Glioma lateralization: Focus on the anatomical localization and the distribution of molecular alterations (Review)

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Abstract. It is well known how the precise localization of glioblastoma multiforme (GBM) predicts the direction of tumor spread in the surrounding neuronal structures. The aim of the present review is to reveal the lateralization of GBM by evaluating the anatomical regions where it is frequently located as well as the main molecular alterations observed in different brain regions. According to the literature, the precise or most frequent lateralization of GBM has yet to be determined. However, it can be said that GBM is more frequently observed in the frontal lobe. Tractus and fascicles involved in GBM appear to be focused on the corticospinal tract, superior longitudinal I, II and III fascicles, arcuate fascicle long segment, frontal strait tract, and inferior fronto-occipital fasciculus. Considering the anatomical features of GBM and its brain involvement, it is logical that the main brain regions involved are the frontal-temporal-parietal-occipital lobes, respectively. Although tumor volumes are higher in the right hemisphere, it has been determined that the prognosis of patients diagnosed with cancer in the left hemisphere is worse, probably reflecting the anatomical distribution of some detrimental alterations such as TP53 mutations, PTEN loss, EGFR amplification, and MGMT promoter methylation. There are theories stating that the right hemisphere is less exposed to external influences in its development as it is responsible for the functions necessary for survival while tumors in the left hemisphere may be more aggressive. To shed light on specific anatomical and molecular features of GBM in different brain regions, the present review article is aimed at describing the main lateralization pathways as well as gene mutations or epigenetic modifications associated with the development of brain tumors.

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Contents

1. Introduction

Glioblastoma is the most common glioma-derived tumor in the central nervous system, especially in the brain (1). The World Health Organization (WHO) classifies central nervous system tumors according to histological, molecular, and prognostic factors (2). Every year, 3-5/100,000 individuals are diagnosed with a brain tumor of which glioblastoma multiforme (GBM) represents the most common form (3). In addition, GBM constitutes the most lethal form of primary brain tumor. According to the WHO, GBM is the Grade IV stage (highest grade) of astrocytoma. The WHO GBM grading was determined according to the core structure, mitotic activity, vascularization, necrosis, proliferation rate, clinical signs, and response to treatment (3,4). Due to its highly heterogeneous structure, radical resection is not possible, resulting in a shortened life expectancy in patients. Despite intensive treatment and surgery in patients with GBM, the overall life expectancy

is 12-15 months (5). Rapid infiltrative growth of GBM cells into peripheral structures causes the disease to progress more aggressively (6).

Revealing the epidemiology, etiology, anatomy, molecular structure and spreading of GBM will provide us with more opportunities to create meaningful treatments and surgical approaches. The aim of the present review is to reveal the lateralization of GBM, the anatomical regions where it is frequently located, the main molecular features in order to associate these characteristics with tumor location and brain anatomy.

2. Lateralization of the brain and functional area

The right and left hemispheres, which are formed by the symmetrical division of the brain into two halves through the fissura longtidunalis, are connected to each other mainly by the corpus callosum and the comissura anterior. Interhemispheric connections occur between areas specialized for the same function in the contralateral cortex (7). However, morphological and physiological differences in the human brain cause significant asymmetries between hemispheres. In most individuals, the right hemisphere appears to be heavier than the left, while the left hemisphere tends to have a denser structure, which may signify that high-level control centers are located on the left (8). This indicates that one side is functionally dominant, and partially or completely responsible for that function, and this tendency is defined as lateralization. For example, in most individuals, speech function is dominant on the left side, while visual and spatial functions are specialized on the right side (9). From a different point of view, the fact that the speech function is dominant on the left side causes this hemisphere to be dominant in other verbal skills, which in most individuals is the left side dominant (8).

Frontal lobe. The frontal lobe is the largest lobe of the brain in terms of volume and contains numerous motor and cognitive control centers (10). It is reported that the systems located on the left side of the frontal lobe are responsible for the cognitive preferences and behaviors given by the existing memory, while the right side is mostly involved in the behaviors directed by the external environment. This indicates that the hemisphere plays a vital role in the healthy processing and assembly of new information cognitively (11).

Parietal lobe. The parietal lobe includes cortical regions related to sensory and language function at the subcortical level, and it is also accepted as an intersection point of white matter pathways related to motor, sensory, language, visuospatial and visual function (12). There is general agreement in the literature that visuospatially-oriented attention is dependent on a network of frontal and parietal areas in the right hemisphere. Visuspatially-oriented attention is also considered to be related to some functions of the right parietal lobe in the production of open-eye movements (13). It has been reported that the parietal cortex tends to be more lateralized on the left side than on the right side (14). Extra-personal and personal spatial neglect can be serious and is often observed in association with the right parietal lobe (15).

Occipital lobe. The occipital lobe is the part of the brain that processes visual data. It is associated with visual-spatial processing, distance and depth perception, color identification, object and face recognition, and memory formation (16). It has been reported that the brain regions involved in visual word processing are lateralized to the left hemisphere, which is considered logical considering that in the majority of individuals, language-related cortical structures are lateralized to the left hemisphere (17). Anatomically, what is called the Yakovlevian torque (occipital bending) is the right hemisphere's tendency to rotate slightly forward relative to the left, which can cause the right frontal lobe to be larger and wider, and the left occipital lobe to be wider and project to the right. This makes the left Sylvian fissure longer and straighter, resulting in a larger planum temporale (an extension of Wernicke's area) (18).

Temporal lobe. The temporal lobe is the part of the brain responsible for various cognitive functions including memory, senses, auditory, language processing, cognition, and semantics (19). Some studies report that while the temporal lobe has a larger area especially on the left side, on the contrary, the cortex thickness is higher on the right side (20,21). The presence of asymmetries in the morphological development of the temporal lobes is considered an important sign of lateralization. The most prominent asymmetry is observed in the peri-Sylvian region and superior temporal sulcus (21).

In general, when the whole brain is examined, it is reported that the total surface area and volume of the left hemisphere are higher, whereas the cortex thickness is higher on the right side (20). Although such lateralization is generally observed, it is also observed that there are differences between the subunits in each lobe (22).

All these data suggest how asymmetries can be found at different levels with different parameters such as regional volume, cortical thickness, connections, cellular and molecular organization, and surface area. The most clearly studied asymmetry is the speech function and it is known to be lateralized to the left side (8,23).

The right hemisphere is less exposed to external influences in its development as it is responsible for the functions necessary for survival. In addition, there is a general dominance of the right hemisphere for all functions except language, therefore the right hemisphere develops earlier (8).

Although genotype probably plays a role in the development of structural asymmetries, lesions in any hemisphere can trigger dominance of the unaffected side due to high plasticity. On the other hand, environmental and/or physiological factors can also cause asymmetries to occur, the best example of which is the right-hand preference due to cultural pressures (18,24).

3. Lateralization of the gliomas within the brain

Considering the complementary functions, the human brain usually has duality, and individuals are categorized as ‘left or right-brained’ according to the dominant hemisphere (25). It is known that a number of different functions, especially the preference for hand use, and lateralization of speech, are located on one side of the cerebrum (right or left) and it is accepted as the dominant hemisphere (26). While the right hemisphere is

primarily associated with nonverbal abilities, the left one is reported to be responsible for verbal memory and language functions (27). It is suggested that evaluating the localization of GBM can be accepted as an indicator in determining the direction of spread (28). While magnetic resonance imaging (MRI) can reveal the characteristic structure of the disease by determining the volumetric information of the tumor and the determination of the anatomical structures that are or may be affected, these determinations are insufficient to reveal the pathophysiology and prognosis (29).

Inskip *et al* (30), in their study conducted on 489 patients with glioma (354 high-grade, 135 low-grade), 197 meningiomas, and 96 acoustic neuromas, did not find a statistical difference between the rates of incidence on the left and right sides, although there was no significant difference between them, in patients with low-grade glioma and meningioma. More specifically, in this study, a more common distribution on the right side compared with the left side was observed, although it was not significant in patients with high-grade and acoustic neuroma. These authors reported that aphasia and mental status changes are more commonly observed in patients with glioma and tumors affecting the left side of the brain. In a study by Jansma and Rutten it was reported that 30 tumors from patients with high-grade glioma were located on the left side and 26 were located on the right side, while 37 patients with low-grade glioma had tumors located on the left side and 16 had tumors located on the right side (31).

In a study by Coluccia *et al* (32) performed on 235 patients, the incidence of tumor spread was as follows: The frontal lobe (left, 29.8%; right, 43.0%), the temporal lobe (left, 42.1%; right, 43.8%), the occipital lobe (left, 15.8%; right, 9.9%), the parietal lobe (left, 35.1%; right, 29.8), the basal ganglia (left, 4.4%; right, 7.4%). These authors also observed that tumors located in the right hemisphere were larger. In the same study, it was reported that the patients with the tumor located on the right had paralysis in the extremities, and the patients with the tumor located on the left had more language problems (63.2% in the right hemisphere and 10.0% in the left hemisphere). There was a decrease in Karnofsky Performance Status after resection in patients with left-sided tumors compared with patients with right-sided lesions. While there was no difference in the overall survival (OS) of the patients regardless of the side, it was reported that there was a decrease in the progression-free survival (PFS) in left-sided patients (7.4 months vs. 10.1 months). The authors stated that the reason for this result was that total resection was performed with less success on the left side.

Appropriate surgical resection is one of the important points in achieving tumor control in GBM. The morbidity risks and reduced quality of life are taken into account when approaching tumors located in the vicinity of or directly within important anatomical regions (33). It has been observed that resection of the dominant hemisphere carries great surgical risks. It has been reported that patients with left temporal lobe glioma experience higher preoperative neurocognitive impairment and demonstrate a more frequent and severe decline in neurocognitive abilities after surgical resection compared with patients with right temporal lobe glioma (34).

In a study involving 507 patients by Ellingson *et al* (35), it was reported that tumors were located to a greater extent on the left side. A relationship between tumor lateralization and OS with an extended survival time of up to 36 months in patients with left-sided tumors compared with the survival time of 12 months observed in patients with tumors affecting the right side, was also oberved in this study. The authors also stated that the lesions were more inclined to be located in the frontal lobe in young patients compared with the elderly (35). In a study by Larjavaara *et al* (36), on 331 patients with glioma, it was reported that tumors were mostly located in the frontal lobe (40%), followed by the temporal lobe (29%), parietal lobe (14%), and occipital lobe (3%), respectively. The authors also stated that the tumor was located more frequently on the right side than on the left (51% on the right and 40% on the left).

One of the most comprehensive studies on lateralization in recent years is the study by Kommers *et al* (37), which was conducted on a total of 1,596 patients with GBM from 13 centers. In this study, the structure of the tumor, its volume, and the structures of the affected brain regions were examined by automatic and manual segmentation with MRI. In the automated segmentations, it was identified that 785 (49.2%) tumors were located on the left side, while 792 (49.6%) were on the right side. In manual segmentation, 794 (49.7%) patients had left-sided tumors, and 799 (50.1%) had right-sided tumors. It was also observed that 19 patients (1.2%) examined by automated segmentation and 3 patients (0.2%) examined by manual segmentation, exhibited no laterality. The authors of this study stated that automatic segmentation produced near-perfect results. In the continuation of the study, cortical and subcortical anatomical formations or anatomical regions in the affected hemisphere were determined in detail.

Based on the study by Kommers *et al* (37), data obtained through automated segmentation revealed that the tumors appeared to be most frequently localized in the insular lobe, frontal lobe and temporal lobe, respectively (37). According to this study, these tumors affected a number of areas of the frontal lobe and were frequently located in the precentral gyrus, with a lesser percentage in the cingulate anterior gyrus and frontal opercular cortex. In the parietal lobe, gliomas were mostly localized in the posterior division of the cingulate gyrus, posterior division of the marginal gyrus, and precuneus cortex. It was observed that the areas involved in the temporal lobe were several. Among these, tumors were often located in the superior temporal gyrus, planum temporale, and central opercular cortex. The incidence of the tumor was mainly observed to be located in the occipital cortex and in the superior and inferior divisions of the lateral occipital cortex. The incidence for each lobe was similar for the cortex structure affected on the right and left sides. Tractus and fascicles involved in subcortical structures appeared to be the corticospinal tract, superior longitudinal I, II and III fascicles, arcuate fascicle long segment, frontal strait tract, and inferior frontal-occipital fascicle. Overall, the eclipse rate of numerous of these structures was high on the right. It should be noted that, except for the arcuate fascicle long segment, the anterior segment was observed significantly higher on the right side than on the left side (37).

Mickevicius *et al* (38) retrospectively studied 113 patients with GBM, hypothesizing that the location of the white matter structures with the tumor was associated with survival. The authors found that OS times were reduced in patients with tumors located in the right anterior thalamic radiation (ATR),

Table I. Studies reporting the lateralization of glioblastoma.

First author(s), year	No. of patients	Brain region	Lateralization		(Refs.)
			Left	Right	
Inskip *et al*, 2003	354 HGG	Entire brain	Left		(30)
	135 LGG	Entire brain	Right		
Ellingson *et al*, 2013	507		Left		(35)
Jansma and Rutten, 2017	56	Entire brain	53.6%	46.4%	(31)
	53	Entire brain	69.8%	30.2%	
Coluccia *et al*, 2018	235	Frontal lobe	29.8%	43.0%	(32)
		Temporal lobe	42.1%	43.8%	
		Parietal lobe	35.1%	29.8%	
		Occipital lobe	15.8%	9.9%	
		Basal ganglia	4.4%	7.4%	
Larjavaara *et al,* 2007	116 (GBM)	Entire brain	44.5%	55.5%	(36)
		Frontal lobe			
		Temporal lobe			
		Parietal lobe			
		Occipital lobe			
Kommers *et al,* 2021	1,596 (Automated segmentation)	Entire brain	49.2%	50.1%	(37)
	1,596 (Manual segmentation)	Entire brain	49.7%	49.6%	

HGG, high grade glioma; LGG, low grade glioma; GBM, glioblastoma mutliforme.

right lower inferior fronto-occipital fasciculus (IFOF), right and left cortico-spinal tract (CST), and corpus callosum (CC). It was also revealed that PFS times were decreased in patients with tumors located in the CST, CC body, right ATR, posterior IFOF, and inferior longitudinal fasciculus (ILF), and PFS times were increased in patients with tumors located in the right genu of CC and anterior IFOF. The main findings of the aforementioned studies are summarized in Table I.

4. Anatomy of brain regions affected by glioblastoma

CS. The CST is a complex system consisting of a series of projection fibers that control spinal cord functions by the brain, including the control of spinal reflexes and motor neuron activity. CST axons (75-90% of the axons) form a crossing at the level of the medulla oblongata and at the level of the midline, called the pyramidal decussation. This signifies that the left side of the brain controls the right side of the spinal cord and is critical for motor functions (39,40). Most CST axons originate from pyramidal neurons in layer V located in the primary motor and sensory cortex (M1 and S1). A pioneer study by Danks *et al* using diffusion tensor imaging (DTI) revealed that the CST originates mainly from the M1 and S1, but also receives input from the supplementary motor areas (SMA) and the ventral and dorsal premotor cortices (PMC). Leaving the neocortex, the CST reaches the brainstem by passing through the posterior limb of the internal capsule and cerebral peduncles before reaching the brainstem in the ventral position. Data obtained through the use of DTI revealed that the CST content originates from 37% M1, 32% S1, 25% SMA, and 7% PMC (41).

The control of complex motor functions such as the selection of movement, making the final decision, initiating the function, and monitoring the process is provided by the SMA. It is known that this area has connections with the precentral gyrus, prefrontal cortex, basal ganglia, limbic system, spinal cord, contralateral SMA, superior parietal cortex, and inferior frontal cortical areas, especially pars opercularis. When Salvati *et al* (42) compared 127 patients with GBM and SMA involvement (Group A) and patients with non-SMA but M1 and CST involvement (Group B), it was reported that group A patients had a higher volume, but there was no change in the OS and PFS durations of the patients.

Superior longitudinal fasciculus (SLF). The primary function of the SLF is to provide communication between the frontal and parietal lobes and partial connections with the temporal lobe. It is accepted that there are two different paths due to its proximity to the arcuate fascicle that connects the posterior temporal lobe and the frontal lobe in the peri-Slyvian region (43,44). Makris *et al* (45) analyzed the SLF by dividing it into four anatomical subsections. SLF I is the dorsal part and provides the connection between the superior parietal and superior frontal lobes. SLF II starts from the angular gyrus, passes over the centrum semiovale on the insula, and ends in the caudal-lateral prefrontal region. SLF III is the ventral part

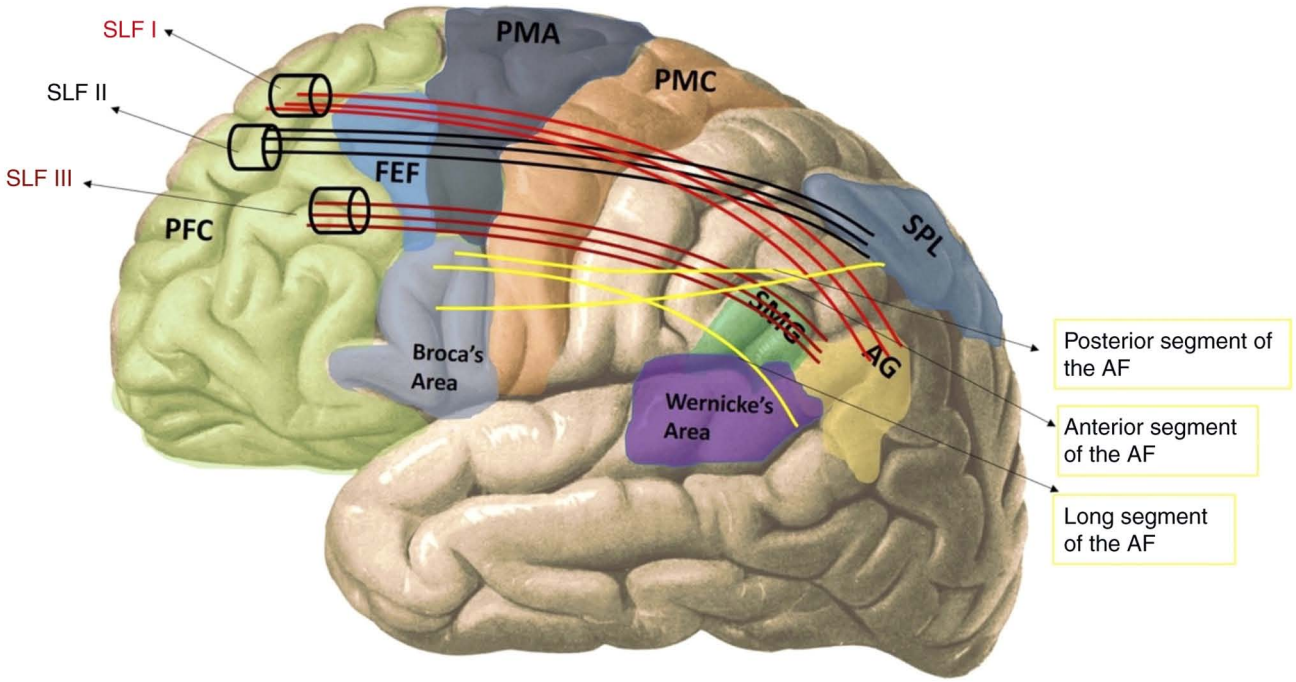

Figure 1. Representation of the SLF I-II-III and the AF [Adapted from Netter Anatomy Atlas Ref (53)]. SLF, superior longitudinal fasciculus; AF, arcuate fasciculus; PMA, premotor area; PMC, primary motor cortex; SPL, superior parietal lobule; FEF, frontal eye field; PFC, prefrontal cortex; SMG, supramarginal gyrus; AG, angular gurys.

of the pathway, and it travels between the anterior part of the angular gyrus, and the supramarginal gyrus, and the ventral premotor and prefrontal areas. The 4th subcomponent of the SLF, identified as SLF IV in earlier studies on non-human primates, corresponds to the arcuate fasciculus (AF). This segment connects the posterior part of the superior temporal gyrus to the lateral prefrontal cortex, running through the caudal extremity of the Sylvian fissure. Nonetheless, the designation of the AF as the 4th component of the SLF is not universally accepted (46,47).

In definitions by Catani and Thiebaut de Schotten, each arcuate fascicle is divided into three parts (long, anterior and posterior) connecting two regions of the Broca, Wernicke, or Geschwind region (inferior parietal lobule) (46). The anterior segment of AF appears to correspond to SLF III and the two terms are used interchangeably. Therefore, although these two bundles are separate structures, some of their subcomponents appear to overlap with each other (47).

Various studies have revealed that the SLF is markedly closer to the cingulum, while it cannot be separated by other SLF structures (SLF I-III and AF) (48,49); in addition, according to Thiebaut de Schotten, the SLF is symmetrical in both hemispheres (50). However, some studies in the literature are not concordant indicating that SLF is greater on the right side than on the left side (47,51), while other studies have claimed that SLF II is dominant on the left side through multiple components (49,52). This anatomical feature may explain the lateralization of the language in the left hemisphere (Fig. 1) (53).

Several studies have demonstrated the occurrence of gliomas and glioblastoma in the SLF region. More specifically, Davtian *et al* (54), presented a case report of a 59-year-old woman with recurrent GBM involving the left medial frontal and cingulate gyri with impairment of the SLF region (54). The authors described that the dissection of the tumor border in contact with the SLF resulted in recurrent speech arrest highlighting how the surgical resection of tumors in this region is not recommended for large lesions (54). Previously, Nakajima *et al* (55), observed visuospatial dysfunction in patients with glioma affecting the right dorsal SLF.

Similarly, Liu *et al* (56), observed cognitive deficits in patients with glioma located in the right SLF temporal part.

Overall, all these data are concordant in demonstrating the cognitive decline (in terms of visuospatial and speech abilities) associated with glioma development in the SLF region.

ILF. The ILF is the white matter structure that provides the reciprocal connection between the temporal-parietal-occipital lobes. It also functions in visual word recognition, connecting the occipital cortex to the posterior occipitotemporal cortices (57). Latini *et al* (58) reported that the main structure of the ILF is located more in the fusiform, lingual, and dorsolateral-occipital regions of the occipital lobe and that these are fixed components. It was revealed that there was no lateralization for the subcomponents of the ILF, but that they were located on the right in total volume (Fig. 2).

As regards the ILF, there are a few studies describing the localization of GBM in this region. Specifically, the postsurgical residual lesion volume located in the left ILF was associated with lexical retrieval impairments supporting the data already described in the aforemetioned section on SLF (59,60).

IFOF. The IFOF is the white matter structure that connects the occipital cortex, temporo-basal areas, superior parietal lobule, and precuneus to the frontal lobe. The region starting from the periphery of the caudate nucleus and extending to the

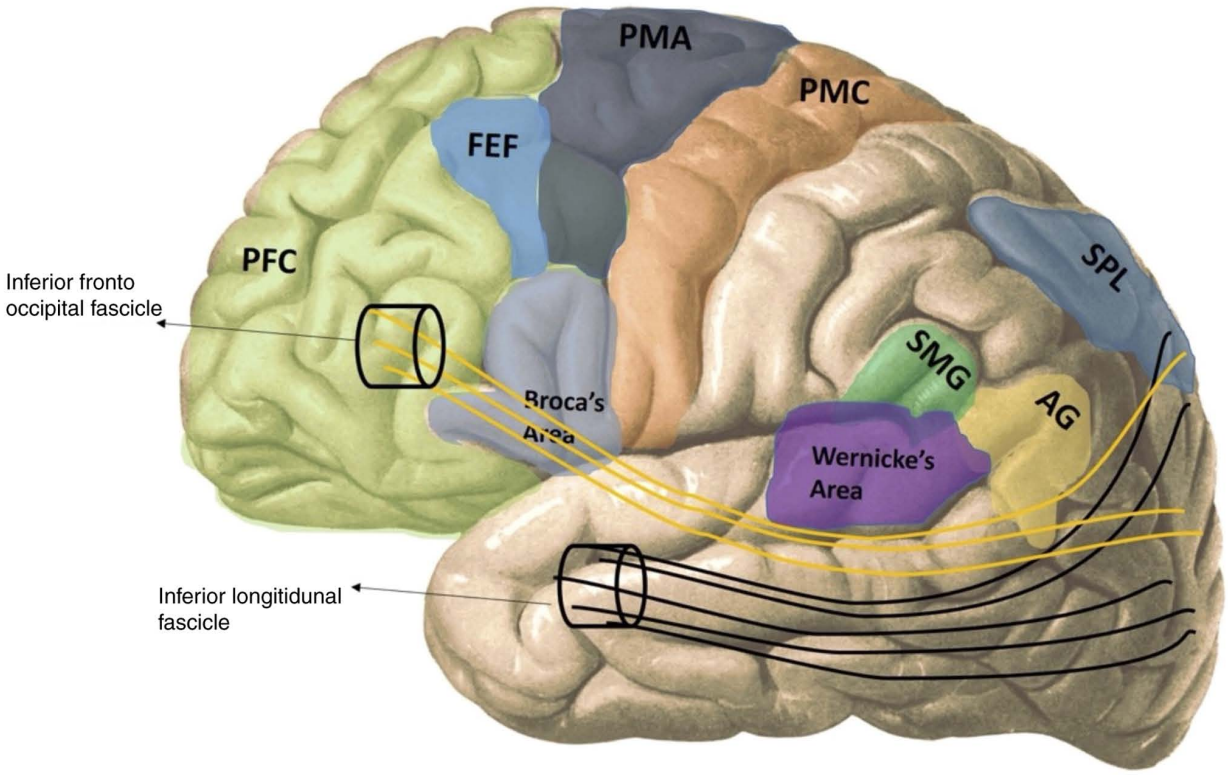

Figure 2. Representation of the inferior fronto-occipital and the inferior longitudinal fasciculus [Adapted from Netter Anatomy Atlas Ref (53)]. PMA, premotor area; PMC, primary motor cortex; SPL, superior parietal lobule; PFC, prefrontal cortex; FEF, frontal eye field; SMG, supramarginal gyrus; AG, angular gurys.

temporal horn of the lateral ventricle is the sub-insular region, and the IFOF is located on the ventral third of this region and the outer side of the external capsule. This pathway is involved in mumerous functions such as language, non-verbal semantic processing, object identification, visual-spatial processing and planning, reading, facial expression recognition, and memory (Fig. 2) (61). Vassal *et al* (62) examined the cortical terminations of IFOF by tractography in 20 healthy individuals to determine individual variations and asymmetry. According to their data, IFOF terminations lateralize over the superior parietal lobule on the right and the inferior frontal gyrus on the left. Altieri *et al* (63) reported that of a total of 23 patients with 38% GBM, 33% oligodendroglioma, and 29% astrocytoma, 57% of tumors were located in the left hemisphere and 43% in the right henisphere. Moreover in this study, this pathway was divided into three parts anatomically: A vertical that runs along the frontal lobe, a horizontal segment that runs along the frontal lobe, and a horizontal segment that runs from the limen insulae. Caminis *et al* (64) reported that 33 lesions of patients with tumors involving the temporal lobe were located on the left side (97%), 14 were medial, 14 were lateral, and 6 were medial and lateral extensions. In total, it was reported that the lesions were directed to the insula in 22 cases.

Frontostriatal tract (FST). The FST connects several cortical areas of the frontal lobe, especially the prefrontal cortex, with the striatum and the thalamus. It is responsible for a wide range of mental, motor, limbic, and cognitive functions (65). In particular, the connections between the caudate nucleus and the frontal cortex have a markedly rigid and clear topographic organization in regionally specific clusters. It is reported that these specific regions are located in the subregions of the ventrolateral, dorsolateral, and orbitofrontal cortex and that there is a similar organizational scheme in both hemispheres (66).

From a different anatomical point of view, two different association fiber structures originating from SMA and connecting with different regions are mentioned in the literature. One is the FST, which connects the pre-SMA to the anterior part of the caudate nucleus, and the other is the fronto-aslant tract, which connects the pre-SMA to the pars opercularis. The FST starts from the caudate nucleus, passes through the lateral ventricle's frontal horn, and terminates in the ipsilateral inferior frontal gyrus (67). The frontal aslant tract is a brain white matter pathway that connects the superior frontal gyrus (SMA, pre-SMA) to the pars opercularis and pars triangularis of the inferior frontal gyrus and the insula (68). Functionally, the left frontal aslant tract is responsible for language and the right for executive functions (69).

An in-depth analysis of the literature does not reveal any studies on glioblastoma involvement in the FST. However, Müller *et al* (70) questioned the possibility of performing neurosurgery for the removal of glioma affecting the caudate nucleus connected to the supplementary motor area through the FST. In this case, the authors discussed the functional role of both the caudate nucleus and the FST that can be indicative of the limits of resection in the case of supracomplete glioma resection (70).

A number of these pathways, which have a complex structure, are still the subject of research. A summary of these aforementioned pathways regarding GBM is included in Table II.

Table II. White matter brain pathways.

Pathway	Connections
Corticospinal tract	Primary motor and sensory cortex to the spinal cord (lower motor neurons)
SLF I	Superior parietal lobe to the superior frontal lobe
SLF II	Angular gyrus to the caudal-lateral prefrontal region
SLF III	Between the anterior part of the angular gyrus, supramarginal gyrus, ventral premotor and prefrontal areas
Inferior longitudinal fasciculus	Between the temporal, parietal and occipital lobes
Inferior fronto-occipital fascicle	Occipital cortex, temporo-basal areas, superior parietal lobule and precuneus to th frontal lobe
Fronto-striatal tract	Between the prefrontal cortex, with the striatum and the thalamus

SLF, superior longitudinal fasciculus.

5. Lateralization of molecular features in glioblastoma

As aforementioned, the lateralization of glioma and glioblastoma has profound anatomical implications that can limit the surgical approaches available due to the impairment of cognitive functions. In addition, it was widely demonstrated that GBM lateralization also has effects on tumor molecular features which influence the pathogenesis of the tumor and the clinical outcomes (71). Despite extensive research efforts, GBM remains a challenge due to its heterogeneity and resistance to treatment, and such heterogeneity is also reflected in the prevalence of molecular alterations observed in the right and left side of the brain (72).

Genomic studies have demonstrated profound differences existing between left and right brain tumors in terms of molecular profiles. Notably, mutations in the isocitrate dehydrogenase 1 (IDH1) gene are more prevalent in tumors located in the frontal lobe, whereas tumors located in the temporal lobe frequently exhibit epidermal growth factor receptor (EGFR) amplification and phosphatase and tensin homolog (PTEN) loss (73,74).

The lateralization of molecular features is not limited only to gene mutations. Notably, DNA methylation, histone modifications, and other epigenetic alterations have exhibited lateralization patterns in GBM (75,76). One of the most common epigenetic alterations observed in cancer, including GBM, is the alteration of DNA methylation (75). The analysis of DNA methylation patterns observed in GBM has revealed region-specific differences in the methylome of GBM, with distinct CpG island methylator phenotype (CIMP) subtypes associated with specific brain regions (75,77). Moreover, differential histone modifications have been observed in GBM located in different brain regions suggesting a putative role of epigenetics in regional tumor heterogeneity and specific subtypes such as the H3 G34 mutant type (78).

In addition to the anatomical and biological lateralization of GBM-associated molecular features, the lateralization of both genetic and epigenetic alterations also has important clinical and therapeutic implications. In this context, the lateralization of molecular features in GBM can be useful to improve the diagnosis and prognosis of this tumor. Indeed, the integration of molecular information with clinical and radio-imaging data could enhance the accuracy of tumor diagnosis and guide personalized treatment strategies. For example, the identification of specific molecular alterations associated with different brain regions could aid in the preoperative prediction of tumor location and facilitate surgical planning (79). In addition, the lateralization of molecular alterations may provide useful prognostic information correlating both side-specific genetic and epigenetic features with the survival outcomes of patients and the route of metastatization (80,81).

Some authors have also proposed to tailor the treatment depending on the lateralization of the molecular features in GBM (82,83). Due to the regional differences observed for the genetic and epigenetic alterations in GBM, targeted approaches could be designed to exploit specific vulnerabilities associated with each brain region. For instance, therapies targeting IDH1 mutations may be more effective in frontal lobe tumors, while targeting EGFR amplification could be more beneficial in temporal lobe tumors (84). In addition, the immune microenvironment and tumor-stromal cell interactions may have a role in the response to immunotherapies and other targeted interventions, however, more in-depth investigations should be performed to fully clarify these complex interactions.

Emerging evidence suggests that specific molecular alterations may exhibit a predilection for GBM located in the right side, left side, frontal lobe or other regions of the brain. This section aims to explore the molecular alterations frequently observed in different areas of the brain in patients with gliomas and glioblastomas, shedding light on their potential clinical and therapeutic implications (Fig. 3 and Table SI).

IDH1 mutations. IDH1 mutations represent one of the most observed molecular alterations in both gliomas and glioblastoma (85,86). A molecular and radio imaging study performed on patients with glioma revealed a higher prevalence of IDH1 mutations in tumors mainly affecting the right hemisphere compared with the left hemisphere (87). However, the precise mechanisms responsible for this lateralization pattern are not widely understood, but can be associated with GBM regional differences in IDH1 expression or genetic predispositions associated with brain asymmetry (88). As a limitation of these findings, the majority of the studies on the detection of IDH

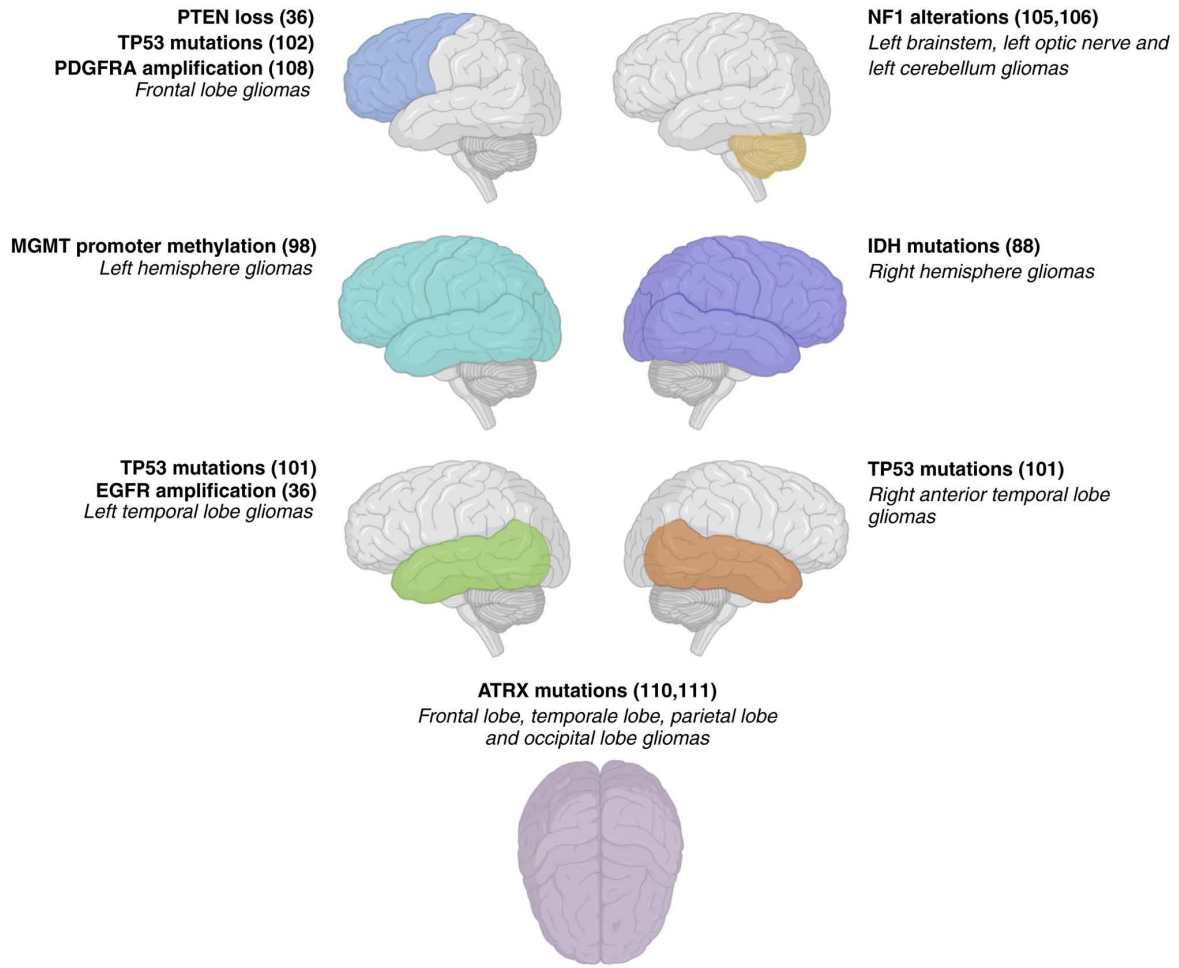

Figure 3. Mapping of the main molecular alterations associated with the development of gliomas and glioblastomas. phosphatase and tensin homolog; PDGFRA, platelet-derived growth factor receptor-α; MGMT, O^6-methylguanine-DNA methyltransferase; NF1, neurofibromin 1; IDH, isocitrate dehydrogenase. Created with BioRender.com.

mutations do not report the right or left lateralization of the mutation but only the brain region affected.

EGFR amplification. Amplification of the EGFR gene is a common genetic alteration observed in glioblastoma (89). Notably, a previous study indicated a higher frequency of EGFR amplification in glioblastoma located on the left temporal lobe of the brain (35). The reasons for this specific lateralization are still under investigation, but could be attributed to variations in the microenvironment or signaling pathways specific to the left hemisphere (90). More importantly, the prevalence of EGFR mutation in GBM may have important prognostic implications as different targeted treatments for EGFR-positive tumors are currently available (91).

PTEN loss. PTEN is a tumor suppressor gene frequently mutated or deleted in glioblastoma. The loss-of-function of PTEN results in the dysregulation of multiple associated signaling pathways involved in cell proliferation, cell survival and apoptosis (92,93). Contrary to what was observed for IDH1 and EGFR, there are no studies describing the specific distribution of PTEN alterations in the two brain hemispheres, however, the study of Ellingson *et al* (35) revealed a higher incidence of PTEN loss in glioblastomas affecting the frontal lobe. However, with regard to this case, the underlying mechanisms for this lateralization pattern require further investigation.

O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation. As regards the lateralization of epigenetics alterations, the MGMT gene encodes a DNA repair protein that can be silenced through the hypermethylation of its promoter (94). MGMT promoter methylation is associated with increased sensitivity to alkylating chemotherapy, such as temozolomide, one of the main drugs used for the treatment of GBM (95,96). Studies have reported a higher frequency of MGMT promoter methylation in left-sided glioblastomas compared with the hypomethylation observed in tumors affecting the right side (97) suggesting how in the left hemisphere epigenetic alterations induced by stromal cells or the microenvironment are more evident compared with the right side (98).

TP53 mutations. A significant fraction of GBM harbor mutations affecting the TP53 gene, which encodes the tumor suppressor protein p53 and plays a key role in the regulation of DNA integrity (99). A previous study reported a higher prevalence of TP53 mutations in gliomas affecting the left medial temporal lobe and the right anterior temporal lobe (100). Another study revealed that p53-mutated glioblastomas were

preferentially located in the frontal lobe near the rostral extension of the lateral ventricles (101). As for the other mutations observed in GBM, the mechanisms responsible for this lateralization remain unclear but it results in the alteration of DNA repair capacity or regional variations in the response to mutagenic factors (102).

Neurofibromin 1 (NF1) alterations. Alterations in the NF1 gene have been implicated in the pathogenesis of gliomas (103). Notably, NF1 acts as a negative regulator of the Ras signaling pathway thus playing a role in the modulation of cell proliferation and cell survival. As described for PTEN, NF1 alterations can affect GBM occurring in different parts of the brain, however, there is a slight preference for the left hemisphere as demonstrated by two independent studies where NF1-mutated gliomas affected the left side of the brainstem, left optic nerve and left cerebellum (104,105).

Platelet-derived growth factor receptor-α (PDGFRA) amplification. Amplification of the PDGFRA gene is a recurrent genetic alteration observed in glioblastoma (106). A previous study has indicated a higher frequency of PDGFRA amplification in H3 G34 diffuse hemispheric gliomas located on both the right and left frontal lobes of the brain (107). However, the specific mechanisms underlying this lateralization pattern remain to be fully elucidated.

ATRX chromatin remodeler (ATRX) mutations. ATRX is a gene involved in chromatin remodeling and it is often mutated in astrocytoma and low-grade glioma (108). Previous studies demonstrated that ATRX mutations can be found both in the right and left hemispheres affecting different brain regions including the frontal lobe, the temporal lobe, the parietal lobe, the occipital lobe, and in rare cases also the brainstem, and the thalamus (108,110).

Overall, understanding the specific right- or left-sided molecular alterations in glioma and glioblastoma has fundamental diagnostic, prognostic, and clinical implications. First of all, the molecular differences observed in right and left tumors could aid the clinical diagnosis performed through imaging techniques and identify potential hidden lesions. Secondly, the precise characterization of the lateralization of molecular alterations may contribute to the development of novel targeted therapies. In particular, the presence of EGFR and TP53 alterations, along with other molecular features, may drive the selection of the correct drug to be administered to the patients. Finally, the definition of the lateralization of a tumor from an anatomical and molecular point of view could improve the management of this tumor.

Notably, different studies are concordant in confirming a more common location of GBM within the frontal lobe and insula with a consequent poor prognosis in terms of PFS times when the tumor is located on the left side of the brain. It was also reported that the white matter structures on the right side are larger in volume, thus the tumors arising in this region are usually of a larger volume. Based on the data obtained in the study by Kommers *et al* it is demonstrated that tumors mainly affect the SLF, ILF, IFOF, AF, FST, and CST regions (however, no statistical comparison depending on the brain side was performed in the study) (37). Considering the anatomical features of these localizations and the areas they connect, it is logical that the major involvements are observed in the frontal-temporal-parietal-occipital lobes, respectively. This supports the hypothesis that the tumor follows the white matter structures during its spreading favored by both direct and indirect mechanisms (for example, mediated by GBM-derived exosomes which induce neurotoxicity in the surrounding structures) (111-113). Although tumor volumes are higher on the right side, some sources state that the prognosis is worse in left-sided patients. However, it should be noted here that there is no difference in OS times, regardless of the localization of tumors. The aforementioned pathways related to GBM and the evaluation of the anatomy of the region for appropriate resection are especially emphasized by surgeons. Some sources state that establishing the location of tumors within brain regions could be useful to determine the prognosis of the disease as well as the surgical decisions (15). In the literature it is reported that regular radiological imaging can be used as a predictor in the evaluation of prognosis by detecting the anatomical and volumetric position of the tumor, necrosis or extent of edema, and pathophysiological changes in patients (16).

Overall, the anatomical data on GBM lateralization, coupled with the growing findings on molecular alterations affecting specific brain regions and epigenetics events involved in GBM development and progression (114,115), may improve the clinical management of patients with GBM and the positive effects on the outcomes of patients. In addition, a deep understanding of both anatomical and molecular lateralization is essential to propose novel effective treatment in GBM, including photoacoustic nanoprobes (116,117).

6. Conclusions

By analyzing the studies reported in the literature, it is not clear if a precise lateralization of brain tumors exists. However, there is strong evidence supporting the anatomical lateralization of both glioma and glioblastoma as well as the molecular lateralization of some key molecular alterations which influence the evolution of tumors and the prognosis of patients. Recently, a broad meta-analysis has collected all the studies reporting the anatomical lateralization of glioma and GBM revealing no specific lateralization patterns in the right or left hemispheres. However, a clear relationship between tumor location in specific brain regions and glioma-associated symptoms were established (118). As regards the lateralization of glioma and GBM molecular features, more robust investigations on this specific topic are needed to establish lateralization patterns of mutations and epigenetics alterations.

In conclusion, these data suggest that the specific evaluation of glioma and GBM localization from both an anatomical and molecular perspective can help clinicians in a number of areas. It may help develop more specific drugs and treatment methods based on different molecular changes in different brain regions. In addition, predicting the location of the tumor and the possibility of spread can provide the physician preliminary information regarding the prognosis of the disease. Another important issue is that technologies such as artificial intelligence can be used in this field. Evaluating

radiological images with artificial intelligence, especially in the early stages, is a topic that can be evaluated in terms of prognosis.

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Authors' contributions

ATs and ATa conceptualized the study. MP, LF, PDM, SG and NTC wrote the original draft of the manuscript. MP, LF, PDM, DAS and ATa provided critical revisions. LF, SG and NTC prepared the tables and figures, conducted the formal analysis, and critically analyzed the literature. Data authentication is not applicable. All authors contributed to the manuscript revision, as well as read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Competing interests

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