CORRELATING PERFUSION MRI MAPS WITH TREATMENT PLANS FOR RE-RADIATION THERAPY IN BRAIN TUMOR PATIENTS

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Abstract

Significance: Contrast-enhanced (CE) and Fluid attenuation inversion recovery (FLAIR) MRI are current standard of care tools for delineating radiation treatment targets in high-grade glioma (HGG) patients. However, in the setting of retreatment, tumor regrowth and non-tumor therapy-related inflammation, known as post-treatment radiation effect (PTRE), have identical MRI appearances. As a result, FLAIR MRI can be an unreliable tool for treatment planning. Surgical biopsy can definitively distinguish recurrent tumors from PTRE but has many disadvantages, namely operative risk and cost. Dynamic Susceptibility-weighted Contrast-Enhanced (DSC) MRI Perfusion can non-invasively detect distinct characteristics of tumor and PTRE through measurements of relative cerebral blood volume (rCBV). PTRE exhibits decreased microvascular density, whereas tumor recurrence displays angiogenesis and microvascular proliferation. Thus, DSC-MRI affords the opportunity to better define tumor burden within and possibly outside of these nonspecific regions.

Objective: To assess the extent with which rCBV maps correlate with re-radiation treatment plans in patients with recurrent tumor in order to identify potential differences in treatment planning.

Design: This study enrolled 8 previously treated HGG patients presenting for re-irradiation of suspected recurrent tumor at a single hospital on an IRB-approved trial. All patients underwent DSC-MRI and routine MRI imaging prior to re-irradiation treatment planning, and underwent treatment as per routine clinical protocol. Following therapy, rCBV and radiation dose maps were overlaid on conventional MR to delineate differences in identified tumor burden.

Results: Of the 8 patients, four rCBV images showed evidence of tumor outside of the RT planning volumes, while the other 4 showed fully treated tumor but with large volumes of uninvolved brain receiving radiation.

Conclusion: DSC-MRI better identified unique regions of potential tumor burden in recurrent HGG patients compared to conventional MRI and could be used to improve radiation treatment planning in re-radiated patients.

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Introduction/Significance

Post-treatment diagnosis and management of high-grade glioma (HGG) patients is a persistent challenge among neuro-oncologists. Current therapy consists of three main modalities: surgery, chemo- and radiation therapy (RT). Although initial treatment is standard for most patients, post-treatment management can vary substantially depending on the individual's course.

Contrast-enhanced MRI (CE-MRI) is the current mainstay for monitoring the HGG response to chemotherapy and RT, and, in conjunction with a neurological exam, is used to define disease progression. Gadolinium-based contrast agents, which normally do not pass through the blood-brain barrier, can indicate the presence of blood-brain barrier disruption, which result in contrast-enhancement of tumors and other lesions. According to the MacDonald criteria, new or enlarging CE-MRI lesions represent increasing tumor burden and suggest treatment failure and poor prognosis.[1,2]

CE-MRI is also used in conjunction with computed tomography (CT) for RT planning. However, early studies identified biopsy-proven tumor cells in the area of MRI T2 abnormalities outside contrast-enhancing CT abnormalities.[16] Due to these concerns, T2 MRI was soon incorporated into RT planning. T2 MRI has the disadvantage of causing CSF to be brighter than the brain, decreasing conspicuity in the regions adjacent to CSF, which led to the development of the fluid attenuation inversion recovery (FLAIR) sequence.[18] FLAIR MRI has the advantage of nullifying the bright CSF signal of T2 MRI and can be used instead of T2 MRI.[17]

CE-MRI and FLAIR are both nonspecific tools for identifying recurrent tumor burden. Specifically, therapy-induced parenchymal injury, called Post-treatment Radiation Effect (PTRE), often develops concurrently with tumor regrowth and mimics its appearance on CE-MRI.[3] It is paramount to distinguish these two as tumor regrowth indicates treatment failure and a need to alter therapy, whereas PTRE changes represent treatment success. Two well documented forms of PTRE are pseudoprogression (pP) and radiation necrosis (RN). Both represent treatment success and predict better prognosis, yet represent erroneous declaration of treatment failure in up to half of cases.[3-4] Thus, tumor progression is often misdiagnosed on conventional MRI, significantly hampering treatment efficacy and survival predictions.

Surgical biopsy definitively distinguishes recurrent HGG from PTRE.[5] However, this dual approach of imaging and biopsy does not account for the wide variability in tumor quantity present in histologic mixtures of PTRE and tumor, an important finding, as the ratio of PTRE to tumor in the lesion may affect prognosis.[6] In fact, studies suggest that quantifying tumor burden provides more meaningful prognostic information than simply reporting its presence, since histologic tumor fraction provides a direct measure of tumor progression that strongly correlates with survival.[7-9] Unfortunately, the disadvantages of surgical biopsy, including medical risk, cost, and potential sampling error, limit clinical application. Furthermore, biopsies cannot be feasibly performed serially and are often not performed until disease progression is pronounced.

Perfusion MRI (pMRI) non-invasively detects HGG and PTRE microvascular characteristics and offers a promising alternative to surgical biopsy.[10-12] This technique is based on the Dynamic Susceptibility-Weighted Contrast-Enhanced (DSC) method, which, in theory, measures Relative Cerebral Blood Volume (rCBV) to detect the differences in microvascular density (MVD) that separate PTRE and tumor growth. PTRE demonstrates decreased capillary perfusion and MVD, while tumor growth typically demonstrates angiogenesis and increased MVD[10].

Use of DSC has been under-utilized to date due to limitations, such as a lack of reliable thresholds and difficulties correcting for blood brain barrier disruptions. However recent improvements in DSC will enable more accurate diagnosis of tumor and PTRE. We have determined how to effectively correct for these inaccuracies, which will allow us to measure rCBV across multiple areas of a CE-MRI lesion to provide regionally specific estimates of tissue microvasculature and identify histologically distinct sub-regions of PTRE and tumor with over 95% accuracy.[13] Additionally, a recent study demonstrated high correlation between rCBV, histologic tumor fraction, and overall survival in a cohort of recurrent glioma patients.[14]

In this study, we focused on the plausibility of incorporating DSC-MRI into the routine diagnosis and management of recurrent HGG patients. Our hypothesis is that rCBV maps will better define tumor burden within and possibly outside these lesions, which may in the future help guide more focused radiation therapy for recurrent gliomas. Our goal was to compare these maps with conventional MRI to identify potential differences in treatment planning.

Materials and Methods

Patients

We recruited patients with recurrent GBM, detected on surveillance MRI, undergoing re-radiation therapy. Prior to enrollment, all study patients had undergone surgery and received temozolomide (TMZ) and radiation therapy (RT) according to the Stupp protocol.[19] We obtained approval from the Institutional Review Board and written informed consent from each subject. CE-MRI and DSC-MRI were obtained concurrently but analyzed and prepared independently of each other prior to comparison.

DSC-MRI Protocol

We used a 3 Tesla MR system for all patients. After antecubital fossa or forearm intravenous catheter placement and 6 minutes prior to the DSC-MRI acquisition, we administered 0.1 mmol/kg Gd-DTPA contrast agent (gadodiamide or gadobenate dimeglumine) preload dose to minimize T1W leakage effects.[22-25] During acquisition, we gave 0.05 mmol/kg bolus at 3–5 cc/sec.[22-25] The DSC-MRI sequence parameters were: Gradient-echo Echo Planar Imaging (EPI) with TR (msec)/TE (msec)/flip angle = 1500–2000/20/60^{o}; FOV 24 × 24 cm, matrix 128 × 128, 5 mm slice; no interslice gap. These parameters yielded an in-plane spatial resolution of 1.8 × 1.8 mm and voxel volumes of 0.02 cm^3. The total Gd-DTPA dose was 0.15 mmol/kg body weight.

Relative Cerebral Flood Volume (rCBV) and rCBV Map Generation

We used an Osirix workstation with IB Neuro and IB Suite (Imaging Biometrics) software to calculate whole-brain rCBV maps from the DSC data, coregistered to stereotactic data. RCBV was calculated based on well-established methods.[22-24] In short, after excluding the first 4 time points of each DSC-MRI series due to saturation effects, we normalized signal intensity (SI) to baseline and converted series to change in relaxivity over time [$\Delta R2^*(t)$] for the entire brain. We generated CBV maps by integrating the area under the $\Delta R2^*(t)$ curve, ending at the time point forty seconds after the nadir SI of the first pass-bolus. All CBV values were corrected for T1W leakage with preload dosing, and a modeling algorithm was used to correct T2/T2*W residual effects.[23] CBV maps were normalized to contralateral normal appearing white matter (NAWM) to create rCBV maps.[22-24]

Image Generation and Analysis

We obtained pre- and postcontrast T1 and T2W stereotactic MRI data sets before DSC-MRI. T1 and T2 FLAIR series were coregistered to produce an anatomic base using IB Suite. Archived anatomic CT scans and RT dosimetry were retrieved and transformed into MR space. rCBV maps were generated from DSC-MRI by tracing hyperintense FLAIR lesions to generate a region of interest (ROI). An rCBV mask was applied to the ROI to produce an rCBV map, which combined with dosimetry, were fused with the T1/FLAIR base to produce the final composite image. We analyzed the images by tracing the prescribed radiation dose and rCBV maps, to establish two volumes of interest (VOI). These were categorized into the following classes: 0) perfect alignment I) complete overlap but dose volume > rCBV volume II) complete overlap but rCBV volume > dose volume III) missed treatment volume. Each class also had 3 subcategories of gradation with A representing 75-100% congruity, B 25-50% and C 0-25%.

Results

DSC-MRI revealed regions of the rCBV map that did not overlap with treatment maps in four out of eight (50%) patients. Of these patients, two had large regions of potential tumor outside of the prescribed radiation dose volume. The remaining 4 patients were judged to have complete overlap of treatment and rCBV maps but with a treatment volume larger than the rCBV-indicated tumor sites. None of the patients were assessed to have either perfect alignment (Class 0) or complete overlap with rCBV volume greater than the treatment volume (Class II).

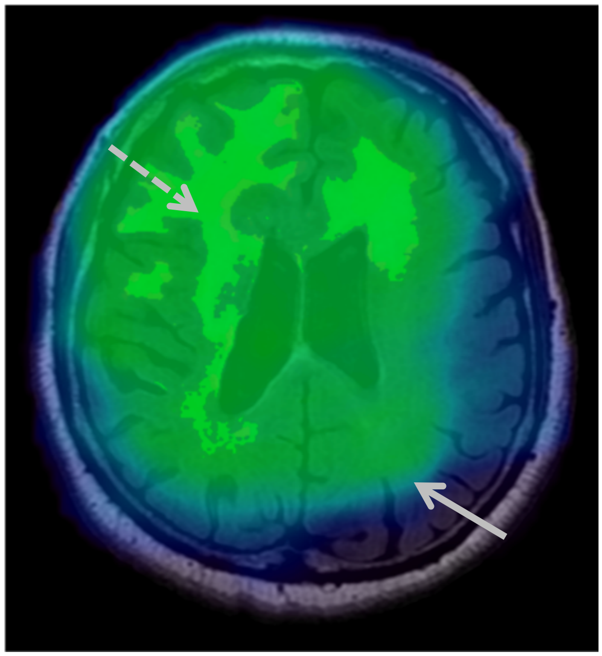

Figure 1: Example of Class 1B.
Image revealing overlap between radiation dose map (solid arrow) and rCBV map (dashed arrow) with target volume > tumor volume.

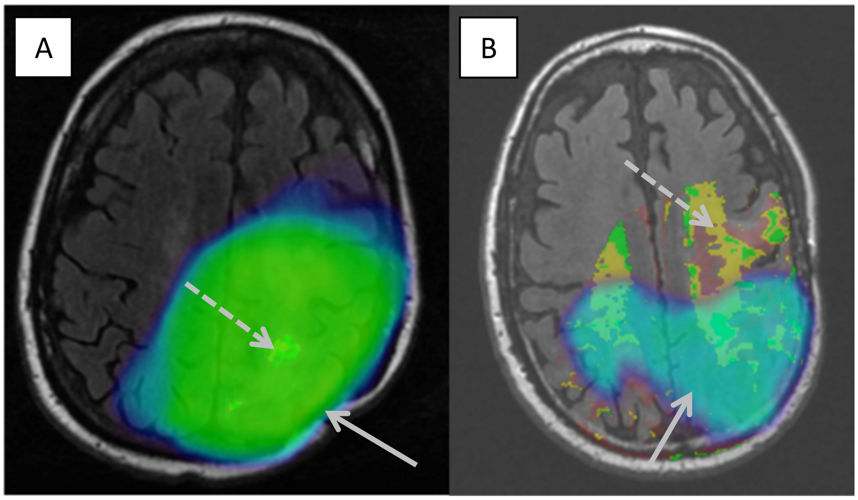

Figure 2: Examples of Class IC and IIIB.
A) Image reveals no missed treatment sites but radiation volume (dashed arrow) is much greater than rCBV volume (solid arrow). B) Image reveals missed treatment sites in bilateral parietal and left frontal lobes, since rCBV maps (dashed arrow) are seen outside RT treatment fields (solid arrow).

Table 1: Results of patient comparison image analysis

Patient	Class
1	IB
2	IIIA
3	IIIA
4	IA
5	IB
6	IIIB
7	IIIB
8	IC

Discussion

DSC-MRI identified four patients who had potentially untreated tumor sites. The other four patients revealed treatment regions that fully encompassed tumor but also showed regions of irradiated normal brain. Unlike previous studies investigating the usage of DSC-MRI in HGG patients, our study focused on areas of recurrence in relation to radiation treatment planning.

While DSC-MRI mostly correlates with radiation treatment plans, they appear to reliably identify regions of potentially untreated tumor. This suggests that DSC-MRI may be a viable tool to better delineate treatment targets during re-radiation therapy in recurrent HGG patients, identifying tumor missed by conventional MRI and sparing normal brain.

Few studies have attempted to investigate the role of DSC-MRI in radiation treatment planning for recurrent tumors. While Pirzkall et al. investigated the use of MR spectroscopy in treatment planning, their cohort consisted of patients undergoing RT for newly-diagnosed gliomas. Hu et al. found that the fraction of tumor burden as defined by rCBV correlated with OS while Schmainda suggested that rCBV is predictive of OS in recurrent HGG patients treated with bevacizumab.[21] Barajas et al. evaluated patients with progressive GBM and found rCBV was significantly higher in patients with recurrent GBM than in patients with PTRE. As such, we chose to compare the spatial extent of DSC-MRI lesions to FLAIR regions and their respective volumes to discover potential changes in treatment planning.

The use of conventional imaging to identify treatment targets leads to inaccurate treatment and likely unintended adverse effects. Currently the standard of care for imaged-based radiation treatment planning is MR fusion with planning CT images. The radiation therapy oncology group recommends gadolinium-enhanced T1 or FLAIR abnormalities + 2cm to determine treatment target volumes.[15] However, neither has been directly compared although both modalities face similar limitations in differentiating tumor and PTRE. Previous studies investigating advanced imaging techniques showed that tumor may not only extend beyond the borders of contrast-enhanced lesions, but also be smaller in overall volume.[25-27] This suggests that the current recommendations for deriving target volumes may both undertreat tumors and overtreat normal brain tissue.

This uncertainty in contrast-enhanced lesion composition presents many challenges when planning effective margins for RT. As a result, the current system of adding a uniform margin presents two potential problems. Firstly, treatment may cover too much normal brain, leading to radiation-induced toxicity, which is related to both radiation dose and volume.[20] Secondly, it may leave small, but significant, areas of tumor outside the treatment area, increasing the likelihood of local recurrence. Thus the goal of any advanced imaging technique would be to identify a margin that is tailored to each patient's tumor spread, presuming that such a technique would improve quality of life and overall survival.

The present study has some limitations. First, the sample size was small, limiting the application of these results to a larger population. Second, because the dosimetry software used at our institution is based of CT imaging, there could have been misregistration errors during the numerous transformations required to develop an anatomic MRI data set from the original dosimetry CT. Finally due to the qualitative nature of the study, several interpretative errors may have been introduced during manual lesion tracing and in the comparison of the coregistered images.

Future Directions

Based on these results, there are many directions to investigate. One important avenue will to explore would be whether these differences in RT treatment s rCBV maps contributed to any change in clinical outcome e.g. overall survival and quality of life. Also follow up imaging may be retrospectively analyzed to see if these regions of potentially untreated tumor were identified as sites of recurrence. Ultimately these studies would be used to support the role of supplementing conventional MRI with rCBV maps in routine clinical practice in order to more accurately treat tumors and improve patient outcomes.

Conclusions

DSC-MRI identifies unique regions of potential tumor burden compared to conventional MRI, potentially identifying tumor missed by conventional MRI and sparing normal brain. This suggests that DSC-MRI may be used to better delineate treatment targets during re-radiation therapy in recurrent HGG patients, improving quality of life and clinical outcomes.

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