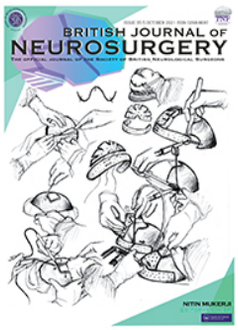

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ORIGINAL ARTICLE

Relationship between molecular characteristics of glioblastoma multiforme and the subventricular zone

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ABSTRACT

Objective: This study aims to assess the relationship between the molecular characteristics of glioblastoma multiforme (GBM) and the subventricular zone (SVZ)

Material and Methods: Eligible patients had their data anonymously collected from an institutional database, including age, sex, preoperative performance status, the extent of tumour resection, anatomical location, *IDH* mutation and *MGMT* methylation status. An Institutional picture archiving and communications system was used for volumetric and morphometric analysis. All measurements were made on T1-weighted magnetic resonance images with gadolinium contrast enhancement. *IDH* wild-type and mutant GBMs were stratified by *MGMT* methylation status. The relationship between tumour volume, distance from the tumour's enhancing edge and the tumour's geometric centre to the SVZ and their molecular characteristics were assessed.

Results: Fifty *IDH* wild-type GBMs were studied. Twenty-three were *MGMT* methylated, Twenty-seven were unmethylated. *IDH* wild-type *MGMT* methylated GBMs were significantly associated with a tumour's enhancing boundary being contiguous to the SVZ ($P < 0.001$). Ninety percent of tumours contiguous to the SVZ were wild-type methylated ($n = 18$) and 10% were unmethylated ($n = 2$). Mean GBM geometric centre distance to SVZ was significantly less for methylated wild-type GBMs compared to unmethylated ($P = 0.025$) and median GBM distance from the tumour's edge of enhancement to the SVZ was significantly shorter in methylated tumours compared to unmethylated ($P < 0.001$). Mean and median distances to SVZ from the edge of enhancement was 3.8 millimetres (mm) and 0 mm, respectively, for wild-type methylated GBMs, while for unmethylated wild-types, 14.6 mm, and 12.5 mm. There was no anatomical localisation of *IDH* wild-type GBMs by *MGMT* methylation status to a cerebral hemisphere or lobe.

Conclusion: *IDH* wild-type GBMs contiguous to the SVZ are highly likely to be *MGMT* methylated. Replication by further studies is required to affirm our results and conclusion.

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Introduction

Glioblastoma multiforme (GBM) is a highly aggressive primary malignant brain tumour. These are the most common malignant brain tumours and account for over 50% of all primary brain tumours and 80% of all primary malignant tumours in the central nervous system (CNS).[1] Despite tremendous advances in the understanding of their genetic and molecular biology, the standard of care treatment has uniformly remained cytoreduction by surgery to remove as much tumour as possible, followed by adjuvant chemoradiotherapy where radiation is delivered in fractions concurrently with oral chemotherapy tablet temozolomide (TMZ), followed by maintenance TMZ for up to 6 months.[2] The prognosis remains abysmal, with overall median survival between 12–18 months; however, individual survival rates are highly varied and dependent on various prognostic factors.[2]

The subventricular zone (SVZ) hosts neural stem cells adjacent to the lateral ventricles' ependymal lining.[3,4] Preclinical work has shown that GBMs have a small subpopulation of cancer stem cells. Like neural stem cells, these cells can proliferate and are the primary driver of recurrence following treatment.[5,6] These GBM cancer stem cells have putative stem cell characteristics: they can self-renew, initiate tumorigenesis, distal migration, and have multilineage potency.[7–9] It was postulated as early as 1942 that neural stem cells might give rise to GBMs.[10] Preclinical evidence shows that neural stem cells in the SVZ can transform into GBMs by oncogenic mutations. These neural stem cells share molecular pathways and genetic similarities to the cancer stem cells within GBM.[11] Clinically, a large proportion of GBMs are diagnosed in proximity to the SVZ.[12] This supports the notion that the SVZ stem cells give rise to a subset of GBMs and the theory at large that GBMs originate from neural stem cell niches.[12]

Understanding the molecular characteristics of GBMs has improved our knowledge of the disease course, response to treatment and allowed for prognostication.[13] GBMs are now accepted as either primary or secondary, both of which are histologically indistinguishable from each other.[13] Mutations in the genes that code for the enzyme isocitrate dehydrogenase, *IDH1* and less commonly *IDH2,* (a key enzyme in the tricarboxylic cycle and

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glutamine metabolism) now unequivocally define a secondary GBM,[13,14] whereas the *IDH* wild type is considered primary GBM that arose de novo as a higher-grade tumour. *IDH* mutated secondary GBMs were lower-grade gliomas that eventually underwent a malignant transformation.[14] These secondary GBMs have a far better prognosis with longer median survivals than *IDH* wild-type primary GBMs.[14] Equally important is O^6-methylguanine-methyltransferase (*MGMT*) gene silencing by methylation.[15] Approximately 50% of all newly diagnosed GBMs are *MGMT* methylated.[15] The *MGMT* gene found on chromosome 10q26 codes for the MGMT protein, a DNA repair enzyme.[15] This protein removes alkyl groups from guanine nucleotide at the O6 position, which is thought to be the site of action of TMZ.[16] Silencing reduces MGMT protein expression leading to decreased DNA repair, rendering these patients more sensitive to TMZ and significantly prolonging survival than unmethylated patients.[16] Thus, in addition to age, preoperative performance status, the extent of tumour resection, molecular characteristics such as *IDH* mutations and *MGMT* methylation are recognised as independent prognostic factors affecting overall survival.[16,17]

Anatomical localisation of these molecular markers has been of interest within the literature as it can aid in preoperative planning and prognostication. *IDH* mutant GBMs are known to have a preferential topographic distribution to single lobes of the brain, typically areas easier to operate in, most commonly within the frontal lobe.[18] However, there is a significant variation and conflicting evidence in the literature about the anatomical localisation of GBMs by their *MGMT* methylation status, with various groups reporting different localisations with regards to lateralisation to a particular cerebral hemisphere, to specific cerebral lobes, and a even a relationship with the SVZ itself.[19–27]

Additionally, the involvement of GBMs with the SVZ is associated with reduced overall survival.[28] Thus, given the importance of the SVZ in harbouring neural stem cells that give rise to a subset of GBMs, the differing evidence about the anatomical localisation of GBM by *MGMT* methylation status, including a possible relationship with the SVZ and poor survival of GBMs associated with the SVZ, it is of interest to assess if there exists a relationship between the molecular characteristics of GBMs and the SVZ. This can add to our knowledge of the underlying biology of GBMs and provide clinical prognostication that may guide management. Our study aimed to evaluate the relationship, if any, between the molecular characteristics of GBMs and their distance in millimetres from the SVZ within our regional neurosurgical institute cohort of GBM patients.

Methods

Patient population

Patients were identified retrospectively, and data were collected after anonymising identifiable information using an electronic institutional database. All consecutive patients diagnosed with GBM between 1st January 2016, to 31st December 2017, were considered for enrolment if they had met our inclusion and exclusion criteria.

Inclusion criteria

1. Adult patients over the age of 18 of either sex.
2. Histologically confirmed diagnosis of GBM.
3. Availability of *IDH* gene mutation and *MGMT* gene methylation status molecular studies.
4. Preoperative T1 weighted gadolinium-enhanced (GdT1) Magnetic Resonance Imaging (MRI) scans for tumour measurements.
5. Postoperative GdT1MRI scan available within 48 hours of surgery to confirm the extent of resection.

Exclusion criteria

1. Patients under the age of 18.
2. Incomplete or poor-quality preoperative MRI imaging to perform volumetric and morphometric analysis.
3. Absence of IDH mutation and MGMT methylation molecular test results.
4. Multifocal GBM and cerebrospinal fluid spread on preoperative MRI.

All appropriate demographic data, including age at presentation, sex, preoperative performance status by Eastern Cooperative Oncology Group Classification (ECOG), were documented. Either immunohistochemistry or next-generation sequencing assesses *IDH* mutation status at our institute. *MGMT* methylation is determined using methylation-specific Polymerase Chain Reaction. Multifocal GBMs on preoperative MRI were excluded. These were defined as two or more independent and separate foci of abnormal enhancement on preoperative MRI. The rationale for exclusion was the difficulty in analysing and standardising measurements on multifocal GBM.[28]

Imaging and measurements

The following imaging measurement protocols were adapted from Young *et al*[28] a similar study where the distance of GBMs from the SVZ was measured. All preoperative GdT1MRI scans were performed using a standard institutional brain tumour imaging protocol on either a 1.5 or 3 Tesla machine. The following measurements were made on preoperative MRI using our institutional picture archive communication system:

1. **Tumour volume**: The volume of abnormal enhancement was measured in cubic centimetres using the ellipsoid volume formula. V=(4/3)*Pi*(a/2)*(b/2)*(c/2). This formula is accepted in the literature to have the highest inter-rater agreement and agreed most with manual segmentation based planimetric tumour volume measurement for glioblastomas.[29] 'a' is the longest measured orthogonal diameter on the axial MRI cut where the tumour appeared to be the largest. 'b' was the second diameter measured on the same slice in the anterior-posterior plane being perpendicular to 'a'. Parameters 'a' and 'b'. The corresponding coronal MRI cut at the point of intersection between 'a' and 'b' was used to measure the longest diameter in the craniocaudal axis, denoted 'c' in the formula. Figure 1 illustrates tumour volume measurement.
2. **Tumour location:** This was defined as the cerebral lobe containing the tumour's geometric centre.
3. **Tumour distance from ventricles**:
   - **Gadolinium edge distance (GdED)** was the closest distance, in millimetres, from any cut on GdT1MRI, from the edge of enhancement to the SVZ and if contrast enhancement was contiguous to the SVZ, GdED = 0.
4. **Gadolinium centre distance (GdCD)** was measured, in millimetres, from the tumour's geometric centre to the SVZ. Figure 2 illustrates both GdED and GdCD.

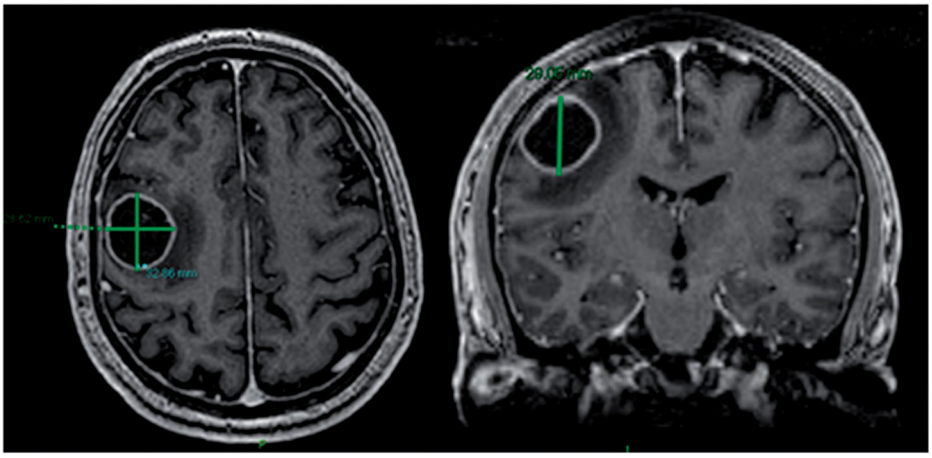

Figure 1. Illustrating Tumour Volume Measurements. Refer to formula in methods section. Axial MRI on left showing 'a'=32.36millimetres, 'b'=28.62millimetre. Coronal MRI on right, 'c'=29.05millemetres. 'a' and 'b' represent the largest diameters in the anterior-posterior and orthogonal plane on axial MRI and 'c' is measured by viewing the corresponding coronal plane at the point of intersection between 'a' and 'b'. 'c' represents the longest diameter in the cranial-caudal axis.

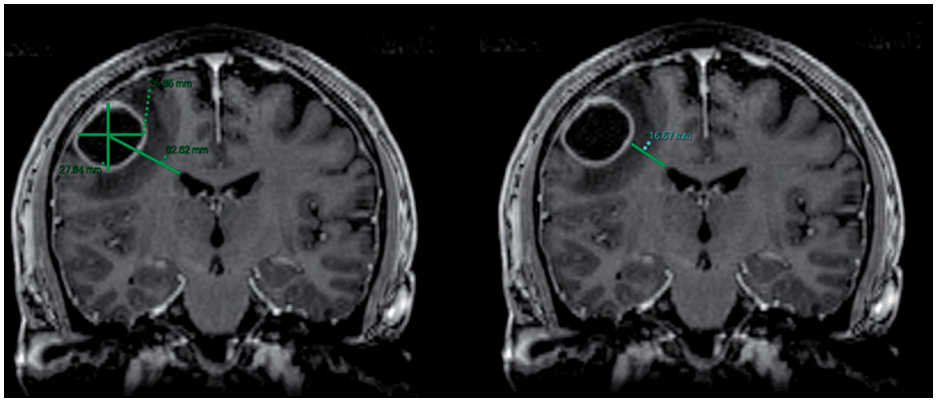

Figure 2. Illustrating Gadolinium Centre Distance, left, and Gadolinium Edge Distance, right. Measurements shown above are in millimetres. GdCD = 32.82millimetres and GdED = 16.67millimetres.

Tumour geometric centre: Defined as the intersection of the largest in-plane anteroposterior and orthogonal diameters on axial GdT1MRI.

Area of SVZ proximity: The closest region of the subventricular zone on GdT1MRI for each patient was identified by dividing the lateral ventricles into its four anatomical regions[30] illustrated by Figure 3:

- Frontal Horn

Body of the Lateral Ventricle
Occipital Horn
Temporal Horn

Extent of Tumour Resection: As documented on the operative notes. At our institution, the extent of resection is categorised as either greater than 90% reduction of preoperative enhancing tumour on a postoperative GdT1MRI acquired within 48 hours. Subtotal resection is classed as less than 90% reduction. Cases where a biopsy was performed, was either by open or stereotactic means.

Results

Fifty-six patients met our inclusion and exclusion criteria. Table 1 summarises patient and tumour characteristics for the entire cohort. The mean age was 60 years. Thirty-two percent of our patients were females, while 68% were male. The median preoperative performance status was 1. There were 50 *IDH* wild-type primary GBMs and six *IDH1* mutant secondary GBMs. Of the 50 primary GBMs, 27 (54%) were MGMT unmethylated, while 23 (46%) were methylated. Among the six *IDH mutant* GBMs, five were methylated, and one was unmethylated. One isolated 19p deletion was found in an *IDH* wild-type *GBM*, and one isolated 19p deletion occurred in an *IDH1 mutant* patient. One 1p/19q co-deletion was found in an *IDH* mutant GBM. 21 GBMs were contiguous with the SVZ. In our series, the most common anatomical location was the parietal lobe (35.7%), followed by the temporal lobe (34%), frontal lobe (23.2%) and occipital lobe (5.4%). One patient had a tumour spanning across the corpus callosum. Due to the small number of *IDH* mutant cases in our cohort and to ensure homogeneity, we excluded these and studied 50 *IDH* wild-type primary GBMs.

Tables 2 and 12 further stratifies measurement parameters by *MGMT* methylation status for the 50 *IDH* wild-type GBMs. Twenty GBMs were contiguous with the SVZ, and of these, 18 (90%) were *MGMT* methylated, while only two (10%) were unmethylated. The mean and median GdED for methylated tumours was 3.8 mm and 0mm, respectively, while for unmethylated tumours, it was 14.6 mm and 12.5 mm, respectively. The mean and median GdCD for methylated tumours were 24.3mm and 24mm, respectively, while 31.5 mm and 32 mm for

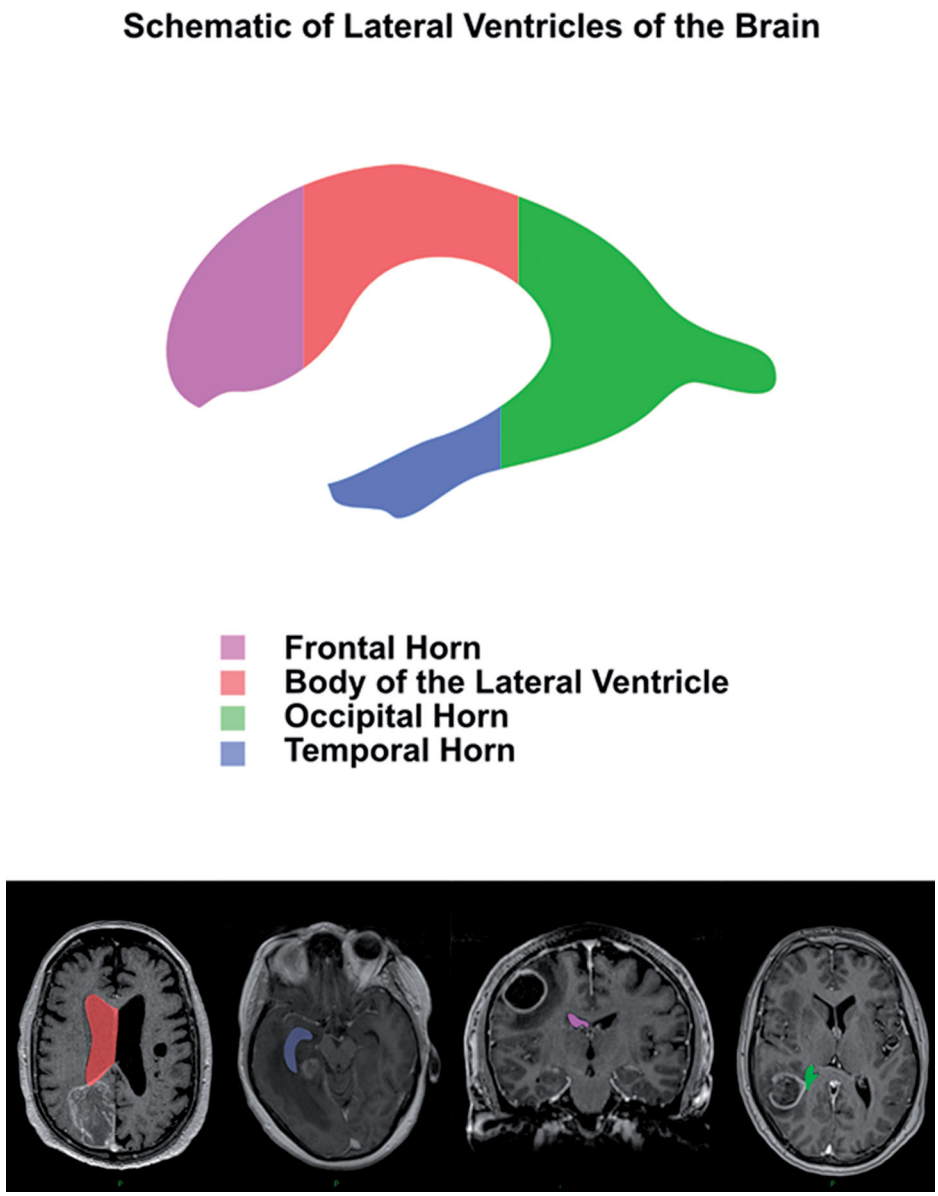

Figure 3. Illustrating Glioblastoma Multiforme's point of subventricular zone contact stratified by the four anatomical regions of the subventricular zone. GdCD. And GdED (distances) to the subventricular zone were measured by the closest anatomical region of the subventricular zone to the tumour.

unmethylated tumours. The mean tumour volume for unmethylated and methylated tumours was 20.2 cubic centimetres (cm^3) and 36.7 cm^3, respectively. The greater than 90% resection rate and subtotal resection rate for unmethylated tumours was 66.7% and 29.6% respectively and was 56.5% and 39.1% for methylated tumours, respectively. Additionally, anatomical locations between *MGMT* methylated and unmethylated *IDH* wild-type tumours are summarised in Table 2.

Statistical analysis

Patient demographic information and variable measurements were entered into and analysed using Statistical Package for Social Sciences (SPSS) Version 27 to assess the relationship between the molecular characteristics and distance from SVZ for the 50 primary GBMs (*IDH* wild type). Independent sample *t*-tests were used to compare normally distributed data, Mann–Whitney U-test for non-parametric data, Pearson's Chi-Squared test, and Fisher–Freeman–Halton exact tests to assess relationships between categorical data. Differences and associations between variables were considered significant if *P*-values were less than 0.05.

GdCD was on average 7.14 mm shorter in MGMT methylated GBMs than those that were unmethylated ($p = 0.025$). Median GdED to the SVZ differed between the two groups ($p < 0.001$), where methylated tumours had a median GdED of 0 mm. In contrast, unmethylated tumours had a median GdED of 12.5 mm. Methylated tumours were, on average, 16.5 cm^3 larger in volume than unmethylated tumours ($P = 0.006$).

There was a significant association between GBM contiguity with the SVZ and MGMT methylation status being positive ($P < 0.001$). No significant association was found between GBM *MGMT* methylation status and the region of SVZ in proximity ($p = 0.17$), nor was there any preferential association between tumours contiguous with SVZ and region of the region of SVZ in proximity ($p = 0.94$). *MGMT* methylation status had no significant localisation association to a particular lobe ($P = 0.6$) or left/right hemispheric lateralisation ($P = 0.78$). *MGMT*

Table 1. Summarises the essential baseline characteristics of our patients, tumour anatomical locations, including the closest region of the SVZ in contact, and molecular profiles.

	Total Patients (%)
Age, at Diagnosis Mean+/-SD= 60 +/- 14; Median= 60	56 (100%)
Sex	
Female	18 (32.14%)
Male	38 (67.85%)
Preoperative Performance (Median = 1)	56 (100%)
Contiguous with Subventricular Zone (GdED = 0 millimetres)	
No	35 (62.5%)
Yes	21 (37.5%)
MGMT Methylation Status	
Unmethylated	
IDH Mutation	
Wild-type	27 (48.2%)
IDH1 mutant	1 (1.7%)
Methylated	
IDH Mutation	
Wild-type	23 (41.2%)
IDH1 mutant	5 (8.9%)
Other Mutations	
None	53 (94.6%)
1p/19q co-deletion	1 (1.7%)
Isolated 19p deletion	2 (3.6%)
Anatomical Location (Cerebral Lobe)	
Frontal	13 (23.2%)
Parietal	20 (35.7%)
Temporal	19 (34%)
Occipital	3 (5.4%)
Corpus Callosum	1 (1.8%)
Closest Region of Subventricular Zone Contact In Contact	
Frontal Horns	9 (16.1%)
Body of Lateral Ventricle	25 (44.6%)
Occipital Horns	17 (30.4%)
Temporal Horns	5 (8.9%)

Preoperative performance status by Eastern cooperative oncology group.

Table 2. Stratifying glioblastoma multiforme study parameters by *MGMT* methylation status for the 50 *IDH* wild-type tumours.

				Count (%)	*p* Value
MGMT Methylation Status	Unmethylated (N = 27)	Extent of Resection	Greater than 90%	18 (66.7%)	0.77
			Less than 90%	8 (29.6%)	
			Biopsy	1 (3.7%)	
	Methylated (N = 23)	Extent of Resection	Greater than 90%	13 (56.6%)	
			Less than 90%	9 (39.1%)	
			Biopsy	1 (4.3%)	
MGMT Methylation Status	Unmethylated	Cerebral Lobe	Frontal	5 (18.5%)	0.6
			Parietal	10 (37%)	
			Temporal	10 (37%)	
			Occipital	2 (7.5%)	
	Methylated (N = 23)	Cerebral Lobe	Frontal	7 (30.4%)	
			Parietal	10 (43.5%)	
			Temporal	5 (21.8%)	
			Occipital	1 (4.3%)	
MGMT Methylation Status	Unmethylated (N = 27)	Subventricular Zone Contact	Frontal Horns	2 (7.4%)	0.17
			Body of Lateral Ventricle	15 (55.6%)	
			Occipital Horns	8 (29.6%)	
			Temporal Horns	2 (7.4%)	
	Methylated (N = 23)	Subventricular Zone Contact	Frontal Horns	6 (26.1%)	
			Body of Lateral Ventricle	7 (30.4%)	
			Occipital Horns	9 (39.1%)	
			Temporal Horns	1 (4.4%)	

methylation status and tumour contiguity with SVZ was not associated with the extent of tumour resection ($P = 0.77$ and $P = 0.91$, respectively).

Discussion

Our study showed that *IDH* wild-type GBMs contiguous to the SVZ are very likely to be MGMT methylated. However, our cohort has no localisation of *IDH* wild-type GBMs by MGMT methylation to a particular cerebral lobe or hemisphere.

Ellingson *et al.* had initially shown in their study cohort that methylated GBMs were lateralised to the left cerebral hemisphere and unmethylated to the right,[22] supported by a further study (conducted by the same group) which had a larger sample, in addition to the patient data from their previous study.[21] Wang *et al.*, however, had found the opposite results of hemispheric lateralisation where methylated GBMs were more commonly found in the right cerebral hemisphere.[27] Eoli *et al.* found no

Table 3. Stratifying glioblastoma multiforme's Centre and edge distances by *MGMT* methylation status for the 50 *IDH* wild-type tumours.

		Mean	Median	*p* Value
MGMT Methylation Status				
Unmethylated (N = 27)	GdED in millimetres (mm)	14.6	12.5	**<0.001***
Methylated (N = 23)	GdED millimetres (mm)	3.8	0	
MGMT Methylation Status				
Unmethylated (N = 27)	GdCD millimetres (mm)	31.5	32.0	**<0.025***
Methylated (N = 23)	GdCD millimetres (mm)	24.3	24.0	
MGMT Methylation Status				
Unmethylated (N = 27)	Tumour Volume in Cubic Centimetres (cm^3)	20.2		**0.006***
Methylated	Tumour Volume in Cubic Centimetres (cm^3)	36.7		

Bold* values indicate statistical significance.

hemispheric lateralisation pattern but anatomical localisation of methylated tumours to parietal and occipital lobes and unmethylated tumours to the temporal lobe.[23] Additionally, studies reported no specific localisation pattern by methylation status to any hemisphere or cerebral lobe.[19,20] However, all of these studies were conducted before the World Health Organisation's (WHO) 2016 updated classification of GBM, when *IDH* mutation status was not an essential diagnostic test as part of routine GBM diagnosis.[13] Ellingson *et al.* had 107 GBMs out of 507 where the *IDH* mutation status was unknown,[21] and the *IDH* mutation status was not mentioned within the other studies.[20,22,23,27] The *IDH* molecular variation in these studies is perhaps the most significant confounder contributing to the discrepancy observed as there is an agreement in the literature about the anatomical localisation of *IDH* mutant GBMs and lower-grade gliomas such as astrocytomas and oligodendrogliomas, of which *IDH* mutants' show a frontal lobe localisation while the wild-type variants do not.[18] *IDH* mutant GBMs also tend to spare 'high-risk' areas of the brain like the hypothalamus, midbrain, and the medulla oblongata.[18] Thus, their inclusion in these studies' cohorts represents a substantial confounder, especially if the *IDH* mutant tumours are different entities arising from a different cell niche.[13,18] Our homogeneous cohort of *IDH* wild-type GBMs showed no anatomical preference of a particular cerebral lobe, nor did they demonstrate laterality to either hemisphere regarding *MGMT* methylation status.

The two recent studies (following 2016 WHO update), both with large cohorts ($N = 398$ and 507), evaluated anatomical localisation of *MGMT* methylation status in a homogenous cohort of *IDH* wild-type, did not find any statistically significant localisation of GBMs, to any hemisphere or cerebral lobes[25,26] and this is in concordance with our results with regards to hemisphere or lobar preference. Similarly, Han *et al.*, in their cohort of 92 *IDH* wild-type GBM patients, supported our results as they could not demonstrate any anatomical localisation to a hemisphere or lobe but stated the SVZ was more frequently spared with MGMT methylated GBMs.[24] This contradicts our results and warrants further research as relatively small sample sizes limit both studies.

We assessed the molecular characteristics of GBMs specifically concerning the SVZ as previously it has been shown from retrospective studies that tumours contiguous with the SVZ have reduced survival[28,31,32]. This is independent of other prognostic factors of GBMs, such as the molecular profile. The reduction in survival in these studies was not a linear association with a tumour's distance from the SVZ, rather a categorical one only associated with tumours directly in contact with the SVZ (GdED = 0). Ahmadipour *et al.*, whilst discussing in their multivariate analysis, state SVZ involvement was a poor prognostic predictor of overall survival.[31] The authors attributed this to the anatomical difficulty and complexity of the area itself as the tumours, in their series, contiguous with the SVZ were larger and naturally relatively more deep-seated to cortical tumours; the authors in this context, also had a statistically higher biopsy or subtotal resection rates which is similar to contemporary literature.[31,33] In our cohort, the mean tumour volume was on average 16.5 cm^3 larger (95% confidence interval, 4.6 cm^3 to 28.3 cm^3) in the *MGMT* methylated group (which constituted 90% of all tumours contiguous with the SVZ) compared to the unmethylated group. Additionally, the proportion of subtotal resection for GBMs contiguous to the SVZ was also higher in our series than those not contiguous. This difference, however, was not statistically significant but could be due to a relatively small sample.

A topographical preference of SVZ contiguous GBMs to be *MGMT* methylated supports the hypothesis of GBMs arising from a specific neural stem cell origin which goes on to become cancer stem cells as opposed to the secondary competing, but the less accepted hypothesis, that any individual cell can accumulate mutations to become a cancer stem cell.[12] We provide evidence that neural stem cells lining the SVZ give rise to a subset of *IDH* wild-type GBMs that are very likely to be *MGMT* methylated. If SVZ does have a propensity to give rise to contiguous GBMs that are *MGMT* methylated but generally have poorer overall survival, this is, in part, a result of the anatomical difficulty of this area to achieve a GTR for these relatively deeply located lesions, along with SVZ GBMs generally having a much larger tumour volume.[31,33] Thus, the presence of these two poor prognostic factors appears to outweigh the benefit that *MGMT* methylation may provide. In such a case, it can be argued that efforts to achieve as great a resection as possible should be made to decompress the tumour without an unacceptable neurological deficit, even if a GTR is not achievable. GBMs are not a homogenous group of aggressive tumours, and we treat different lines of distinct tumours. *MGMT* methylation itself is a favourable prognostic factor for patients. It would be desirable for such patients to preserve their quality of life and improve progression-free survival with safe surgery and adjuvant treatment. Survival can be relatively long in methylated patients if performance status is good (0-1 on ECOG classification) and TMZ with radiotherapy are administered. In one of the largest series of unresectable de novo *IDH* wild-type (biopsy only) GBMs ($N = 177$), Hamdan *et al.* showed that despite no resection,

MGMT methylated patients with good performance status (0–1), receiving TMZ with radiotherapy, followed by six months of TMZ have a median overall survival of 18.5 months which is nearly twice that of biopsy only unstratified patients (9.4 months).[34] It would be interesting for future studies to evaluate the progression and overall survival benefit *MGMT* gives, if any, in the case of SVZ contiguous GBMs.

In addition to the anatomical complexity, which may lead to a lower extent of resection, and larger tumours size,[31,33] the SVZ itself may also represent an environment more biologically hostile as its' microenvironment has been shown to play a critical role in resistance to radiotherapy.[35] Concurrent to this is clinical evidence that GBMs contiguous SVZ have smaller progression-free and overall survival.[28,31,32] Goffart *et al.* transplanted intracranial xenografts of human GBM cells from the SVZ in mice models and identified the chemokine CXCL12 responsible for radioprotection.[35] Preclinical pharmacological inhibition of this molecule has been shown to prevent tumour recurrence by preventing the development of tumour vasculature needed for recurrence following radiotherapy.[36] Evers *et al.* showed that GBM patients who had higher doses of radiotherapy (>43Gy) delivered bilaterally to the SVZ had an 8 month longer progression-free survival compared to those that received a reduced dose ($P = 0.028$).[37] It would be useful to study further how to target the SVZ and the GBM cancer stem cells responsible for recurrence, be it by new radiation therapy paradigms to the SVZ or more novel pharmacological agents targeting critical biological molecules responsible for recurrence.

A significant clinical benefit of accurately predicting GBMs' methylation status radiographically means that the result can be incorporated into treatment decisions when the laboratory result is not available. This can be for patients where the tumours' diagnostic sample was not large enough to perform *MGMT* methylation test or for patients whose results are indeterminate, as can be the case in 20% of GBM patients where pathological analysis depends upon the location of the GBM.[15] In developing countries where government-funded hospitals do not pay for GBM molecular profiling,[38] clinicians can more accurately guide patients who cannot afford *MGMT* gene methylation testing regarding prognosis.

Limitations and future recommendations

We analysed a homogenous cohort of *IDH* wild-type GBMs. The retrospective nature of the study, however, may introduce subconscious selection bias. We acknowledge the possibility that any difference that we could not demonstrate but have been found in other papers discussed, such as hemispheric lateralisation or cerebral lobe localisation by *MGMT* methylation status, could be attributed to a relatively smaller sample. Also, while the linear formula-based assessment is an acceptable method for assessing GBM volume, manual segmentation remains the gold standard,[29] and superior automated software programmes replace manual segmentation.[39] Neither of these was available to us. In addition, their were 142 GBM patients during the study duration who could not studied either due to absence of pre or postoperative imaging, lack of *MGMT* methylated or *IDH* gene mutation results. In our study and similar literature on the topic,[31,33] the SVZ contiguous tumours had a larger preoperative volume. It may be that larger GBMs generally are more likely to touch the SVZ, representing a significant bias that needs to be addressed. We acknowledge that the rim of enhancement of GdT1MRI might not represent the actual boundary of GBM. Therefore, in the future, studies should incorporate several MRI sequences with histological validation and with larger data sets and multiple observers making measurements whilst blinded to the molecular profile being studied.

Conclusion

IDH wild-type GBMs in direct contiguity to the SVZ are very likely to be *MGMT* methylated. However, further studies addressing the limitations we have described are required to validate our findings and affirm our conclusion.

Ethical approval

Institutional Review Board approval was not required due to retrospective nature of study. All patient data was kept anonymous and no identifiable information is present.

Disclosure statement

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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