sheath of the nerve in the region of the epineurium. Some tumors do tend to concentrate in the region of the perineurium. Various tumors have a propensity for involving different compartments. Perhaps it is better simply to accept the term and not to dwell on its derivation. It is key, however, to understand that we are referring to tumor selectively traveling along a nerve away from a primary lesion.

Exactly why tumor follows the nerve is also unclear. Various theories have been proposed. Perhaps the nerve represents the line of least resistance forming a natural channel through anatomy otherwise difficult to traverse. Intraneural lymphatics have been suggested as a pathway. Because endothelial cells are not seen bordering the traveling tumor, however, this theory is not accepted. There have always been theories that something in the nerve causes the tumor to grow in the vicinity of the nerve. One such theory has focused on various growth factor binding sites. This is particularly pertinent to the current article, because the desmoplastic variant of melanoma described by the authors has shown strong immunologic staining for growth factor receptor p75 (1). During development, Schwann cells migrate to and along a nerve partly because of an interaction between nerve growth factor and a binding site on the Schwann cells called nerve growth factor receptor p75. Adenoid cystic carcinoma has also (in a very small series) shown affinity for the stain for p75 (2). Perhaps the malignant cells use a mechanism similar to the Schwann cells to invade and then travel along the nerve. More work is needed to define exactly why various malignancies follow nerves, but the fact that they do follow nerves has been clearly established. Adenoid cystic carcinoma from the minor and major salivary glands, lymphoma, melanoma, squamous cell carcinoma, and others have all been identified as having the potential to follow nerves.

The radiologist's goal is to be able to identify the

perineural spread. The responsibility of detection of this phenomenon falls directly to imaging. There may be symptoms, but frequently enough there is no suggestion that a nerve is involved. The radiologist must always examine the neural routes connecting to the primary site. The neural pathway must be assessed through its entire course, not just in the vicinity of the tumor. The neural foramina and their associated fat pads are examined by using CT or more commonly MR imaging. With high-spatial-resolution MR imaging, the actual nerve is often seen surrounded by fat or, within the foramina, surrounded by a small perineural vascular plexus. Obliteration of the fat below a foramen, enhancement of the nerve, or enlargement of a nerve, foramen, or canal is considered evidence of tumor involvement. Alternatively, lack of these positive findings is evidence that tumor has not reached a certain level.

There are differences in opinion regarding the best imaging techniques for diagnosis or exclusion of perineural spread. Many, perhaps most, radiologists prefer MR imaging with fat-suppression techniques to identify the enhancing nerve. I would like to take this opportunity to lobby for an alternative approach. At our institution, we prefer pre- and postgadolinium sequences done without fat suppression to evaluate perineural spread at the skull base. The coronal high-spatial-resolution (512 × 338 matrix, 200-mm field of view) postgadolinium T1-weighted image is particularly useful, showing foramen rotundum, Vidian's canal, foramen ovale, and their respective nerves along with the gasserian ganglion and Meckel's cave. Pregadolinium T1-weighted images show the fat pads through which the nerves approach the neural foramina. Tumor obliterates the high signal intensity of the fat. Indeed, even after intravenous contrast agent administration, tumor is never as hyperintense as fat. With a tight narrow window, one can make contrast-enhancing tumor blend with fat, but with a wider window, the enhancing tumor and fat can be separated. Within the foramina and canals, there is no fat. There may be fat in the osseous medullary space next to the foramen, but not within the foramen itself. With a high matrix and a wide window, the actual nerve can often be identified, size can be measured, and enhancement can be detected. The involved nerve is lighter gray (the "evil" gray) compared with the darker normal nerve. Use of fat suppression can lead to problems in assessing the skull base neural foramina. Susceptibility proves a significant issue, particularly in the area of the sphenoid sinus. If the sphenoid sinus is large, air is immediately adjacent to the foramen rotundum, foramen ovale, and Vidian's canal. The nerve is separated from the air by a very thin plate of bone. The change from air to tissue alters the local field enough to change the resonant frequency very slightly. The change is often great enough to push the water peak into the suppression range of frequency-selective fat-suppression techniques. Suppression of the signal intensity causes the signal void of the sinus to enlarge slightly, or "bloom," obscuring the key foramina. One need only try to visualize the enhancing mucosa along the wall of the sinus to see this effect. With a high-resolution, high-matrix sequence, the nerves are well seen and evaluated without fat suppression. The appropriate imaging approach is a matter of opinion and will depend on the preference of the radiologist. Either the fat-suppression technique or the non-fat-suppressed strategy is acceptable, as long as the radiologist can identify the target foramen and appropriately decide whether or not the nerve is normal or abnormal. If the foramen is obscured and the radiologist cannot reliably make a decision, the examination should be considered incomplete.

When should we look for perineural spread? Certainly we should look for signs of perineural growth in any patient with a known malignancy. We are also responsible for identifying the phenomenon even in patients without a known tumor. There are several situations when that scenario is particularly important.

In any patient imaged for facial paralysis, the study must follow the facial nerve into the parotid gland. We cannot be satisfied with a "brain" study or even a temporal bone examination. The gland should be examined for a tumor, and one should carefully examine the fat pad at the stylomastoid foramen where the facial nerve exits the temporal bone.

A second situation is less obvious but perhaps more important simply because it is so easy to overlook. In any patient referred because of facial pain, the radiologist should look carefully for perineural spread. It is crucial to examine the pterygopalatine fossa, the branch point of V2, for obliteration of fat and for enlargement of the connecting foramina. An even more subtle abnormality originates in the parotid gland. A tumor originating deep within the parotid may not be palpable. The tumor, usually adenoid cystic carcinoma, can grow along the auriculotemporal nerve, a branch of the third division of the trigeminal nerve (3). Passing along the posterior aspect of the mandible, the lesion follows the nerve through the fat just medial to the lateral pterygoid muscle and into foramen ovale. After transiting the foramen, the tumor reaches the gasserian ganglion, the common target of perineural spread along any division of the trigeminal nerve. Involvement of the ganglion affects fibers from the second division of the trigeminal nerve, resulting in facial pain. The clinician may suspect sinus inflammation and order a sinus CT. The radiologist must look carefully at the fat just medial to the lateral pterygoid muscle and at the tissue wrapping around the posterior aspect of the upper mandible (condylar neck and ramus). Abnormal soft tissue obliterating the fat planes in this area may be the only suggestion of this most subtle, but potentially devastating, disease process.

In summary, the concept of perineural tumor spread is a crucial one when interpreting images of the head and neck. The radiologist absolutely must be able to follow and evaluate the neural pathways when imaging patients with known head and neck cancer and must know the key landmarks for detecting or excluding perineural spread. Strategies for imaging

can vary but at least consider using non-fat-suppressed high-spatial-resolution images for this crucial evaluation. The habit of examining the key landmarks even when evaluating imaging findings in patients without known cancer will allow the radiologist to make a real difference in patients with subtle disease.

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Is CT Perfusion Ready for Prime Time?

Depends on whom you ask. Technically, CT perfusion (CTP) of the brain is relatively easy to perform on the newest generation of ultrafast CT scanners. Generating meaningful images and data and then interpreting these data in a clinically relevant manner is a more difficult task. Two groups of neuroradiologists seem to have emerged: 1) the CTP cheerleaders, who believe CTP could (or even should) be a part of routine brain imaging, especially in the acute stroke setting, and 2) the CTP cynics, who are still waiting for more proof to be convinced that CTP will change the workup of patients with cerebrovascular disorders.

As occurs with most new neuroradiologic techniques, the avalanche of articles championing CTP has officially begun. Most of the early articles discussing and generally advocating this technique have appeared in vendor-supported journals (vendors like new techniques for obvious reasons) or as a part of "advanced imaging of stroke" review articles. (I, too, am not immune from writing such articles [1]). In attendance at the 2003 American Society of Neuroradiology meeting in Washington, DC, were neuroradiology luminaries preaching the gospel of CTP as a holy grail in the brain attack workup of stroke patients. In addition to review articles, scientific studies of CTP have begun to appear in peer-reviewed journals, and several groups have begun to employ CTP on a routine clinical basis. These groups have reported their preliminary sensitivity and specificity of CTP compared with other techniques, such as MR diffusion and perfusion (2), and have attempted to establish the clinical utility of this technique (3, 4). In addition, methodological advances are creeping into the literature (5). These studies usually have high physician and technologist person-hours invested into creating quality CTP images with highly trained people interacting with the data. It is with this backdrop that Fiorella et al's article "Assessment of the Reproducibility of Postprocessing Dynamic CT Perfusion Data" appears in the current issue of the *AJNR*.

Fiorella et al take a slightly different, yet very practical, approach to evaluating this new technique. Rather than looking at this technique with the best possible product achievable and then evaluating the utility of the technique, they took a stab at evaluating the clinical practicality of CTP. Specifically, the au-thors aimed to assess the reproducibility of the postprocessing step in the analysis of CTP data in a group of 20 patients. Three technologists measured four variables: arterial input function (AIF), venous function (VF), preenhancement interval (PREI), and postenhancement image (POEI). The other potential variables, such as region of interest location for the cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) measurements, were removed by the fact that identically sized predetermined locations were already chosen by a neuroradiologist. Despite a "technologist outlier," the authors showed high intraclass and interclass correlations for the calculated CBV, CBF, and MTT values. Also, the AIFs, VFs, and PREIs chosen by the technologists were similar. The POEIs, however, were often markedly different, leading to differences in the appearance of the CTP maps. Thus, the within-subject standard deviations actually showed clinically significant levels of variability within the maps. The authors, therefore, conclude that, although there is high correlation between region-of-interest measurements in the CTP maps, the degree of agreement may not be sufficient to allow the use of quantitative values in the clinical practice, but that postprocessing parameter optimization will naturally reduce the variability observed in this study.

Of course, such conclusions have important implications to our clinical practice. This study attempts to mimic everyday practice in which a technologist will undoubtedly be the interface between the data acquisition and image analysis. In most clinical centers, it is just not practical to have only the neuroradiologists perform all of the data manipulations. Fiorella et al know this and appropriately remove the neuroradiologist from the postprocessing step. They point out that the postprocessing techniques must be reproducible across technologists in order for the technique to have clinical practicality.

So the question remains: is CTP ready for prime time? Without question, CTP provides the clinician with more knowledge about the underlying perfusion and cerebrovascular status of the patient. The idea of using perfusion as a tool to evaluate the brain is not a new concept. It really got off the ground with MR imaging, first by using bolus gadolinium injection and

later arterial spin labeling techniques. In fact, diffusion-perfusion mismatches were touted several years ago as possibly being the diagnostic tool that identifies the holy grail of stroke imaging—the ischemic penumbra. Although it was possible to perform MR perfusion relatively easily, it was (and is) still not clear which perfusion images should be evaluated: the blood flow images, the blood volume images, or the MTT images. Also, time to peak and other summary parameter images could be created. Another question also arose about whether quantified cerebral blood maps were necessary or whether qualitative maps suffice. Such questions were never fully answered when CTP techniques emerged and allowed a more practical technique in the emergency room setting.

CT affords the opportunity of one-stop shopping in the emergency room setting, and because "time is brain" in the acute stroke setting. Practically speaking, CT definitely has an advantage over MR imaging. A routine CT, CT angiography, CTP protocol may ultimately prove to be the protocol in most centers, and such a protocol would allow a rapid assessment of the anatomy, vascular patency, and regional hemodynamic status on an individual basis. Thus, one can easily envision a CT protocol that might guide clinicians in the early stages of an infarct rather than simply basing decisions on population studies. As already mentioned, some centers are already using such a protocol to stratify patients into different treatments.

As Fiorella et al show in their study, however, there are some inherent problems with the CTP technique, and each facility must attempt to attain uniformity in performing these studies. Their article represents a necessary step along the pathway of critically evaluating CTP as a potential diagnostic tool.

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