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The Four Ps of Acute Stroke Imaging: Parenchyma, Pipes, Perfusion, and Penumbra

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Neuroimaging and Cartography: Mapping Brain Tumors

Cartography: The art or technique of making maps.

Map: A representation, usually in a plane surface, of a region. To plan or delineate in detail, to explore or make a survey.

Although MR images are currently of exquisite resolution, as neuroradiologists we all acknowledge that confidently mapping the margins of primary brain tumors is very difficult. Malignant gliomas tend to extend beyond their enhancement into areas of high T2 signal that most of us initially assume to represent edema. This behavior is typical of primary gliomas, and at our institution, if proton MR spectroscopy (MRS) shows elevated choline (Cho) outside of the area of enhancement, we generally nearly always exclude the diagnosis of a solitary metastasis (these are well-marginated lesions without neoplastic infiltration of edema). As neuroradiologists, our primary role is that of mapping the extent of a tumor and then predicting the histologic findings. The former is important because the success of many current and future therapies will depend on it. Currently, the extent of the initial research based on information obtained from imaging studies is still the factor that contributes the most to the patient's prognosis (1). Apart from MR imaging, what can we do to map tumors?

Magnetization transfer rates (MTR) show higher values in higher-grade gliomas than in edema. Radiation necrosis shows low MTR but in a similar range as tumors (2). Thus, MTR cannot be used to map treated tumors. We attempted to use apparent diffusion coefficients (ADC) to separate tumors from edema and normal tissue (3). In our experience, ADC could not reliably distinguish between tumor and edema. It is possible that diffusion tensor imaging will show altered anisotropy in areas of tumor infiltration, but preservation of anisotropy in regions of edema where the white matter tracts are not destroyed. MRS is yet another technique that may be used to map tumor margins. Up until now, the major limitations of MRS are that 1D and 2D techniques suffer from partial averaging effects and limited spatial resolution.

In this issue of the *AJNR*, Dowling et al (page 604) take an important step in establishing MRS as a promising technique to map tumor extension. They obtained 3D MR spectra in 28 brain tumors and correlated the histologic findings from specific sites to the corresponding voxels. From their results we learn the following:

1. If *N*-acetyl aspartate (NAA) is normal, the tissue is normal. Conversely, abnormal NAA correlates with abnormal tissue regardless of the underlying histologic findings.
2. When a lesion contained a Cho level that was larger than NAA and larger than normal Cho, tumor was always present.
3. The level of Cho correlated with the percentage of tumor in the specimen.
4. Non-detectable to near-normal levels of NAA and Cho were seen in areas of gliosis/necrosis.
5. Areas of similar appearance and enhancement may show different spectra and different histologic findings.

On the basis of these data, it seems that MRS is a worthy method that may be used to map tumor margins, identify areas with the highest malignancy, and serve to guide biopsy, identify residual tumor after surgery, and identify recurrent tumor after treatment.

Despite these exciting possibilities, the study by Dowling et al also has some limitations. Their data were correlated retrospectively, and it is not clear if in an a priori analysis of MRS will perform similarly (although I have the impression that it will). The studies loaded into the imaging-guided surgery device were not the same as those used to guide the placement of the MRS grid. Indeed, in some patients, considerable time elapsed between biopsy and MRS; thus, the correlation between these two may not be entirely accurate. Some authors believe that neuronavigation systems do not identify deep tumor reliably (4). This is attributable to deformation of the brain after craniotomy and shifting of the structures. It is, thus, possible that brain shift may also have introduced some degree of sampling error in Dowling's patients. Not all biopsies were obtained from the most abnormal-appearing spectra; therefore, the histologic grade of some lesions may have been underestimated. The authors clearly point out that volume of tissue obtained comprises only a small percentage of the size of the MRS voxels. At present, the lack of commercially available 3D MRS packages also limits the widespread use of the technique. The authors correctly point out that MRS and MR imaging may be performed in one setting. It is unclear if the MRS studies were guided by and obtained after contrast administration. They observed that Cho levels tended to be higher in tumors grade II and III but slightly lower in glioblastoma multiforme. This is counterintuitive and is probably related to partial volume effects.

In very few years, MRS has matured and become clinically feasible in most MR units. Because many other techniques, such as MTR and ADC maps, are limited in the mapping of brain tumors, careful prospective studies using MRS are needed. The study of Dowling et al supports my impression that MRS provides good tissue characterization and is very helpful in the mapping of brain tumor margins. We need to incorporate the information obtained from MRS into imaging-guided surgery devices to obtain full benefit of these exciting techniques. Detailed mapping of tumor margins are needed before robotic brain surgery becomes clin-

ically feasible. Mapping of tumors will also he critical for the placement of intralesional chemotherapy, delivery of viral vectors or stem cells, and guiding of stereotatic radiosurgery. Because the brain cannot adequately remove necrotic detritus, mapping of necrosis is also important. Identification of exact locations of brain damaged by tumor may lead to implantation of neuronal and glial precursor cells, which may minimize deficits. It seems that, as neuroradiologists and brain cartographers, we are moving in the right direction.

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MRS Imaging of Gamma Knife Treatment for Gliomas: From Metabolite Ratios to Therapeutic Rationale

In this issue of the *AJNR*, Graves et al (page 613) describe serial 3D proton MR spectroscopic (MRS) imaging and conventional postcontrast T1-weighted MR imaging in 18 adult patients with gliomas prior to and after MR-targeted gamma knife radiosurgery. Their main results summarized below were in general agreement with many prior single-voxel MRS studies in that increased choline (Cho) and decreased *N*-acetylaspartate (NAA) were evident in areas of recurrent tumor, whereas Cho was reduced in patients who responded to therapy and who underwent stable follow-up MR examinations. The authors adopted a rigorous definition with a contralateral brain reference for tumor-suggestive MRS voxels as those in which normalized Cho (nCho) was elevated and normalized NAA (nNAA) was decreased by at least 2 SD of the corresponding normal metabolite distribution. As experience increases, analyses of sensitivity, specificity, and area under the receiver-operator characteristic curve for this definition of tumor-suggestive MR spectra, and for threshold (cutpoint) values of nCho and the Cho/NAA ratio in gamma-knife treated cases, with histologic correlations, would be enlightening.

Changes at 1 and approximately 5 months in the median values of nCho, nNAA, and the Cho/NAA ratio within the gamma knife target were tabulated for patients with radiographic (MR) outcomes compatible with stable disease, local recurrence contiguous with the target, or recurrence remote from the target. A trend toward reduced median nCho was seen within the gamma knife target in the first postoperative month in all outcome groups, and at 5 months for patients with stable disease and local radiographic recurrence. In light of prior reports regarding changes in Cho and NAA in irradiated gliomas and in normal brain, and of radiobiological data regarding normal glial and neuronal radioresistance, the authors suggested that changes in nCho and nNAA levels within the gamma knife target could reflect changes in glial and neuronal cell densities after cell death induced by high-dose radiation. Similarly, a trend toward a progressive drop in the median Cho/NAA ratio within the gamma knife target from baseline to 5 months postoperatively was observed in the stable and in the remote recurrence groups. An explanation for this serial fall in Cho/NAA suggested by the authors may be a corresponding progressive drop in the fraction of viable neoplasm as a consequence of high-dose radiation, perhaps of greater clinical significance than individual nCho and nNAA levels. Although confirmation of these hypotheses with scheduled serial biopsies in patients with glioma would be impractical, serial biopsies and direct correlation of nCho, nNAA, and Cho/NAA with: 1) histologic measurements of tumor fraction, necrotic fraction, and mitotic index; 2) markers of apoptosis and angiogenesis required for neoplastic growth; and 3) levels of oncogene and suppressor expression may be insightful in future studies with animal models.

Regarding radiographic recurrence, high values of median Cho/NAA were evident in regions of new contrast enhancement for both local and remote recurrence groups at 1 and 5 months postoperatively. Biopsy confirmed residual/recurrent glioma in six patients with local or remote radiographic recurrence. Presuming that gliomas in the patients who underwent biopsy were most refractory to treatment, it is of interest that Cho/NAA values on final follow-up spectra were all greater than median 5-month postoperative values for new regions of contrast enhancement. The observation that in nine cases an MR spectroscopic abnormality preceded a coincident increase in postcontrast enhancement by 1 to 2 months suggests an expanding role for MRS in postoperative monitoring.

Although not stated explicitly in the article, the

authors suggest definitions for metabolic outcomes to therapy in their narration of the number of patients in whom at least one tumor-suggestive voxel was found over the 3D MRS field of view. A possible definition for a metabolic response to gamma knife therapy would be the absence of any tumor-suggestive MRS voxels in a volume of interest, either within the target or the surrounding brain. Conversely, metabolic residual/recurrent disease could be defined as the presence of at least one tumor-suggestive voxel in a volume. Two questions arise relative to the metabolic response of gliomas to gamma knife irradiation, given the apparent conceptual paradox of a focal irradiative treatment for an often refractory and diffusely infiltrating neoplasm. First, speaking to the effect of gamma knife irradiation on the targeted tissue only, one may ask, ''Does the number of patients with no tumor-suggestive MRS voxels within the MR-derived target at final follow-up differ from that at pre-gamma-knife baseline?'' The reported data suggest a trend at final follow-up toward fewer patients with at least one tumor-suggestive voxel inside the gamma knife target (11 vs four patients). With a larger sample size, one may consider a contingency table with mutually exclusive states (metabolic response vs metabolic residual/recurrence) in the rows (baseline pre-gamma-knife) and columns (final follow-up) amenable to analysis with McNemar's matched χ^2 method that may demonstrate a significantly improved metabolic outcome within the target.

Speaking to a possible lack of metabolic response to gamma knife irradiation outside of the MR-derived target, one may ask an analogous second question, ''Does the number of patients with no tumor-suggestive MRS voxels outside of the MR-derived target at final follow-up differ from that at pre-gamma-knife baseline?'' The reported data suggest a similar number of patients with metabolic residual/recurrent disease outside of the target at pre-gamma-knife baseline and final follow-up (10 vs 11 patients). If contingency tables or other analyses were to demonstrate a significant metabolic response within, but no change outside of, the MR-derived target, on average, a logical extension might be to combine MRS and MR findings in the formulation of the gamma knife target, as was done with Graves et al's patient 13. Similar analyses may prove insightful for necrosis-suggestive MRS voxels determined with lipid/lactate resonances.

The many strengths of Graves et al's article include: high clinical relevance for medical centers conducting or contemplating a gamma knife service; a heterogeneous study population with respect to glioma type, grade, and prior therapy typical of recruitment into emerging treatment techniques; flexible and reproducible lesion sampling with small MRS voxels localized in three dimensions; gamma knife–treating physicians blinded to MRS results to reduce study bias; and straightforward definitions of MRS tumor-suggestive voxels and radiographic response to gamma knife irradiation. The few limitations of their article include: a small study sample that precluded statistical analyses to confirm or refute significant changes after radiosurgery in metabolite levels both within and outside of gamma knife targets, and both within (intra-) and between (inter-) radiographic outcome groups; unavailable post-gamma-knife histologic outcome for 12 of 18 patients; and unreported (or unreferenced) information regarding patient tolerance and technical success of combined MR and 3D MRS examinations.

As more patients are recruited, subgroup analyses may suggest different optimal gamma knife targeting algorithms or doses for patients with different histologic grades of glioma, or for those who have received prior cytotoxic therapy. Finally, further studies might extend the reporting of other outcome measures such as survival curves, and perhaps perform randomization to study arms that include or exclude gamma knife irradiation.

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The Four Ps of Acute Stroke Imaging: Parenchyma, Pipes, Perfusion, and Penumbra

Stroke imaging and intervention are advancing at a dramatic and welcome pace. Triage of acute stroke patients and choice of treatment are increasingly driven by advanced imaging findings. The fresh perspective of new imaging techniques like fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging help us rediscover basic principles of stroke pathophysiology. Getting back to these basics lets us analyze and reorganize the imaging approach so that each critical component in the ischemic process is assessed.

In this issue, Maeda et al (page 632) report that focal intravascular abnormalities are commonly seen on FLAIR sequences in acute stroke patients. Their 11 patients were studied by both FLAIR and diffusion-weighted images within 6 hours of symptom onset. All proved to have acute infarctions: 10 of 11 already had parenchymal changes on diffusion-weighted images at baseline, and the other case manifested similar findings a few days later. The central finding was that eight of 11 cases also showed abnormal intravascular signal on FLAIR

images in the arterial territory leading to the infarcted parenchyma shown by diffusion-weighted imaging. In one case, a subtle intravascular abnormality was even seen by use of FLAIR before diffusion-weighted imaging showed positive findings. In the three cases with negative imaging findings, the vessels affected were probably too small to see. This article adds to the growing literature attesting to the value of FLAIR in the evaluation of stroke, already known to be helpful for detection of subarachnoid hemorrhage and for non-acute ischemic lesions adjacent to spinal fluid spaces (1, 2). How often this intravascular sign might be seen as a false-positive finding, such as an artifact or slow flow (but not frank ischemia), is left for future studies.

Maeda et al's undoubtledly useful observations about vascular signal changes in acute stroke should come as no surprise. Although acute imaging has traditionally focused on damage to the end organ, the brain, findings in the brain parenchyma are really the end result of a predictable chain of vascular events. When a vessel becomes occluded, and collaterals are insufficient, this leads to a perfusion defect. If the perfusion defect is of sufficient degree and duration, infarction will occur. This sequence of events leading up to brain infarction can be organized into a few critical steps, and new imaging techniques stand ready to assess each of these critical components.

One practical way to help organize and recall each of the key steps is to remember the four Ps of stroke: parenchyma, pipes, perfusion, and penumbra. Consideration and measurement of each of the four Ps, in their correct order, are necessary to understand the cause and potential treatment options for stroke in a particular patient. Comprehensive neurovascular imaging protocols using CT or MR imaging can now measure each of these 4 Ps within minutes after the patient arrives at the hospital. And each of the Ps has its own imaging story to tell.

Parenchyma

The first task of imaging is to divide the strokes into ischemic (85%) or hemorrhagic (15%) subtypes. Distinction of hemorrhage versus infarction is the initial critical branch point in acute stroke triage, and directs care toward medical therapy or tailored intervention such as endovascular aneurysm coiling or thrombolysis. Hemorrhage is most efficiently excluded by CT, but can also be reliably assessed using MR imaging, which includes both T2*-weighted and FLAIR sequences. Parenchymal ischemic changes can be detected in most patients within several hours by either CT or routine MR (T2-weighted or FLAIR) sequences. But by far the most sensitive way to detect acute infarction is through diffusion-weighted imaging, which is able to clearly show ischemic changes beginning within minutes to a few hours after symptom onset (3). The novel tissue contrast mechanism of diffusion-weighted imaging and its ''light bulb'' bright signal of infarction make it a robust and reliable method for anyone on the stroke team. Diffusion-weighted imaging interpretation does not require the detailed scrutiny required of the intravascular FLAIR findings reported by Maeda et al. With increasing stroke awareness, many more patients are being seen in the first minutes to hours after stroke onset. At these time points, a positive diffusion scan usually means infarction has already occurred, but reversibility of diffusion defects has been seen in children and after thrombolysis. In the future, sodium MR imaging may give a firmer prediction of absolutely dead tissue versus likely infarcted brain.

Pipes

Stroke begins as a vascular event on either a large or small scale, and the ''pipes'' of this mnemonic refer to the large arteries (or veins) ultimately causing either hemorrhage or infarction. The ''pipes'' seen by imaging are grossly visible vessels on the order of 0.5 mm or larger—the aortic arch, carotid and vertebral vessels of the neck, the major branches of the circle of Willis, and the proximal cortical branches. Identifying a lesion in the ''pipes'' has important therapeutic implications for understanding the source of thrombi or emboli, identifying sites for potential thrombolysis, and assessing gross collateral flow patterns. On CT scans, we have some indirect signs to assess disease in the ''pipes'', such as the hyperdense artery sign (thrombus), and some direct methods, such as CT angiography (vessel narrowing or occlusion). MR imaging has a richer set of signs related to the ''pipes'': loss or alteration of intravascular signal (flow) voids (4), stasis of gadolinium in slow-flowing territories (5), and loss of flow-related enhancement on MR angiography. Maeda et al's finding of intravascular high signal on FLAIR images is a natural extension of these well-known MR concepts—ie, lack of flow voids and presence of either intravascular thrombus or very slow flow, leading to high arterial signal.

Perfusion

The third P, perfusion, indicates the sum total cerebral blood flow arriving at a particular brain region at a given moment in time, both via normal routes and recruited collaterals. It is not sufficient to know at what level the ''pipes'' are occluded: it is the individual variation in collaterals, vascular autoregulation, and resulting net perfusion that means brain survival or infarction. An internal carotid or middle cerebral artery occlusion in one patient may be an incidental finding, provided there are good collaterals; but in the next, it may lead to a devastating or fatal infarction. The difference lies in the time course of occlusion and the potential collateral pathways, not the site of vessel occlusion

per se. Single-photon emission CT, xenon CT, CT perfusion, and perfusion-weighted MR imaging all offer the opportunity to noninvasively assess this component (6).

Penumbra

The fourth P, penumbra, is ultimately the most important in ischemic stroke, and is the focus of all the preceding Ps. One working definition of the penumbra is brain tissue that is ischemic but not yet infarcted, and is therefore at risk for further damage unless flow is rapidly restored. Although present treatment methods cannot be expected to reverse infarction that has already occurred, detection of a perfusion-diffusion mismatch gives us a realistic target for potential intervention (7). The key to detection of the penumbra is not based on a single imaging feature, but by integration of all three of the preceding Ps: the site of vessel occlusion (the pipes), the extent and degree of oligemia at that moment (perfusion), and the mismatch between this perfusion defect and the brain already infarcted (parenchyma). New imaging observations such as those shown by Maeda et al help us recognize these sometimes subtle but critical signs in the four-P stroke pathway so that appropriate therapy can be undertaken.

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Enhancing Our Understanding of Multiple Sclerosis: Tracking Contrast-enhancing Plaques with MR Imaging

Contrast enhancement in the brain of patients with multiple sclerosis (MS) is known to be very sensitive in detecting acute, inflammatory MS plaques. It has been reported that contrast-enhanced MR imaging shows active new lesions four to 10 times more frequently compared with clinically defined relapses. Despite this, there is a paucity of literature on the natural history of enhancing new brain lesions. Thus, the expected time course of development and subsequent regression of enhancing plaques is poorly understood. In the report by He and colleagues in this issue of the *AJNR* (page 662), the researchers attempt to broaden our understanding of the longitudinal evolution and morphology of enhancing MS plaques. But, why is it important to understand the natural history of contrast-enhancing lesions?

The presence of enhancing lesions in the brain of patients with MS has great significance for several reasons. First, in the imaging evaluation of patients presenting with symptoms for the first time, the presence of an enhancing new lesion may help to establish dissemination of lesions in time; a major criteria for diagnosis of MS. Tracking of enhancing lesions over time may also help to document disease activity and thus, aid in treatment planning or in determining response to therapy. Contrast-enhanced lesions can also help in diagnosing the most likely etiology when the imaging appearance is ambiguous, such as when there is a question between possible tumor versus a tumefactive MS lesion. In the latter example in particular, knowledge of the expected time of resolution of enhancement is of primary importance. Finally, contrast-enhanced MR imaging provides a major focus of analysis for testing of new drugs or other proposed new therapies for MS. In fact, the United States Multiple Sclerosis Society Task Force has recommended that T2-weighted and contrast-enhanced T1-weighted sequences be used as primary measures of efficacy in clinical treatment trials of new MS therapies because of the documented sensitivity of these techniques for showing progression of structural brain disease in MS (1).

He and colleagues report their analysis of a retrospective series of 25 patients in whom they identified 301 new enhancing lesions. Of these lesions, 93% disappeared within 6 months. Only seven lesions (2.3%) showed persistent enhancement in excess of 6 months. Time course analysis in the remaining 4.7% of enhancing lesions was deemed indeterminate, because the follow-up interval between successive scans was greater than 6 months. Thus, the authors conclude that enhancement in MS plaques resolves within 6 months in the overwhelming majority of lesions. This is potentially

important documentation and supports observations from several prior reports. However, these results should be scrutinized carefully. From a casual reading of this report, one might infer that the overwhelming majority of enhancing MS plaques persist for a prolonged period, up to 6 months, before normalizing. But is this really the case?

The present study does not evaluate a sufficient number of time points between onset of enhancement and 6 months to determine how many plaques resolve in less than 6 months. To try to address this important question one must refer to other reports from the literature. Studies by McFarland et al (2) and Simon et al (3) (both of which He and colleagues also reference in their report) have suggested that most enhancing MS lesions in the brain characteristically undergo more rapid changes over periods of days to weeks. This time course and pattern fits with our clinical experience and implies that one can generally use a relatively short follow-up interval of 4 to 6 weeks to look for resolution or significant decrease of enhancement in questionable cases of MS. In a study by Smith et al (4), approximately 75% of enhancing lesions disappeared in less than 1 month, whereas 20% continued to enhance for greater than 1 month. Only a small minority (5%) showed persistent enhancement at 3 to 4 months. It must be pointed out that He does address this more rapid evolutionary time course of enhancing plaques and cites the study by Harris et al (5) in their discussion that showed 95% of new enhancing lesions normalized within 8 weeks of onset. My concern is that this fact might be overlooked by a casual reading of He et al's report, which emphasizes the smaller proportion of enhancing plaques that persist. Additionally, in this same series reported by Harris et al, no lesions continued to enhance after 16 weeks. Therefore, I do agree with the present report that it is important to document the fact that there is a measurable (although a minority) number of patients who demonstrate persistent contrast enhancement up to and, on rare occasions, in excess of 6 months.

Because of the broad range of time intervals and variable numbers of sequential MR images used in many MS studies, the statistics can often be confusing. This is not necessarily the fault of the authors, however. Nearly all of the studies on which these natural history statistics are based are retrospective in nature. Detection of enhancing lesions in MS is both technique- and dose-related. In many studies, including this one, there has not been a prospective attempt to incorporate natural history analysis and time course of enhancement in the study design. Thus, they lack uniformity in the intervals between successive MR imaging studies. There may also be great variability in the MR imaging techniques, in the patient population selection (relapsing remitting disease versus secondary progressive disease versus primary progressive MS), and in the contrast dose and the time interval between injection and imaging. The most valuable data regarding natural history of enhancing lesions as well as of T2 lesions comes from the early studies evaluating new drug therapies, including interferon beta-1b and interferon beta-1a. These were performed with rapid serial imaging in placebo-controlled (ie, untreated) patient populations. It is unlikely that new natural history studies of enhancing plaques in untreated MS patients will be done since there are now multiple FDA-approved drug regimens available for treatment of MS. Many appear efficacious, and it would therefore be unjustified and unethical to withhold treatment to perform such a study.

Thus, in view of the constraints that limit our ability to analyze the natural time course of contrast enhancement, this study does provide important documentation and useful information about resolution of contrast enhancement in MS plaques. This is a time-consuming study involving retrospective review of 140 MR examinations with many unavoidable variables and tracking of over 300 new enhancing lesions across serial studies. He and colleagues are to be commended for performing their retrospective analysis.

It is also important to emphasize another major point that He et al make in their report. Namely, that one must be aware that lesion activity and progression of MS disease are not limited to definition of contrast enhancement. Despite the fact that enhancing MS plaques are sensitive in detecting new, active lesions and form a major imaging marker for determining response to therapy or efficacy of new drugs; much activity is taking place that is not necessarily defined by enhancement alone. Although not perfect, contrast-enhanced MR imaging is still very valuable as a diagnostic tool and is far more sensitive than is the clinical examination alone in defining disease activity and predicting progression. Nevertheless, the clinical radiologist should understand the limitations and controversies surrounding enhancing lesions. Studies have shown good correlation between presence and number of enhancing lesions and the occurrence of clinical relapse. However, other studies have shown weak correlation between enhancing lesions and disability or impairment at 1 and 2 years as measured by Expanded Disability Status scores (6). Thus, studies of T2 lesion burden, magnetization transfer changes, and MR spectra remain important research tools that are essential for continuing our understanding and evaluation of multiple sclerosis.

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