

Physiological and anatomical imaging of brain tumor by magnetic resonance imaging; emerging clinical applications around tumor metabolism

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ABSTRACT

Brain tumors (BTs) are among the scariest of health conditions; in fact, the BT epidemiology consortium has called them an orphan disease because research funding is limited. The related potentials and challenges from the perspectives of technology, physics, and biology as well as clinical application of the ultrahigh field MR systems are different from those systems operated at 3 T, 1.5 T, or lower field strength. The integration risk, preparation of surgical means and course of intraoperative electrophysiological procedures are important. These novel imaging methods increase the specificity to a noninvasive approach of cerebral tumors and help the neurosurgeon in the assessment of resection and function preservation.

KEY WORDS: Brain tumors, Angiogenesis, Physiological imaging, Diffusion weighted imaging, Perfusion weighted imaging.

1. INTRODUCTION

Epidemiology of Brain Tumors and Imaging Modalities: Brain tumors (BTs) are among the scariest of health conditions; in fact, the BT epidemiology consortium has called them an orphan disease because research funding is limited. They are relatively rare, developing in approximately 16.5 per 100,000 people in the United States each year (Leydon, 2000). The most common types are gliomas and meningiomas. Gliomas are usually malignant (cancerous), while 90% of meningiomas are benign (non-cancerous). Glioblastoma multiforme is the most deadly, with a 5-year survival rate of 3.3%. However, some malignant types have 5-year survival rates of more than 70%; benign tumors can also cause serious illness or death, depending on their size and location. Although many risk factors have been examined over the past several decades, there are few consistent findings, possibly because of small sample sizes in individual studies and differences between studies in patients, tumor types and methods of classification (Parkin, 2005). The distribution of tumor types varies substantially by age group. In Sweden, tumors in pediatric patients aged ≤ 15 years; which is very different compared with adult patients, in whom high-grade. Universal, age-standardized death for major malignant BTs is ≈ 2.8 per 100,000 population for men and 2.0 per 100,000 population for women (GLOBOCAN). Like incidence rates, the estimated mortality is higher in more developed countries (men, 4.1 per 100,000; women, 2.7 per 100,000) than in less developed countries (men, 2.2 per 100,000; women, 1.6 per 100,000). Changes in tumor classification and coding likely are responsible for some of the increases in incidence for BTs histologies, such as oligodendroglioma and astrocytoma, and not otherwise specified. To the central nervous system (CNS) belong a heterogeneous group of glial and non-glial rare cancers. 4.1% Embryonal tumours and 0.1% choroid plexus carcinoma; incidence rates vary widely across European regions especially for astrocytic tumours ranging from 3/100,000 in Eastern Europe to 5/100,000 in United Kingdom and Ireland (Crocetti, 2012). Yearly occurrence rate of 4.8 per 100,000 for astrocytic, 0.4 for oligodendroglial, 0.2 for ependymal and embryonal tumours and less than 0.1 for choroid plexus carcinoma. During the past decade, tremendous progress has been made in magnetic resonance imaging (MRI), which has revolutionized our understanding of normal brain functioning as well as neoplastic disorders (Fatehi, 2016b). Many of the new MRI methods allow the investigation of metabolic and physiological aspects of brain neoplasm and tumors, thereby supplementing conventional MRI, which provides excellent structural information. Advanced MRI techniques using different contrast principles, have been incorporated into the clinical routine in order to aid tumor diagnosis. Currently, advanced MRI techniques either are already available or will soon be widely available. Diffusion weighted imaging (DWI) and perfusion-weighted imaging (PWI) has become the essential elements of integrated MR examination in the BTs setting. While these methods were only research tools a few years ago, they now have the potential to replace computed tomography (CT) (Fatehi, 2016). In other hand, over the last 30 years there has been much interest in using imaging to identify, quantify, and monitor change in the vascular architecture and function of tumors, particularly in tracking response to antiangiogenic therapy. Initial CT, MRI, or PET studies assessing angiogenesis in preclinical models of cancer and in patients were not available till the late 1980s. Subsequent to a stable upsurge in papers to around 200 per year, attention in imaging angiogenesis trails and therapeutic reserve was more powered in the early 2000s, inhibition became clear in renal, colorectal, non-small cell lung, hepatocellular, ovarian, and other cancers (Rajendran, 2003).

Clinical studies have mapped and quantified drug-target interaction for VEGF inhibitors and av integrin– targeted agents (Weissleder and Mahmood, 2001). This research not only shows proof of mechanism but also helps to map the variation in drug target expression. In contrast, most studies that image angiogenesis quantify and map aspects of the microenvironment at the phenotypic level, rather than the molecular level. These methods are also expensive and require investment of time from both patients and scientists.

DWI: Diffusion is considered the result of the random movement of water molecules (Gharib Salehi, 2016, Rahmani Tanha, 2016). Diffusion occurs at equal rates in all directions inside an isotropic medium; hence, water mobility is considered to be anisotropic. Specifically, The modern-day concept of cerebral edema remains largely based on the theory of Klatzo, who in 1967 proposed two fundamentally different types of edema, cytotoxic and vasogenic. In cytotoxic edema, the chief mechanism is related to intracellular swelling due to sodium influx after energy pump failure at the cell membrane level. The net result of cytotoxic edema is marked decrease in extracellular space and, hence, marked reduction in ADC measurement seen in the setting of acute cerebral infarct. In vasogenic edema, however, there is increase in extracellular space volume, because of disturbance of vascular permeability, which enables the indiscriminate escape of plasma fluid and protein. Unlike cytotoxic edema, vasogenic edema implies reactive changes rather than permanent cellular damage and, hence, is reversible. In brain tumors, peritumoral edema is mainly based on imaging definition of different components of tumor in relation to the presence or absence of contrast enhancement after the administration of intravenous contrast agent. In general, the nonenhancing area of abnormality surrounding the enhancing tumor core is referred to as peritumoral edema. In metastatic brain tumors or noninfiltrative primary tumors such as meningioma, the peritumoral edema is synonymous with vasogenic edema, where there is increased extracellular water due to leakage of plasma fluid and usually invading along the white matter tracts. Imaging-based localization of scattered and random areas of tumor infiltration within the peritumoral edema in gliomas is a daunting, if not impossible, task because infiltrated tumor cells are barely identifiable even at histologic evaluation at a microscopic level, a resolution that is far beyond what anatomic MRI can provide. Differentiation between vasogenic and infiltrative edema has been attempted with DWI on the foundation of the evidence that water diffusivity is facilitated to a greater degree in vasogenic than in infiltrative edema due to absence of intervening tumor cells in the former. The real challenge, however, is to localize tumor-infiltrated regions among the area of vasogenic edema so that potential therapy can be directed to these sites without subjecting unnecessary toxicity on the entire peritumoral edema, most of which is vasogenic in nature. Several reports have shown that ADC values are not helpful in differentiating tumor and tumor related brain edema. Although there was one report showing statistically significantly different ADC values between the 2 types of edema in 2 different tumor types (gliomas vs. metastatic tumors), it is unlikely that ADC alone will be able to discriminate pure white matter water as in vasogenic edema from brain water with scattered foci of microscopic and isolated tumor cells as in infiltrative edema because of the inherent limitation of spatial resolution of DWI. In addition, Tissues with high cellularity have a low ADC because the mobility of water protons is impaired. In tumors of malignancy. Low-grade gliomas tend to have a higher ADC compared with high-grade lesions. The ADC value seems to be inversely related to tumor cellularity and grading. T2-FLAIR hyperintense and/or nonenhancing tissue may imply a high grade malignancy as well; this has opened new frontiers in neuroimaging, setting the pace for DWI application in neuro-oncology. DWI therefore represents a promising tool for preoperative grading, postoperative assessment of glial tumors, differential diagnosis between recurrences or in the assessment of therapeutically response injury. Conversely, DWI has not still explored its full potential; it is currently being used as detector of pathology, but new oncological applications as prediction of tumor response or early post treatment motorization have to be completely explored (Takenaka, 2009).

PWI: This physiological technique is a relatively new MRI strategy. Ischemic core and the surrounding brain regions, thereby complementing the information derived from DWI. PWI displays micro vascular hemodynamic. Blood flow in the cerebral vascular network can be measured by quantitation of hemodynamic parameters like the regional cerebral blood flow (rCBF) and the regional cerebral blood volume (rCBV). Based on these premises and knowing that micro vascular proliferation is one of the most important histopathological criteria when determining the malignancy of gliomas, PWI has rapidly been established a valuable tool for assessing tumor angiogenesis. PWI permits no invasive in vivo study of tumor prognosis, particularly in gliomas. Two perfusion techniques are used: arterial spin labeling (ASL, without contrast media) and dynamic susceptibility contrast (DSC) enhanced perfusion imaging. The ASL signal uses blood normally circulating in the vascular bed as endogenous tracer. Blood is labeled in special sequences for the identification and quantification. In addition, ASL uses endogenous arterial water as a diffusible tracer. There is continuous exchange of water between blood and brain tissue, and therefore proximal spine labeling results in the changes of total magnetization of brain tissue in an imaging slice. Tagged and nontagged images are obtained and absolute cerebral blood flow (CBF) is calculated. Different ASL techniques have been proposed, namely continuous ASL (CASL), pulsed ASL (PASL) and pseudo-CASL.^{30–32} Notwithstanding the spin labeling technique, clinical ASL must be just obtained from the latest commercial high-field MRI, instantly processed

on operating console or offline, and must provide absolute quantification data for more active clinical application. ASL provides direct quantification of CBF in contrast with DSC PWI, which needs a complicated algorithm for absolute quantification. Territorial ASL, applied in stroke imaging or vascular variants in normal brain, and its further application in brain tumor imaging is expected. DSC technique is known as contrast agent bolus tracking and employs exogenous tracer (i.e. Gadolinium) as paramagnetic contrast media administered by rapid infusion during the acquisition of ultrafast MR sequences. Gadolinium, which alters the magnetic susceptibility of blood. Under a pathological perfusion (i.e. hyperacute ischemic lesion) the signal decrease is attenuated or delayed, or varies in relation to grading (as in brain tumors). Important quantitative parameters that characterize PWI include: Mean Transit Time (MTT, the average time spent by the blood in the cerebral vascular bed) and Time to Peak (TTP, the time taken from the start of bolus injection to the maximum signal intensity) Yet, the most robust quantitative parameter is rCBV, which represents tumor angiogenesis. In brain tumors, perfusion MRI proposes to measure the degree of tumor angiogenesis and capillary permeability, both of which are important biologic markers of malignancy, grading, and prognosis, particularly in gliomas. Brain tumor vasculature plays critical roles not only in supplying nutrients and oxygen to tumor cells but also in providing a roadmap for tumor infiltration and complex feedback loop with tumor hypoxia and necrosis. It is of utmost importance to understand the complex biology of brain tumor angiogenesis to gain insight into the development of malignancy and strategies to combat tumor growth. To that end, various PWI methods strive to provide noninvasive and robust surrogate markers of tumor angiogenesis and capillary permeability. PWI- to study and quantify brain tumor vasculature. Accurate CBF measurements in clinical patients who have neoplastic (and vascular) cerebral disease remain a serious imaging challenge, regardless of magnetic field strength or even imaging modality. Quantitative CBF values are frequently considered to weigh the risks and benefits of surgical versus medical (chemotherapy) management. Strong positive correlation between tumor rCBV and astrocytoma grading. rCBV ratios were calculated on the solid portion of the tumor, on peritumoral area, as well as on the contralateral normal white matter, respectively. The results showed that higher rCBV ratios were present in both solid portions and peritumoral imaging (Kajimoto, 2003).

DISCUSSION

Structural imaging of brain tumors has evolved from a purely anatomy-based discipline to one that incorporates morphologic irregularity with physiologic alterations in extracellular compartment kinetics, cellular metabolism, and hemodynamics (Cha, 2006). Tremendous progress and widespread clinical use of physiology-based MRI have become an essential part of the diagnostic armamentarium to diagnose, guide surgery, monitor therapy response, and predict prognosis of patients with brain tumor. The incorporation of physiologic MRI such as DWI and PWI, as part of the mainstream clinical imaging protocol to provide meaningful and clinically relevant end points and biomarkers for clinical trials and assessment of malignancy (Rahmani Tanha, 2016). PWI main advantages are relative noninvasiveness as well as qualitative and quantitative capability of assessment of ischemic or tumoral hemodynamics. PWI in the latter aids in grading and better differentiation in diagnostics as well as in pre-therapeutic planning. Thanks to this novel technique the course of treatment, both after chemo- as well as radiotherapy in combination with surgical treatment, may be optimized. As advances in MR technology take place, the role of PWI in the care of neuro-oncologic patients is likely to increase, and may eventually permit reliable, noninvasive assessment of a patient's prognosis and response to therapy. More efforts are to be made in order to improve ASL techniques that allow measuring perfusion without contrast media administration; the advantages are that completely noninvasive absolute CBF measurements are possible and that multiple repeated measurements can be obtained to evaluate one or more interventions (Wolf and Detre, 2007).

2. CONCLUSION

The characterization of tumoral and peritumoral tissue microstructure, according to water diffusion and perfusion results, lead to increased diagnostic value. The wide range of metabolic, functional and structural data derived from advanced MRI techniques if thoroughly evaluated and combined with other clinical and imaging findings might be the key to optimize diagnosis and treatment. Finally, the integration risk, planning of surgical routes and direction of conventional, intraoperative electrophysiological procedures. These novel imaging methods increase the specificity to a noninvasive approach of cerebral tumors and help the neurosurgeon in the assessment of resection and function preservation.

Conflict of Interest: Authors have no conflict of interests.

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