DTI fiber-tracking parameters adjacent to gliomas: the role of tract irregularity value in operative planning, resection and outcome

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Abstract

Background: The goal of glioma surgery is maximal tumor resection associated with minimal post-operative morbidity. DTI-FT is a standard application of white-matter (WM) visualization for diagnosis and surgical planning but assumes a descriptive role since the main DTI parameters showed limitations in clinical use. New quantitative measurements were recently applied to describe WM architecture adjacent the tumor that can be adopted as predictive values and guide for safe tumor resection.

Methods: This is a prospective multicentric study on a series of glioma-patient who performed magnetic resonance imaging (MRI) with pre-operative diffusion tensor imaging-tractography (DTI-FT). We examined DTI parameters of FA (mean, min-max), MD, and the shape-metric TI grade measured in the brain adjacent tumor area, comparing it with the surgical series' clinical, radiological, and outcome data.

Results: The population consisted of 118 patients, with a mean age of 60.6 years. 82 patients suffering from high-grade gliomas (69.5%), and 36 from low-grade gliomas (30.5%). A significant inverse relationship exists between the FA mean value and grading ($p=0.001$). The relationship appears directly proportional regarding MD values ($p=0.003$) and TI values ($p=0.005$). FA mean and MD values are susceptible to significant variations with tumor and edema volume ($p=0.05$). TI showed an independent relationship with grading regardless of tumor radiological features and dimensions, with a direct relationship with grading, ki67% ($p=0,05$), PFS ($p<0.001$), and EOR ($p<0.01$).

Conclusion: FA, MD and TI are useful predictive measures of clinical behavior of glioma and especially TI could potentially be helpful for tumor grading identification and surgical planning.

Index

Abbreviations

Central nervous system (CNS), World Health Organization (WHO), glioblastoma (GB), Genome-wide Complex Trait Analysis (GCTA), isocitrate dehydrogenase (IDH), low grade glioma (LGG), high-grade gliomas (HGG), histone chaperone α-thalassemia mental retardation X-linked (ATRX),
overall survival (OS), Extent of resection (EOR), 5-aminolaevulinic acid (5-ALA), white matter (WM), Magnetic resonance imaging (MRI), fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), DTI Fiber tracking (DTI-FT), cortico-spinal tract (CST), generalized q-sampling imaging (GQI), q-space diffeomorphic reconstruction (QSDR), region of interest (ROI), fiber assignment by continuous tracking (FACT), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), Karnofsky performance scale (KPS), gross total resection (GTR), functional MRI (fMRI), fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), tract irregularity (TI), radiotherapy (RT), standard deviation (SD), tensor shape (CL), planar isotropy coefficients (CP), spherical isotropy coefficients (CS), fiber density index (FDi), Progression-free survival (PFS), magnetization-prepared rapid acquisition gradient echo (MPRAGE).

1.1 Gliomas: definition and epidemiology

Gliomas are the most common primary neoplasms of the central nervous system (CNS) in adults [1,2]. They are typically distinct for their astrocytic or oligodendrocytic origin and are categorized according to the World Health Organization (WHO) grade [3]. Approximately 85,000 individuals in the United States and 5/100000 in Europe are diagnosed with a primary brain tumor each year [4], of which approximately 80% to 85% of these are gliomas, which diffusely infiltrate the brain parenchyma. The incidence of glioblastoma (GB), the most common malignant primary brain tumor in adults, increases after the age of 40 and peaks in adults aged 75 to 84 years. Lower-grade diffuse gliomas usually affect patients younger than 50 years old and are further subclassified into astrocytomas and oligodendrogliomas [2].
Less than 5% of adults with a malignant brain tumor report a family history of brain tumors or have a cancer predisposition syndrome. However, the contribution of heritability to brain tumor formation is likely higher, based on germline sequencing and analysis using Genome-wide Complex Trait Analysis (GCTA). Prior exposure to ionizing radiation to the CNS, usually during treatment for another cancer, such as childhood leukemia, is considered a risk factor for brain tumors. Exposure to low-frequency electromagnetic fields is not an established risk factor. No high-quality evidence demonstrates an association between cellular telephone use and brain tumor formation. In an international case-control study of 4533 glioma patients and 4171 controls, a history of respiratory allergies, asthma, or eczema was associated with a statistically significant lower risk of glioma. Those with glioma (229 patients) are also less likely than controls (289 patients) to report a history of varicella virus (adjusted OR, 0.59 [95% CI, 0.40-0.86]) and have lower levels of immunoglobulin G to varicella virus [5].

Since identifying key molecular alterations that provided a definitive prognosis and led to the 2021 WHO classification of CNS tumors, understanding of glioma behavior has rapidly evolved [6]. The mutations in isocitrate dehydrogenase (IDH) 1 and 2 are present in all of the adult grade 2 and 3 gliomas, and the use of 1p/19q codeletion for classification is now limited to the oligodendroglioma distinction. Further, new molecular key factors were discovered to improve distinction and to better predict the prognosis. As such, low grade glioma (LGG) encompasses all grade 2 and 3 tumors, while high-grade gliomas (HGG, grade 4) is definitely identified with the IDH-wild type mutation or the new additional molecular characterization. With this definitive shift in the understanding of lower-grade gliomas, disease management is being redefined in the setting of emerging molecular-genetic biomarkers [7].

1.2 Glioma pathogenesis

Comprehensive molecular profiling has dramatically mutated the diagnostic neuropathology of brain tumors. Diffuse gliomas are now classified by highly recurrent biomarkers instead of histo-morphological characteristics. The advent of molecular profiling technology has altered neoplastic disease classification, delineating more biologically and clinically uniform entities that often transcend conventional histopathological categorization [8]. This is particularly evident in brain tumor taxonomy, where this fundamental shift in approach has led to both the refinement of existing diagnostic categories and the creation of several novel tumor types (Fig. 1).

Table 1 2021 WHO Classification of Tumors of the Central Nervous System. Provisional Entities are in Italics

World Health Organization Classification of Tumors of the Central Nervous System, fifth edition
Gliomas, glioneuronal tumors, and neuronal tumors
Adult-type diffuse gliomas
Astrocytoma, IDH-mutant
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted
Glioblastoma, IDH-wildtype
Pediatric-type diffuse low-grade gliomas
Diffuse astrocytoma, *MYB*- or *MYBL1*-altered
Angiocentric glioma
Polymorphous low-grade neuroepithelial tumor of the young
Diffuse low-grade glioma, MAPK pathway-altered
Pediatric-type diffuse high-grade gliomas
Diffuse midline glioma, H3 K27-altered
Diffuse hemispheric glioma, H3 G34-mutant
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
Infant-type hemispheric glioma
Circumscribed astrocytic gliomas
Pilocytic astrocytoma
High-grade astrocytoma with piloid features
Pleomorphic xanthoastrocytoma
Subependymal giant cell astrocytoma
Chordoid glioma
Astroblastoma, *MN1*-altered
Glioneuronal and neuronal tumors
Ganglioglioma
Desmoplastic infantile ganglioglioma / desmoplastic infantile astrocytoma
Dysembryoplastic neuroepithelial tumor
Diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters
Papillary glioneuronal tumor
Rosette-forming glioneuronal tumor
Myxoid glioneuronal tumor
Diffuse leptomeningeal glioneuronal tumor
Gangliocytoma
Multinodular and vacuolating neuronal tumor
Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease)
Central neurocytoma
Extraventricular neurocytoma
Cerebellar liponeurocytoma

Fig. 1 The list shows the tumor types included in the last WHO 2021 classification of Brain Tumors

Neoplastic categories based on the histopathological features of astrocytes and oligodendrocytes have been revised and optimized with the integration of disease-defining molecular markers, stratifying biologically, clinically, and prognostically distinct entities in adult and pediatric populations. Moreover, above and beyond tumor classification, these developments have revealed novel pathogenic mechanisms involving epigenetic regulator genes not previously been implicated in oncogenesis.

Historically, diffuse gliomas have been classified solely based on histological characteristics into HGG, lower-grade astrocytomas, or oligodendrogliomas, with a portion of lower-grade tumors expressing both glial phenotypes (oligoastrocytomas). Histological diagnosis of HGG was performed based on central pseudopallisading necrosis and microvascular proliferation (**Fig. 2**). In contrast, diffuse astrocytomas and oligodendrogliomas were typically characterized by moderately increased cellularity, small nuclear atypia, low mitotic activity, absence of necrosis, and microvascular proliferation [9].

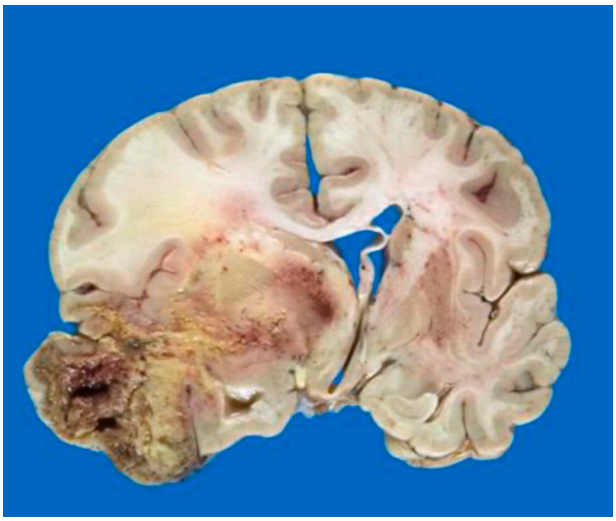


Fig. 2 A histological sample of glioblastoma of temporal lobe in a formalin specimen slice. Is appreciable the intra-tumoral necrosis and hemorrhagic area with abnormal vascularization.

Morphology alone does not sufficiently predict clinical behavior, with tumor progression varying notably across each histological subtype. More recently, the WHO, informed by large genomic profiling studies like the Cancer Genome Atlas [10], has extensively revised diffuse glioma classification to incorporate highly penetrant molecular abnormalities.

As mentioned earlier, gene mutations encoding isocitrate dehydrogenase enzymes (IDH1 and IDH2) IDH represent the main distinction node between high-grade (IDH wild-type) and lower-grade IDH-mutated forms. Other key biomarkers, such as H3 histone

monomers (H3F3A and HIST1H3B), and the histone chaperone α-thalassemia mental retardation X-linked (ATRX), induce disruptions in normal epigenetic functionality, revealing previously unappreciated oncogenic mechanisms [11].

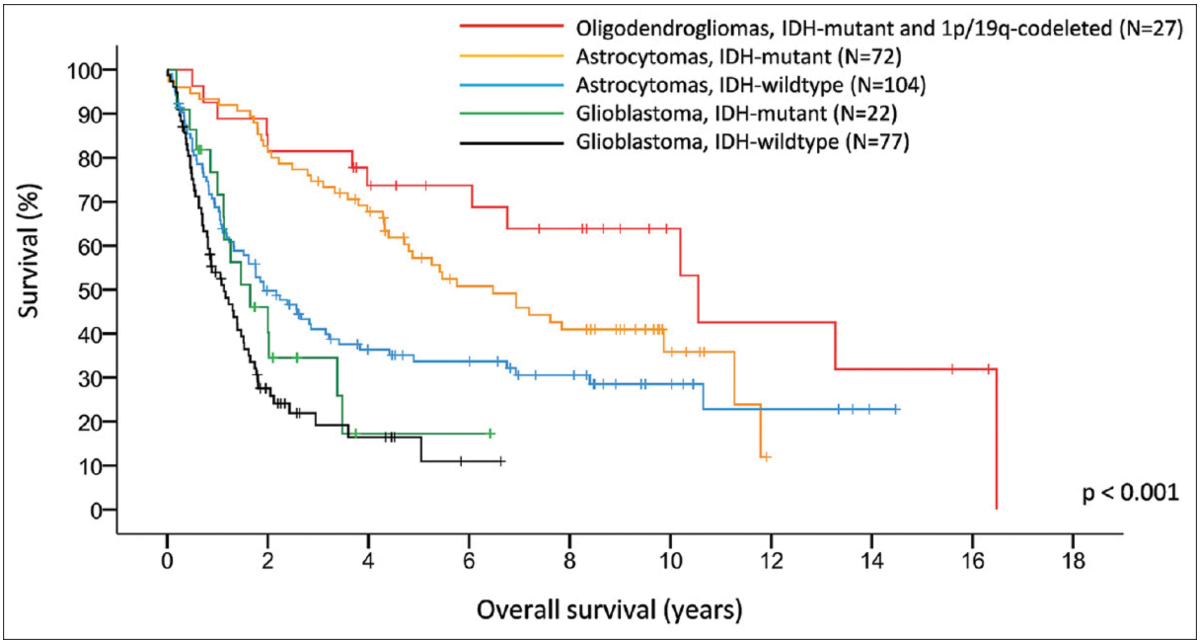
IDH mutations, as codified in the WHO 2021 [3], designate predominantly lower-grade (WHO grade 2 and 3) diffuse gliomas distinct from IDH-wildtype GB, the archetypical WHO grade 4 primary brain tumors. IDH-wildtype GBM almost invariably arises de novo in a fully malignant state characterized by the aggressive histopathological features of microvascular proliferation and necrosis, and although exclusively low-grade morphology is occasionally encountered, rapid clinical progression is the rule. GB and WHO grade 4, with histologically LGG, possess highly infiltrative patterns, such as gliomatosis cerebri growth patterns with widespread involvement [9].

IDH-mutant gliomas, while ultimately deadly, typically progress at a more measured pace through repeated cycles of treatment and recurrence before emerging as high-grade lesions.

In adults, IDH-mutant gliomas are further subcategorized by coincident deletion of chromosomal arms 1p and 19q (1p/19q codeletion). Oligodendrogliomas, WHO grades 2 and 3, are now defined by the concurrent IDH mutation and 1p/19q codeletion, and while ultimately deadly, can be associated with extended clinical course, with median survival times exceeding 8 years. By contrast, IDH-mutant astrocytomas, WHO grades 2 and 3, do not harbor 1p/19q codeletion, instead featuring combined loss-of-function mutations in ATRX and TP53 in the vast majority of cases and exhibit a somewhat more aggressive biological behavior than their oligodendroglial counterparts. WHO 2021 now also recognizes a grade 4 IDH-mutant astrocytoma, effectively replacing the glioblastoma, IDH-mutant diagnostic category established in WHO 2016 [12]. IDH-mutant astrocytomas, WHO grade 4, exhibit the defining molecular features of their lower-grade counterparts along with microvascular proliferation, necrosis, and/or homozygous deletion in CDKN2A/B, the latter having been repeatedly associated with unfavorable prognosis within this glioma subclass [13].

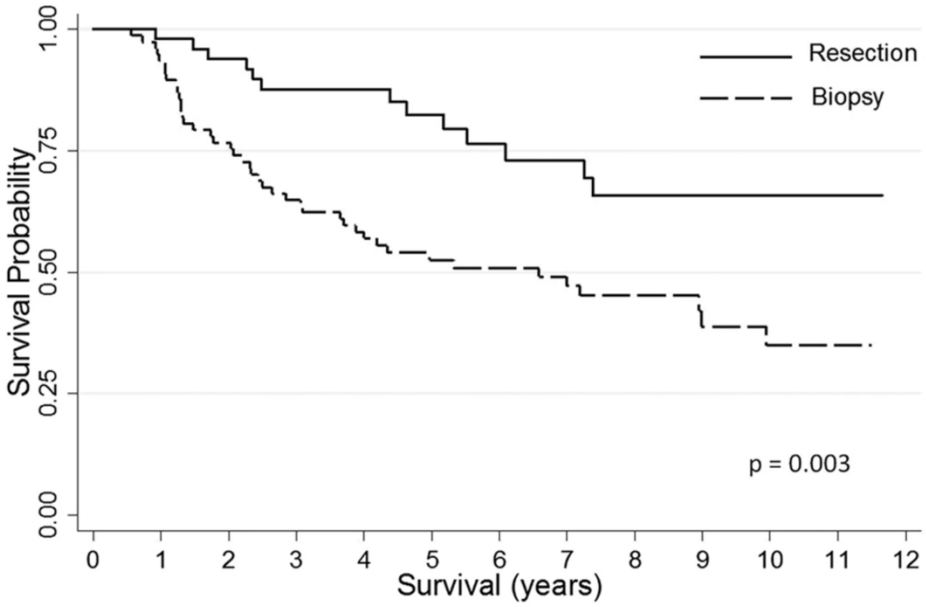
1.3 Treatment and Prognosis

The prognosis of the glioma patient is influenced mostly by the molecular profile, extent of surgical resection, age, and initial and postoperative performance status [14].
Survival varies significantly by grade across all glioma subtypes and expression of key biomarkers (**Fig. 3**) [15].



GB has the poorest overall survival (OS), with only 0.05% to 4.7% of patients surviving 5 years past diagnosis and a median survival of approximately 15 months [16], while gliomas with an oligodendroglial component have increased survival, as opposed to those with an astrocytic component. Age is significantly associated with survival after diagnosis for all glioma, but the effect is most pronounced for GB [17].

Despite the remarkable improvement in understanding the pathogenesis of gliomas, the first therapeutic step remains surgery. It was demonstrated in population-based parallel cohorts that early surgical resection is associated with better OS than biopsy and watchful waiting [2] (**Fig. 4**).



Therefore, it is necessary to maintain an appropriate balance between maximal surgical resection and the risk of neurological damage contributed to the patient [18]. The goals of surgery are maximal tumor removal associated with minimal post-operative morbidity and maximal patient functional preservation. Surgery is important since it relieves symptoms and provides accurate histological and molecular diagnosis. Extent of resection (EOR) remains a critical determinant of oncologic outcomes for patients with high- and low-grade glioma [19]. Realizing the true benefit of neurosurgical resection requires a balance between surgical cytoreduction and preservation of neurological function. This surgical concept is defined as "Maximal safe resection" and "Neuro-oncological balance" [1].

But while there is the issue of a balance between surgical radicality and preservation of function, fully understanding what it means to perform a total resection and understanding whether all functions, including higher cognitive functions, have been preserved has not yet been achieved.

At first, it is known that the carcinogenic process and mutations leading to the tumor-disease phenotype are already initiated by surrounding cells beyond the contrast-enhancing tumor visible on MRI. Supratotal resection is the emerging concept within GB-surgery, which aims to achieve a more extensive resection of the tumor than is possible with conventional techniques. The technique involves the removal of more than 100% of the visible tumor tissue, which means that the surgeon removes not only the tumor itself but also some surrounding healthy brain tissue [20]. This may be accomplished with 5-aminolaevulinic acid (5-ALA)-guided tumor tissue elimination, using intraoperative MRI

for non-enhancing residual tumors, or resection until improvement in clinical outcome is achieved [21].
Neuronavigation using 5-ALA fluorescence and microsurgical techniques have been developed to enable maximal safe neurosurgical tumor resection and minimize the neurological consequences of glioma surgery [22]. Further, in glioma radiotherapy treatment planning, a margin of 15–25 mm is typically applied to the edge of the gross tumor to create the CTV, and a further 5 mm is added to generate a safety margin [23]. This raises the probability of progression-free recession and survival while lowering the likelihood of recurrence, but on the other side can notably increment the risk of functional damage [24] and treatment-related cerebral necrosis.

Second, within the neurosurgical planning, the definition of what brain tissue must be considered "eloquent" is still mostly based on a classic localizationist model, which assumes that cortical areas are specialized for specific aspects of neurological functions. On the other hand, this model is now outdated, and cognitive neuroscience research suggests that every cognitive and motor function depends on complex neuroplastic networks connecting many cortical areas by means of long- and short-association white matter (WM) fibers [25]. According to this connectionist model, cortical and subcortical functional interplay may be highly variable among human beings and can reorganize in response to brain damage, such as a relatively slow-growing tumor mass. These neuroplastic properties might explain why, despite bearing an extensive mass located close or within brain tissue considered to be critical according to the classic localizationist model, patients with brain tumors usually display very mild or even no neurological deficit at presentation and can maintain this status even after surgery with extensive tumoral and peritumoral tissue resection [26]. Preserving cortical and subcortical function is important for better postoperative outcomes and improved quality of life; thus, the concept of neuroplasticity should be considered for accurate presurgical planning, but the full translation of this factor from basic to clinical neuroscience is still lacking because of an incomplete understanding of its mechanisms [27]. Currently, it is still impossible to predict its impact on the postsurgical outcome based on an objective measure of how much the brain of the patient has already reorganized in response to the tumor and may still reorganize after surgery. From this point of view, cortical and subcortical structures show different plastic potential. The cortex seems to have great neuroplastic potential, and it can reorganize effectively in the case of brain tumors, while white-matter bundles seem to have low plastic potential, and extensive surgical resections might depend mainly on white-matter boundaries rather than on the cortical extension of the tumor [28].

In conclusion, although the goal of maximal safe resection is clear, it is often difficult in clinical practice to identify the correct planning because the limit of a maximum EOR is unclear, and the preservation of neurological function is undefined. Indeed, it is apparent that the preservation of movement circuits is dictated by well-defined cortical areas and projections. Targeting areas of language and, even more so, paraverbal areas and higher functions such as memory, computation, and cognitive functions are far more difficult given the lack of specific areas, complexity, and redundancy of circuits involved.

1.4 Diagnosis and imaging

Gliomas are a heterogeneous group of tumors that exhibit variable treatment response and patient prognosis. The paradigm shift of using molecular profiles to guide glioma classification, prognosis, and potentially targeted treatment has important implications even for neuroradiology.
Magnetic resonance imaging (MRI) is the most important exam to study brain tumors. Imaging phenotypes using conventional and advanced MRI sequences have been shown to predict tumor behavior and genotype and allow the facilitation of personalized treatment. A broad diagnosis of glioma is often first suggested by imaging in the differential diagnosis, with detailed subclassification left to neuropathologists after detailed tissue analysis (**Fig. 5**).

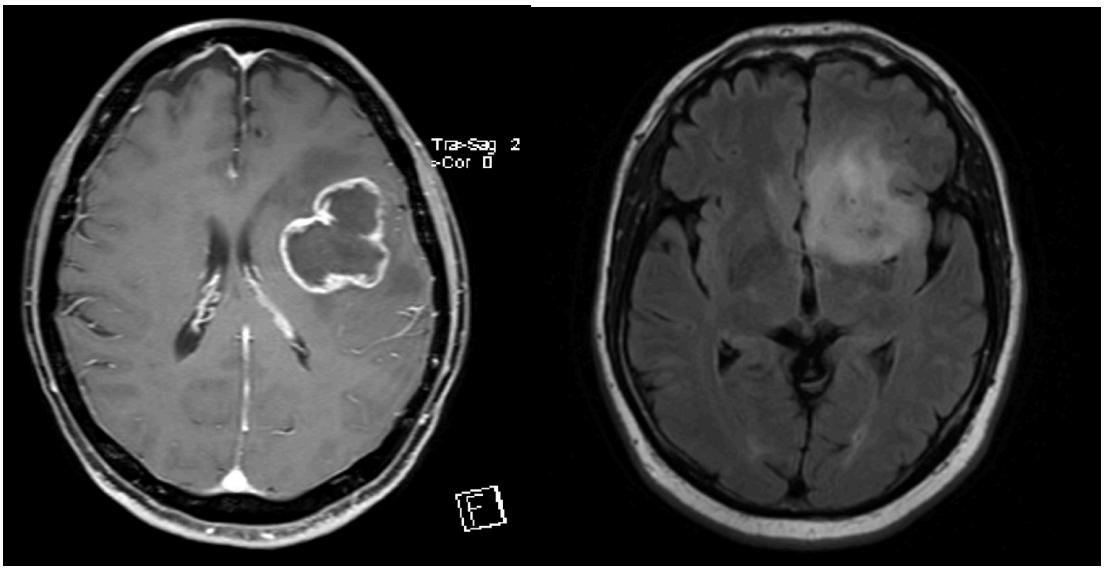


Fig. 5 The image on the left shows a T1-weighted MRI axial sequence documenting the presence of an intra-axial contrast-enhancing tumor attributable to a glioblastoma. The figure on the right does not capture contrast but shows the presence of hyperintensity in T2-weighted and FLAIR suggesting the diagnosis of a low-grade glioma

However, a number of imaging and sequence findings can predict molecular subtypes and allow for a more precise subgroup diagnosis suggested in preoperative imaging [29]. MRI spectroscopy is one of the most used in gliomas, whereas high choline/N-acetyl-aspartate ratio and choline/creatinine ratio argue for tumor invasion and high grading [30].
MRI plays an important role in diagnosing adult gliomas and is the necessary first step in surgical planning and procedure. Technically, the true supra total resection is defined as excision past all discernible and visible MRI-specific abnormalities, including fluid-attenuated inversion recovery (FLAIR) borders [24]. Surgical planning has benefited greatly from these advances in neuroimaging. Yet, there remain a number of barriers preventing accurate determination of tumor pathology using noninvasive means alone. One of these barriers is certainly the estimation of the correct extent of tumor extension in the context of the WM and the alterations it entails.

1.5 The imaging study of white matter

Tumor-related WM change is usually detected at a late stage when the mass effect or prominent edema is present [31]. Several pivotal works have shown that glioma growth appears typically along WM tracts [32]. Because gliomas spread along the WM without causing noticeable changes in routine MRI, tumor extent can be larger than in contrast-enhancing sequences [31-34]. Information about whether the tumor has invaded the WM tract could have significant implications for the planning of surgical procedures or radiotherapy [31]. Phenotypically, the macroscopic tumor volume is still accepted, notably for GB, as the volume is limited by the contrast-enhanced boundary on MRI [34], which defines the gross tumor volume for surgery and radiotherapy [35]. Further, conventional MRI techniques provide purely anatomical information without data regarding CNS connectivity. The ability to visualize important WM tracts in the brain enables neurosurgeons to better guide their surgical approach and resection [33].
Magnetic resonance multidirectional diffusion-weighted imaging (DWI) tractography allows in vivo indirect reconstruction of WM fibers and can perform digital anatomical dissections of WM bundles [26] (**Fig. 6**).

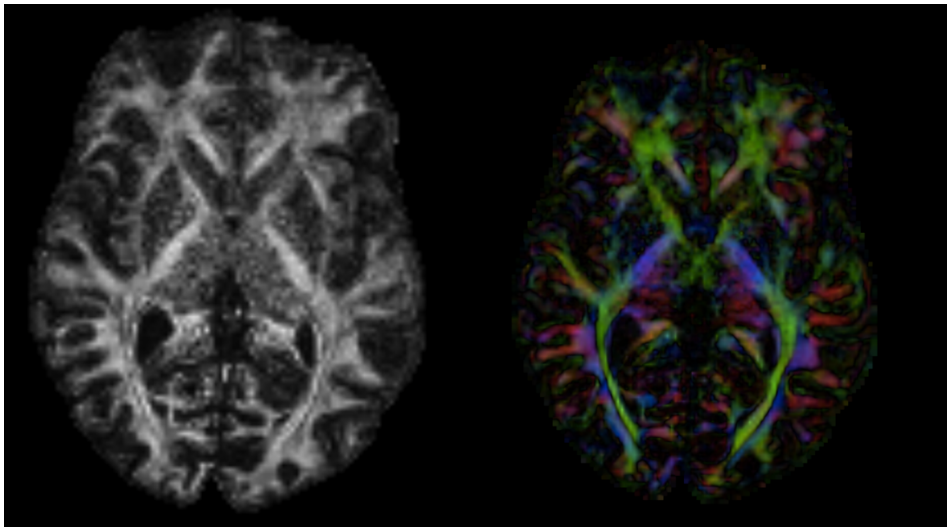


Fig. 6: The image shows the basic acquisition of Magnetic resonance multidirectional diffusion-weighted imaging (DWI) tractography before the post-processing fiber-reconstruction

Different DWI tractography acquisition protocols, postprocessing methods, and reconstruction algorithms are currently used with different accuracy levels [26]. The simplest DWI tractography method is based on deterministic tracing based on voxel main diffusion direction estimated with tensor modeling [diffusion tensor imaging (DTI)].
DTI is a form of DWI in MRI that assesses physiological water directionality and motion, providing images of important WM tracts within the CNS [36].
DTI measures water diffusion properties of neural tissue and can be used to approximate functionally relevant anatomical WM tracts in the brain.
Within the context of intracranial tumor diagnosis and treatment, DTI tractography or DTI Fiber tracking (DTI-FT) is currently used for preoperative surgical planning to define areas to excise, maximize the surgical resection, avoid damage association and projection fibers located near the tumor, to preoperatively differentiates tumor pathology, intraoperative estimation of brain shift, improving postoperative functionality scores, assessing postoperative morbidity and mortality using preoperative information (Fig. 7).

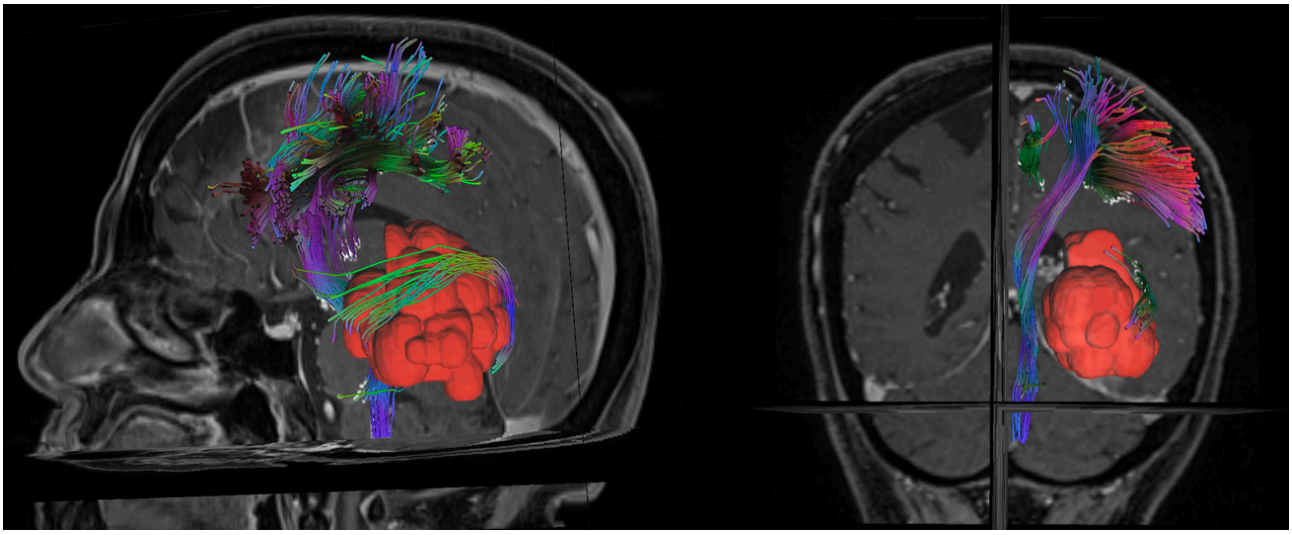


Fig. 7 The image shows a DTI-FT that documented the relationships between the main eloquent fibers (in blue the cortispinal tract and in green the arcuate fasciculus) with an intra-axial tumor.

Despite the diverse clinical applications for DTI within neurosurgical oncology, the method remains underutilized and lacks Level I evidence support [37].
Moreover, it is still unclear if subcortical variability could have a role in postoperative outcomes and if it could be useful for the neurosurgeon to predict the risk of neurological deficits [26]. In conclusion, the necessary imaging for the preoperative study of the patient with GB is undoubtedly the MRI, where through the study with DTI and tractography, it is possible nowadays to estimate the relationship between the tumor mass and the eloquent WM fibers, allowing to be able to estimate the risk of postoperative neurological damage, plot the best possible surgical trajectory, and verify the relationships within white-matter connections endowed with function.

2.1 DTI fiber tracking (DTI-FT)

DTI-FT are MRI techniques based on the concept of anisotropic water diffusion in myelinated fibers, which enable three-dimensional reconstruction and visualization of WM tracts [38]. DTI-FT has been used to visualize specific fiber bundles in the proximity of brain lesions or those influenced by them. Space-occupying lesions, particularly infiltrating ones such as gliomas, may exert various effects on WM tracts, which DTI-FT can depict.
DTI-FT provides information about the normal course, the displacement or interruption of WM tracts around a tumor, and the widening of fiber bundles caused by edema or tumor infiltration can be detected. Some research groups have used DTI tractography to visualize the spatial relationship between lesions adjacent to the sensorimotor system and cortico-spinal tract (CST) for presurgical planning and functional prediction [39]. Others have

used DTI-FT findings for intraoperative guidance by loading data provided by DTI tractography into the neuronavigation system [40].
Images are acquired using a clinical MRI unit (1.5- or 3-T systems) with a standard head coil. DTI is performed using a single-shot EPI sequence. Echo planar imaging is a fast-acquisition technique that reduces motion-related artifacts. Single-shot EPI is commonly used instead of multishot EPI despite its poorer spatial resolution because it has a shorter acquisition time, a superior signal-to-noise ratio, and less motion-related distortion. The degree of diffusion weighting, represented as the b-value, is determined by a sensitizing gradient scheme of strength, duration, and temporal spacing. Diffusion gradient weighting can be done in as few as 6 orientations/ directions and in as many as 512, which is the capacity of many imaging systems. Most groups acquire between 6 and 55 directions (or volumes), with more encoding directions increasing the required scan time but decreasing the variance in tensor model parameters and the signal-to-noise ratio [33,41] (**Fig. 8**).

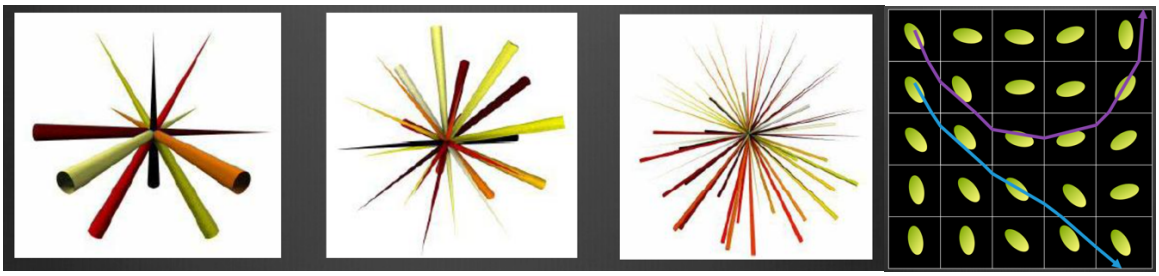


Fig. 8 In this scheme is showed some different number of gradient directions useful to perform a reliable fiber-track reconstruction

Many software are available for mapping and showing the brain connections. DSI Studio is a tractography software tool that maps brain connections and correlates findings with neurological disorders. For clinical research, the "DSI-studio software" is the most adopted since it has been used in more than 1,400 publications and top-tier journals [42] (Fig. 9).

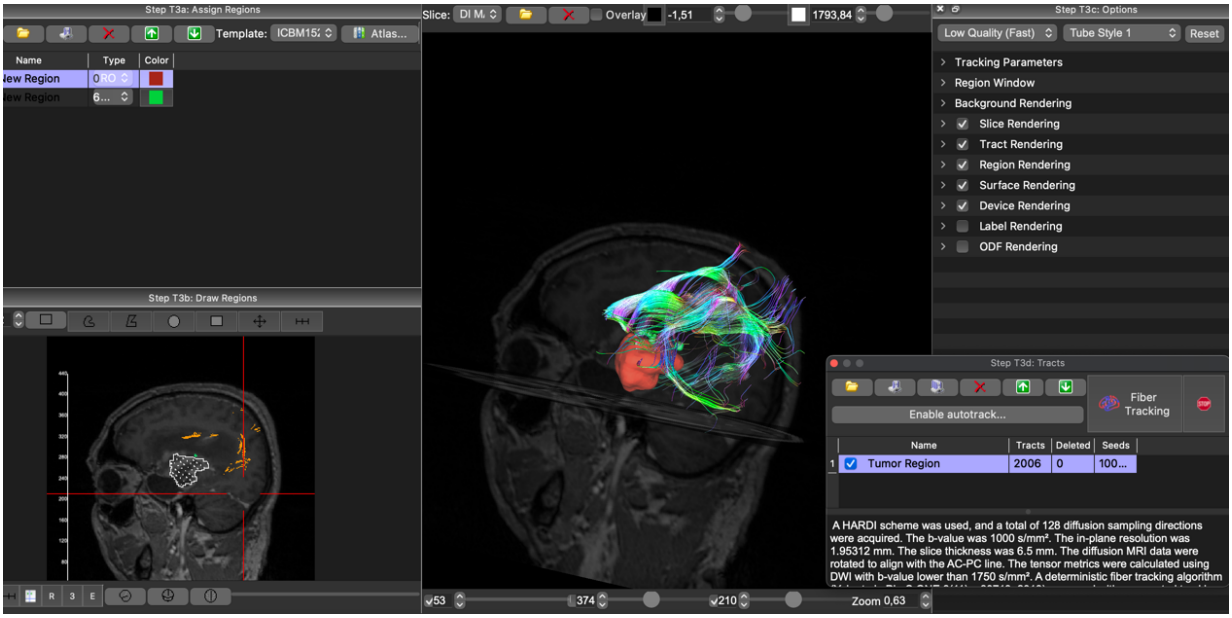


Fig.9 The image shows the graphic user interface of DSI studio

It is a collective implementation of several diffusion MRI methods, including DTI, generalized q-sampling imaging (GQI), q-space diffeomorphic reconstruction (QSDR), diffusion MRI connectometry, and generalized deterministic fiber tracking.
DTI measurements are obtained using either region of interest (ROI) analysis or tractography. ROI analysis is based on operator experience and is sometimes difficult to reproduce in areas with brain tumors or edema. Frequently, DTI-FT can be performed first to localize the tracts, and then ROI analysis can be used based on the previously identified tracts, thereby reducing selection biases of the ROI [33,36,41].
Tractography can be performed via the deterministic or probabilistic method. The deterministic method initiates fiber trajectories using fiber assignment by continuous tracking (FACT) of user-defined voxels.
Various factors, including noise, patient movement, and image artifact, can create uncertainty in DTI measurements; these uncertainties can be adjusted for by using the probabilistic method, in which an additional quantification of the probability of connection between 2 points is performed, allowing the depiction of a greater portion of WM tracts. The probabilistic method is advantageous in areas of lower anisotropy, such as small tracts and crossing fibers, as well as in gray matter.

The combined use of deterministic and probabilistic systems in the analysis of DTI-FTI allows the identification of different types of WM tracts with anatomical detail comparable to reality [43].
WM fiber tracts are traditionally divided into association fibers that connect cortical areas within the hemisphere; projection fibers that connect cortical areas to the deep nuclei,

brainstem, cerebellum, and spinal cord; and commissural fibers that interconnect similar cortical areas of opposite hemispheres. The association fibers commonly visualized on DTI are the cingulum, superior and inferior frontooccipital fasciculus, uncinate fasciculus, superior longitudinal fasciculus (SLF), and inferior longitudinal fasciculus (ILF) [36]. The projection fibers visualized on DTI-FT include the corticospinal, corticobulbar, and corticopontine projection fibers; the commissural fibers seen on DTI-FT include the corpus callosum and anterior commissure. In certain cases, other less commonly used tracts may be identified, such as the optic pathways or fiber tracts within the brainstem [33].
In conclusion, DTI is a special MRI technique that can identify the location of WM tracts important for speech/language/visual/motor functions. The location of WM pathways is the most frequent reason surgery is halted early to avoid compromising patient function. DTI is the only method available to visualize functionally important WM tracts in the vicinity of a tumor before surgery and can be fused with standard intra-operative navigation systems to enable visualization of the spatial location of the tracts during surgery, allowing removal of tumors in close proximity.

2.2 Evolution of DTI for Neurosurgical Use

Ongoing technological advances have led to widespread interest in functional neuroimaging for the preoperative planning of glioma surgery [44]. The motivation behind this interest can be traced directly to the hypothesis that more precise mapping of neurological function will improve the extent of resection, mitigate morbidity, and broaden surgical indications for lesions in classically eloquent areas.
The first authors to integrate the use of fiber tracking into intraoperative navigation were Coenen et. Al. [45] in 2001, in 4 patients undergoing resection of both intra- and extra axial tumors using a diffusion-weighted mapping without diffusion tensor was used to visualize the pyramidal tracts for intraoperative navigation. Several studies followed [46,47], and most investigators applied direct stimulation to verify the fidelity of DTI-FT. In 2003, Kamada et al. [34] used DTI and direct fiber stimulation to confirm the accuracy of DTI in the intraoperative identification of the corticospinal tract in 6 patients with intraaxial lesions. In 2004, Berman et al. [46] combined DTI and direct cortical stimulation in 11 patients undergoing glioma resection. These investigators found that DTI-FT maintained a high degree of correlation with the descent of motor tracts from the cortex to the cerebral peduncle [48]. This same group also reported on the in vivo detection of WM tracts involved in speech and naming using DTI derived from direct cortical stimulation during resection of a left frontotemporal glioma [33].

In 2005, Nimsky et al. [48] described 37 patients undergoing supratentorial glioma surgery in whom both pre- and intraoperative DTI were performed. These authors analyzed WM-tract shifting and bidirectional (outward and inward) shifting of tracts. They found that the amount of WM tract shift corresponded well with the brain shift of the "deep tumor margin" [49].

In 2007, Wu et al. [50] performed a rare prospective randomized controlled trial to evaluate the impact of DTI versus standard neuronavigation in patients with gliomas involving the pyramidal tracts. The authors reported on a consecutive series of 238 patients, with 118 randomized to a group undergoing DTI-FT integrated into neuronavigation during resection and 120 randomized to a group undergoing standard MRI protocols and standard neuronavigation. The 6-month performance scores were assessed in 96.34% of enrolled patients. The Karnofsky performance status (KPS) scores among patients with either low- or high-grade gliomas were significantly higher in those who had undergone DTI than in those who had undergone standard neuronavigational resection. Additionally, the overall rates of gross total resection (GTR) in the DTI group (118 cases, 72% GTR) were significantly higher than in the control group that underwent standard neuronavigation (120 cases, 51.7% GTR, $p = 0.002$).

This study is a key component of the neurosurgical literature for several reasons. First, it is one of very few Class I (prospective randomized controlled) studies to link outcomes of glioma surgery with neurosurgical technique. Second, it shows benefits in increasing OS, EOR, and 6-month KPS scores in the DTI-aided high-grade glioma group.

The current literature demonstrated that integrating anatomical and functional information is useful for surgical planning and intra-operative procedures. Multimodal navigation, which refers to lesion localization and resection assistance, may include direct cortical and subcortical stimulation and functional MRI (fMRI) and DTI sequences. Often, these imaging modalities can be used simultaneously and allow for intraoperative overlay of both functional and anatomical spatial relationships.

2.3 Tractography main parameters

DTI is an important method to evaluate the structure of WM structures, but although most studies have demonstrated the usefulness of this technique in neurosurgical planning, the validity of the information provided remains to be confirmed, as a potential underestimation of the effective size of fiber bundles by DTI-FT has been demonstrated [1]. DTI-FT currently assumes descriptive value toward pathology by

lacking validated quantitative data and values useful for diagnosis and preoperative study.

DTI-FT provides potentially useful information about diffusion measurements and enables the calculation of several parameters from DTI [51]. The four diffusion coefficients, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), are derived from mathematical modeling and provide information and indicators when assessing the imaging studies of glioma. The table resumes the most used parameters for research (**Table 1**).

No.	Name	Metrics	Method	Interpretation	Changes
1	FA	Fractional anisotropy	Diffusion tensor imaging (DTI)	Axonal integrity	↓ demyelination, inflammation, edema, axonal loss
2	AD	Axial diffusivity	Diffusion tensor imaging (DTI)	Axonal density	↓ axonal loss
3	RD	Radial diffusivity	Diffusion tensor imaging (DTI)	Myelination	↑ demyelination
4	MD	Mean diffusivity	Diffusion tensor imaging (DTI)	Edema and cell infiltration	↑ vasogenic edema, ↓ cytotoxic edema
5	QA	Quantitative anisotropy	Q-space imaging	Axonal density	↓ axonal loss
6	ISO	Isotropy	Q-space imaging	Edema	↑ edema
7	RDI	Restricted diffusion imaging	Q-space imaging	Inflammation	↑ cell infiltrations
8	NRDI	None-restricted diffusion imaging	Q-space imaging	Edema	↑ edema (inflammation)

The study of glioma-DTI found significant differences in FA, MD, and other DTI coefficients in many WM regions where no signal changes in conventional MRI were found [52]. These changes are related to tumor invasion and development, and more emphasis is placed on the analysis of the dispersion values of FA, MD, and others of one or more WM fiber pathways but lacking an overall voxel-wise data inspection [52]. FA and MD improve the accuracy and reliability based on a traditional fiber bundle analysis [53] for several reasons:

1) FA is a regularly studied parameter as it reflects the directionality of brain-fiber tracts and correlates with cell density and proliferation activity [54].

Various cellular structures—for example, cell membranes and intracellular organelles—impede the random motion of water molecules in the brain and cause them to move with directionality called “anisotropy” [33,36].

This biological property is essential to understanding DTI because the directionality of water molecules as they move within WM tracts is a key component of fiber tracking. The orientation of WM tracts causes anisotropy because water diffuses in a direction parallel to the axonal fibers due to the myelin sheaths, which create a barrier to the diffusion of water

perpendicular to the axonal membranes. Collectively, this information is known as the "diffusion tensor," a 3D ellipsoid model of water diffusion. The diffusion tensor directly represents the direction (anisotropy) of water and indirectly represents the orientation of WM fibers. It is described as a 3D ellipsoid and is subjected to a linear algebraic procedure known as "diagonalization"[41].

FA is calculated from the standard deviation of the 3 eigenvalues ($l1 \geq l2 \geq l3$), which are measures of the magnitude of diffusion, and subsequently by 3 eigenvectors (v1, v2, v3), which are orthogonal to each other and represent the direction of diffusion.

The value of FA ranges from 0 (isotropy with 0 net direction) to 1 (maximum anisotropy along 1 eigenvector). This directionality is typically presented in a color-coded map or via fiber tractography, whereby the color indicates directionality and brightness is proportional to the FA. A general convention is to color code the projection fibers (blue) coursing from superior to inferior (for example, the corticospinal tract), the association fibers (green) coursing anterior to posterior (for example, the arcuate fasciculus), and the commissural fibers (red) coursing laterally (for example, the corpus callosum) (Fig. 10)

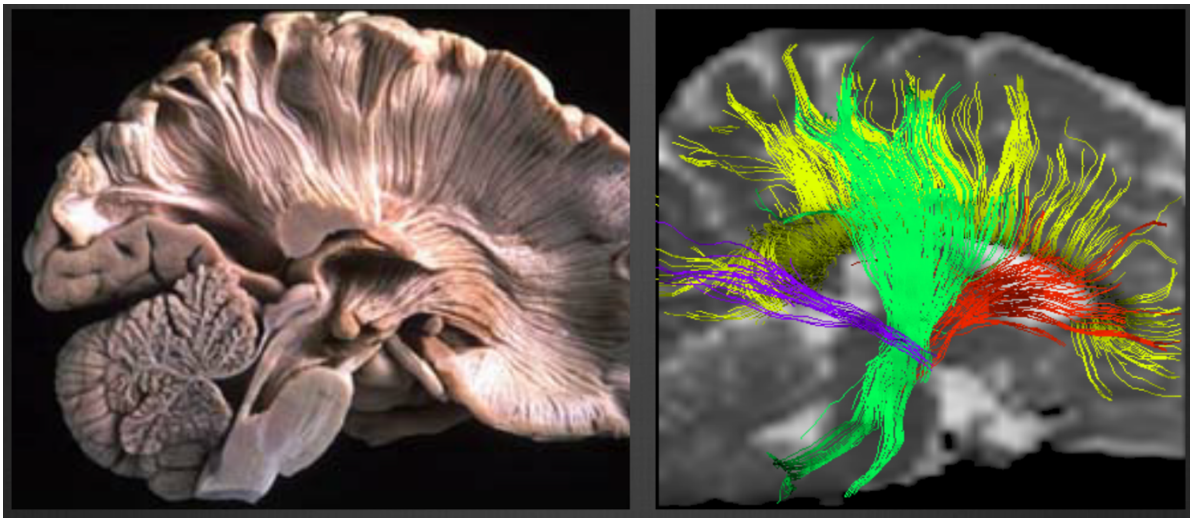


Fig. 10 The image shows the general conventional color code to identify projection fibers (blue), the association fibers (green) and the commissural fibers and a comparison with anatomical preparation

Considering it is a well-known biomarker for WM integrity, some authors decided to measure FA [55] to evaluate the post-surgical neurological deterioration risk correlating to the extent of resection and WHO grade in brain tumors [56]. WM integrity measured with FA predicted neurological decline when a lesion was present in a not-eloquent area [56]. Higher WM integrity of the non-dominant hemisphere was even associated with a higher incidence of neurological decline, while at the same time, it was associated with better preoperative neurological performance. There are several possible explanations for these

findings. First, a lowered FA might indicate impending or proceeding neuroplasticity effects, protecting patients from further neurological damage. Also, plasticity might be triggered by WM damage to the projection fibers and manifest elsewhere [57].

2) If FA is the measurement of the tendency of water to diffuse in one direction (anisotropy), MD measures the magnitude of diffusion. MD is comparable and mathematically equivalent to the ADC in standard DWI. It is calculated as the mean of the 3 eigenvalues, representing the directionally averaged diffusivity of water, which is affected by changes in the structure of brain tissue. Changes in the MD value of the WM skeleton are caused by tumor-related symptoms such as secondary epilepsy and brain edema. It is known that an increased MD is due to a reduction in the number and/or volume of cells and a compensatory increase in the extracellular space of WM [32,58]. Previous studies on DTI in patients with epilepsy have shown that MD may be a more accurate quantitative indicator [53,58]. MD of tumor regions is the DTI parameter that differed significantly between patients with and without epilepsy [59].

The DTI diffusion coefficient showed various limitations for the validity in clinical use. Discordance between tractography and intraoperative direct stimulation may result from an accumulation of errors at each stage of DTI, beginning from MR distortions during the acquisition of the tensor information all the way to registration during surgery. False negatives can occur in tractography (a fiber can be missed), or false positives can occur, and it is difficult to control them [60]. Underlying anatomical differences in fibers, including size, can translate into different FA values. Further, peritumoral brain edema reduces the ability of early DTI standard methods to perform peritumoral tracking because the signal from free water competes with the signal from WM. In these cases, it is possible to retrieve invalid FA and MD threshold values [61]. These concerns raise the possibility that tractography can identify a tract that has been made redundant by the effects of a nearby glioma, leading the surgeon to perform a subtotal resection or even dissuading the surgeon entirely from tackling the tumor.

2.4 New quantitative DTI-parameters: the shape descriptors

Gliomas are white matter pathologies that grow in the context of the white matter. It is known that most fibers in the supratentorial compartment are associative type in which a clear eloquent function regarding brain cognitive function is often unknown [62].

The most used network analysis tackled the structure-function correlation from a panoramic view, but the shape characteristics and topological pattern of the connecting bundles were mostly ignored, particularly the association pathways in the human brain that control most of the cognitive functions. While there are existing shape analysis studies focused on specific applications [63,64], there is yet a comprehensive study utilizing shape analysis to investigate the structural characteristics of the human association pathways. To bridge this information gap was applied a comprehensive shape analysis, including length, area, volume, and shape metrics, to investigate the shape characteristics of the human association pathways. Shape analysis has been widely used in computer vision in various applications to achieve an imaging understanding of an object [65]. The analysis provides the "shape descriptor"—a quantitative measurement that describes one part of the shape characteristics as length, area, and volume. Yeh FC [66] recently introduced a useful quantification of the length metrics, including length, span, diameters of the bundle, and radius of the innervation regions. Based on these metrics, we further derived "shape metrics," which are unit-free indices, including curl, elongation, and irregularity, to describe the shape characteristics of the association pathways (**Table 2**).

Descriptors	Definition
Length (mm)	$\frac{1}{n}\sum_{i=1}^{i=n}\sum_{t=1}^{t=m_i-1}\|v_i(t)-v_i(t+1)\|_2$
Span (mm)	$\sum_{i=1}^{i=n}\|v(1)-v(m_i)\|_2$
Diameter (mm)	$2\sqrt{\frac{volume}{\pi \times length}}$
Radius (mm)	$\frac{1.5}{N_e}\sum_{i=1}^{i=N_e}\left\|E_i-\frac{1}{N_e}\sum_{j=1}^{j=N_e}E_j\right\|_2$
Surface Area (mm^2)	$N_s \times voxel\ spacing^2$
Volume (mm^3)	$N \times voxel\ volume$
Trunk Volume (mm^3)	$N_t \times voxel\ volume$
Curl	$\frac{length}{span}$
Elongation	$\frac{length}{diameter}$
Irregularity of the bundle surface	$\frac{surface\ area}{\pi \times diameter \times length}$
Irregularity of the end surface	$\frac{\pi \times radius^2}{area\ of\ the\ end\ surface}$

Length metrics | Area metrics | Volume metrics

Bundle: trajectory form=$\{v_i(t) \mid i = 1,2,3,\dots n\}$, voxelized form=$\{V_i \mid i = 1,2,3,\dots N\}$

End surface: voxelized form=$\{E_i \mid i = 1,2,3,\dots N_e\}$

N_t is the number of "trunk bundle" voxels.

N_s is the number of tract surface voxels.

Table 2: List of shape descriptors and their definitions

Examining the reliability of these metrics using the intra-class correlations. These reliability results revealed some information, such as left-right asymmetry in fibers and between-subject variations for the association pathways. The derived metrics further achieved moderate to good test-retest reliability.

The parameters that quantify the most descriptive features are length, span, curl, volume, diameter, elongation surface, and area. These values are specific and closely related to the characteristics of the beam itself, which may have different sizes between the two hemispheres or high interindividual variability. But focusing on the surface area, it is noteworthy that this parameter here will inevitably include the innervation area around a ROI. Based on a cylinder model, Yeh FC [66] proposed a new descriptor called "irregularity" or tract irregularity (TI) which is defined as

$$irregularity = surf\ ace\ area\ (8)\ \pi \times diameter \times length$$

Irregularity is conceptually similar to convexity and concavity. A surface area much larger than the expected cylinder surface suggests higher shape irregularity. The rest of the shape analysis then utilized the two end surfaces of a track bundle. The end surfaces were determined by anisotropy and angular threshold used in the fiber tracking (**Fig. 11**)

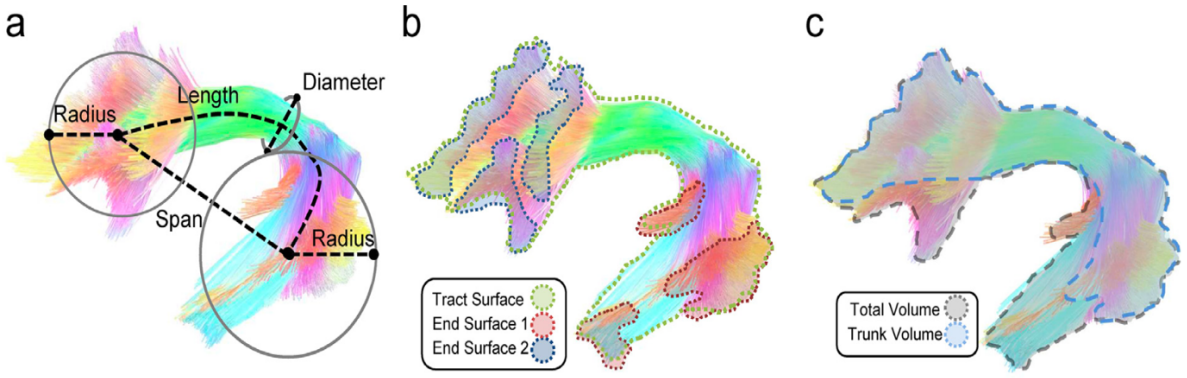


Fig. 11: Shape analysis of a bundle. (a) The length metrics include length, span, diameter, and radius of the innervation region. The length measures the length of the bundle trajectory, whereas the span measures the absolute distance between two ends of the bundle. The diameter estimates the average bundle diameter. The radius uses a circular model to estimate the coverage of the innervation regions. (b) The area metrics include total track surface area and area of the two end surfaces. (c) The volume metrics include total volume and trunk volume.

By integrating with shape analysis, these parameters offer new option for WM analysis. It can be used in neurological, psychological, and psychiatric studies to investigate the correlation between WM architecture correlates and abnormal brain functions, with the hope of deciphering how structure defines brain functions [66].

2.5 Clinical Use of the DTI-parameters

The WM fibers that come into relationship with the tumor are inevitably distorted, depreciated, and (especially in aggressive forms such as GB) infiltrated by the mass, but the extent to which this distortion occurs is greatly affected by several variables, including the grading, tumor volume, brain edema, and lobe involvement. If, for the large projection fibers, the alteration and distortion entity turns out to be intuitable from a quantifiable clinical symptom (the neurological deficit from pyramidal bundle injury, for example), it is not so simple for an association tract that surrounds the tumor and may be involved in superior cognitive function.
Studying the relationship between the extent of distortion of WM bundles and the volume of edema in relation to tumor size may help to discriminate how aggressive and infiltrating a tumor is before a surgical procedure and to estimate whether there is a predictive relationship on the molecular status of the tumor that can be estimated before the surgical procedure [31] (**Fig. 12**)

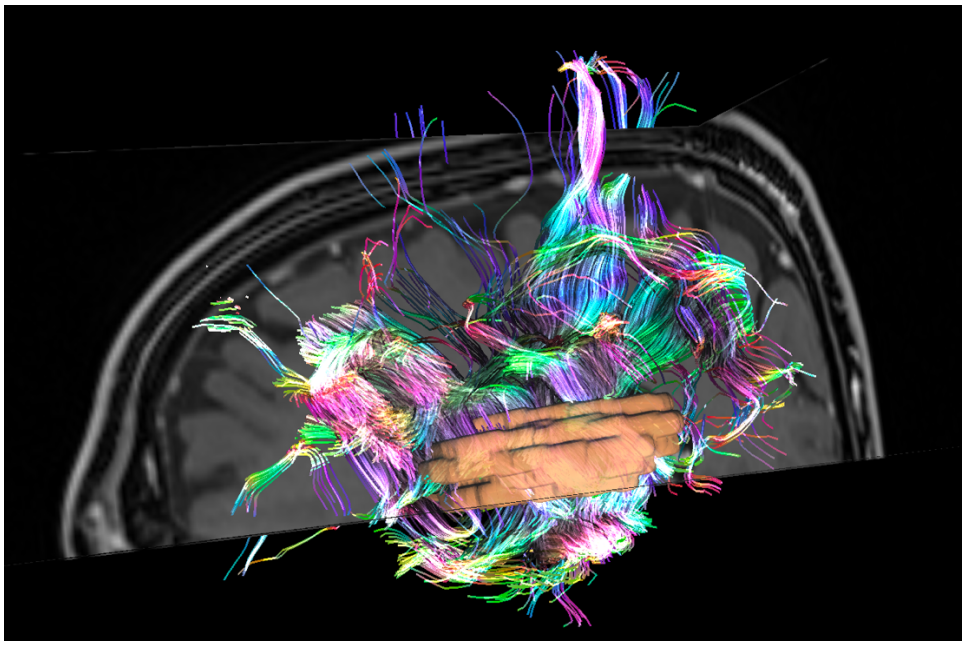


Fig. 12 This DTI-FT reconstruction shows how the WM fibers around the tumor are distorted, depreciated, and in this case of GB infiltrated by the mass

Numerous researches focused on the verification of the feasibility of DTI parameters in glioma grading and prognostication, which seemed to be informative for determining the optimal target containing the highest cell density when considering biopsy, radiotherapy (RT), or surgical resection [47].
The basic hypothesis for such grading was that the DTI metrics within solid tumors would be determined by a balance between factors increasing the degree of the directionality of water diffusion, such as high cellularity and/or vascularity, and factors decreasing the degree of the directionality of water diffusion, such as fiber destruction or infiltration.
The main DTI metric statistical descriptors are mean FA (ratio), median FA (ratio), maximum FA, and FA variation [maximum standard deviation (SD) and range], which were advocated to be useful in glioma grading [67].
Glioma size, infiltration, and edema are usually related to decreased mean FA, and a study comparing radiation damage and tumor infiltration found that the apparent diffusion coefficient in regions of a tumor infiltration was reduced when compared to radiation damage, which was related to an excessive number of tumor cells. Notably, a study comparing radiation damage and tumor infiltration found that ADC in the regions of tumor infiltration was reduced compared to radiation damage, which was related to an excessive number of tumor cells [68]. This has led some researchers to use DTI image data to help detect tumor boundaries and infiltration. The mass-occupying effect may lead to an abnormal WM skeleton and can guide the surgeon to a supra-marginal resection.

In the aggressive forms such as GB, though there was the destruction of WM fibers causing the decrease of FA compared with normal-appearing WM, its value did not decrease to extremely low because the increase in cell density and vascularity gave directionality to the water diffusion in extracellular space resulting in compensation of decreased FA; on the contrary, with regard to LGG, cells were loosely and randomly arranged in fibrillary matrix, where water diffused almost freely in all direction thus leading to the significant increase of FA. Besides, increased MD would be correspondingly observed due to the increased extracellular spaces and decreased cellularity. Evidence supporting the aforementioned assumptions could be found from early glioma grading research on astrocytoma, which suggested that the mean FA values of HGG, anaplastic astrocytoma, diffuse astrocytoma, and pilocytic astrocytoma were largely affected by histopathologically confirmed cellularity and/or vascularity [33], and higher grade of astrocytoma tended to present lower FA value.

Inoue et al.[69] demonstrated that FA, rather than MD, efficiently detects the disparity between LGG and HGG. Antithetically, like DTI research in other aspects, there was

always disagreement regarding the clinical value of various metrics. Research on the combination of DTI and MR spectroscopy suggested that FA was uncorrelated and even contradictorily higher in LGG, whereas ADC value significantly correlated with the histological grading, and lower ADC indicated HGG. Different authors concluded that DTI might not be useful for preoperative differentiation, whereas they still contended that FA value rendered a better correlation with histopathologic parameters [70].

Recently, some researchers [55,71] diverted their attention to the periphery of the glioma, claiming that those areas in the vicinity of the glioma contained a considerable amount of preserved fiber tracts due to its less extent of fiber infiltration and disruption; hence, the FA value should be significantly higher in LGG than HGG. The highlight of these studies was that the heterogeneity of glioma and metrics normalization had been considered by using the regional (median or mean) FA value and metric ratio for the statistic comparison [55].

To achieve a more precise and objective grading of glioma based on DTI metrics, White et al. [70] hypothesized that the solid parts within HGG would have a greater variation of FA based on its intrinsic heterogeneous nature. In their research, the FA statistical descriptors, including maximum FA, FA range, and maximum SD of FA, were compared between LGG and HGG. The results demonstrated that these values of grade II glioma were significantly lower than those for HGG ones, and they speculated that the tumor components with maximum standard deviation (SD) or high maximum FA might reflect regional heterogeneity of histopathology and/or the more malignant foci.

DTI metrics were also considered applicable for surgical planning to perform an adequate tumor resection and might be related to the survival prediction when being correlated with the Ki-67 index, a marker of proliferation in glioma.

Other research indicated that some unconventional DTI-derived metrics such as tensor shape measures—tensor shape (CL), planar and spherical isotropy coefficients (CP and CS), and p, L, AD, and fiber density index (FDi) [56] or irregularity tract index (TI) [66] could potentially be helpful for tumor grading and surgical planning, whereas due to the limited number of related results, a rush conclusion should not be drawn.

In contrast to other functional imaging techniques not routinely used for clinics, DTI has gradually been considered a standard application in combination with structural imaging for glioma patients' diagnosis and surgical planning. However, the limitation of DTI should always be remembered when admiring the colorful portrayal of WM from tractography and evaluating its metrics for clinical research. DTI-based analysis remains a challenging technology based on complex data acquisition and geometrical models that rely on many assumptions. Moreover, methodological and artificial aspects can provide

erroneous diffusion measurements that do not appropriately reflect microstructure information and may finally lead to misinterpretation of the results [56]. To overcome these limitations, a call for a universal protocol regarding image acquisition to post-processing is mandatory. DTI Challenge, an image processing contest organized at the Medical Image Computing and Computer Assisted Intervention conference, demonstrated a large variability of tractography results on the same neurosurgical cases among international teams using different algorithms, platforms, and software [72]. This community-based effort aimed at providing a standardized evaluation of tractography algorithms.

THE STUDY

3.1 Background

Gliomas are the most common primary neoplasms of the CNS in adults [1,2]. The prognosis of the glioma patient is influenced by the molecular profile, extent of surgical resection, age, and performance status [14]. Despite the remarkable improvement in understanding the pathogenesis of gliomas, the first therapeutic step is surgery. EOR remains a critical determinant of oncologic outcomes for patients with high- and low-grade glioma [19]. The goals of surgery are maximal tumor resection associated with minimal post-operative morbidity and maximal patient functional preservation. Realizing the true benefit of neurosurgical resection requires a balance between surgical cytoreduction and preservation of neurological function in the modern concept of "Neuro-oncological balance" [1]; but fully understanding what it means to perform a total resection and understanding whether all functions, including higher cognitive functions, have been preserved has not yet been achieved. DTI-FT is gradually considered a standard application in combination with structural imaging for glioma-patient diagnosis and surgical planning. DTI-FT has been used to visualize specific fiber bundles, which are in the proximity of brain lesions or those influenced by them. Gliomas may exert various effects on white matter (WM) tracts, which DTI-FT can depict. The WM fibers that come into relationship with the tumor are inevitably distorted, depreciated, and infiltrated, but the extent to which this distortion occurs is greatly affected by several variables, including the grading, tumor volume, brain edema, and lobe involvement [31] (Fig. 13).

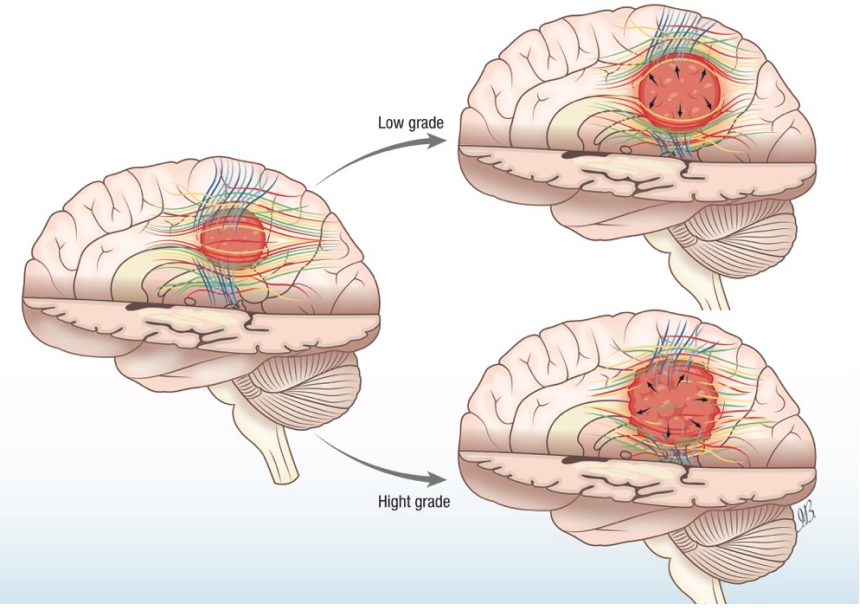


Fig. 13: The figure shows the different WM-alterations developed in different grading tumor-growth

For these reasons, DTI-FT assumes a descriptive role toward pathology by lacking validated quantitative data and values useful for diagnosis and preoperative study. The DTI diffusion parameters showed various limitations for the validity in clinical use since methodological aspects and tumor features can provide erroneous diffusion measurements that do not appropriately reflect microstructure information and may finally lead to misinterpretation of the results [56]. The most commonly used metrics, FA and MD, could be invalidated in these cases [61].
These concerns raise the possibility that DTI-FT can identify a tract that has been made redundant by the effects of a nearby glioma, leading the surgeon to perform a subtotal resection or even dissuading the surgeon entirely from tackling the tumor. It is known that most fibers in the supratentorial compartment are associative type in which a clear eloquent function regarding brain cognitive function is often unknown [62]. The most used network analysis tackled the structure-function correlation from a panoramic view, but the shape characteristics and topological pattern of the connecting bundles were mostly ignored, particularly the association pathways in the human brain that control most of the cognitive functions. To bridge this information gap was applied a comprehensive shape analysis, including length, area, volume, and shape metrics of white-matter tracts, to investigate the shape characteristics of the human association pathways. Shape analysis provides the "shape descriptor"—a quantitative measurement that describes one part of the shape characteristics as length, area, and volume. Yeh FC [66] recently introduced a useful quantification of the length metrics, including length, span, diameters of the bundle, and radius of the innervation regions. The derived "shape metrics" include curl, elongation, and irregularity to describe the shape characteristics of the association pathways. The new descriptor called "irregularity," defined as a numerical ratio between the surface area, diameter, and length of a specific fiber, could offer a new option for WM analysis and can be used to investigate the correlation between WM architecture and abnormal brain functions [66] in the context of a brain tumor. This simple metric could help to detect tumor boundaries and infiltration. The mass-occupying effect may lead to an abnormal WM skeleton and can guide the surgeon to obtain a safety supra marginal resection. This new DTI metric and the standard quantitative parameters used could potentially be helpful for tumor grading identification and surgical planning.

3.2 Objective of the study and purpose

This study proposes to test the validity of the main quantitative parameters of DTI-FT in establishing the grading and behavior of a series of glioma patients. We compare the

clinical, morphological, molecular, and outcome parameters of glioma patients and establish the predictive values of FA, MD with the combined use of the shape descriptor "tract irregularity" measured in the bundles surrounding the tumor, in the supramarginal space, with the aim to identify useful parameters to planning the tumor resection during the neuronavigation. The hypothesis is to identify in the relations between FA, MD, and TI the areas of WM beyond the contrast-enhancing margins that are already considered damaged and nonfunctional, thus allowing safe supramarginal resection of the tumor.

3.3 Material and Methods

This is an observational prospective study performed on a surgical series of brain tumor patients treated in the neurosurgical department of Policlinico Umberto I of Rome, Molinette Hospital of Turin, and Santa Maria Goretti Hospital of Latina, Italy. Consensus about diagnosis, treatment, and related information was obtained under written informed consent approved by the Institutional Review Board of our Institution (IRB: 6961, prot. 0296/2023).

Population study

All subjects with radiological diagnosis suggestive of glioma and candidate for surgery were enrolled from March 2018 to December 2022, with the following inclusion criteria:

- *Age > 18 years;*
- *Patients with unilateral supra-tentorial tumor with no history of inflammatory or degenerative brain disease;*
- *Patients with histological diagnosis of glioma, following the WHO 2021 classification fo brain tumors;*
- *Performance status measured using Karnofsky performance scale (KPS) > 70;*
- *Patients who performed functional magnetic resonance imaging (MRI) with diffusion tensor sequences (DTI) and fiber-tracking (tractography) study within 7 days before surgery;*
- *All the patients included in the study were newly diagnosed brain tumor at their first surgery.*

We excluded patients who did not agree to or could not undergo the functional MRI examination or for whom the radiological examination could not be performed with the volumetric standards required for the analysis (explained below).

Patient Selection

Data acquisition and analysis were approved by the institutional ethics committee (6961 prot. 0296/2023 of Policlinico Umberto I, Rome, Italy) and performed according to the data protection guidelines, including pseudonymization of personal data.
For all the included patients, we recorded clinical data such as age, gender, and clinical onset.
We reported radiological information such as tumor site (identifying major lobe involvement, deep-seated or superficial location), tumor volume, edema volume, edema-tumor ratio, radiological and surgical morphology (distinguished between solid, cystic or necrotic lesion), and the presence of a hemorrhagic lesion. (**Fig. 14, 15 and 16**).

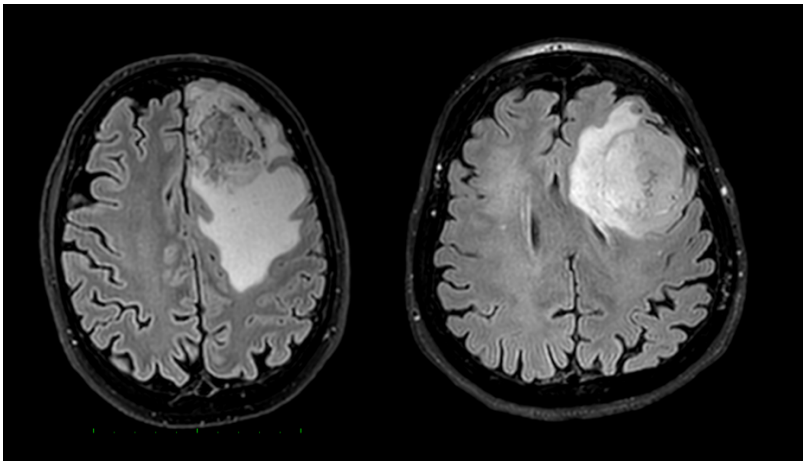


Fig. 14: The image shows an example of different edema volume retrieved by two different patients with the same diagnosis

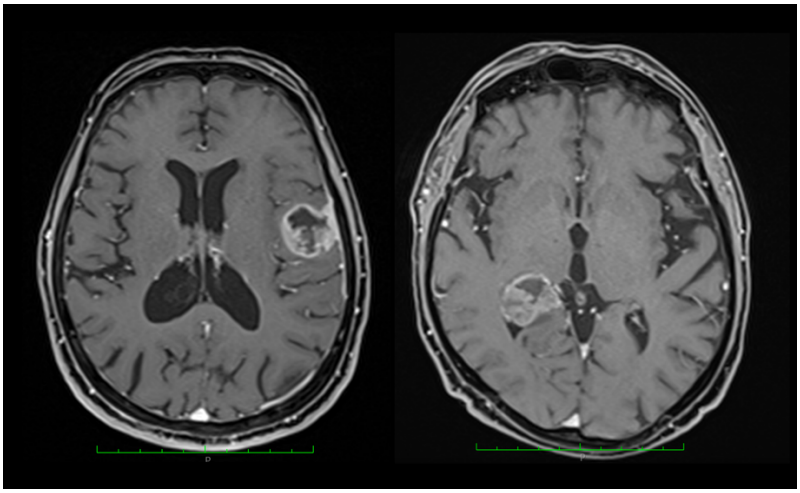


Fig. 15: The image shows an example of different surgical site retrieved by two different patients with the same diagnosis (superficial on the left and deep)

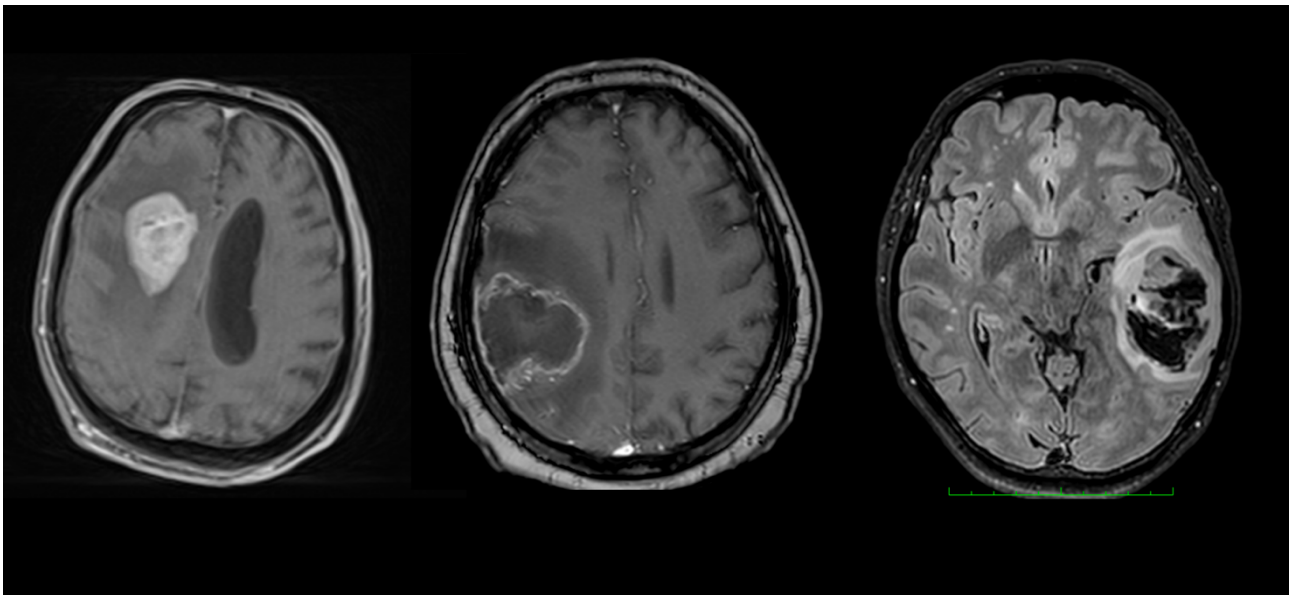


Fig. 16: The image shows an example of different surgical morphology of the different gliomas distinct between solid, cystic and hemorrhagic lesion

We reported tumor grading in accordance with the updated version of the 2021 WHO classification of brain tumors [3], distinguishing between high-grade (grade 4) and low-grade (grade less than 4) tumors (**Fig. 17**).

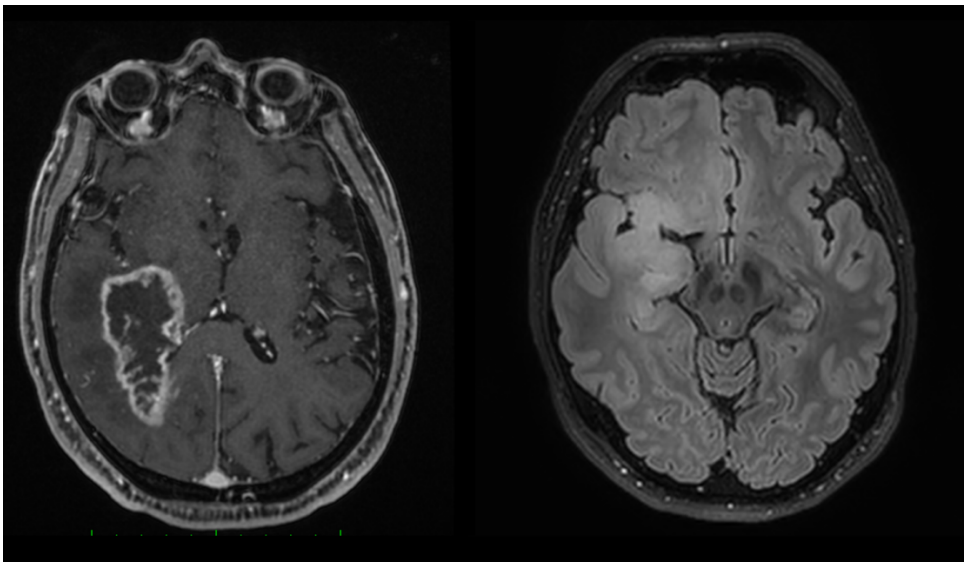


Fig. 17: The image shows an example of the different grading suggested by MRI-imaging

Immunohistochemistry was routinely performed in the Department of Neuropathology of our University Hospital, reporting ki-67%, EGFR expression status, MGMT, p53, ATRX and antibody anti-IDH1 R132H (Dianova, DIA H09; 1:50).

Progression-free survival (PFS) was recorded in months, and it was estimated as the interval between the date of diagnosis and the estimated date of progression revealed by the follow-up MRI imaging. Overall Survival (OS) was recorded in months; it was measured from the date of diagnosis to the date of death or the date of last contact if alive. The digital database of our Institutions obtained clinical information, whereas OS data were obtained by a telephone interview.
A special clinical focus was on the performance status expressed as the KPS scale: such parameter was considered, as previously observed [14], as associated with OS. In particular, it was recorded in four different moments: 1. Before surgery, 2. At 30 days after surgery 3. At the end of the adjuvant treatment, 4. At the last follow-up evaluation.

Image Acquisition

All the patients included underwent a brain MRI scan, including a high field 3 Tesla volumetric study within 7 days before surgery with the following sequences: T2w, FLAIR, isotropic volumetric T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) before and after intravenous administration of paramagnetic contrast agent; diffusion tensor sequences (DTI) with 3D tractography fiber tracking and functional MRI (fMRI).
The images characteristics were: field of view = 240 mm; matrix 512 × 512; 3D T1, repetition time (TR) = 8.8 ms, echo time (TE) = 3.5 ms, voxel size = 0.469 mm side, slice thickness = 1.4 mm; axial T2 axial, Spin Echo, TR = 9000 ms, TE = 80 ms, voxel size = 0.469 mm side, slice thickness = 4 mm; sagittal 3D FLAIR, TR = 9000 ms, TE = 141 ms, voxel size = 0.5 mm side, slice thickness = 1 mm; DTI, TR = 7000 ms, TE = 81 ms, matrix 256 × 256, voxel size = 1 mm side, slice thickness = 3.5 mm, b = 1000 s/mm^2.
Volume of the contrast-enhancing lesion was calculated by drawing a region of interest (ROI) in a Volumetric enhancing post-contrast study weighted in T1 (a multi-voxel study), conforming to the margins of the contrast-enhancing lesion, using the free-hand assisted tool with software Horos (LGPL license at horosproject.org v3.3.6, sponsored by Nimble Co LLC d/b/a Purview in Annapolis, MD USA) [42,73]. Peri-tumoral brain edema (PBE) volume was calculated by drawing a ROI conforming to the hyperintense signal borders on the T2-weighted and Fluid Attenuated Inversion Recovery (FLAIR) sequences and subtracting the previously calculated tumor volume. All volumes were measured in cm^3 before anti-edemigen therapy.

The relationship between tumor and brain edema was reported as the numerical ratio between the two values according to the formula:

$$\frac{\text{Tumor Volume (cm}^3\text{) + Edema Volume (cm}^3\text{)}}{\text{Tumor Volume (cm}^3\text{)}} = \text{Edema/tumor ratio}$$

The criteria for DTI acquisition were guided by the interdisciplinary team and depended on the eloquent location of the tumor, suspected histopathological malignancy, patient compliance, and eligibility for functional MRI and other complementing tools.
DTI was acquired using a single-shot echo-planar imaging diffusion tensor imaging (DTI) sequences with equal settings (TR/TE = 7010/102 ms; FOV = 222 × 222 mm2; matrix 112 × 112; 50 slices without gap; slice thickness 2.7 mm; 32 non-collinear directions, b- value = 1000 s/mm2) using a dedicated head coil. Reconstruction with fiber-tracking required for each image set at least one acquisition with 9 scalar volumes.

Tractography

For tractography for all data, the open-source validated [74] software DSI studio (https://dsi-studio.labsolver.org/) and BrainLab iPlan software (BrainLAB Inc., Feldkirchen, Germany) have been used. For definition and evaluation of ROI feasibility, metric analysis we used these two tractography applications of different complexity to ensure cross-software validity.
MRI objects consisted in three volumes, manually contoured (slice by slice) with a ROI positioned manually. The seed ROI was placed outlining with the tool “free-hand drawing” region to be drawn freehand" the edges of the contrast-enhancing signal around the tumor (**Fig. 18**).

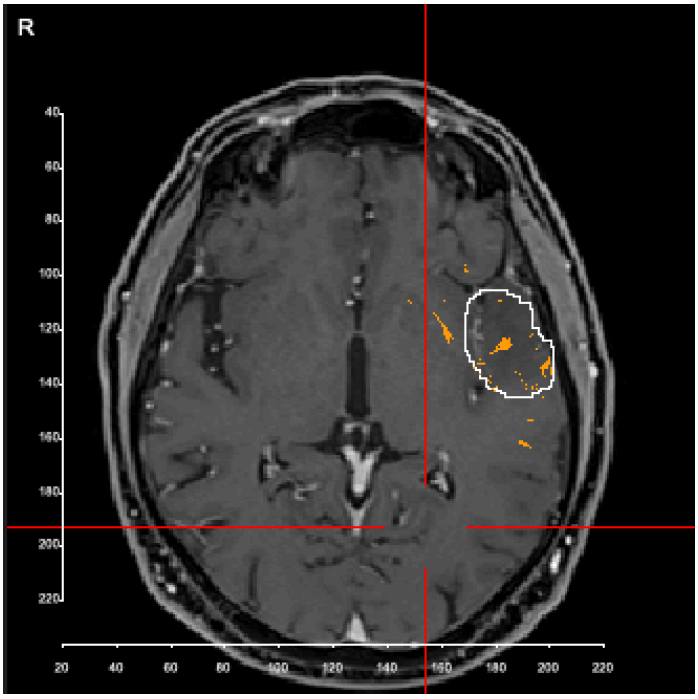


Fig. 18: The figure shows the MRI objects manually contoured (slice by slice) with a ROI positioned manually. The seed ROI was placed outlining with the tool "free-hand drawing" region to be drawn freehand" the edges of the contrast-enhancing signal around the tumor

We defined the ROIs margin based upon the tracts 'obligatory pathways, derived from literature [75], own experiences in peritumoral tractography and following the limits of the brain adjacent tumor (BAT) area.
Following the current clinical practice [55], the BAT volume was defined as the region adjacent to the gross tumor volume, which contains signal abnormalities on T2-weighted and FLAIR sequences. The minimum streamline length was set to 30 mm, and the maximum streamline length was set to 250 mm. The tractogram was examined by an experienced neurosurgeon and an experienced neuroradiologist.
The fiber tracking was filtered by the ROI at the evaluation. Unharmed and dislocated tracts were categorized as "unaffected". Then, the FA mean, FA max, FA min, MD, and Irregularity of tract (TI) values within the volumes were extracted. The deviation for each value was less than 0.006, drawn by two different operators on the two different software to ensure the cross-validity.

Treatment

All the procedures were performed with an infrared-based Neuronavigator (Brainlab, Kick® Purely Navigation), in a standard neurosurgical theatre with a standard operative

microscope. On the first postoperative day, the patients underwent a CT scan to evaluate major early complications and a volumetric Brain MRI scan to evaluate the EOR.
For all the included patients whose lesions were non-eloquently located, a standard total intravenous anesthesia protocol with Propofol (1 mg/kg) and Remifentanil (0,5 μg/kg/min) has been used.
The surgical technique to remove 100% of the mass it was accomplished with 5-ALA-guided tumor tissue elimination [22], using neuronavigation for non-enhancing residual tumors [21].

For lesions involving the motor cortices and language-related functional cortices, a standard Full Awake Surgery protocol was routinely performed with the aid of Intraoperative Neuromonitoring [76] realized with the use of bi- and monopolar stimulating probes, respectively, for the cortical and subcortical mapping. If intraoperative neuromonitoring or Awake surgery were performed, no muscle relaxants were administered.
In general, it was intra-operatively judged necessary to stop tumor excision when:
1. white matter appeared free of disease in any aspect of the surgical cavity and without 5-ALA signal,
2. despite a directly visualized or Navigation-proven remnant, neuromonitoring or intra-operative neuropsychological testing outlined a risk for postoperative motor morbidity [56].

The EOR was assessed by an experienced neuroradiologist in postoperative MRI within 72 hours.

Statistical Analysis

Statistics were performed using SPSS Statistics 25 (IBM, Armonk, NY, USA). Normality distribution was tested after D'Agostino-Pearson. Comparisons between nominal variables were made with the Chi-squared test. Comparisons between nominal and quantitative variables were made with t-students. The EOR means were compared with One-way and Multivariate ANOVA analysis, Contrast analysis, and Post-Hoc Tests. Continuous variable correlations have been investigated with Pearson's Bivariate correlation. The threshold of statistical significance was considered $p < 0.05$.

The potential source of Bias and Study size

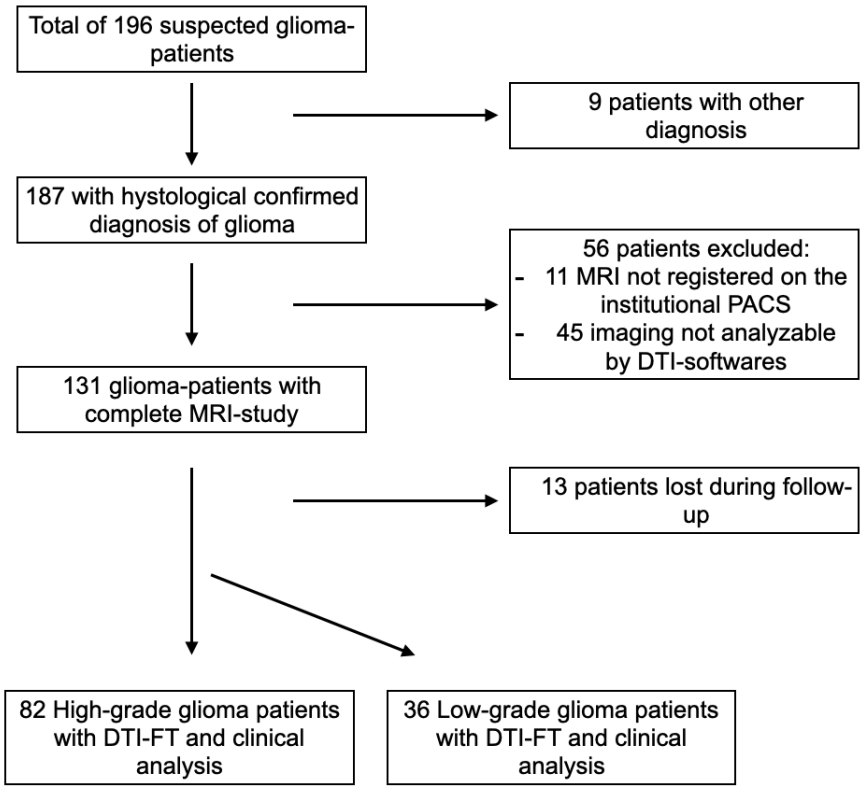
We addressed no missing data since incomplete records were exclusion criteria. A potential source of bias is expected to derive from the exiguity of the sample, which nevertheless, in regards to the endpoints selected, presents an excellent post-hoc statistical estimated power (difference between two independent means; $1-\beta = 0.9488$ for α 0.05 and effect size 0.5), thus providing extremely reliable conclusions.

The informed consent was approved by the Institutional Review Board of our Institution. Before the surgical procedure, all the patients gave informed, written, explicit consent after appropriate information. Data reported in the study have been completely anonymized. No treatment randomization has been performed for its observational nature. This study is consistent with Helsinki's declaration of Ethical principles for medical research to humans.

3.4 Results

Population study

196 patients underwent surgery for radiologically suspected intracranial gliomas between March 2021 and December 2022 in our institutions. Applying inclusion and exclusion criteria, the final collection includes 118 surgical-treated glioma patients (**Fig. 19**).



The population consisted of 78 males (66.1%) and 40 females (33.9%), with a mean age of 60.6 years (min=18, max=80). The tumors involved the frontal lobe in 68 cases (57.6%), the temporal lobe in 38 cases (32.2%), and the parietal lobe in 30 cases (25.4%). No cases of lesions involving the occipital lobe were collected. Gliomas had deep localization with ventricular involvement in 50 cases (42.4%) and superficial paracortical localization in 68 cases (57.6%). The tumors on MRI presented several morphologies with solid lesions in which the contrast enhancement or FLAIR signal was homogeneous in 67 cases (56.7%), cystic lesions in 35 cases (29.6%), and necrotic lesions in 16 cases (13.6%). We identified signs of bleeding in the tumor context in 8 patients (6.8%).
With regard to clinical onset, most patients clinically debut with seizures and/or focal deficits (both in 37 patients, 31.4%). Speech and cognitive disorders or dizziness were

found in 35 patients (29.7%). 9 patients had incidental radiological diagnosis during follow-up for other diseases or screening (7.6%). All details on patient demographics are summarized in **Table 1**.

Table 1 - Population study

Patients: 118			
Gender			
	M	78	66,1%
	F	40	33,9%
Age			
	Mean	60,6	
	Min-Max	18-80	
Lobe involvement			
	Frontal	68	57,6%
	Temporal	38	32,2%
	Parietal	30	25,4%
	Occipital	0	0%
Location			
	Deep/ periventricular	50	42,4%
	Superficial/ convexity	68	57,6%
Morphology			
	Solid	67	56,7%
	Cystic	35	29,6%
	Necrotic	16	13,6%
Hemorragic		8	6,8%
Clinical debut			
	Focal deficit	37	31,4%
	Seizure	37	31,4%
	Cognitive deficit	35	29,7%
	Incidental	9	7,6%

Radiological and clinical outcome

In the series, 82 patients were found to have high-grade gliomas (WHO 4, 69.5%), and 36 patients had low-grade gliomas (WHO 1,2,3, 30.5%). All details on series data are summarized in Table 2.

Table 2 - Outcome and Values

Patients: 118			
Grading			
	High-Grade	82	69,5%
	Low-grade	36	30,5%
Tumor volume (mm3)	Mean	29,1	
Edema volume (mm3)	Mean	26,05	
Tumor-edema ratio	Mean	1459	
Extent of resection	GTR	53	44,9%
IDH		37	31,4%
ki67%	Mean	27%	
EGFR expression		18%	
P53 overexpressed		25	21,2%
KPSpre	Mean	85	
KPSpost	Mean	80	
KPSfu	Mean	65	
PFS	Mean	20	
OS	Mean	27	
FAmean		0,248	
FAmax		0,523	
FAmin		0,1	
MD		1,52	
Irregularity of tract		10,41	

The mean tumor volume was 29.1 cm^3 with no significant differences regarding grading (26.9 cm^3 in high-grade gliomas and 34.1 cm^3 in low-grade gliomas, respectively, p=0.22). The mean volume of PBE was 26.05 cm^3 in this case, with a significant difference between high-grade and low-grade tumors (28.8 cm^3 versus 14.9 cm^3, respectively, p=0.05). There were no significant differences in tumor-edema ratio (310 versus 180, p=0.25). Immunohistochemically, the mean percentage of ki67 is 27%, with a significant difference between grading (35% in high-grade gliomas and 7.5% in low-grade, p<0.001, respectively). EGFR is expressed in 18% of the population, and p53 was over-expressed in 25 patients (21.2%), both in the high-grade gliomas group.

From the clinical outcome point of view, patients had a mean preoperative KPS of 85 with no significant difference in grading (85 for high-grade gliomas versus 90 for low-grade, p=0.12).

The mean KPS had significant differences between the two groups of tumors at postoperative (80 versus 90), post-adjuvant therapy (80 versus 90), and at the last follow-up (65 versus 90), with high-grade tumors presenting consistently lower values. High-grade glioma patients presented a mean PFS of 8 months after surgery versus 26 months for low-grade glioma patients. OS shows a mean of 15 months for high-grade after the procedure versus 48 months for low-grade (indicating that of the series at final evaluation, 80% of patients were alive). Group analysis details are summarized in **table 3**.

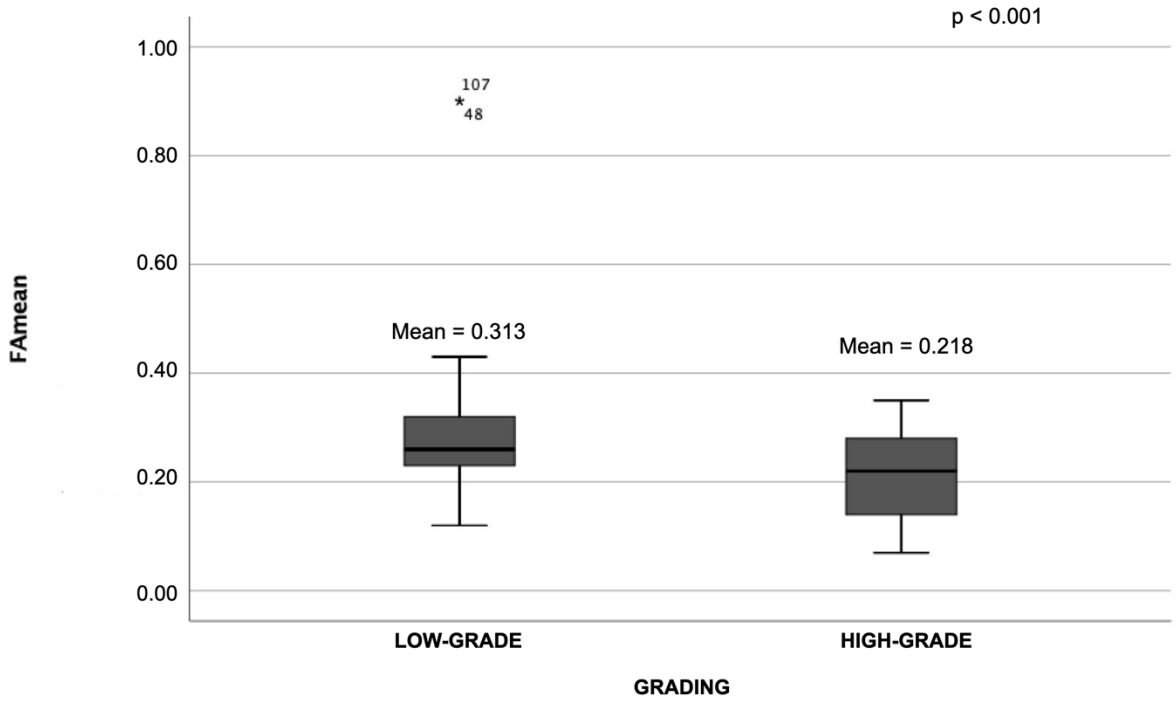
Table 3

		High-grade (82)	Low-grade (36)	P-value
Gender				
	M	58	18	
	F	24	16	
Age				
	Mean	63,5	54	
Lobe involvement				
	Frontal	46	20	
	Temporal	30	8	
	Parietal	20	8	
	Occipital	0	0	
Location				
	Deep/ periventricular	38	12	
	Superficial/ convexity	44	24	
Morphology				
	Solid	40	30	
	Cystic	28	6	
	Necrotic	14	0	
Hemorragic				
Clinical debut				
	Focal deficit	26	8	
	Seizure	28	17	
	Cognitive deficit/ language	8	28	
	Incidental	28	8	
Tumor volume (mm3)	Mean	26,9	34,1	0,22
Edema volume (mm3)	Mean	28,8	14,9	0,05
Tumor-edema ratio	Mean	310	180	0,25
Extent of resection	GTR	42	16	
ki67%	Mean	35	7,5	<0,01
KPSpre	Mean	85	90	0,12
KPSpost	Mean	80	90	0,03
KPS post-RT		80	90	0,02
KPSfu	Mean	65	90	0,001
PFS	Mean	8	26	<0,01
OS	Mean	15	48	<0,01
FAmean		0,218	0,313	0,01
FAmax		0,53	0,51	0,6
FAmin		0,10	0,12	0,6
MD		1,12	0,87	0,05
Tract irregularity (TI)		11,14	8,44	0,05

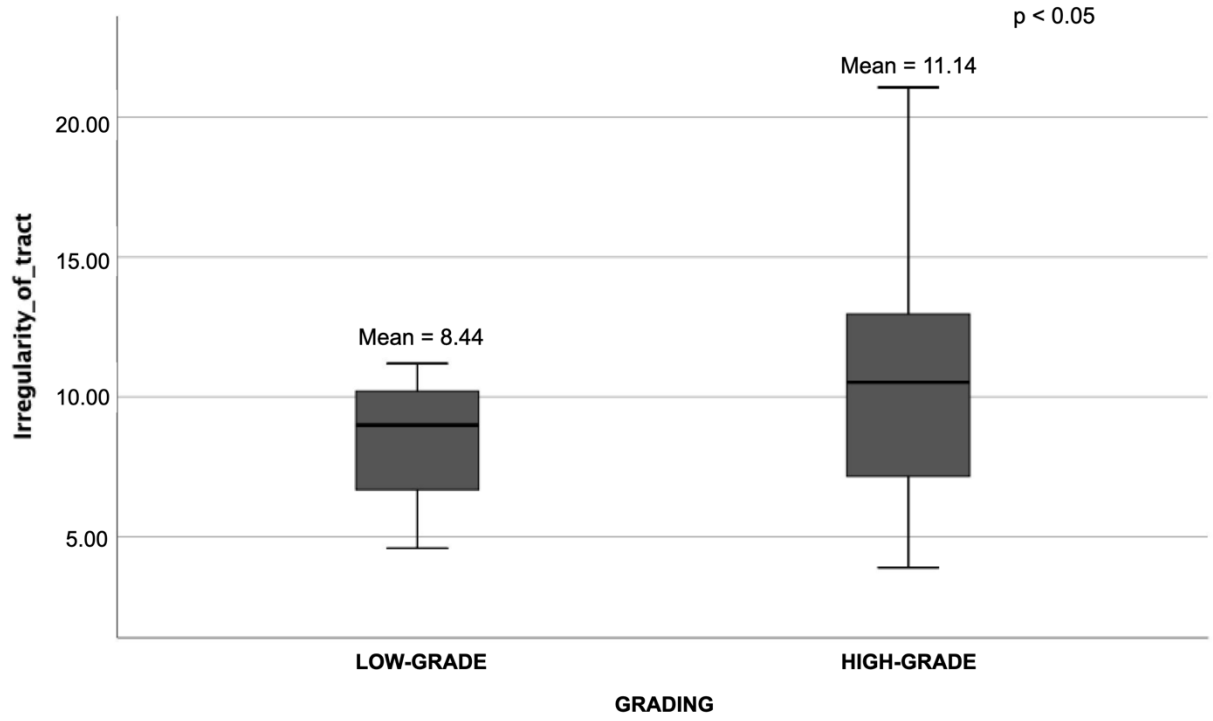
Analysis of quantitative tractography parameters

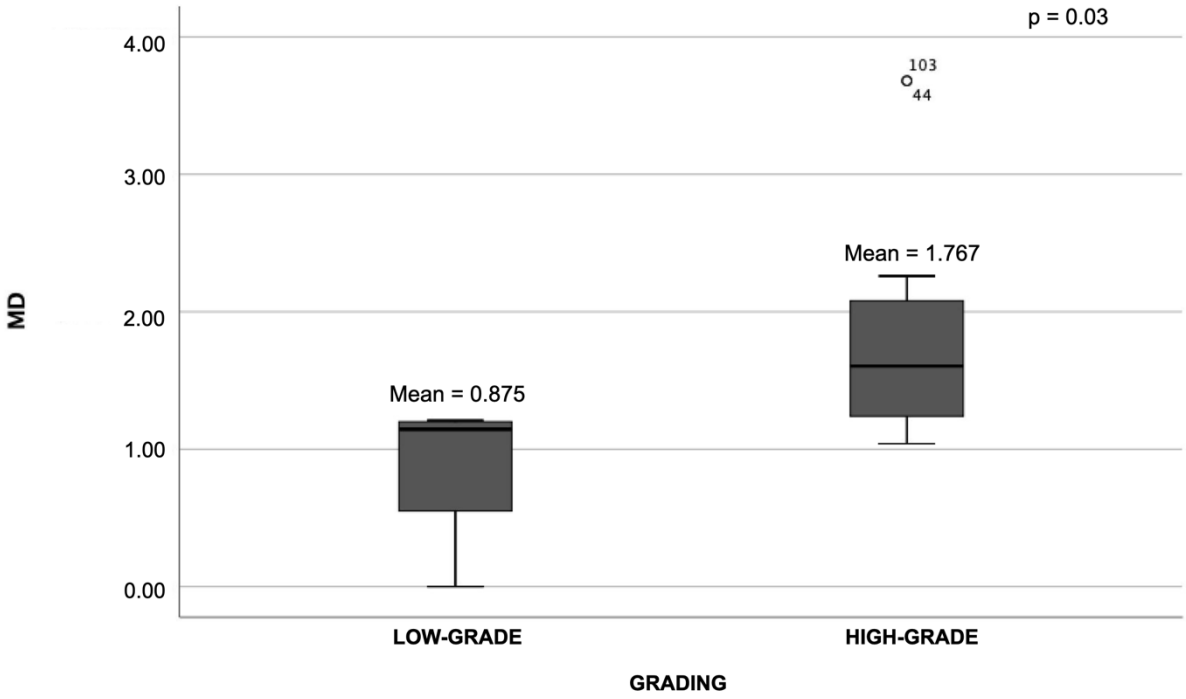
We examined the values of FA mean, FA max, FA min, MD, and TI grade measured at the level of the through fibers around of the tumor lesion, comparing it with the surgical series' clinical, radiological, and outcome parameters.

We identified that there is a significant inverse relationship between the FA mean value and grading (FA mean 0.313 for low-grade gliomas versus FA mean 0.218 for high-grade gliomas, p=0.001), showing that a low-grade lesion is likely to result in greater distortion of WM fibers than the aggressive high-grade gliomas. **Graph 1**



In contrast, the relationship appears to be directly proportional regarding MD values (0.875 in low-grade gliomas versus 1.767 in high-grade gliomas, p=0.003, **Graph 2**) and TI values (8.44 in low-grade gliomas versus 11.14 in high-grade gliomas, p=0.005, **Graph 3**).

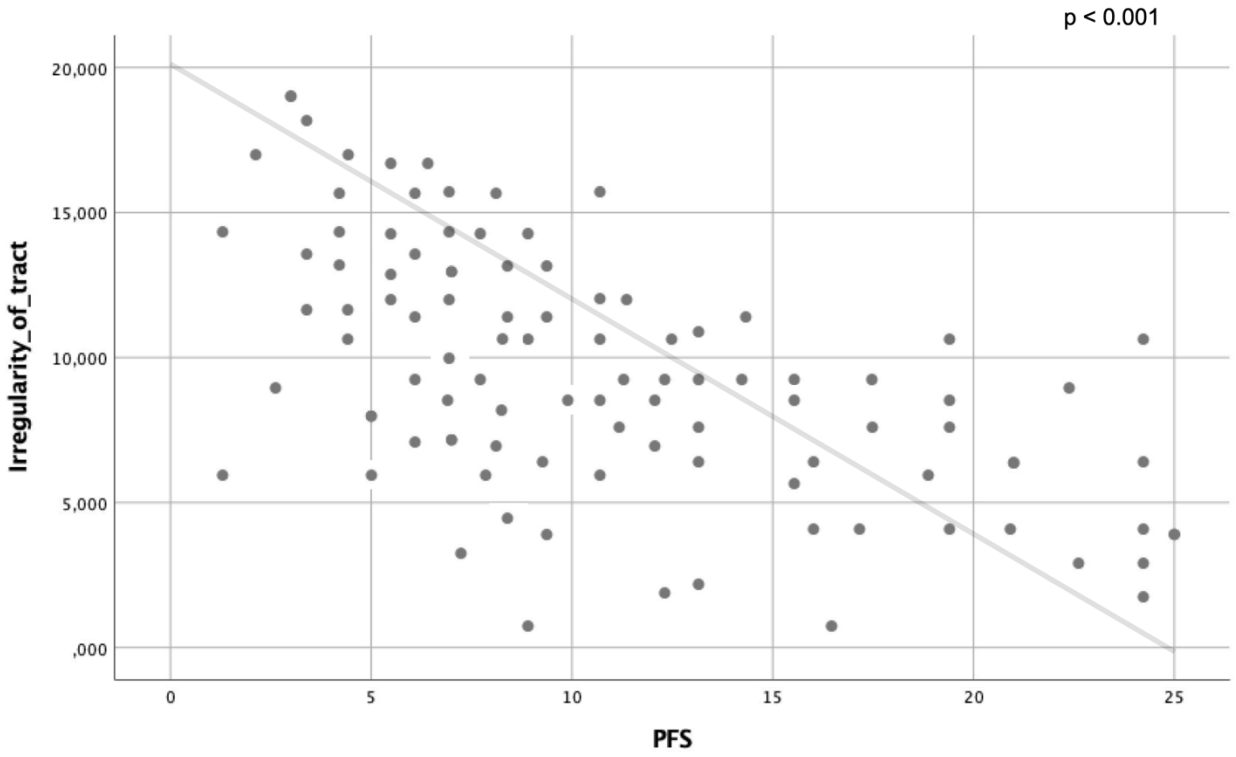




We evaluated, in a multivariate analysis, the other parameters that may affect these values, such as tumor size, PBE volume and ratio, surgical site, and lesion features (solid, cystic, and necrotic).

There were no significant differences between FAmean, MD, and TI values regarding the surgical site and tumor characteristics such as hemorrhage, necrosis, and cystic aspect (p=1). On the other hand, with regard to tumor size and especially PBE, it shows that FA

mean and MD values are susceptible to significant variations with a linear correlation between FA and tumor and edema volume (p=0,05) and MD and edema volume (p=0,06). In this evaluation, FA mean and MD values correlate with each other in a significant proportional manner (p=0.02).
The only value that showed an independent relationship with the degree of aggressiveness of the tumor regardless of tumor radiological features and dimensions is TI, which has a direct relationship with grading, ki67% (p=0,05), and PFS (p<0.001, **Graph 4**).

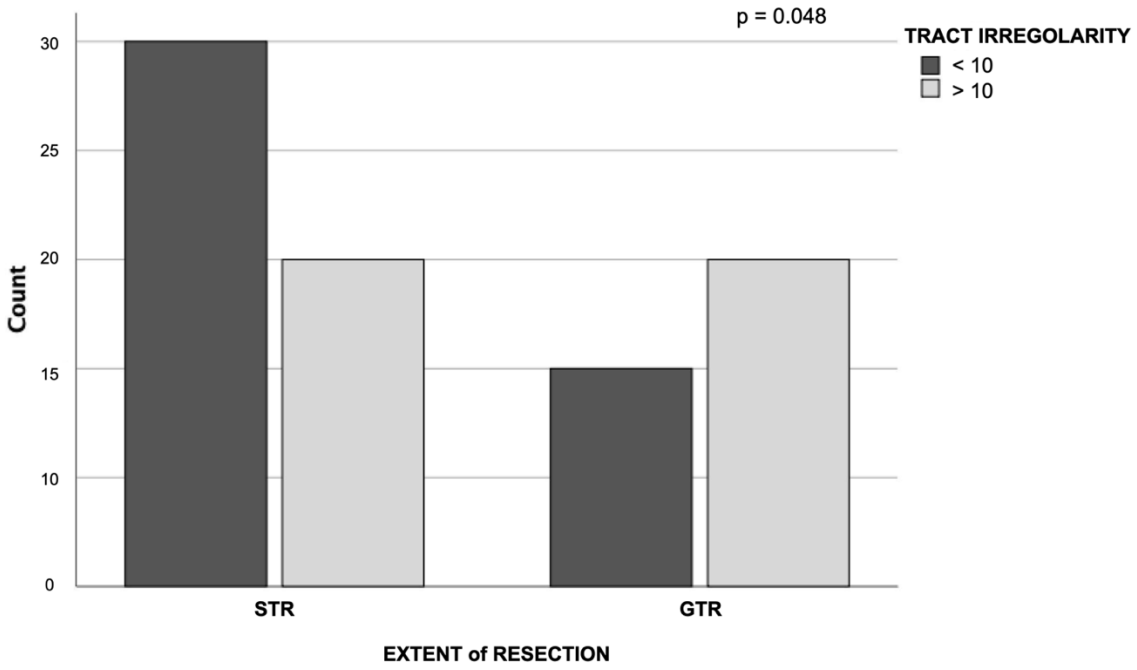


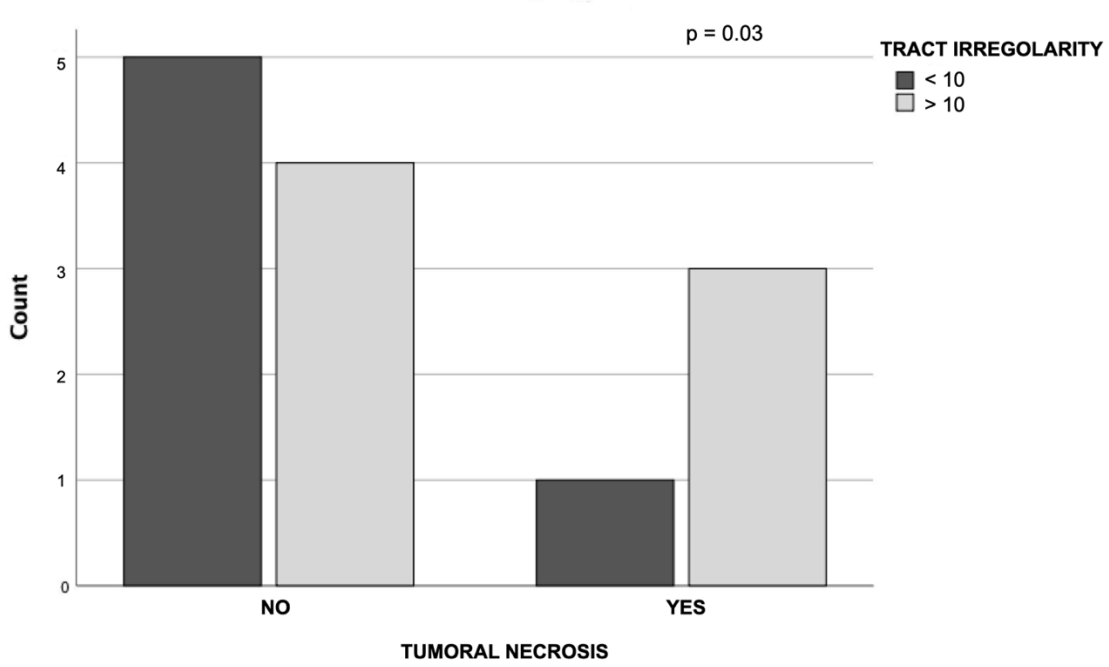
Tracts irregularity analysis

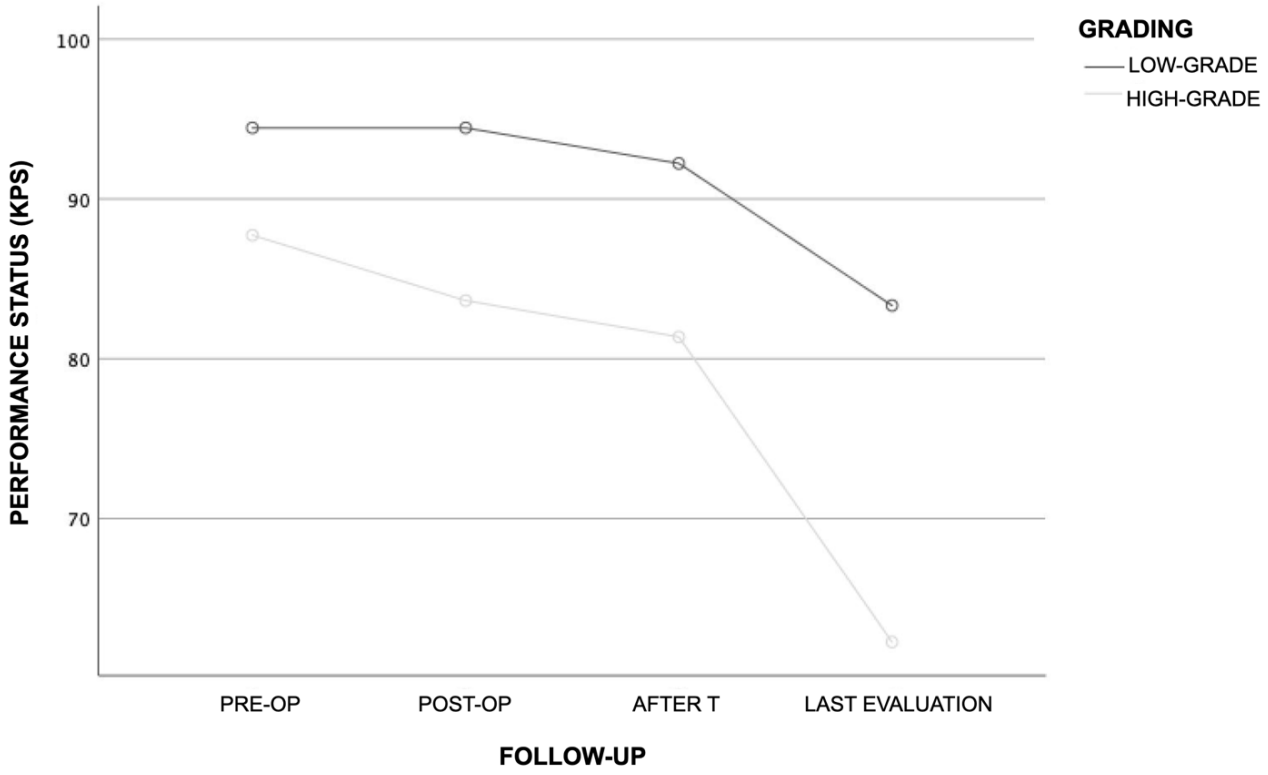
We hypotheses that TI could be an indirect measure of WM alteration and degradation with regard to fibers that are still present and recognized by tractography but are impaired and probably nonfunctional.
We, therefore, related TI values to EOR. In particular, considering only low-grade tumors, there is a significant relationship between TI value and EOR with a higher percentage of GTR for higher TI values (Mean 11.2 for GTR versus Mean 8.9 for NTR, p<0.01). This is probably because high TI values correspond to areas of altered WM texture and density capable of guiding the surgeon into marginal resection.
WM enveloping the tumor and distorting its neighboring bundles in terms of obvious high TI values also has a significant clinical impact on tumor onset with seizures (patients with

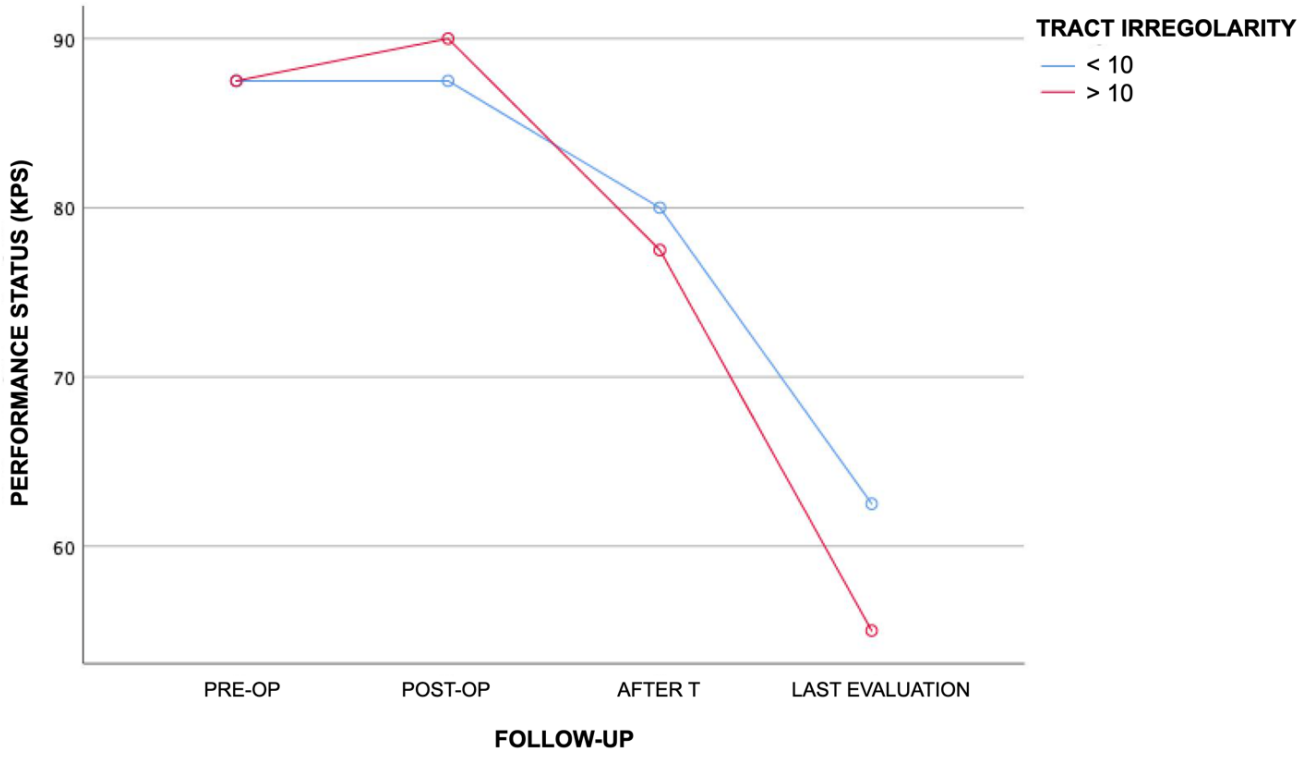
clinical onset of seizure have TI mean 14.46 compared to focal onset or incidental diagnosis with TImean= 7.98)

We identified 10 as the threshold value of TI and performed binomial analysis on the clinical and outcome parameters. We showed that high TI (>10) correlates with greater tumor aggressiveness (with high correlation with the presence of intratumoral necrosis, p=0,03. Graph 5), achievement of GTR (p= 0.048), Graph 6) obvious reduction in patient performance status during follow-up and in PFS in a similar manner of grading (**graph 7A and B**).






GRADING
LOW-GRADE
HIGH-GRADE
PERFORMANCE STATUS (KPS)
100
90
80
70
PRE-OP
POST-OP
AFTER T
LAST EVALUATION
FOLLOW-UP


TRACT IRREGOLARITY
< 10
> 10
PERFORMANCE STATUS (KPS)
90
80
70
60
PRE-OP
POST-OP
AFTER T
LAST EVALUATION
FOLLOW-UP

3.5 Discussion

Gliomas are intra-axial infiltrating brain tumors, whereas the boundaries within the perilesional WM are difficult to define [26]. It is accepted that the best prognosis can be reached by aiming at the most radical tumor resection possible and preserving a good postoperative neurological status [68,77]. Consequently, the EOR within the possibly infiltrated but normal-appearing brain tissue must avoid damaging critical normal functioning cortical areas and their WM connections.
In the glioma imaging study, DTI-FT offers an optimal visualization of WM tracts, revealing infiltration and displacement by the tumor to hypothetically inform surgical planning (**Fig. 19**).

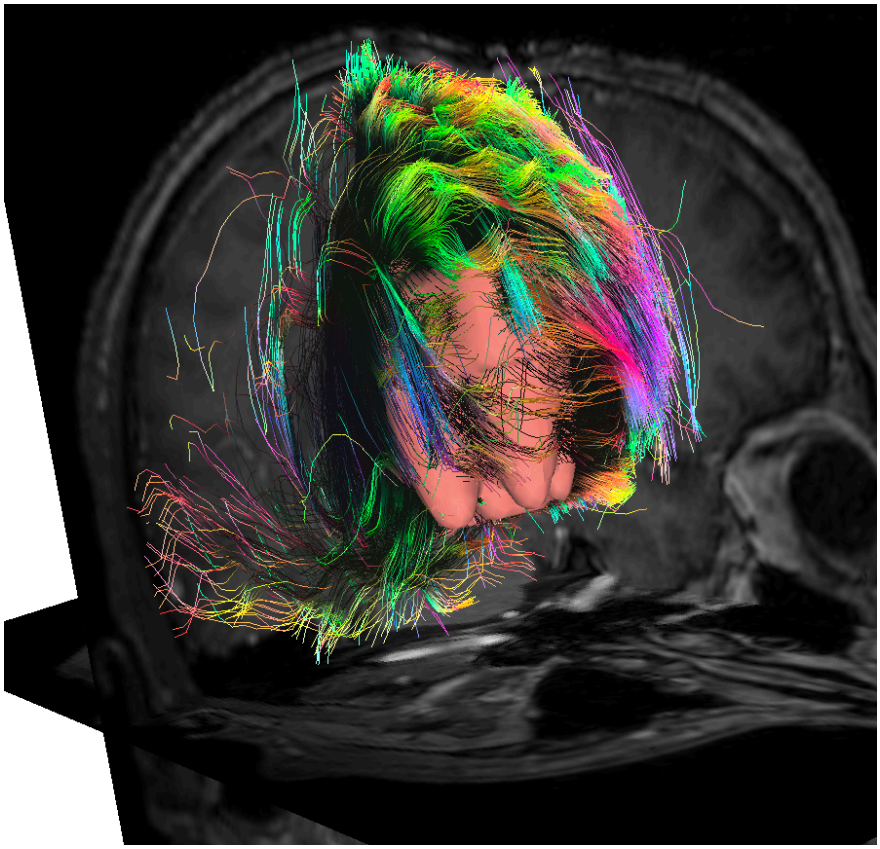


Fig. 19 The image show a DTI-FT reconstruction from our series with WM-fibers around the lesion

Until now, tractography has been considered a descriptive imaging modality and less a functional and operative tool [78].
Recent research [55,71] diverted their attention on DTI-FT analysis to the periphery of the glioma, claiming that the BAT contained a considerable amount of preserved but altered fiber tracts with less infiltration and disruption. The basic hypothesis is that DTI metrics around solid tumors are determined by a balance between factors that increase the degree

of directionality of water diffusion (the "anisotropy"), such as high cellularity [33] and/or vascularization [36], and factors that decrease the degree of directionality, such as fiber destruction or infiltration [55]. The use of diffusion metrics promises to make DTI-FT a grading-predictive tool and a more precise aid in guiding the EOR by studying the BAT area.
We described here the first prospective clinical study that follows the progress of patients treated for glioma and evaluates the predictive value of DTI metrics measured around the tumor.

Histologically, it is well known that tumor cell density decreases up to several centimeters from the macroscopic tumor volume, and previous analyses [47] have shown that high fiber density values are inversely correlated with tumor cell number and infiltration into the macroscopic tumor volume. In the BAT, the density of DTI fibers correlates with the mean FA value, which reflects the directionality of brain fiber tracts and correlates with their density and proliferation activity [54].
We identified that the FA mean value tends to decrease in the area around the tumor in the HGGs (without ever reaching value=0) while the value of MD tends to increase.
With these results, we confirmed the hypotheses previously posed by several nonclinical functional studies [55,70] that supported the possibility that FA mean tended to be significantly higher in the LGG than in the HGG, hypothesizing that this was due to greater heterogeneity of solid parts within the latter. The inverse relationship between the FA mean value and grading demonstrates that an LGG is likely to result in greater distortion of WM fibers than the HGG. In HGG, though there was the destruction of WM fibers causing the decrease of FA compared with normal-appearing WM, its value did not decrease to extremely low because the increase in cell density and vascularity gave directionality to the water diffusion in extracellular space resulting in compensation of decreased FA (thus eliminating the possibility of obtaining a false negative response); on the contrary in LGG, cells were loosely and randomly arranged in fibrillary matrix, where water diffused almost freely in all direction thus leading to the significant increase of FA. Besides, increased MD would be correspondingly observed due to the increased extracellular spaces and decreased cellularity [33].

The main reliability problem of the DTI metric statistical descriptors [67] is that the extent of fiber density, directionality, and distortion is greatly affected by several variables, including tumor volume, brain edema, and the tumor site location. If, for the large projection fibers, the alteration and distortion entity turns out to be intuitable from a quantifiable clinical symptom (the neurological deficit from pyramidal bundle injury, for

example), it is not so simple for an association tract that surrounds the tumor and may be involved in superior cognitive function. With this study, we show that glioma size and edema are correlated with FA mean and MD, and we confirm in part the results of the study by Kinoshita et. al [68] who had found that an apparent diffusion coefficient in regions of tumor infiltration largely affected these variables.
Research on the combination of DTI and MR spectroscopy suggested that FA was uncorrelated and even contradictorily higher in LGGs [56], while ADC value correlated significantly with histologic grading and lower ADC indicated HGG, concluding that DTI may not be useful for preoperative differentiation precisely because of the presence of variable PBE volume [70].

This has led some researchers to detect other metrics that improve the study of tumor boundaries and infiltration. With the introduction of the shape metrics, Yeh FC [66] introduced an interesting quantification of WM tracts around a ROI to better investigate the shape characteristics of the human association pathways, permitting the study of the extent of distortion of fibers in relation to tumor and edema volumes [31].
Specifically, the TI value [66] could potentially be helpful for tumor grading and surgical planning, which seems more objective and validatable. TI demonstrated an independent relationship with the degree of aggressiveness of the tumor regardless of tumor radiological features and dimensions, also showing a relationship with grading, ki67% (the main marker of proliferation cellular index), EOR, and PFS. We also find it very interesting that at high TI values (with an identified threshold of 10), there were more patients in our case series who achieved a GTR. This, in our opinion, suggests that likely areas around the tumor with high WM irregularity are more likely to be appreciated as phenotypically altered by the surgeon, who is more likely to proceed with resection. We suggest that a high TI value corresponds to areas of altered WM consistency that favor the surgeon to provide a larger excision by obtaining GTR results more frequently (Fig. 20). Further, TI values correlate inversely with PFS, suggesting that it is an indirect measure of microscopic tumor infiltration.

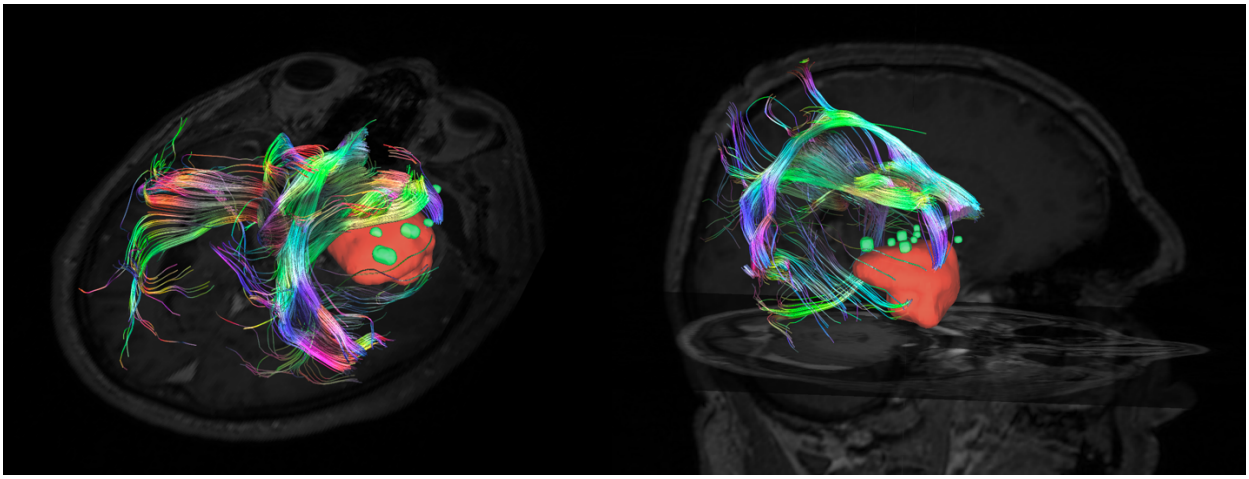


Fig. 20 In this figure we showed with green-dotted signs the area of major TI around the tumor that hypothetically could be safety debulk during surgery

In conclusion, DTI-based analysis remains a challenging technology based on complex data acquisition and geometrical models that rely on many assumptions. Methodological and artificial aspects can provide erroneous diffusion measurements that do not appropriately reflect microstructure information and may finally lead to misinterpretation of the results [56,57];

DTI fiber-tracking parameters and shape metrics used together promise a quantitative value in preoperatively predicting the EOR, giving patients a more informed prognosis of their surgical outcome [51]. We believe that DTI-based functional neuronavigation helps to plan aggressive resection of DTI-FT-defined abnormalities [24] and can offer precise intraoperative imaging guidance to achieve a greater chance of improving progression-free and overall survival [79] (**Fig. 21**).

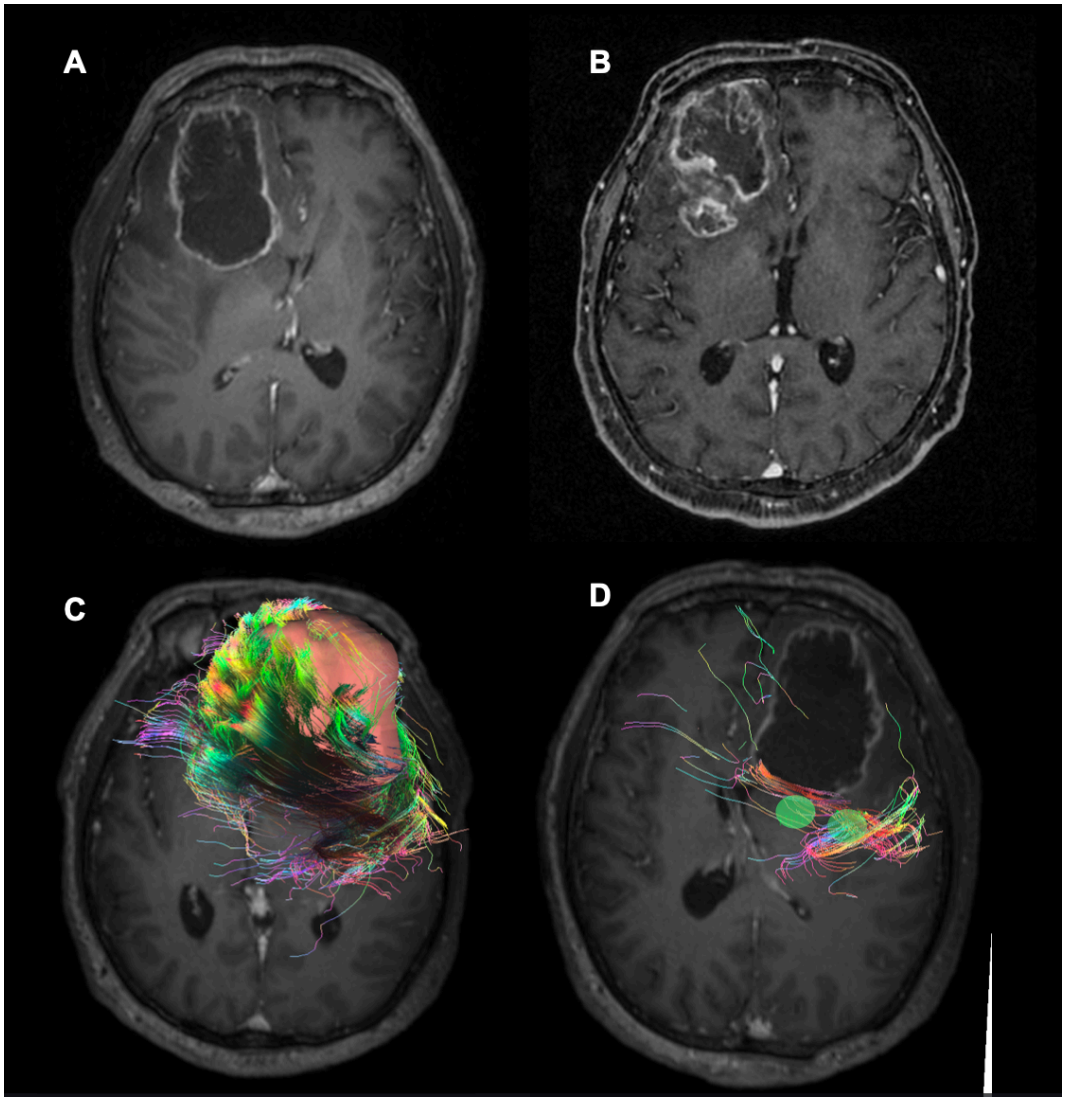


Fig. 21 We present an illustrative case of a 57-year-old patient treated surgically with total excision of a right frontal glioblastoma (A) who experienced disease recurrence 7 months after diagnosis (B). In a retrospective analysis of pre-operative DTI, we note very low mean values of FA (mean 0.004) and high mean values of MD (mean 0.45) and TI (mean 7.022) around the tumor (C). If we mark the areas of highest expression of TI (green areas) we observe that they are located right at the point of highest growth of recurrence and where the bundles are most irregular (D).

The value of TI, combined with FA mean and MD parameters, measured at different locations of some small ROIs positioned around the tumor, could easily suggest the areas of apparently intact WM that can be resected without leading to significant functional impairment in the patient.

Under this aspect, the growing interest in artificial intelligence methods could enable the detection of real tumor boundaries, suggesting an optimal topographically directed molecular analysis of tissue, and planning follow-up strategies of treatments [55]. Further recent studies evaluated the application of augmented reality for WM analysis finding a generally positive response and potential clinical uses dependent upon the future developments of the system [80].

3.6 Further studies and limitations

The main limitation of this study is that it is a nonrandomized observational study with a limited number of patients. Although highly valued for its clinical applications, the validity of quantitative measurement of various DTI metrics is impaired by several factors: for example, the echo-planar imaging sequence used for DWI acquisition is subject to many artifacts. Therefore, the application of quality control tools to correct the raw DWI data is recommended as a first step before post-processing procedures in any DTI study. In addition, there appears to be some variability in the metrics results processed by the different software available for research [56]. We have observed, using two of the major software available for studying diffusion metrics (Brainlab I-plan and DSI studio), that the differences in the values are small and negligible; however, we believe that other software may actually provide more variability in the results. It is critical that clinicians know the limitations and potential pitfalls inherent in this technique when making clinical decisions based on DTI in glioma management.

3.7 Conclusion

In contrast to other functional imaging techniques not routinely used for clinics, DTI has gradually been considered a standard application in combination with structural imaging for glioma patients 'diagnosis and surgical planning. This is the first study to analyze the predictive value of key quantitative parameters of DTI, such as FA mean, MD in relation to tumor volumes, edema and patient outcome, showing that these factors need to be considered together to be standardized for future studies and suggesting the use of TI as main shape metric to add its specificity and improve surgical resection.

3.8 Disclosures

Data Availability

The dataset generated and analyzed during the current study is not publicly available or retrieved for National databases because it results from institutional internal research of all treated cases of gliomas in our Hospitals (Policlinico Umberto I of Rome and Molinette

Hospital of Turin). The original dataset is available from the corresponding author upon reasonable request.

Compliance with ethical standards

Funding: This study was not funded by any association.

Conflict of Interest: We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
This article does not contain any studies with animals performed by any of the authors.

Informed consent: Informed consent was obtained from all individual participants included in the study. The patient has consented to the submission of this review article to the journal.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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