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CT Perfusion of Head and Neck Cancer: Why We Should Care versus Why Should We Care!

S.K. Mukherji and J.A. Castelijns

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the inability of conventional MR imaging measures to quantify the extent and to define the nature of MS tissue damage. These techniques, including T1 and T2 relaxation times (RT), magnetization transfer (MT) MR imaging, diffusion tensor MR imaging, and proton MR spectroscopy, allow us not only to grade the severity of damage in macroscopic T2-visible lesions, but also to detect and grade subtle damage in regions with normal signal intensity on conventional dual-echo scans. At present, only a few studies have applied such techniques to try to define the in vivo MR correlates of DAWM in patients with MS.[2-4] These studies have demonstrated consistently that DAWM abnormalities are somewhat in between those measured in macroscopic T2-visible lesions and those seen in the NAWM, in T1 and T2 RT,[4] fractional anisotropy (FA),[4] and MT ratio (MTR).[2,3] So far, there has been no attempt to define DAWM features in patients with MS with a multiparametric, quantitative MR imaging approach.

Against this background, the study by Vrenken et al,[7] published in the current issue of the *American Journal of Neuroradiology*, represents an important step forward, because it applies a set of quantitative MR imaging techniques, likely characterized by a good specificity toward the possible pathologic substrates of MS, to assess the extent of tissue damage associated with DAWM. This might ultimately lead to the identification of additional useful surrogate markers for in vivo monitoring of MS evolution and treatment efficacy.

In this study, the authors wished to characterize, by using a region-of-interest analysis, DAWM abnormalities in 17 patients with chronic MS by combining T1 RT, MTR, FA, and mean diffusivity (MD). It is remarkable that they also explored differences in these previous quantities between patients with secondary-progressive (SP) and primary-progressive (PP) MS. Consistent with previous studies,[1-4] DAWM values were intermediate between those of the NAWM and those of T2-visible lesions when the whole sample of patients was considered.

The most intriguing finding of this study is, however, that related to the analysis of DAWM changes in the 2 progressive clinical phenotypes of the disease. Such an analysis revealed that T1 RT and MTR changes in the DAWM from patients with PPMS were less pronounced than in patients with SPMS. Several studies compared the extent of brain involvement between patients with SPMS and PPMS[8-10] by using different quantitative MR-based techniques and assessing different tissue compartments (ie, lesions, NAWM, gray matter). In general,[8,10] albeit not always,[9] these studies detected more severe abnormalities in patients with SPMS than in patients with PPMS. Most of these previous studies, however, applied a histogram-based approach to derive MR-quantities from a large part of the brain (eg, the whole WM), which also included the so-called DAWM and, hence, were unable to provide specific pieces of information on the extent of damage occurring in the DAWM.

Although it is not possible to draw definitive conclusions from a single study in which a snapshot of an heterogeneous process that is dynamic with time has been obtained, the results of the present study are important because they suggest that, compared with patients with SPMS, patients with PPMS not only have fewer and smaller T2-visible lesions,[11] as well as less severe NAWM damage, but they also have milder pathologic changes in the DAWM. If confirmed by other studies, possibly with larger patient samples, this finding would indicate that the possible explanation for the severity of clinical disability typically observed in patients with PPMS is likely because of spinal cord damage[8,12] and/or inefficient cortical reorganization,[13,14] rather than the extent of brain structural damage.

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M. Filippi
M.A. Rocca
Neuroimaging Research Unit
Institute of Experimental Neurology
Division of Neuroscience
Scientific Institute and University Ospedale San Raffaele
Milan, Italy

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EDITORIAL

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CT perfusion (CTP) provides the unique ability to noninvasively quantify the microvascular blood flow of tissue. Most neuroradiologic applications have been focused on brain perfusion with specific emphasis on stroke, vasospasm, and

cerebrovascular reserve. There have also been several oncologic investigations suggesting that CTP parameters of blood flow (BF), blood volume (BV), mean transit time, and capillary permeability (CP) may be beneficial in assessing both intracranial and extracranial neoplasms.[1-5] Early reports have suggested that head and neck squamous cell carcinoma (HNSCC) with elevated BV has a greater likelihood of complete response when treated with nonsurgical organ-preservation therapy (NSOPT).[4] Other studies have suggested that serial reductions in BV and BF provide an objective and quantitative method of identifying tumors that have initially responded to neoadjuvant chemotherapy.

In the March issue of the *American Journal of Neuroradiology*, Šurlan Popovič et al[6] and Bisdas et al[7] present 2 important investigations, which substantially add to our understanding of the ability of CTP to predict "up-front" response to NSOPT and play a possible role in treatment monitoring. In the first article, Šurlan Popovič et al suggested that certain pretreatment CTP parameters (BF and CP) are predictive of local control with NSOPT and introduced the concept of BV/BV mismatch for helping predict response. In the second article, Bisdas et al demonstrated that serial reductions in BV during treatment were predictive of response, whereas progressive elevations in BV were identified in nonresponders and are consistent with previously published reports.

The next obvious question is "so what?" or "why should we care?" To answer these questions, we must first understand how treatment regimens for HNSCC and other malignancies are determined. The preferred treatment options for most malignancies are based on population estimates that have resulted in the best local control and cure rates for the population as a whole. A patient can then attempt to assess his or her own probability of cure from the various treatment choices on the basis of these population estimates. Thus, the individual treatment regimens are essentially "fixed" regimens, and one can argue that the patient is the "variable," often leading to the saying "the patient failed therapy" as opposed to "the treatment failed the patient."

We have learned the hard way that the best chance to cure cancer is to eradicate the tumor on the initial treatment attempt. The likelihood of long-term cure in a recurrent tumor or one that never completely responded is poor, with reported salvage rates for HNSCC not exceeding 20%. In the past, the preferred treatment regimens have been based on the initial Tumor, Node, Metastases (International Union Against Cancer) staging. These are anatomic assessments of the tumor size and spread. More recent developments have resulted in more biologically targeted therapy, with newer chemotherapy agents targeted to specific proteins overexpressed by certain tumors (bevacizumab, vascular endothelial growth factor; cetuximab, epidermal growth factor).

These advances herald the age of individualized therapy, with specific treatment regimens designed to treat the unique biologic characteristics of each tumor. The next, and some would argue the most important step, is to attempt to determine the response of a tumor during treatment as opposed to the "wait and see" approach. Biologic imaging information, such as that obtained with CT/perfusion MR imaging or MR imaging diffusion techniques, which can predict if a tumor is less likely to respond to a certain NSOPT treatment regimen, would warrant an alternative treatment such as surgery. Similarly, biologic information suggesting that a tumor is not responding to NSOPT during treatment would warrant treatment modification, such as dose escalation and adjuvant chemotherapy or surgical resection. For residual or recurrent disease, salvage surgery may be available as a curative treatment for only a limited number of patients. However, complication rates of salvage surgery after radiation therapy (RT) are high, with wound-healing problems as a well-known complication in patients treated with radiation. Moreover, the locoregional recurrence rate after salvage surgery (without the option of postoperative irradiation) is high. Therefore early identification of nonresponders to RT would avoid the morbidity and cost of a futile extensive RT and possible complications of salvage surgery after RT in a substantial number of patients. In those patients, survival may improve if RT is abandoned and salvage surgery is performed, including the possibility of postoperative radiation. This tailored approach has the potential for increasing local control and overall survival with fewer complications.

The results of the CTP initial investigations are promising and suggest that CTP has the ability to predict response to NSOPT. A recent investigation indicated that BF and BV were directly correlated with microvascular density (MVD), confirming that CTP can be used as a noninvasive surrogate marker for measuring MVD and potentially tissue hypoxia. The next step is to validate these findings and attempt to correlate the biologic imaging and histologic changes. In recent similar studies exploring the predictive value of diffusion in patients with HNSCC, Kim et al[8] and Galbán et al[9] showed that diffusion MR imaging may also have predictive value both pretreatment and shortly after the start of therapy for the results of chemoradiation. The ability to accurately determine the response of a tumor during any NSOPT and to modulate the dose at this time, as opposed to our current "watch and wait" approach, should be the hallmark of individualized therapy. Šurlan Popovič et al[6] and Bisdas et al[7] have made very important scientific contributions, which take us 1 step closer to the "Holy Grail" of cancer treatment.

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S.K. Mukherji
Departments of Radiology, Otolaryngology, Head and Neck Surgery, Radiation Oncology, and Periodontics and Oral Medicine
University of Michigan Health System
Ann Arbor, Michigan
J.A. Castelijns
Department of Radiology
VU University Medical Center
Amsterdam, the Netherlands

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EDITORIAL

Are Neuroimaging Findings in Novel Influenza A(H1N1) Infection Really Novel?

Novel H1N1 (referred to as "swine flu" earlier) is a new influenza virus causing illness in humans. This virus was first detected in people in Mexico and the United States in April 2009. It is spreading worldwide from person-to-person, probably in much the same way as the spread of regular seasonal influenza. The latter can be associated with neurologic complications,[1,2] but the frequency with which these occur with the novel influenza A(H1N1) virus infection is unknown. Neurologic sequelae such as seizures, encephalopathy, or encephalitis within 5 days of the initial illness were reported in 4 children with H1N1 infection for the first time in Dallas, Texas.[3] Brain imaging findings were normal in these children.

The first case of neuroimaging abnormalities in H1N1 infection was reported in a child from Texas presenting with imaging features of acute necrotizing encephalitis.[4] Subsequently, 2 more cases of encephalitis associated with H1N1 infection have been reported by Haktanir from Turkey[5] and Ormitti et al from Italy.[6] Neuroimaging findings in influenza-associated encephalopathy might be normal, but in severe cases, abnormalities can include diffuse cerebral edema and bilateral thalamic lesions.[2] Lack of evidence of H1N1 viral infection in the CSF suggests that neurologic manifestations might be an indirect effect of respiratory tract infection, similar to the ones observed in influenza A and B viral infections.[1,2]

The imaging findings may resemble those of acute necrotizing encephalitis or may present as encephalitis with hemorrhage and typically involve the bilateral thalami as seen in all 3 case studies.[4-8] These imaging features have also been described in Arbovirus encephalitis and may overlap these conditions.[9] These case studies suggest that imaging may be abnormal in H1N1-associated encephalitis with normal CSF; and in the presence of flu-like symptoms in the endemic zones, H1N1-associated encephalitis should be considered as an important differential diagnosis. Because these patients are known to recover completely with treatment, early recognition of H1N1-associated encephalitis will result in early institution of therapy specific to H1N1 and will possibly help in reducing the associated morbidity and mortality.

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R.K. Gupta
Department of Radiodiagnosis
Sanjay Ghandhi Postgraduate Institute of Medical Sciences
Lucknow, India

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