Thesis

Surgery of Intrinsic Brain Tumors in the Superior Frontal Gyrus

submitted by

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Zusammenfassung

Hintergrund

Der Gyrus frontalis superior (SFG) beherbergt die supplementär-motorische Region (SMA), die für die Planung, Initiierung und Ausführung von Sprache und Motorik von entscheidender Bedeutung ist und maßgeblich in kognitive/neuropsychologische Schaltkreise eingebunden ist. Aufgrund der weitreichenden Vernetzung des SFG und der SMA stellt die Resektion hirneigener Tumoren eine signifikante Herausforderung dar, um postoperative Defizite weitgehend zu vermeiden bzw. zu minimieren. Ziel dieser Studie war es, die transienten und permanenten neuro(psycho)logischen Defizite von Patient*innen mit hirneigenen Tumoren im SFG zu untersuchen. Hierbei lag der Schwerpunkt auf dem transienten Charakter des SMA-Syndroms und auf der Korrelation zwischen verschiedenen Parametern und dem Bestehen von postoperativen neuro(psycho)logischen Defiziten.

Methoden

Die Datenerhebung erfolgte mittels retrospektiver Krankenaktendurchsicht der behandelten Patient*innen. Zu den erhobenen Daten gehörten das präoperative Tumorvolumen, die Seite des Tumors, die Art der Operation (wach oder unter Allgemeinanästhesie), der WHO ZNS Grad, der Karnofsky Performance Status (KPS), sowie die Wiederaufnahme der präoperativ durchgeführten beruflichen Tätigkeit. Exakte Tests nach Fisher, Chi-Quadrat-Unabhängigkeitstests und binäre logistische Regressionsmodelle wurden verwendet, um statistisch signifikante Korrelationen zu analysieren. *P*-Werte < 0.05 wurden als statistisch signifikant beurteilt.

Ergebnisse

Es wurden 31 Patient*innen, die zwischen 2018 bis 2023 aufgrund eines Tumors im Gyrus frontalis superior operiert wurden, eingeschlossen. Davon hatten 21 (67,7%) Patient*innen einen linksseitigen und zehn (32,3%) einen rechtsseitigen Tumor. Einundzwanzig (67,7%) Patient*innen wurden mittels Wachoperation operiert, die übrigen zehn (32,3%) wurden unter Allgemeinanästhesie operiert. Die Analyse der transienten und permanenten neuro(psycho)logischen Defizite zeigte keine statistisch signifikanten Korrelationen mit dem präoperativen Tumorvolumen oder der Seite des Tumors. Auch gab es keinen statistisch signifikanten Zusammenhang mit der Resektion des Gyrus frontalis medius (MFG), des Gyrus cinguli (CG) oder von Fasern des Corpus callosum (CC). Die Art

der Operationen (p = 0,027) und WHO ZNS Grad (p = 0,028, p = 0,044) präsentierten sich hingegen als statistisch signifikante Prädiktoren, vor allem permanente neuro(psycho)logische Defizite betreffend.

Schlussfolgerungen

Diese Studie hat den transienten Charakter des SMA-Syndroms untermauert und die Bedeutung von Wachoperationen bei der Behandlung von hirneigenen Tumoren hervorgehoben. Dies gilt vor allem, um postoperative neuro(psycho)logische Defizite zu minimieren bzw. zu vermeiden und somit ein optimales Gleichgewicht zwischen neuroonkologischen Ergebnissen und gesundheitsbezogener Lebensqualität zu gewährleisten.

Abstract

Background

The superior frontal gyrus (SFG) is home to the supplementary motor area (SMA), which is essential in the planning, initiation and execution of language and motor function, and is heavily involved in cognitive / neuropsychological circuits. Due to the vast interconnectedness of the SFG and SMA, resection of intrinsic brain tumors thus poses a significant challenge to avoid surgically induced morbidity and postoperative deficits. The aim of this study was to explore transient and permanent neuro(psycho)logical outcomes of patients with primary brain tumors in the SFG, particularly focusing on the transient nature of the SMA syndrome and assessing the correlation of varying parameters and the subsequent development of postoperative neuro(psycho)logical deficits.

Methods

Data were gathered by means of retrospective chart review. Data evaluated included preoperative tumor volume, tumor laterality, type of surgery (awake versus asleep), WHO CNS grade, Karnofsky Performance Status (KPS) and return to work. Fisher's Exact Tests, Chi-Square tests of independence, and binary logistic regression models were used to assess statistically significant correlations. *P*-values < 0.05 were considered statistically significant.

Results

Thirty-one patients were included from 2018 to 2023, 21 (67.7%) with left-sided tumors, ten (32.3%) with right-sided tumors. Twenty-one (67.7%) patients underwent awake surgery, ten (32.3%) were operated on asleep. Examining neuro(psycho)logical deficits, there were no statistically significant correlations with preoperative tumor volume, laterality, resection of the middle frontal gyrus (MFG), cingulate gyrus (CG), or fibers of the corpus callosum (CC). Type of surgery ($p = 0.027$) and WHO CNS grade ($p = 0.028$, $p = 0.044$) were statistically significant predictors, especially for permanent deficits.

Conclusions

This study has underscored the transient nature of the SMA syndrome and reiterated the importance of awake surgery for primary brain tumors, especially to mitigate postoperative neuro(psycho)logical deficits to ensure the best balance between neurooncological outcome and health-related quality of life.

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List of Abbreviations

CT	Computed Tomography
MRI	Magnetic Resonance Imaging
AZ	Astrocytoma
ODG	Oligodendroglioma
GB	Glioblastoma
EP	Ependymoma
CNS	central nervous system
LGG	low-grade glioma
HGG	high-grade glioma
WHO	World Health Organization
MGMT	O^6-methylguanine-DNA methyltransferase
CSF	cerebrospinal fluid
5-ALA	5-Aminolevulinic acid
ioNM	intraoperative neuromonitoring
ioNN	intraoperative neuronavigation
ioMRI	intraoperative MRI
PpIX	protoporphyrin IX
PNS	peripheral nervous system
SSEPs	Somatosensory Evoked Potentials
MEPs	Motor Evoked Potentials
BAEPs	Brainstem Evoked Potentials
VEPs	Visual Evoked Potentials
EMG	electromyography
EEG	electroencephalography
DW-MRI	diffusion-weighted MRI
DTI	diffusion tensor imaging
CSD	constrained spherical deconvolution
EBRT	conventional fractionated external beam radiotherapy
IMRT	intensity-modulated radiotherapy
TMZ	temozolomide
CCNU	lomustine
PCV	procarbazine, lomustine (CCNU) and vincristine

SFG	superior frontal gyrus
MFG	middle frontal gyrus
IFG	inferior frontal gyrus
SFS	superior frontal sulcus
IFS	inferior frontal sulcus
PrCG	precentral gyrus
PCG	postcentral gyrus
PrCS	precentral sulcus
CS	central sulcus
SMA	supplementary motor area
MFG	middle frontal gyrus
CC	corpus callosum
CG	cingulate gyrus
mRS	Modified Rankin Scale
KPS	Karnofsky Performance Status
TN(P)D	transient neuro(psycho)logical deficits
PN(P)D	permanent neuro(psycho)logical deficits
OAZ	Oligoastrocytoma
GTR	gross total resection
STR	subtotal resection
FAT	frontal aslant tract
SLF-I	superior longitudinal fasciculus I
TMS	transcranial magnetic stimulation

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I. Introduction

i. Intracranial tumors

Intracranial tumors represent a category of neoplasms that describes a heterogenous ensemble of tumors, which are often grouped together despite their significant differences in etiology, treatment, and prognosis. Furthermore, they are poorly understood by patients and their relatives, regularly causing anxiety about associated morbidity, mortality and lethality. Consequently, the clear definition of the various subgroups of intracranial tumors is of vital importance to adequately inform patients and their families about the best course of treatment and to provide a truthful prognosis.

Intracranial tumors can largely be separated into two groups:

- Extra-axial tumors
- Intra-axial tumors

Extra-axial tumors (Figure 1) describe neoplasms that are external to the brain parenchyma, while intra-axial tumors are located within the brain tissue itself. Common examples of extra-axial tumors include meningiomas, pituitary tumors, and cranial nerve tumors such as vestibular schwannomas. Metastases of extra-cranial neoplasms and intrinsic brain tumors belong to the group of intra-axial tumors (Figure 2).

Figure 1 – Extra-axial tumors

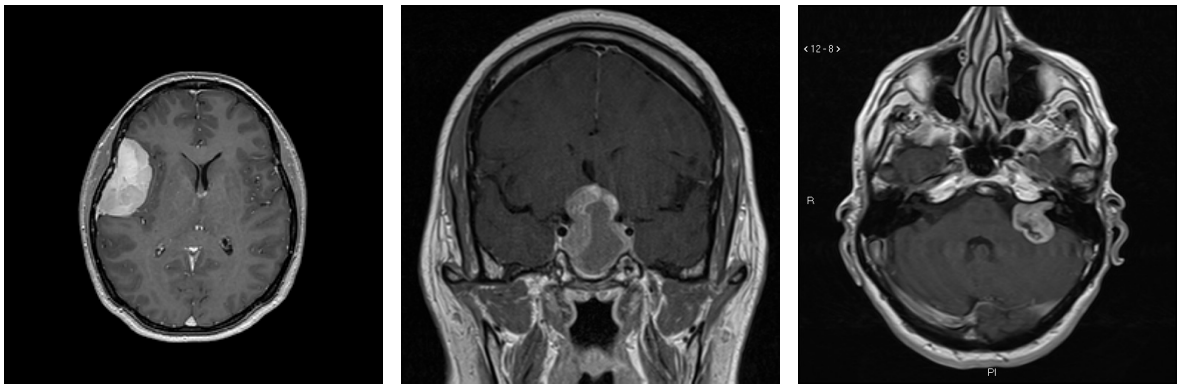

Figure 1. Extra-axial tumors are shown. The pictures show a meningioma (left (1)), a pituitary adenoma (middle (2)), and a vestibular schwannoma (right (3)).

Figure 2 – Intra-axial tumors

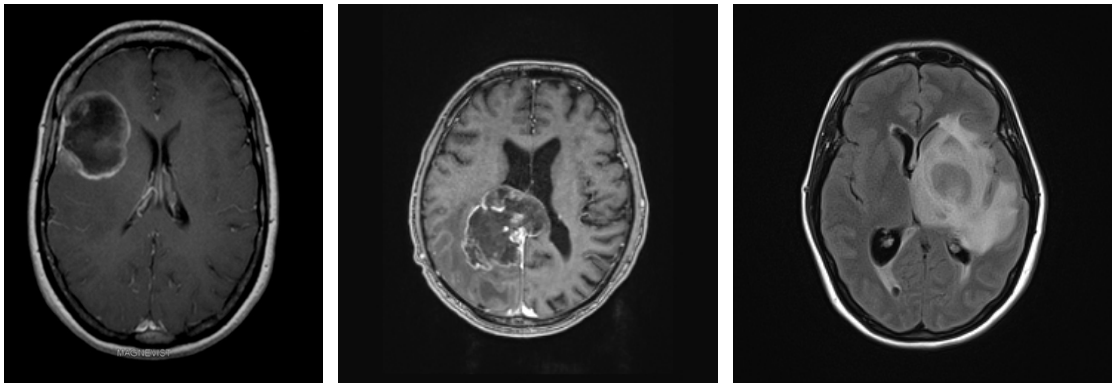

Figure 2. Intra-axial tumors are shown. The pictures show a metastasis from lung cancer (left (4)), a glioblastoma (middle (5)), and a central nervous system (CNS) lymphoma (right (6)).

Due to the heterogeneous etiology of intracranial tumors, their treatment, outcome and prognosis vary widely. Depending on tumor entity, histopathological and molecular pathological features, current symptoms, patients' age and comorbidities, careful consideration must be placed on the implementation of the correct treatment modalities. For instance, stable or slow-growing meningiomas diagnosed incidentally can be clinically and radiologically observed, not necessitating immediate treatment and leading to no reduction of life expectancy. In contrast, low-grade gliomas (LGG) and high-grade gliomas (HGG) generally should be surgically resected wherever possible as this can decrease current symptoms and increase overall survival if a certain resection threshold is reached (7, 8). Due to the location of some gliomas or patients' age or comorbidities, surgery is not always advised. In these cases, radiotherapy and/or chemotherapy may be a viable alternative treatment modality. Depending on the WHO CNS grade of gliomas, life expectancy can vary widely from ten to 15 or more years in the case of well-controlled LGG (7, 9, 10) to just a few months in aggressive progressed HGG (11, 12).

Nevertheless, intracranial tumors may present very similarly clinically regardless of the type of tumor patients are diagnosed with. Common symptoms and reasons for initial clinical consultation can be divided into three categories: category one includes nonspecific symptoms such as headaches, vertigo, fatigue, nausea, and vomiting, or reduction of cognitive capacity. Category two includes focal neurological symptoms such as focal or generalized seizures, sensorimotor deficits, worsening or loss of vision or field of vision, speech difficulties, language difficulties (motor or sensory aphasia, dyslexia, dysgraphia). The third category includes neuropsychological disorders such as working memory problems, short term memory problems, and personality changes.

Despite the variety of possible symptoms that intracranial tumors can cause, a considerable number of patients are, in fact, asymptomatic, and the diagnosis of their intracranial tumor is based on an incidental finding on either a Computed Tomography (CT) scan or a Magnetic Resonance Imaging (MRI) scan (13).

ii. Intrinsic brain tumors

A subgroup of intra-axial intracranial tumors are intrinsic brain tumors, which, like cerebral metastases, are located within the brain tissue itself, but in contrast, directly arise from brain tissue, and thus are considered primary or intrinsic brain tumors, whereas metastases are considered secondary brain tumors.

Depending on the tissue tumors arise from and their molecular signature, the following intrinsic brain tumors can be differentiated:

- Astrocytomas
- Oligodendrogliomas
- Glioblastomas
- Ependymomas
- Medulloblastomas

Astrocytomas (AZ), oligodendrogliomas (ODG), glioblastomas (GB), and ependymomas (EP) are commonly referred to / grouped as gliomas. Gliomas arise from glial cells that form the supportive and connective tissue found within the CNS. Glial cells include astrocytes, oligodendrocytes and ependymal cells, which are also the namesakes for the respective and specific types of gliomas. These cells can be differentiated microscopically allowing for the correct diagnosis to be made. In addition to the microscopic presentation of these cells, molecular diagnostics are of critical importance in correctly diagnosing intrinsic brain tumors.

The following paragraphs will discuss the histopathological and molecular pathological diagnostics, clinical presentation, radiological presentation, and prognosis of the different subtypes of gliomas present in our study cohort (AZ, ODG, GB, and EP).

a) Astrocytomas

Astrocytomas arise from astrocytes, which account for the majority of glial cells in the CNS, and play a role in cerebral metabolism, structural, homeostatic, and neuroprotective tasks (14-16). They can further be subcategorized into protoplasmic astrocytes, fibrous astroglia, and varicose projection astroglia (14).

Histopathologically astrocytomas, just as other types of gliomas, can be classified as either low-grade or high-grade gliomas that represent WHO CNS grades 1 and 2, and 3 and 4, respectively. Low-grade astrocytomas show signs of mild nuclear atypia, low mitotic activity, and no necrosis, whereas high-grade tumors show an increased mitotic rate, microvascular proliferation, and necrosis (17). Astrocytomas of WHO CNS grades 1 to 4 as well as their key molecular features are shown in Table 1.

Table 1 – Astrocytomas: WHO CNS grade and key features

Astrocytoma WHO CNS grade	Key molecular features
Pilocytic astrocytoma (Grade 1)	BRAF fusion
Astrocytoma, IDH-mutant (Grade 2)	IDH1/2 mutation, TP53 mutation, ATRX loss
Astrocytoma, IDH-mutant (Grade 3)	IDH1/2 mutation, TP53 mutation, ATRX loss + increased mitotic rate
Astrocytoma, IDH-mutant (Grade 4)	CDKN2A/B homozygous deletion, necrosis, microvascular proliferation

Table 1. Astrocytomas and their respective WHO CNS grades and key features (17, 18) are shown.

The clinical presentation of patients with astrocytomas varies a lot. Focal or generalized seizures are common and occur especially in patients with low-grade cortically located astrocytomas (19, 20). Other symptoms include focal neurological deficits, such as sensorimotor deficits and speech difficulties, and cognitive or personality changes, which are most commonly found in tumors of the frontal lobe. In addition, patients can present with unspecific headaches, nausea and vomiting due to the increased intracranial pressure that may be present.

Radiological presentation commonly allows for suspected classification into low-grade gliomas (LGG) or high-grade gliomas (HGG). In MRI, LGG typically present with T2 and FLAIR hyperintensity, no contrast enhancement in T1, and usually show minimal acute mass effect despite potentially growing to a substantial size. Conversely, HGG usually present with a ring-shaped contrast enhancement in T1, necrosis, edema, and irregular tumor margins (21-23).

The prognosis and life expectancy of patients varies depending on the tumor's WHO CNS grade and its location. In general, O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, younger age, and gross total resection or even supramaximal resection portray better prognosis, while CDKNA/B deletion and subtotal resection are associated with worse prognosis. The accuracy of life expectancy prediction varies a lot and has been

a controversial and evolving topic among the worldwide neurosurgical community. Approaches of treatment and specifically surgical strategy differ significantly from center to center, which gives rise to potential differences in the prediction of life expectancy.

b) Oligodendrogliomas

Oligodendrogliomas arise from oligodendrocytes, yet their diagnosis does not primarily depend on histopathological features, which include perinuclear clearing, delicate and branching capillaries, and frequent calcifications (24), but on molecular pathological considerations instead. According to the WHO CNS 2021 classification two requirements must be met to diagnose an oligodendroglioma (17):

1. IDH1 or IDH2 mutation
2. 1p/19q co-deletion

If either of these requirements is not present, a tumor cannot be classified as an oligodendroglioma but would be considered either an astrocytoma, if the 1p19q co-deletion is missing, or as a glioblastoma if the tumor is IDH wildtype. Interestingly and in contrast to astrocytomas, oligodendrogliomas can only be considered a WHO CNS grade 2 or 3; there are no grade 1 or grade 4 oligodendrogliomas.

As is the case with astrocytomas, the presentation of patients with oligodendrogliomas varies a lot. Focal or generalized seizures can occur, so can focal neurological deficits, such as sensorimotor or speech difficulties, and nonspecific headaches, nausea and vomiting can be present due to the tumor's mass effect.

Radiologically oligodendrogliomas present similarly to astrocytomas. This means that they usually present as hypointense and with no contrast enhancement in T1. However, contrast enhancement in T1 can be present for both ODG CNS grade 3 as well as for ODG CNS grade 2. The latter, however, does not reliably predict malignant transformation. In T2 and FLAIR hyperintensity can be observed (Figure 3). Oligodendrogliomas are often associated with calcifications, which can be seen on CT imaging (Figure 3).

Prognosis and life expectancy are best for oligodendrogliomas followed by astrocytomas and glioblastomas. This is mainly because ODG's IDH mutation and 1p19q co-deletion compare favorably to the genetic sequence of both astrocytomas and glioblastomas (25, 26).

Figure 3 – CT and MRI scans of oligodendrogliomas

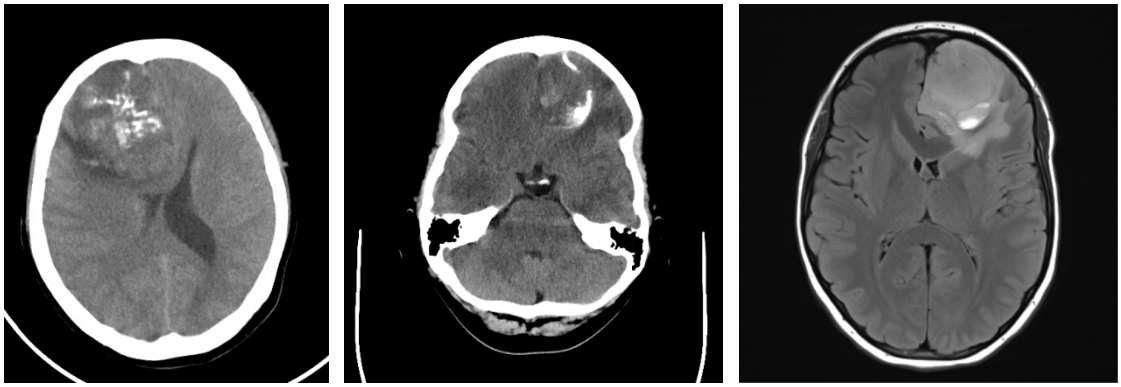

Figure 3. CT and MRI scans of oligodendrogliomas are shown. The left (27) and middle (28) CT scan show calcifications, the MRI (right) shows moderate mass effect (28).

c) Glioblastomas

Glioblastomas are WHO CNS grade 4 glial tumors characterized by and known for their inherent poor prognosis and life expectancy. For the diagnosis of a glioblastoma both histopathological and molecular pathological requirements need to be met. The histopathological requirements are (29):

1. High cellularity, nuclear atypia and pleomorphism
2. High mitotic rate
3. Microvascular proliferation
4. Necrosis (often associated with pseudopalisading of tumor cells around the necrosis)

In addition, the following molecular pathological requirements need to be met (29):

1. TERT promoter mutation
2. EGFR gene amplification, or
3. Combined whole chromosome 7 gain and whole chromosome 10 loss
4. IDH wildtype

Additionally, MGMT promoter methylation is regularly regarded as it is a critical prognostic marker; tumors with a methylated MGMT promoter have a better prognosis due to their better response to chemotherapy agents like temozolomide and are generally associated with increased overall survival (30).

The clinical presentation of patients with glioblastomas is somewhat similar to that of patients with other intrinsic brain tumor entities, however, it does differ slightly. Patients with glioblastomas tend to be older with a peak age of onset in the seventh decade of life.

Focal and generalized seizures tend to be less common and clinical presentation is often due to symptoms, which are associated with acute mass effect of the tumor leading to increased intracranial pressure. Such symptoms include nonspecific headaches, nausea, and vomiting.

While the clinical presentation can be similar to that of both astrocytomas and oligodendrogliomas, the radiological presentation is different, especially when compared to low-grade glial tumors. On T1-weighted MRI scans, there is usually a ring-shaped contrast enhancement with a hypointense center indicating necrotic processes. On T2-weighted scans, the tumor and surrounding edema present hyperintense (Figure 4). Some glioblastomas cross the midline due to their very aggressive growth and have a characteristic butterfly-like shape (Figure 4).

Figure 4 – MRI scans of glioblastomas

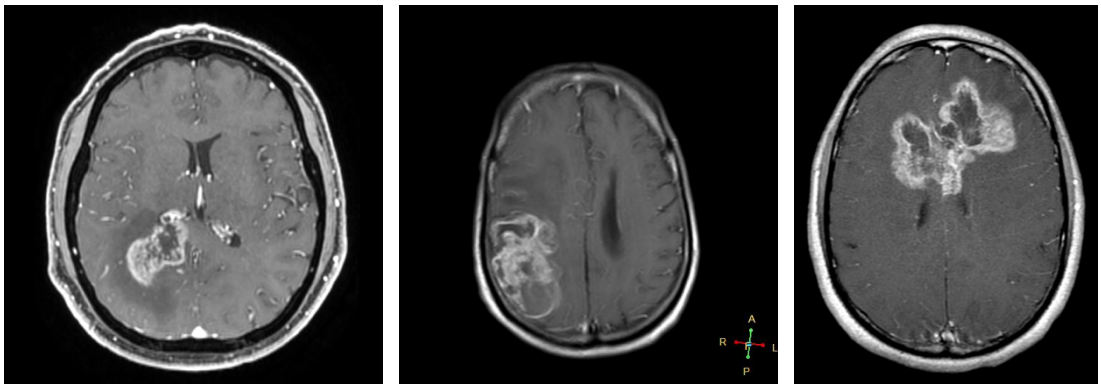

Figure 4. MRI scans of glioblastomas are shown. The left (31) and middle (32) scan show ring-shaped irregular contrast enhancement on T1-weighted scans, central hypointensity as a sign of necrosis and irregular tumor margins; the right (33) scan shows a butterfly glioblastoma.

The prognosis for patients with glioblastomas is known to be very poor. Statistics vary, yet the median overall survival is reported to sit between a few months and two years (11). Long-term survival is rare, with only 0.71% of patients still alive at the ten-year mark as reported by Tykocki and Eltayeb (12).

d) Ependymomas

Ependymomas arise from ependymal cells that line the ventricles of the brain as well as the central canal of the spinal cord. Their classification takes into account both histopathological characteristics and molecular pathological characteristics coupled with specific anatomical locations. The histopathological aspects typical of ependymomas are (34):

1. Perivascular pseudorosettes
2. True ependymal rosettes

In contrast to astrocytomas and oligodendrogliomas, and to some extent glioblastomas, ependymomas are not routinely graded using a numerical grading system of 1 to 4. Instead, they are primarily classified by integrating molecular pathological features alongside anatomical tumor location, as shown in Table 2.

Table 2 – Anatomical location & molecular pathological aspects of ependymomas

Anatomical location	Molecular pathological aspects
Supratentorial EP	ZFTA fusion-positive
	YAP1 fusion-positive
Posterior fossa EP	Group A
	Group B
Spinal EP	MYCN-amplified
	Other subtypes (e.g. myxopapillary EP)

Table 2. Anatomical locations and the molecular pathological aspects of ependymomas are depicted (34).

The clinical presentation of patients with ependymomas is similar to that of patients with astrocytomas, oligodendrogliomas, or glioblastomas. Common symptoms are focal or generalized seizures as well as focal neurological deficits or cognitive deficits. In addition, nonspecific headaches, nausea and vomiting can occur. Due to ependymomas originating from the lining of ventricles, and thus their vicinity to the ventricular system, symptoms of acute hydrocephalus can occur if the circulation and drainage of cerebrospinal fluid (CSF) are impaired or obstructed. These symptoms include severe headaches, nausea, vomiting, balance and gait disturbances, confusion, and incontinence. Spinal ependymomas can cause back pain and sensorimotor deficits. In addition, bowel or bladder dysfunction can occur.

Radiological imaging usually shows ependymomas as well-demarcated masses. On T1-weighted scans ependymomas present as iso- to hypointense. In contrast, on T2-weighted

scans they can be observed as hyperintense. If contrast agent is administered, enhancement in T1 is common (Figure 5).

Figure 5 – MRI scans of ependymomas

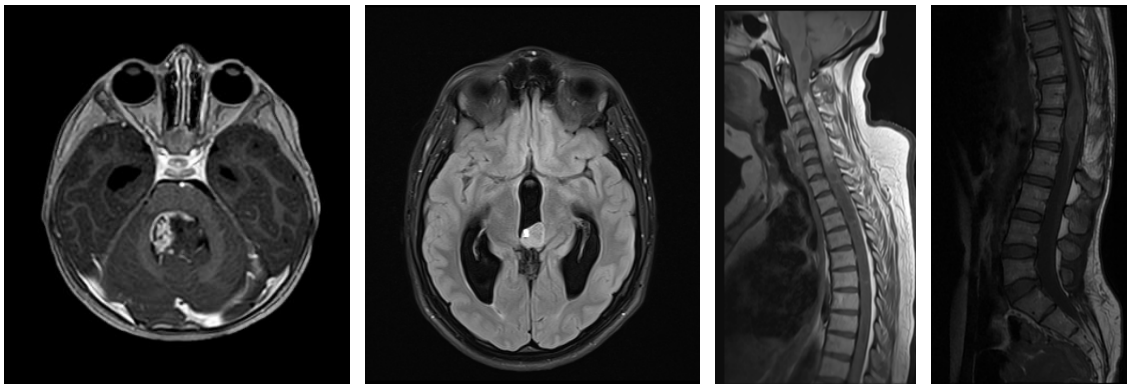

Figure 5. MRI scans of ependymomas are shown. The left (35) scan shows a posterior fossa EP, the middle (36) scan shows a supratentorial EP, and the two scans on the right (37, 38) show spinal EPs.

Generally, predictions of prognosis and life expectancy cannot simply be drawn from or assumed by WHO CNS grading, as grading is no longer applied to every ependymoma. Much more important are the molecular features and anatomical location that can be seen in Table 2. Thus, it can generally be concluded that in supratentorial ependymomas, ZFTA-fusion positive tumors are associated with more aggressive growth (39), while in infratentorial/posterior fossa ependymomas group B tumors (40, 41), which are more common in adults, have better prognosis compared to group A tumors, more commonly found in young children (40-42). In spinal ependymomas, MYCN-amplified tumors are associated with aggressive growth and poorer outcomes when compared to other types of spinal ependymomas (39).

iii. Surgery of gliomas

Gliomas are a major reason for significant morbidity and lethality. Hence, neurooncology has repeatedly reconsidered available treatment options to decrease disease burden and to increase progression-free survival, overall survival and health-related quality of life.

To this day, the surgical resection of gliomas is pivotal for oncological control and in the alleviation of present symptoms.

a) The role of the extent of resection

As is the case with many other types of benign or malignant tumors, the goal of surgery is to remove as much tumor as possible. This is directly associated with progression-free survival and overall survival.

Wherever possible, gross total resection should be carried out, as many studies have shown that more extensive resection is associated with better prognosis for both LGG and HGG (43, 44); several studies have concluded that an extent of resection of at least 80% should be targeted to have a statistically significant survival benefit for patients, especially for HGG (Figure 6) (8, 45, 46).

Maximizing the extent of resection is therefore of utmost importance, yet due to the brain's delicate nature and our somewhat limited understanding of it and how specific surgical intervention may cause postoperative neuro(psycho)logical deficits, neuroscientists and neurosurgeons have been considering different treatment options to best prevent patients from sustaining new neuro(psycho)logical deficits after intervention or treatment.

Figure 6 – Impact of extent of resection on survival

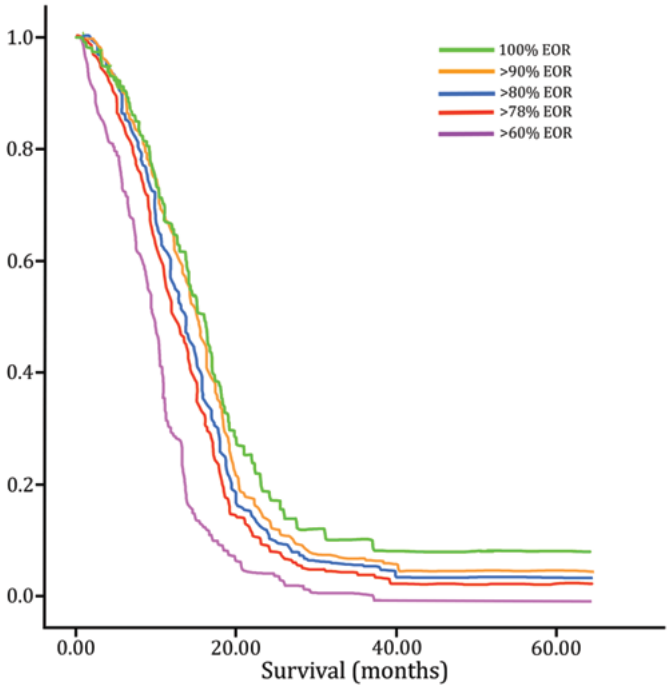

Figure 6. Survival curves for differing extents of resection from Sanai et al. (45) are shown.

b) Awake surgery

Awake surgery has been established as a means to intraoperatively assess and evaluate a patient's neuro(psycho)logical function aiming to avoid causing significant surgically induced deficits. This approach is only possible as the brain itself does not register pain; it is only the surrounding tissue that registers pain, which can be controlled with adequate anesthesia.

Before surgery careful planning and preoperative exams need to be completed to ensure that this technique is a viable approach for the patient from a surgical point of view considering the tumor's location and the potential benefits from performing awake surgery, but also from a patient's psychological point of view ensuring their wellbeing throughout the procedure.

Depending on the center, different surgical approaches are chosen. Some centers rarely perform awake surgeries, not supporting the previously published literature arguing for its superiority in preserving patients' neuro(psycho)logical function. Those who do perform awake surgery usually choose one of two techniques:

1. Asleep-Awake-Asleep
2. Awake-Awake-Awake

The first technique allows for maximum patient comfort while not compromising on testing and evaluation opportunities. The patient is sedated via general anesthesia or sedoanalgesia for the initial surgical steps, i.e., positioning, scalp incision and preparation, and craniotomy. Anesthesia is then reduced and stopped, and the patient is awakened. Once awake, intraoperative brain mapping commences. The surgeon then uses direct cortical electrical stimulation to create a map of the surgical area. This is done in unison with the patient being attended to by a neuropsychologist, who helps the patient perform specific tasks that are indicative of the neuro(psycho)logical function assumed to be present in the brain area currently being assessed. These tests include spontaneous conversation, naming tasks, the Stroop test, finger-tapping, other fine motor movement tests, describing changes in sensation, or even playing musical instruments. If patients speak more than one language, the tests focused on speech and language understanding may be carried out in all languages a patient is proficient in.

In contrast, the second technique does not put the patient under general anesthesia at all, thus avoiding initial drowsiness after awakening the patient, which may delay the

surgery. However, undergoing a craniotomy while awake may not be the most pleasant feeling, even if painless. In addition, the awake-awake-awake technique can cause the patients to become tired more quickly as they have been awake and secured in this position for longer than their counterparts who undergo the asleep-awake-asleep technique.

Once the patient has been awoken (asleep-awake-asleep) and/or after the initial steps of surgery as well as the initial intraoperative mapping, tumor resection commences while the neuropsychologist monitors the patient's neuro(psycho)logical function and wellbeing. If the patient suddenly shows signs of possible deficits, resection is stopped, and mapping is continued to further map the area. Subcortically, electrical stimulation is carried out to proceed the extent of resection to the functional borders without risking surgically induced deficits. Once the full extent of the planned resection is carried out or the patient is no longer able to continue testing or functional borders have been reached the patient is sedated again in the case of the asleep-awake-asleep technique or stays awake in case of the awake-awake-awake technique.

During both awake and asleep surgery, the following techniques and tools may be used to avoid causing new postoperative neuro(psycho)logical deficits:

- 5-aminolevulinic acid (5-ALA)
- Intraoperative neuromonitoring (ioNM)
- Intraoperative neuronavigation (ioNN)
- Intraoperative MRI (ioMRI)

These tools shall be explained and discussed in the following sections.

c) 5-Aminolevulinic acid

5-Aminolevulinic acid (5-ALA) naturally occurs as a precursor in the heme biosynthesis pathway. However, it can also be administered, which leads to an intracellular accumulation of protoporphyrin IX (PpIX). This chemical compound is fluorescent and especially accumulates in high concentrations in malignant glioma cells, but not in healthy brain tissue (47-49).

5-ALA is administered orally about three hours before anesthesia in a dose of 20mg/kg (47, 50). During surgery the surgical microscope is switched to a violet-blue excitation light, which leads to the emission of a pink to red fluorescence by the tumor allowing for better visualization of the tumor and thus a greater extent of resection to be

achieved. As a result, patients undergoing surgery with the use of 5-ALA show increased progression-free survival (47).

Worthy of note is that 5-ALA is less effective in LGG, as they show decreased fluorescence or none at all. This, however, allows the surgeon to assess in real time whether the tumor that is being removed is likely low- or high-grade. In addition, the use of 5-ALA may aid in the detection of focal intratumoral areas of malignant transformation (51). However, there can be molecularly diagnosed glioblastomas that show no sign of 5-ALA uptake as well as oligodendrogliomas of both WHO CNS grade 2 and 3 that do emit fluorescence despite their lack of malignancy.

Figure 7 – Intraoperative use of 5-ALA

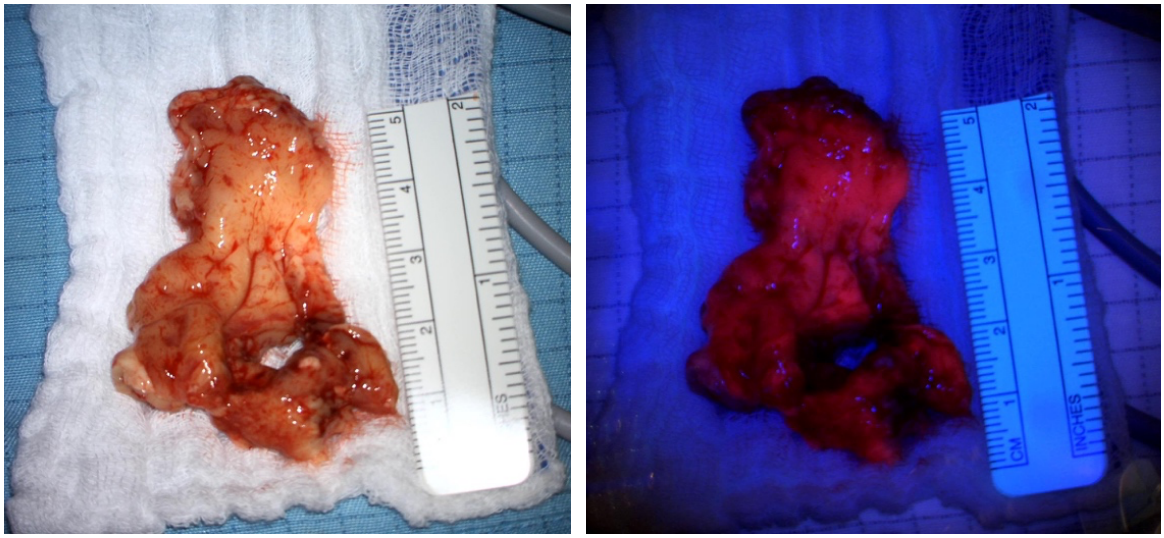

Figure 7. A surgical specimen with the use of 5-ALA is shown; on the left normal microscopic light is used, whereas on the right violet-blue excitation light is used which causes pink fluorescence representing intratumoral areas of malignant transformation.

d) Intraoperative neuromonitoring

Intraoperative neuromonitoring (ioNM) is the use of real-time electrophysiological methods to assess and evaluate, as well as preserve neurological function of the CNS and/or peripheral nervous system (PNS). The goal of ioNM is to decrease the likelihood of surgically induced neurological deficits by immediately alerting the surgical team of electrophysiological changes (52, 53). De Witt Hamer et al. (54) have shown that the use of ioNM significantly reduces the risk of causing patients surgically induced neurological deficits; with use of intraoperative stimulation mapping, 3.4% of patients experienced new postoperative deficits, whereas without its use the percentage increased to 8.2%.

ioNM includes several techniques:

- Somatosensory Evoked Potentials (SSEPs)
- Motor Evoked Potentials (MEPs)
- Brainstem Auditory Evoked Potentials (BAEPs)
- Visual Evoked Potentials (VEPs)
- Electromyography (EMG)
- Electroencephalography (EEG)

Depending on the tumor's location, different modalities are used to preserve neurological function and avoid inducing new deficits. Benefits of ioNM include the reduction of surgically induced neurological deficits and early detection of injury, thus enabling quick and preemptive countermeasures (52, 53).

Limitations include the fact that not all electrophysiological changes are of clinical significance, and conversely, not all clinical deficits may show up as electrophysiological changes during surgery.

e) Intraoperative neuronavigation

Intraoperative neuronavigation (ioNN) uses computer assistance to guide and help neurosurgeons localize and navigate in real-time while operating. Its goal is to facilitate orientation in the CNS and especially aid in the resection of intrinsic brain tumors due to their inherent similarity in appearance to healthy brain tissue. It is often referred to or described as a sort of GPS for the brain when explaining its use and to patients.

ioNN requires the following steps:

- Preoperative neuroimaging with MRI and/or CT
- Preoperative registration and calibration
- Tracking systems (electromagnetic or optical)
- Visualization of navigation probe on the workstation

Considering its capabilities, ioNN is commonly used in the following types of interventions and surgeries:

- Surgical removal of brain tumors
- Surgery of highly delicate CNS areas (e.g., brainstem)
- Biopsies
- Pituitary surgery
- Epilepsy surgery

- Complex spine surgery

ioNN allows for real-time spatial orientation within the surgical area and gives the surgical team a better understanding of where exactly their instruments are located. It can improve the extent of resection and may reduce operative time, as well as reoperation rates. Furthermore, ioNN can integrate preoperative functional imaging allowing for more advanced surgical planning and safer resection to prevent causing new postoperative neuro(psycho)logical deficits (55, 56).

However, the inevitable brain shift that occurs with surgery, first, after opening of the dura and the subsequent involuntary CSF "drainage", and second, after commencing, tumor resection, for example, reduces the accuracy of the ioNN, even though it could initially be calibrated to an accuracy of less than one millimeter (55-57). In addition, the use of ioNN requires high-quality imaging and expensive workstations as well as specialized training.

f) Tractography

Tractography is a neuroimaging modality that makes use of diffusion-weighted MRI (DW-MRI) to create three-dimensional reconstructions of subcortical white matter tracts and to visualize them. It is based on water molecules tending to diffuse along the direction of axons rather than across them, which is referred to as anisotropy (58).

Tractography can be achieved by use of various approaches, the most commonly used to date is diffusion tensor imaging (DTI), which looks at the overall orientation of diffusion within a voxel and creates a tensor upon the anisotropy observed. DTI is one method of deterministic tractography, which is rather easily available and does not require much time to use. However, DTI runs into problems when there is crossing of fibers, diffusion abnormalities or other gross pathologies (59).

Next to deterministic approaches, there are new advanced methods, such as constrained spherical deconvolution (CSD) (60), which is considered a probabilistic approach. These approaches estimate the likelihood of two brain areas being connected, rather than assuming one path as is the case with deterministic approaches. This way, probabilistic algorithms are better at depicting fiber tracts that cross, kiss, or branch (61). They also show improved results when assessing regions with diffusion abnormalities. Despite their advantages, probabilistic algorithms are computationally intensive and may create false-positive fiber tracts.

Using reconstructions created by tractography and integrating them into ioNN allows for improved navigation, increased extent of resection (62), decreased operative time (63), and decreased likelihood of causing new neuro(psycho)logical deficits by transecting subcortical white matter connections (62, 64, 65).

However, the variability in software algorithms decreases the reproducibility, thereby making the reconstructions to some extent dependent on the software and user who created the tracts (66).

iv. Radiotherapy and chemotherapy

While surgery proves to be an important aspect in the treatment of many intrinsic brain tumors, both for LGG and HGG, it regularly does not suffice and supportive treatment or, in some instances, standalone treatment with radiotherapy and/or chemotherapy is required as part of a multimodal treatment approach.

Radiotherapy is usually employed postoperatively to control residual tumor and/or to lower the risk of tumor recurrence. Radiotherapy is typically administered as conventional fractionated external beam radiotherapy (EBRT). This allows for delivery of high radiation dosages to the desired brain area, i.e., tumor, while sparing healthy brain tissue. Advanced modalities such as intensity-modulated radiotherapy (IMRT) and proton therapy have been shown to improve dose conformity and reduce toxicity (67, 68).

The most widely used chemotherapeutic, especially for HGG, is temozolomide (TMZ). Stupp et al. (67) have shown that TMZ with radiotherapy followed by six cycles of adjuvant chemotherapy with TMZ improved overall survival significantly when compared to radiotherapy alone. As discussed, tumors with methylated MGMT promoters show better prognosis; this is because tumors with methylated MGMT promoters respond better to chemotherapy with TMZ (69).

In contrast, adjuvant chemotherapy for LGG is less straightforward. Buckner et al. (70) and Bell et al. (71) have demonstrated that combined radiotherapy and chemotherapy with PCV, including procarbazine, lomustine (CCNU) and vincristine, is statistically significantly associated with increased progression-free survival. Interestingly, this effect is most pronounced when IDH-mutation and 1p19q co-deletion are present, thereby concluding that oligodendrogliomas respond better to adjuvant treatment with radiotherapy and chemotherapeutic treatment with PCV (72).

In summary, both adjuvant radiotherapy and chemotherapy remain key treatment modalities for LGG and HGG.

v. Anatomical aspects

a) The frontal lobe

The frontal lobe is the largest lobe of the cerebrum and plays a vital role in many neuro(psycho)logical functions, including motor movement, speech and cognitive abilities. Anatomically it is one of the lobes with distinctive subdivisions allowing for the identification of the same brain areas across individuals.

At large, the frontal lobe is located anterior to the central sulcus and separated from the temporal lobe by the Sylvian fissure or lateral sulcus (Figure 8). Anatomically, the frontal lobe can be subdivided into three gyri located in an anterior-posterior direction; the superior frontal gyrus (SFG) (Figure 11), the medial frontal gyrus (MFG), and the inferior frontal gyrus (IFG), which are separated from one another by the superior frontal sulcus (SFS) and the inferior frontal sulcus (IFS), respectively (Figure 9). In addition to these three gyri there is the precentral gyrus (PrCG), which is separated from the aforementioned gyri and the postcentral gyrus (PCG) by the precentral sulcus (PrCS) and central sulcus (CS), respectively (Figure 9). Additionally, the frontal pole and orbital gyri (Figure 9) are sometimes considered separate gyri/frontal areas.

In some instances, neurosurgical nomenclature is used where the PrCG and PCG are considered the central lobe and are thus not part of the frontal lobe, in which case the posterior border of the frontal lobe would be defined as the PrCS instead of the CS.

Figure 8 – Frontal lobe

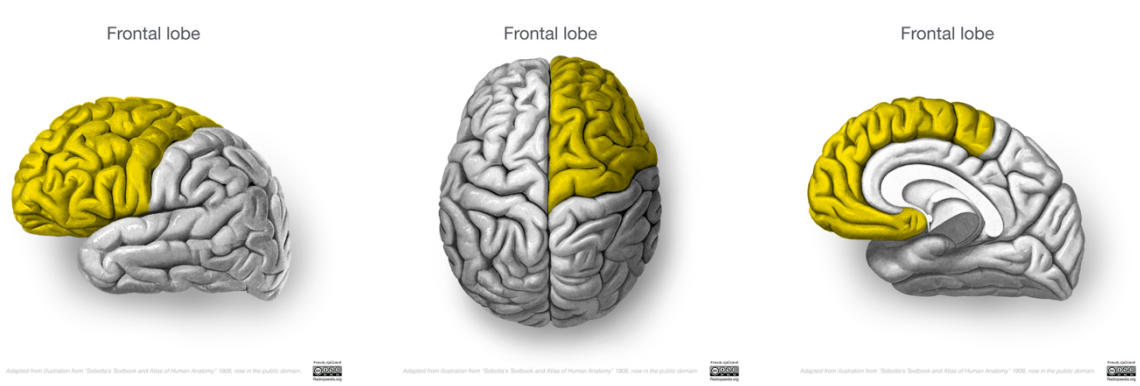

Figure 8. A lateral (73), dorsal (74) and medial (75) view of the frontal lobe is shown.

Figure 9 – Gyri and sulci of frontal lobe

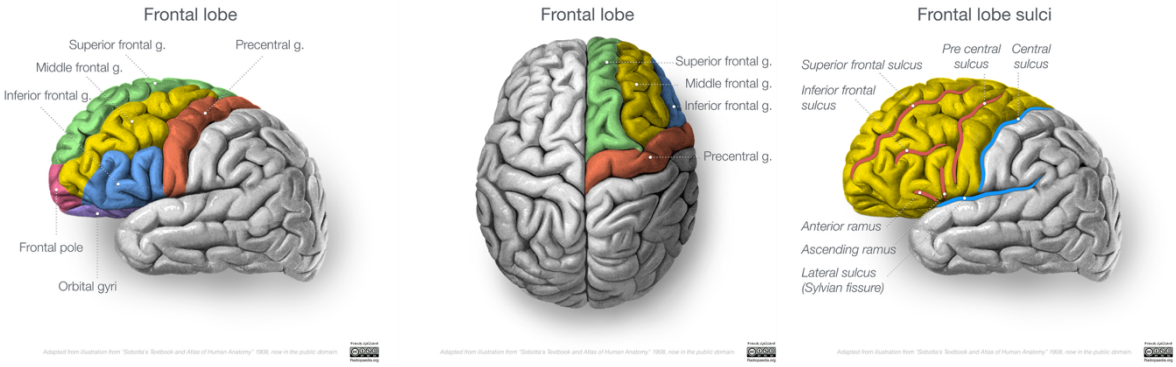

Figure 9. Lateral (73) and dorsal (74) views of the frontal lobe's gyri, and a lateral view of the frontal lobe's sulci (73) are shown.

The frontal lobe can furthermore be subdivided into functionally distinct regions, including the prefrontal cortex, premotor cortex, primary motor cortex, and Broca's area.

Broca's area is typically referred to as the home of speech and language production and is primarily located in the left IFG. It is specifically important for articulation; damage to this area may lead to motor aphasia, characterized by impaired speech production with mostly preserved comprehension and understanding (76).

The prefrontal cortex describes the anterior-most aspect of the frontal lobe and can be subdivided into the ventromedial, dorsolateral and orbitofrontal cortex. It is especially important for executive / cognitive functions such as working memory, decision-making, emotional regulation, and social cognition (77).

The primary motor cortex is located in the PrCG and is primarily responsible for the execution of voluntary movements. The different muscle groups are represented in somatotopic order using the homunculus (Figure 10).

Figure 10 – Motor homunculus

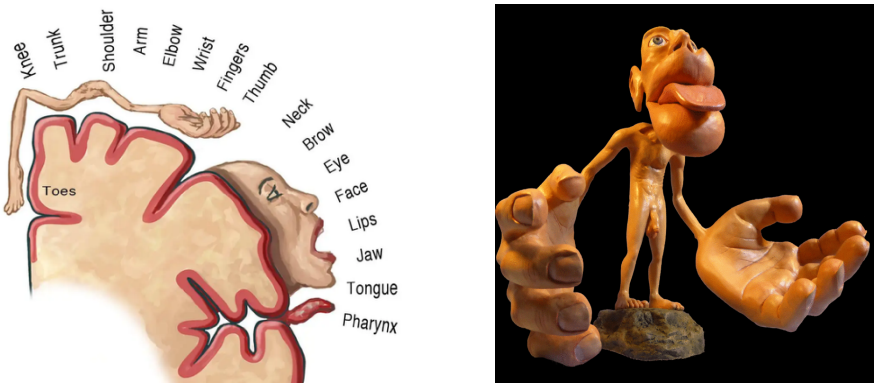

Figure 10. A representation of the motor homunculus on the cortex (78) of the PrCG and a model (79) of the homunculus are shown.

The premotor cortex is directly anterior/adjacent to the primary motor cortex and therefore located in the SFG. It is heavily involved in the planning, initiation and coordination of motor movement (80).

b) <u>The superior frontal gyrus</u>

The superior frontal gyrus (SFG) (Figure 11) is home to the premotor cortex and is bounded medially by the interhemispheric fissure, laterally by the SFS and posteriorly by the PrCS.

Figure 11 – Superior frontal gyrus

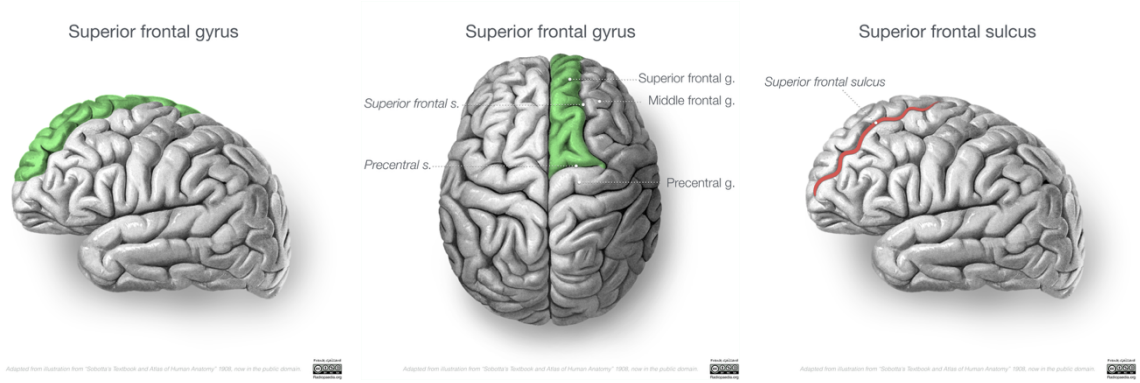

Figure 11. Lateral (73), dorsal (74) views of the SFG, and a lateral view of the SFS (73) are shown.

Next to the premotor cortex, the SFG is also home to the supplementary motor area (SMA) (Figure 12), which is located in the posterior-most and medial aspect of the SFG (81, 82).

Figure 12 – Supplementary motor area

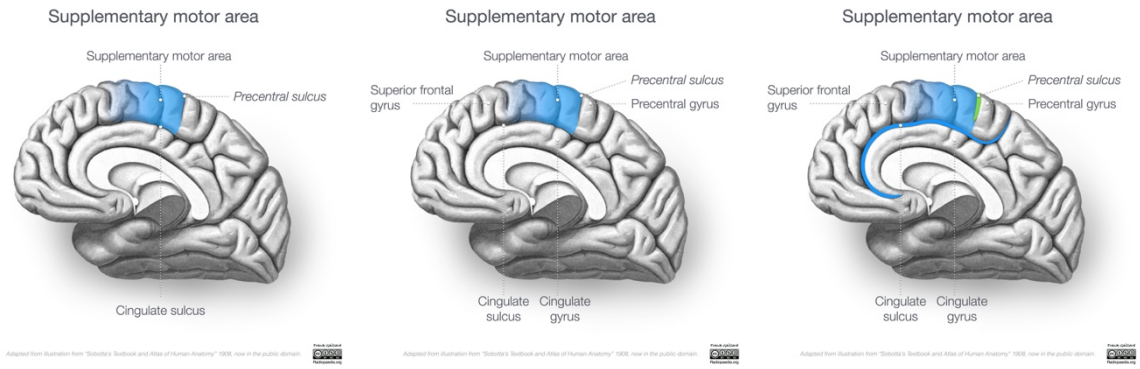

Figure 12. The SMA and its bordering anatomical structures are shown (83).

c) <u>The supplementary motor area</u>

The supplementary motor area (SMA) (Figure 12) plays a crucial role in the initiation, planning and execution of motor and speech function (84) and is linked to neuro(psycho)logical/cognitive abilities (85, 86).

The SMA can further be divided into the SMA-proper and pre-SMA. The SMA-proper is primarily linked to motor function (87), while the pre-SMA is especially involved in language and cognitive function (88). Therefore, the surgical resection of brain tumors in this area provides ample risk for neuro(psycho)logical deficits.

The SFG, and particularly the SMA, is a common site for intrinsic brain tumors, such as low-grade and high-grade gliomas (89), necessitating further research into specific outcomes of surgical resection of intrinsic brain tumors in this cerebral area. While several studies have looked at postoperative transient and permanent neurological deficits of both LGG and HGG, there has been little research specifically addressing postoperative outcomes of tumors in the SFG and SMA. In addition, to the best of our knowledge, there has been no study yet addressing the postoperative neuropsychological outcome in patients with such tumors. This portrays a relevant gap in the literature as such deficits may profoundly impact patients' health-related quality of life.

Understanding what the general surgical outcome of patients with tumors located in the SFG and SMA is, may aid in improving shared decision-making allowing for better individualized treatment plans and enabling surgeons to better manage postoperative expectations, both by the patients as well as by the treating physicians. As neurosurgical treatment decisions increasingly try to include health-related quality of life considerations

and focus on the patient as a whole, ensuring the availability of accurate prognostic data about transient and permanent neuro(psycho)logical sequelae is ever more important.

vi. Objective of this work

The aim of this study was to explore the surgical outcome and the postoperative neuro(psycho)logical deficits of patients with an intrinsic brain tumor in the SFG. In addition, we evaluated the impact of preoperative tumor volume, WHO CNS grade, laterality of the tumor (left versus right SFG) and the type of surgery (awake versus asleep), resection of the middle frontal gyrus (MFG), resection of fibers of the corpus callosum (CC), or the resection of the cingulate gyrus (CG) on the presence of postoperative transient and permanent neuro(psycho)logical deficits. Further, we assessed whether the presence of transient deficits is a predictor of permanent deficits.

II. Methods

i. Study design and setting

After obtaining the approval from the Ethics Committee of the Medical University of Graz, Austria, we performed a retrospective study on patients diagnosed with intrinsic brain tumors in the SFG. We included all patients who underwent surgery for a confirmed intrinsic brain tumor at the Department of Neurosurgery at the Medical University of Graz between January 2018 and June 2023. A total of 31 patients were included in this retrospective analysis.

Patients with non-intrinsic brain tumors, such as metastases or meningiomas, were excluded from the study due to the significant difference in etiology, surgical technique, and expected outcome for these patients (Table 3). Another exclusion criterion was primary tumor location other than the SFG, as this study focused on postoperative neuro(psycho)logical deficits arising from tumors in this particular area. Both, patients who underwent surgery for the first time and patients who had surgery due to tumor recurrence, were included in the study. If treatment was due to tumor recurrence and the patient's first surgery was before the study timeline, these data were also included in the study to provide accurate information on the patient's history and to be able to best compare surgical interventions.

All 31 patients were operated on by one of three surgeons, with 26 of the 31 patients operated on by the same surgeon. Depending on the laterality of the lesion, shared decision-making and other patient-specific criteria function-guided awake surgery with neuropsychological testing or function-guided surgery under general anesthesia with intraoperative neuromonitoring was performed.

Table 3 – Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Primary tumor location in SFG	Primary tumor location other than SFG
Underwent surgical treatment between 1 January 2018 and 30 June 2023	Did not undergo surgical treatment between 1 January 2018 and 30 June 2023
Intrinsic brain tumor	Other treatments (without surgical resection)
First surgery or surgery for tumor recurrence	Meningiomas
	Metastases

Table 3. Inclusion and exclusion criteria of the present study are shown.

ii. Data collection

Data gathering was conducted using a retrospective chart review. Data were extracted from openMEDOCS, the data recording system of the University Hospital of Graz and the Medical University of Graz.

Data evaluated in the study included preoperative and postoperative neurological exam results, standardized neurological examination and the Karnofsky Performance Status (KPS) (90). Preoperative and postoperative MRI assessed (residual) tumor volume, (residual) tumor contrast enhancement and exact (residual) tumor localization. Further data included surgical reports, return to work, intra- and postoperative complications, histopathological and molecular pathological diagnoses, necessity for further surgical interventions and adjuvant radio- and/or chemotherapy. Characteristics of the study population are depicted in Table 4.

Figure 13 – Karnofsky Performance Status

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disable; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Figure 13. The Karnofsky Performance Status scale definitions are shown.(90)

iii. Assessment of neuropsychological deficits

In all instances, neuropsychological examination was performed before surgery, on postoperative day one and upon discharge. Further examinations were performed during routine follow-up visits in the neurosurgical outpatient clinic and/or during neurooncological appointments for adjuvant radio- and/or chemotherapy, three months and 12 months postoperatively, respectively.

iv. Primary and secondary endpoints

The primary endpoints of the study were the rates of postoperative transient and permanent neuro(psycho)logical deficits that can be attributed to the surgical removal of the tumor that the patients presented with.

The secondary endpoints of the study were defined as possible correlations between preoperative tumor volume, WHO CNS grade, laterality of tumor, type of surgery (awake versus asleep), resection of the middle frontal gyrus (MFG), resection of the corpus callosum (CC), or the resection of the cingulate gyrus (CG) and the incidence of transient and/or permanent neuro(psycho)logical deficits.

v. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 28 and Python Version 3.13.3. Missing numerical data were excluded from the analysis. Descriptive statistical analysis was performed to further describe the study population and assess its treatment outcomes.

Binary logistic regression models were created to assess a possible statistical association between tumor volume determined on preoperative MRI scans and postoperative transient or permanent neuro(psycho)logical deficits.

For assessment of relationships between categorical variables, such as WHO CNS grade, resection of the CG and/or CC and/or MFG, laterality of tumor and type of surgery (awake versus asleep) concerning the presence of postoperative transient or permanent neuro(psycho)logical deficits, Chi-Square tests of independence or Fisher's Exact Tests were used. Probability values of $p \leq 0.05$ were considered statistically significant.

Table 4 – Study population demographics

ID	Age	Awake surgery	Side	Diagnosis	WHO CNS grade	Tumor volume (cm^3)	TN(P)D	PN(P)D	KPS (12 months post-op.)
SFG1	31	Y	L	ODG	2	120.89	Y	N	100
SFG2	40	Y	L	ODG	2	87.31	Y	N	100
SFG3	32	Y	L	AZ	2-3	50.1	N	N	90
SFG4	83	N	R	GB	4	72.49	Y	N	60
SFG5	37	Y	L	ODG	2	31.89	N	N	90
SFG6	27	Y	R	ODG	2	23.11	Y	N	100
SFG7	50	Y	L	AZ	3	88.95	Y	N	90
SFG8	41	Y	L	GB	4	7.02	Y	N	100
SFG9	71	Y	L	GB	4	19.42	Y	N	90
SFG10	72	N	R	GB	4	8.03	Y	Y	60
SFG11	38	N	L	OAZ	2	12.88	N	N	100
SFG12	24	Y	L	AZ	3	65.57	N	N	100
SFG13	35	N	L	GB	4	102.61	Y	Y	40
SFG14	56	N	L	OAZ	2	20.95	N	N	100
SFG15	50	Y	L	OAZ	2	10.82	N	N	90
SFG16	20	Y	L	EP	3	27.77	N	N	100
SFG17	17	Y	L	ODG	2	12.22	Y	N	100
SFG18	30	Y	L	AZ	4	107.63	Y	N	100
SFG19	41	Y	L	AZ	2	8.21	Y	N	100
SFG20	63	Y	L	ODG	3	67.4	N	N	90
SFG21	52	Y	R	AZ	2-3	16.55	Y	N	100
SFG22	59	Y	L	GB	4	15.91	Y	N	80
SFG23	55	Y	L	ODG	3	143.02	Y	N	90
SFG24	34	Y	R	AZ	3	36.03	N	N	100
SFG25	40	Y	L	AZ	2	10.9	Y	N	100
SFG26	31	N	R	AZ	2	13.34	Y	N	100
SFG27	58	N	R	ODG	2	37.74	Y	N	100
SFG28	25	Y	L	AZ	2	21.05	N	N	100
SFG29	33	N	R	AZ	3	114.58	N	N	90
SFG30	75	N	R	GB	4	19.58	Y	Y	40
SFG31	71	N	R	GB	4	55.6	Y	N	60

Table 4. Demographics of the study population are shown. TN(D)P = transient neuro(psycho)logical deficits, PN(D)P = permanent neuro(psycho)logical deficits, Y = yes, N = no, L = left, R = right, ODG = Oligodendroglioma, AZ = Astrocytoma, GB = Glioblastoma, OAZ = Oligoastrocytoma, EP = Ependymoma, m = missing.

III. Results

Between 1 January 2018 and 30 June 2023, 31 patients presented to the Department of Neurosurgery at the Medical University of Graz for diagnosis and subsequent surgical resection or re-resection of intrinsic brain tumors primarily located in the SFG.

i. Study population

The demographic data of the 31 patients are listed in Table 4. The study population was predominantly female with 20 (64.5%) patients being female and the remaining eleven (35.5%) being male (Figure 14). The mean age at the date of the (first) surgery was 45.2 ± 17.9 years. Analysis of the preoperative tumor volume showed a mean volume of 31.35 cm^3 and a median of 16.50 cm^3 (7.66 – 104.17 cm^3). The average postoperative hospital stay amounted to eight days with a median of six days (4 – 36 days). Twenty-one (67.7%) patients presented with a tumor localized in the left SFG, whereas ten (32.3%) patients were diagnosed with an intrinsic brain tumor in the right SFG (Figure 15). Astrocytomas (35.5%) and Oligodendrogliomas (25.8%) of varying WHO CNS grades alongside Glioblastomas (25.8%) accounted for the vast majority of cases (87.1%) (Figure 16). Other tumor entities (12.9%) included Oligoastrocytomas, which are not found in the current WHO CNS tumor classification anymore, and one Ependymoma.

Figure 14 – Sex distribution

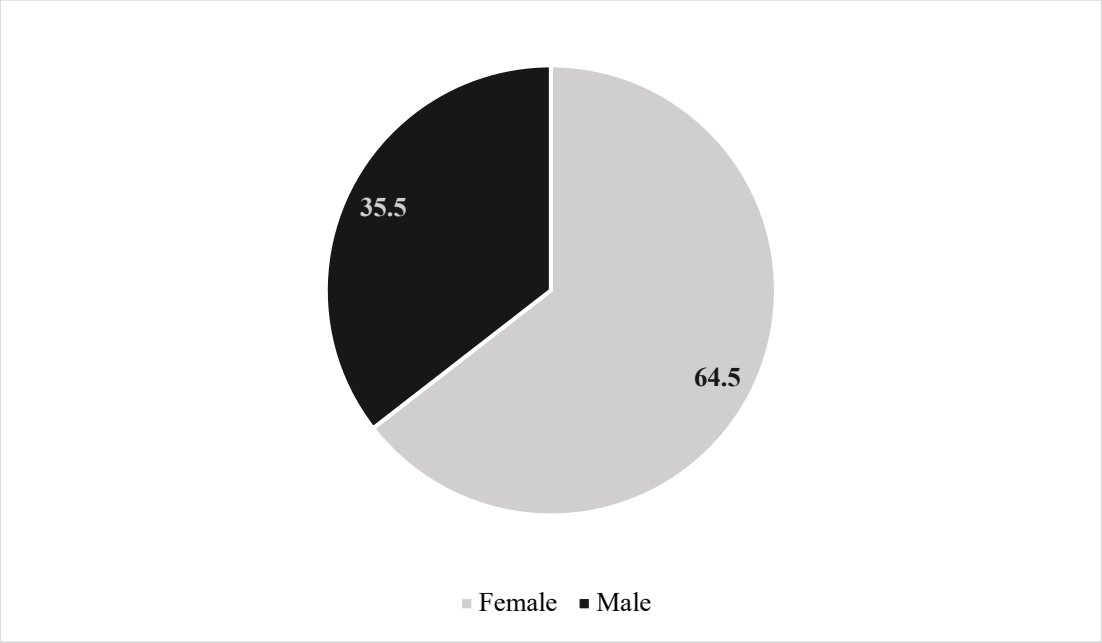

Figure 14. The sex distribution among the study population is shown. Twenty (64.5%) patients were female, whereas eleven (35.5%) were male.

Figure 15 – Laterality of tumors

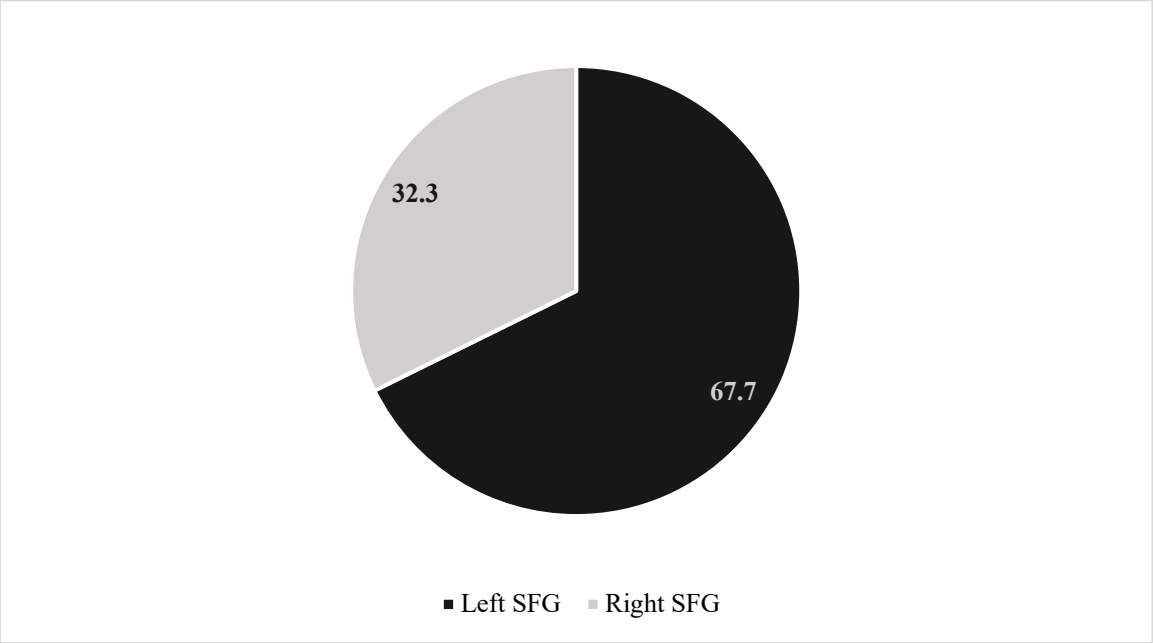

Figure 15. The laterality of tumors in the study population is shown. Twenty-one (67.7%) tumors were located in the left SFG, whereas ten (32.3%) were located in the right SFG.

Figure 16 – Tumor entities

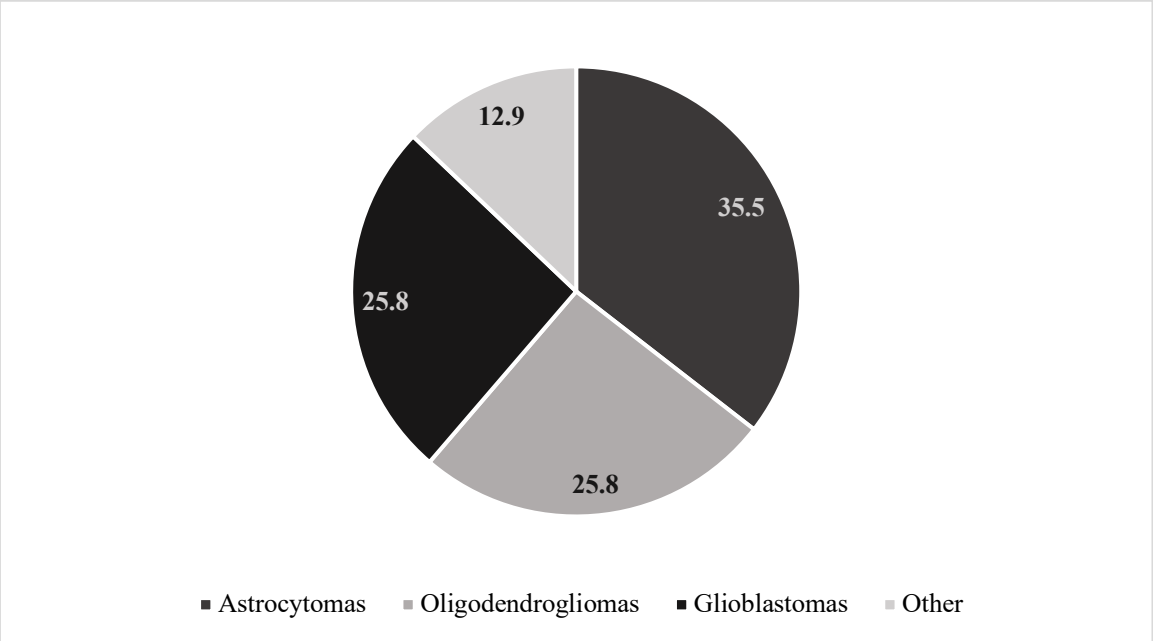

Figure 16. The percentage of tumor entities is shown. Astrocytomas of varying WHO CNS grades were the most common with 35.5%, followed by oligodendrogliomas (25.8%) of varying WHO CNS grades and glioblastomas (25.8%).

ii. Clinical presentation and preoperative considerations

Eighteen (58.1%) patients initially presented with a seizure, either in the form of a generalized tonic-clonic seizure (61.1%) or a focal seizure (38.9%) (Figure 17), presenting as either a speech arrest or difficulty, involuntary motor function, or intermittent sensory disturbances.

During the examination upon hospital admission 22 (71.0%) patients were completely neurologically intact and did not show any symptoms.

Contrast enhancement of preoperative T1-weighted MRI was present in 12 (38.7%) tumors, eight later diagnosed as glioblastomas, one as an astrocytoma WHO CNS grade 4, one as an astrocytoma WHO CNS grade 3, one as an oligodendroglioma WHO CNS grade 3, and one as an ependymoma WHO CNS grade 3. Preoperative tumor volume determined on preoperative MRI ranged from 7.02 cm^3 to 143.02 cm^3 with a median of 27.77 cm^3 and a mean of 46.12 ± 39.89 cm^3 (mean ± SD).

Figure 17 – Clinical presentation and seizures

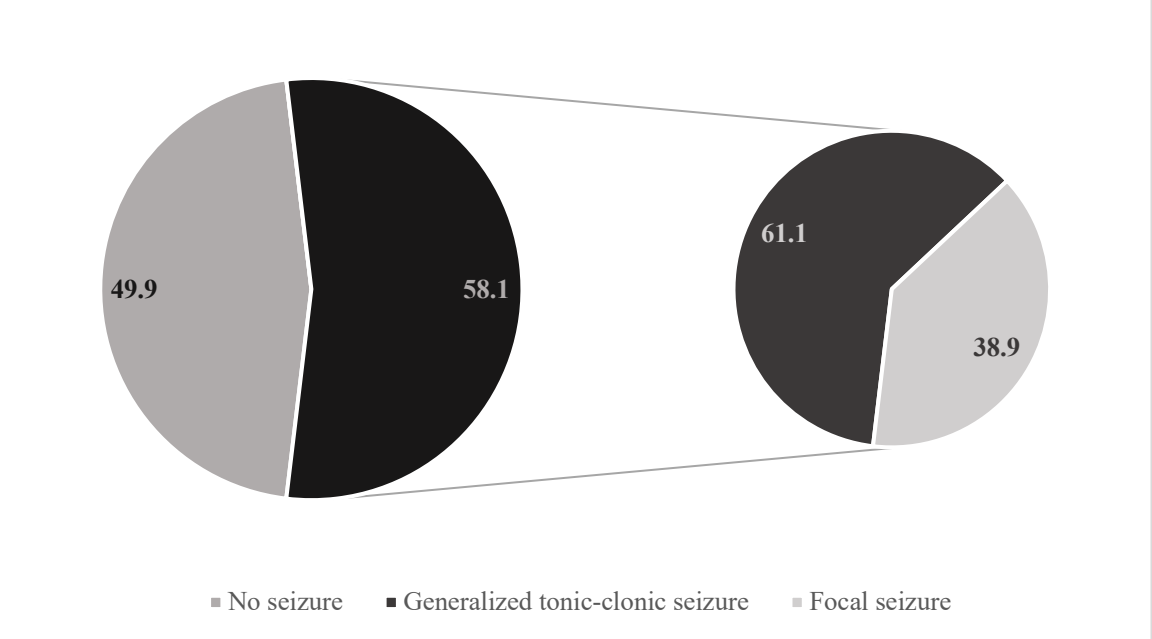

Figure 17. The percentage of patients with initial clinical presentation with seizures is shown. Eighteen (58.1%) initially presented with a seizure, eleven (61.1%) of which with a generalized tonic-clonic seizure, and seven (38.9%) with a focal seizure.

iii. Surgical strategy

All patients underwent open microscopic surgery with the goal of maximum safe resection. By means of shared decision-making 21 (67.7%) patients were operated on awake to facilitate the aforementioned goal (Table 4, Figure 18). Of these 21 patients, 18 (85.7%) had a left-sided tumor and three (14.3%) had a right-sided tumor (Table 4, Figure 15, Figure 18).

Intraoperative neuromonitoring was conducted in all but three cases. In contrast, during awake surgery, cortical and subcortical electrical stimulation lead to, for example, involuntary motor function, motor inhibition, and somatosensory or speech and language disturbances.

Due to tumorous infiltration into neighboring structures, the CG, CC and MFG had to be removed in parts (or fully in case of the MFG) in several patients. The CG was removed partially or in its majority in 16 (51.6%); the CC was removed partially in 14 (45.2%) and the MFG was removed partially and fully in eight (25.8%) and two (6.5%) patients, respectively. Surgical complications arose in two (6.5%) patients – one CSF fistula and one rebleeding.

Figure 18 – Type of surgery and laterality of tumor

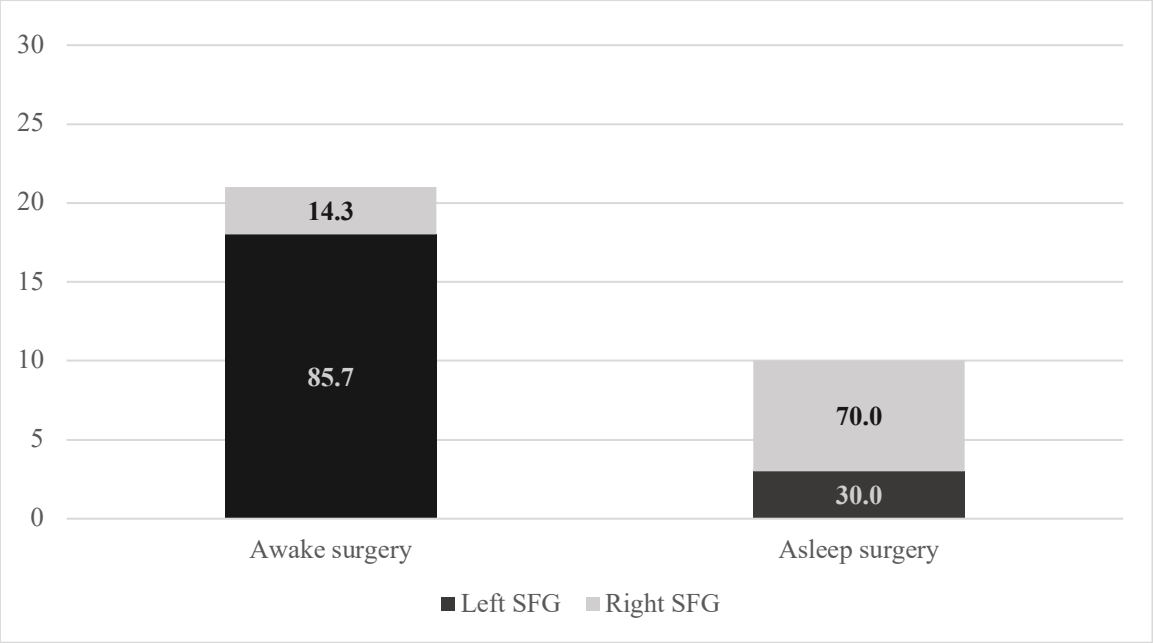

Figure 18. The number of patients operated on awake versus asleep is shown. Twenty-one (67.7%) patients underwent awake surgery, and ten (32.3%) underwent asleep surgery. Of the 21 patients operated on awake, 18 (85.7%) presented with a tumor in the left SFG, and three (14.3%) with a

tumor in the right SFG. Conversely, of the ten patients that underwent asleep surgery, three (30.0%) presented with a tumor in the left SFG, and seven (70.0%) presented with a right-sided tumor.

iv. Postoperative outcomes and considerations

Gross total tumor resection (GTR) was achieved in 22 (71.0%) patients (Figure 19). The remaining nine (29.0%) patients underwent subtotal resection (STR) to maintain neuro(psycho)logical function (Figure 19).

Transient neuro(psycho)logical deficits were present in 20 (64.5%) patients, including symptoms characteristic of SMA syndrome such as mutism, aphasia, contralateral hemiparesis/hemiplegia, psychomotor slowing, and concentration difficulties (Table 5 and Figure 20). Most of these patients improved significantly during the remaining hospital stay with all but three patients having no neuro(psycho)logical deficits by the postoperative 12-month follow-up mark (Table 5 and Figure 20). These three patients were the only patients with permanent neuro(psycho)logical deficits, including one with persistent left-sided hemiparesis of both the upper and lower left extremity and two with persistent psychomotor slowing (Table 5).

The median KPS score at three months and 12 months postoperatively was 90% and 100%, respectively (Range: 60% to 100% and 40% to 100%, respectively).

Adjuvant therapy was administered to 19 (61.3%) patients, with combined radiotherapy and chemotherapy being the choice in 17 (89.5%) cases. All eight glioblastomas were treated with combined radiotherapy and chemotherapy. Seven of eleven (63.6%) astrocytomas received some form of adjuvant therapy, with six receiving combined radiotherapy and chemotherapy, and one treated solely with radiotherapy. Three of eight (37.5%) oligodendrogliomas were treated with postoperative radiotherapy and chemotherapy.

After (the first) surgery, patients returned to their preoperative line of work in 21 (80.8%) cases, whereas five (19.2%) patients did not return to work (Figure 21). Five patients were excluded from this analysis as they had already retired before having surgery.

Figure 19 – Extent of surgical resection

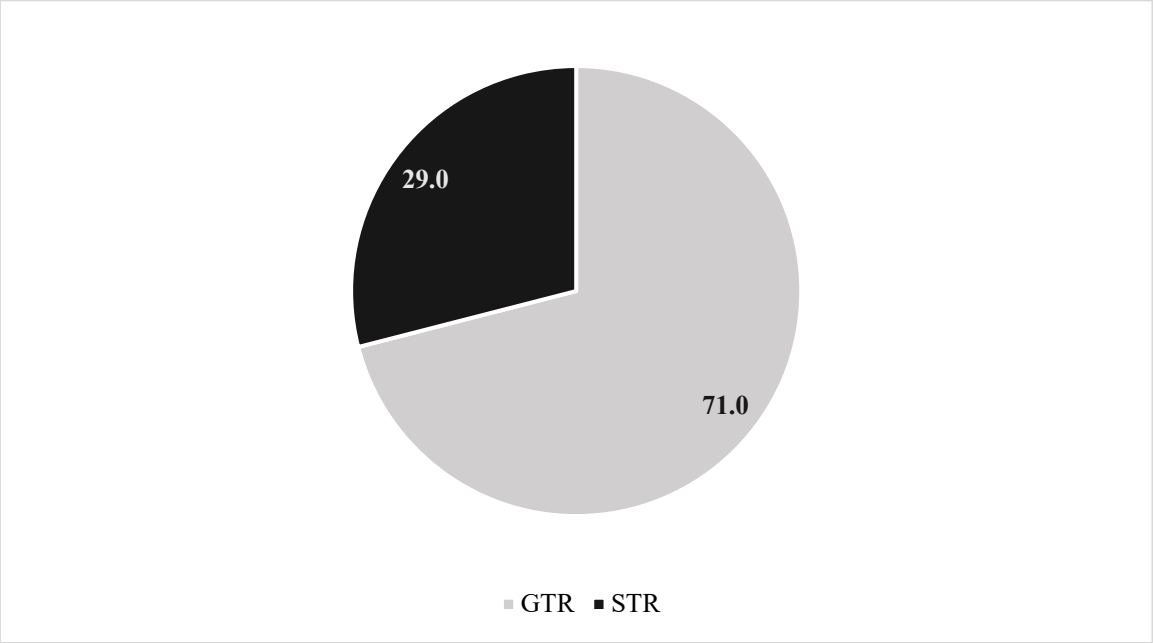

Figure 19. The percentage of patients with GTR and STR is shown. In 22 (71.0%) patients GTR was attainable, whereas in nine (29.0%) patients only STR was possible due to functional limits.

Figure 20 – Transient and permanent neuro(psycho)logical deficits

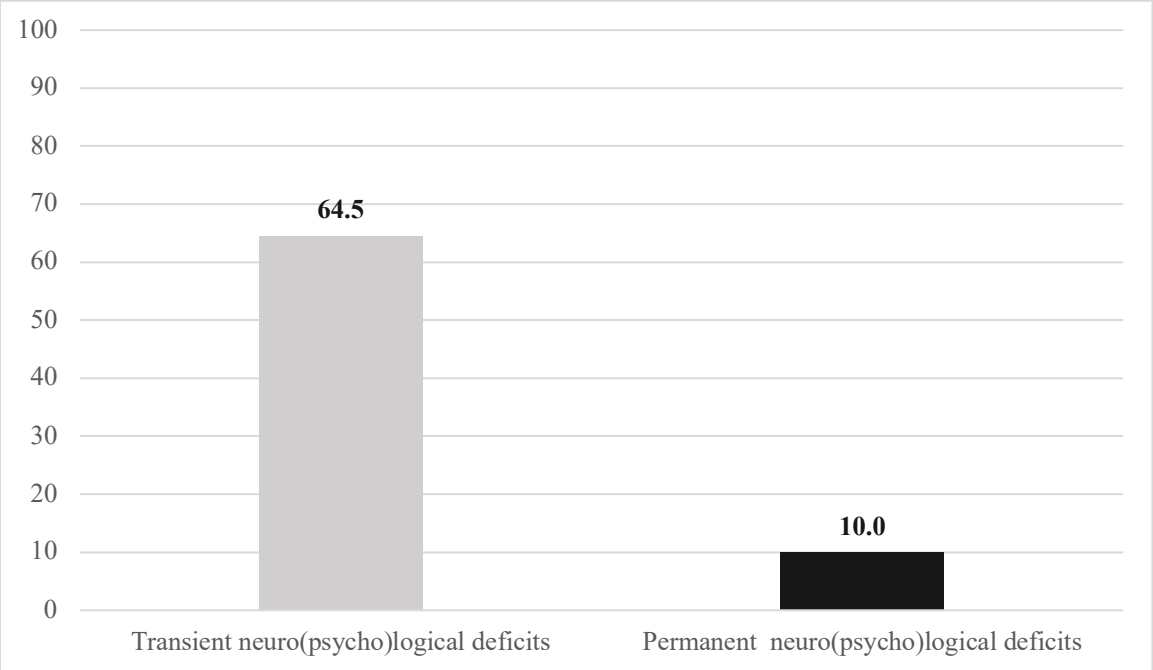

Figure 20. The percentage of deficits is shown. Transient and permanent neuro(psycho)logical deficits were present in 20 (64.5%) patients and three (10.0%) patients, respectively.

Figure 21 – Return to work

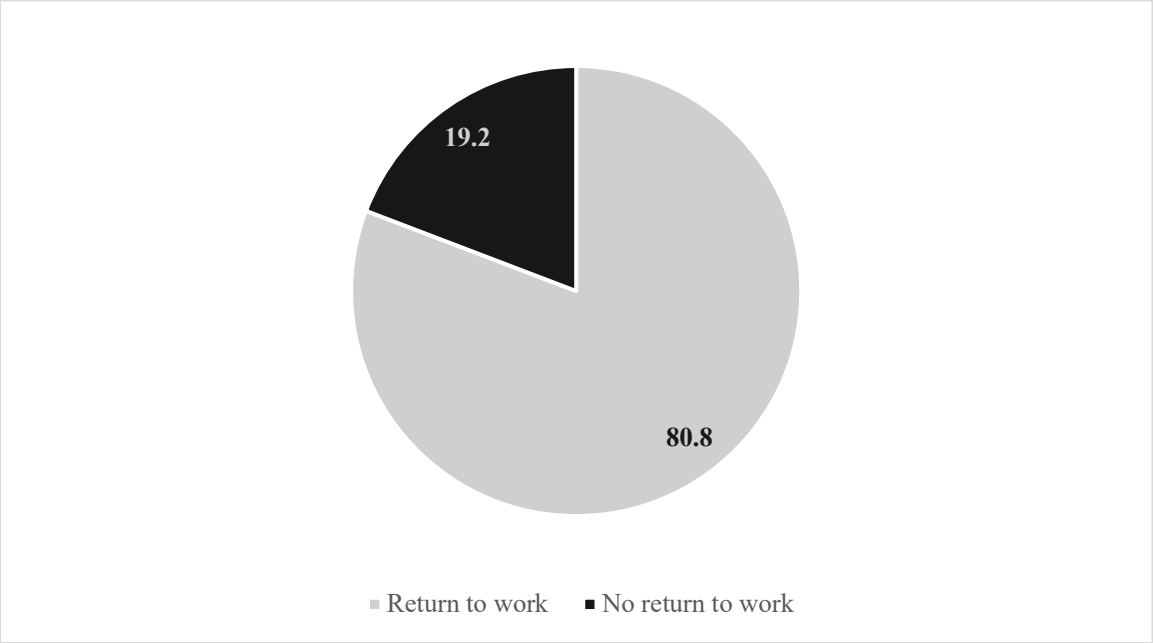

Figure 21. The percentage of patients with their respective return to work status is shown. Twenty-one (80.8%) patients returned to work, five (19.2%) did not return.

Table 5 – (Post)operative outcomes

ID	Surgical complications	TN(P)D	PN(P)D	Resection of CG	Resection of CC	Resection of MFG	Post-op. hospital stay
SFG1	--	Nearly complete aphasia; language-dominant SMA syndrome	--	partially	partially	fully	8 days
SFG2	--	Word-finding difficulty	--	partially	partially	partially	6 days
SFG3	--	--	--	--	partially	--	6 days
SFG4	--	Severe hemi-syndrome (SMA syndrome)	--	--	--	--	5 days
SFG5	--	--	--	partially	partially	--	5 days
SFG6	--	Mnestic and concentration difficulty	--	--	--	partially	5 days
SFG7	--	Psychomotor slowing, reduced drive, emotional blunting	--	partially	--	--	5 days
SFG8	--	Mild word-finding difficulty, slight right-sided weakness	--	--	--	--	5 days

SFG9	--	Mild word-finding difficulty	--	--	--	--	5 days
SFG10	--	Left-sided hemiplegia	Left-sided hemiparesis	partially	partially	--	15 days
SFG11	CSF fistula	--	--	partially	--	--	17 days
SFG12	--	--	--	--	--	--	7 days
SFG13	--	Word-finding difficulty, psychomotor slowing	Psychomotor slowing	partially	partially	--	8 days
SFG14	--	--	--	--	--	--	5 days
SFG15	--	Mutism, limited spontaneous speech, reduced resilience	--	partially	partially	--	7 days
SFG16	--	--	--	--	--	--	4 days
SFG17	--	Speech initiation problems, word-finding difficulty, fine motor impairment of right hand	--	--	partially	--	8 days
SFG18	--	Word-finding difficulty, poverty of speech, executive dysfunction	--	--	partially	partially	5 days
SFG19	--	Speech initiation problems, speech production difficulty, delayed motor response of right side	--	partially	partially	--	5 days
SFG20	--	--	--	partially	--	--	5 days
SFG21	--	Poverty of speech, emotional blunting	--	--	--	--	9 days
SFG22	--	Word-finding difficulty, right-sided leg-predominant hemiataxia	--	--	--	--	5 days
SFG23	Rebleeding	Slight right-sided hemiparesis, aphasia	--	partially	partially	partially	35 days
SFG24	--	--	--	--	--	partially	4 days

SFG25	--	Aphasia, right-sided hemiplegia	--	--	--	--	6 days
SFG26	--	Psychomotor slowing, decreased responsiveness	--	partially	--	--	5 days
SFG27	--	Tiredness, delayed responsiveness, left-sided hemiparesis	--	partially	--	partially	7 days
SFG28	--	--	--	--	--	--	36 days
SFG29	--	--	--	partially	partially	partially	7 days
SFG30	--	Severe word-finding difficulty, psychomotor slowing, disorientation	Psychomotor slowing, confusion	partially	partially	fully	6 days
SFG31	--	Personality change, psycho-motor slowing	--	partially	partially	partially	5 days

Table 5. (Post)operative outcomes of the study population are shown. TN(D)P = transient neuro(psycho)logical deficits, PN(D)P = permanent neuro(psycho)logical deficits, m = missing.

v. Tumor recurrences and re-resection

Seven (22.6%) patients underwent multiple resections up until 30 June 2023; five underwent a total of two surgeries (including the first resection), and two patients underwent a total of three surgeries (initial surgery + two further resections).

In all instances, indication for surgery was made upon follow-up MRI scans showing tumor recurrence or residual tumor progression. None of the patients showed preoperative clinical deterioration. Preoperative tumor volume before the second surgery was again determined on preoperative MRI and ranged from 7.66cm^3 to 104.17cm^3 with a median of 16.50cm^3.

Transient and permanent neuro(psycho)logical deficits were present in four of seven (57.1%) and two of seven (28.6%) patients, respectively.

vi. Tumor volume and neuro(psycho)logical deficits

Binary logistic regression models were created to assess whether preoperative tumor volume determined on MRI predicted transient and permanent postoperative neuro(psycho)logical deficits.

The first model was not statistically significant as can be seen by $p = 0.111$ (Table 6), therefore indicating that preoperative tumor volume cannot be assumed to be a predictor for postoperative transient neuro(psycho)logical deficits.

The second model was statistically significant, therefore indicating that preoperative tumor volume can be assumed a predictor for postoperative permanent neuro(psycho)logical deficits. For each unit increase in tumor volume, the odds of experiencing postoperative permanent neuro(psycho)logical deficits decreased by 89.3% (Exp(B) = 0.107, $p < 0.001$) (Table 6).

vii. WHO CNS grade and neuro(psycho)logical deficits

A Chi-Square test of independence was performed to assess whether the WHO CNS grade predicted transient neuro(psycho)logical deficits. The test resulted in a $X^2(3) = 9.14$, $p = 0.028$ (Table 6) suggesting a statistically significant association. Post-hoc pairwise comparisons using standardized residuals revealed no significant residuals, as no standardized residual exceeded the ±1.96 threshold, indicating that no specific WHO CNS grade was significantly associated with the presence of transient neuro(psycho)logical deficits.

A similar test was performed to assess whether the WHO CNS grade predicted permanent neuro(psycho)logical deficits. The test resulted in a $X^2(3) = 8.12$, $p = 0.044$ (Table 4) suggesting a statistically significant association. Post-hoc pairwise comparisons using standardized residuals revealed that the relationship between WHO CNS grades and postoperative permanent neuro(psycho)logical was particularly significant for tumors of WHO CNS grade 4, where the standardized residual exceeded ±1.96 (2.3). Other comparisons did not show statistically significant results.

viii. Resection of CG and neuro(psycho)logical deficits

A Fisher's Exact Test was performed to analyze whether the partial resection of the cingulate gyrus, and thereby the cingulum, predicted transient neuro(psycho)logical deficits. The test indicates there is no statistically significant association, $p = 0.716$ (Table 6).

Equally, the test analyzing a possible correlation between the partial resection of the CG and the incidence of permanent neuro(psycho)logical deficits also did not indicate a statistically significant correlation, $p = 0.226$ (Table 6).

ix. Resection of CC and neuro(psycho)logical deficits

Once more, a Fisher's Exact Test was performed to assess whether the partial resection of the CC would predict transient neuro(psycho)logical deficits. The result indicates there is no statistically significant association, $p = 0.707$ (Table 6).

Likewise, the test assessing whether the partial resection of the CC would be a predictor of permanent neuro(psycho)logical deficits also did not suggest a statistically significant association, $p = 0.081$ (Table 6).

x. Resection of MFG and neuro(psycho)logical deficits

The Chi-Square test of independence performed to gauge a possible correlation between the resection of the MFG and the occurrence of transient neuro(psycho)logical deficits did not suggest a statistically significant association, $p = 0.371$ (Table 6).

Correspondingly, a Chi-Square test of independence was performed to assess whether the resection of the MFG would predict permanent neuro(psycho)logical deficits; the result does not favor a conclusion of a statistically significant association, $p = 0.101$ (Table 6).

xi. Laterality of tumor and neuro(psycho)logical deficits

A Fisher's Exact Test was performed to assess whether the laterality of the tumor (left versus right SFG) predicted transient neuro(psycho)logical deficits. The test indicates there is no statistically significant association, $p = 0.262$ (Table 6).

Similarly, the test assessing whether the laterality of the tumor (left versus right SFG) predicted permanent neuro(psycho)logical deficits also did not suggest a statistically significant association, $p = 0.237$ (Table 6).

xii. Type of surgery and neuro(psycho)logical deficits

A Fisher's Exact Test was performed to assess whether the type of surgery (awake versus asleep) predicted transient neuro(psycho)logical deficits. The test indicates there is no statistically significant association, $p = 1.000$ (Table 6).

In contrast, the test assessing whether the type of surgery (awake versus asleep) predicted permanent neuro(psycho)logical deficits suggested a statistically significant association, $p = 0.027$ (Table 6). All patients ($n = 3$, 10.0%) who experienced permanent neuro(psycho)logical deficits after their first surgery were operated under general anesthesia.

xiii. Transient and permanent neuro(psycho)logical deficits

A Fisher's Exact Test was performed to assess whether transient neuro(psycho)logical deficits predicted their persistence, and, therefore, the existence of permanent deficits. The test indicates there is no statistically significant association, $p = 0.535$ (Table 6).

Table 6 – Prediction analysis

Predictor	Outcome	Test	*p*-value
Preoperative tumor volume	TN(P)D	Binary logistic regression	0.111
	PN(P)D		< 0.001*
WHO CNS grade	TN(P)D	Chi-Square test of independence	0.028*
	PN(P)D		0.044*
Resection of CG	TN(P)D	Fisher's Exact Test	0.716
	PN(P)D		0.226
Resection of CC	TN(P)D	Fisher's Exact Test	0.707
	PN(P)D		0.081
Resection of MFG	TN(P)D	Chi-Square test of independence	0.371
	PN(P)D		0.101
Tumor laterality	TN(P)D	Fisher's Exact Test	0.262
	PN(P)D		0.237
Type of surgery	TN(P)D	Fisher's Exact Test	1.000
	PN(P)D		0.027
Transient neuro(psycho)logical deficits	PN(P)D	Fisher's Exact Test	0.535

Table 6. Prediction analysis. TN(D)P = transient neuro(psycho)logical deficits, PN(D)P = permanent neuro(psycho)logical deficits. Statistically significant predictors are indicated with *.

IV. Discussion

In this study, we looked at a specific patient cohort with intrinsic brain tumors primarily located in the SFG and their treatment and subsequent outcome. We examined the frequencies of not only transient and permanent neurological deficits (91), but also those of neuropsychological deficits (92).

We explored the type of postoperative neuro(psycho)logical deficits and their development over time with special consideration of symptoms associated with the resection of the SMA, which is located in the SFG (81), and the subsequent development of SMA syndrome.

Additionally, we analyzed whether factors such as preoperative tumor volume, WHO CNS grade, resection of the CG and/or CC and/or MFG, type of surgery – awake versus asleep (93-95) – and laterality (96, 97) of tumor (left SFG versus right SFG) were predictors of postoperative neuro(psycho)logical deficits, either solely transient or permanent or both. Further, we looked at whether the presence of transient neuro(psycho)logical deficits was associated with their persistence over time, and thus, the presence of permanent deficits.

i. The supplementary motor area and the SMA syndrome

Functional anatomical consideration of the SFG places special emphasis on the SMA, which is often affected during surgical resection of intrinsic brain tumors in the frontal lobe. It can further be divided into the pre-SMA and SMA-proper, and occupies the posterior-most aspect of the SFG (81, 82), primarily located on the medial aspect of the SFG, just anterior to the leg presentation of the precentral gyrus (84). The SMA plays an important role in the initiation, planning and execution of motor and speech function (84), thereby being of important consideration in surgery of the frontal lobe and is consequently to be monitored closely using intraoperative direct cortical and subcortical electrical stimulation, especially during awake surgery. The SMA has also been linked to various neuropsychological or cognitive functions, such as working memory and attention (85, 86), which present an understudied aspect that has so far not been paid enough attention to. Keeping in mind its important role in motor and language functioning as well as cognitive processes, its preservation during surgery should be considered to avoid postoperative neuro(psycho)logical deficits.

Postoperative neuro(psycho)logical deficits can generally be classified into transient and permanent deficits, by their very definition affecting patients' postoperative recovery and quality of life significantly. Our study shows that 20 (64.5%) patients experienced some form of transient postoperative neuro(psycho)logical deficits, which could be attributed to the surgical resection as most of these deficits had not been present prior to surgery. These deficits included language and speech disturbances, motor deficits, such as contralateral hemiparesis or even hemiplegia, fine motor deficits, and psychomotor slowing. These symptoms have been described as classic symptoms of the SMA syndrome. Depending on the predominance of either motor or language deficits, the SMA syndrome can further be classified into a motor-dominant or language-dominant SMA syndrome (87). Even though the importance of the SMA in cognitive processes has been shown, a specific subclassification, such as "cognitive-dominant" or "neuropsychologically-dominant" has not yet been established. This distinction dependent on the primary neurological deficits can largely be made by assessing which part of the SMA has been resected during surgery. If it was primarily the SMA-proper that was resected, patients tend to experience a motor-dominant SMA syndrome, whereas primary resection of the pre-SMA tends to cause a language-dominant SMA syndrome alongside cognitive or neuropsychological deficits (87, 88).

Previous studies, such as by Peraud et al., have shown a similarly high percentage of initial postoperative neuro(psycho)logical deficits as the numbers presented by us. In their case, patients showed new or more pronounced motor or speech deficits in 83.3% and 64.3% of cases, respectively (91). They compared their findings to a similarly high rate (89%), which was reported by Zentner et al. (98). Numbers published by Young et al. were relatively similar to ours, with 60.7% of patients developing SMA syndrome (99). In contrast, a more recent study by De Maria et al. published in 2025 observed postoperative neuro(psycho)logical deficits in only 42% of their patient cohort (100). This difference in the incidence of the SMA syndrome following surgical resection of the SMA has been previously discussed by Samuel et al. (101), showing a wide range of initial deficits associated to SMA syndrome spanning from 23% to 100%.

Interestingly, Duffau et al. observed there to sometimes be a delayed onset of SMA syndrome (102), meaning no neuro(psychological) deficit was observed when tumor resection was completed, yet the patient still developed SMA syndrome within 30 minutes of the end of the operation. We also observed this phenomenon routinely as intraoperative

monitoring and testing during awake surgery do not show any deficits, yet patients regularly awake with classical symptoms of SMA syndrome. According to Duffau et al. there are two hypotheses that could explain this phenomenon (102). First, there is sufficient residual activity in an oscillatory neural loop by means of the thalamocortical (103) and corticocortical (104) networks for the execution of function to take place but not its initiation. Another explanation for this could be an immediate yet short-term neuroplasticity mechanism, which is based on now-exposed parallel networks. The unmasking of intracortical networks (105) could therefore facilitate the assumption of neuro(psycho)logical function, thereby explaining the lack of neurol(psycho)logical deficits during or immediately after surgical resection. However, this reorganization may at first only yield temporary compensatory mechanisms as it may be able to assume the transient execution of function but not its re-initiation. Furthermore, these newly uncovered networks may postoperatively be inhibited – thus leading to the development of SMA syndrome – due to postoperative edema or idling neurons (102).

Several studies have shown that most patients' SMA syndrome is transient and does not necessarily lead to permanent neuro(psycho)logical deficits (106, 107), as was first described by Laplane et al. in 1977 (108). However, Baker et al. demonstrated that some patients do, in fact, experience persisting deficits (109). This can also be observed in our study cohort, as three (10.0%) patients had permanent deficits. This corresponds to a decrease of 85% when comparing the number of patients with transient to the number of patients with permanent deficits. This is also supported by our analysis showing no statistically significant association between the presence of transient deficits and their persistence in the form of permanent deficits (Fisher's Exact Test, $p = 0.535$). Due to this mostly transient nature of the SMA syndrome questions about recovery, its underlying processes and the likelihood of said recovery need to be asked to best plan the surgical resection by maximizing the extent of resection while maintaining neuro(psycho)logical function.

ii. SMA syndrome recovery and connectomic cerebral organization

In our study cohort, only three patients (10.0%) experienced permanent neuro(psycho)logical deficits. This is in stark contrast to the initial percentage of deficits, which saw 20 (64.5%) patients suffer from transient deficits. This suggests that only 15% of patients have persisting neuro(psycho)logical deficits. It can therefore be concluded that most patients experiencing postoperative SMA syndrome, even with severe

neuro(psycho)logical deficits, can expect to fully or largely recover within a few weeks to months after surgery (87, 106, 107, 110, 111). Purely neurological deficits do on average resolve more quickly than their neuropsychological or cognitive counterparts, with most of the neurological function returning or starting to return within the first one to two weeks after surgery. Meanwhile, cognitive deficits may take a bit longer to recover. Nevertheless, this recovery potential highlights the plasticity of the human brain, which is hypothesized to be linked to the functional connectivity of the SFG, thus reiterating connectomic cerebral organization (112), especially interhemispheric connectivity (113, 114).

The SMA-proper is part of a motor, language and cognitive network that involves the ipsilateral pre-SMA, the lateral premotor cortex, the primary motor cortex as well as the contralateral pre-SMA and SMA-proper and the corpus callosum (106, 115). Especially the connections to and via the CC have been shown to play a pivotal role in quicker and complete recovery, thereby supporting the hypothesis that contralateral homologous cerebral areas are of vital importance in compensating the loss of function induced by surgical removal of a specific brain area (113). It can therefore be assumed that the (partial) resection of the CC, but also of the CG and MFG, for oncological control of the disease may lead to a decreased likelihood of recovery concerning surgically-induced neuro(psycho)logical deficits. Our results do not concur with this hypothesis as there was no statistically significant correlation between the partial resection of the CC and either transient or permanent neuro(psycho)logical deficits (Fisher's Exact Test, $p = 0.707$, $p = 0.081$). The latter p-value, $p = 0.081$, which describes the possible correlation between the partial resection of the CC and the development of permanent deficits, is relatively close to the 5% mark of statistical significance, suggesting there is a possible correlation, albeit not statistically significant in our study cohort.

These findings further emphasize a much-discussed topic within neurosurgery, namely connectome-based neurosurgery, which rejects the traditional localizationalist theory of cerebral organization and expands on the associationist theory of cerebral organization. The localizationalist view assumes the brain to have "critical", or often referred to as "eloquent", cortical areas, that are responsible for a certain neurological function (112). The prime example of this is the motor speech area, first described by Broca, and traditionally assumed to be the home of speech production and specifically located in the IFG. These localizationalist principles lead to the cerebral concept that the same neurological functions are located in the same or similar kind of areas across individuals, thereby creating a map of

critical areas to avoid and safe areas that can be targeted during surgery. Another prominent brain area is Wernicke's area, located in the posterior aspect of the superior temporal gyrus and serving as a complementary part to Broca's area, which is important for speech comprehension. Its namesake is responsible for the associationist view of functional neuroanatomy believing in connections between "critical" or "eloquent" areas and associating cerebral functions to this subcortical connection. The paradigm of the "connectomic" cerebral organization, however, disagrees with the idea of eloquent cortical areas and mere connections between them, but suggests that white matter tracts serve for network-level processing and give rise to complex cerebral function (112, 116), and therefore serve as much more than just linkages between mostly independent brain areas.

It is therefore apparent that to reduce postoperative neuro(psycho)logical deficits, special attention should be placed on subcortical mapping and white matter tract preservation. Thus, it can be concluded that the reason why the SMA syndrome is mostly transient and not permanent is due to the resilience of the network the SMA is part of and not due to its cortical redundancy. This is underscored by the fact that a significant percentage of patients, 23% to 100% (101), do experience immediate postoperative deficits. Future research, such as the work by Ille et al. (117), is needed to assess how such networks can be used to improve postoperative outcomes for patients or speed up their recovery and rehabilitation.

iii. The connectomic organization of the SFG

The SFG has, by virtue of its functional anatomical aspects and previous research works, been assumed and proven to have numerous subcortical connections, which according to the connectomic cerebral organization may play an important role in selected network-level neuro(psycho)logical functions. As the deficits associated with SMA syndrome include motor, language and cognitive deficits, special attention should be given to the surrounding subcortical fiber tracts, which have repeatedly been studied and analyzed in post-mortem brains using Klingler dissection.

One domain of the SMA syndrome is represented by possible speech difficulties such as mutism or speech production difficulties. According to the localizationist view the motor speech area, commonly referred to as Broca's area, is located in the IFG, and thereby theoretically out of reach during resection of tumors in the SFG. However, dissection and tractography allow for the identification of the frontal aslant tract (FAT) whose fibers commence within the superolateral aspect of the SFG and end in the frontal operculum and

pars triangularis of the IFG (82). The FAT can therefore be considered a major part in why resection of the SMA may cause (mostly transient) speech production difficulties, but also difficulties in neuropsychological/cognitive domains such as working memory, social community tasks, or attention (118). In addition, it has been shown that close resection to the FAT can cause motor impairment (119). Thus, if the resection of the SMA is necessary for oncological control, careful consideration should consequently be placed on how the resection is carried out in order to best prevent postoperative deficits. Considering the direction of the motor fibers, coronal cuts parallel to the precentral and postcentral gyri should be made to decrease the likelihood of causing major deficits (120). The importance of the FAT in the development of SMA syndrome was demonstrated by Young et al. (99), with all patients whose FAT was resected developing SMA syndrome. Interestingly, preserving the FAT did not prevent the occurrence of an SMA in all cases, suggesting other subcortical fiber tracts to be involved in the pathogenesis, too.

Further subcortical connections can be observed with the cingulum. Its fibers originate from the medial surface of the SFG and continue within the CG to either terminate in the precuneus, or in the parahippocampal gyrus and uncus after having curved around the splenium of the CC (82). Various neuropsychological/cognitive and emotional processes have been attributed to the cingulum. For example, targeting the anterior cingulum can be considered for patients with chronic pain, whereas the temporal aspect of the cingulum has been associated with mnestic deficits. The cingulum has also been shown to play a part in emotion and mood and hence was commonly targeted in psychosurgery (121). It is therefore reasonable to assume that resecting the CG would lead to the presence of postoperative neuro(psycho)logical deficits and could consequently contribute to the development of SMA syndrome. There was no statistically significant correlation between the (partial) resection of the CG and postoperative transient or permanent neuro(psycho)logical deficits (Fisher's Exact Test, $p = 0.716$, $p = 0.226$). This could be explained by two hypotheses: First, the majority of our patients underwent awake surgery enabling the surgeon to identify the local functional boundaries and thus limit the likelihood of postoperative transient or permanent neuro(psycho)logical deficits induced by the resection of the CG. Second, the transient nature of the SMA syndrome may suggest that the resection of the CG may indeed contribute to the occurrence of neuro(psycho)logical deficits in select cases, however, a statistically significant correlation cannot be attributed due to the high likelihood of recovery of patients with SMA syndrome.

In addition, the SFG, primarily its most posterior aspect, is connected to the superior parietal lobule and precuneus via the superior longitudinal fasciculus I (SLF-I).(112, 122) The functional contribution of the SLF-I is still not understood in its entirety. Through its connections with the medial and superior parietal regions, the dorsal premotor region and the SMA, it is presumed to contribute to the regulation of higher motor function.(123) Its surgical disruption can consequently be assumed to have an impact on the development of SMA syndrome.

Finally, the SFG is heavily connected to its contralateral counterpart through callosal fibers of the genu and body of the CC. Interestingly, more anteriorly found fibers project horizontally through the genu of the CC to terminate within the frontal poles, whereas more posteriorly located fibers project vertically through the body of the CC to connect the two SFGs (82). Connections via the CC have been shown to facilitate and accelerate recovery of neuro(psycho)logical function following surgery (113). Despite this our results do not show a statistically significant correlation between the partial removal of the CC and the presence of postoperative transient or permanent neuro(psycho)logical deficits (Fisher's Exact Test, $p = 0.707$, $p = 0.081$). Our hypotheses about why the resection of the CG and the lack of a statistically significant correlation with the occurrence of postoperative neuro(psycho)logical deficits, can be assumed for the CC as well. However, the *p*-value describing the correlation between the resection of callosal fibers and permanent neuro(psycho)logical deficits is approaching the 5% mark of statistical significance, which may indicate a possible correlation, albeit not statistically significant in our study cohort.

Considering the thorough subcortical white matter connections that the SFG has, it can be assumed that these networks substantially contribute to patients' recovery potential from surgically induced SMA syndrome.

iv. The necessity of awake surgery

The laterality of the tumor (left versus right SFG) was not shown to be a predictor of either transient or permanent neuro(psycho)logical deficits in our dataset.

Laterality was, however, an important consideration in whether awake or asleep surgery was performed, as 18 of 21 (85.7%) patients with a left-sided tumor were operated on awake, in contrast to three of ten (30.0%) patients with a right-sided tumor. The primary reason for this disparity lies in the fact that in the majority of patients speech function is primarily located within the left hemisphere, causing the likelihood of this subset of patients

undergoing awake surgery to be much higher when compared to patients with right-sided tumors. However, this approach should be reconsidered as it has been demonstrated that the right frontal lobe is especially important for higher cognitive functions (124), which can now – in comparison to the past – also be tested and monitored during awake surgery.

Our data suggest that awake surgery decreases the likelihood of patients' sustaining permanent neuro(psycho)logical deficits. All patients who experienced permanent deficits (n = 3, 10.0%) did undergo surgery under general anesthesia. A Fisher's Exact Test has yielded a significant correlation, $p = 0.027$, thus suggesting awake surgery to decrease the likelihood of permanent deficits. This concurs with previously published literature (54, 125-127).

As discussed, our study shows a similar percentage of postoperative transient neuro(psycho)logical deficits as other previously published studies; however, our percentage of permanent neuro(psycho)logical deficits is considerably higher than a recent study published by Bauman et al. (128). They report permanent new deficits in only 3% of patients, whereas we report a permanent deficit rate of 10.0%. This may be due to most studies only focusing on purely neurological deficits (91, 100, 128), and not considering neuropsychological deficits. If we solely consider permanent neurological deficits and do not include neuropsychological deficits, our permanent deficit rate decreases from 10.0% to 3.2%. Preserving neuropsychological and cognitive function is, however, of great importance to the health-related quality of life patients are experiencing after surgical treatment (129), which in turn has proven to be a prognostic factor for overall survival (130, 131). This may furthermore be of wider economic consideration when patients, particularly with LGG, are able to return to their preoperative line of work and are thus able to contribute to a population's economy and are not reliant on social welfare programs and/or family members to financially support them.

Considering the SMA's important role in networks facilitating language and motor function as well as cognitive and neuropsychological aspects, we encourage awake surgery to be considered regularly as it allows to best monitor and preserve neuro(psycho)logical function during surgery (54, 125-127) and, consequently, leads to an improvement of postoperative health-related quality of life (129) as well as increased overall survival (130, 131).

v. Study strengths and limitations

It should be noted that this study must be interpreted within the confines of several methodological limitations. Most of these are inherent to our study's retrospective design. Retrospective chart review includes limitations such as inconsistent charting and subsequent missing data. This was largely mitigated as nearly all the patients included in our study were operated on by one of the authors as either the primary or assistant surgeon. Consequently, parts of the missing data could be completed after initial data extraction allowing for more reliable and conclusive data analysis.

A further limitation is the – in general terms – relatively small sample size of 31 patients. However, in a neurosurgical context this can also be regarded as one of the strengths of our study, as we included 31 patients with a homologous location of different types of intrinsic brain tumors, allowing for specific location-dependent analysis and conclusions about postoperative outcomes to be drawn. Still, we hope to expand our study in the future to increase the statistical power even further.

In addition, the inclusion of postoperative transient and permanent neuropsychological deficits, next to "classic" neurological deficits, is largely missing in currently available literature. Therefore, our study provides an important additional layer knowledge about patient management, which should be taken into consideration routinely.

vi. Suggestions for future research

Even though the sample size of 31 patients can be regarded as a strength of our present study, further research about this topic by means of including more patients should be done to confirm or disprove our hypotheses. An interesting aspect to further evaluate is the resection of parts of the CC and its possible correlation with the occurrence of postoperative permanent neuro(psycho)logical deficits; at the present time no statistically significant correlation was found, however, the p-value was approaching the 5% mark of statistical significance, emphasizing the importance of further research.

Considering the thorough subcortical white matter connections of the SFG and their importance in network-level execution of neuro(psycho)logical functions, a thorough analysis into the exact localization of the FAT, SLF-I, CG, and callosal fibers assessed by means of intraoperative cortical and subcortical electrical stimulation during awake surgery in comparison to advanced preoperative tractography imaging could be an important step of understanding the functional anatomy and connectivity of the SFG better.

Another interesting aspect would be the determination of recovery time of patients with SMA syndrome, specifically focusing on whether there is a difference in duration and timing between neurological deficits and neuropsychological deficits. Another aspect could be the differentiation between neurological deficits and neuropsychological deficits dependent on the subcortical white matter tracts resected during surgery, possibly allowing for more accurate postoperative deficit prediction, enabling surgeons to better inform patients about what can be expected during the immediate and long-term postoperative period.

Past research has shown that transcranial magnetic stimulation (TMS) can be beneficial in the recovery of patients having undergone brain tumor resection (117). Whether the use of TMS could benefit patients by, for example, reducing the recovery time when sustaining surgically induced SMA syndrome, should be studied.

V. Conclusion

In summary, our retrospective study discusses the surgery and outcomes of intrinsic brain tumors in the SFG, primarily focusing on the associated SMA syndrome that may arise with the resection or surgical manipulation of the SMA.

Next to “classic” postoperative neurological deficits, we also considered neuropsychological deficits, which were transiently present in 64.5% and permanently in 10% of patients. We found a statistically significant correlation between the type of surgery (awake versus asleep) and the presence of permanent neuro(psycho)logical deficits, suggesting the superiority of awake surgery. Conversely, we did not find a statistically significant correlation between the presence of transient and their persistence and, thus, the presence of permanent neuro(psycho)logical deficits, thereby underscoring the likelihood of full recovery after sustaining postoperative SMA syndrome.

We anticipate that more data will be collected in the future to provide further individualized treatment plans for patients that focus on both neurological as well as neuropsychological/cognitive outcomes to ensure the best balance between oncological outcome and health-related quality of life.

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