Magnetic Resonance Imaging Mapping of Brain Tumor Burden: Clinical Implications for Neurosurgical Management: Case Report

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BACKGROUND AND IMPORTANCE: Distinction of brain tumor progression from treatment effect on postcontrast magnetic resonance imaging (MRI) is an ongoing challenge in the management of brain tumor patients. A newly emerging MRI biomarker called fractional tumor burden (FTB) has demonstrated the ability to spatially distinguish high-grade brain tumor from treatment effect with important implications for surgical management and pathological diagnosis.

CLINICAL PRESENTATION: A 58-yr-old male with glioblastoma was treated with standard concurrent chemoradiotherapy (CRT) after initial resection. Throughout follow-up imaging, the distinction of tumor progression from treatment effect was of concern. The surgical report from a redo resection indicated recurrent glioblastoma, while the tissue sent for pathological diagnosis revealed no tumor. Presurgical FTB maps confirmed the spatial variation of tumor and treatment effect within the contrast-agent enhancing lesion. Unresected lesion, shown to be an active tumor on FTB, was the site of substantial tumor growth postresection.

CONCLUSION: This case report introduces the idea that a newly developed MRI biomarker, FTB, can provide information of tremendous benefit for surgical management, pathological diagnosis as well as subsequent treatment management decisions in high-grade glioma.

KEY WORDS: Brain tumor, Neurosurgery, Fractional tumor burden (FTB), MRI, Pseudoprogression, Relative cerebral blood volume (rCBV), Case report

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Distinction of brain tumor progression from treatment effect on postcontrast magnetic resonance imaging (MRI) is an ongoing challenge in the management of brain tumor patients. Especially after chemoradiation therapy (CRT), the inability to distinguish true progression from treatment effect (a.k.a. pseudoprogression) is common,[1,2] thus making treatment decisions difficult, including if and when to repeat surgery. Moreover, especially in a treated tumor, postcontrast MRI cannot reliably guide the surgeon to active tumor sites. As a possible solution, a newly emerging MRI biomarker called fractional tumor burden (FTB) has demonstrated the ability to distinguish high-grade brain tumor from treatment effect,[3–5] with the fraction of tumor burden predictive of overall survival.[3,6,7] Described here is the report of a patient whose presurgical FTB was predictive of the localized tumor response as well as adjacent tumor progression, suggesting the utility of FTB to guide surgery, pathological diagnosis as well as follow-up treatment management.

ABBREVIATIONS: 5-ALA, 5-aminolevulinic acid; **CRT,** chemoradiation therapy; **DSC,** dynamic susceptibility contrast; **FTB,** fractional tumor burden; **srCBV,** standardized relative cerebral blood volume; **TMZ,** temozolomide; **TTF,** tumor treating field

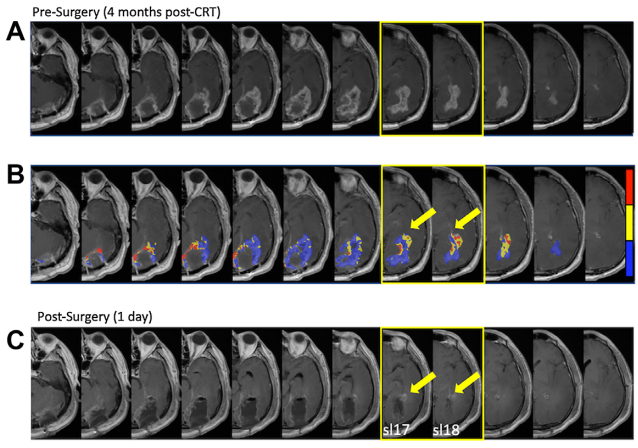

FIGURE 1. *Pre- and postsurgery MRI.* **A**, *Postcontrast T1-weighted MRI obtained approximately 4 mo after the completion of CRT and just prior to resurgery.* **B**, *Corresponding maps of FTB superimposed on the postcontrast T1-weighted MRI images. The FTB maps show areas of active tumor (red), treatment effect (blue) as well as a transitional zone (yellow).* **C**, *Postsurgical T1-weighted MRI showing extent of resection. Highlighted in a yellow box are image slices 17 and 18 that show regions of active tumor, as indicated by FTB, which were not resected.*

CLINICAL PRESENTATION

Patient Information

A 58-yr-old male with bilateral optic neuropathy presented with a brain lesion on follow-up MRI. He subsequently underwent gross-total resection and was diagnosed with glioblastoma, IDH wild type, O^6-methylguanine-DNA methyltransferase (MGMT) unmethylated, and intact alpha-thalassemia/mental retardation syndrom X-linked (ATRX). He was treated with standard concurrent chemoradiation therapy (CRT) with temozolomide (TMZ) followed by adjuvant TMZ and tumor treating fields (TTFs), which were initiated approximately 5 wk following CRT completion. The patient provided informed written consent to participate in this Institutional Review Board (IRB)-approved Health Insurance Portability and Accountability Act (HIPAA)-compliant study.

Clinical Imaging Studies

Throughout treatment, the patient remained asymptomatic neurologically. Following CRT, the patient was imaged with MRI at 1, 2, and 4 mo following CRT with a persistent differential diagnosis of treatment effect vs tumor. At 4 mo post-CRT, postcontrast T1-weighted imaging (Figure 1A) showed significant "foamy enhancement" surrounding the surgical cavity deemed to be suggestive of treatment effect. There was also a significant amount of edema around the enhancement that did not improve over time. Also given the tumor's unfavorable molecular markers, the patient was recommended for surgical resection.

Advanced Imaging

Dynamic susceptibility contrast (DSC) MRI was acquired throughout the patient's treatment. From the DSC, standardized relative cerebral blood volume (srCBV) maps were created from which a voxel-wise determination of tumor burden, within a contrast-agent enhancing lesion, can be mapped. These maps, referred to as FTB maps, allow spatial discrimination of high-grade tumor from treatment effect and are based on multisite studies where spatially matched tissue biopsies were used to validate sRCBV thresholds.[3–5] Specifically, srCBV thresholds were used to classify enhancing voxels as either treatment effect (srCBV < 1.0) or tumor admixture (srCBV > 1.0) with srCBV > 1.6 indicating $>88\%$ probability of tumor.[4] Thus, 3 distinct regions are delineated and indicated by blue (treatment effect), yellow, and red regions comprising the FTB maps presented in this report (software provided by Imaging Biometrics LLC was used to create the srCBV, deltaT1, and FTB maps). Following CRT and just prior to resurgery, FTB maps revealed varying proportions of these 3 distinct regions within the contrast enhancement (Figure 1B). The patient underwent resection without the guidance of FTB maps.

Surgical Findings

At 4 mo following the completion of CRT, the lesion was significantly debulked using stereotactic guidance. Intraoperatively, it was described as "extremely vascular" and "typical for recurrent high-grade glioma." After reasonable resection, intraoperative MRI was performed, which showed a significant amount of residual contrast enhancement. The lesion was further dissected until a normal-appearing brain was perceived in all directions.

Pathological Analysis

Tissue specimens (35 cm^3 in volume) were evaluated with hematoxylin and eosin staining. No tumor was present. Microscopic examination showed necrotic brain tissue, fibrous tissue, and thick-walled vessels consistent with treatment effect.

Postoperative Course

MRI performed postoperative day 1 demonstrated significant debulking with a small amount of residual contrast enhancement (Figure 1C). As indicated by the FTB maps, blue (treatment-effect) regions were predominant in the resected lesion (Figure 1B), which may explain the pathological diagnosis of no tumor present. Enhancing regions that remained, which are predominantly red/yellow on the FTB maps (Figure 1C, yellow arrows), correspond to the regions that demonstrated rapid progression in the subsequent months (Figure 2A).

The patient continued with the same course of treatment, which included adjuvant TMZ and TTF. However, compliance with TTF was generally poor, averaging 62% of "ON" time throughout the treatment period. Subsequent to imaging findings at 3 and 4 mo following redo resection, lomustine and then bevacizumab were initiated, respectively, as a result. After the

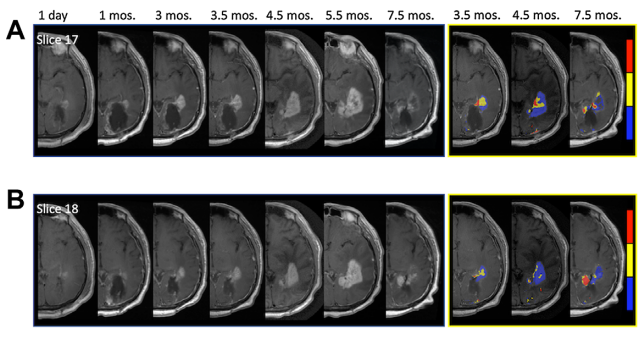

FIGURE 2. *Postcontrast T1-weighted MRI of slices 17 and 18* **A**, *(see Figure 1) obtained at 1 d, 1 mo, 3 mo, 3.5 mo, 4.5 mo, 5.5 mo, and 7.5 mo after resurgery. The location of unresected active tumor, as indicated by the FTB in Figure 1, became the site of substantial growth of the enhancing lesion over time.* **B**, *Corresponding FTB maps were also available at 3.5, 4.5, and 7.5 mo after surgery and concomitant with and after the time of treatment change. The focus of active tumor initially, followed by a decreasing extent of viable tumor, as indicated in blue, is consistent with an initial response to the change in treatment.*

change in treatment, MRI revealed improvement in postcontrast enhancement (Figure 2B). In addition, FTB maps obtained at 3.5, 4.5, and 7 mo postsurgery, coincident with and following the treatment change, show an initial focus of active tumor followed by a decrease in viable tumor over time suggestive of a response to treatment. Subsequent surgeries to obtain additional tissue were not performed.

DISCUSSION

Key Results

This report describes a first example of how a newly emerging MRI biomarker, FTB, can be of benefit to surgical management and pathological diagnosis. Creation of FTB maps is based on previous studies validating the rCBV threshold used to distinguish high-grade brain tumor from treatment effect for the creation of FTB. More recent studies demonstrated the relevance of FTB to predict outcomes[5–7] and guide clinical decisions.[8] Introduced here is the idea that FTB can likewise be useful for guiding surgery and diagnosis.

Limitations

The FTB maps were obtained retrospectively. A prospective assessment of FTB is necessary to fully validate the accuracy and utility of FTB for surgical guidance.

Interpretation

The noted discrepancy between the pathological diagnosis of treatment effect and the surgical report of highly vascular tumor underscores the idea that FTB can provide important spatial information to reconcile these differences and thus direct sampling toward active tumor. Though the site-specific clinical progression for the presented case supports this application, prospective validation of tumor extent will be necessary to further refine this technique.

Generalizabilty

As with other biomarkers, such as 5-aminolevulinic acid (5-ALA) fluorescence-guided surgery and contrast-enhanced ultrasound,[9] which can achieve a higher rate of complete glioma resection, FTB can likewise improve the extent of tumor resection by providing the added distinction between tumor and treated tissue. FTB may also be used in conjunction with techniques such as magnetic resonance spectroscopy (MRS), which can be used to noninvasively determine the isocitrate dehydrogenase mutation status in gliomas.[10] Specifically, by identifying regions of tumor and avoiding regions of necrosis, as guided by FTB maps, MRS may prove sufficiently reliable, eliminating the need for invasive biopsy sampling altogether.

CONCLUSION

This case report introduces the idea that an advanced MRI biomarker such as FTB can provide information of tremendous benefit for surgical management, pathological diagnosis as well as subsequent treatment management decisions in high-grade glioma cases where both tumor recurrence and treatment effect are possible diagnoses.

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Disclosures

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