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Glioblastoma radiomics: can genomic and molecular characteristics correlate with imaging response patterns?

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Abstract

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Compliance with ethical standards

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent For this type of retrospective study formal consent is not required.

Conflict of interest The authors declare that they have no conflict of interest.

Purpose—For glioblastoma (GBM), imaging response (IR) or pseudoprogression (PSP) is frequently observed after chemoradiation and may connote a favorable prognosis. With tumors categorized by the Cancer Genome Atlas Project (mesenchymal, classical, neural, and proneural) and by methylguanine-methyltransferase (MGMT) methylation status, we attempted to determine if certain genomic or molecular subtypes of GBM were specifically associated with IR or PSP.

Methods—Patients with GBM treated at two institutions were reviewed. Kaplan-Meier method was used to estimate overall survival (OS) and progression-free survival (PFS). Mantel-cox test determined effect of IR and PSP on OS and PFS. Fisher's exact test was utilized to correlate IR and PSP with genomic subtypes and MGMT status.

Results—Eighty-two patients with GBM were reviewed. The median OS and PFS were 17.9 months and 8.9 months. IR was observed in 28 (40%) and was associated with improved OS (median 29.4 vs 14.5 months $p < 0.01$) and PFS (median 17.7 vs 5.5 months, $p < 0.01$). PSP was observed in 14 (19.2%) and trended towards improved PFS (15.0 vs 7.7 months $p = 0.08$). Tumors with a proneural component had a higher rate of IR compared to those without a proneural component (IR 60% vs 28%; $p = 0.03$). MGMT methylation was associated with IR (58% vs 24%, $p = 0.032$), but not PSP (34%, $p = 0.10$).

Conclusion—IR is associated with improved OS and PFS. The proneural subtype and MGMT methylated tumors had higher rates of IR.

Keywords

Imagingresponse; Pseudoprogression; TCGAsubtype; Glioblastoma; Radiomics

Introduction

Glioblastoma (GBM) is a highly aggressive primary brain tumor that affects approximately 12,000 patients in the USA each year [1]. While survival has improved over the past two decades due to introduction of more effective therapies like temozolomide addition to radiation and surgery and TTFields treatment, most patients will still succumb to the disease within 2 years of diagnosis [2, 3]. In spite of the generally poor prognosis, 5-year survival is now being reported in some patients [4]. Clinical and genetic prognostic factors including performance status, O⁶-methylguanine-DNA-methyltransferase (MGMT) methylation status, and isocitrate dehydrogenase (IDH) mutational status have been identified that predict for improved survival [4–6]. Radiogenomic prognostic factors remain more elusive, but are actively being investigated [7, 8].

Prior studies have suggested that both imaging response (IR) to radiotherapy and the presence of pseudoprogression (PSP) are imaging features that portend a better prognosis [9, 10]. MGMT methylation has been tied to PSP, but this has not been a universal finding [10]. What genetic or biologic factors might lead to GBM IR after chemoradiotherapy also remains unknown.

The goal of the present two-institution study of patients with GBM treated with modern treatment modalities is to assess the relationships between imaging changes, clinical

outcomes, and genomic subtypes of GBM. We specifically evaluated the effect of PSP and IR on progression-free survival (PFS) and overall survival (OS).

Methods

Patient population

Between 2005 and 2012, 82 patients with GBM were treated with combined modality therapy at Wake Forest Baptist Medical Center (WFBMC) ($N=50$) or the Swedish Medical Center (SMC) ($N=41$) with tissue blocks preserved for genomic sequencing. Patients were included for review if they underwent surgery followed by adjuvant radiation therapy for a previously untreated GBM and had adequate documentation of follow-up and clinical outcomes. At both institutions, adequate tumor cellularity and a representative tissue block of tumor were determined prior to RNA sequencing. At WFBMC, electronic medical records and imaging were used to retrospectively determine clinical outcomes. The same group of investigators evaluated a prospectively collected database of patients treated at SMC [11]. De-identified information including surgery, radiation therapy, chemotherapy, clinic notes and imaging reports, and pathology samples were available for review. Imaging studies were available for patients on The Cancer Imaging Archive (TCIA) website maintained by the National Institute of Health [12]. The institutional review board for WFBMC approved this study.

Adjuvant therapy

Patients were treated at both institutions to approximately 59.4–60 Gy employing a treatment technique with an initial volume of 46 Gy with a cone down to 60 Gy. At WFBMC, intensity-modulated radiotherapy (IMRT) was only used to spare critical structures, such as the optics, whereas the majority of patients treated at SMC were treated with IMRT as the primary treatment technique. Fractionation schedules varied between 1.8 and 2.0 Gy at each institution. Concurrent and adjuvant temozolomide was prescribed to the majority of patients.

Patient follow-up and response assessment

Follow-up surveillance imaging was performed at 4–6 weeks after completion of adjuvant therapy to determine a baseline, and then every 2 months for the first 6 months thereafter unless clinical circumstances dictated otherwise. After the first year, subsequent MRIs were performed on a q3 monthly basis, unless patients developed new or progressive neurologic symptoms warranting an earlier MRI.

IR, stable or progressive disease, or PSP was assessed after the completion of adjuvant therapy. PSP was assessed by the Response Assessment in Neuro-Oncology criteria [13]. PSP was defined as a transient or non-progressive increase in size of enhancement over the course of two scans or development of new contrast enhancement within the treatment volume (46 Gy isodose line) [13].

IR was defined as a 25% decrease in the volume of enhancement as previously reported by Barker et al. [9]. Stable or progressive disease was scored by the absence of an IR or a

progressive clinical decline which does not require imaging to confirm progression of disease. Advanced imaging techniques, such as perfusion imaging or diffusion-weighted imaging, were not employed to determine IR or PSP.

Genomic analysis

At WFBMC, genomic techniques for data processing and evaluation were previously described by Holmes et al. [14]. In brief, Affymetrix Human Exon 1.0 ST GeneChips (Affymetrix, Santa Clara, CA) and Infinium HumanMethylation (HM) 450 BeadChip from Illumina (Illumina, San Diego, CA) were used for genomic analysis of fresh frozen tissue from the Brain Tumor Center of Excellence Tumor Bank at WFBMC [15]. Of note, tissue banking was performed predominantly on patients with tumor resection as opposed to stereotactic biopsy as the latter tended to yield an insufficient quantity of tissue. The QIAGEN DNA purification kit and TRizol Reagent from Invitrogen were used for genomic DNA and total RNA isolation. The Affymetrix expression console was used to perform analysis of raw data, and the Partek Genomics Suite 6.6 software was used to quantile normalize the data.

At the SMC, genomic analysis was performed in collaboration with the Ben and Catherine Ivy Center for Advanced Brain Tumor Treatment. Each tumor sample was analyzed using 840 transcripts from the RNA-Seq data as per Verhaak et al. [16]. Probes were designed to overlap with corresponding Affymetrix array probe when possible. Tissue banking was performed only on samples with at least 25% viable cells of core tumor at a high density of cells (50–100 cells/100 μm^2) and tumors were sampled in multiple different sections. For a given tumor, if different cellular tumor samples exhibited distinct subtypes, the tumor was classified as a mixture of its subtypes. A detailed overview of techniques used in the SMC cohort is available online [17].

Tumors undergoing genomic analysis were clustered into clinically relevant gene expression-based molecular classification including The Cancer Genome Atlas (TCGA) subtypes [16]. DNA methylation profiles for these samples were evaluated for MGMT using immunohistochemistry (IHC) [18, 19]. IDH mutations were assessed in both cohorts with IHC.

Statistics

The data from the two institutions were combined for analysis of patient outcomes for PFS and OS. Median follow-up and time-to-event outcomes were defined from the time of diagnosis to the time of most recent follow-up or to the event of interest. The Kaplan-Meier method was used to estimate PFS and OS. Univariate Cox proportional hazards models (UVA) were constructed for both PFS and OS for all putative predictor variables. Statistically significant predictor variables ($p < 0.10$) on univariate analysis were included in multivariate Cox proportional hazards models (MVA) which were constructed to estimate hazards for mortality and PFS. Statistical analysis was performed using R version 3.2.1 software (R Foundation for Statistical Computing, Vienna, Austria).

Fisher's exact test was used to assess the relationship between IR and PSP by TCGA subtype (mesenchymal, classical, neural, and proneural) and molecular features (MGMT

methylation status and IDH mutational analysis). At SMC, tumors could be classified as a mix of two separate GBM subtypes or as a single subtype (i.e., classical mixed with mesenchymal or classical alone). To account for this heterogeneity of tumors as well as classification techniques, IR and PSP analyses based on TCGA subtype were organized by TCGA subtype component vs not (i.e., tumors from WFBMC and SMC with a mesenchymal component vs tumors without a mesenchymal component).

Results

Ninety-one patients were treated at the two institutions, 50 at WFBMC, and 41 at SMC. Tumor blocks from nine patients from the WFBMC cohort were not sequenced for genomic data due to insufficient cellularity in the tissue block, leaving 41 tumors for analysis. Eight patients from the SMC cohort were excluded from the analysis due to omission of adjuvant radiation therapy ($N = 6$), inadequate documentation/followup ($N = 2$), and one sample was from a recurrent tumor. Of the 74 remaining patients, median age, use of concurrent TMZ, and median cycles of adjuvant TMZ were similar between the cohorts (Table 1). Patients in the SMC cohort had a numerically higher rate of gross total resection compared to patients treated at WFBMC ($p = 0.052$). Median KPS was different between the two groups 80 vs 90 ($p = 0.001$). MGMT methylation was detected in 32 patients (46%); 8 (10%) tumors carried an IDH mutation.

For the entire population, the median PFS was 8.9 months (95% CI 7.0–10.9) and median OS was 17.9 months (95% CI 14.5–25.2). There were no significant differences in PFS ($p = 0.46$) or OS ($p = 0.33$) between the two cohorts (Table 1). Median follow-up was 17.8 months (95% CI 14.5–23.8) using the reverse Kaplan-Meier method.

Effects of imaging response and pseudoprogression on clinical outcomes

An IR was observed in 27 patients (37.5%) of the population (Table 1). An IR was associated with improved PFS (median 17.7 [95% CI 12–34] vs 5.5 [3.9–7.9] months, $p < 0.01$) (Fig. 1a) and a longer median OS (29.4 months [20.2–NR] vs 14.5 [11.6–20.6] months $p < 0.01$) (Fig. 1b). PSP was observed in 14 patients (19%); 10 (71%) patients with PSP were MGMT methylated. Patients with PSP had a numerically higher median PFS of 15.0 (95% CI 8.9–29.9) vs 7.7 (95% CI 5.3–10.3) ($p = 0.08$) (Fig. 2a). Patients with PSP had similar survival of 23.8 months (95% CI 18.7–36.1) vs 15.7 (95% CI 12.1–25.4) ($p = 0.36$) compared to those without PSP (Fig. 2b).

Univariate and multivariate analysis

A UVA was performed evaluating significant factors affecting progression and mortality. After multivariate analysis for mortality, IR was associated with a reduced hazard for death (HR = 0.36 95% CI 0.19–0.69, $p = 0.002$) as well as MGMT methylation status (HR = 0.31 95% CI 0.16–0.60, $p < 0.001$). TCGA subtypes were not associated with survival (Table 2). For PFS, IR and PSP were independently associated with improved PFS after multivariate analysis (HR = 0.20 95% CI 0.10–0.39, $p < 0.001$) and (HR = 0.52 95% CI 0.28–0.99 $p = 0.046$), respectively (Table 3).

Correlation of imaging response and PSP with genomic and molecular subtypes

Sixty-eight tumors (92%) had TCGA subtype data available. Tumors with a proneural component had a 60% IR rate compared to tumors without a proneural component (28%) ($p = 0.03$) (Table 4). Analysis of IR between classical, neural, and mesenchymal tumors did not demonstrate any statistically meaningful relationship between IR and TCGA subtype (Table 4). There was no statistically significant association observed between any TCGA subtype and PSP. MGMT methylation status was associated with a higher rate of IR compared to MGMT unmethylated tumors (56% vs 24%, $p = 0.003$) and a numerically higher rate of PSP (34% vs 16%, $p = 0.099$). IDH status was not associated with IR or PSP.

Discussion

Our findings reveal that tumors that exhibit an IR after adjuvant therapy have a demonstrably improved PFS and OS. After multivariate analysis, PSP and IR were both associated with a reduced hazard for PFS in GBM. Furthermore, the proneural subtype and MGMT methylated tumors were more likely to exhibit an IR after adjuvant therapy compared to other subtypes. Conversely, progressive or stable disease after adjuvant therapy without an IR could suggest aggressive histology that is MGMT unmethylated and could help triage appropriate salvage or adjuvant therapy. To our knowledge, this is the first study attempting to link imaging characteristics with genomic and molecular subtypes of GBM.

Recent efforts to improve the accuracy of diagnosing progression from pseudoprogression have been underway, as conventional MRI does not have a high predictive value in distinguishing PSP from true progression [20]. Investigators are focusing on trying to improve the specificity for PSP with novel MRI sequences such as diffusion- and perfusion-weighted imaging, as well as PET and MR spectroscopy [21–23]. Moreover, higher order statistical analysis incorporating multiparametric imaging sequences as well as genomic data is additionally being investigated. Qian et al. recently reported on a machine learning algorithm that integrates conventional MRI sequences with novel imaging sequences such as diffusion tensor imaging and genomic data to improve diagnostic accuracy for PSP [24].

Marrying imaging features with genomic features may play an increasing role in the management of GBM. Radiomics provides an immense amount of information to analyze, through MR spectroscopy and FDG-PET. With the clinical approval in the USA for NexGen sequencing of all malignant brain tumors, more molecular and genotypic information will be available for patients at time of initial diagnosis [25]. The ability to distinguish specific patterns of response and anticipated outcomes based on molecular markers and genomic sequences will become more feasible and relevant. While our study is limited to conventional MRI without perfusion imaging, it represents an initial attempt to bridge this gap between radiologic responses and genomic features of tumors. Further efforts with more advanced imaging techniques should attempt to expand the findings suggested by this work.

There are several limitations to the current study. As a retrospective review, it is subject to patient selection bias, particularly with patients for whom genomic data and follow-up information were available. Our findings are limited to hypothesis generation. Additionally, it is known that tumors have significant TCGA intratumoral heterogeneity, as 14 patients in

the SMC cohort had mixed TCGA subtypes within the same tumor. The effect of heterogeneity on IR could not be adequately assessed due to the low number of patients in each cohort. These tended to be patients with tumor resection as opposed to stereotactic biopsies, given the amount of tissue necessary to perform genomic analysis and for patients that were able to follow up for appointments. There are differences in institutional approaches to treating GBM that are difficult to capture with a retrospective analysis.

Conclusion

Imaging responses and PSP are favorable features associated with outcomes in GBM. Tumors with a proneural component or MGMT methylation have a higher rate of IR; we did not find significant correlations between PSP and genomic subtype of tumors. As NexGen sequencing becomes more commonplace for glioma, assessing imaging response patterns based on molecular features will become increasingly relevant and may be able to categorize features of tumors

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Fig. 1.
a Kaplan-Meier curves for progression-free survival for patients with an imaging response vs those without an imaging response after adjuvant therapy for GBM. PFS 17.7 vs 5.5 months $p < 0.01$. **b** Kaplan-Meier curves for overall survival for patients with an imaging response vs those without an imaging response after adjuvant therapy for GBM. Median OS 29.4 vs 14.5 months $p < 0.01$

Fig. 2.

a Kaplan-Meier curves for progression-free survival for patients with observed pseudoprogression vs those without pseudoprogression after adjuvant therapy for GBM. Median PFS 15.0 vs 7.7 months, $p = 0.08$. **b** Kaplan-Meier curves for overall survival for patients with observed pseudoprogression vs those without pseudoprogression after adjuvant therapy for GBM. Median OS 23.8 months vs 15.7 months, $p = 0.36$

Table 1

Baseline characteristics for patients included in the entire population and for each cohort. ***Wake Forest Baptist Medical Center (WFBMC), **Swedish Medical Center (SMC), The Cancer Genome Atlas (TCGA), temozolomide (TMZ), O6-methylguanine-DNA methyltransferase (MGMT), isocitrate dehydrogenase (IDH)

Characteristic	All (N = 41)	IQR or percentage	WFBMC (N = 74)	IQR or percentage or standard deviation []	SMC (N = 33)	IQR or percentage or standard deviation []	p value
Median age (years)	60.4	51.4–66.15	59.9	51.7–68.5	61	51–65	0.69
KPS	90	80–90	80	70–90	90	80–100	0.001
Dead	62	84	37	90	25	76	0.17
Surgery							0.052
Biopsy	1	1.4	1	2	0	0	
Subtotal resection	28	38	20	49	8	25	
Gross total resection	45	61	20	49	25	75	
Total dose of radiation (Gy) (mean [standard deviation])	59.7	59.4–60	60.0	[0.23]	59.3	[2.91]	0.16
Intensity-modulated radiotherapy	49	66	17	41.5	32	97	< 0.01
Concurrent TMZ	72	97	39	95	33	100	0.57
Adjuvant TMZ	57	81	33	81	27	82	0.39
Median cycles of adjuvant TMZ	4	1–6	4	1–6	4	1–7	0.55
TCGA subtypes*							NA
Neural			7	17	12	36	
Proneural			7	17	7	21	
Mesenchymal			21	51	12	36	
Classical			6	15	14	42	
Not available			0	0	4	12	
Mixed			NA		15	45	
MGMT methylated	32	46	21	53	11	38	0.34
IDH	8	11	4	10	4	13	1
Imaging assessment							
Pseudoprogression	14	19	8	20	6	18	0.47
Imaging response	27	38	16	41	11	33	0.67
Median PFS (months)	8.9	7–10.9	9.4	4.18–18.25	7.8	3.6–16.1	0.46
Median OS (months)	17.9	14.5–25.2	17.9	14.5–32.3	16.2	12.1–25.2	0.33

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For the XYZ cohort's TCGA analysis, multiple samples from each tumor were subtyped, which allowed for heterogeneity and a mixed tumor sample.
*
All subtypes are represented in the table

Table 2

Cox proportional hazard ratios for variable influencing mortality. Univariate variables with a hazard ratio p value < 0.10 were included in multivariate model. Imaging response was associated with a reduced hazard for mortality

Variable	Univariate analysis			Multivariate analysis		
	HR (95% CI)	p value		HR (95% CI)	p value	
Institution	1.29 (0.77–2.15)	0.330				
Age	1.02 (1.00–1.04)	0.100		1.00 (0.98–1.03)	0.691	
KPS	0.96 (0.94–0.99)	0.004		0.99 (0.96–1.02)	0.568	
GTR vs subtotal/bx (ref)	0.63 (0.39–1.02)	0.058		0.78 (0.45–1.37)	0.393	
Concurrent TMZ	0.27 (0.06–1.13)	0.074		0.60 (0.11–3.43)	0.570	
Adjuvant TMZ	0.21 (0.11–0.39)	< 0.001		0.22 (0.10–0.46)	< 0.001	
MGMT methylated	0.31 (0.17–0.56)	< 0.001		0.31 (0.16–0.60)	< 0.001	
IDH mutated	0.58 (0.23–1.44)	0.238				
Classical	0.99 (0.42–1.57)	0.984				
Neural	0.82 (0.42–1.57)	0.542				
Proneural	1.04 (0.56–1.96)	0.901				
Mesenchymal	1.33 (0.79–2.21)	0.281				
Imaging response	0.38 (0.21–0.67)	0.001		0.36 (0.19–0.69)	0.002	
Pseudoprogression	0.75 (0.41–1.38)	0.358				

Cox proportional hazard ratios for variable influencing progression-free survival. Univariate variables with a p value < 0.10 were included in multivariate model. Pseudoprogression and imaging response were associated with improved progression-free survival

Table 3

Variable	Univariate analysis			Multivariate analysis		
	HR (95% CI)	p value		HR (95% CI)	p value	
Institution	0.88 (0.54–1.44)	0.609				
Age	1.00 (0.99–1.02)	0.621				
KPS	0.98 (0.96–1.00)	0.073		0.99 (0.97–1.02)	0.695	
GTR vs subtotal/bx (ref)	0.72 (0.44–1.18)	0.191				
Concurrent TMZ	0.47 (0.11–1.96)	0.296				
Adjuvant TMZ	0.42 (0.23–0.75)	0.004		0.29 (0.15–0.57)	< 0.001	
MGMT methylated	0.20 (0.11–0.38)	< 0.001		0.23 (0.12–0.2)	< 0.001	
IDH mutated	0.49 (0.20–1.22)	0.126				
Classical	1.30 (0.73–2.31)	0.366				
Neural	0.93 (0.49–1.75)	0.821				
Proneural	0.93 (0.49–1.75)	0.846				
Mesenchymal	0.94 (0.51–1.74)	0.171				
Imaging response	0.32 (0.18–0.54)	< 0.001		0.20 (0.10–0.39)	< 0.001	
Pseudoprogression	0.59 (0.33–1.07)	0.084		0.52 (0.28–0.99)	0.046	

Table 4

Imaging response rates and pseudoprogression rates when stratifying by MGMT and IDH subtypes as well as between genomic subtypes. Comparison for imaging response and pseudoprogression was TCGA subtype (Classical, Neural, Proneural, Mesenchymal) vs all other TCGA subtypes. Two-sided *p* values calculated by Fischer's exact test. The Cancer Genome Atlas (*TCGA*), temozolomide (*TMZ*), O⁶-methylguanine-DNA-methyltransferase (*MGMT*)

	<i>N</i>	Imaging response (%)	<i>p</i> value	Pseudoprogression (%)	<i>p</i> value
MGMT methylated	32	56	0.003	60	0.099
MGMT non-methylated	37	24		24	
IDH mutant	8	63	0.14	25	1
IDH wildtype	64	34		23	
TCGA subtype					
Classical	17	29	0.77	35	0.34
Neural	14	36	1	14	0.49
Proneural	15	60	0.033	20	0.74
Mesenchymal	31	26	0.2	26	1