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Comparison of clinical, radiographic and genomic alterations between histologic and molecular glioblastoma, *IDH*-wildtype

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Abstract

Background. Glioblastoma *IDH*-wildtype (GBM) may be diagnosed histologically (hGBM) or based on molecular features when microvascular proliferation and histologic necrosis are absent (mGBM). Clinical and radiographic distinction between hGBM and mGBM remains unclear.

Methods. 101 hGBM cases were matched to 109 mGBM cases by age, sex, year of diagnosis, and *TERT* promoter mutation (*TERT*p) status. Clinical outcome, radiographic, and molecular features were compared across mGBM and hGBM.

Results. Median time from first MRI to diagnosis was longer for mGBM versus hGBM (34 vs 7 days, $p < .001$). mGBM more often presented with seizures (51% vs 26%, $p < .001$), gliomatosis pattern (12% vs 2%, $p = .005$), basal ganglia involvement (17% vs 0%, $p < .001$). Contrast enhancement appeared on MRI for 98% (96/98) of hGBM and 50% (54/107) of mGBM ($p < .001$). mGBM with non-enhancing MRI were rarely multifocal (2% vs 30%, $p < .001$). mGBM harbored fewer total copy number alterations (median 20 vs 16.5, $p = .029$), less often had *EGFR*amp (34% vs 48%, $p = .051$), isolated chromosome 10 loss (84% vs 96%, $p = .013$), and *CDKN2A/B* homozygous deletion (56% vs 77%, $p = .005$). Median overall survival was longer for mGBM (2.16 vs 1.44 years, $p < .001$), and for mGBM without MRI contrast enhancement versus hGBM with enhancement (3.11 vs 1.62 years, adjusted $p = .003$). mGBM without +7/–10 or without CDKN2A/B homozygous deletion had longer survival and time-to-progression versus hGBM with these alterations.

Conclusion. mGBM with MRI enhancement may represent undersampled or early/evolving hGBM. mGBM that are non-enhancing, present with seizures, prolonged time to diagnosis, absent CDKN2A/B alteration or +7/–10 may represent other IDH-wildtype entities.

Key Points

- mGBM is not always early/evolving or undersampled classic histologic glioblastoma.
- mGBM has better survival in matched case comparison with histologic glioblastoma.
- mGBM with prolonged presentation, seizures, and no enhancement on MRI may represent other IDH-wildtype glioma entities.

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Importance of the Study

Clinical experience and several reported observations suggest heterogeneity among lower histologic grade, diffuse IDH-wildtype astrocytic tumors with molecular features of glioblastoma (mGBM). There are methodological limitations to prior studies observing no overall survival differences between histologic GBM (hGBM) and mGBM. This study is unique as hGBM patients were matched to mGBM patients by age at diagnosis, sex, year of diagnosis and *TERT* promoter mutation to minimize bias. Findings affirm that mGBM with enhancement on MRI at diagnosis likely represents under-sampled or early/evolving hGBM. Findings suggest caution in mGBM diagnosis, prognosis and clinical trial inclusion for patients with non-enhancing MRI lesions, basal ganglia involvement, long symptom profile, seizures, only *TERT* promoter mutation as a defining molecular feature, absence of *CDKN2A/B* homozygous deletion, combined gain of chromosome 7 and loss of chromosome 10, or low copy number alteration. Some of these patients may have significantly better survival.

In the 2021 WHO classification of central nervous system tumors, the integrated diagnosis of glioblastoma, *IDH*-wildtype (GBM) incorporates morphologic and molecular features.[1] As a result, a GBM diagnosis can be defined purely on a morphologic basis if classic morphologic features including microvascular proliferation or histologic necrosis are identified in a diffuse astrocytic glioma (hGBM). However, if microvascular proliferation or histologic necrosis are both absent, a GBM diagnosis can be made if the tumor is *IDH*- and histone H3-wildtype and exhibits at least one of the following molecular alterations (mGBM): *TERT* promoter mutation (*TERT*p), *EGFR* amplification (*EGFR*amp), or combined whole gain of chromosome 7 and loss of chromosome 10 (+7/–10). The equivalence of this integrated diagnosis was based on reports showing that hGBM patients have similar survival outcomes as mGBM patients who do not display classic morphologic features but have molecular alterations that are associated with poor outcomes.[2-7]

Several observations suggest that there is heterogeneity among lower histologic grade diffuse astrocytic tumors with molecular features of GBM. These features include prolonged delays to diagnosis and primary presentation with seizure,[5] diffuse gyriform expansile non-enhancing T2 signal lesions,[8-10] and less frequent or only patchy enhancement without features of radiographic necrosis on MRI.[11,12] This contrasts to the fairly uniform clinical presentation of focal neurologic symptoms of just days to weeks in duration, and typical imaging features with mass like necrotic enhancement with hGBM.[13] Certain molecular patterns may distinguish mGBM subtypes. For example, it has been observed that mGBM patients defined by *TERT*p mutation alone have improved survival.[14,15]

Without comprehensive molecular characterization, other *IDH*-wildtype tumor types may be misdiagnosed as mGBM. These include diffuse pediatric type glioma with *MYB* alterations,[16] tumors with *BRAF* alteration[17] such as pleomorphic xanthoastrocytoma or epithelioid GBM (subtype E),[18] diffuse astrocytoma with *FGFR3*::*TACC3* fusion,[19,20] and diffuse glioma with gliomatosis cerebri growth patterns, *TERT*p,[21] and a distinct epigentic profile (subtype F).[22]

There are limitations to the prior studies that observed no difference in overall survival between hGBM and mGBM. These studies report relatively small retrospective single or multi-institutional mGBM cohorts, compared with much larger historical hGBM cohorts. As such, inherent biases related to cohort selection, data acquisition, and follow-up may confound results. The goal of this study was to compare clinical, imaging, and molecular features across cohorts of matched mGBM and hGBM patients. Our experimental design matched hGBM to mGBM to account for potential confounders such as sex, age at diagnosis, year of diagnosis and *TERT*p status. *TERT*p status was important to include as a matching variable since it was shown that patients with *TERT*p have older age of diagnosis and worse survival compared to *TERT* wildtype.[23] Presenting symptoms, radiographic features, treatment, and survival were compared across hGBM and mGBM. Our overall hypothesis was that hGBM and mGBM are not single homogeneous clinical entities. While mGBM can represent undersampled hGBM in some instances,[24] or early presentations in evolution to hGBM,[25] we hypothesized that there are patients with mGBM that have clinical, molecular, imaging features, and outcomes that are significantly different from hGBM. Further characterization of mGBM is important for refinement of expected prognosis and treatment approaches, including appropriate consideration for clinical trial eligibility.

Methods

Patient Selection and Data Acquisition

The Mayo Clinic Institutional Review Board approved this study, and all patients provided written informed consent. The Mayo Clinic Neuro-Oncology Biobank was used to identify a cohort of 113 mGBM patients diagnosed between 1993 and 2021. A cohort of hGBM from the Biobank were optimally matched to the mGBM cohort based on age at diagnosis, sex, year of diagnosis, and TERTp status. TERTp matching was performed since tumors that have *TERT*p were shown to be significantly older and have poorer outcome than tumors without have *TERT*p23; thus, our design aimed to account for *TERT*p as a potential confounder. After matching, clinical and MRI features were manually extracted by a single reviewer (DHL) blinded to diagnosis (Tables 1 and 2). Unblinded reviewers (A.M. and S.S.) abstracted treatment data, including radiation therapy, Optune use, temozolomide, and extent of resection (biopsy only, subtotal, gross total). Exclusion criteria were applied after manual review. Exclusion criteria for mGBM patients were cases with any lesion where location was primarily in midline structures (n = 2) and patients whose tumor had a histone

Table 1. Demographic, clinical, and treatment characteristics of mGBM and hGBM patients.

	mGBM (*N* = 109)	hGBM (*N* = 101)	*p*-value
Demographics			
Sex (male)	68 (62.4)	67 (66.3)	.55
Median age (range)	62 (18, 91)	61 (35, 83)	.94
Clinical presentation			
Iincidentally discovered	12 (11.0)	2 (2.0)	.009
First symptom			
Seizures	55 (50.5)	26 (25.7)	<.001
New onset progressive headache	11 (10.1)	32 (31.7)	<.001
New onset cognitive deficit	17 (15.6)	16 (15.8)	.96
New onset focal neurological deficit	30 (27.5)	44 (43.6)	.015
Days from first symptom to pathological diagnosis			.018
Median (range)	52 (2, 11,119)	34 (1, 1370)	
At diagnosis, regions of involvement			
Frontal	57 (52.3)	38 (37.6)	.033
Temporal	57 (52.3)	38 (37.6)	.033
Parietal	21 (19.3)	38 (37.6)	.003
Occipital	4 (3.7)	7 (6.9)	.29
Corpus callosum	15 (13.8)	7 (6.9)	.11
Basal ganglia	19 (17.4)	0 (0.0)	<.001
Brainstem	6 (5.5)	2 (2.0)	.18
Cerebellum	1 (0.9)	1 (1.0)	.96
Gliomatosis pattern (3 or more lobes involved)	13 (11.9)	2 (2.0)	.005
Gliomatosis at progression	5 (4.6)	1 (1.0)	.18
Leptomeningeal progression	3 (2.8)	3 (3.0)	.92
Treatment			
Extent of resection			<.001
Gross total resection	22 (20.2)	66 (65.3)	
Partial resection	48 (44.0)	25 (24.8)	
Biopsy	39 (35.8)	10 (9.9)	
Received radiation therapy (%)	95 (89.6)	89 (92.7)	.44
Received temozolomide (%)	89 (84.0)	82 (87.2)	.51

Comparisons were made across groups using the χ^2 test or Kruskal-Wallis test, as appropriate. Values are *n* (%) unless indicated.

H3 mutation ($n = 0$). For both cohorts, patients who only had tissue diagnosis related to a recurrence and not a primary tumor were excluded ($n = 2$ for mGBM and n=12 for hGBM). After exclusion criteria there was a total of 109 mGBM and 101 hGBM used for all comparative analyses.

Tumor mutation testing using the Mayo Clinic Neuro-Oncology Expanded Next-generation Sequencing Gene Panel was available for 81 hGBM and 69 mGBM patients. In the remainder, *IDH* status was determined by immunohistochemistry or targeted sequencing, and *TERT*p status was determined by targeted sequencing. Copy number data from the Mayo Clinic Chromosomal Microarray were available for 73 hGBM and 62 mGBM patients. If copy number profiling was not performed, *EGFR*amp was inferred upon review of the Mayo Neuro-Oncology Expanded Next-generation Sequencing Gene Panel (RBJ). The clinical copy number results were reviewed by at least two clinical laboratory technologists and at least one ACMG Board-certified clinical laboratory geneticist and were scored based on American College of Medical Genetics and Genomics (ACMG) guidelines.[26] The copy number alterations were summed to define the total number of alterations (copy number complexity). *MGMT* promoter methylation was evaluated using the Mayo Clinic Real-Time Methylation-Specific PCR Assay that interrogates downstream CpG sites 79-86.

Statistical Analysis

Patient characteristics, radiographic findings and genomic alterations were compared between mGBM and hGBM using the χ^2 test or Kruskal-Wallis test, as appropriate. Cumulative survival probabilities were estimated using the Kaplan-Meier method. The association of mGBM and hGBM with overall survival and time-to-progression was assessed overall and subset to patients who received standard of care using Cox proportional hazards regression adjusting for age

Table 2. Radiographic characteristics of index MRI* of 109 mGBM and 101 hGBM patients. Index MRI was the MRI done closest to, but within 30 days, of surgical diagnostic procedure.

	mGBM (*N* = 109)	hGBM (*N* = 101)	*P*-value
Time from first MRI to pathologic diagnosis (days)			<.001
N	107	98	
Median (range)	34 (1, 4581)	7 (0, 929)	
Was the index MRI the first MRI?			<.001
No	48 (44.9)	14 (14.4)	
Yes	59 (55.1)	83 (85.6)	
Number of MRIs between first MRI and index MRI			.31
0	27 (56.3)	5 (45.4)	
1	11 (22.9)	5 (45.4)	
2	7 (14.6)	0 (0)	
>2	3 (6.3)	1 (9.1)	
Index MRI, contrast enhancement			<.001
No	53 (49.5)	2 (2.0)	
Yes	54 (50.5)	96 (98.0)	
Index MRI, contrast enhancement with necrosis			<.001
No	35 (65)	15 (16)	
Yes	19 (35)	81 (84)	
Index MRI, multifocal			.23
No	90 (84.1)	88 (89.8)	
Yes	17 (15.9)	10 (10.2)	
Index MRI, regional mass effect			<.001
No	70 (66.0)	21 (21.4)	
Yes	36 (34.0)	77 (78.6)	
First MRI when index MRI was not the first MRI, contrast enhancement present			.039
No	48 (82.8)	8 (57.1)	
Yes	10 (17.2)	6 (42.9)	
First MRI when index MRI was not the first MRI, multifocal			.79
No	54 (94.7)	13 (92.9)	
Yes	3 (5.3)	1 (7.1)	
First MRI when index MRI was not the first MRI, contrast enhancement with necrosis			.55
No	8 (80)	4 (67)	
Yes	2 (20)	2 (33)	
First MRI when index MRI was not the first MRI, regional mass effect			.64
No	45 (80.4)	12 (85.7)	
Yes	11 (19.6)	2 (14.3)	

Comparisons were made across groups using the χ^2 test or Kruskal-Wallis test, as appropriate.
Values are *n* (%) unless indicated.

at diagnosis and sex. Progression was defined radiographically. Standard of care (SOC; yes/no) was defined as having a biopsy, partial resection or gross total resection followed by radiation therapy and temozolomide (either concurrent only, concurrent and adjuvant, or adjuvant only). Groups with less than five patients were excluded from all survival analyses. There was one patient in each of the cohorts diagnosed in 2005, and three patients in each cohort diagnosed between 1993 and 2005, and accordingly, in addition to variation in standard of care during those years, these patients were excluded from adjusted survival analysis. $p < .05$ was considered statistically significant.

Results

Cohort Demographics

The mGBM and hGBM groups were matched by year of diagnosis, sex, age at diagnosis, and *TERT*p status (Table 1): 62% (68/109) of mGBM and 66% (67/101) of hGBM patients were male. Median age of the mGBM group was 62 and 61 for hGBM. *TERT*p mutation was present at initial diagnosis in 93% mGBM and 95% hGBM patients, noting that hGBM were matched to mGBM by *TERT*p status.

Clinical Presentation

Table 1 summarizes the clinical data collected. There were significant differences in patterns of presentation when comparing mGBM with hGBM cohorts. The time from first symptom to pathological diagnosis was longer for mGBM versus hGBM (median 52 vs 34 days, $p = .018$). There were several mGBM patients with long latencies to diagnosis (Figure 1a). mGBM patients were more likely to present with seizures (51% vs 26%, $p < .001$), be discovered incidentally (11% vs 2%, $p = .009$), have basal ganglia involvement (17% vs 0%, $p < .001$), and have a gliomatosis pattern (defined as three or more brain regions involved; 12% vs 2%, $p = .005$). hGBM patients were more likely to present with new onset of progressive headache (32% vs 10%, $p < .001$) and new onset of focal neurologic deficits (44% vs 28%, $p = .015$).

Imaging Features

Time from first MRI to pathological diagnosis was longer for mGBM in comparison to hGBM (median 34 vs 7 days, $p < .001$; Table 2), with several mGBM patients experiencing long latency from first MRI to diagnosis (Figure 1b). Consequently, the first MRI was the index MRI (MRI done closest to, but within 30 days, of surgical diagnostic procedure) in 86% of hGBM and 55% of mGBM ($p < .001$; Table 2).

Table 2 summarizes and Figure 2a (top rows) illustrates the distribution of major imaging features across the 109 mGBM and 101 hGBM patients. Contrast enhancement was present on the index MRI (performed 30 days or less prior to pathologic diagnosis) for 98% (96/98) of hGBM and 51% (54/107) of mGBM ($p < .001$). When the first MRI was not the index MRI, contrast enhancement was present on the first MRI for 43% (6/14) of hGBM and 17% (10/58) mGBM ($p = .039$).

Regional mass effect on index MRI was more common in hGBM versus mGBM (79% vs 34%, $p < .001$; Table 2). This difference relates to the difference in the presence or absence of any enhancement on MRI. Features of radiographic necrosis (often associated with regional mass effect) occur only in the presence of contrast enhancement on MRI. In considering only patients with any contrast enhancement on MRI, radiographic necrosis was present in 84% (81/96) of hGBM, and only 35% (19/54) of mGBM ($p < .001$). As by definition mGBM does not have histologic necrosis, unless accounted for by sampling error in all 19 cases (unlikely), this finding suggests that radiographic necrosis on MRI does not necessarily equate to histologic necrosis morphologically.

Analyses were performed within the mGBM cohort. mGBM patients with contrast enhancement on index MRI were significantly less likely to have seizures prior to diagnosis versus mGBM patients that did not have contrast enhancement on index MRI (33% versus 68%, $p < .001$; Supplementary Table S1). mGBM patients with contrast enhancement on index MRI were more likely to present with focal neurological deficit (41% versus 15%, $p = .003$), and more likely to have a mutlifocal pattern ofT2 signal changes (30% versus 2%, $p < .001$) than mGBM patients without contrast enhancement on MRI. That is, mGBM without enhancement on index MRI were rarely multifocal.

Molecular Features

Figure 2a illustrates and Supplementary Table S2 summarizes the distribution of the primary diagnostic molecular alterations (*TERT*p, *EGFR*amp, +7/–10) as well as other molecular alterations for the mGBM and hGBM cohorts. *EGFR*amp was more frequent in hGBM versus mGBM (48% vs 34%, $p = .051$), as was isolated loss of chromosome 10 (96% vs 84%, $p = .013$), and *CDKN2A/B* homozygous deletion (77% vs 56%, $p = .005$). No significant differences between groups were observed for *TERT*p ($p = .47$, reflecting the matched study design) or combined +7/–10 ($p = .18$). There was no significant difference between hGBM and mGBM in the frequency of *TERT*p as the only defining molecular alteration (20% versus 11%, respectively, $p = .12$). The frequency of *MGMT* promoter methylation was also not observed to be different between hGBM and mGBM (31% vs 45%, $p = .16$).

The total number of copy number alterations (as a proxy for chromosome copy number complexity) are summarized in Figure 2b and illustrated in Supplementary Figure S1,

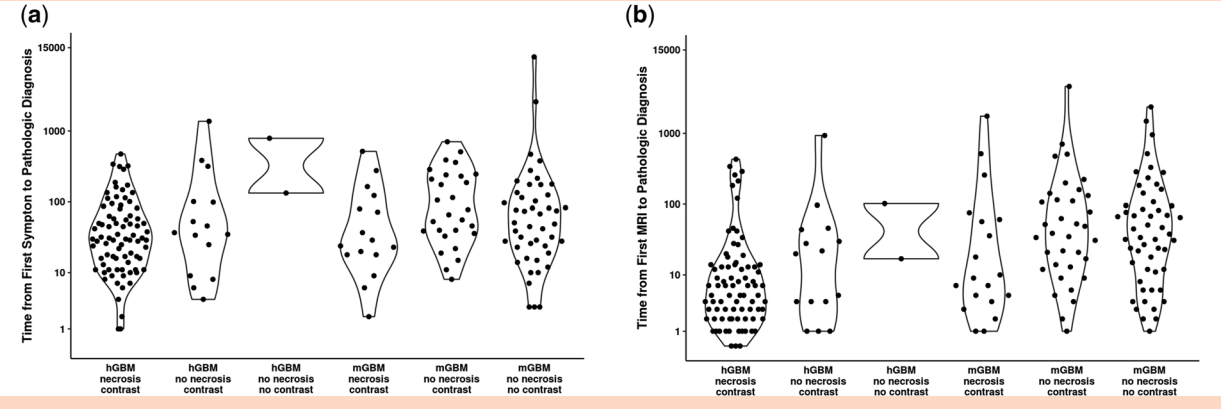

Figure 1. (a) Time from first symptom to pathological diagnosis, and (b) time from first MRI to pathologic diagnosis, in days, across hGBM and mGBM by pattern of enhancement on index MRI.

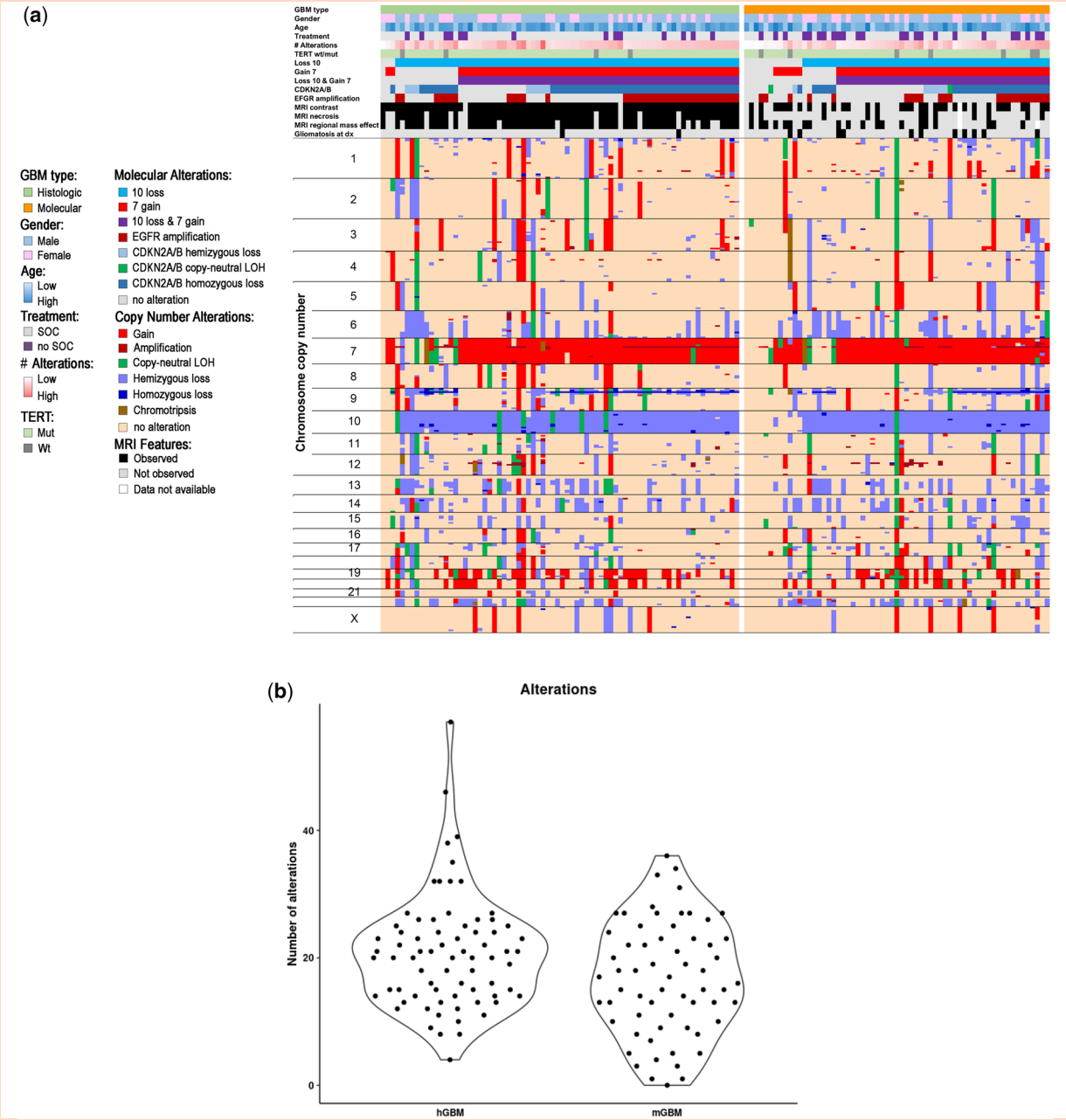

Figure 2. (a) Comparison of clinical features, index MRI features, and molecular alterations across mGBM and hGBM patients. (b) Comparison of copy number complexity across mGBM and hGBM patients.

where subjects are sorted by the total number of alterations. The median total number of copy number alterations was larger for hGBM versus mGBM (20 vs 16.5, $p = .029$).

Treatment Following Diagnosis

Extent of resection was significantly different between the two groups ($p < .001$), with biopsy and partial resection more common in mGBM and gross total resection more common in hGBM (Table 1). The frequency of radiation therapy and temozolomide were not significantly different between mGBM and hGBM ($p = .44$ and 0.51, respectively). Of the 19 mGBM patients with enhancement and radiographic necrosis on index MRI, five had biopsy, nine had partial resection, and five had gross total resection of the contrast enhancing tumor (data not shown).

Overall Survival and Time-to-progression

The median overall survival for mGBM was significantly longer than hGBM (2.16 vs 1.44 years, $p < .001$ adjusted for age, sex and SOC; Figure 3a). Three- and five-year overall

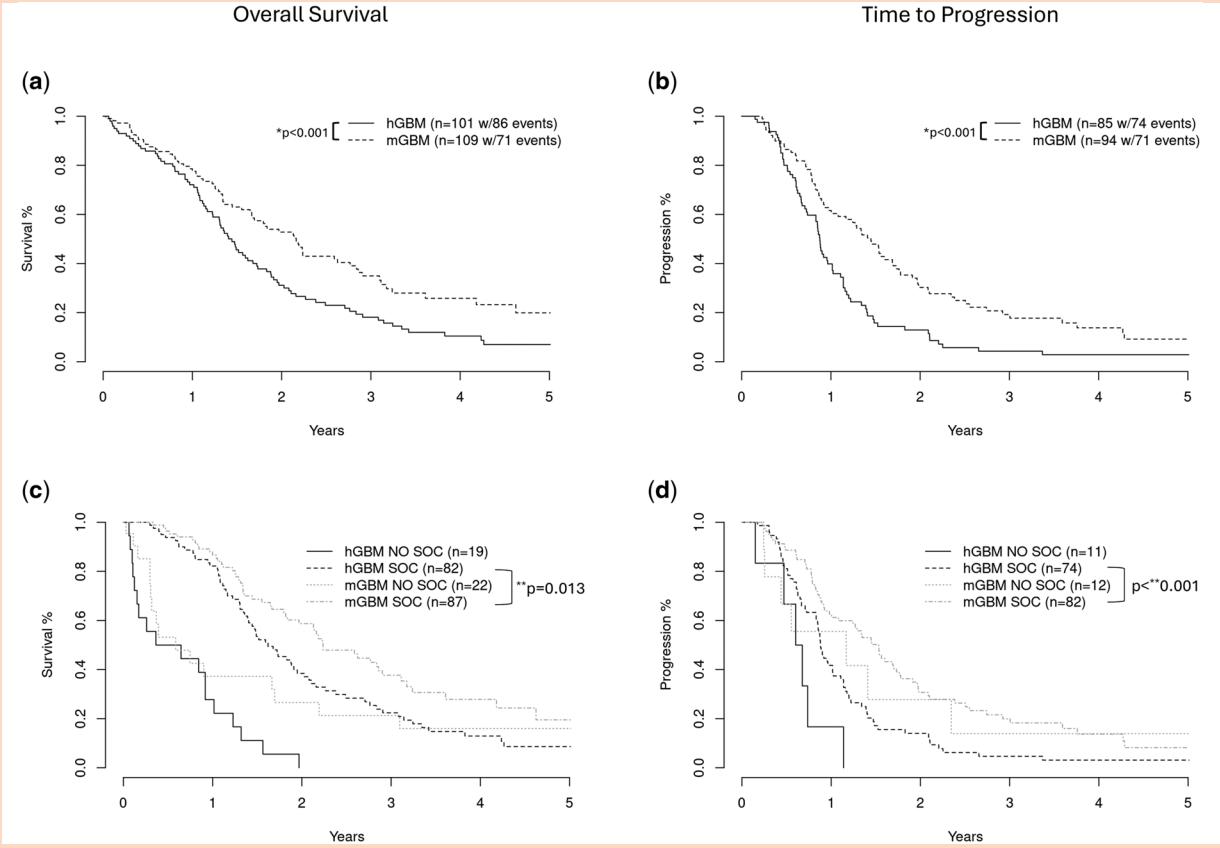

Figure 3. Kaplan-Meier curves comparing hGBM versus mGBM across all patients for (a) overall survival, (b) overall survival by standard of care (SOC), (c) time-to-progression, and (d) time-to-progression by SOC. *p-values from Cox proportional hazards regression adjusted for age at diagnosis, sex and SOC. **p-values from Cox proportional hazards regression adjusted for age at diagnosis and sex.

survival rate was 35% and 20% for mGBM, 18% and 7% for hGBM, respectively. The median time-to-progression for mGBM was also longer than hGBM (1.45 vs 0.88 years, $p \leq 0.001$ adjusted for age, sex and SOC; Figure 3b). Figure 3c and d demonstrate that patients who received standard of care had improved outcomes in comparison to patients who did not receive standard of care for both hGBM and mGBM. Consequently, among patients who received SOC, the median overall survival was significantly longer for mGBM versus hGBM (2.24 vs 1.62 years, adjusted $p = .013$; Figure 3c), and the median time-to-progression was also significantly longer for mGBM versus hGBM (1.53 vs 0.88 years, adjusted $p < .001$; Figure 3d).

As noted above, 98% of hGBM had contrast enhancement on index MRI at diagnosis in comparison to 51% of mGBM. Among patients who received SOC, the median overall survival was significantly longer for mGBM that did not have contrast enhancement on MRI versus hGBM with contrast enhancement on MRI (3.11 vs 1.62 years, adjusted $p = .003$; Figure 4a). There was no significant difference in overall survival between mGBM with enhancement on MRI and hGBM with enhancement on MRI (adjusted $p = .26$). When enhancement was present on MRI, presence of radiographic necrosis was not significantly associated with overall survival (Figure 4b). The median time-to-progression was significantly longer for mGBM with contrast enhancement on MRI versus hGBM with contrast enhancement on MRI (1.45 vs 0.88 years, adjusted $p = .016$; Figure 4c). The median time-to-progression was also significantly longer for mGBM that did not have contrast enhancement on MRI versus hGBM with contrast enhancement on MRI (1.56 vs 0.88 years, adjusted $p = .003$). When enhancement was present on MRI, mGBM with radiographic necrosis had a significantly longer time-to-progression than hGBM with radiographic necrosis (1.54 vs 0.88 years, adjusted $p = .048$; Figure 4d).

Overall survival was also evaluated by individual tumor molecular alterations, as well as in the subset of patients that had *TERT*p as the only defining tumor molecular alteration. All analyses were performed only among patients that received SOC and were adjusted for age at diagnosis and sex. mGBM patients with *TERT*p as the only defining molecular alteration did not have a statistically significant difference in median overall survival compared to mGBM patients with additional defining molecular alterations such as *EGFR*amp and/or +7/–10 (median not reached vs 2.14 years, adjusted $p = .10$; Supplementary Figure S3a). mGBM patients who did not have +7/–10 had significantly improved median overall survival in comparison to hGBM with +7/–10 (median not reached vs 1.49 years, adjusted $p = .004$; Supplementary Figure S3b). Similarly, mGBM patients who did not have *CDKN2A/B* homozygous deletion had significantly improved median overall survival in comparison to hGBM with

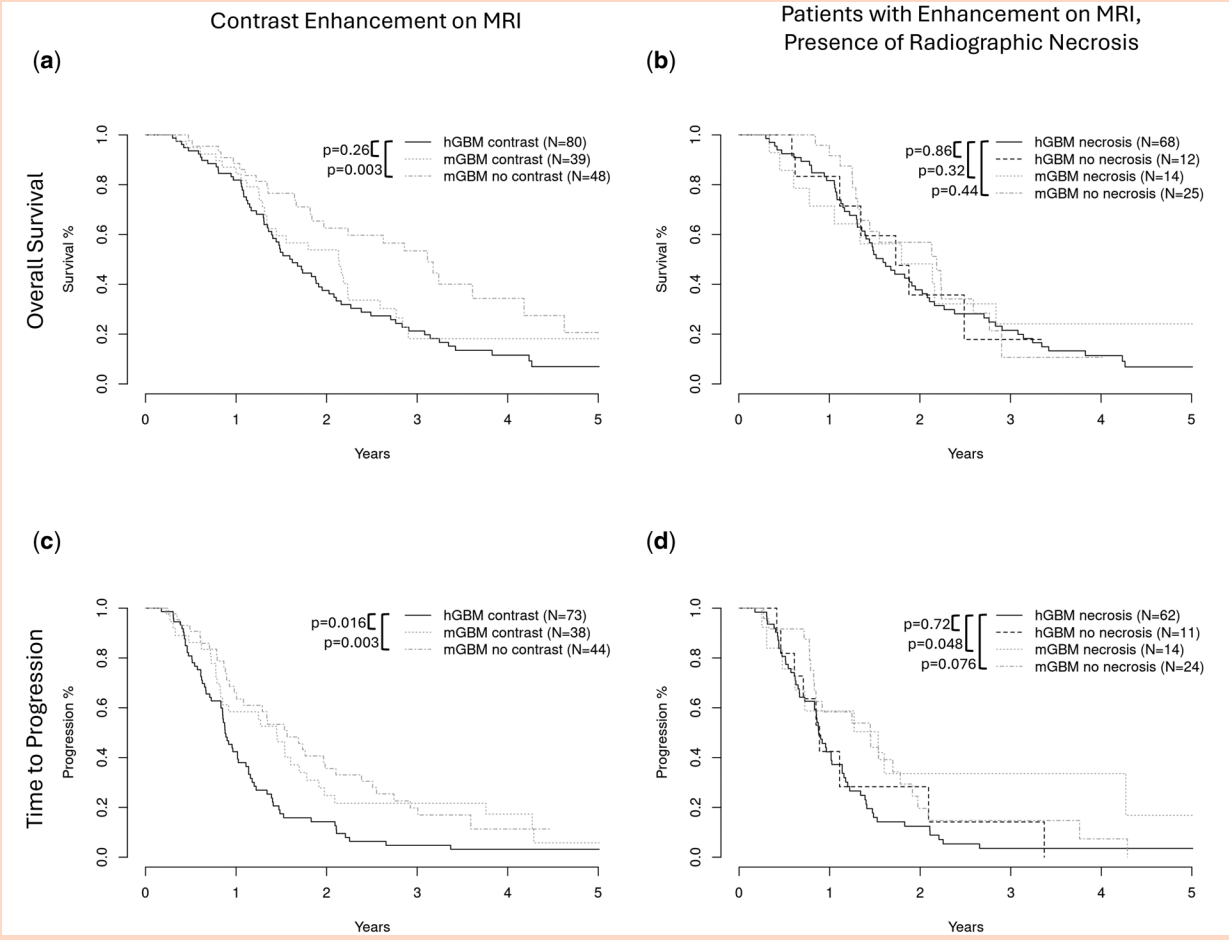

Figure 4. Kaplan-Meier curves comparing hGBM and mGBM patients across the subset of patients who received standard of care (SOC): (a) overall survival by contrast enhancement on index MRI, (b) overall survival for the subset of patients with contrast enhancement on index MRI, by presence of radiographic necrosis on MRI, (c) time-to-progression by contrast enhancement on index MRI, and (d) time-to-progression for patients with contrast enhancement on index MRI, by presence of radiographic necrosis on MRI. *p*-values from Cox proportional hazards regression, adjusted for age at diagnosis and sex. There were only 2 hGBM that did not have contrast enhancement on index MRI; thus, they were excluded from (a) and (c).

CDKN2A/B homozygous deletion (median not reached vs 1.48 years, adjusted $p < .001$; Supplementary Figure S3c). There was no significant difference in median overall survival between mGBM patients who did not have *EGFR*amp versus hGBM with *EGFR*amp (2.24 vs 1.88 years, adjusted $p = .079$; Supplementary Figure S3d).

Time-to-progression was also evaluated by individual tumor molecular alterations among patients that received SOC, adjusted for age at diagnosis and sex. mGBM patients with *TERT*p as the only defining molecular alteration did not have a statistically significant difference in median time-to-progression compared to mGBM patients with additional defining molecular alterations such as *EGFR*amp and/or +7/–10 (0.90 vs 1.34 years, adjusted $p = .80$; Supplementary Figure S3e). mGBM patients with +7/–10 had significantly longer median time-to-progression in comparison to hGBM with +7/–10 (1.34 vs 0.88 years, adjusted $p = .029$; Supplementary Figure S3f). Similarly, mGBM patients who did not have +7/–10 had significantly longer median time-to-progression in comparison to hGBM with +7/–10 (1.08 vs 0.88 years, adjusted $p = .014$). mGBM patients who did not have *CDKN2A/B* homozygous deletion had significantly longer median time-to-progression in comparison to hGBM with *CDKN2A/B* homozygous deletion (1.62 vs 0.87 years, adjusted $p = .002$; Supplementary Figure S3g). There was a significant difference in median time-to-progression between mGBM patients who did not have *EGFR*amp versus hGBM with *EGFR*amp (1.54 vs 0.87 years, adjusted $p = .004$; Supplementary Figure S3h), as well as between mGBM patients with *EGFR*amp versus hGBM with *EGFR*amp (1.53 vs 0.87 years, adjusted $p = .052$).

Discussion

The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) Update 3 concluded that the outcomes of IDH- and H3-wildtype lower-grade diffuse astrocytic glioma with either +7/–10, *EGFR*amp, or *TERT*p were sufficiently similar

to classify as equivalent to hGBM.[2] However, they cautioned that other glioma subtypes, for example, pleomorphic xanthoastrocytoma, ganglioglioma, high grade astrocytoma with piloid features (HGAP) and others should be excluded. Louis et al. also urged caution in the molecular diagnosis of GBM in young adults age groups.[1] The cIMPACT-Now group also advised that *CDKN2A/B* homozygous deletion was not sufficient to be included as a diagnostic marker for GBM because it is observed in different diagnostic entities and not always associated with uniformly poor outcome.

Since that cIMPACT-NOW publication, much attention has been focused on understanding the disease course of mGBM. Tesileanu et al. observed no statistically significant median overall survival difference between 71 mGBM and 197 hGBM patients that were obtained across three medical centers in the Netherlands.[5] Importantly, the study excluded mGBM patients with ring-enhancing MRI features consistent with radiographic necrosis to minimize pathological undersampling bias. The study did not observe a statistically significant difference in median overall survival between 22 mGBM patients that were defined based on *TERT*p only (ie, without +7/–10 or *EGFR*amp) compared with 197 hGBM patients.

Berzero et al. identified 302 mGBM patients (47 morphologic grade 2 and 255 morphological grade 3) from the OncoNeuroTek (the tumor bank of the Pitié-Salpêtrière Hospital, Paris) database who were diagnosed between 1989 and 2020 and for whom data on *TERT*p, *EGFR*amp and +7/–10 were available.[14] mGBM patients with morphologic grade 2 tumors had a significantly longer median overall survival than morphologic grade 3 (42 vs 17 months, $p < .001$). The overall survival was longer in the subset of grade 2 mGBM patients where *TERT*p mutation was the sole molecular feature (median overall survival was 88 months). Berzero et al.[14] also reported that grade 2 mGBM tumors had a lower frequency of molecular alterations, including *EGFR*amp, +7/–10, and *CDKN2A/B* homozygous deletion in comparison to grade 3 mGBM tumors. Based on this work it was suggested that grade 2 *IDH*-wildtype tumors with only *TERT*p as the primary defining alteration should not be classified as GBM.[14,15] Stichel et al. also suggested caution about *IDH*wt tumors when *TERT*p was the only identifying alteration.[4] Richardson et al.[27] observed a similarly prolonged survival for 36 *IDH*-wildtype diffuse astrocytoma, grade 2 morphology, that did not harbor any of the three defining molecular alterations (median overall survival of 100.6 months). These tumors had less total copy number variation, less frequent homozygous deletion of *CDKN2A*, less frequent *PTEN* and *PIK3CA* alterations, and more frequent *NF1* alterations. By contrast, these authors did not observe a survival difference between patients with morphologically defined grade 2 and grade 3 who met any criteria for mGBM. We did not observe a statistically significant difference in the frequency of *TERT*p as the only defining molecular alteration across hGBM versus mGBM ($p = .12$). Additionally, we did not observe a statistically significant difference in overall survival in mGBM patients where *TERT*p was the only molecular alteration versus mGBM patients with additional alterations ($p = .10$). However, there were only 13 mGBM patients who had *TERT*p as the sole defining molecular alteration and only five had an event. Thus, a larger cohort and longer follow up are needed to further evaluate the outcome in mGBM patients with *TERT*p as the only defining molecular alteration.

Zhang et al.[24] reviewed the characteristics and outcomes of 38 mGBM patients prospectively identified at the University of California San Francisco (UCSF) between 2015 and 2021. Five of the 38 patients showed enhancement and radiographic necrosis on imaging at diagnosis and were characterized as likely pathologic under-sampled hGBM. Grade 2 morphology was identified in 17/38, and grade 3 in 21/38. The overall median survival was 23.8 months (95% CI: 20.7-39.6): 38 months for those with morphologic grade 2, and 20 months for those with morphologic grade 3. The authors reported a survival experience comparable between the five tumors with radiographic necrosis on imaging at diagnosis and the remaining 33 as a basis for concluding that mGBM represents early or evolving GBM. Ramos-Fresnedo also reviewed radiographic and pathological features for five mGBM patients at time of recurrence and concluded that mGBM may be hGBM in evolution.[25]

While there is evidence to suggest that some mGBM may represent an early or evolving GBM, there are radiographic characteristics and presenting symptoms that support the hypothesis that a subset of mGBM patients may represent a separate entity. Izquierdo et al. analyzed 40 *IDH*-wildtype astrocytomas (19 grade II and 21 grade III) with *TERT*p that were diagnosed between 2011-2017: 9/39 had *EGFR*amp and +7/–10 was not reported.[9] Contrast enhancement of any type was observed in 27%, a gliomatosis pattern was observed in 43%, and T2 signal highlighting a gyriform pattern (T2 signal restricted to cortex) on fluid attenuated inversion recovery (FLAIR) sequences was observed in 33%. Patterns of progression were assessed in 17 cases with two clearly divergent courses: (1) rapid evolution to ring-enhancing necrotic lesions typical of hGBM in 10 cases, and (2) slow progression that lasted years in seven cases. Mesny et al. from the same institution evaluated the significance of the gyriform pattern of T2 signal change on MRI in 31 mGBM patients diagnosed between 2017 and 2020 (mGBM was defined by *TERT*p or *EGFR*amp; +7/–10 was not reported).[10] The gyriform pattern was observed in 16/31 (52%) of mGBM and 40/294 (14%) of hGBM ($p < .001$); the gyriform pattern was seen in 64% of cases with gliomatosis pattern versus 10% of those without ($p < .001$). We similarly observed that a gliomatosis pattern on imaging at presentation was six times more likely in mGBM, affirming these observations. Our sample size did not permit evaluating associations between gliomatosis pattern and specific molecular markers or outcome, particularly the occurrence of *TERT*p without +7/–10 or *EGFR*amp, that is, potentially consistent with the recently described High Grade Glioma Subtype F by Muench et al.[22] Moreover, we did not attempt to identify specific patterns of T2 signal change during blinded MRI review in this report.

Our findings affirm previous observations that mGBM is twice as likely to present with seizures, enhance on contrast MRI in half of cases, and that features of radiographic necrosis on imaging occur in a minority (18%) of cases. A distinguishing feature of mGBM that has not been previously reported is the delayed time from first symptom and first imaging to pathologic diagnosis: median 52 vs 34 days ($p = .018$) for first symptom, and median 34 vs 7 days ($p < .001$) for first MRI. While the

natural history for GBM from early initiation to diagnosis is not truly known, occasional chance clinical encounters of serial imaging in patients with hGBM demonstrate a uniformly rapidly progressive course, distinct from the protracted time to diagnosis for a significant subset of mGBM patients, particularly those presenting with seizures and indeterminate non-enhancing T2 signal lesions.

The median overall survival in our cohort of mGBM patients was 2.16 years, versus 1.44 years for hGBM, which is in line with historical data.[28] The 5-year survival rate was 20% for mGBM and 7% for hGBM. Median time-to-progression for mGBM patients was significantly longer than hGBM, 1.45 versus 0.88 years. These observations have greater significance if considered in view of the lower frequency of extent of resection for mGBM, where maximally safe resection is currently considered foundational in glioma care.[11]

Our observation of improved survival in mGBM patients presenting without contrast enhancement on MRI has not previously been reported. mGBM patients with enhancement on MRI had overall survival similar to hGBM and the presence or absence of radiographic necrosis was not significantly associated with outcome. This supports other reports that mGBM patients with enhancing tumors are likely under sampled or early evolving GBM. Conversely, mGBM patients with non-enhancing MRI tumors had significantly longer survival than hGBM with enhancing tumors. These mGBM patients had longer delays in diagnosis and were more likely to present with seizures. This implies that there is underlying biology with one or more subsets within mGBM as presently defined that requires further study.

This study is unique among previously published comparisons between mGBM and hGBM as the comparison is based on a design that matched on age at diagnosis, sex, year of diagnosis and *TERT*p to minimize biases that might affect the results. However, there are limitations in this study. The mGBM patients were identified over a long period where neuropathology practices were evolving, particularly with the use of copy number assessment, mutation analysis, and methylation analysis for clinical diagnosis, and therefore a complete molecular data set was not uniformly available for all cases. Next-generation sequencing data for specific mutations and fusions were not available for most cases; for example, *FGFR3* fusions, implicated as identifying a subgroup with prolonged survival, may have been missed. Diagnosis for patients in this series predated routine or even special case availability of methylation analysis. Morphologic grading of mGBM cases was not uniformly performed nor was clinical performance status at diagnosis routinely quantified in either cohort, thus obviating the ability to compare morphologic grade 2 vs 3 in mGBM or outcomes by performance status as prior published work has highlighted. mGBM patients were identified over a long period of time where SOC changed. We defined SOC as any surgery combined with any radiation and any temozolomide. While the frequency of radiation and temozolomide therapy, nor *MGMT* promoter mutation status, was not statistically different between mGBM and hGBM, extent of resection was significantly different. mGBM patients were significantly less likely to receive gross total resection than hGBM. In addition to less optimal volume reduction surgery in mGBM, for cases prior to 2021 and certainly prior to the 2016 WHO classification, mGBM patients may also receive less intense therapy such as lower dose radiation or shorter chemotherapy. Taken together, these should have negatively bias outcomes for mGBM patients.[11] Overall, due to the retrospective nature of the design, the survival analyses require validation in a more modern treatment era.

In summary, this report confirms that mGBM as presently defined in the 2021 WHO Classification are not a uniform entity equivalent to hGBM. Our study validates the importance of comprehensive molecular analysis for any adult with an *IDH*-wildtype diffuse astrocytic glioma, particularly those not meeting traditional morphologic criteria for GBM. Our results also further validate that mGBM with contrast enhancement on MRI are more likely to represent under-sampled or early evolving hGBM, particularly in the presence of combined +7/–10 or *CDKN2A/B* homozygous deletion. We observed that mGBM cases were less likely to have *EGFR*amp and isolated loss of chromosome 10, and had lower copy number complexity. We additionally observed that mGBM without +7/–10 or without *CDKN2A/B* homozygous deletion had better overall survival. mGBM patients without contrast enhancement on MRI were more likely to present as unifocal T2 signal lesions, with long symptom profile and seizures. These patients are less likely to be under-sampled or early evolving GBM and may represent other *IDH*-wildtype entities. These patients should be (1) advised of a potential clinical course that may not be the same as hGBM, and managed accordingly, and (2) either excluded or stratified correspondingly in GBM clinical trials so that analyses can be performed separately for mGBM and hGBM.

Our findings are in line with the recently published cIMPACT-NOW update 11 report: "Recommendations regarding the IDH- and H3-wildtype diffuse high-grade gliomas include: (1) use caution assigning CNS WHO grade 4 (diagnosis of Glioblastoma, IDH-wildtype) to a "TERT promoter only", histologically low-grade, IDH-wildtype tumor; (2) EGFR gene amplification and +7/–10 chromosome copy number alterations should not be used as solitary defining features for diagnosing high-grade gliomas as Glioblastoma, IDH-wildtype in patients <40 years of age; (3) Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype should be considered in the differential diagnosis in adults, especially those <40 years of age; (4) PDGFRA alteration, EGFR alteration, or MYCN amplification count as key molecular features of Diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype only in patients <25 years."[29] Future efforts should be directed to additional comprehensive molecular characterization of mGBM including refinement of methylation profiling, stratified by presenting clinical and imaging features and relevant treatment differences, with the goal of further clarification of the WHO classification for glioma. This highlights the importance of analyzing a large mGBM cohort, with appropriate follow-up and where possible serial sampling over disease course.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords

clinical and radiographic features | molecular glioblastoma IDH-wildtype | survival

Author Contributions

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Conflict of Interest Statement

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