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Advanced imaging techniques in brain tumors

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Abstract

Perfusion, permeability and magnetic resonance spectroscopy (MRS) are now widely used in the research and clinical settings. In the clinical setting, qualitative, semi-quantitative and quantitative approaches such as review of color-coded maps to region of interest analysis and analysis of signal intensity curves are being applied in practice. There are several pitfalls with all of these approaches. Some of these shortcomings are reviewed, such as the relative low sensitivity of metabolite ratios from MRS and the effect of leakage on the appearance of color-coded maps from dynamic susceptibility contrast (DSC) magnetic resonance (MR) perfusion imaging and what correction and normalization methods can be applied. Combining and applying these different imaging techniques in a multi-parametric algorithmic fashion in the clinical setting can be shown to increase diagnostic specificity and confidence.

Keywords: *MR perfusion; MR permeability; MR spectroscopy; brain tumors.*

Introduction

Perfusion, permeability and magnetic resonance spectroscopy (MRS) are now widely used in the research and clinical settings. In the clinical setting, qualitative, semi-quantitative and quantitative approaches such as review of color-coded maps to region of interest (ROI) analysis and analysis of signal intensity curves are being applied in practice. There are several pitfalls with all of these approaches. Some of these shortcomings are reviewed, such as the relative low sensitivity of metabolite ratios from MRS and the effect of leakage on the appearance of color-coded maps from dynamic susceptibility contrast (DSC) magnetic resonance (MR) perfusion imaging and what correction and normalization methods can be applied. These shortcomings have important clinical implications as even qualitative perfusion maps are altered significantly by the leakiness of a lesion[1]. The relative advantages for T1 dynamic contrast-enhanced (DCE) MRI are compared with T2* DSC MRI in the estimation of perfusion and permeability metrics in the clinic.

The role of perfusion, permeability and MRS in the characterization of tumor biology and different pathologies is reviewed[2–4]. Differentiating between recurrent tumor and therapeutic necrosis is often a challenge. The role of advanced imaging and the effects of antiangiogenic therapies on tumor microvasculature/microenvironment resulting in changes in diffusion, perfusion and MRS are reviewed. With antiangiogenic therapies, we are seeing tumors that appear to respond to therapy in terms of a diminution of contrast enhancement, however the tumor appears to be still present, a phenomenon called 'pseudoresponse'[5]. An entity called 'pseudoprogression', which is seen more commonly as a result of therapy with temozolomide and radiation for high-grade gliomas, is discussed[2–4,6,7]. Combining and applying these different imaging techniques in a multi-parametric algorithmic fashion in the clinical setting can be shown to increase diagnostic specificity and confidence[8,9].

First-pass T2* DSC MRI versus steady state T1 DCE MRI (combined approach)

First-pass pharmacokinetic modeling (FPPM) is used to calculate vascular permeability (K^{trans}) from the same

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DSC MRI data used to calculate relative cerebral blood volume (rCBV). FPPM uses an exact expression for tissue contrast concentration assuming that contrast exists in two interchanging compartments (plasma and extravascular, extracellular space)[10,11].

Due to the complexity of angiogenesis, the accuracy and reproducibility of different perfusion MRI techniques for the measurement of vascular permeability has been under discussion recently. The primary issues are that vascular permeability may be 'non-flow limited' or 'flow limited'[12] and that the first pass of contrast measures only the permeability in the first pass, which is likely to be different to permeability measured in the steady state, whereby measurement of bidirectional exchange between two interchanging compartments (plasma and extravascular, extracellular space) can be characterized.

Recently, Cha *et al*. compared vascular permeability measurements, K^{trans} using steady state T1-weighted (ssT1) with first-pass $T2^*$-weighted ($fpT2^*$) MR imaging methods in gliomas and meningiomas[13]. The $fpT2^*$ K^{trans} was highly correlated with ssT1 K^{trans} in gliomas but not in meningiomas. Further investigation is likely to demonstrate that there may be two types of vascular permeability: very high vascular permeability (which is flow related and can be characterized in the first pass) versus steady state permeability (which is not necessarily flow limited and more proportional to the surface area product), which may be characterized using steady state techniques. As a result some centers including our own, are utilizing both ssT1 and fpT2* methods for obtaining perfusion metrics in gliomas[14]. Indeed, there are some inherent advantages to T1 techniques for obtaining perfusion and permeability metrics, such as the ability to estimate fractional blood volume (fBV) or CBV in the setting of susceptibility from post-surgical blood products or lesions in the temporal lobes or skull base. Three-dimensional T1-weighted dynamic sequences and novel techniques using iterative analysis to estimate permeability and perfusion have been demonstrated[15,16].

Clinical applications of perfusion MR and MR spectroscopy

MR spectroscopy and improving the specificity

MRS is sometimes limited by its apparent low specificity. Increased choline (Cho)/creatinine (Cr) ratio is identified in numerous intracranial pathologies. To increase specificity, it is important to compare the abnormal spectrum with one from the contralateral normal brain. Increased Cho levels in comparison with the contralateral normal Cho, i.e. Cho_{Abn}/Cho_n, is in keeping with tumoral disease, with higher Cho levels indicating higher glioma grade. On the other hand, a decrease in Cho_{Abn}/Cho_n would more likely favor non-neoplastic pathology, such as ischemia, encephalitis, radiation necrosis or a tumefactive demyelination lesion[4,17].

Histologic grading: limitations with neuropathology and World Health Organization (WHO) Classification in measuring tumor angiogenesis with CBV, CBF and permeability

The existence of multiple approaches to pathologic classification of human glioma implies that there is a lack of consensus among experts as to which is the single best approach[18–23]. These multiple grading systems do, however, agree on the histologic parameters that are important in the determination of glioma biology, namely hypercellularity, pleomorphism, vascular endothelial proliferation, mitotic activity and necrosis.

There have been numerous publications demonstrating the relatively low reproducibility of this system. Coons *et al*.[24] demonstrated that 4 observer concordance is 52%, 3 observer concordance is 60% and after 3 common reviews and agreement on pathologic features, the 4 observer concordance improved minimally to 69% and 3 observer concordance to 75%. Furthermore, there are other issues affecting pathologic reproducibility that must also be considered: (1) because only a few small samples of tissue are assessed, particularly from stereotactic biopsy, the most malignant portion of a tumor may not be sampled; (2) it may be difficult to obtain a range of samples if the tumor is inaccessible to the surgeon (in eloquent brain); (3) there are numerous classification/grading systems used in different institutions; (4) the dynamic nature of tumors of the central nervous system, with at least 50% de-differentiating into more malignant grades[25,26].

Despite these shortcomings, the WHO classification scheme remains the standard reference for guiding therapy and predicting prognosis in patients with brain tumors. Recently, Law et al.[3] compared the value of rCBV measurements in predicting tumor biology, using patient outcome as the gold standard. In this study, patients with the histopathologic diagnosis of high-grade gliomas (HGGs) and low-grade gliomas (LGG) from stereotactic biopsy and resection could be stratified into 2 groups based on rCBV. The Kaplan–Meier curve demonstrated that progression-free survival within the LGG group with ($rCBV < 1.75$) and ($rCBV > 1.75$) rCBV groups was significantly different ($p < 0.0001$). Similarly, when comparing HGGs, there was a significant difference in progression in HGGs with high ($rCBV > 1.75$) versus low rCBV ($p < 0.0001$). Lesions with low baseline rCBV (<1.75) demonstrated stable tumor volumes when followed over time and lesions with high baseline rCBV (> 1.75) demonstrated progressively increasing tumor volumes over time. These results demonstrates that rCBV measurements from DSC MRI may overcome some of the limitations of the current

histologic methods to provide an additional prognostic factor for tumor biology.

DSC MRI increases the sensitivity and predictive value in predicting glioma grade compared with conventional contrast-enhanced MRI[2]. In clinical practice, 95–100% sensitivity has been reported for differentiating HGG from LGG using thresholds of 1.75 and 1.5 for rCBV, respectively[2,27]. In the same studies, 57.5–69% specificity can be achieved using the same threshold values. Law *et al*.[2] reviewed 160 glioma patients, of whom 120 were HGGs and 40 were LGGs. The relatively lower specificity is due in part to the high number of false positives. Several LGGs with elevated rCBV can be misclassified as HGGs, giving more false positives.

Recently Danchaivijitr *et al*. demonstrated that in transforming LGG, DSC MRI perfusion imaging can demonstrate significant increases in rCBV up to 12 months before contrast enhancement is apparent on T1-weighted MR images[28]. Thus, an increase in microvascular density occurs well in advance of blood–brain barrier leakage reflcted by pathologic contrast enhancement. rCBV increase is therefore likely to provide an earlier non-invasive indicator of malignant progression and may likely indicate this 'angiogenic switch'.

Guiding stereotactic biopsy and radiosurgery

The rationale for using perfusion MRI to guide stereotactic brain biopsy is again based on the usefulness of these techniques in defining the most vascular regions of the tumor[29]. Most biopsies are guided with contrast-enhanced T1-weighted MR or computed tomography (CT) images[30], which only reflect blood–brain barrier disruption and may not indicate the most malignant or vascular region of the tumor. Often the region of highest vascularity and hence malignancy is found within the region of T2 signal abnormality and not necessarily within the region of contrast enhancement.

Therapeutic monitoring

The differentiation of therapy-induced necrosis (radiation and/or chemotherapy) from recurrent or residual tumor is challenging, both from a clinical point of view and from conventional MR imaging. Unfortunately, most of the time in clinical practice and at histopathology, both of these entities coexist. After all, it is primarily in the setting of residual tumor that the patient is receiving adjuvant radiation or chemotherapy.

Perfusion (rCBV) and vascular permeability seem to be measuring different pathophysiologic changes in the brain. As a result there are some instances whereby there are not only spatial differences in the distribution of the rCBV versus permeability but changes in one metric may be better than the other for differentiating between radiation necrosis and recurrent tumor.

Data recently reported in the randomized EORTC 22981/26981–NCIC CE.3 (European Organization for Research and Treatment of Cancer/National Cancer Institute of Canada) phase III trial on patients newly diagnosed with glioblastoma (GBM) given temozolomide (TMZ) plus radiotherapy (RT) have provided a new standard of care[31]. Since the introduction of chemoradiotherapy with temozolomide as the new standard of care for patients with glioblastoma, there has been an increasing awareness of post-therapeutic progressive and enhancing lesions on MR imaging, noted immediately after the end of treatment, which are not related to tumor progression, but which are a treatment effect[6,32–35]. This so-called therapy-induced enhancement/encephalitis or pseudoprogression, which can occur in up to 20% of patients who have been treated with temozolomide chemoradiotherapy, can explain about half of all cases of increasing lesions and enhancement after the end of this treatment[6]. These lesions decrease in size or stabilize without additional treatment and often remain clinically asymptomatic[6]. These findings suggest that pseudoprogression represents a continuum between the subacute radiation encephalitis/reaction and treatment-related necrosis. The mechanisms behind these events have not yet been fully elucidated, but the likelihood is that chemoradiotherapy causes a higher degree of (desired) tumor-cell and endothelial-cell killing. This increased cell kill might lead to secondary reactions, such as edema and abnormal vessel permeability in the tumor area, mimicking tumor progression, in addition to subsequent early treatment-related necrosis in some patients and milder subacute radiotherapy reactions in others[6].

Advanced neuroimaging findings in pseudoprogression have not yet been published but preliminary findings suggest a decrease in CBV values and an increase in vascular permeability (as well as increase in choline levels), in keeping with the proposed pathophysiology previously described. These findings usually appear in the first 3 months of treatment, earlier than the typical time period in which radionecrosis is described, and usually regress 6–9 months following the initial commencement of temozolomide and radiation therapy and possibly other chemo-radiation regimes. Further research is needed to establish reliable imaging parameters that distinguish between true tumor progression and pseudoprogression or treatment-related necrosis. Certainly it is critical to determine which parameter better differentiates early pseudoprogression from early progressive lesions, as the management approaches are completely different for each situation.

Perfusion MRI as biomarkers for novel antiangiogenic agents

Malignant gliomas, particularly recurrent anaplastic gliomas and glioblastoma multiforme (GBM) are highly

refractory to therapy. A key feature of malignant gliomas, such as GBM, is their tendency to infiltrate surrounding tissues. This invasive property often precludes total surgical resection and makes it difficult to treat with radiation without damaging normal brain parenchyma. Because of the difficulty in obtaining total eradication, patients with GBM have a median survival of less than 1 year, despite aggressive treatment. Of the approximately 35,000 Americans diagnosed with primary brain cancer each year, almost half with high-grade (WHO class III–IV) gliomas will succumb to their disease within 2 years if treated and in less than 6 months if untreated. This extremely poor prognosis has not changed despite 30 years of research, technological progress, and clinical trials. Whereas concomitant use of radiation and temozolomide has been recently defined as the standard first-line approach for therapy for newly diagnosed grade 4 gliomas[31], the conventional treatment of recurrent high-grade glial tumors remains ill-defined.

These gliomas are highly vascular and are likely the result of the tumoral upregulation of angiogenic growth factors, such as vascular endothelial growth factor (VEGF). VEGF is secreted by tumor cells and acts in a paracrine manner on the VEGF receptors (VEGFRs) on endothelial cells to stimulate endothelial-cell proliferation, migration, and survival. The importance of VEGF is highlighted by the fact that the degree of vascularization has been linked to prognosis in gliomas and other solid tumors, and VEGF levels in glioblastomas have been correlated with tumor blood vessel density, invasiveness, and patient prognosis[36].

Antiangiogenic therapy in gliomas is desirable for multiple reasons, including the prominent role of angiogenesis in glioblastoma growth and proliferation. The accessibility of intravascular VEGFR localized to endothelial cells circumvents the challenge of delivering the drug to the tumor beyond the impermeable blood–brain barrier. In addition to the potential for direct antitumor effects, antiangiogenic therapy has been shown to prune abnormal vessels and 'normalize' existing vasculature, which may paradoxically improve drug and oxygen delivery to the tumor for a period of time following drug administration. Ideally, this window of normalization can lead to a temporary improvement in tumor oxygenation and blood flow, which may enhance the effectiveness of radiation therapy and chemotherapy. In addition, anti-VEGF therapy has been shown to reduce cerebral edema through elimination of VEGF, which may reduce the need for steroid use and have a beneficial impact on neurologic function[36].

One of the few agents currently approved by the US Food and Drug Administration is bevacizumab (Avastin). Bevacizumab is a humanized murine monoclonal antibody against the VEGF receptor and was approved in February 2004 for first-line use against metastatic colorectal cancer when used with 5-fluorouracil-based chemotherapy. There are promising data regarding its use in other cancers, including renal cell carcinoma, non-small cell lung, pancreatic, and breast cancers[37]. Current phase II and phase III studies are testing its efficacy in these and other tumor types. However, published data on the role of bevacizumab in primary brain tumors are much more limited. Although bevacizumab seems to have some activity as a single agent, no studies have shown that bevacizumab confers a survival advantage when used without cytotoxic chemotherapy, suggesting that sequestration of circulating VEGF is not sufficient to produce antitumor activity and that bevacizumab may be able to potentiate the effects of cytotoxic chemotherapy[36]. Fine has recently demonstrated in a phase II study that patients with glioblastoma treated with bevacizumab alone had a response rate of 60% and a 6-month progression-free survival (PFS) rate of 30%[38]. These response and PFS rates are similar to the published data on bevacizumab plus irinotecan, suggesting that most of the radiographic response and clinical benefit may be attributable to bevacizumab and that eliminating irinotecan may improve the tolerability of the therapy.

Vredenburgh *et al*. published the first phase II study of patients treated with bevacizumab and irinotecan and showed an overall radiographic response rate of 63% based on MacDonald criteria, against 5% or 6% with the traditional treatments[39,40]. More important, the 6-month PFS rate was much higher that published in historic series, reaching 30% in the GBM group treated with bevacizumab and irinotecan, whereas historically it was reported to be around 15%; however, it is still unclear if this new treatment improves overall survival[40].

One study demonstrated a 50% conventional MR imaging response rate in 14 patients with recurrent HGGs. Of these patients, 4 died (mean survival after treatment 116 days), 2 of whom had what the authors described as 'mixed progressive disease' and the other two with 'partial response', suggesting that radiographic improvement does not correlate well with clinical outcome[41].

There is also evidence that VEGF receptor inhibitors may have activity. In a recent phase II study of the pan-VEGF receptor inhibitor, AZD2171, in recurrent GBMs, the radiographic response rate was approximately 50%, and 6-month PFS rate was 27%. In most patients, relative tumor vessel size significantly decreased as early as 1 day after the onset of AZD2171 treatment as well as vascular permeability.

Although the results suggest benefit from the combination of bevacizumab and irinotecan, there are cases that do not respond. This could be due to the heterogeneity in the vascular response to bevacizumab or because of other independent patient characteristics that make them less likely to respond to therapy[42]. These characteristics include differences in the molecular profiles among those with primary and secondary GBM. Also the tumor escape from anti-VEGF therapy may involve other growth factors important for angiogenesis,

including VEGF-C, VEGF-D, placental growth factor, platelet-derived growth factor, and basic fibroblast growth factor[36].

Recent evidence has demonstrated that a subset of patients treated with bevacizumab and irinotecan may develop non-enhancing tumor progression without evidence of an increase in tumor vascularity[36,43]. Experimental evidence has shown that glioma tumors treated with the anti-VEGFR-2 antibody DC-101 demonstrated an increase in the number and total area of small satellite tumors[44]. Tumor cells were found to have migrated along blood vessels over long distances to eventually reach the pial surface and spread in the subarachnoid space, a process known as cooption vascular[44]. The results suggest that in a therapeutic situation, whereby angiogenesis is inhibited, tumors cells can coopt preexistent cerebral vessels to provide their blood supply before they induce neovascularization and this may be demonstrated in the MR image as an increase in the hyperintense surface area on fluid attenuated inversion recovery (FLAIR) sequences. Again there is no standard method to quantify this pattern of progression radiographically. Normally there is no increase in the CBV values, even though spectroscopy can show high choline levels and diffusion-weighted images show low levels of apparent diffusion coefficient (ADC). This results in another entity called pseudoresponse. Recurrent gliomas treated with antiangiogenic agents may demonstrate a decrease in contrast enhancement, however, over time the tumor is seen to recur, so the initial antiangiogenic effect is not a true response but a pseudoresponse to therapy, almost a 'super-steroid' effect on the contrast enhancement[5].

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