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Clinical study

Diagnostic utility of restriction spectrum imaging (RSI) in glioblastoma patients after concurrent radiation-temozolomide treatment: A pilot study

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ABSTRACT

Discriminating between tumor recurrence and treatment effects in glioblastoma patients undergoing radiation-temozolomide (RT/TMZ) therapy remains a major clinical challenge. Here, we report a pilot study to determine the utility of restriction spectrum imaging (RSI), an advanced diffusion-weighted MRI (DWI) technique that affords meso-scale resolution of cell density, in this assessment. A retrospective review of 31 patients with glioblastoma treated between 2011 and 2017 who underwent surgical resection or biopsy over radiographic concern for tumor recurrence following RT/TMZ was performed. All patients underwent RSI prior to surgical resection. Diagnostic utility of RSI for tumor recurrence was determined in comparison to histopathology. Analysis of surgical specimens revealed treatment effects in 6/31 patients (19%) and tumor recurrence in 25/31 patients (81%). There was general concordance between the measured RSI signal and histopathologic diagnosis. RSI was negative in 5/6 patients (83%) in patients with histological evidence of treatment effects. RSI was positive in 21/25 patients (84%) in patients with tumor recurrence. The sensitivity, specificity, positive and negative predictive values of RSI for glioblastoma recurrence were 84%, 86%, 95%, and 60%, respectively. Histopathologic review showed agreement between the RSI signal and cellularity of the tumor specimen. These data support the use of RSI in the evaluation of treatment effects versus tumor recurrence in glioblastoma patients after RT-TMZ therapy.

1. Introduction

Glioblastoma is the most common primary malignancy of the central nervous system, with an incidence of 2–3 per 100,000 [1]. The current standard of care for glioblastoma involves surgical resection, followed by fractionated radiotherapy (RT) and adjuvant chemotherapy with the alkylating agent temozolomide (TMZ) [2,3]. Treatment response and disease recurrence are typically assessed using serial contrasted MRI studies. New regions of contrast enhancement on these MRIs often represent tumor growth [4]. However, differentiating between tumor growth and treatment effects, including pseudoprogression (a self-limiting process that occurs within weeks to three months of initial treatment) and radiation necrosis (a progressive lesion that occurs months to years after initial treatment and typically requires intervention), remains challenging with conventional MRI [4,5]. Regions of contrast enhancement generally represent areas of disrupted blood-brain barrier, which can occur secondary to tumor growth or treatment effects [6]. Considering this, current guidelines for interpretation of MR images taken within 12 weeks of concurrent RT/TMZ treatment recommend against imaging-based diagnosis of tumor recurrence or progression, unless confirmed by histopathology [7].

Restriction spectrum imaging (RSI) is an advanced form of diffusion-weighted imaging (DWI) [8,9]. Compared to conventional DWI, which employs a single gradient in the assessment of molecular diffusion, RSI collects data over a range of diffusion gradient strengths, diffusion times, and diffusion weighting factors (b-values) [10]. The integration of this spectrum of signals affords dis-

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crimination of intracellular water diffusion relative to extracellular water diffusion. Histologically, signals of intracellular diffusion correlate with regional cellularity [8,11]. As such, RSI offers biologic information of a fundamentally different nature relative to contrast enhancement imaging. When applied to tumor surveillance, appearance of new RSI signals may serve as a biomarker for tumor recurrence [12]. RSI has shown promise for differentiating tumor grade and treatment responses for multiple tumor types [13–16]. Here, we test the hypothesis that RSI may be useful in the assessment of radiation effect versus tumor recurrence for post-RT/TMZ glioblastoma patients.

2. Methods

2.1. Patients

An Institutional Board Review (IRB 130601) approved retrospective data review of prospectively enrolled glioblastoma patients treated between 2011 and 2017 at the University of California, San Diego was performed to identify patients who: 1) developed new regions of contrast enhancement on MRIs taken after RT/TMZ treatment, 2) underwent RSI before surgical resection or biopsy of the contrast enhancing region, and 3) underwent surgical resection or biopsy, yielding specimens derived from regions of contrast enhancement. All patients underwent standard of care treatment, with clinical decisions (including initial treatment and post-treatment surveillance imaging) made after case review in a brain tumor board consisting of two neurosurgeons, two radiation oncologists, a neuro-radiologist, and a neuropathologist. Patient age, sex, histopathology, and RSI imaging characteristics were recorded.

2.2. Imaging and analysis

Pre- and post-gadolinium MRI as well as RSI imaging was performed as previously described [14], with all patients imaged using the same protocol. Specifically, images were obtained on a 3T Signa Excite HDx scanner (GE Healthcare, Milwaukee, Wisconsin). For RSI, a single-shot pulsed gradient spin-echo EPI sequence was used (TE/TR = 96 ms/17 s, FOV = 24 cm, matrix = 96 × 96 × 48) with 4b-values (b = 0, 500, 1500, and 4000 s/mm^2) with 6, 6, and 15 diffusion directions for b = 500, 1500, and 4000, respectively (approximate scan time ~8 min). Details of this RSI model were as previously reported [8]. RSI signal analysis was performed based on parameters reported by Kothari et al. [17]. RSI signal map was co-registered to 3D T1 post-contrast volume using the Amira software package (Visage Imaging, San Diego, California).

To determine a threshold value for defining an RSI positivity with clinical translatability, MR images with regions of interest (ROIs) with RSI signals that were quantitatively 1.2, 1.5, 1.7, 2.0, and 2.5-fold that of the contra-lateral cortex were visually reviewed by three independent reviewers. The reviewers were asked to select the minimal signal intensity that allowed consistent discrimination between ROI and the contralateral cortex. Uniform consensus of discrimination by the three reviewers was found when the ROI harbored RSI signals greater than 2-fold that of the contra-lateral cortex. In this context, RSI positivity was defined as signal greater than 2-fold higher than that seen in the contra-lateral cortex.

Post-contrast MRI and RSI images were co-registered prior to import into a Brainlab surgical navigation device (Brainlab, Munich, Germany). ROIs with RSI positivity (defined as described above) were contoured for surgical biopsy or resection. For lesions that were not accessible to open resection, biopsy at the center of the region of RSI positivity was performed [18]. For lesions amenable to surgical resection, the RSI positive region was located using the Brainlab probe and removed for pathologic analysis prior to resection of the remainder of the contrast enhancing region. In cases where RSI was negative, the entirety of the contrast enhancing region was removed whenever possible. Surgical specimens secured from these regions were analyzed by a board-certified neuropathologist, with pathologic diagnoses reviewed by the senior author. Findings and images from the formal pathology report were recorded.

2.3. Statistics

Correlative analysis between RSI positivity and histopathologic findings were performed. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for RSI positivity using histopathologic findings of radiation effect and tumor recurrence as the gold standard. Analyses were performed using Stata version 11.2 (StataCrop, College Station, Texas).

3. Results

3.1. Clinical information for study subjects

Pertinent clinical information of the study cohort is shown in Table 1. The age distribution of the study cohort ranged from 29 to 70 years, with a mean age of 58 (+12 years). Eighteen patients were male (58%), and 13 were female (42%). The age distribution and slight male dominance in the study cohort is generally consistent with the epidemiology of glioblastoma. Sixteen of the 31 patients (52%) underwent stereotactic needle biopsy, while the remaining 48% underwent open surgical resection. Surgical specimens from six of the 31 patients (19%) showed findings consistent with treatment effects and no evidence of tumor recurrence. Histopathology of the remaining twenty-five patients (81%) showed evidence consistent with tumor recurrence (with variable levels of admixed treatment effects also seen). The proportion of patients who underwent needle biopsy versus open resection was comparable in patients diagnosed with treatment effects (4 biopsy, 2 open surgery) and tumor recurrence (12 biopsy, 13 open surgery).

3.2. RSI positivity and histopathologic diagnosis

Overall, 21 of the 31 patients (67%) showed RSI positivity within regions of new contrast enhancement found on MRIs taken after RT/TMZ treatment. The proportion of patients with RSI positivity within regions of new contrast enhancement was comparable between patients who underwent needle biopsy and open resection. Of the six glioblastoma patients with tissue confirmed treatment effects, RSI was predominantly negative. Specifically, five of the six patients showed no evidence of RSI positivity in the contrast enhancing region. Of the twenty-five patients with tissue confirmed tumor recurrence, RSI was positive in 21 subjects (84%). Estimates of statistical parameters supporting the diagnostic utility for RSI are shown in Table 2. The sensitivity, specificity, positive and negative predictive values of RSI for glioblastoma recurrence were 84%, 86%, 95%, and 60%, respectively.

3.3. Histopathologic correlation with RSI

The histopathology of surgical specimens was reviewed for cases where the RSI signal was discrepant with the histologic diagnosis. Specifically, we reviewed histologic images for the one case of RSI positivity in a patient who suffered from radiation effects, as

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Table 1
Summary of patient demographics, histopathology, RSI results, and tissue sampling methodology.

Subject	Age	Sex	Pathology	RSI+	Surgery (S)/Biopsy (B)
1	29	M	Recurrence	+	B
2	63	M	Recurrence	–	S
3	64	F	Treatment Effects	–	B
4	56	F	Recurrence	+	S
5	65	M	Recurrence	–	B
6	57	M	Recurrence	+	S
7	62	F	Recurrence	+	B
8	47	M	Treatment Effects	–	S
9	53	M	Recurrence	+	S
10	58	M	Recurrence	+	S
11	31	F	Recurrence	+	B
12	51	M	Recurrence	+	S
13	71	M	Recurrence	+	S
14	50	M	Recurrence	+	B
15	67	M	Recurrence	+	B
16	79	F	Recurrence	+	B
17	59	M	Treatment Effects	–	B
18	67	M	Recurrence	–	B
19	55	M	Recurrence	+	B
20	72	M	Treatment Effects	–	S
21	62	M	Recurrence	+	S
22	39	M	Recurrence	+	S
23	72	F	Recurrence	+	B
24	63	M	Recurrence	+	S
25	66	M	Recurrence	+	S
26	37	F	Recurrence	+	B
27	57	M	Recurrence	–	S
28	66	M	Recurrence	+	S
29	73	M	Treatment Effects	–	B
30	57	M	Recurrence	+	B
31	64	F	Treatment Effects	+	B

Table 2
Diagnostic utility of RSI for GBM recurrence.

	Estimate	CI
Sensitivity	84%	64–95%
Specificity	86%	42–97%
Positive Predictive Value (PPV)	95%	77–99%
Negative Predictive Value (NPV)	60%	37–79%

well as the four patients who suffered from tumor recurrence despite negative RSI signals. Four patients in whom the RSI signal was concordant with the histologic diagnosis were also randomly selected for analysis.

In the four RSI-signal concordant patients, there was excellent agreement between RSI positivity and cellularity of the contrast enhancing region. Fig. 1 shows MRI and histopathologic images of subject 29 who developed an area of contrast enhancement distant to the original surgical site that showed RSI positivity. The region was surgically excised. Histologic analysis of the specimen secured from this second site revealed a highly cellular glioblastoma. Fig. 2 shows the corresponding images of subject 8, who developed an area of progressively enlarging contrast enhancement adjacent to the left temporal resection site. There was no RSI signal, but the region was resected due to progressive enlargement over four independent MRI studies. Histologic analysis of the resected specimen showed regions of hypo-cellularity without evidence of tumor recurrence.

Conversely, Fig. 3 shows representative MRI and histologic images from an RSI-discordant patient (subject 2) who suffered tumor recurrence in which the RSI signal was negative. Although histologic analysis in this patient largely revealed regions of radiation effect, there were small islands of rare tumor cells (inferior aspect of the histology image) that ultimately led to a diagnosis of recurrent tumor. Finally, Fig. 4 shows representative images from the lone patient (subject 6) who was found to have treatment effects on histopathologic analysis, but a positive RSI signal. In this patient, histopathology revealed regions of high density reactive astrocytes (i.e. gliosis) interwoven with regions of radiation effect.

These correlative studies suggest a general agreement between RSI signal and cellularity. However, small islands of microscopic glioblastoma growth can occur in regions that otherwise show a paucity of cells (resulting in a general RSI negativity). Similarly, treatment effects can be associated regions with high-density reactive astrocytes, resulting in RSI positivity.

4. Discussion

Differentiating treatment effects from tumor recurrence is an ongoing clinical challenge in the management of glioblastoma patients. Here we assessed the utility of RSI, a multi-spectral, multi-directional form of DWI, as a tool to capture local tumor and cellular architecture in glioblastoma patients after standard of care RT/TMZ treatment. In general, there was a good correlation between RSI signal and histopathologic diagnosis, with a sensitivity and specificity of 84% (CI: 63–95%) and 86% (42–100%), respectively. Based on our cohort, estimates of positive predictive value and negative predictive value of RSI positivity for glioblastoma recurrence were 95% (CI: 77–99%) and 60% (CI: 37–79%), respectively. Moreover, careful review of selected histopathologic samples from patients in this study demonstrated a general agreement between the RSI signal and the cellularity of the tumor specimen. Specifically, histology in cases where tumor recurrence was observed despite negative RSI showed small islands of microscopic glioblastoma growth in regions that were otherwise devoid of cell content. Conversely, the one case where treatment effects were associated with a positive RSI signal showed a high density of reactive astrocytes. These results support the utility of RSI in assessing regional cell density in glioblastoma patients after RT/TMZ treatment, with the caveat that cellularity is not a perfect proxy for tumor recurrence.

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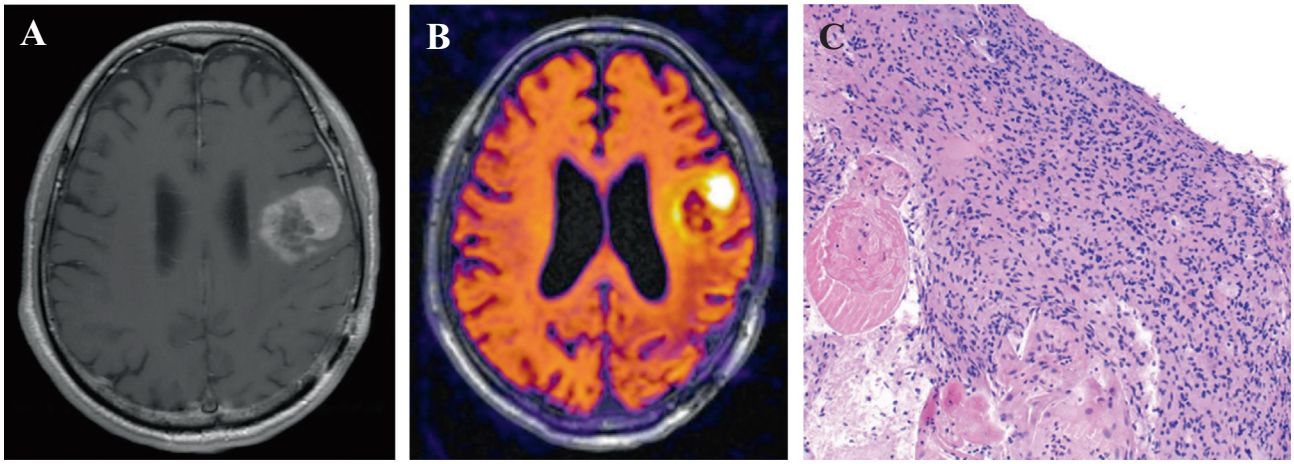

Fig. 1. RSI positivity in a patient with glioblastoma recurrence (true positive). Representative images from a patient who developed an area of contrast enhancement distant to the original surgical site that showed RSI positivity. T1 post-contrast enhancement MRI is shown in (A). Positive RSI signal is shown in (B). Histopathology of the resected specimen (C) demonstrated findings consistent with a highly cellular glioblastoma.

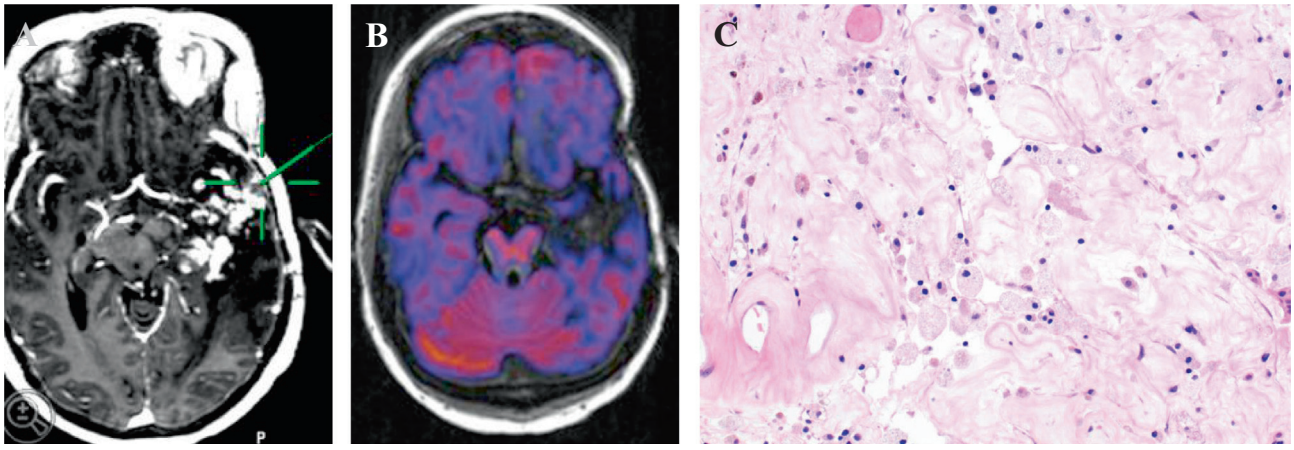

Fig. 2. RSI negativity in a patient with treatment effects (true negative). Representative images from a patient who developed a progressively enlarging contrast enhancing area adjacent to the site of a previously resected left temporal tumor. T1 post-contrast enhancement MRI is shown in (A). Negative RSI signal is shown in (B). Histopathology of the resected specimen (C) demonstrated findings consistent with treatment effects, without evidence of tumor recurrence.

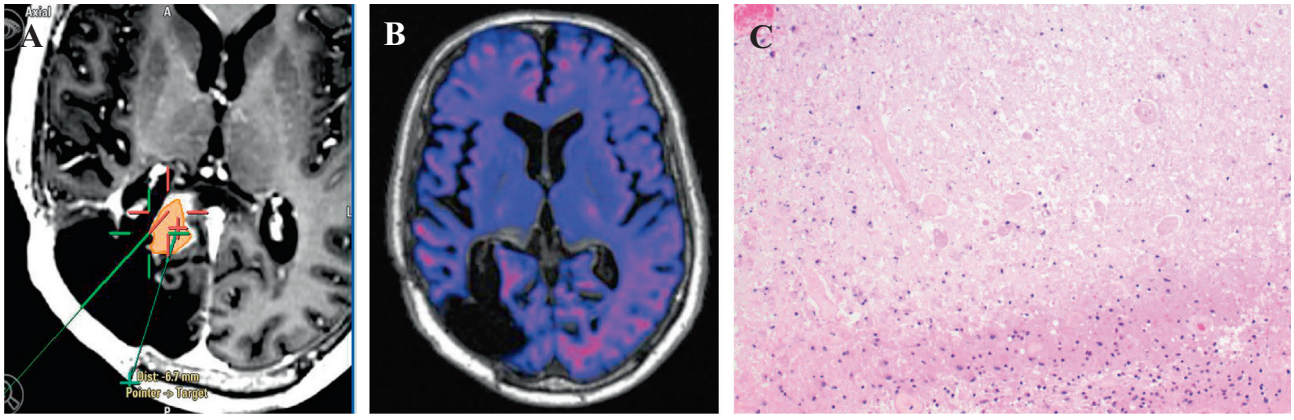

Fig. 3. RSI negativity in a patient with tumor recurrence (false negative). Representative images from a patient who developed a progressively enlarging contrast enhancing area adjacent to a right occipital surgical site. T1 post-contrast enhancement MRI is shown in (A). Negative RSI signal is shown in (B). Histopathology of the resected specimen (C) largely demonstrated radiation effects, however, small areas of tumor cells (inferior aspect of image) were observed, consistent with tumor recurrence.

Assessment of tumor recurrence versus treatment effects after RT/TMZ fundamentally determines the subsequent clinical course for glioblastoma patients. As such, there has been significant effort invested in the development and testing of imaging biomarkers that facilitate this assessment. CT and conventional MRI have nonetheless largely proven to be insensitive to this delineation

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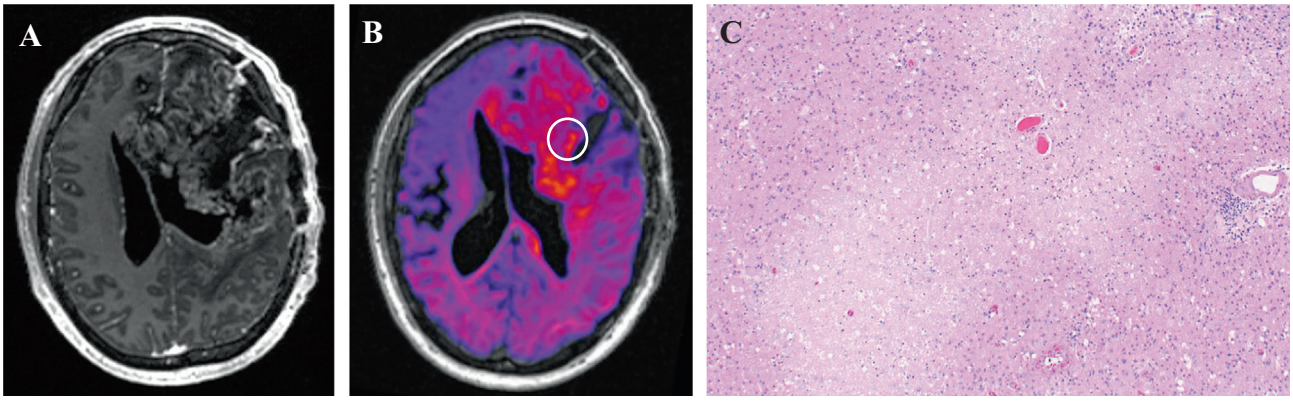

Fig. 4. RSI positivity in a patient with treatment effects (false positive). Representative images from a patient who developed progressive enlargement of a contrast enhancing area surrounding a left frontal resection cavity. T1 post-contrast enhancement MRI is shown in (A). Positive RSI signal is shown in (B). Histopathology of the resected specimen (C) demonstrated intermixed high-density reactive astrocytes (i.e. gliosis) and radiation effects, without evidence of tumor recurrence.

despite some authors suggesting that certain lesion features, such as involvement of the corpus callosum or periventricular white matter, new contrast-enhancement post-treatment, or a "Swiss cheese" appearance, may favor treatment effects over tumor recurrence [19]. Other efforts range from theoretic, such as textural analysis of multi-parametric MRI [20], to more established, including MR perfusion and spectroscopy [21], diffusion weighted imaging (DWI) [22], single-photon emission computed tomography (SPECT) [23], and positron emission tomography (PET) [24,25]. The reported sensitivity and specificity of these approaches for differentiating recurrent tumor from treatment effects is nonetheless varied (PET: 65–81% sensitivity and 40–94% specificity; MR perfusion: 50–100% sensitivity and 45–100% specificity; MR spectroscopy: 36–94% sensitivity and 55–100% specificity), in addition to the common limitation of poor spatial resolution across all three platforms [19]. Given the complexity of glioblastoma physiology *in vivo* [26], it is likely that informative imaging assessments will require synthesizing information from imaging modalities that reflect distinct but complimentary biologic properties that proxy tumor recurrence, such as the cellularity data obtained through RSI.

The presented data should be interpreted in the context of the limitations and biases inherent to our retrospective design [27] and the single institutional nature of our study. While MR scanner specifications vary amongst manufacturers, reproducibility should be expected if the RSI protocol reported here is applied to an MR scanner of the same manufacturer. Additionally, the performance of RSI relative to more traditional DWI/ADC imaging for delineating tumor recurrence from treatment effects warrants further investigation. Such work is currently on-going. Another consideration involves the subjective nature of histopathologic diagnoses, and the inherent limitations of tissue analysis for the identification of potentially sparsely distributed tumor cells within an area of treatment effect [28]. Despite the inherent limitations of histopathology, it remains the most widely accepted diagnostic standard [29]. Finally, while the sample size of our study is limited, it represented a genuine effort to study the application of a novel imaging modality on a rare disease with high case fatality. Accordingly, the dataset required collection over a six-year study period in a large university setting. Our work is nonetheless comparable in size to recently published studies assessing the efficacy of other imaging modalities for differentiating tumor recurrence from treatment effects [20,22–24].

Despite the various limitations discussed, our study forms a foundation for future RSI studies in post-treatment glioblastoma patients. Specifically, future studies should be designed with a focus on validation of the presented results, including time-to-progression. Consideration should also be given to the collection of pertinent molecular information including Methyl-Guanine Methyl Transferase (MGMT) promoter methylation and Isocitrate Dehydrogenase (IDH) mutation status. Finally, scrutiny of whether sufficient tumor is sampled through stereotactic biopsies in future study designs is also warranted.

5. Conclusion

Our results provide pilot data suggesting that RSI may yield useful information pertaining to the cellularity of contrast enhancing regions in glioblastoma patients subsequent to RT/TMZ treatment. This RSI data potentially harbors diagnostic utility in determining whether the enhancement is related to treatment effects or tumor recurrence.

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