



Commentary: Pitfalls in the Neuroimaging of Glioblastoma in the Era of Antiangiogenic and Immuno/Targeted Therapy

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A commentary on

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The profoundly aggressive nature of glioblastoma multiforme (GBM) leads to a dismal prognosis, with an overall survival of 15 months with standard surgery and chemoradiation (1, 2). Innovative therapeutic approaches are required to make meaningful survival advances. Therefore, efforts are underway to harness the immune system, target molecular signaling pathways, and even inhibit cell division utilizing alternating electric fields. These new therapies impact the follow-up neuroimaging in ways we are just beginning to understand. Immunotherapies, targeted therapies, antiangiogenic therapy, and tumor-treating fields (TTFields) are discussed, with a brief review of existing challenges in response assessment for these patients, along with some potential solutions.

The evaluation and optimization of novel techniques affecting the tumor microenvironment and signaling is under active investigation, including redirected T lymphocytes (chimeric antigen receptor T-cell, CAR-T), immune checkpoint inhibitors (nivolumab), growth factor/receptor inhibitors and vaccines (i.e., rindopepimut, dendritic cell vaccines), oncolytic virotherapy (i.e., poliovirus), among others (3–7). The harnessing of immune response involves inflammatory sequela which complicates the appearance on neuroimaging. Recognition of these factors has influenced the refinement of response assessment criteria as reflected in the immunotherapy Response Assessment in Neuro-Oncology, with lengthening of the expected window of pseudoprogression from 3 to 6 months, and extending the follow-up interval to confirm radiographic progression from 4 weeks to 3 months (8).

There is a paucity of data evaluating physiologic and metabolic imaging parameters in these patients, necessitating more studies to maximize the potential of advanced imaging tools in detecting elusive disease and redefining response in these patients.

Diffusion weighted imaging (DWI) utilizing apparent diffusion coefficient (ADC) has shown value in immunotherapy-treated GBM. Specifically, minimum ADC values from enhancing areas could differentiate between inflammation and progressive tumor in dendritic cell immunotherapy patients (9). In patients treated with anti-programmed cell death (PD-1) agents (nivolumab and pembrolizumab), after an initial 6-month period of suspected inflammatory hypercellularity, stabilization, and decrease in volumes of intermediate ADC areas correlated with response (10). Diffusion tensor imaging metrics such as fractional anisotropy (FA), linear, planar, and spherical anisotropy coefficients (CL, CP, and CS, respectively) have been shown to characterize tumor microenvironments at the cellular and subcellular level (11–13). These

techniques were applied to GBM following standard therapy, and a combination of FA, CL, and maximum relative cerebral blood volume (rCBVmax) had the highest accuracy in identifying true progression (area under the curve 0.91) (12). This multiparametric analysis may allow more accurate assessment following immunotherapy compared to conventional imaging (Figure 1). Perhaps in the future, techniques such as diffusion kurtosis imaging, diffusion spectrum imaging and restriction spectrum imaging (RSI) may allow even further characterization of subtleties of response assessment (14–18).

The targeted anti-vascular endothelial growth factor antibody bevacizumab has drastic effects on tumor vasculature and subsequent imaging. Diffusion has been widely studied in the evaluation of bevacizumab-treated tumors with somewhat complex results, though overall a trend demonstrating increasing restricted diffusion corresponds with worse prognosis in this setting (19–22). RSI has been shown to be less affected by bevacizumab-related changes in T2/FLAIR signal compared to standard DWI and may add specificity to the response assessment following antiangiogenic therapy (18).

Magnetic resonance spectroscopy (MRS) can also add utility in the response assessment of these patients. MRS has been evaluated to assess response to bevacizumab, differentiation

of pseudoprogression from true progression, and the genetic profiling of gliomas (23–25). Elevated lipid and low choline/*N*-acetyl aspartate (NAA) ratios have been reported in association with pseudoprogression (24, 26). Early experience with whole-brain echo-planar spectroscopic imaging following standard therapy also shows higher Cho/Cr and Cho/NAA ratios in patients with true progression compared to pseudoprogression, with further improved discriminatory accuracy with multivariate logistic regression analyses (27). The added value of MRS in the immunotherapy setting is yet to be determined.

Tumor-treating fields utilize alternating electric fields to inhibit mitosis (28, 29) and was FDA approved for recurrent GBM in 2011 and for newly diagnosed GBM in 2015 (30, 31). Initial experience utilizing advanced imaging techniques demonstrates decreased FA, Cho/Cr ratio, and rCBVmax, along with increased ADC within the first 2 months in patients treated by TTFields (32, 33). Understanding the imaging findings in patients treated with TTFields requires further investigation, to see if and how the appearance and timing of pseudoprogression and true progression in these patients differ from tumors treated with standard therapy and immunotherapy.

The devastating prognosis of GBM which has only been modestly improved by recent efforts is a testament to the exceedingly

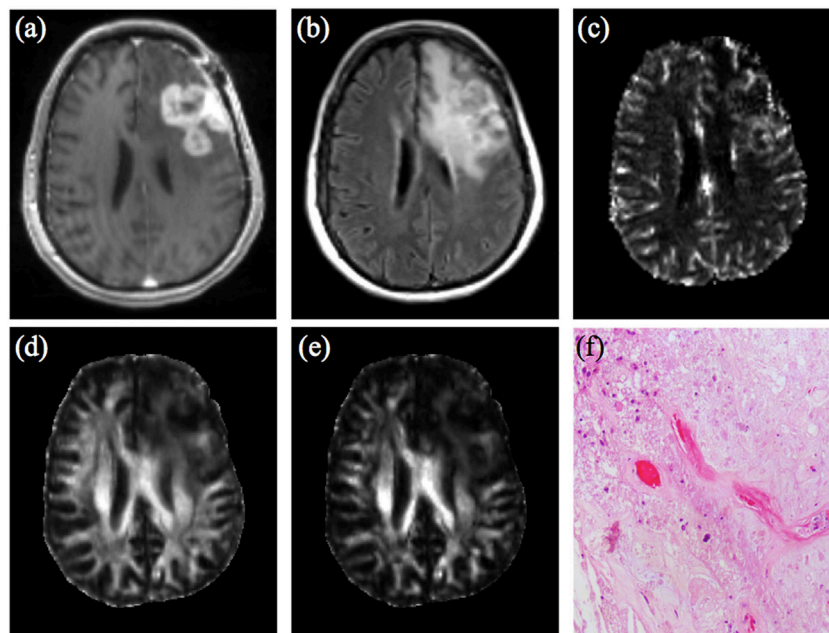


FIGURE 1 | 47-year-old woman with GBM, status post gross total resection and chemoradiation, treated with dendritic cell vaccine immunotherapy (ICT-107) (four vaccine treatments over 2 months prior to this imaging.) **(A)** Contrast-enhanced T1-weighted image shows large lobulated nodular enhancing lesion measuring 4.5 cm × 2.8 cm at site of previously resected GBM which had increased from prior scans. **(B)** FLAIR images demonstrate a large area of associated T2/FLAIR signal abnormality in the left hemisphere. **(C)** DSC shows elevated rCBV from the enhancing region of the tumor. Overall constellation of these conventional and advanced imaging findings were concerning for true progression. Logistic regression model combining rCBVmax with FA **(D)** and CL **(E)** according to analysis used in Wang et al. *AJNR* 2016 did not meet criteria for true progression (rCBVmax 4.396, FA 0.112, CL 0.0418) (12), suggesting a significant component of treatment-related changes. However immunotherapy was discontinued due to concern for progression. **(F)** Pathology from surgical resection performed 2 weeks later demonstrates predominant treatment effect (~80%) with hyalinization of vessels and tissues, geographic necrosis, and macrophage infiltration. Recurrent infiltrating glial tumor cells with marked nuclear pleomorphism were also present, comprising approximately 20% of the specimen. Abbreviations: GBM, glioblastoma multiforme; FLAIR, fluid attenuation inversion recovery; DSC, dynamic susceptibility contrast; rCBV, relative cerebral blood volume; rCBVmax, maximum relative cerebral blood volume; FA, fractional anisotropy; CL, linear anisotropy coefficient.

adaptive behavior of this tumor, with the best currently available overall survival of 20.5 months with TTFields in addition to standard therapy (31). As a result, the evolving standard of care will likely require a multimodality approach incorporating TTFields and immunotherapy with surgery, radiation, and chemotherapy, the optimal combination of which is still being defined. These new therapies have the capability to mask and/or mimic disease on conventional images and, therefore, imaging evaluation is challenging. Advanced MR techniques have shown potential to further differentiate true progression from pseudoprogression, though efforts to understand these subtleties are early in development. There are barriers to adopt these imaging tools into clinical workflow, including added time for scanning and processing data, which often requires subspecialized knowledge and/or software that is not readily available. Optimizing understanding and use of readily available imaging data such as ADC values may provide added value without added acquisition or processing time. Efforts should also be made to create user friendly applications to process and interpret advanced MRI data. Furthermore, computation of multiparametric radiomic data may allow distillation of many

imaging variables into a clinically relevant synthesis, potentially aiding in response assessment (34). Close collaboration with neuropathology, neurosurgery, and neuro-oncology is also critical in the optimization of response assessment. For example, the quantification of a pathologic specimen's proportion of tumor vs. treatment effects [i.e., the histologic analysis used in Wang et al. (12)], and the use of image-matched specimens can further elucidate tissue composition and define treatment response. Continued multidisciplinary efforts are necessary to better define treatment response and guide therapy in patients with GBM.

AUTHOR CONTRIBUTIONS

AS: first author; SW: MRI image processing, figure, and technical input; PG: neuropathology and figure input; and SM: senior author.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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