The Utility of Multi-Parametric MRI for Radiotherapy Planning in Gliomas

Mekhail Anwar and Daphne Haas-Kogan*
Department of Radiation Oncology, University of California San Francisco School of Medicine and UCSF Benioff Children's Hospital, USA

Abstract

Patients with high-grade gliomas have poor overall survival despite significant efforts to improve multi-modality treatment. Tumor heterogeneity, dynamic changes during treatment and peritumoral invasion render the optimal delineation of target volumes for radiotherapy challenging. Although traditional clinical imaging modalities can identify gross disease, advanced imaging techniques are needed to identify tumor heterogeneity and microscopic invasion. Multi-parametric imaging sequences such as perfusion, diffusion and spectroscopy can be employed to characterize the cellular properties of both gross tumor as well as microscopic disease within anatomically normal tissue. In this review we explore the utility of these imaging techniques in guiding radiotherapy planning for gliomas. With the ability to precisely shape and target radiation dose, the use of these imaging modalities to plan radiation therapy has promise in increasing efficacy and limiting toxicities of radiotherapy for gliomas.

ABBREVIATIONS

CNI: Choline to NAA Index; CBV: Cerebral Blood Volume; %recov: Percent Recovery; FA: Fractional Anisotropy; ADC: Apparent Diffusion Coefficient

INTRODUCTION

The potential morbidity of surgical resection of gliomas, combined with the inability to rigorously clinically evaluate the burden of disease, has increased the importance of imaging in defining the extent of disease, both gross and microscopic, as well dynamically assessing the response to therapy. With the advent of MRI, more accurate delineation of gross disease in both high- and low-grade gliomas is available, yet the extent of microscopic disease is still unknown. Furthermore, the ability to predict, as well as dynamically assess treatment response, using imaging is not well established. New MRI imaging modalities, consisting of physiologic and metabolic imaging, have made progress in addressing these needs. In this review we will discuss the advances in multiparametric MRI in assessing tumor extent, prognosis and response. This information can then be used to guide treatment in a multidisciplinary treatment setting.

HISTOPATHOLOGY OF GLIOMA: TUMOR HETEROGENEITY AND PERITUMORAL INVASION

Advances in radiotherapy have enabled significant flexibility in the spatial distribution of dose, and the current challenge for clinicians is to define where to appropriately target radiotherapy. The design of radiotherapy plans for gliomas, both for dose and margins, is complicated by tumor heterogeneity and invasion into surrounding normal brain parenchyma, respectively. Within the area of gross disease, gliomas are known to be heterogeneous in both their histologic characteristics [1,2] as well as their molecular expression [3] and this can be seen in the corresponding imaging [4]. Higher-grade gliomas necessitate a greater dose for tumor control, and therefore tumor heterogeneity can lead to the need for areas of focally increased dose. The concept of dose-painting [5], whereby foci of increased dose within the tumor are intentionally planned, can potentially address this by appropriately targeting higher dose focally within the gross tumor volume.

Similarly, a lower dose may be appropriate for areas of microscopic invasion, but defining areas of microscopic invasion remains a challenge. Whereas the proliferation rate positively correlates with tumor grade, local invasion can be seen with gliomas regardless of clinical grade [6,7]. The invasive nature of even low-grade gliomas implies that this invasive phenotype is acquired early in tumorigenesis, and invasion often proceeds along white matter tracts [8]. Other patterns of spread include perivascular and subpial spread as well as perineuronal satellitosis [8]. Therefore, in addition to targeting the gross tumor volume, and the high-grade areas within it, an appropriate dose must be given to the tissue with microscopic invasion. New MRI imaging technologies offer promise in addressing both of these areas.
MAGNETIC RESONANCE IMAGING FOR GLIOMA

Advances in imaging, notably the introduction of MRI into standard clinical practice, have enabled greater accuracy in delineating tumor volumes. Malignant gliomas (grade III and IV) typically enhance due to breakdown of the blood brain barrier enabling extravasation of contrast into the brain tissue, whereas lower grade gliomas (II) may not enhance on T1 imaging [9]. Although delineation of gross disease has been strengthened with MRI, the invasive nature of gliomas makes it difficult to define appropriate treatment margins based on anatomic imaging alone [10]. Burger [11] showed that foci of GBM could be found more than 2 cm from the contrast enhancing lesion (CEL) on CT, and Halperin [12] found tumor as far as 3 cm from the peritumoral edema. Additionally, debate remains on whether T2 signal changes represent tumor invasion or edema. Biopsies done on untreated patients after imaging showed that the T1 CEL corresponded to gross tumor involvement, but isolated tumor cells could be found not only within the T2 lesion, but outside of it, in normal appearing brain parenchyma [13,14]. Studies of stereotactic biopsies taken from outside the T2 region [15,16] have shown viable tumor cells as far as 4 cm away from the T2 lesion. Because of this highly invasive behavior, surgical resection is employed to treat the entire extent of disease. The uncertainty in tumor extent beyond the gross disease has led to various strategies in defining both radiotherapy dose and margins for gliomas. A key example of the debate on this topic can be recognized in the competing guidelines for radiotherapy of malignant gliomas, with the RTOG based in the United States recommending 45 Gy to the T2 lesion plus a 2 cm margin (with a boost to the T1 lesion), while Canadian and European groups generally recommend 60 Gy to the T1 lesion with a 2-3 cm margin [17]. Therefore, there is a need for improved imaging to delineate subclinical disease to enhance radiotherapy targeting.

MULTIPARAMETRIC IMAGING IN GLIOMA

In addition to the traditional anatomic MR sequences, new methods of obtaining both physiologic and metabolic information can provide information on the cellular characteristics of voxels, potentially identifying subclinical disease as well as further defining tumor heterogeneity. Specifically, physiologic information consists of perfusion and diffusion imaging, which assesses the characteristic blood flow and water movement properties, respectively, of an individual voxel. Perfusion imaging traditionally consists of a measure of the amount of blood passing through a voxel (Relative Cerebral Blood Volume, rCBV) and the level of leakiness of that vasculature. Gross tumor results in notoriously leaky neovascularity, increasing the rCBV. Furthermore, studies have shown an association between high-grade gliomas and rCBV magnitude [4,18]. Diffusion imaging consists of measuring both the directionality of water diffusion as well as its magnitude. By measuring diffusion gradients in multiple directions, the preferential direction of water motion can be determined. This tends to be higher along the direction of white matter tracts, and forms the basis for tractography, whereby connectivity of different regions in the brain are mapped though neural pathways. The magnitude of the directionality is captured in a parameter called the fractional anisotropy (FA). Consistent with tumor invasion that disrupts white matter tracts, the FA is decreased in areas of tumor involvement [19]. The apparent diffusion coefficient (ADC) is a measure of the magnitude of diffusion, and can be decreased with gross tumor involvement [20] and increasing tumor grade due to increased cellularity, but increased with subclinical involvement due to edema. Figure 1 illustrates an example of multiparametric imaging in a patient diagnosed with GBM.

Cellular metabolism can be used to identify cells with an increased turnover rate, indicative of tumor involvement. Although PET is the most commonly used modality in metabolic cancer imaging, the high background activity in the brain and poor resolution complicates its use in spatially defining gliomas. Magnetic resonance spectroscopy, or MRS, can be used to identify specific metabolites based on the shift in proton...
spectra. Specifically, MRS has shown utility in identifying choline (Cho, a membrane component and neurotransmitter increased in tumor), N-acetylaspartate (NAA, a neuronal metabolite), creatine (Cre, an indicator of cellular metabolism), and lactate (increased in anaerobic metabolism) [21]. The choline to NAA ratio is increased in gliomas, with a larger ratio corresponding to higher cellular density [22] and grade [23]. MRS parameters have been shown to have direct correlation with pathologic samples [24,25], and the choline signal on MRS is positively correlated with the Ki-67 labeling index, a molecular marker of proliferation [26]. Studies examining the extent of spectroscopic abnormalities have shown that they extend beyond anatomic T1 and T2 sequences, likely representing infiltrative disease [21,27]. Therefore, use of these physiologic and metabolic parameters can help identify areas of tumor not within the anatomic T1 and T2 sequences while further categorizing voxels within the gross tumor, enabling risk-adapted radiotherapy planning to all involved voxels.

**Imaging Findings as a Function of Treatment Response and Outcome**

In addition to giving insight into tumor grade and extent of invasion, multiparametric imaging has also been used to predict treatment response and prognosis. This may result from both identifying more aggressive tumor, as well as areas not in the T1 and T2 lesions and therefore suboptimally treated. Dynamic changes in perfusion, from pre- to post-radiotherapy, were shown to be predictive of progression-free survival in patients with high-grade gliomas treated with the standard regimen of 60 Gy with concurrent and adjuvant temozolamide [28] and an anti-angiogenic agent [29]. Other studies have shown that changes in rCBV during the first weeks of radiotherapy can predict survival [30,31]. Similarly, diffusion changes, even within the first 3 weeks, have been shown to predict time to progression and overall survival [32-34]. Specifically, these studies found that patients with a greater volume of tumor that had increased ADC 3 weeks into treatment had significantly longer survival (52.6 vs. 10.9 months, p<0.003) [35]. The increased ADC is thought to be indicative of reduction in cell density, representing a response to treatment that will later manifest as a reduction in tumor size. Parameters obtained from metabolic imaging with MRS also have predictive value [36]. Therefore, not only can multiparametric MRI help define the target volume and dose distribution but dynamic changes in these parameters can help predict outcome. This introduces the paradigm of temporally modulated radiotherapy, whereby the radiotherapy plan is adjusted based on parameter dynamics throughout treatment.

**Future Directions for Imaging in Brain Tumors**

Despite radiotherapy’s long standing role in the treatment of gliomas, and trials varying both the dose and spatial distribution of radiotherapy, overall survival remains 12-16 months [37] and recurrence continue to be largely local [38-40]. One explanation for central tumor recurrences in malignant gliomas could be the result of an expansion of suboptimally treated tumor cells groups that infiltrated the adjacent brain [8]. Furthermore, the heterogeneity within the gross tumor and large extent of invasion surrounding may not be adequately targeted by current radiotherapy guidelines based on anatomic T1 and T2 MRI sequences. Therefore, multiparametric imaging should be incorporated into radiotherapy planning, potentially boosting dose to radioresistant foci and adequately covering surrounding invasive disease. Additionally, imaging during treatment may enable modification of the radiotherapy plan based on areas not responding to treatment. With the advent of MRI integrated with radiotherapy delivery (ViewRay [41], Elekta [42]), there is potential to visualize changes in these parameters in real-time. Real-time, risk-adapted radiotherapy planning based on multiparametric imaging for gliomas should be evaluated in a prospective clinical trial.

**ACKNOWLEDGEMENT**

Funding sources: The Nancy and Stephen Grand Philanthropic Fund (DHK); The V Foundation (DHK).

**REFERENCES**


