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Association of Diffusion and Anatomic Imaging Parameters with Survival for Patients with Newly Diagnosed Glioblastoma Participating in Two Different Clinical Trials[1]

Qiuting Wen*†,2, Laleh Jalilian*2, Janine M. Lupo*, Yan Li*, Ritu Roy§,¶, Annette M. Molinaro§,¶, Susan M. Chang§, Michael Prados§, Nicholas Butowski§, Jennifer Clarke§ and Sarah J. Nelson*†,‡

*Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA United States; †UCSF/UCB Joint Graduate Group in Bioengineering, University of California, San Francisco, San Francisco, CA United States; ‡Department of Bioengineering and Therapeutic Sciences, University of California, San Francisco, San Francisco, CA United States; §Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA United States; ¶Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA United States

Abstract

PURPOSE: To evaluate the time course and association with survival of anatomic lesion volumes and diffusion imaging parameters for patients with newly diagnosed glioblastoma who were treated with radiation and concurrently with either temozolomide and enzastaurin (TMZ+enza cohort) or temozolomide, erlotonib, and bevaciumab (TMZ+erl+bev cohort). *MATERIALS AND METHODS:* Regions of interest corresponding to the contrast-enhancing and hyperintense lesions on T2-weighted images were generated. Diffusion-weighted images were processed to provide maps of apparent diffusion coefficient, fractional anisotropy, and longitudinal and radial eigenvalues. Histograms of diffusion values were generated and summary statistics calculated. Cox proportional hazards models were employed to assess the association of representative imaging parameters with survival with adjustments for age, Karnofsky performance status, and extent of resection. *RESULTS:* Although progression-free survival was significantly longer for the TMZ+erl+bev cohort (12.8 vs 7.3 months), there was no significant difference in overall survival between the two populations (17.0 vs 17.8 months). The median contrast-enhancing lesion volumes decreased from 6.3 to 1.9 cm^3 from baseline to the postradiotherapy scan for patients in the TMZ+enza cohort and from 2.8 to 0.9cm^3 for the TMZ+erl+bev cohort. Changes in the T2 lesion volumes were only significant for the latter cohort (26.5 to 11.9 cm^3). The median apparent diffusion coefficient and related diffusion parameters were significantly increased for the TMZ+enza cohort (1054 to 1225 $\mu m^2/s$). More of the anatomic parameters were associated with survival for the TMZ+enza cohort, whereas more diffusion parameters were associated with survival for the TMZ+erl+bev cohort. *CONCLUSION:* The early changes in anatomic and diffusion imaging parameters and their association with survival reflected differences in the mechanisms of action of the treatments that were being given. This suggests that integrating diffusion metrics and anatomic lesion

Address all correspondence to: Sarah J. Nelson, PhD, Department of Radiology and Biomedical Imaging, UCSF, 1700 4th St, Byers Hall, Box 0775, UCSF, San Francisco, CA 94143-0775.
E-mail: sarah.nelson@ucsf.edu

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[2]These authors contributed equally to this work.

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volumes into the Response Assessment in Neuro-Oncology criteria would assist in interpreting treatment-induced changes and predicting outcome in patients with newly diagnosed glioblastoma who are receiving such combination treatments.

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Introduction

Glioblastoma (GBM) is the most malignant primary malignant brain tumor in adults. The standard of care for patients with newly diagnosed GBM consists of surgery, radiotherapy (RT), and temozolomide (TMZ). In a recent phase III trial, patients treated in this manner had significantly improved overall survival (OS) compared with patients who received RT alone [1]. The median overall survival obtained with this treatment was 15 months [1]. A number of different therapeutic agents that are expected to have a synergistic effect with RT and TMZ have been considered [2–6], with the goal of improving outcomes for patients with GBM. Assessment of early response to these combination treatments is complicated by their different mechanisms of action and the impact that they have on standard magnetic resonance (MR) imaging parameters [7].

Enzastaurin is a protein kinase C β-inhibitor that is reported as having a direct antitumor effect through the suppression of tumor cell proliferation and induction of apoptosis, and indirect effects that are expressed by the inhibition of tumor-induced angiogenesis [8]. Preclinical reports have shown that it is synergistic with radiation and induces apoptosis in glioma model systems [9]. These data provided the rationale for a recent phase II clinical trial of RT, TMZ, and enzastaurin in patients with newly diagnosed GBM. Although the clinical outcome data for patients from this study have already been reported [3], the role of advanced imaging parameters in assessing efficacy and predicting outcome has not yet been presented.

Another agent of interest for combination therapy is bevacizumab, which is a humanized monoclonal vascular endothelial growth factor (VEGF)–blocking antibody that normalizes vascular permeability and regulates angiogenesis [10]. Preliminary studies of bevacizumab in patients with recurrent GBM have shown a dramatic decrease in the size of the enhancing lesion and an increase in progression-free survival (PFS) [11–13]. This led to a number of clinical trials of patients with GBM that combined bevacizumab with standard RT and chemotherapy. The biological hypotheses that have driven these analyses are that combination treatment would normalize tortuous tumor vasculature, improve the delivery of chemotherapeutics, and hence provide improved overall survival [14].

The disadvantage of treatments such as enzastaurin and bevacizumab is that they cause changes in anatomic imaging characteristics, which can make it difficult to use conventional methods for assessing response to therapy. For example, agents that reduce proliferation may result in a clinical assessment of stable disease, whereas antiangiogenic agents decrease the size of the contrast-enhancing lesion (CEL), but this does not necessarily signify a reduction in bulk tumor [11]. Another complication of anti-VEGF agents that have been reported is to result in increased tumor invasiveness that is expressed by an increase in the size of the region of T2 hyperintensity rather than the changes in the enhancing lesions [15]. Although the Response Assessment in Neuro-Oncology criteria include consideration of changes in the T2 lesion as part of the definition of response to therapy [16], it is not clear whether such changes are specific to recurrent tumor or represent nonspecific RT-induced changes in normal white matter.

Diffusion-weighted imaging has been proposed as an adjunct to standard anatomic imaging because it can provide new information about response to therapy through the evaluation of parametric images that reflect variations in tissue composition and architecture [17–19]. The most widely considered variable is the apparent diffusion coefficient (ADC), which is sensitive to an increase in tumor cellularity, formation of necrosis, and the presence of vasogenic edema. Other variables of interest are the fractional anisotropy (FA), which describes variability in the directionality of diffusion, and eigenvalues (EV1 and EVrad), which provide information on the magnitude of the preferred (longitudinal) direction of diffusion and average perpendicular components. These reflect local variations in tissue properties associated with unregulated cell growth and changes in the extracellular environment. The hypotheses of interest are that a decrease in FA reflects breakdown of normal brain structure and that the magnitude of EV1 and EVRAD may be more sensitive to such changes than the ADC alone.

Metrics describing pretreatment and early changes in diffusion within the CEL have been reported as predictors of response to therapy in brain tumors [17–22]. These include the evaluation of histograms of ADC at single time points [20,21] and the functional diffusion map (fDM), which describes changes between ADC values on a pixel-by-pixel basis in overlapping regions of the CEL from two successive scans [17,18]. Although these methods have been applied to the assessment of agents such as bevacizumab [19,22], the relatively small size of the CEL in follow-up scans means that they do not meet the cutoff criterion of 3 to 4 cm^3 that was originally defined for this type of analysis [17,18].

The purpose of this study was to compare the patterns of early changes in anatomic and diffusion parameters for patients with newly diagnosed GBM who had received advanced imaging examinations and had been participating in two different clinical trials. The hypothesis was that the metrics considered would provide information about the effectiveness of the treatments being considered. Scans were obtained at baseline and at three follow-up time points. Imaging parameters derived from these scans were evaluated to see if they were associated with PFS and OS.

Methods

Study+ Population

A total of 75 patients with newly diagnosed GBM (WHO grade IV) who had received advanced imaging examinations and had participated in phase II clinical trials at UCSF were evaluated in this study. Their diagnosis was based upon histological analysis of tissue from surgical