Aus der Klinik für Neurochirurgie
der Heinrich-Heine-Universität Düsseldorf
Komm. Direktor: Prof. Dr. med. Jan Frederick Cornelius

The influence of awake craniotomy and intraoperative neurophysiological monitoring in the overall survival of patients diagnosed with Glioblastoma
A single centered retrospective analysis

Dissertation

zur Erlangung des Grades eines Doktors der Medizin
der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

vorgelegt von

Marian Preetham Suresh Babu

2023

Als Inauguraldissertation gedruckt mit Genehmigung der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf

gez.:
Dekan: Prof. Dr. med. Nikolaj Klöcker
Erstgutachter: Prof. Dr. med. Michael Sabel
Zweitgutachter: Prof. Dr. med. Bernd Turowski

Obstacles are those frightful things you see when you take your eyes off the goal

- Hannah More

Dedicated to Sarah Suresh

My wife and my best friend

Summary

Surgical resection of the tumour is critical to treating glioblastomas. As the surgical settings for operating on glioblastomas have evolved, modern monitoring techniques, such as awake craniotomy and intraoperative neurophysiologic monitoring, have been incorporated. Using these state-of-the-art monitoring techniques, surgeons can operate on eloquent-area tumours without increasing postoperative morbidity. This study aims to analyse retrospectively the progression-free survival (PFS), overall survival (OAS) and post-operative outcomes of patients diagnosed with glioblastoma who underwent surgical resection between 2004 and 2018 in the university hospital of Duesseldorf under different surgical settings. A total of 1010 patients were analysed, 631 of which were considered eligible. Of these, 150 patients underwent a biopsy and were considered to have unresectable tumours. Of the 481 patients who underwent surgery, 160 were operated under general anaesthesia, 71 were operated awake with 60-Hz bipolar stimulation, 145 were operated with intraoperative neuromonitoring (IONM), and 105 were operated with a combination of awake and IONM.

We found that the number of biopsies decreased significantly with the incorporation of awake surgeries and intraoperative IONM. However, the extent of resection (EOR) achieved under different operative techniques showed no statistical significance favouring a particular operating setting. The National Institute of Health Stroke Scale (NIHSS), Karnofsky Performance Scale (KPS), progression-free survival and overall survival were analysed for the surgical cohort of 481 patients, as well as those who received adjuvant radio and chemotherapy according to the STUPP- protocol and those with IDH wild-type tumours with adjuvant STUPP therapy. The three-month KPS and NIHSS in patients operated with IONM and with a combination of awake and IONM was better than that of the patients operated without monitoring. PFS and OAS were not influenced by operating technique.

Based on the analysis, we observed that the incorporation of surgeries combining awake and IONM did not negatively influence the NIHSS or KPS. Instead, the significant decrease of biopsies suggested that the operability of eloquent tumours has increased considerably since the incorporation of awake and IONM surgeries. Thus, this study showed that using awake and IONM in surgeries increases the possibility of operating eloquent-area tumours without causing significant post-operative surgical morbidity for the patient.

Zusammenfassung

Ein entscheidender Aspekt bei der Behandlung von Glioblastomen ist die operative Entfernung des Tumorgewebes. Das operative Vorgehen bei der Behandlung von Glioblastomen hat sich konstant weiterentwickelt, indem neue moderne Monitoringtechniken wie Wachkraniotomie oder intraoperatives neurophysiologisches Monitoring (IONM) entwickelt wurden. Indem diese Monitoringtechniken als Goldstandard eingeführt wurden, ist es möglich geworden, auch Tumore in eloquenten Arealen ohne Steigerung der postoperativen Morbidität zu operieren. Als Ziel dieser Studie wurden retrospektiv das progressionsfreie Überleben (PFS), die Gesamtüberlebenszeit (OAS) und das postoperative Outcome von Patienten mit zwischen 2004 und 2018 am Universitätsklinikum Düsseldorf operierten Glioblastomen betrachtet. Insgesamt wurden 1010 Patienten zwischen 2004 und 2018 analysiert. 631 Patienten konnten eingeschlossen werden, von denen 150 lediglich eine Biopsie erhalten hatten. Patienten, welche lediglich biopsiert worden waren, wurden als inoperabel definiert. Bei den übrigen 481 Patienten wurde der Tumor reseziert. 160 Patienten wurden in Intubationsnarkose, 71 wach mit 60 Hz Stimulation, 145 mit IONM und 105 sowohl wach als auch mit IONM operiert. Seit Einführung moderner Monitoringtechniken ist die Anzahl der Biopsien signifikant zurückgegangen. Der Vergleich des Resektionsgrades (EOR) zeigte keine Signifikanz. Die NIHSS (National Institutes of Health Stroke Scale), der Karnofsky-Index (KPS), die PFS und OAS wurde bei der gesamten operativen Kohorte (481 Patienten), bei Patienten, welche operiert worden und adjuvante Strahlen- und Chemotherapie nach STUPP-Protokoll erhalten hatten, sowie bei Patienten, bei welchen zusätzlich zur Operation und STUPP-Schema immunhistologisch ein IDH Wildtyp festgestellt worden war, analysiert. Patienten, welche mit IONM oder wach/IONM operiert worden waren, hatten im Vergleich zu Patienten ohne Monitoring drei Monate nach Operation sowohl eine besseren NIHSS als auch eine bessere KPS. PFS und OAS wurden durch unterschiedliche Monitoringtechniken nicht beeinflusst. Zusammenfassend können wir feststellen, dass die Einführung von Wachoperationen in Kombination mit IONM keinen negativen Einfluss auf NIHSS oder KPS hat. Anhand des signifikanten Rückgangs von Biopsien sehen wir, dass die Operabilität von Tumoren in eloquenten Gehirnarealen erhöht wurde. Diese Studie zeigt, dass Wachoperationen und IONM das Operieren von Tumoren in eloquenten Arealen ohne signifikant negativen Einfluss auf die postoperative Morbidität möglich macht.

Abbreviations

18 FET	O-(2-[18F] fluoroethyl)-1-tyrosine
2-HG	2-hydroxyglutaric acid
5-ALA	5-Aminolevulinic acid
ANOVA	Analysis of variance
CDKN	Cyclin-dependent kinase inhibitor
CNS	Central nervous System
CT	Computer tomography
EEG	Electroencephalogram
EGFR	Epidermal growth factor receptor
EMG	Electromyography
EOR	Extent of resection
FGS	Fluorescence-guided surgery
Fig.	Figure
G	Gray
GA	General anaesthesia
GBM	Glioblastoma
GTR	Gross total resection
Hz	Hertz
ICD	International Classification of Diseases
IDH	Isocitrate dehydrogenase
IONM	Intraoperative neuromonitoring
kHz	Kilohertz
KPS	Karnofsky Performance Scale
m2	Square metres
mA	Milliampere
MEP	Motor-evoked potential
MGMT	O6- methylguanine-DNA methyltransferase
min	Minutes
mm	Millimetres
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NIHSS	National Institute of Health Stroke Scale
nm	Nanometres
OAS	Overall survival
PDMS	Patient data management systems
PET-MRI	Positron emission tomography–magnetic resonance imaging
PFS	Progression-free survival
PpIX	Protoporphyrin IX

PTEN	Phosphatase and tensin homolog
QOL	Quality of life
SPSS	Statistical Package for the Social Sciences
SSEP	Somatosensory evoked potential
TERT	Telomerase reverse transcriptase
TTF	Tumour treating fields
UKD	*Uniklinikum Düsseldorf*
VEGF	Vascular endothelial growth factor
WHO	World Health Organisation

INDEX

1 Introduction

Glioblastoma multiforme (GBM), one of the most aggressive forms of primary tumours of the central nervous system, has a grim prognosis despite maximum treatment. Recurrence of GBM following a surgical resection is nearly inevitable, and its management is typically not standardised but rather case dependent (Lc *et al.*, 2006). Therefore, constant research is needed to identify novel treatment strategies that increase the overall survival period of patients while ameliorating their quality of life (QOL). Currently, the standard of care for patients with GBM comprises surgical resection followed by radio and chemotherapy (Wang *et al.*, 2019).

Since GBM is an infiltrating tumour, surgical excision is often challenging. However, maximising the resection of the tumour plays a key role in the prognosis of the disease (Gerstner *et al.*, 2010; Molinaro *et al.*, 2020). Since the inception of awake craniotomy in glioma surgery, as well as the implementation of real-time monitoring aids, such as intraoperative neuromonitoring (IONM) and 5-Aminolevulinic acid (5 ALA), neurosurgeons have improved the extent of resection while preserving patients cognitive functions (Krieg *et al.*, 2012). However, whether the extent of resection and preservation of cognitive function can be improved further, whether the implementation of awake craniotomy and IONM have rendered the resection of eloquent-area tumours more safely resectable and whether these surgical techniques play a role in improving the QOL and overall survival (OAS) of patients with glioblastomas have yet to be determined. This retrospective study aims to investigate these questions.

1.1 Glioblastoma multiforme

1.1.1 Definition, aetiology and epidemiology

Glioblastoma is the most aggressive form of glioma and the most common primary malignant brain tumour, accounting for 16% of primary brain and central nervous system (CNS) neoplasms (Davis, 2016). In the USA, the average age-adjusted incidence of GBM is 3.2 per 100,000 population (Qt *et al.*, 2015). GBM is primarily diagnosed at older ages, with a median age of diagnosis of 64 years. It is also more prevalent in men than women. GBM is uncommon in children, accounting for approximately only 3% of all brain and CNS tumours reported among patients 0–19 years old (Jp *et al.*, 2014).

The aetiology of most malignant gliomas remains unclear, and the effects of formaldehyde, electromagnetic fields and nonionizing radiation have no correlation to the development of GBM (Davis, 2016). Hereditary syndromes, such as Li-Fraumeni syndrome and neurofibromatosis types 1 and 2, and therapeutic irradiations to the skull and brain in childhood have a predominant risk for glioma development. Since the overall incidence is low and no other major risk factors are known, gliomas may develop *de novo* within few weeks or months, and no screening for gliomas has yet been implemented (Batchelor *et al.*, 2017).

1.1.2 WHO classification of gliomas

WHO CNS tumour grades	
Tumour types	WHO grade
Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH mutant	II
Anaplastic astrocytoma, IDH mutant	III
Glioblastoma, IDH wildtype	IV
Glioblastoma, IDH mutant	IV
Diffuse midline glioma, H3 K27M mutant	IV
Oligodendroglioma, IDH mutant and 1p/19q codeleted	II
Anaplastic oligodendroglioma, IDH mutant and 1p/19q codeleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III

Table 1: WHO classification of astrocytic and oligodendroglial tumors, adapted from (Louis *et al.*, 2016)

In 2016, the World Health Organisation (WHO) revised the classification of CNS tumours (Table 1). For gliomas, the 2007 classification was based largely on the histological appearance of the tumour cells, while the 2016 classification identified these tumours based upon their molecular genetics (Louis et al., 2016). According to the classification, GBM are classified as grade IV gliomas—a highly malignant type of gliomas. Though the microscopic histopathological criteria for diagnosing GBM remained the same, the new classification system instituted molecular markers that

significantly influence the prognosis of patients diagnosed with GBM (Louis *et al.*, 2007; Batchelor *et al.*, 2017).

According to the 2016 classification, GBM can be broadly divided into isocitrate dehydrogenase (IDH)-wildtype glioblastomas and IDH mutant glioblastomas. IDH is a rate-limiting enzyme found in the Krebs cycle, and IDH 1 and 2 have recently been recognised as a notable potential therapeutic target in patients with gliomas. Because IDH mutations produce high levels of 2-hydroxyglutaric acid (2-HG), they inhibit the proliferation of glioma stem cells (Huang *et al.*, 2019).

IDH-wildtype glioblastomas have a rapid onset. They are typically characterised by telomerase reverse transcriptase (TERT) promoter mutations, epidermal growth factor receptor (EGFR) amplification and phosphatase and tensin homolog (PTEN) mutation. Due to the absence of a low-grade precursor, IDH-wildtype GBM are typically considered primary or *de novo* GBM (Batchelor *et al.*, 2017). Around 90% of all GBM fall under this category (Nobusawa *et al.*, 2009).

IDH mutant glioblastomas typically arise from an antecedent WHO grade II or WHO grade III glioma. Their median age of appearance is 44 years (Batchelor *et al.*, 2017). Due to their malignant evolution from pre-existing gliomas, they are considered secondary GBM (Louis *et al.*, 2016). These gliomas have a significantly better prognosis than wildtype glioblastomas.

Another important molecular marker is the O^{6-} methylguanine-DNA methyltransferase (MGMT) gene, which is located on the chromosome 10q26.3 and encodes the enzyme expressed in DNA repair. MGMT is a repairing gene that acts on the O^6 position of guanine at the DNA level, antagonising the alkylating effects of drugs such as temozolomide (Wick et al., 2014). Epigenetic silencing of the MGMT gene by promoter methylation reduces the MGMT protein expression and thereby increases the sensitivity of alkylating chemotherapeutics (Hegi *et al.*, 2005). Therefore, the presence of MGMT gene-promotor methylation is a positive prognostic factor for chemotherapy (Mansouri *et al.*, 2019).

Histology	WHO 2016	Grade	WHO 2021	Grade
Oligodendroglioma	Oligodendroglioma, IDH mutant and 1p/19q-codeleted	WHO grade II	Oligodendroglioma, IDH mutant and 1p/19q-codeleted	CNS WHO 2
Anaplastic oligodendroglioma	Anaplastic oligodendroglioma, IDH mutant and 1p/19q-codeleted	WHO grade III	Oligodendroglioma, IDH mutant and 1p/19q-codeleted	CNS WHO 3
Diffuse astrocytoma	Diffuse astrocytoma, IDH-wildtype or IDH mutant	WHO grade II	Astrocytoma, IDH mutant	CNS WHO 2
Anaplastic astrocytoma	Anaplastic astrocytoma, IDH-wildtype or IDH mutant	WHO grade III	Astrocytoma, IDH mutant	CNS WHO 3
Glioblastoma	Glioblastoma, IDH-wildtype or IDH mutant	WHO grade IV	Glioblastoma, IDH-wildtype	CNS WHO 4
Astrocytoma			Astrocytoma, IDH-mutant and CDKN2A/B homozygous deletion	CNS WHO 4
Astrocytoma			Glioblastoma, IDH-wildtype and TERT promotor mutation, EGFR amplification or gain/loss of chromosome 7/10	CNS WHO 4

Table 2: A comparison of the WHO classification of gliomas from 2021 and 2016, adapted from (Huang, 2022)

In 2021, the WHO published the fifth edition of the classification system for CNS tumours, which incorporated considerable changes to the 2016 version. Though an in-depth analysis of the classification system is beyond the scope of this dissertation, certain key concepts must be mentioned. The grading system no longer utilises Roman numerals but rather has adopted the Hindu-Arabic numeral system. According to the 2021 classification, glioblastomas are diffuse astrocytic gliomas without mutations on the IDH genes or histone H3 genes. They are characterised by the presence of TERT promoter mutation, EGFR gene amplification and/or the gain of chromosome 7 combined with the loss of chromosome 10 as part of the cytogenetic signature. The former 'IDH mutant glioblastomas—grade IV' are now referred to as 'IDH mutant astrocytoma—grade 4'.
In the 2021 classification, the cyclin-dependent kinase inhibitor (CDKN) gene plays an important role in the diagnostic criteria. Furthermore, the homozygous deletion of the CDKN2A/B locus is a molecular marker of grade-4 IDH mutant astrocytoma. This deletion correlates to the aggressive nature of IDH mutant grade 4 astrocytoma and poor outcomes. Differentiating grade-2 and grade-3 IDH mutant gliomas has become increasingly challenging, however, warranting new trials enrolling patients with both grades (Weller *et al.*, 2021) (Table 2).

1.1.3 Clinical presentation and imaging

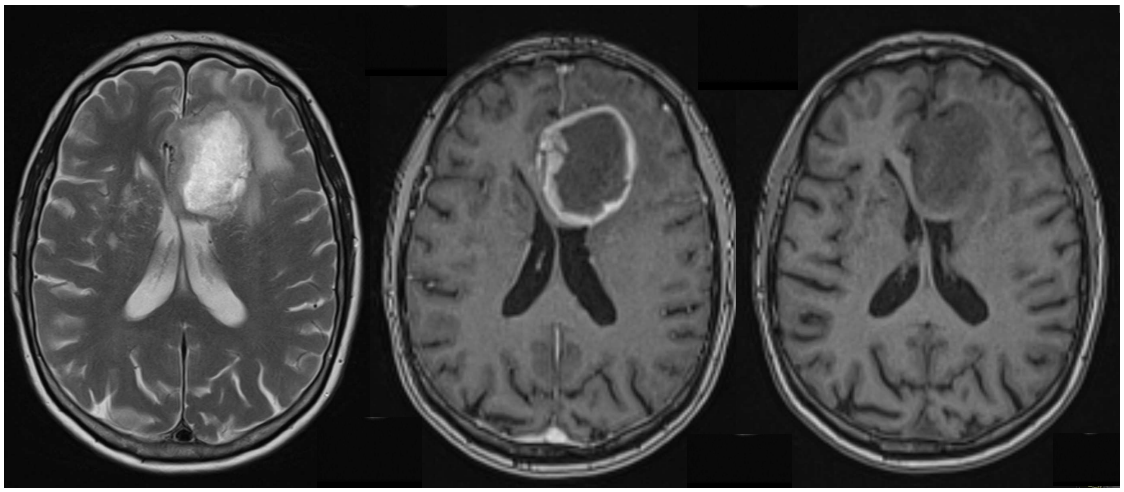

Fig. 1: GBM appearance on an MRI. From left to right: T2, T1 with contrast and T1 without contrast *(Courtesy : Prof. M. Sabel, University hospital of Duesseldorf)*

For *de novo* glioblastomas, the clinical history is typically short, with symptoms appearing after 3 months. According to Hanif *et al.*, the symptoms appear via three distinct mechanisms. First is the direct effect of necrosis of the brain tissue caused by the

tumour; depending on the location of the tumour, patients experience cognitive problems, sensory or motor aphasia, weakness or hemianopsia.

The second mechanism is the mass effect of perifocal oedema due to tumour progression, the hallmark feature of which is headaches, which are found in 30–50% of patients with GBM. The final mechanism is the onset of seizures, which are typically correlated to the location of the tumour. These seizures typically have a focal onset and can be simple-partial, complex-partial or generalised seizures (Hanif *et al.*, 2017).

Magnetic resonance imaging (MRI) is the standard method used for the radiological diagnosis of gliomas; computer tomography (CT) is only used when an MRI is not possible. For example, patients with pacemakers who are unable to receive an MRI undergo CT with contrast instead. Since the adoption of magnetic resonance angiography (MRA), cerebral angiography has nearly become obsolete. MRA is useful especially when the tumour has close contact to vital vascular structures (Batchelor *et al.*, 2017).

GBM appear hyper-intense on T_2 weighted images and hypo- or isointense on T_1 weighted images. Post-contrast T_1 weighted images show an irregular peripheral contrast enhancement associated with a central non-contrast enhancing area consistent with necrosis. This is the characteristic appearance of GBM on MRI (Fig. 1). T_2-weighted fluid-attenuated inversion recovery (FLAIR) images suggest the extent of oedema and tumour infiltration beyond the contrast enhancement (Abd-Elghany *et al.*, 2019; Shukla *et al.*, 2017).

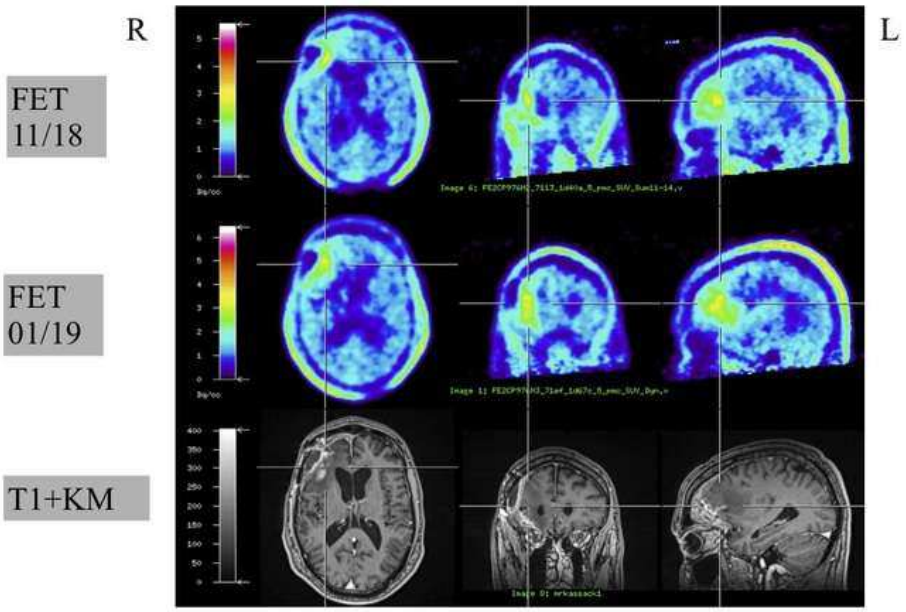

Fig. 2: 18FET PET-MRI ***(Courtesy : Prof. M. Sabel, University hospital of Duesseldorf)***

Positron emission tomography–MRI (PET-MRI) is used widely to differentiate radiation necrosis and pseudo-progress from tumour progress. O-(2-[18F] fluoroethyl)-1-tyrosine (18FET) is a widely used radioactive tracer in PET-MRI. Approximately 95% of high-grade gliomas, including glioblastomas, display a significant uptake of 18FET; thus, 18FET has a high sensitivity for tumour detection (Verger and Langen, 2017) (
Fig. 2).

The uptake ratio of 18FET is different for various grades of gliomas, thus enabling oncologists and neurooncologists to determine treatment strategies depending on the grades of the glioma (Rapp *et al.*, 2013). Besides radiation necrosis, which is observed in MRI after radiation therapy, another confounding factor for the determination of tumour progress is pseudo-progress. Pseudo-progressions mimic the MRI characteristics of tumour progress. They typically occur within the first 3 months after completing adjuvant therapy and are observed in almost 60% of cases. While MRI cannot provide a conclusive diagnosis, 18FET-PET can identify the presence of pseudo-progress to an accuracy of 96% (Zikou *et al.*, 2018).

1.2 Standard of care in glioblastoma therapy

1.2.1 Surgery

The primary hallmark of GBM therapy is surgery, which aims at gross total resection (GTR). The extent of resection (EOR) is the most important predictor for treatment-related outcomes; an EOR of ≥ 98% has been found to improve survival significantly (Fernandes *et al.*, 2017). Therefore, the aim of surgery is to achieve the maximum possible resection while preserving the patient's QOL. The location of the tumour plays a major role in achieving GTR, and achieving GTR for tumours located in the eloquent areas (e.g., motor cortex, sensory cortex, supplementary motor cortex, basal ganglia, insula) is challenging. The morphology of GBM also impacts GTR. Since GBM are highly infiltrative tumours, finding a clear border between the tumour and healthy brain tissue can be difficult. Fluorescence-guided surgery (FGS), intraoperative neuromonitoring and awake craniotomy are techniques that provide better control for surgeons operating on eloquent-area tumours, thereby maximising the EOR (Skjøth-Rasmussen, Engelmann and Brennum, 2017).

A detailed description of the frequently used monitoring techniques implemented in the surgery of glioblastomas is given below.

1.2.1.1 Fluorescence-guided surgery

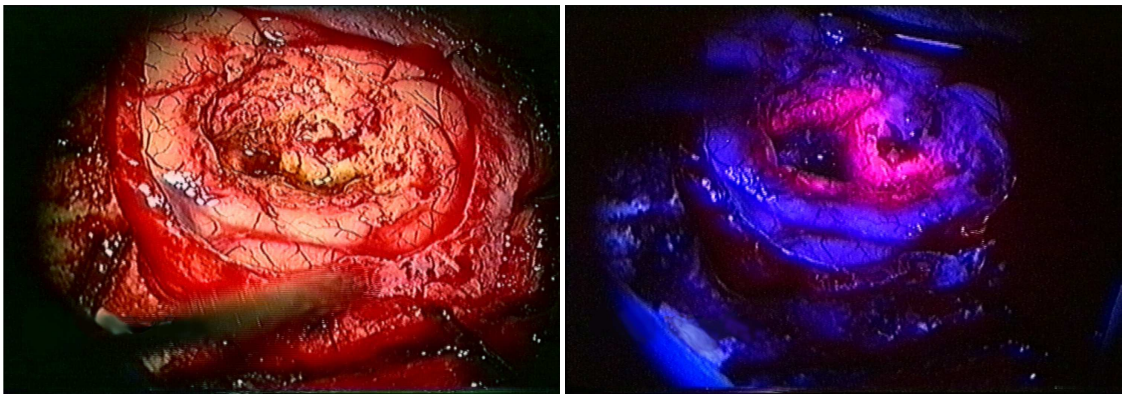

Fig. 3: Fluorescence-guided surgery with 5-ALA in GBM. ***(Courtesy: Prof. M. Sabel, University Hospital of Duesseldorf)***

In FGS, fluorescent dyes are used to define resectable boundaries between the tumour and normal tissue (Fig. 3). For glioma surgery, 5-Aminolevulinic acid (5-ALA) is the most commonly used fluorescent dye. Dr Walter Stummer first described the use of 5-ALA for resecting high-grade gliomas (Stummer *et al.*, 1998). A natural metabolite in the human body, 5-ALA is produced by the haemoglobin metabolic pathway. Exogenously administered 5-ALA has a good penetration of the blood-brain barrier and tumour interface, and malignant gliomas metabolise 5-ALA into protoporphyrin IX (PpIX), a fluorescent metabolite. PpIX has a red-violet fluorescence when excited with a 405-nm wavelength blue light, which enables FGS for gliomas. Strong fluorescence corresponds to more proliferating tumours with high tumour densities, while weak fluorescence corresponds to infiltrating tumours with medium tumour densities.

Though 5-ALA has become a vital tool for increasing the EOR in malignant glioma surgery, the fluorescence should be interpreted carefully. For example, patients who have recurrent malignant gliomas and have thus completed adjuvant therapy can display false-positive fluorescence, which corresponds histopathologically to radio necrosis. Furthermore, the administration of 5-ALA to the patients is crucial, as PpIX typically peaks 4 h after oral ingestion of 5-ALA. Therefore, adopting the optimal time window for administration of 5-ALA is crucial for maximum fluorescence. Another phenomenon that influences fluorescence is ‘photo bleaching’, or the loss of fluorescence due to prolonged exposure under blue or white light (> 25 min. with blue light and > 87 min.

with standard white light). However, photo bleaching does not significantly affect the EOR since the tumour bed is revealed in layers by resection and usually is covered with a film of blood. Finally, the size of the craniotomy plays a role in the visualisation of fluorescence. Small craniotomies, in which blue light penetration is hindered, can cause reduced fluorescence visualisation. Thus, while 5-ALA is a good tool, experienced interpretation of the fluorescence is of great importance (Hadjipanayis, Widhalm and Stummer, 2015; Stummer *et al.*, 1998).

1.2.1.2 Awake Craniotomy

Awake craniotomy has been used to treat brain disorders for a long time; archaeological findings have shown that trephinations were practiced before the advent of anaesthesia. For example, skulls unearthed in Peru showed complete healing in 55% of 214 patients (Bulsara, Johnson and Villavicencio, 2005). However, modern awake craniotomy was established by Wilder Penfield and André Pasquet, who published a landmark paper on the anaesthetic and surgical considerations of awake craniotomy in 1954 (Penfield, 1954). In 1988, Archer *et al.* published the first large study to document the results of conscious-sedation analgesia during awake craniotomy (Archer *et al.*, 1988). Then, in 1992, Silbergeld *et al*. introduced short-acting sedative propofol with antiemetic and amnestic properties to awake craniotomy. Later, remifentanyl was used to render analgesia to patients (Hans *et al.*, 2000).

Awake craniotomy has especially been widely used in the field of glioma surgery to localise the eloquent areas in real time and thus achieve maximal possible resection while reducing the patient's functional morbidity (Fig. 4). In 1994, Haglund *et al*. showed the feasibility of language testing in 40 patients with left-sided temporal lobe gliomas by utilising cortical and subcortical stimulations to test the language areas. Their study showed that resections can be maximised and post-operative language deficits can be minimised under awake conditions (Haglund *et al.*, 1994). Since their study, the practice of awake craniotomies has evolved significantly. The use of anaesthetics, such as propofol and fentanyl, and regional scalp blocks have increased the safety and practicability of awake craniotomy. In the largest single-surgeon experience on awake craniotomies to be published, the authors concluded that awake craniotomy can be safely performed in glioma surgery in spite of comorbidities like obesity, history of seizures, tumour location and tumour pathology (Hervey-Jumper *et al.*, 2015). Furthermore, Gerritsen *et al.* suggested that a better EOR can be achieved with fewer minor late post-

operative complications under awake craniotomy than under general anaesthesia (Gerritsen *et al.*, 2019). However, although awake craniotomy has arguably become the gold standard for tumour resection in eloquent-area gliomas, certain considerations and precautions should be taken. Intraoperative seizures are a frequently occurring complication of awake craniotomy. Use of intraoperative cold water and antiepileptic drugs is imperative. Additionally, anxiety and panic disorders and the patient's compliance during the awake procedure must be accounted for and pre-operatively assessed (Shinoura *et al.*, 2011). Thus, communication and teamwork are essential between the patient, neurosurgeon, anaesthesiologist and neurophysician to conduct a successful awake craniotomy.

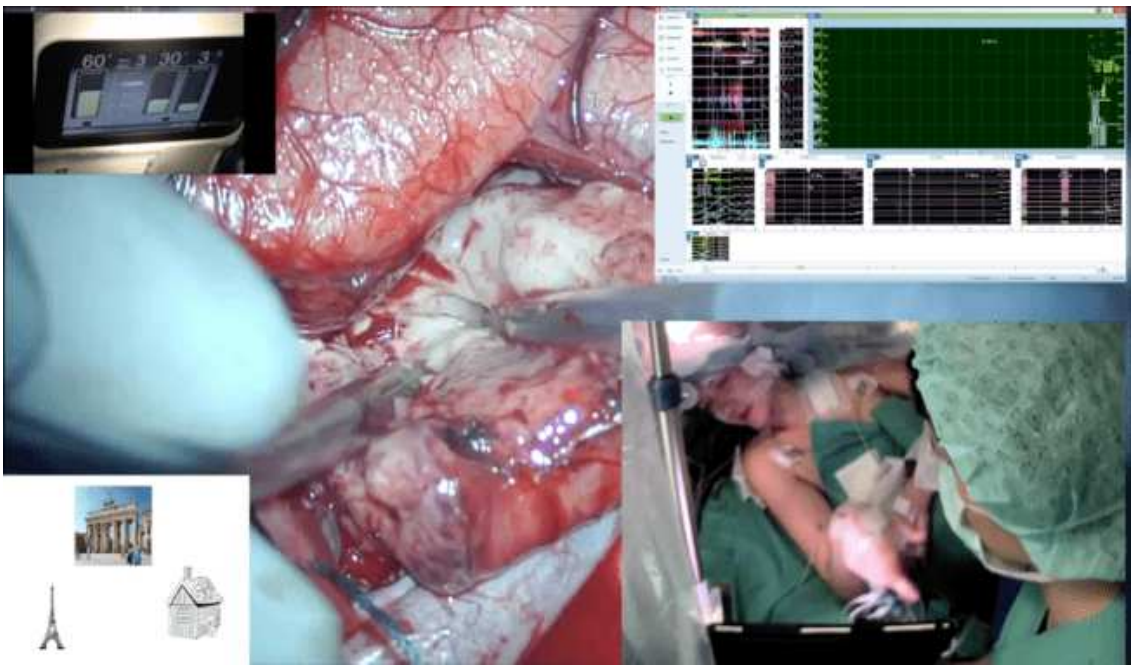

Fig. 4: Awake surgery with IONM and Neurophysiological testing. ***(Courtesy : Prof. M. Sabel, University hospital of Duesseldorf)***

1.2.1.3 Intraoperative neurophysiological monitoring

IONM is an important tool for monitoring the neurological status of patients during resection of highly eloquent tumours in glioma surgery. IONM was first used in 1930, when direct cortical stimulation was used to identify the motor cortex for an epilepsy surgery. The technique was widely adopted in the 1980s when IONM machines were developed (Kim *et al.*, 2013).

Eliciting a motor or sensory response requires electrical stimulation of the cortex. This stimulation is achieved using a constant current stimulator, which delivers the same amount of current irrespective of the impedance caused by the cortical and subcortical

surface. This provides the surgeon more control over the delivery of the stimulating current. Constant voltage stimulators, in contrast, vary the administering current depending on the impedance of the brain surface. Thus, a low impedance causes the release of higher amounts of current, which can compromise patient safety.

Monopolar and bipolar stimulation are the two primary methods of cortical stimulation. A bipolar probe has two tips that are separated from each other by 6–10 mm. Depending on the surgeon's preference, bipolar probes have either straight tips or ball tips. As the name suggests, monopolar probes have a single stimulating tip that functions in accordance with a reference electrode, which is typically placed frontally. These probes also have both straight and ball tips; straight tips have a width of 2–3 mm, and ball tips have a width of 2–5 mm. The distribution of the electric fields during stimulation differs between monopolar and bipolar probes. Monopolar probes produce a spreading electric field that provides increased spatial orientation as far as stimulation is concerned. However, the current densities decrease in the areas surrounding the reference electrode. Bipolar stimulation produces a more direct and specific stimulation, but the current is distributed only between the two probes, which provides more information regarded the actual stimulated area but less information regarding the surrounding surface. Thus, monopolar and bipolar stimulation are used in an alternating fashion to attain specific spatial information for mapping. The stimulating current is typically between 25 and 60 Hz, with short pulse frequencies of 20 mA set as the maximum stimulation intensity for safety reasons (Szelényi *et al.*, 2010).

IONM is crucial for mapping and monitoring the motor cortex and corticospinal tract and preserving their integrity while achieving maximum EOR. To map the motor cortex and corticospinal tract, motor-evoked potential (MEP) is needed. Stimulation is achieved either through transcranial electrical stimulation using corkscrew scalp electrodes placed in a 10/20 fashion or through direct cortical stimulation achieved using strip electrodes placed subdurally, away from the site of resection, perpendicular or close to the assumed location of central sulcus. Alternatively, stimulation can be achieved via subcortical stimulation using bipolar or monopolar stimulators. Stimulation is achieved through constant anodal stimulation with a train of five stimuli and an interstimulus interval of 4–5 milliseconds. For the elicited stimulation, specific recording sites are chosen, include the contralateral abductor hallucis, abductor pollicis, tibialis anterior and flexor muscles of the forearm. Before resection, baseline stimulation values are obtained followed by continuous monitoring, with recordings completed every 120 seconds. When approaching

the proximity of the corticospinal tract, stimulation is usually started at 15 mA and continued until 5mA. When MEP is stable at 5 mA, resection is typically stopped; this corresponds to an approximate distance of 5 mm to the proximity of the corticospinal tract (Grossauer, Parpaley and Koeck, 2017).

Somatosensory-evoked potential (SSEP) monitors the primary sensory cortex by stimulating peripheral nerves along the somatosensory afferent pathways that lead to the primary somatosensory cortex. Stimulation of the median or ulnar nerve for upper limbs or the posterior tibial or peroneal nerve for lower limbs is chosen, and recordings are gathered from electrodes placed either subdurally on the cortex or on the scalp. Phase reversal, a technique in which the difference of polarity changes in recorded, is used to detect the location of the central sulcus. When the somatosensory cortex is approached from the motor cortex, the polarity of SSEP recording changes; this determines the anatomical location of the central sulcus.

Furthermore, SSEP amplitude and latency change have well-documented correlation with cerebral blood flow; changes of more than 50% reveal an imminent threat of vascular damage, which, if not reversed, can cause permanent damage. Since SSEP waveforms are highly sensitive to anaesthesia regimens, glioma surgery with IONM does not recommend inhalation gas anaesthetic as it can produce false-positive SSEP waveform changes (Pamir, Black and Fahlbusch, 2010; Grant, Farrell and Silbergeld, 2002).

1.2.2 Adjuvant therapy for glioblastomas

The Stupp protocol, which includes concomitant and adjuvant chemotherapy plus radiotherapy, has become the standard of care for adult patients up to 70 years of age who have been diagnosed with glioblastoma. This protocol comprises combined radio-chemotherapy for 6 weeks. During this period, patients receive a radiation dose of 2 Gy from Monday–Friday, resulting in a total radiation of 60 Gy. Additionally, the patients receive simultaneous temozolomide at a dosage of 75 mg/m² of body surface per day for 7 days. The 6 weeks of concomitant therapy are followed by a 6-week adjuvant therapy of temozolomide comprising 150–200mg/m² for 5 out of 28 days (Stupp *et al.*, 2005). One of the adverse side effects of temozolomide is bone marrow suppression, and patients present with thrombocytopenia and neutropenia. Therefore, frequent blood analysis is mandatory to monitor patient values. If acute decrease of thrombocytes is observed, temozolomide must be stopped, and platelet transfusion must be performed. Another

common side effect of temozolomide is nausea and vomiting. As prophylaxis, patients receive 2 mg of granisetron with temozolomide. Patients also receive treatment with cotrimoxazole to prevent infections from *Pneumocystis carinii*, which is prevalent due to neutropenia.

In 2019, Herrlinger *et al.* published the results of a randomized, open-label phase three trial comparing the efficacy of a combination of lomustine and temozolomide to temozolomide only in patients with newly diagnosed GBM with MGMT methylation.

Their results found a median survival of 48.1 months in the combination therapy group compared to 31.4 months in the group that received temozolomide alone. Thus, the results supported the feasibility of combination therapy in the MGMT methylated population (Herrlinger *et al.*, 2019). However, elderly patients with GBM have a far worse prognosis. Although radiotherapy and chemotherapy are feasible, patients aged 70 years and above experience more adverse effects from the adjuvant therapy than younger populations (Minniti, Lombardi and Paolini, 2019; Berger *et al.*, 2021).

Treating recurrent glioblastomas is also challenging, and no standards have yet been identified. Instead, most treatment regimens have been developed from retrospective data. Individual factors must be considered prior to treatment, including age, the Karnofsky Performance Scale (KPS) and the National Institute of Health Stroke Scale (NIHSS).

Re-resection is typically considered. Though resection has increased morbidity when considering the preservation of neurological functions, studies have found a significant increase in the OAS of patients who underwent repeated surgery than those who did not (Lu *et al.*, 2018).

Re-radiation is also typically feasible for patients with a KPS more than 60%, a tumour size of up to 40 mm and a PFS of at least 6 months. Fractionated stereotactic radiotherapy with a total dose of 30–36 Gy is the common approach for recurrent GBM (Dhermain *et al.*, 2004; Combs, Debus and Schulz-Ertner, 2007).

The Optune system (Novocure, St. Helier, Jersey Isle, UK) uses an alternating electric frequency of 200 kHz to create tumour-treating fields (TTF) that penetrate the cell walls of cancer cell division, thus leading to apoptosis (Topfer and Farrah, 2016). Transducers are placed on the patient's shaved head and connected to a portable battery unit, which patients can transport with them. In a phase three trial, Stupp *et al*. evaluated the superiority of TTF compared to chemotherapy of recurrent GBM and found no significant increase in OAS (Stupp *et al.*, 2012). However, TTF is still an alternative for patients who do not tolerate the side effects of chemotherapy.

Several options have been explored for chemotherapy. Nitrosourea-based regimes like lomustine (CCNU) have shown efficacy with a PFS of 6 months, according to randomized trials that tested the protein kinase C-ß inhibitor enzastaurin and the vascular endothelial growth factor (VEGF) receptor inhibitor cediranib (Wick *et al.*, 2010; Batchelor *et al.*, 2013).

Temozolomide is also used as an adjuvant therapy for recurrent glioblastomas. Enrico Francheschi *et. al* found that in patients with treatment-free intervals of 5 months, temozolomide had an 8-month median PFS compared to the 5.8-month median of the nitrosurea group (Franceschi *et al.*, 2018).

Bevacizumab is a monoclonal antibody that acts as an angiogenesis inhibitor. Wick *et al*. assessed the efficacy of the combination therapy of bevacizumab and lomustine compared to monotherapy of lomustine. Their study showed a 2.7-fold longer PFS in the combination group. However, no survival advantage from the combination therapy was observed (Wick *et al.*, 2017).

Despite many different strategies for treating patients with GBM, the prognosis is still poor. The median survival of patients with newly diagnosed GBM is only 14.6 months, with 2-year survival rates of only 27.2%. Thus, novel therapy modalities are needed. One such novel therapy is vaccination with dendritic cells. Dendritic cells help produce autologous cytotoxic effector T-cells, which kill tumour cells (Rapp *et al.*, 2018). Hsu *et al*. applied dendritic cell vaccination in a trial studying patients with B-cell lymphoma (Hsu *et al.*, 1996). Regarding GBM specifically, several studies that have been conducted since 2000 have provided encouraging results regarding OAS. Furthermore, a national prospective multicentre, open-label, randomized phase two study is underway in hospitals located in the German state of Nord Rhine-Westphalia in the vicinity of Duesseldorf. This study aims to investigate the clinical efficacy of dendritic cell vaccination in patients with GBM (Rapp *et al.*, 2018).

1.3 Aim and objective of the study

This study aims to retrospectively analyse the post-operative outcome of patients diagnosed with glioblastomas between 2004 and 2018 in the University Hospital of Duesseldorf and operated under different operative and monitoring settings in terms of neurological status, the extent of tumour resection, PFS and OAS.

2 Material and methods

2.1.1.1 Patient recruitment and sample description

After receiving approval from the ethics committee of the University Hospital of Duesseldorf, retrospective patient recruitment was undertaken. All patients with glioblastomas operated and diagnosed in the University Hospital of Duesseldorf between 2004 and 2018 were recruited. Systematic retrospective data collection was performed for data from 01 January 2004 to 31 December 2018. Patient follow-up of the recruited cohort was conducted through 31 October 2020. Patient recruitment was conducted through 'Medico', the local patient data management system (PDMS). Using the C71 classification code from the International Classification of Diseases (ICD), search criteria were created to generate a list of all cerebral neoplasms. From this list, all patients with a diagnosis of glioblastomas were selected, resulting in 1010 patients from 2004–2018.
Further filtering of the cohort was conducted using the following specific exclusion criteria:

- All patients who only had a documented follow-up period of less than or equal to 3 months. This criterion excluded 247 patients.
- Patients in whom the first surgical procedure was conducted outside the University Hospital of Duesseldorf. This criterion excluded 73 patients.
- Patients with incomplete clinical data. This excluded 44 patients.
- Patients who were not 18 years of age at the time of diagnosis. This excluded 15 patients.

After the exclusion criteria, a cohort of 631 eligible patients remained. Of these patients, 150 received biopsies. The remaining 481 patients underwent surgical resection. Biopsies were typically performed for the following patients:

- Those in whom the tumour had a very eloquent location, where surgical resection without increased morbidity was nearly impossible.
- Those with pre-existing conditions with increased risk of an elaborate surgical resection.

In this study, the biopsied patients were included to analyse their distribution from 2004–2018, to compare their frequencies in correlation to the implementation of different operative settings over the years and to compare their prognoses with the rest of the cohort.

Data collection involved analyses of specific variables, including operative settings, IDH and MGMT statuses, tumour location and eloquence, PFS, OAS, adjuvant therapy, extent of resection, KPS and NIHSS scores before surgery, at the time of discharge and at 3 months follow-up.

The 481 operated patients were further classified into three sub-groups based on their IDH statuses. Group one included 14 IDH mutated patients. Group two included 320 IDH-wildtype patients, and group three comprised 147 patients without a known IDH status. Within the subgroups, the patients were further classified as MGMT methylated, unmethylated and unknown. According to the new classification, IDH mutated GBM were referred to as IDH mutant astrocytoma grade 4.

From the surgical cohort, 427 patients received post-operative radio-chemotherapy (i.e., STUPP). Of the 320 IDH-wildtype patients, 296 received STUPP and 12 of the 14 patients with mutated IDH statuses received STUPP. In addition to the statistical analyses for the entire cohort, specific sub-group statistical analyses were performed for those patients who were IDH-wildtype and had received post-operative STUPP (Fig. 5)..

All 481 patients received pre- and post-operative MRI to assess the EOR. EOR was calculated for all except for two patients because of multilocular and diffuse tumour characteristics without a significant margin of tumour delineation.

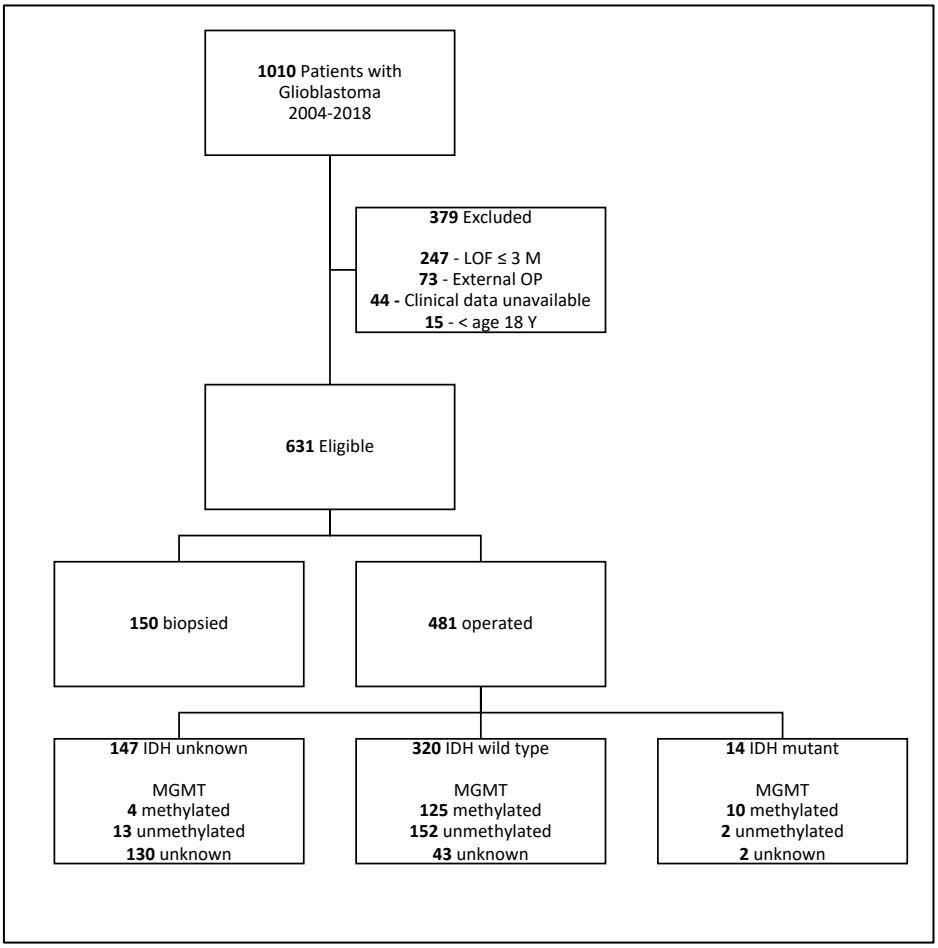

Fig. 5: Flowchart of patient recruitment.

2.2 Operative techniques

Since this study aimed to compare the different operative and intra-operative monitoring modalities, the patients were analysed according to the type of operating setting to which they were subjected. The types of surgical settings were as follows:

- GA: general anaesthesia only with no added monitoring modalities.
- Awake: awake craniotomy with 60-Hz bipolar cortical stimulation to define the eloquent areas and achieve safe resection margins.
- IONM: the patient is completely asleep throughout the entire surgery and received SSEP, MEP and EEG monitoring.
- IONM/awake: this method incorporates both awake craniotomies and IONM. Patients are operated in an awake fashion with SSEP, MEP and EEG monitoring.

The type of surgical setting was determined by the surgeon considering the neurological and physical status of the patient. It was also vastly influenced by the year of diagnosis. For example, GBM diagnosed before 2007 received almost only GA, as other above-

mentioned monitoring modalities were not in use at the University Hospital of Duesseldorf before then.

2.3 NIHSS and Karnofsky Performance Score

The National Institutes of Health Stroke Scale (NIHSS) was devised to measure stroke-related disorders. Although it was designed to assess the neurological deficits and outcomes of acute stroke, the scale has also been used in other neurological diseases to document the outcomes. The scale has 11 assessment criteria. The first criterion is divided in to three subgroups, and the fifth and sixth criteria are each divided into two subgroups. Thus, the scale has 15 individual parameters. The scale evaluates the patient's level of consciousness, ability to verbalise, visual field loss, extraocular movements, motor strength, ataxia, dysarthria and sensory loss. On the scale, 0 is the best result, indicating no neurological deficits, while the maximum score of 42 is related to an extremely severe neurological disorder ('Tissue Plasminogen Activator for Acute Ischemic Stroke', 1995; Brott *et al.*, 1989).

In our study, the NIHSS of all patients was evaluated before surgery, after surgery at the time of discharge and 3 months after surgery during follow-up (Table 3, Table 4).

The modified National Institutes of Health Stroke Scale score			
1a.	Level of consciousness	0 =	Alert; keenly responsive
		1 =	Not alert, but arousable by minor stimulation
		2 =	Not alert; requires repeated stimulation
		3 =	Unresponsive or responds only with reflex
1b.	Level of consciousness questions: What is the month? What is your age?	0 = 1 = 2 =	Answers two questions correctly Answers one question correctly Answers neither question correctly
1c.	Level of consciousness commands: Open and close your eyes. Grip and release your hand.	0 = 1 = 2 =	Performs both tasks correctly Performs one task correctly Performs neither task correctly
2.	Best gaze	0 = 1 = 2 =	Normal Partial gaze palsy Forced deviation
3.	Visual	0 = 1 =	No visual loss Partial hemianopia

		2 =	Complete hemianopia
		3 =	Bilateral hemianopia
4.	Facial palsy	0 =	Normal symmetric movements
		1 =	Minor paralysis
		2 =	Partial paralysis
		3 =	Complete paralysis of one or both sides
5.	Motor arm 5a. Left arm 5b. Right arm	0 =	No drift
		1 =	Drift
		2 =	Some effort against gravity
		3 =	No effort against gravity; limb falls
		4 =	No movement
6.	Motor leg 6a. Left leg 6b. Right leg	0 =	No drift
		1 =	Drift
		2 =	Some effort against gravity
		3 =	No effort against gravity; limb falls
		4 =	No movement
7.	Limb ataxia	0 =	Absent
		1 =	Present in one limb
		2 =	Present in two limbs
8.	Sensory	0 =	Normal; no sensory loss
		1 =	Mild to moderate sensory loss
		2 =	Severe to total sensory loss
9.	Best language	0 =	No aphasia; normal
		1 =	Mild to moderate aphasia
		2 =	Severe aphasia
		3 =	Mute, global aphasia
10.	Dysarthria	0 =	Normal
		1 =	Mild to moderate dysarthria
		2 =	Severe dysarthria
11.	Extinction and inattention	0 =	No abnormality
		1 =	Visual, tactile, auditory, spatial or personal inattention
		2 =	Profound hemi-inattention or extinction
Total score = 0–42.			

Table 3: NIHSS, adapted from (Lyden *et al*., 2001)

NIHSS	Stroke Severity
0	No stroke symptoms
1–4	Minor stroke
5–15	Moderate stroke
16–20	Moderate to severe stroke
21–42	Severe stroke

Table 4: Grades of NIHSS, adapted from (Lyden *et al.*, 2001)

David A. Karnofsky and Joseph H. Burchenal introduced the Karnofsky performance scale (KPS) in a 1949 book titled *The clinical evaluation of chemotherapeutic agents in cancer*. The KPS helps define a patient's functional status and has 11 points, each corresponding to a percentage; 100% is the best functional status while 0% essentially describes the death of the patient. In addition to describing patients' functionality, the KPS is also a strong prognostic factor for a variety of tumour entities (Lyden *et al.*, 2001). We used the KPS to assess the functionality of all our patients before surgery, after surgery at the time of discharge and 3 months after surgery during follow-up (Table 5).

100	Normal, no complaint, 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.
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/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance. (In bed more than 50% of the time)
30	Severely disabled, hospitalisation is indicated although death is not imminent. (Almost completely bedfast)
20	Hospitalisation necessary, very sick, active supportive treatment necessary. (Totally bedfast and requiring extensive nursing care by professionals and/or family)
10	Moribund, fatal processes progressing rapidly. (Comatose or barely arousable)
0	Dead.

Table 5: KPS, adapted from (Péus, Newcomb and Hofer, 2013)

2.4 Extent of resection and eloquence

In the treatment of GBM, the EOR plays a major a role in the patient's prognosis; many studies have shown that maximising the EOR provides a survival advantage for patients with GBM. In 2012, Bloch *et al*. emphasised the need for achieving maximum EOR. In our study, the EOR also played a pivotal role in the outcome of different operating techniques. As suggested by Bloch *et al*., we defined a resection of 95% or greater of tumour volume as GTR. Tumour resection less than 95% was considered partial resection (Bloch *et al.*, 2012). Most tumour volumetry with manual image segmentation was performed using the Brain Lab licensed software. Volumetry for tumours with good circumscribed borders was measured using the ABC/2 formula (Kwak, Kadoya and Suzuki, 1983; Kothari *et al.*, 1996), a simplified version of the volume of an ellipsoid.

$$4/3\ \pi \times (A/2) \times (B/2) \times (C/2).$$

- A- Greatest diameter of the tumour/haemorrhage in the axial plane.
- B- Diameter of the tumour/haemorrhage 90° to A on the axial plane.
- C- Total number of CT or MRI slices with the tumour/haemorrhage multiplied to the slice thickness corresponding to the height of the tumour/ haemorrhage.

The tumour volume is measured in cubic centimetres or millilitres. The ABC/2 formula was originally conceptualised for quick and accurate measurements of intracerebral hematomas, and this formula can also be used to measure meningiomas and acoustic neurinomas (Opalak *et al.*, 2019; Bathla *et al.*, 2017). Sreenivasan *et al*. suggested that the simplified formula can also be used for measuring tumour volume in gliomas. However, the formula is only usable for GBM with good delineated tumour borders, not for larger tumours (Sreenivasan *et al.*, 2016). Contrast-enhancing tumours in pre- and post-operative T1-weighted MRI images were measured in our study.

Although maximising EOR is important, preserving and striving to improve the neurological function of patients is of greater importance. The location of the tumour plays a pivotal role in this function; maximising the EOR and preserving neurological functionality in eloquently located tumours is challenging. Although the entire brain can be considered of eloquence, we defined eloquence based on several studies as brain regions that when damaged, could cause a serious observable and quantifiable neurological deficit. These included the right and left pre- and post-central cortex, the basal ganglia, primary visual cortex (calcarine cortex), Wernicke's area and areas of speech. Of the 481 operated patients, 405 had eloquently located tumours (Kahn, Lane

and Sagher, 2017; Talabaev *et al.*, 2020; Sawaya *et al.*, 1998; González-Darder *et al.*, 2010).

2.5 PFS and OAS

Since glioblastomas are not curable, progress of the disease is inevitable. Thus, defining the progression of the disease and differentiating it from pseudo-progress are relevant for determining the therapeutical strategies. Changes in MRI are widely used for deducting and documenting this progress. In 1990, Macdonald *et al*. published an objective radiological assessment to define the progress of high-grade gliomas (Macdonald *et al.*, 1990).

In 2013, Chinot *et al.* published revised updated assessment criteria for glioblastomas. To assess the progress, we used the revised Response Assessment in Neuro-Oncology (RANO) criteria (Wen *et al.*, 2010; Chinot *et al.*, 2013). PFS is defined as the span of time between the surgical procedure and the day before the detection of progress in the MRI (Table 6). OAS is defined as the span of time from the surgical procedure to the last documented follow-up or death of the patient.

Criteria	Macdonald	RANO
Complete response[a]	▪ Disappearance of all enhancing measurable and non-measurable disease (sustained for ≥ 4 weeks) ▪ No new lesions ▪ No corticosteroids ▪ Clinically stable or improved	▪ Disappearance of all enhancing measurable and non-measurable disease (sustained for ≥ 4 weeks) ▪ Stable or improved non-enhancing (T2/FLAIR) lesions ▪ No new lesions ▪ No corticosteroids (physiologic replacement doses only) ▪ Clinically stable or improved
Partial response[a]	▪ ≥ 50% decrease of all measurable enhancing lesions (sustained for ≥ 4 weeks)[b] ▪ No new lesions ▪ Stable or reduced corticosteroid dose ▪ Clinically stable or improved	▪ ≥ 50% decrease of all measurable enhancing lesions (sustained for ≥ 4 weeks)[b] ▪ No progression of non-measurable disease ▪ Stable or improved non-enhancing (T2/FLAIR) lesions[c] ▪ No new lesions

		▪ Stable or reduced corticosteroid dose compared with time of baseline scan ▪ Clinically stable or improved
Minor response[a]	▪ Not applicable	▪ Only applies to low-grade gliomas
Stable disease[a]	▪ Clinically stable ▪ Does not qualify for complete response, partial response or progression	▪ Does not qualify for complete response, partial response or progression ▪ Stable non-enhancing (T2/FLAIR) lesions[c] ▪ Stable or reduced corticosteroid dose ▪ Clinically stable or improved
Progression[d]	▪ ≥ 25% increase in enhancing lesions[b] ▪ Any new lesion ▪ Clinical deterioration	▪ ≥ 25% increase of enhancing lesions on stable or increasing doses of corticosteroids[b] ▪ Significant increase in non-enhancing (T2/FLAIR) lesions[e] (not caused by comorbid events) ▪ Any new lesion ▪ Clear clinical deterioration (not attributable to other causes from the tumour or changes in corticosteroid dose) ▪ Clear progression of non-measurable disease

[a] Response is designated only if all the following criteria are met.
[b] Measured by sum of the products of perpendicular diameters.
[c] On same or lower dose of corticosteroids.
[d] Progression is designated if any of the following criteria are met.
[e] On stable or increasing doses of corticosteroids.

Table 6: Definition of progress according to (Chinot *et al.*, 2013)

2.6 Statistical analyses

Descriptive statistics and the mean, median with interquartile ranges and standard deviation were calculated using the statistical function available in Microsoft Excel. Bar and line graphs generated from Excel were used to extrapolate the values graphically. For special statistical analyses, the Statistical Package for the Social Sciences (SPSS) was

used. A Pearson chi square test was used to determine whether the frequencies of different surgical techniques were statistically significant when compared to others.

The one-way analysis of variance (ANOVA) is used to test the statistical significance of the differences in means of three or more independent groups. It is the extension of the student's t-test, which determines the statistical significance of means in two independent groups. The one-way ANOVA was used to test the statistical significance of EOR, NIHSS and KPS in different surgical settings. Although this test allowed us to determine the statistical significance of the means of the independent groups, repeated-measure ANOVA was required to test the relationship of the means between the independent groups, as repeated-measure ANOVA is an analysis of dependencies.

To analyse the distribution of survival, the Kaplan-Meier survival curve was used to determine the distribution of PFS and OAS.

2.7 Ethical approval

This monocentric retrospective study was registered at the University Hospital of Duesseldorf with the identification number 2018-03-4640 and was approved by the local committee for clinical research with the study number 2018-79-RetroDEuA. After two amendments to the original ethics commission approval (Amendment numbers: 2018-79_1, 2018-79_2), data collection was conducted until 31 October 2020. All data were pseudo-anonymised, and the decryption key was irreversibly destroyed after data collection. The retrospective study was conducted in compliance with the Helsinki Declaration under conditions of good scientific and clinical practice.

3 Results

3.1 Descriptive statistics

Of the 1010 patients analysed from 2004–2018, 631 were considered eligible for the study. Of these, 150 were biopsied. The remaining 481 patients underwent surgical resection. Out of these 481 patients, 303 were male, and 178 were female. Furthermore, 334 patients had a known IDH status, 320 patients were IDH-wildtype, and 14 were IDH mutated.

Although our study only included patients with glioblastomas and the 14 IDH mutated patients were referred to as IDH mutant astrocytoma grade 4 according to the 2021 WHO classification, we still included these 14 patients in our study because the data acquisition and interpretation occurred before the updated classification was published.

Of the 481 patients, 139 were MGMT methylated, 167 were MGMT unmethylated, and the remaining 175 had no known MGMT status. A total of 405 patients had eloquently located tumours. KPS and NIHSS before and after surgery and at 3 months follow-up were calculated respectively with median values and their respective interquartile ranges. Out of 481 patients, 427 received post-operative radio therapy with concomitant and adjuvant temozolomide (STUPP protocol). A subgroup statistical analysis of the cohort with known IDH statuses was performed. In the cohort with known IDH status, 206 were male, and 128 were female. KPS and NIHSS before and after surgery and at 3 months follow-up were also calculated. Descriptive patient characteristics were tabulated for the entire operative cohort of 481 patients as well as the subgroup of 334 patients with known IDH status (Table 7).

Characteristic	Cohort (n = 481)			IDH known (n = 334)		
Sex			%			%
Male	303	/481	63.0	206	/334	61.7
Female	178	/481	37.0	128	/334	38.3
Age at diagnosis, y			%			
Mean (SD)	60.6	(12.6)		60.9	(12.9)	
Median (IQR)	61.0	(52.8–70.0)		61.0	(52.0–71.0)	
Range	23.0	- 89.0		23.0	- 89.0	
< 65 y	281	/481	58.4	188	/334	56.3
≥ 65 y	200	/481	41.6	146	/334	43.7
Diagnosis year			%			%

Before 2010	116	/481	24.1	1	/334	0.3
2010 and after	365	/481	75.9	333	/334	99.7
Surgical techniques			%			%
GA	160	/481	33.3	53	/334	15.9
Awake	71	/481	14.8	38	/334	11.4
IOMN	145	/481	30.1	140	/334	41.9
Awake/IOMN	105	/481	21.8	103	/334	30.8
ALA			%			%
Administered	452	/481	94.0	320	/334	95.8
Not administered	29	/481	6.0	14	/334	4.2
IDH Status			%			%
Wildtype	320	/481	66.5	320	/334	95.8
Mutant	14	/481	2.9	14	/334	4.2
Unknown	147	/481	30.6	0	/334	0.0
MGMT status			%			%
Methylated	139	/481	28.9	135	/334	40.4
Unmethylated	167	/481	34.7	154	/334	46.1
Unknown	175	/481	36.4	45	/334	13.5
Radio chemo			%			%
Administered	427	/481	88.8	308	/334	92.2
Not administered	54	/481	11.2	26	/334	7.8
Tumour location by lobe			%			%
Frontal	159	/481	33.1	116	/334	34.7
Parietal	90	/481	18.7	60	/334	18.0
Temporal	135	/481	28.1	83	/334	24.9
Occipital	29	/481	6.0	16	/334	4.8
Insular	7	/481	1.5	6	/334	1.8
Basal Ganglia	7	/481	1.5	6	/334	1.8
Corpus Callosum	17	/481	3.5	14	/334	4.2
Multilocular	33	/481	6.9	30	/334	9.0
Cerebellar	2	/481	0.4	1	/334	0.3
Pontine	2	/481	0.4	2	/334	0.6
Tumour location by side			%			%
Bilateral	15	/481	3.1	14	/334	4.2
Left	223	/481	46.4	154	/334	46.1
Right	243	/481	50.5	166	/334	49.7
Eloquence			%			%
Eloquent	405	/481	84.2	305	/334	91.3
Not eloquent	76	/481	15.8	29	/334	8.7
Before 2010			%			%
Eloquent	75	/116	64.7	1	/1	100.0
Not eloquent	41	/116	35.3	0	/1	0.0
2010 and after			%			%

Eloquent	330	/365	90.4	304	/333	91.3
Not eloquent	35	/365	9.6	29	/333	8.7
Extent of resection, % by volume						
Mean (SD)	96.1	(8.6)		96.3	(8.1)	
Median (IQR)	100.0	(96.2–100.0)		100.0	(96.6–100.0)	
Range	38.2	- 100.0		38.2	- 100.0	
KPS before surgery			%			%
< 60	12	/481	2.5	6	/334	1.8
60	9	/481	1.9	5	/334	1.5
70	44	/481	9.1	14	/334	4.2
80	112	/481	23.3	57	/334	17.1
90	175	/481	36.4	152	/334	45.5
100	129	/481	26.8	100	/334	29.9
Median KPS (IQR)	90	(80-100)		90	(90-100)	
KPS after surgery			%			%
< 60	6	/481	1.2	3	/334	0.9
60	11	/481	2.3	5	/334	1.5
70	45	/481	9.4	14	/334	4.2
80	126	/481	26.2	65	/334	19.5
90	173	/481	36.0	145	/334	43.4
100	120	/481	24.9	102	/334	30.5
Median KPS (IQR)	90	(80–95)		90	(80–100)	
KPS after 3 months			%			%
< 60	17	/470	3.6	8	/329	2.4
60	20	/470	4.3	12	/329	3.6
70	53	/470	11.3	27	/329	8.2
80	112	/470	23.8	69	/329	21.0
90	168	/470	35.7	130	/329	39.5
100	100	/470	21.3	83	/329	25.2
Median KPS (IQR)	90	(80–90)		90	(80–100)	
NIHSS before surgery			%			%
< 5	450	/481	93.6	317	/334	94.9
5–10	29	/481	6.0	16	/334	4.8
➢ 10	2	/481	0.4	1	/334	0.3
Median NIHSS (IQR)	1	(0–2)		1	(0–2)	
NIHSS after surgery			%			%
< 5	457	/481	95.0	318	/334	95.2
5–10	18	/481	3.7	13	/334	3.9
> 10	6	/481	1.2	3	/334	0.9
Median NIHSS (IQR)	1	(0–2)		1	(0–2)	
NIHSS after 3 months			%			%
< 5	432	/470	91.9	302	/329	91.8

5–10	35	/470	7.4	24	/329	7.3
> 10	3	/470	0.6	3	/329	0.9
Median NIHSS (IQR)	1	(0-2)		1	(0-2)	
Progression-free survival (PFS), m						
Mean (SD)	11.6	(13.8)		10.9	(11.6)	
Median (IQR)	7.0	(4.0–13.0)		7.0	(4.0–13.0)	
Range	1.0	- 147.0		1.0	- 104.0	
Overall survival (OAS), m						
Mean (SD)	19.9	(19.1)		18.4	(16.9)	
Median (IQR)	14.0	(8.0–23.0)		13.0	(8.0–22.0)	
Range	4.0	- 147.0		4.0	- 118.0	

Table 7: Descriptive statistics

3.2 Changes in surgical characteristics from 2004-2018

With Microsoft Excel, bar graphs were plotted to describe the distribution of the annual prevalence of glioblastomas in the University Hospital of Duesseldorf from 2004–2018. The annual distribution also included the 14 IDH mutant patients that were newly referred to as IDH mutant astrocytoma grade 4. The highest number of GBM (n = 104) occurred in 2015, while the least (n = 27) occurred in 2005. The mean number of GBM diagnosed from 2004–2018 was 67.3 (SD 21.2) (**Fig. 6**). A year-wise extrapolation of the surgical techniques was represented using a line graph to understand better the changes in surgical settings over time. Towards the end of 2011, the number of surgeries with only GA decreased considerably. In 2007, awake surgeries were implemented with 60-Hz stimulation, and their numbers steadily increased until 2011. IONM and the combination of IONM and awake surgeries were implemented in 2010, and over time, this became the standard of surgical care for patients. As IONM increased, GA decreased considerably. Based on the graphical representation, 2010 marked a pivotal change in defining the standard of care for surgery for patients with GBM. (Fig 7). The chi square test showed that the prevalence of biopsies decreased significantly after 2010. The chi square test also showed the statistically significant increase of awake, IONM and IONM/awake surgical settings after 2010 (Table 8 and Table 9).

The first studies on the impact of IDH status on the overall survival of GBM patients were published in 2009. After 2010, defining the IDH status became a standard parameter incorporated into histopathological findings. A separate graph extrapolating the surgical

techniques used in patients with known IDH statuses was created for better comparison (Fig. 8).

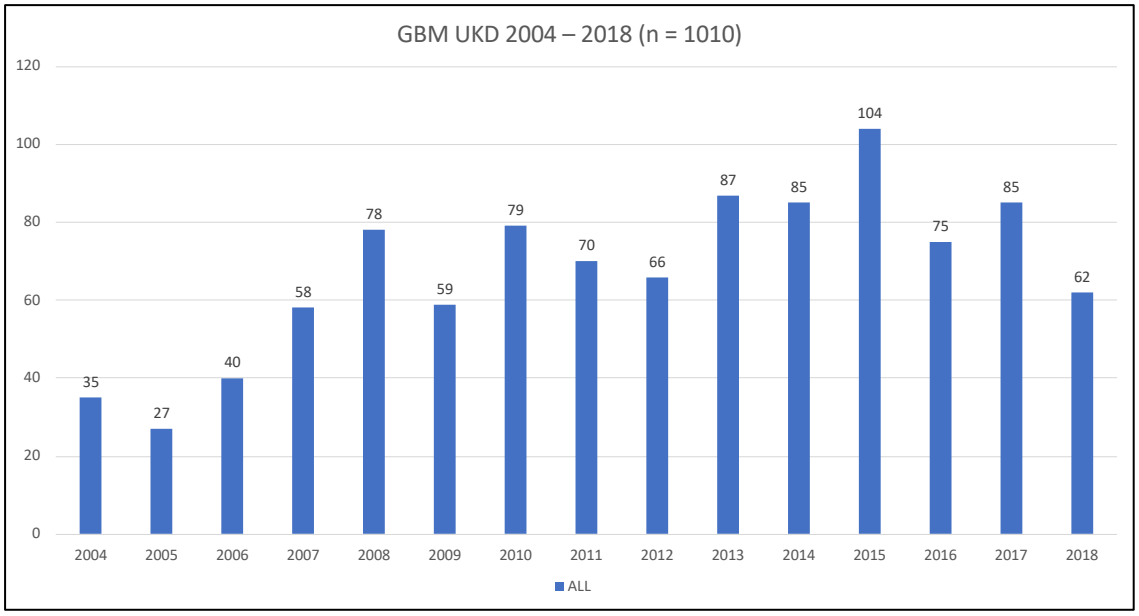

Fig. 6: All glioblastomas operated in UKD from 2004–2018

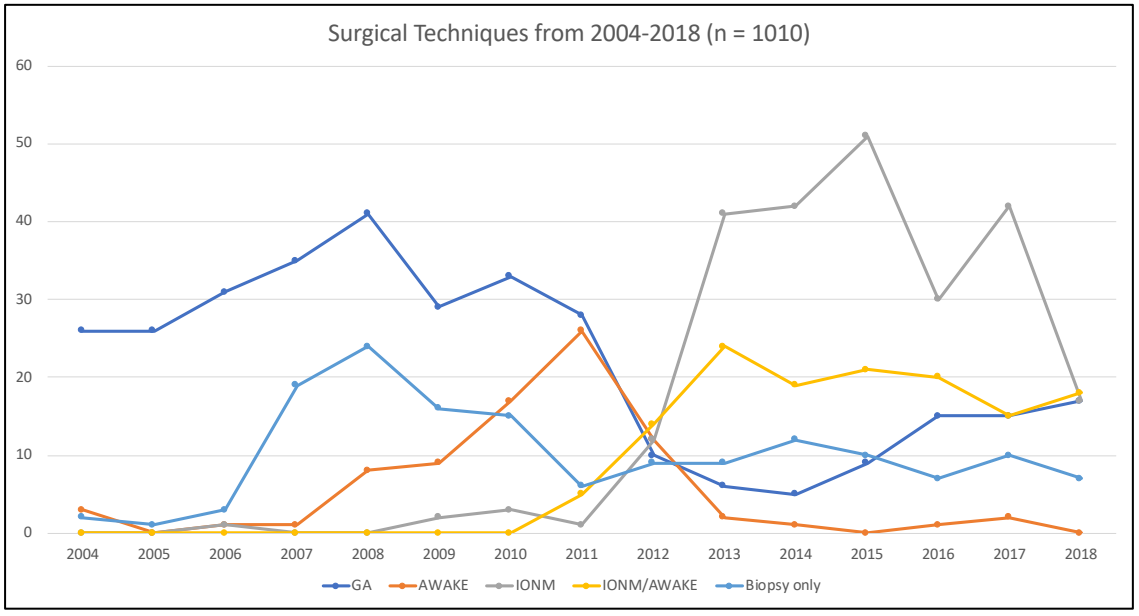

Fig. 7: Line graph of patients (n = 1010) divided by surgical technique from 2004–2018

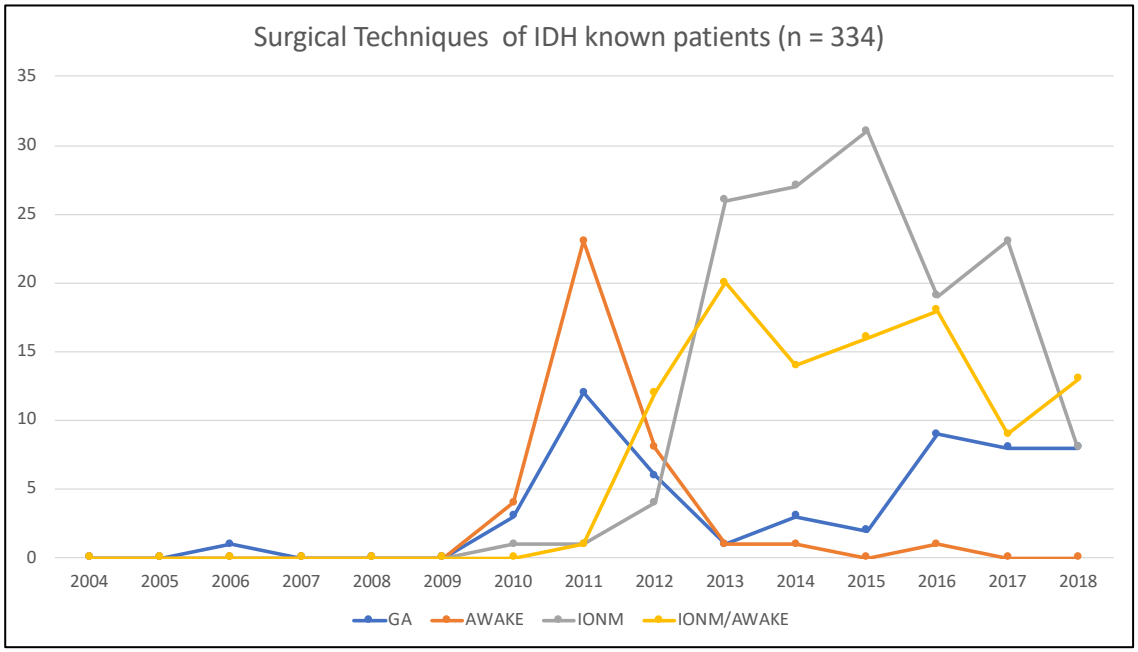

Fig. 8: Line graph patients (IDH known) (n = 334) divided by surgical technique from 2004–2018

Pearson chi square test

Biopsy compared to all other surgeries in UKD (excluding external surgeries)

Before 2010 vs. 2010 and after

			Before 2010	2010 and after	Total
Surgical technique	Biopsy	Count	65	85	150
		Expected count	44.5	105.5	150.0
	All other surgeries	Count	213	574	787
		Expected count	233.5	553.5	787.0
Total		Count	278	659	937
		Expected count	278.0	659.0	937.0

p = < 0.0001

Table 8: Pearson chi square test, biopsy compared to all other surgeries in UKD, before 2010 vs. 2010 and after

Pearson chi square test GA compared to all other surgical techniques (awake, IONM, IONM/awake) Before 2010 vs. 2010 and after					
			Before 2010	2010 and after	Total
Surgical technique	Other techniques	Count	25	436	461
		Expected count	124.8	336.2	461.0
	GA	Count	188	138	326
		Expected count	88.2	237.8	326.0
Total		Count	213	574	787
		Expected count	213.0	574.0	787.0
p = < 0.0001					

Table 9: Pearson chi square test, GA compared to all other surgical techniques (awake, IONM, IONM/awake), before 2010 vs. 2010 and after

3.3 The distribution of eloquent tumours

Bar charts were used to extrapolate the distribution of eloquently located tumours operated from 2004–2018. The lowest number of eloquently located tumours was found in 2004 and 2005 (n = 11). In 2015, the highest number of eloquent tumours were operated (n = 49) (Fig. 9 and Fig. 10) . The chi square test showed that since 2010, the number of surgeries operated on eloquently located tumours increased significantly, which corresponded directly to the increase of IONM and IONM/awake surgeries ($p < 0.0001$) (Table 10). To observe the possibility of a selection bias for patients operated under GA, a chi square test was performed. Since 2010 marked the incorporation of additional monitoring during surgeries, the number of patients operated under GA before and after 2010 were compared. The selection of GA for patients was not biased by the location of the tumour ($p = 0.184$)(Table 11)

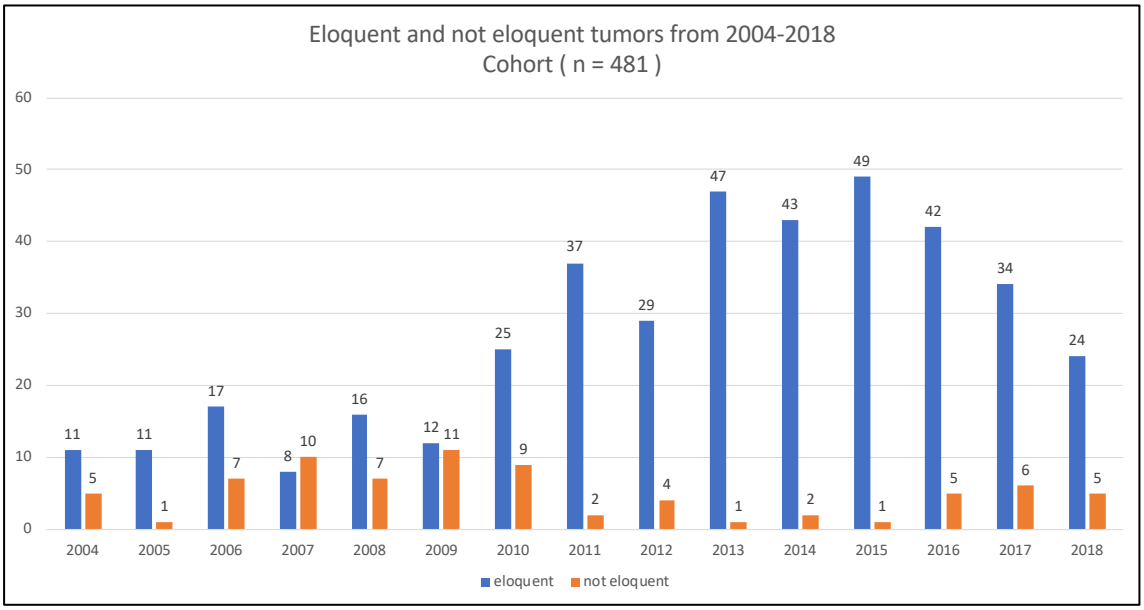

Fig. 9: Bar graph of eloquent and not eloquent tumors (cohort, n = 481) from 2004–2018

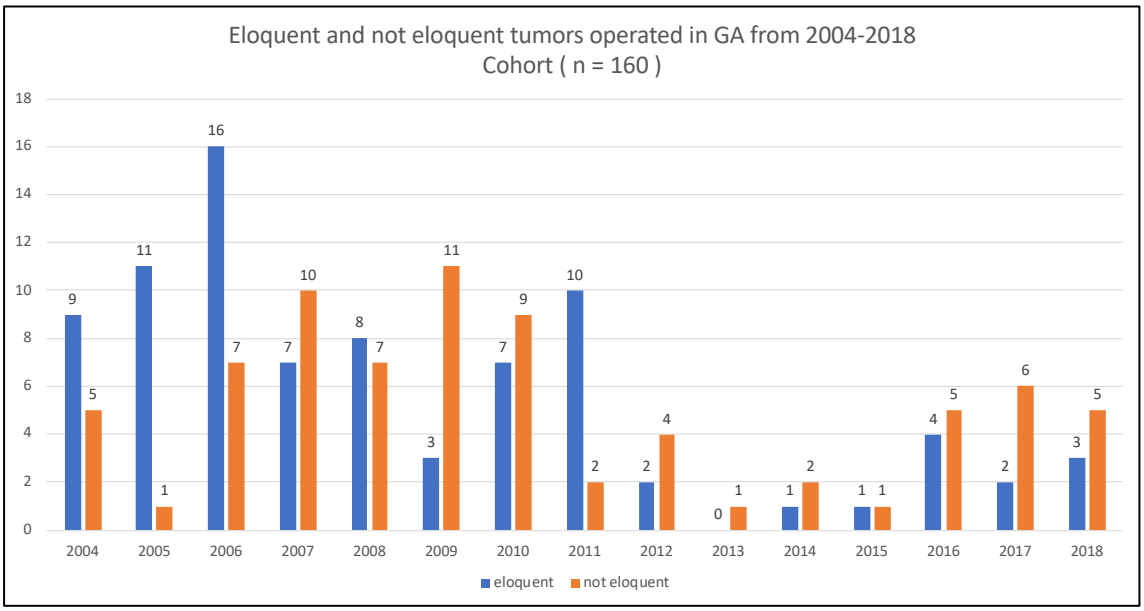

Fig. 10: Bar graph of eloquent and not eloquent tumors operated in GA (n = 160) from 2004–2018

Pearson chi square test

Eloquent and not eloquent tumours

Before 2010 vs. 2010 and after

			Before 2010	2010 and after	Total
Eloquence	Eloquent	Count	75	330	405
		Expected count	97.7	307.3	405.0
	Not eloquent	Count	41	35	76
		Expected count	18.3	57.7	76.0
Total		Count	116	365	481
		Expected count	116.0	365.0	481.0

$p < 0.0001$

Table 10: Pearson chi square test, eloquent and not eloquent tumours, before 2010 vs. 2010 and after

Pearson chi square test

Eloquent and not eloquent tumours operated in GA

Before 2010 vs. 2010 and after

			Before 2010	2010 and after	Total
Eloquence	Eloquent	Count	54	30	84
		Expected count	49.9	34.1	84.0
	Not eloquent	Count	41	35	76
		Expected count	45.1	30.9	76.0
Total		Count	95	65	160
		Expected count	95.0	65.0	160.1

$p = 0.184$

Table 11: Pearson chi square test, eloquent and not eloquent tumors operated in GA, before 2010 vs. 2010 and after

3.4 Extent of resection

The percentile values of the mean, median and range were calculated for the EOR for the entire cohort of surgical resection and also for the cohort with a known IDH status. The mean value for both cohorts was ≈ 96% with respective interquartile ranges ≈ 96.2–100% (Table 7).

Of the 481 patients who underwent a surgical resection, 373 patients (76%) had a GTR, while the remaining 108 (22%) had a partial resection. Of the patients who were operated under GA, 128 (80%) had a GTR, and 32 (20%) had a partial resection. In the awake setting, 56 patients (79%) had a GTR, and 32 (21%) had a partial resection. In the IONM setting, 108 patients (74%) had a GTR, and 37 (26%) had a partial resection. Finally, in those operated with IONM/awake, 81 (77%) had a GTR, and 24 (23%) had a partial resection.

To test how the different operative settings affected maximal EOR, a one-way ANOVA was performed. No statistical significance ($p = 0.404$) was found regarding the EOR and different surgical settings. A box plot was created to represent the results for the EOR for various surgical settings. Fig .11 represents the cohort of all surgically resected patients, and Fig. 12 represents the cohort with a known IDH status. Additionally, the subcohort analysis of patients with known IDH statuses found no statistical significance ($p = 0.138$) regarding the EOR and different surgical settings.

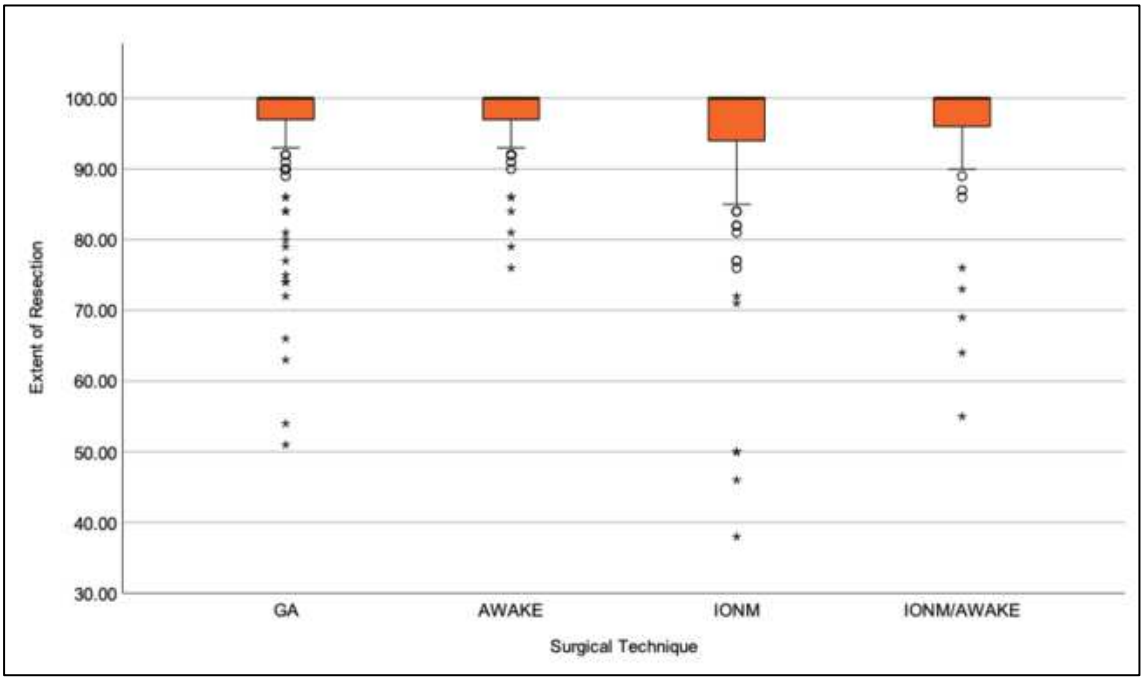

Fig. 11: Boxplot, EOR compared with different surgical techniques of all cohort patients (n = 478); one-way ANOVA (p = 0.404)

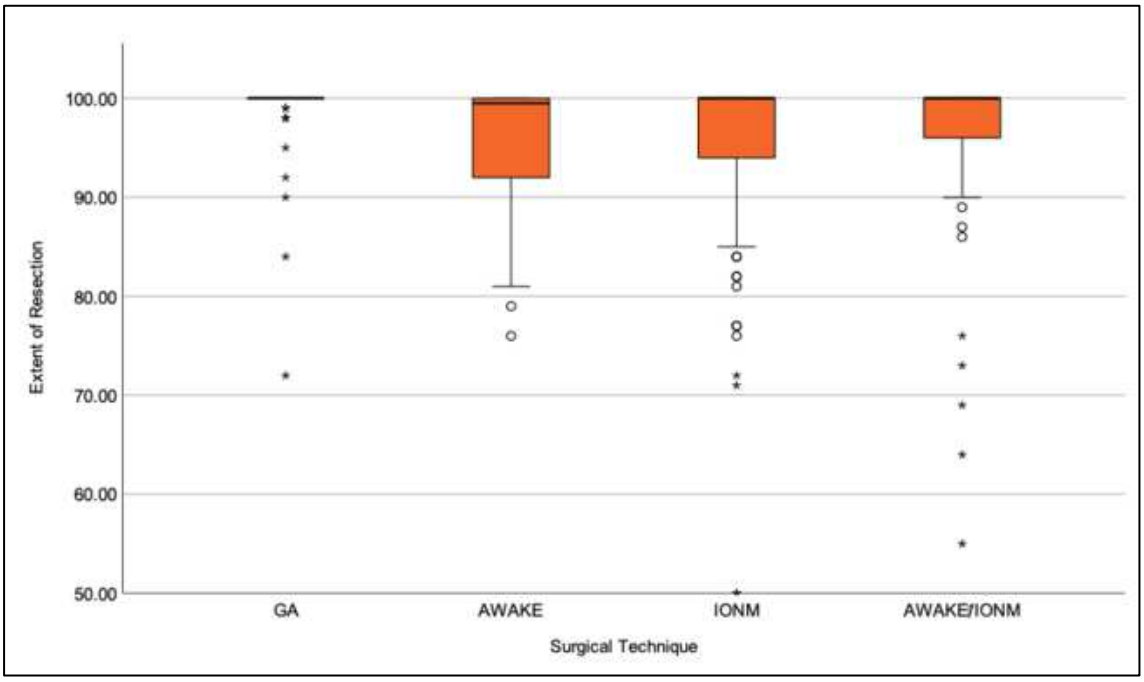

Fig. 12: Boxplot, EOR compared with different surgical techniques of all patients with known IDH (n = 332); one-way ANOVA (p = 0.138)

3.5 NIHSS and KPS

NIHSS and KPS were documented at three different times for all patients who underwent surgery:

- Before surgery,
- At the time of discharge and
- Three months after surgery.

A one-way ANOVA was used to assess the means of the NIHSS and KPS for the different times as they related to the different operative settings. Bonferroni correction was utilised to address the error that may have occurred during multiple comparisons to analyse the changes of NIHSS and KPS statistically over the different times.

For better comparison, sub-cohort analyses of NIHSS and KPS were also completed as follows:

- NIHSS and KPS of patients who received STUPP (n = 427)
- NIHSS and KPS of patients with IDH-wildtype with STUPP (n = 291)

3.5.1 NIHSS for the entire patient cohort (n = 481)

3.5.1.1 One-way ANOVA at different times

Before surgery

The boxplot diagram analysing NIHSS before surgery showed statistically significantly higher values of NIHSS scores for patients operated in GA compared to those who underwent the other operating settings (Fig.13 and Table 12).

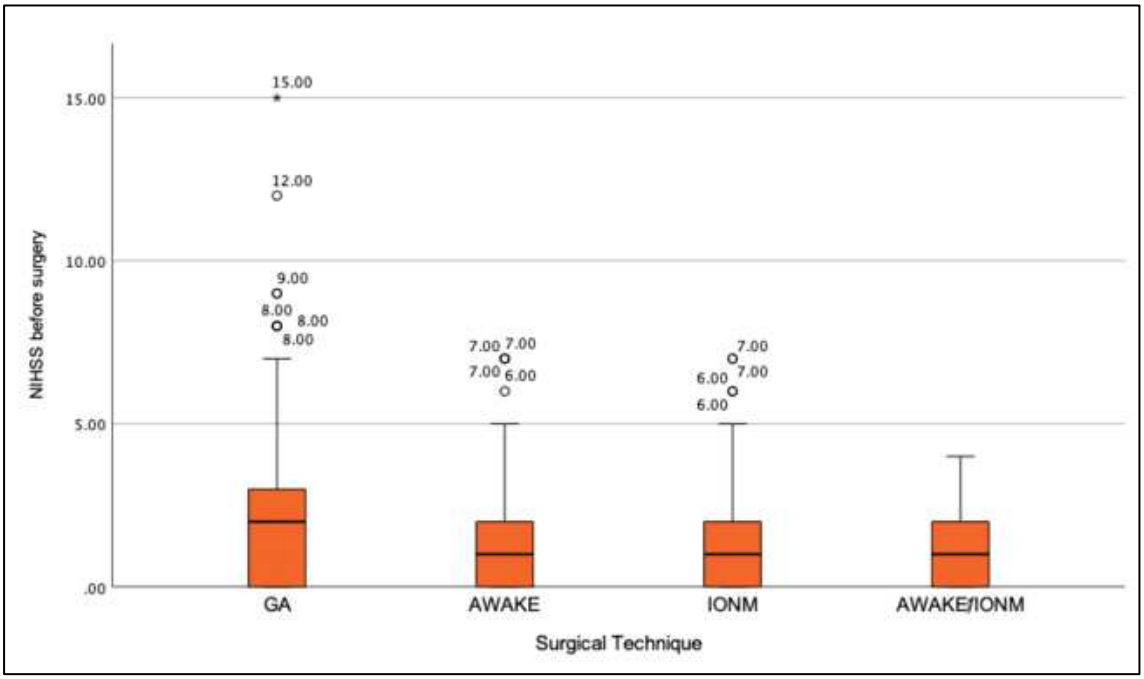

Fig. 13: Boxplot, NIHSS before surgery for all patients

One-way ANOVA		
NIHSS before surgery for all patients		
GA compared to other surgical techniques		*p value*
GA	Awake	0.044
	IONM	0.005
	IONM/Awake	< 0.0001

Table 12: One-way ANOVA, NIHSS before surgery for all patients, GA compared to other surgical techniques

After surgery

As seen in Fig. 14 and Table 13, patients operated under the awake setting had a significantly higher NIHSS after surgery compared to those operated under the other settings.

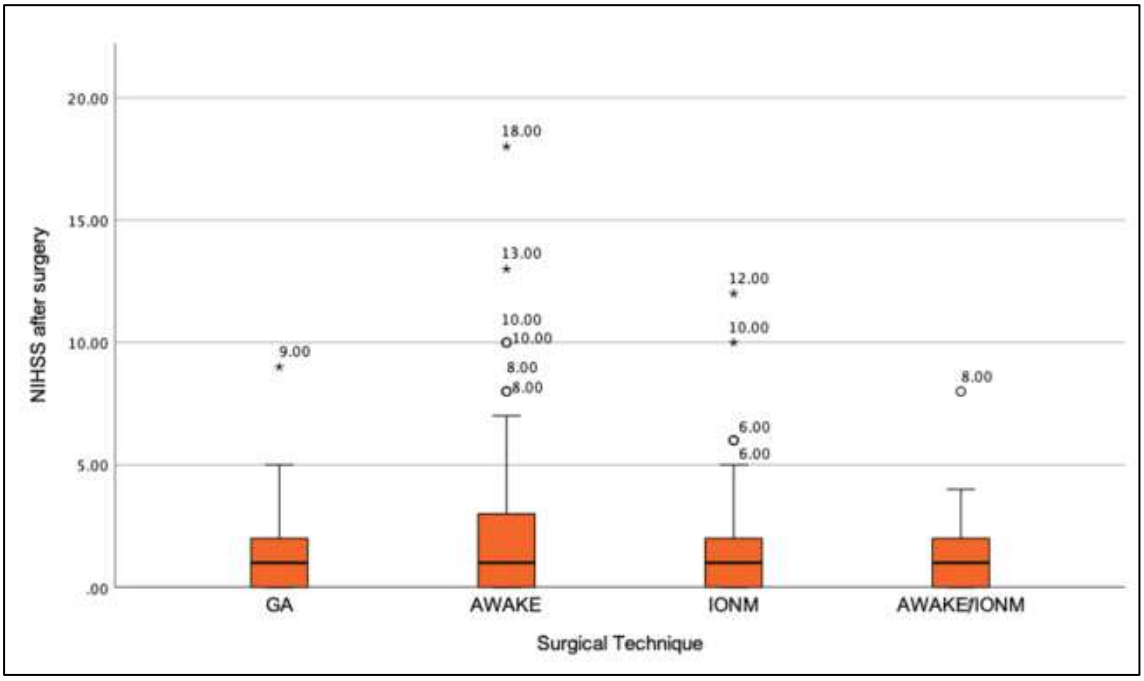

Fig. 14: Boxplot, NIHSS after surgery for all patients

One-way ANOVA		
NIHSS after surgery for all patients		
GA compared to other surgical techniques		*p value*
GA	Awake	0.005
	IONM	1.000
	IONM/awake	0.216

Table 13: One-way ANOVA, NIHSS after surgery for all patients, GA compared to other surgical techniques

Three months after surgery

The three-month follow-up showed a tendency of statistical significance for patients operated in the awake setting to have higher values of NIHSS compared to other patients. No statistically significant variation of NIHSS was observed in patients operated under GA, IONM or IONM/awake compared to the other times recorded (Fig. 15 and Table 14).

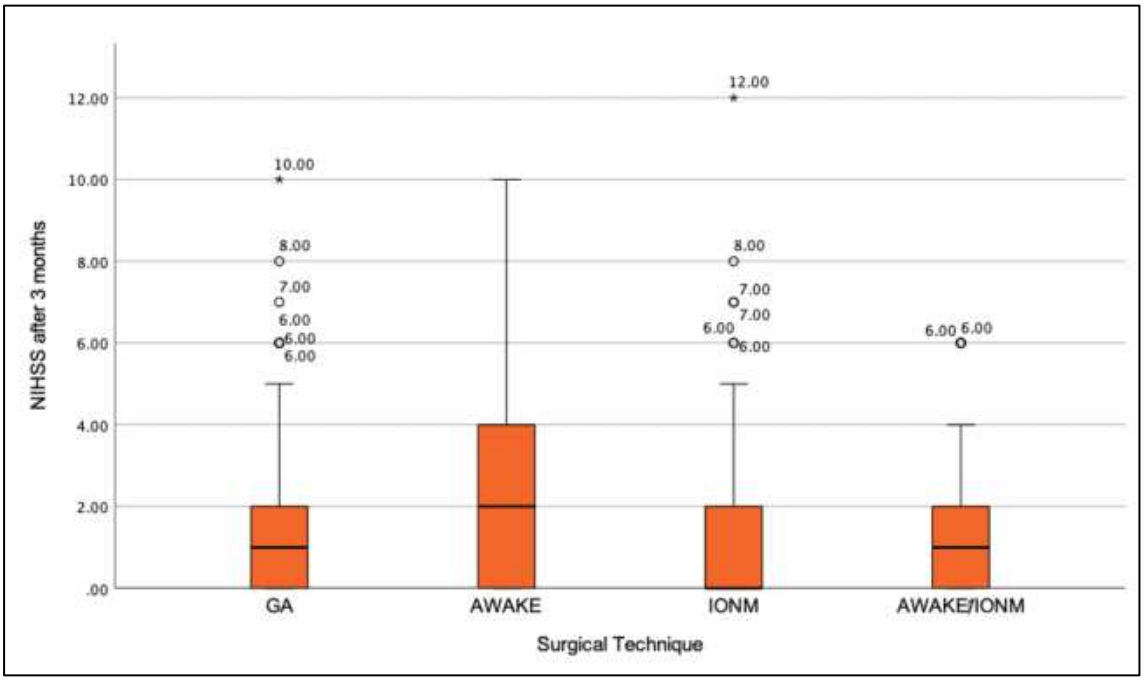

Fig. 15: Boxplot, NIHSS three months after surgery for all patients

One-way ANOVA		
NIHSS three months after surgery for all patients		
GA compared to other surgical techniques		*p value*
GA	Awake	0.044
	IONM	1.000
	IONM/awake	1.000

Table 14: One-way ANOVA, NIHSS three months after surgery for all patients, GA compared to other surgical techniques

3.5.2 NIHSS for all patients with STUPP (n = 427)

3.5.2.1 One-way ANOVA at different times

Before surgery

In the sub cohort of patients who received adjuvant STUPP, patients operated in GA had a comparatively higher pre-operative NIHSS value compared to those operated under IONM or IONM/awake. With a *p*-value of 0.13, no significant difference was found between awake and GA (Fig. 16 and Table 15)

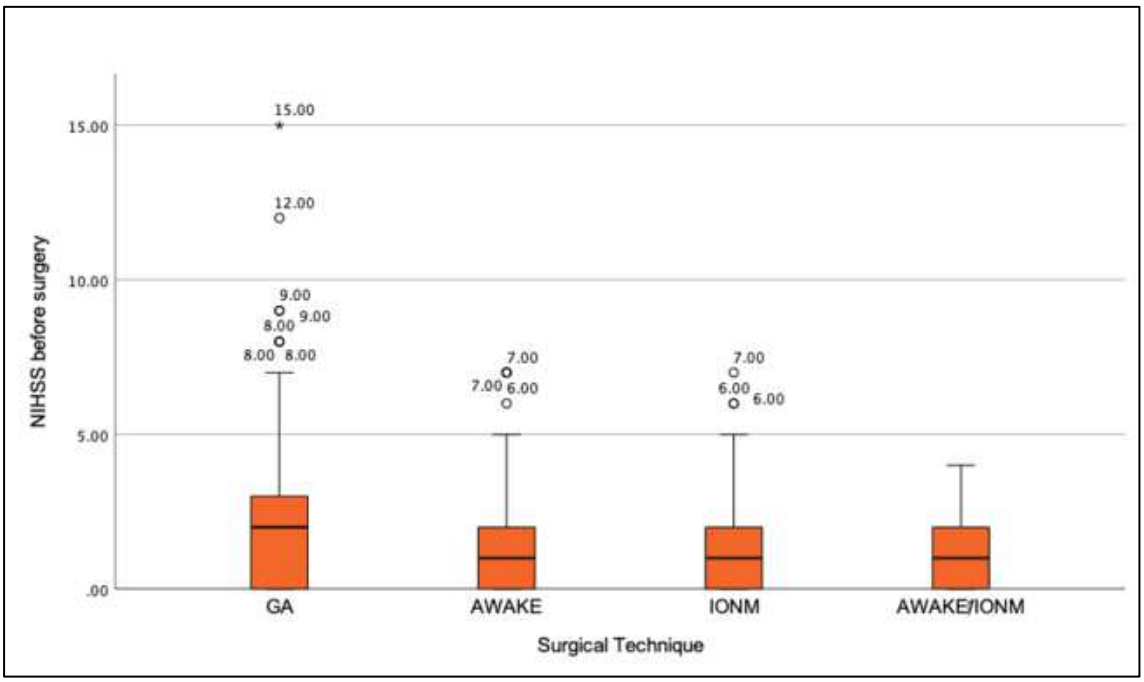

Fig. 16: Boxplot, NIHSS before surgery for all patients with STUPP

One-way ANOVA		
NIHSS before surgery for all patients with STUPP		
GA compared to other surgical techniques		*p value*
GA	Awake	0.130
	IONM	0.008
	IONM/awake	< 0.0001

Table 15: One-way ANOVA, NIHSS before surgery for all patients with STUPP, GA compared to other surgical techniques

After surgery

We observed an increase in the post-operative NIHSS in patients operated under awake settings, and this increase was statistically significant compared to the other surgical settings (Fig. 17 and Table 16)

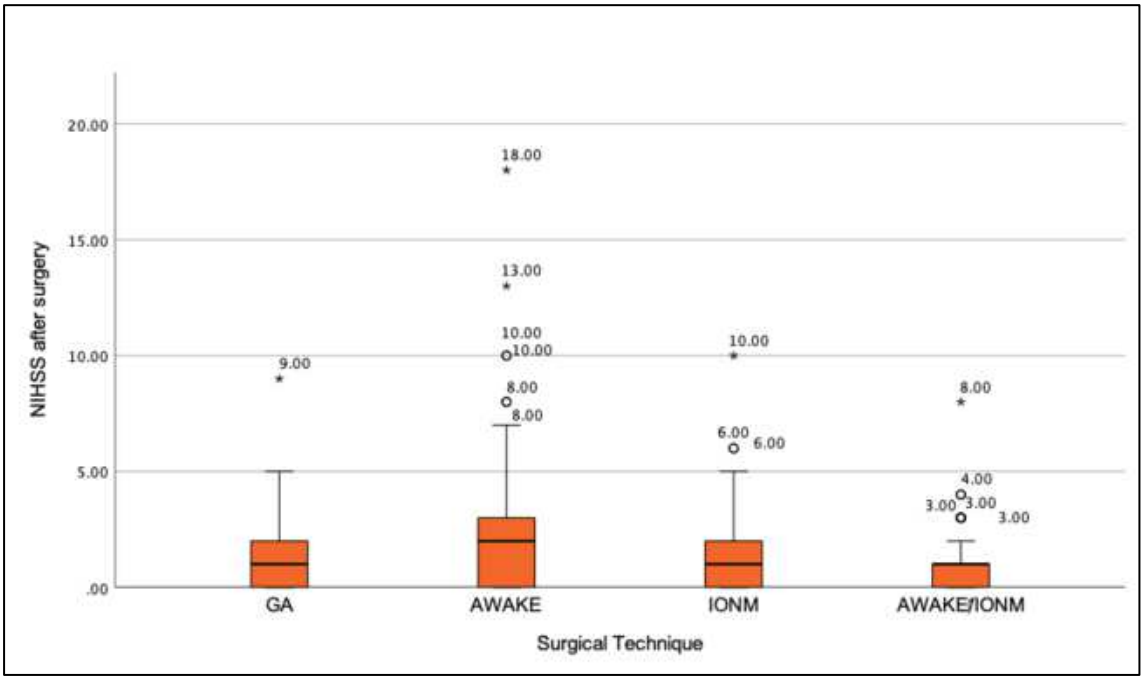

Fig. 17: Boxplot, NIHSS after surgery for all patients with STUPP

One-way ANOVA		
NIHSS after surgery for all patients with STUPP		
GA compared to other surgical techniques		*p value*
GA	Awake	0.001
	IONM	1.000
	IONM/awake	0.204

Table 16: One-way ANOVA, NIHSS after surgery for all patients with STUPP, GA compared to other surgical techniques

Three months after surgery

The three-month follow-up also showed that awake surgeries had significantly higher values of NIHSS compared to the other operating techniques (Fig. 18 and Table 17)

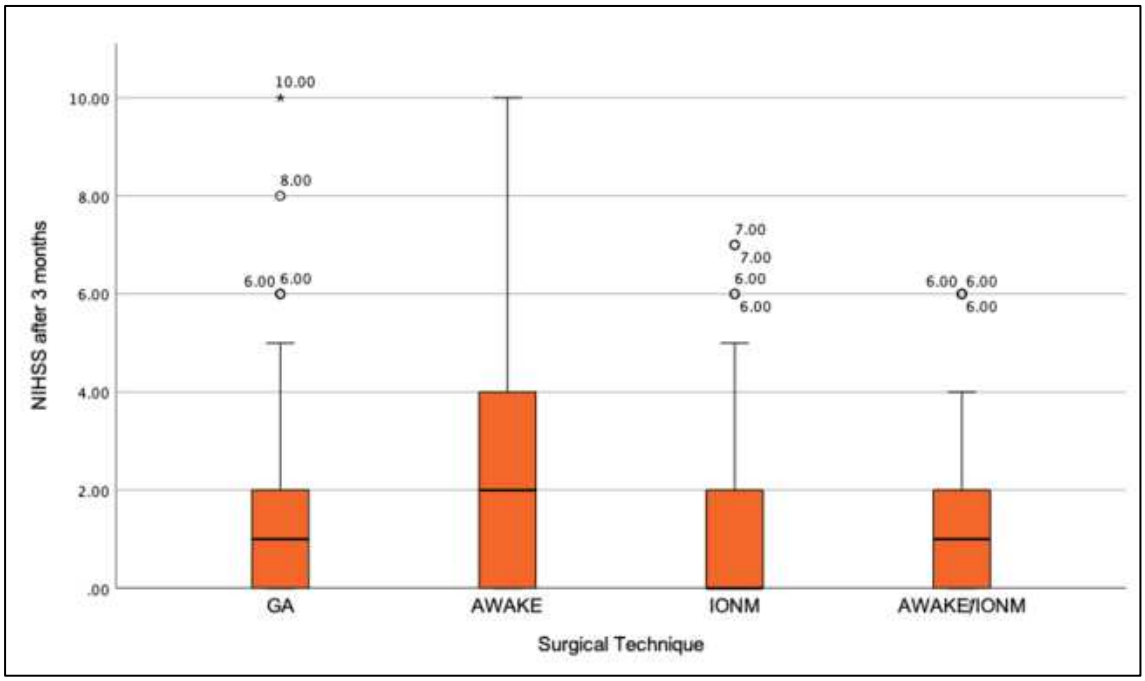

Fig. 18: Boxplot, NIHSS three months after surgery for all patients with STUPP

One-way ANOVA		
NIHSS three months after surgery for all patients with STUPP		
GA compared to other surgical techniques		*p value*
GA	Awake	0.013
	IONM	0.727
	IONM/awake	1.000

Table 17: One-way ANOVA, NIHSS three months after surgery for all patients with STUPP, GA compared to other surgical techniques

3.5.3 NIHSS with IDH-wildtype and STUPP (n = 291)

3.5.3.1 One-way ANOVA at different times

Before surgery

In the second sub cohort analysis of patients with IDH-wildtype GBM who received adjuvant STUPP (n = 291), the pre-operative NIHSS values showed no statistically significant values for the different operating settings (Fig. 19 and Table 18)

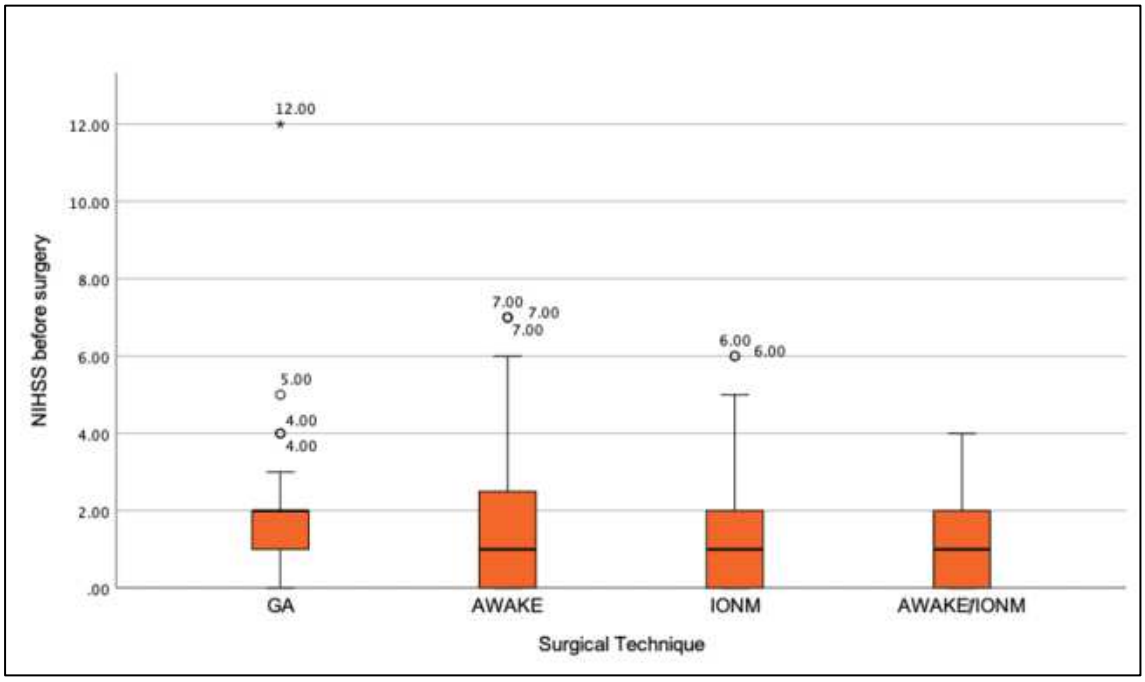

Fig. 19: Boxplot, NIHSS before surgery for all patients with STUPP and IDH-wildtype

One-way ANOVA		
NIHSS before surgery for all patients with STUPP/IDH-wildtype		
GA compared to other surgical techniques		*p value*
GA	Awake	1.000
	IONM	0.889
	IONM/awake	0.033

Table 18: One-way ANOVA, NIHSS before surgery for all patients with STUPP and IDH-wildtype, GA compared to other surgical techniques

After surgery

No statistical significance was observed in the post-operative NIHSS values comparing GA, IONM or IONM/awake. However, the awake setting showed significantly higher NIHSS values in the post-operative period (Fig. 20 and Table 19)

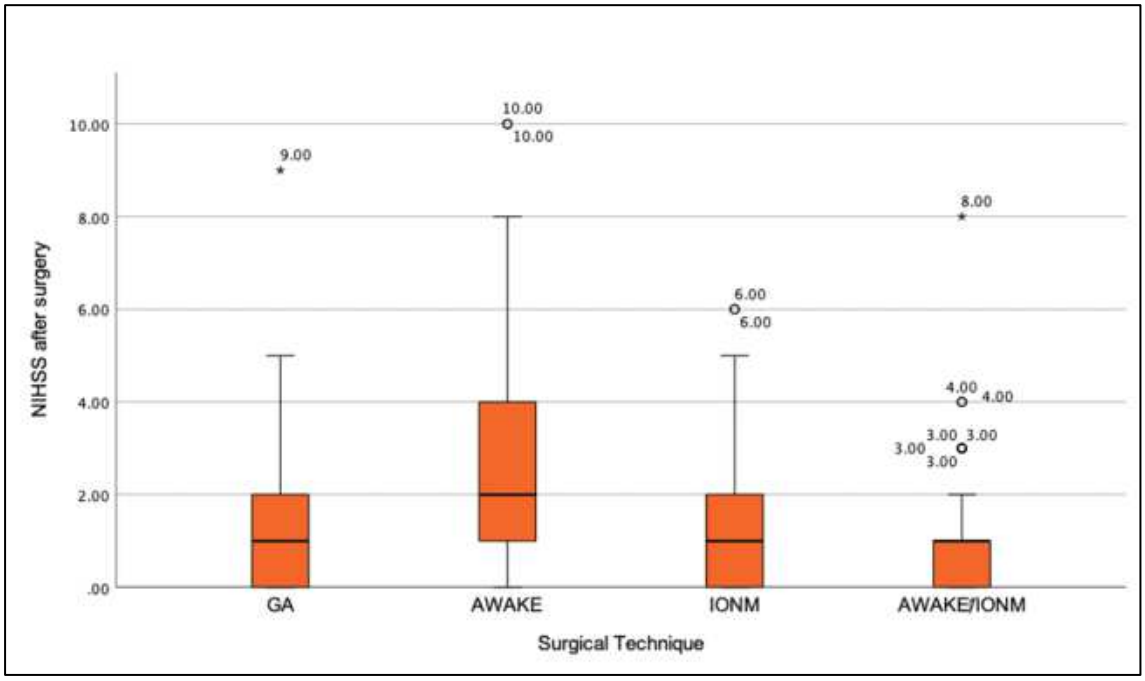

Fig. 20: Boxplot, NIHSS after surgery for all patients with STUPP and IDH-wildtype

One-way ANOVA		
NIHSS after surgery for all patients with STUPP/IDH-wildtype		
GA compared to other surgical techniques		*p value*
GA	Awake	0.001
	IONM	0.899
	IONM/awake	0.149

Table 19: One-way ANOVA, NIHSS after surgery for all patients with STUPP and IDH-wildtype, GA compared to other surgical techniques

Three months after surgery

Comparably similar results were also observed in the three-month follow-up period; the awake setting had a significantly higher NIHSS value ($p = 0.004$), while the other three surgical settings showed no significant change in the NIHSS values (Fig. 21 and Table 20)

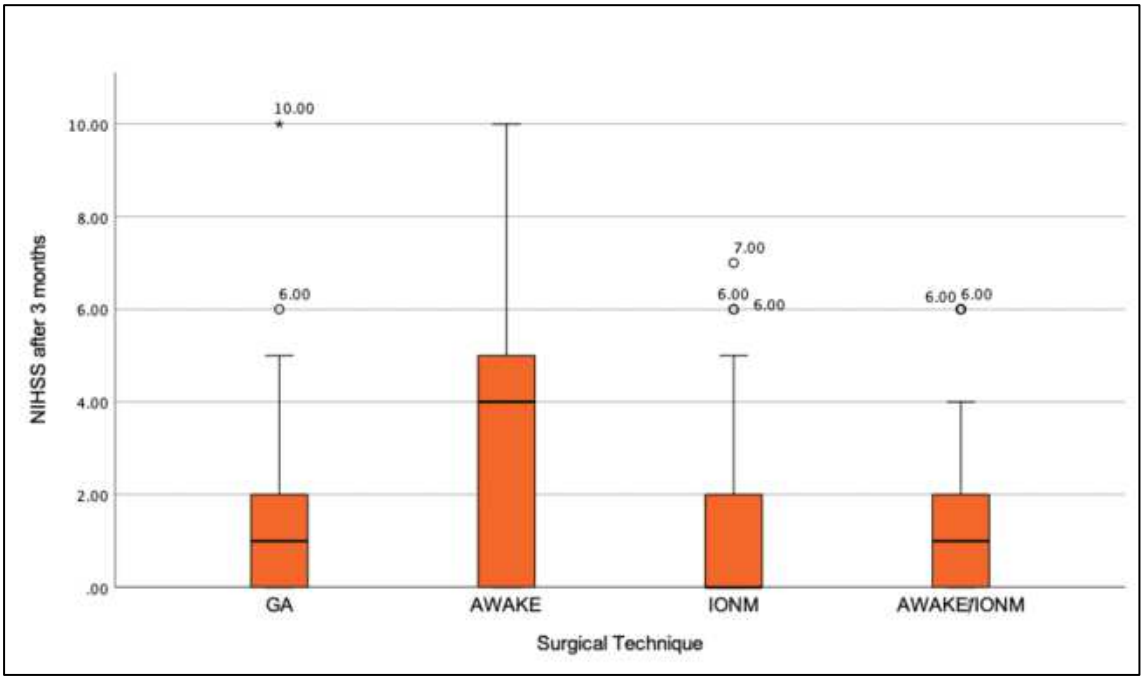

Fig. 21: Boxplot, NIHSS three months after surgery for all patients with STUPP and IDH-wildtype

One-way ANOVA		
NIHSS three months after surgery for all patients with STUPP/IDH-wildtype		
GA compared to other surgical techniques		*p value*
GA	Awake	0.004
	IONM	0.988
	IONM/awake	1.000

Table 20: One-way ANOVA, NIHSS three months after surgery for all patients with STUPP and IDH-wildtype, GA compared to other surgical techniques

3.5.4 KPS for entire patient cohort (n = 481)

3.5.4.1 One-way ANOVA at different times

Before surgery

One-way ANOVA with a box plot diagram revealed that patients operated under IONM and IONM/awake settings had significantly higher pre-operative KPS compared to those operated in GA and awake settings (Fig. 22 and Table 21)

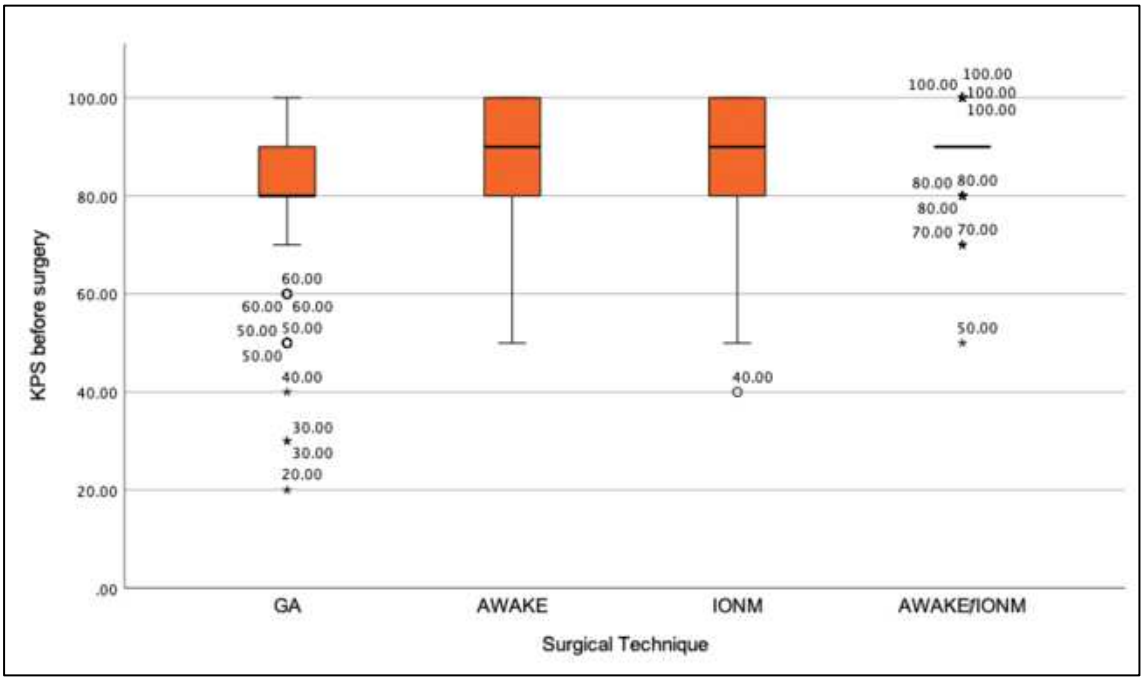

Fig. 22: Boxplot, KPS before surgery for all patients

One-way ANOVA		
KPS before surgery for all patients		
GA compared to other surgical techniques		*p value*
GA	Awake	0.086
	IONM	< 0.0001
	IONM/awake	< 0.0001

Table 21: One-way ANOVA, KPS before surgery for all patients, GA compared to other surgical techniques

After surgery

Post-operative analysis showed that the patients operated under IONM, and IONM/awake settings experienced no deterioration in terms of their KPS score. However, a significant decrease of the KPS score was observed in patients operated under the awake setting, while the KPS score for those operated under GA increased (Fig. 23 and Table 22)

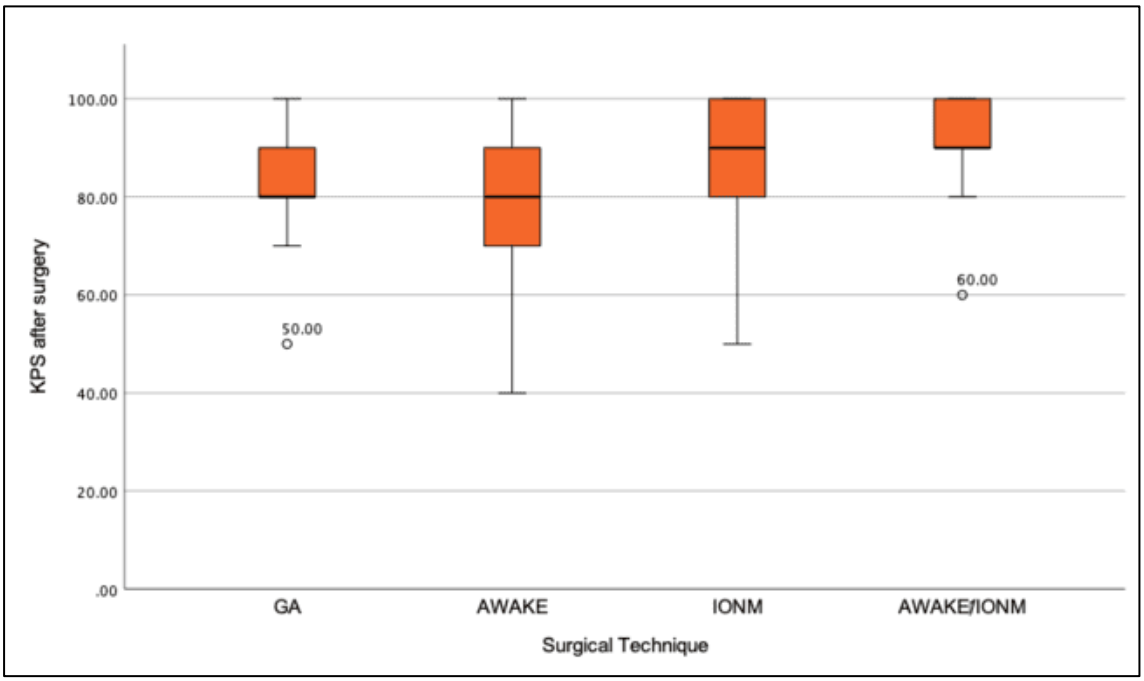

Fig. 23: Boxplot, KPS after surgery for all patients

One-way ANOVA		
KPS after surgery for all patients		
GA compared to other surgical techniques		*p value*
GA	Awake	< 0.0001
	IONM	< 0.0001
	IONM/awake	< 0.0001

Table 22: One-way ANOVA, KPS after surgery for all patients, GA compared to other surgical techniques

Three months after surgery

The three-month follow-up showed consecutively and significantly higher values of KPS for the IONM and IONM/awake settings compared to those of the GA setting as calculated using the Bonferroni method. However, the awake setting showed a significantly lower KPS score compared to GA (Fig. 24 and Table 23)

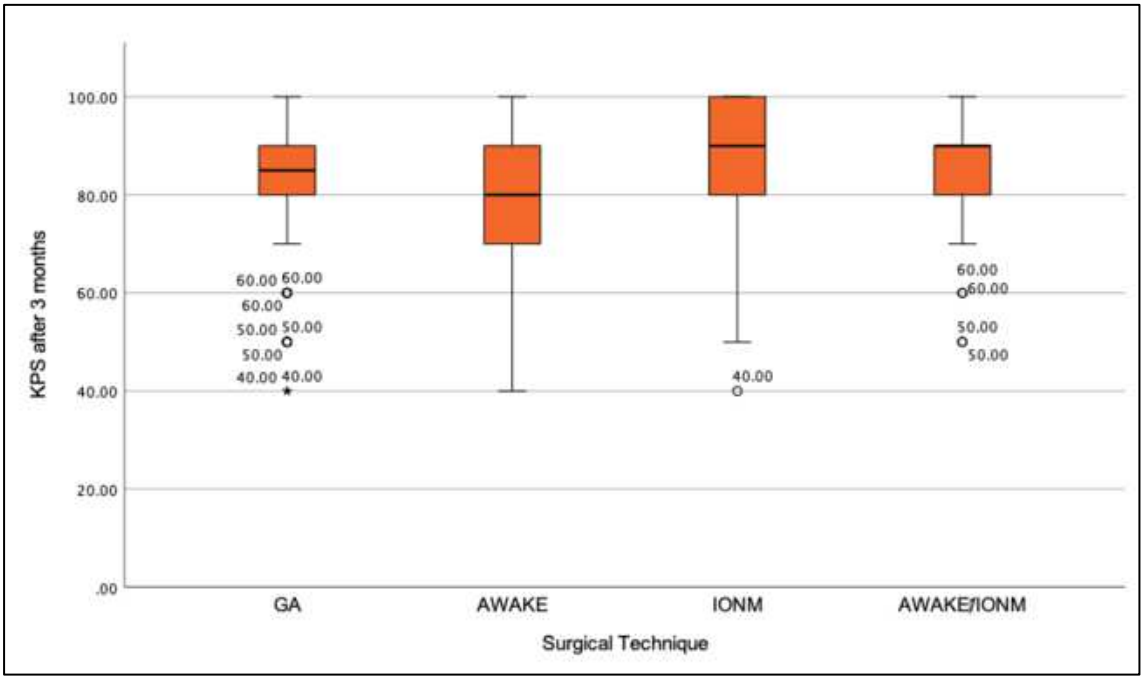

Fig. 24: Boxplot, KPS three months after surgery for all patients

One-way ANOVA		
KPS three months after surgery for all patients		
GA compared to other surgical techniques		*p value*
GA	Awake	0.012
	IONM	0.004
	IONM/awake	0.021

Table 23: One-way ANOVA, KPS three months after surgery for all patients, GA compared to other surgical techniques

3.5.5 KPS for all patients with STUPP (n = 427)

3.5.5.1 One-way ANOVA at different times

Before surgery

In the subcohort analyses of patients who received adjuvant STUPP, the results were comparable, with patients operated under IONM and IONM/awake settings having a significantly higher KPS score before surgery compared to those operated under GA and awake (Fig. 25 and Table 24).

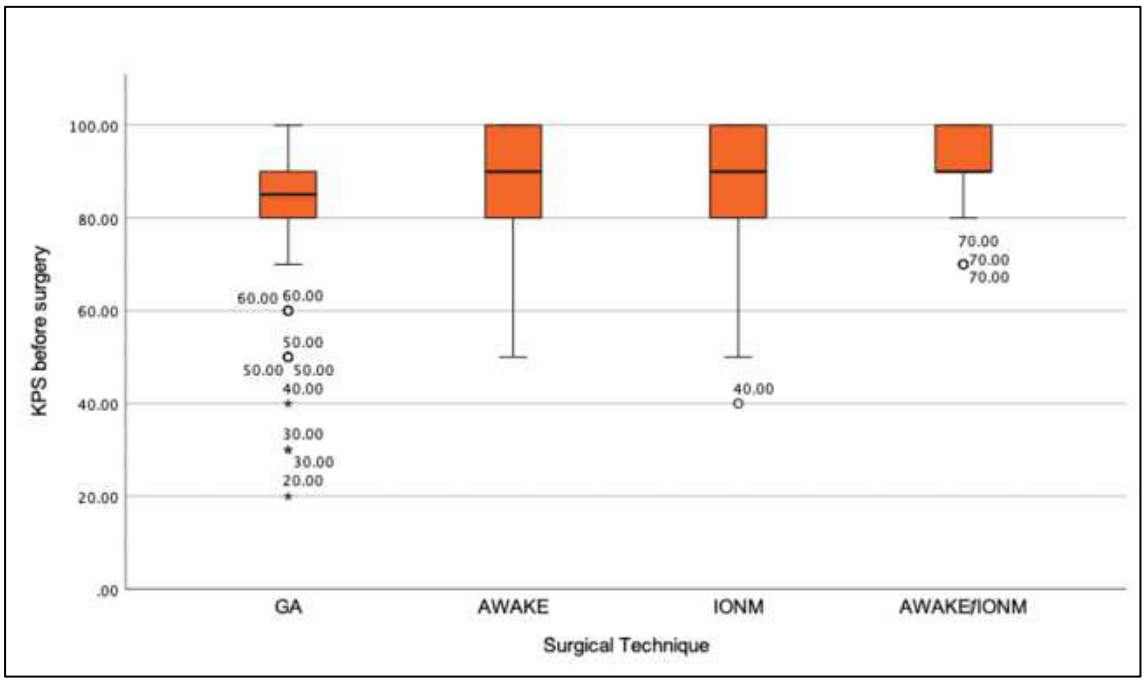

Fig. 25: Boxplot, KPS before surgery for all patients with STUPP

One-way ANOVA		
KPS before surgery for all patients with STUPP		
GA compared to other surgical techniques		*p value*
GA	Awake	0.259
	IONM	< 0.0001
	IONM/awake	< 0.0001

Table 24: One-way ANOVA, KPS before surgery for all patients with STUPP, GA compared to other surgical techniques

After surgery

Post-operative KPS was shown to be significantly higher in the patients operated with IONM and IONM/awake. The AWAKE group had significantly lower KPS levels comparatively (Fig. 26 and Table 25).

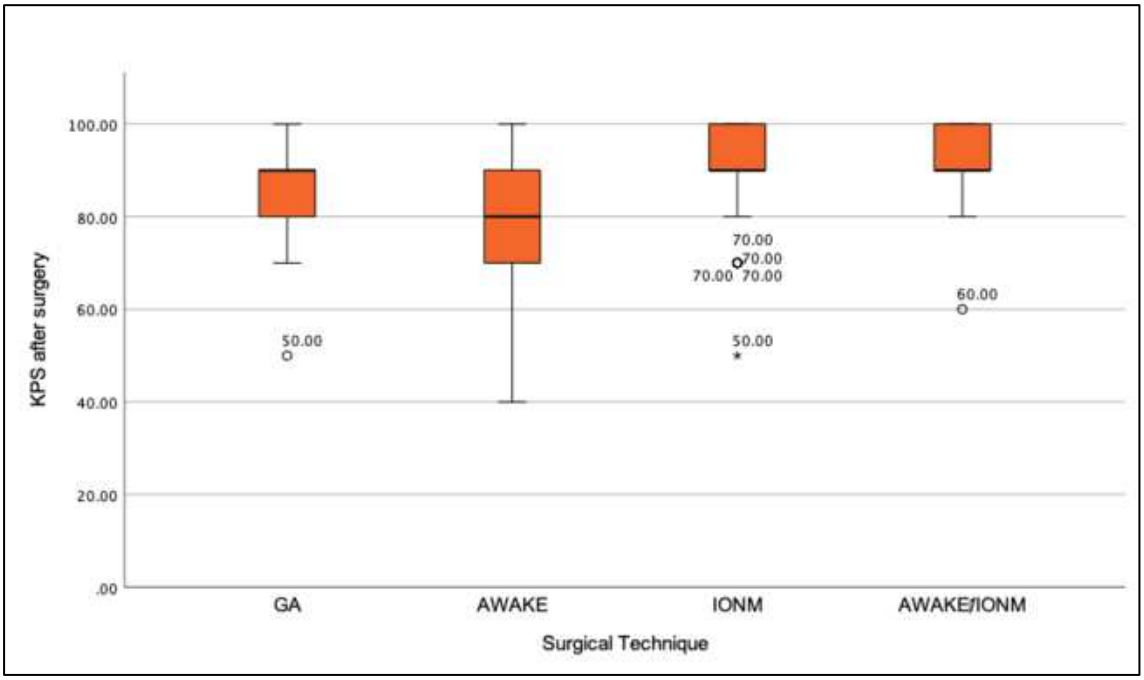

Fig. 26: Boxplot, KPS after surgery for all patients with STUPP

One-way ANOVA		*p value*
KPS after surgery for all patients with STUPP		
GA compared to other surgical techniques		
GA	Awake	< 0.0001
	IONM	< 0.0001
	IONM/awake	0.001

Table 25: One-way ANOVA, KPS after surgery for all patients with STUPP, GA compared to other surgical techniques

Three months after surgery

The three month follow-up analyses mirrored the results of those from the post-operative period, with IONM and IONM/awake showing higher values of KPS and the awake cohort showing significantly lower KPS scores comparatively (Fig. 27 and Table 26) .

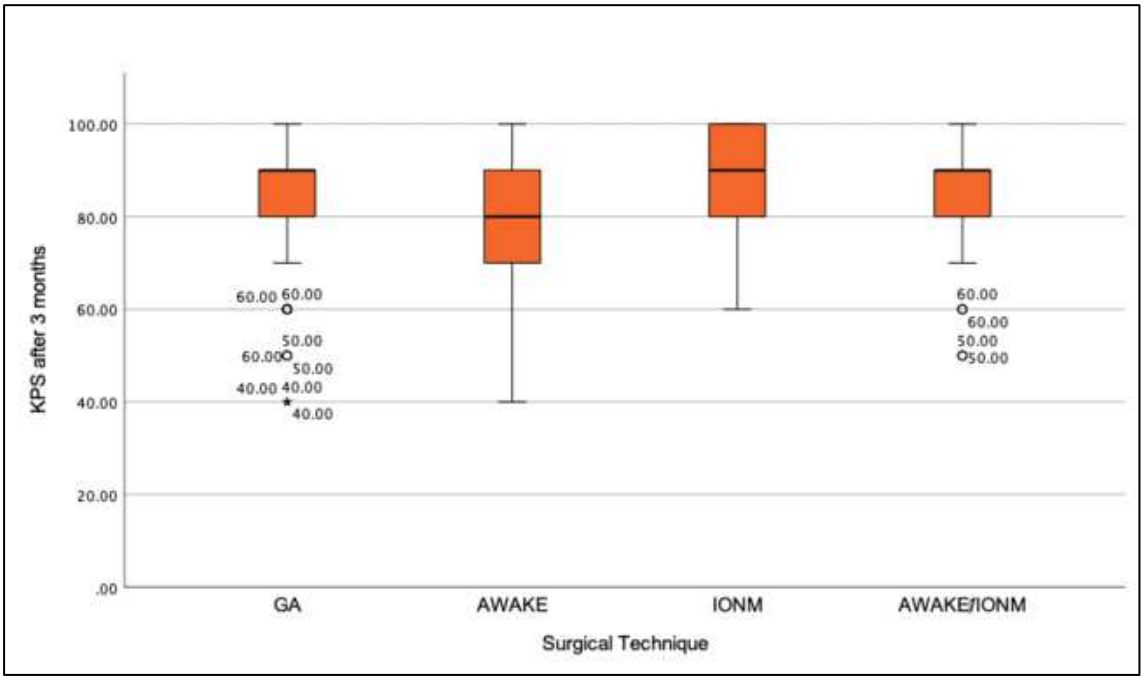

Fig. 27: Boxplot, KPS three months after surgery for all patients with STUPP

One-way ANOVA ***KPS three months after surgery for all patients with STUPP***		
GA compared to other surgical techniques		*p value*
GA	Awake	0.001
	IONM	0.002
	IONM/awake	0.049

Table 26: One-way ANOVA, KPS three months after surgery for all patients with STUPP, GA compared to other surgical techniques

3.5.6 KPS for patients with IDH-wildtype and STUPP (n = 291)

3.5.6.1 One-way ANOVA at different times

Before surgery

The subcohort analysis of patients with IDH and STUPP showed no significant difference in the KPS score when comparing the different operating techniques before surgery (Fig. 28 and Table 27).

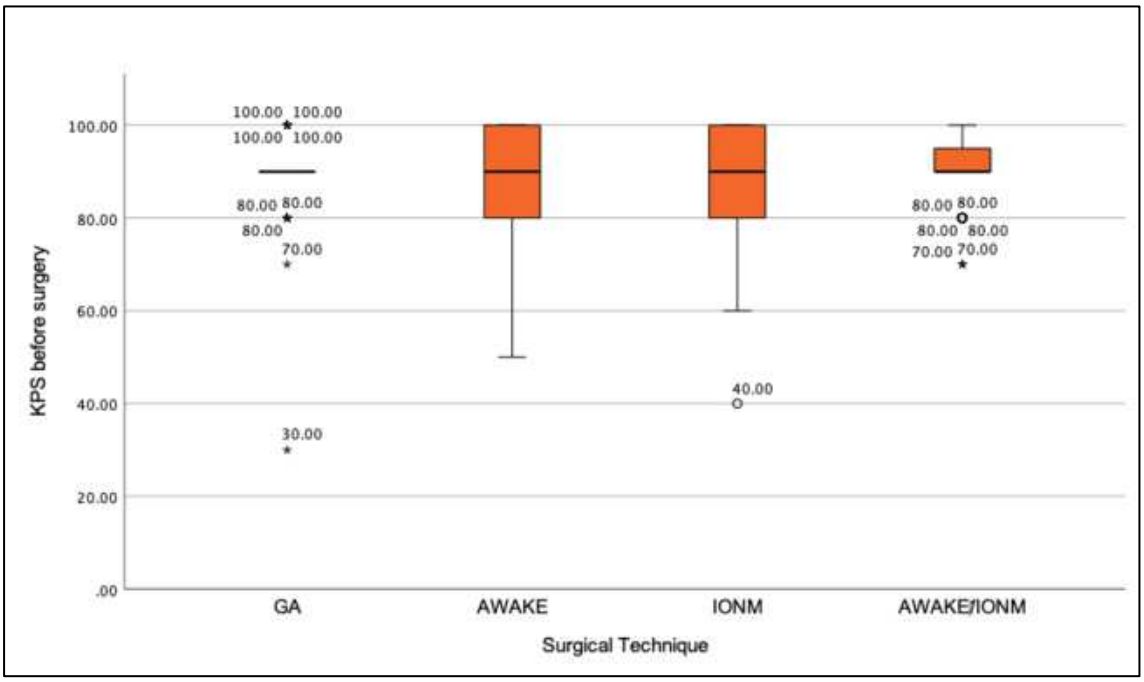

Fig. 28: Boxplot, KPS before surgery for all patients with STUPP and IDH-wildtype

One-way ANOVA		
***KPS before surgery for all patients with STUPP and IDH-wild*type**		
GA compared to other surgical techniques		*p value*
GA	Awake	1.000
	IONM	1.000
	IONM/awake	1.000

Table 27: One-way ANOVA, KPS before surgery for all patients with STUPP and IDH-wildtype, GA compared to other surgical techniques

After surgery

However, the post-operative results showed a significant decrease in the KPS score of those operated awake, while IONM and IONM/awake showed no significant change of KPS compared to the pre-operative period (Fig. 29 and Table 28).

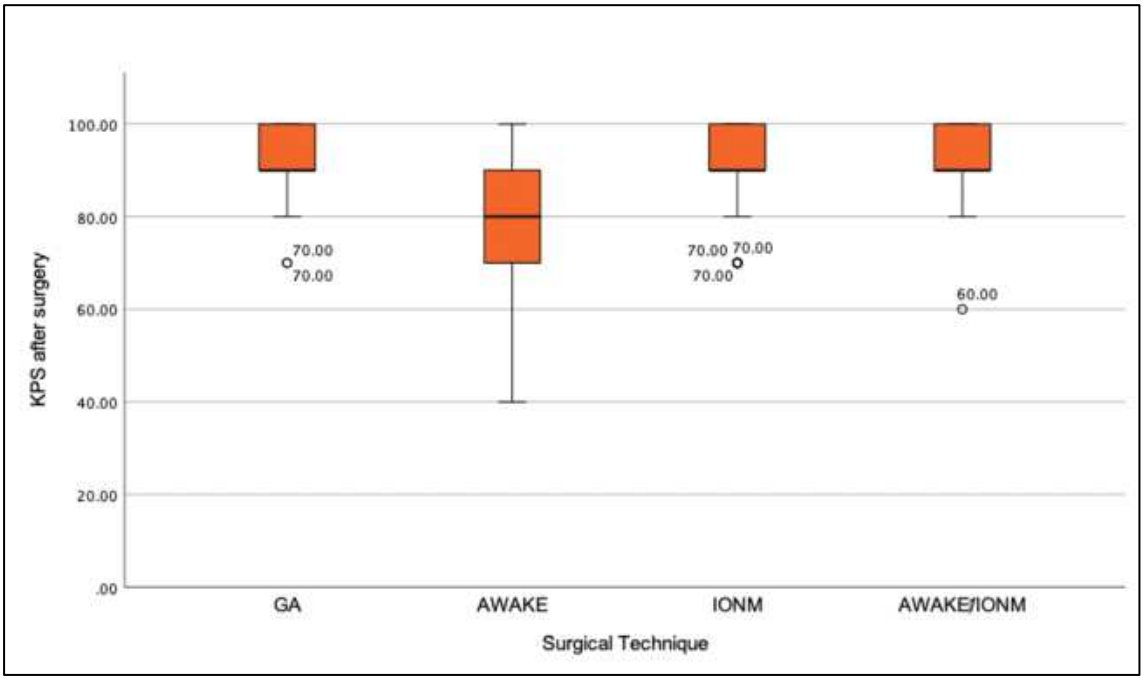

Fig. 29: Boxplot, KPS after surgery for all patients with STUPP and IDH-wildtype

One-way ANOVA ***KPS after surgery for all patients with STUPP and IDH-wild*type**		
GA compared to other surgical techniques		*p value*
GA	Awake	< 0.0001
	IONM	1.000
	IONM/awake	1.000

Table 28: One-way ANOVA, KPS after surgery for all patients with STUPP and IDH-wildtype, GA compared to other surgical techniques

Three months after surgery

As expected, the results from the three-month follow-up mirrored that of the post-operative period (Fig. 30 and Table 29).

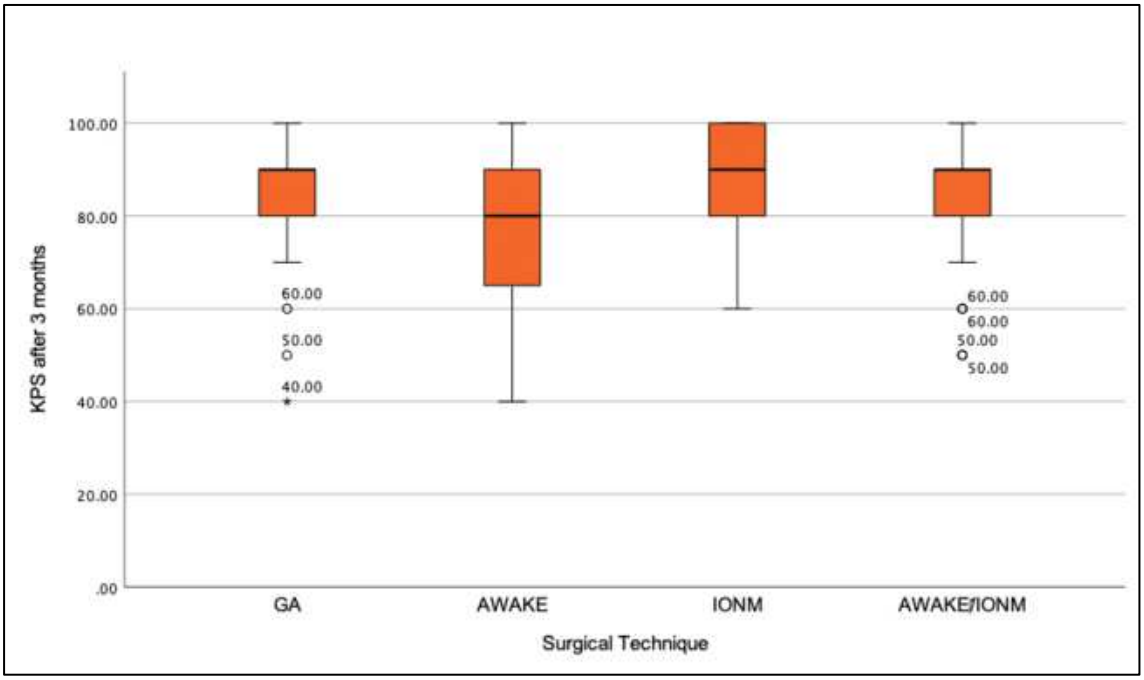

Fig. 30: Boxplot, KPS three months after surgery for all patients with STUPP and IDH-wildtype

One-way ANOVA		
***KPS three months after surgery for all patients with STUPP and IDH-wild*type**		
GA compared to other surgical techniques		*p value*
GA	Awake	0.002
	IONM	0.225
	IONM/awake	0.920

Table 29: One-way ANOVA, KPS three months after surgery for all patients with STUPP and IDH-wildtype, GA compared to other surgical techniques

3.6 PFS and OAS

To calculate the PFS and OAS, a Kaplan-Meier survival curve was plotted for the different operative settings. Subgroup analyses were also performed for the patients who received adjuvant STUPP and those with IDH-wildtype with adjuvant STUPP.

3.6.1 Kaplan-Meier curves for PFS

Fig. 31 shows the Kaplan-Meier curve for the PFS of the entire cohort. With a *p*-value of 0.749, no significance was found regarding the PFS of the different surgical settings. Fig. 32 and Fig. 33 show the PFS Kaplan-Meier curves for the subgroups that received STUPP and those with IDH-wildtype and STUPP, respectively. No significance in the PFS was observed while comparing the different operating techniques.

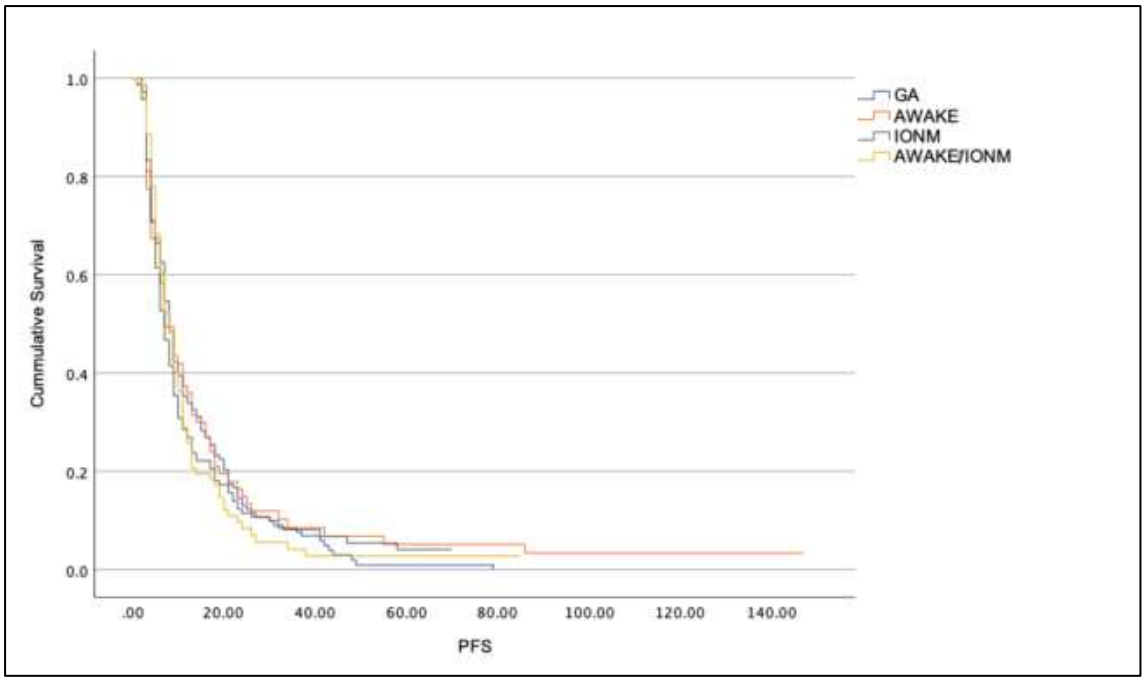

Fig. 31: Kaplan-Meier curve for the PFS for all patients, $p = 0.749$

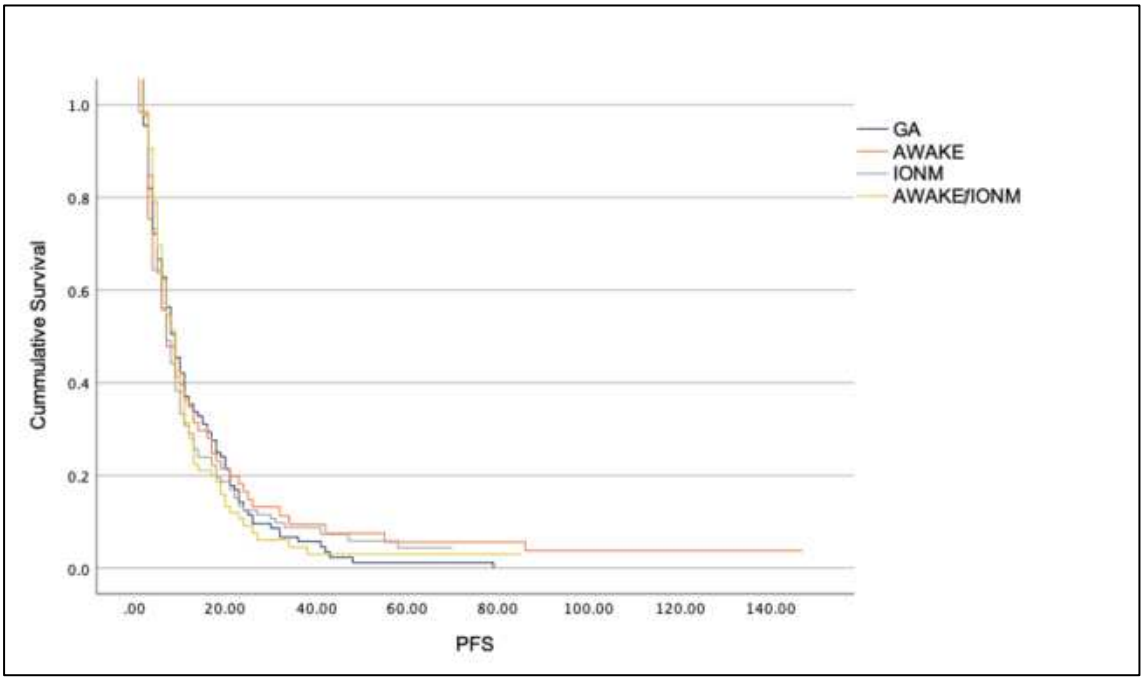

Fig. 32: Kaplan-Meier curve for the PFS of all patients with STUPP, $p = 0.923$

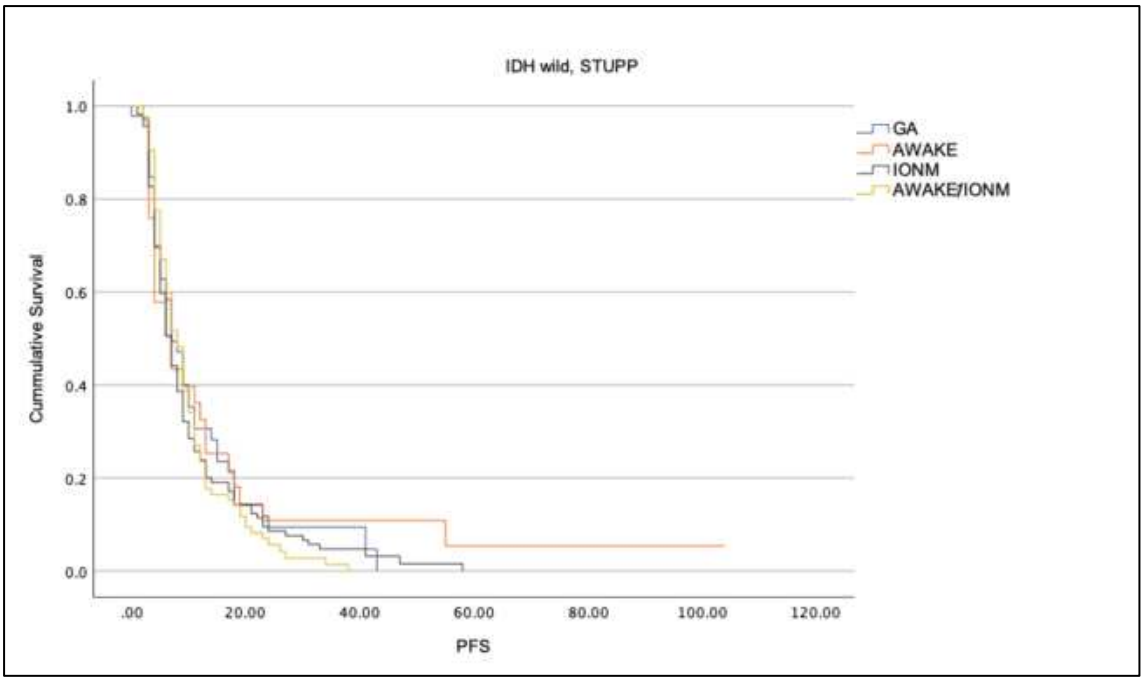

Fig. 33: Kaplan-Meier curve for the PFS of patients with STUPP and IDH-wildtype, $p = 0.737$

3.6.2 Kaplan-Meier curves for OAS

A Kaplan-Meier curve was plotted to extrapolate the OAS for all included patients, for patients who received STUPP therapy and for those with IDH-wildtype GBM who received adjuvant STUPP therapy. With a *p*-value of 0.034 for the entire patient cohort and for the subgroup that received STUPP, a significance of increased OAS for patients operated with GA was observed (Fig. 34 and Fig. 35). However, in the subcohort of patients with IDH-wildtype receiving STUPP, neither of the operating techniques were found to increase OAS (p = 0.199) (Fig. 36).

A separate Kaplan-Meier curve was used to compare biopsies to surgeries; this revealed that the patients with biopsies had a significantly lower OAS compared to their surgical counterparts (Fig. 37).

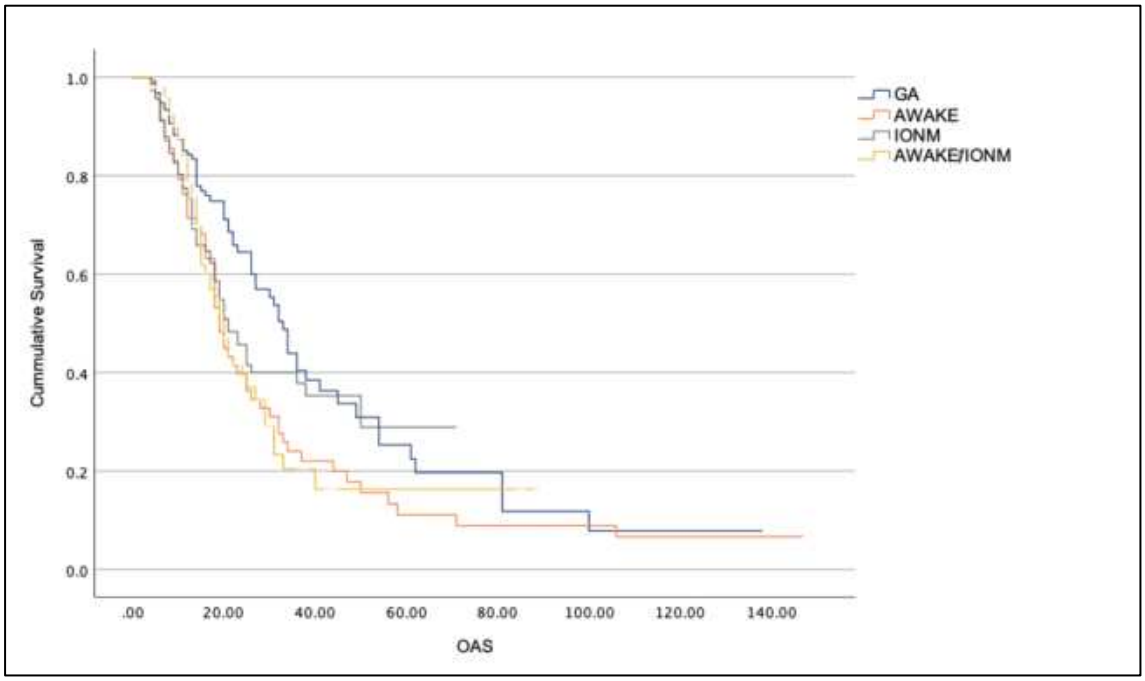

Fig. 34: Kaplan-Meier curve for the OAS for all patients, p = 0.034

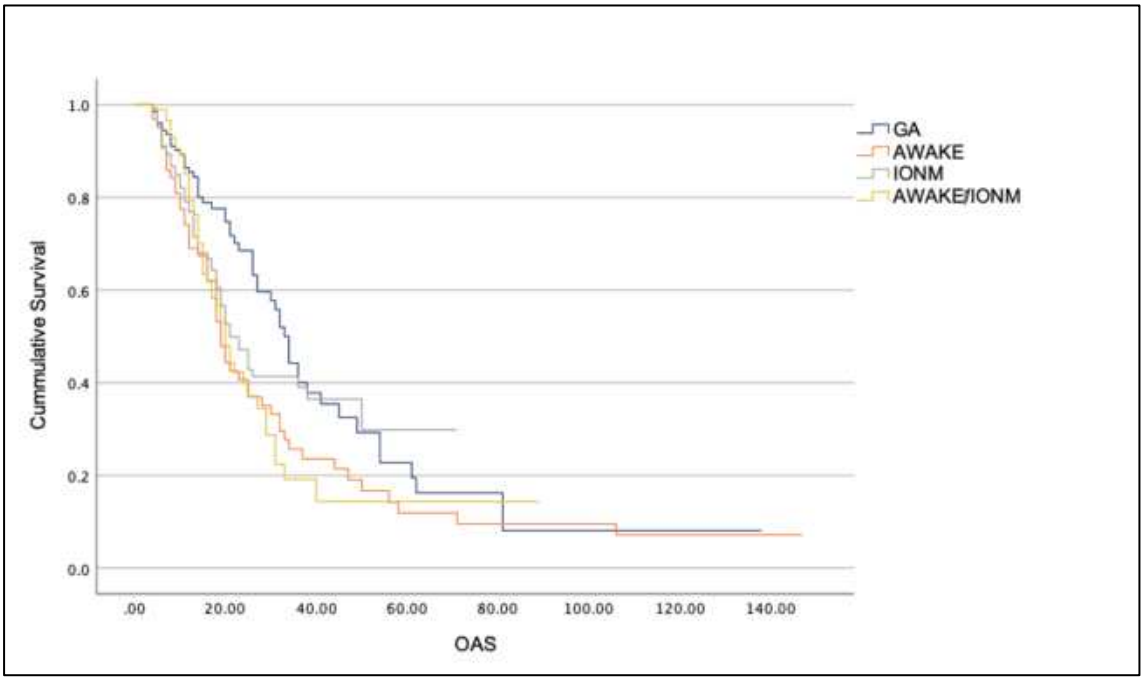

Fig. 35: Kaplan-Meier curve for the OAS for patients with STUPP, $p = 0.034$

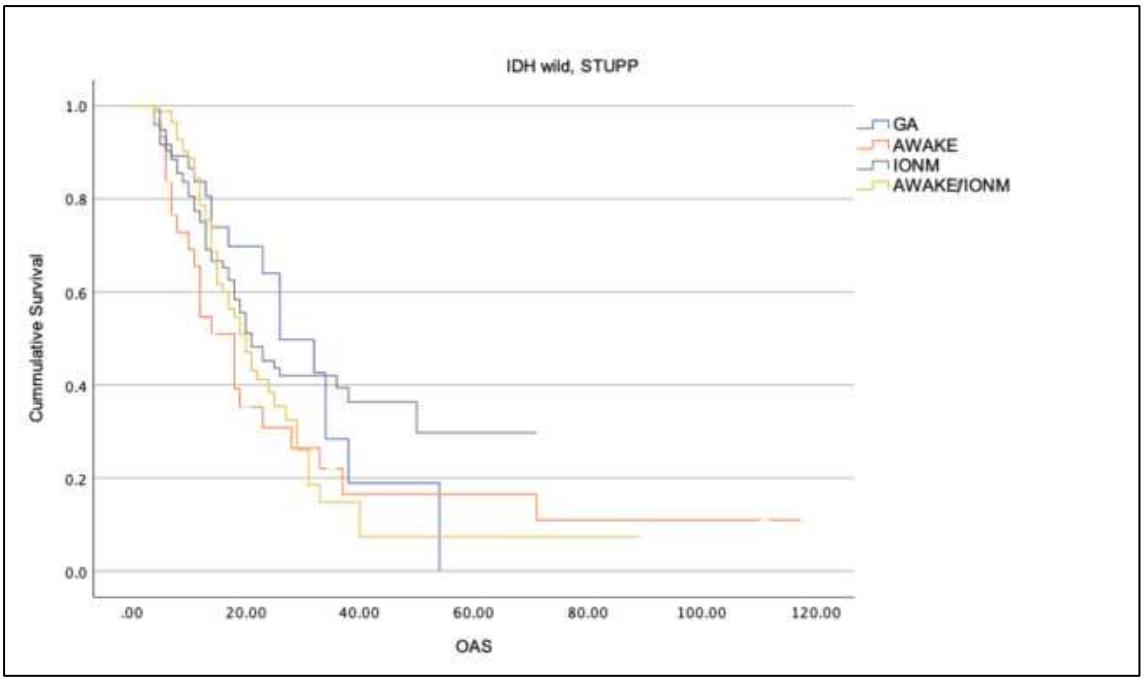

Fig. 36: Kaplan-Meier curve for the OAS of IDH-wildtype with STUPP, $p = 0.199$

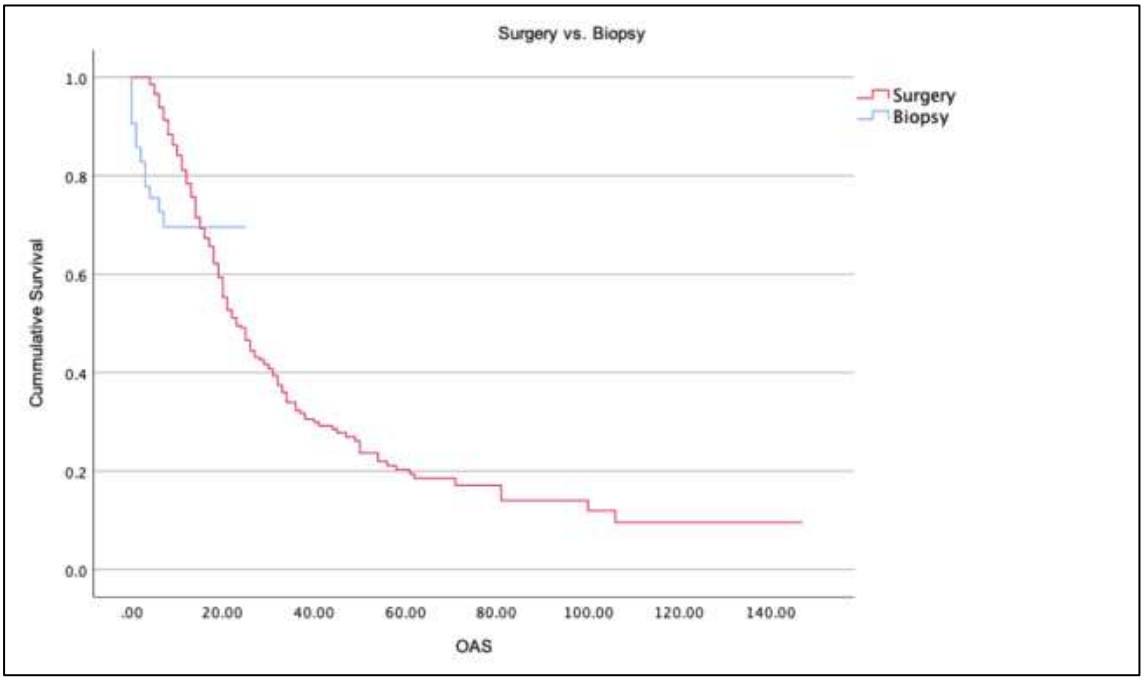

Fig. 37: Kaplan-Meier curve for the OAS of biopsy vs. surgery (GA, awake, IONM or IONM/awake), $p < 0.001$

4 Discussion and conclusion

4.1 Discussion

The standards for surgical treatment of GBM have evolved considerably. In our monocentric study, we found significant changes in the intraoperative monitoring techniques since 2004 (Fig. 7 and Fig. 8). We observed three 'phases': (1) virtually no monitoring until 2007, (2) introduction of awake craniotomies as the only monitoring technique in 2008 and (3) introduction of IONM in 2010.

In our retrospective study, which spanned 2004–2018, we aimed to quantify statistically the influence of elaborate intraoperative monitoring methods, such as awake craniotomies and neurophysiological monitoring, on the immediate effects and long-term prognosis of patients with eloquently located GBM.

In 2006, Kurimoto *et al.* presented a case report on the safe resection of GBM in the dominant gyrus angularis when performed awake. They concluded that awake craniotomies with the help of neuro-navigation provide the best possibility to resect eloquently located GBM (Kurimoto *et al.*, 2006).

Awake craniotomies with 60-Hz bipolar stimulation provide functional control on the cortical and subcortical level of a wide array of neurological functions, particularly language functions. Thus, the importance of awake craniotomies has been recognised in the surgical management of eloquently located low-grade gliomas. However, the implications of this technique for eloquently located GBM have not yet been well established. A meta-analysis by Zhang *et al*. concluded that awake craniotomies produce acceptable rates of gross total resection as well as lower rates of persistent neurological deficits (Zhang *et al.*, 2020). However, the drawback of this technique is dependence on the patient's compliance and the elicitation of seizures.

IONM has proved to be a good alternative for monitoring somatosensory and motor functions, and it provides 'active monitoring' (monopolar stimulation) of cortical or subcortical motor functions. Regarding the resection of unilateral corpus callosum GBM and butterfly GBM, Cui *et al.* proposed that a multimodal approach involving intra-operative MRI, neuro-navigation and IONM played a crucial role in safe resection (Cui *et al.*, 2021).

Both awake craniotomies and IONM have an important role in the resection of eloquently located GBM. This study aimed to determine whether both techniques could be combined

and performed safely on patients with eloquently located GBM. Saito *et al.* suggested that using IONM helps maximise resection and minimise the risk of permanent post-operative neurological deficits with awake craniotomies, as it provides surgeons more control in monitoring the eloquent areas (Saito *et al.*, 2018). En route to answering this question, we considered several decisive parameters, including EOR, NIHSS, KPS, PFS and OAS.

In our study, of the 481 patients who underwent surgical resection, 78% had a GTR, while the remaining 22% had a partial resection. The mean extent of resection was ≈ 96% from all four operating settings. Although minor differences in the EOR occurred amongst the four operating settings as expected, we did not find any statistical significance in the EOR of a particular operating setting (Fig. 11 and Fig. 12). Thus, the implementation of IONM and awake procedures or their combination did not negatively impact the EOR of eloquently located GBM.

Patient outcomes were assessed by NIHSS and KPS scores. Additionally, subcohort analyses were performed for patients who received STUPP therapy after surgery (n = 427) and for those with IDH-wildtype with concomitant STUPP therapy (n= 291) to check for possible bias that could have been caused by the IDH status and the implementation of adjuvant therapy. In all three subcohorts, we observed that the NIHSS scores for patients operated under IONM or IONM/awake were not significantly altered in the post-operative period or during the three-month follow-up, which implied that both techniques are safe for patient use and cause no added neurological deterioration. Both post-operatively and during the three-month follow-up, only patients operated under awake had a significant increase in NIHSS scores. Regarding KPS scores, no deterioration in the performance of the patients operated with IONM or IONM/awake was found at the post-operative period or during the three-month follow-up. However, those operated awake had a significant decrease in their KPS scores at the post-operative period and during the three-month follow-up.

One of the reasons for post-operative decrease of KPS in awake only surgeries we postulate is the extent of patient compatibility during awake procedures as well as the lack of IONM, which prevents passively monitoring somatosensory and motor functions. This, in turn, may lead to transient deterioration of the neurological functions post-operatively. Trinh *et al.* suggested that one of the reasons for the deterioration of the neurological condition in patients operated in awake settings post-operatively and during the three month follow-up is injury of the subcortical structure correlated with significant

changes in diffusion-weighted imaging in post-operative MRI (Trinh *et al.*, 2013). Furthermore, Zhang *et al*. concluded that the rate of neurological deficit in patients operated in an awake fashion is relatively higher. However, the neurological deficits are transient, getting better after the three months. (Zhang *et al.*, 2020). Comparatively, awake had a GTR of 79% compared to 74% for IONM and 77% for IONM/awake. We hypothesize that the slightly higher GTR of awake surgeries may have been due to the decisive difference of tissue that should be preserved to reduce post-operative patient deterioration. Incorporating IONM did cause a slight decrease in the GTR but also resulted in better post-operative patient outcomes. Due to the relatively low patient cohort in the awake technique in our retrospective study, however, this hypothesis cannot be fully supported.

PFS and OAS served to observe the long-term outcomes. A mean PFS of 11.6 months was seen in the entire cohort, and a mean PFS of 10.9 months was observed in those with known IDH status. The Kaplan-Meier curve for PFS that compared the different operating settings showed no significant superiority of the surgical setting. This was a significant finding; although GA had a slightly higher GTR percentile of 80% compared 79%, 74% and 77% for awake, IONM and IONM/awake, respectively, in terms of EOR, no observed increase of PFS favoured patients operated only with GA (Figs. 31, 32 and 33). This finding agreed with those of previous studies. Although factors like EOR and post-surgical radio chemotherapy did play a significant role in the PFS of patients, the type of surgical setting did not (Abedi *et al.*, 2021).

A mean OAS of 19.9 months was seen in the entire cohort, and the mean OAS in those with known IDH status was 18.4 months. The Kaplan-Meier curve of the OAS for the entire patient cohort and for those with STUPP therapy showed the significance of OAS for those operated with GA. However, this result must be interpreted judicially. GA was mostly implemented in patients before 2010, when the significance of IDH status on the prognosis of GBM was still under investigation. The patients operated in GA in these two cohorts comprised mostly unknown IDH statuses. Amongst these patients, statistical outliers had an OAS of more than the expected normal average life expectancy, which we postulate to be that of IDH mutated patients causing a statistical bias favouring GA. However, in the cohort with IDH-wildtype and STUPP therapy, OAS did not significantly favour any surgical settings (Figs. 34, 35 and 36).

Another important result was the comparison of biopsies to surgeries. In our study, 150 of the included 631 patients underwent biopsies. In accordance with many studies,

patients who undergo biopsies have significantly bad prognosis, but this is not something we wanted to prove within the premises of our dissertation. Our study examined the prevalence of biopsies between 2004 and 2018.

The ratio of biopsies compared to surgeries decreased significantly after 2010, when the incorporation of IONM and IONM/awake drastically increased (Table 8). In 2010, the surgical excision of eloquently located tumors also significantly increased. Thus, IONM and IONM/awake positively impacted the resection of eloquently located GBM.

4.2 Limitations

This study had certain limitations. First, it was based on retrospective data rather than a randomised acquisition of data, which caused the presence of bias and confounders. The acquisition of date was also limited as many patients were not retrospectively reproduceable after a follow-up of 6 months due to limited documentation and the absence of regular visits.

The surgical settings, which the surgeons chose based on patient compliance and tumour location, were also influenced by the time of diagnosis. For example, GA with 5-ALA fluorescence was the standard of surgical care earlier in the timeframe of the study, while more modern monitoring approaches, such as IONM and awake craniotomies, were implemented later. This resulted in an uneven allocation of patients under the various groups of surgical settings.

Furthermore, a partial bias was present in the choice of surgical setting. Compliant patients with a good pre-operative neurological status were mostly chosen for awake/IONM surgeries. Additionally, GBM diagnosed before the standardised incorporation of IDH statuses could have included IDH mutated tumours, which have a better prognostic factor.

4.3 Conclusion

Although many publications have promoted the use of IONM and awake craniotomies in the resection of GBM in smaller patient cohorts, no documented report, to our knowledge has systematically reviewed the implications of different surgical settings and statistically compared the patient outcomes, conclusively arguing for the constant use of IONM and awake craniotomies for resection of eloquent GBM. We observed that, since the incorporation of awake surgeries and intraoperative IONM, the number of biopsies has

decreased significantly. The extent of resection amongst the different operative techniques showed no statistical significance favouring a particular operating setting. The three-month KPS and NIHSS scores in patients operated with IONM and with IONM/awake was better than that of those operated only in awake settings. PFS and OAS were not influenced by the operating technique. Based on the analysis, we observed that the incorporation of awake surgeries in combination with IONM did not negatively influence the NIHSS and KPS. The significant decrease in biopsies showed that the operability of eloquent tumours has considerably increased since the incorporation of awake and IONM surgeries. Thus, using IONM and IONM/awake surgical settings rendering safe resection of eloquent GBM with minimal post-operative morbidity is feasible. This study also showed that using awake surgeries and IONM increases the possibility of operating more eloquently located tumours without causing any significant post-operative surgical morbidity for the patient.

5 References

Abd-Elghany, A.A. *et al.* (2019) 'Radiological characteristics of glioblastoma multiforme using CT and MRI examination', *Journal of Radiation Research and Applied Sciences*, 12(1), pp. 289–293. Available at: https://doi.org/10.1080/16878507.2019.1655864.

Abedi, A.A. *et al.* (2021) 'A Prognostic Model for Glioblastoma Patients Treated With Standard Therapy Based on a Prospective Cohort of Consecutive Non-Selected Patients From a Single Institution', *Frontiers in Oncology*, 11, p. 597587. Available at: https://doi.org/10.3389/fonc.2021.597587.

Archer, D.P. *et al.* (1988) 'Conscious-sedation analgesia during craniotomy for intractable epilepsy: a review of 354 consecutive cases', *Canadian Journal of Anaesthesia*, 35(4), pp. 338–344. Available at: https://doi.org/10.1007/BF03010852.

Batchelor, T.T. *et al.* (2013) 'Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma', *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, 31(26), pp. 3212–3218. Available at: https://doi.org/10.1200/JCO.2012.47.2464.

Batchelor, T.T. *et al.* (eds) (2017) *Oxford textbook of neuro-oncology*. First edition. New York, NY: Oxford Universiy Press (Oxford textbooks in clinical neurology).

Bathla, G. *et al.* (2017) 'Calculating the Tumor Volumes in Vestibular Schwannomas: Are the ABC/2 and Volumetric Methods Comparable?', *Otology & Neurotology*, 38(6), pp. 889–894. Available at: https://doi.org/10.1097/MAO.0000000000001423.

Berger, K. *et al.* (2021) 'Age-stratified clinical performance and survival of patients with IDH-wildtype glioblastoma homogeneously treated by radiotherapy with concomitant and maintenance temozolomide', *Journal of Cancer Research and Clinical Oncology*, 147(1), pp. 253–262. Available at: https://doi.org/10.1007/s00432-020-03334-3.

Bloch, O. *et al.* (2012) 'Impact of extent of resection for recurrent glioblastoma on overall survival: Clinical article', *Journal of Neurosurgery*, 117(6), pp. 1032–1038. Available at: https://doi.org/10.3171/2012.9.JNS12504.

Brott, T. *et al.* (1989) 'Measurements of acute cerebral infarction: a clinical examination scale', *Stroke*, 20(7), pp. 864–870. Available at: https://doi.org/10.1161/01.str.20.7.864.

Bulsara, K.R., Johnson, J. and Villavicencio, A.T. (2005) 'Improvements in brain tumor surgery: the modern history of awake craniotomies', *Neurosurgical Focus*, 18(4), pp. 1–3. Available at: https://doi.org/10.3171/foc.2005.18.4.6.

Chinot, O.L. *et al.* (2013) 'Response assessment criteria for glioblastoma: practical adaptation and implementation in clinical trials of antiangiogenic therapy', *Current Neurology and Neuroscience Reports*, 13(5), p. 347. Available at: https://doi.org/10.1007/s11910-013-0347-2.

Combs, S.E., Debus, J. and Schulz-Ertner, D. (2007) 'Radiotherapeutic alternatives for previously irradiated recurrent gliomas', *BMC cancer*, 7, p. 167. Available at: https://doi.org/10.1186/1471-2407-7-167.

Cui, M. *et al.* (2021) 'Combined use of multimodal techniques for the resection of glioblastoma involving corpus callosum', *Acta Neurochirurgica* [Preprint]. Available at: https://doi.org/10.1007/s00701-021-05008-6.

Davis, M. (2016) 'Glioblastoma: Overview of Disease and Treatment', *Clinical Journal of Oncology Nursing*, 20(5), pp. S2–S8. Available at: https://doi.org/10.1188/16.CJON.S1.2-8.

Dhermain, F. *et al.* (2004) '[Role of radiotherapy in recurrent gliomas]', *Bulletin Du Cancer*, 91(11), pp. 883–889.

Fernandes, C. *et al.* (2017) 'Current Standards of Care in Glioblastoma Therapy', in S. De Vleeschouwer (ed.) *Glioblastoma*. Brisbane (AU): Codon Publications. Available at: http://www.ncbi.nlm.nih.gov/books/NBK469987/ (Accessed: 27 September 2020).

Franceschi, E. *et al.* (2018) 'Temozolomide rechallenge in recurrent glioblastoma: when is it useful?', *Future Oncology*, 14(11), pp. 1063–1069. Available at: https://doi.org/10.2217/fon-2017-0681.

Gerritsen, J.K.W. *et al.* (2019) 'Awake craniotomy versus craniotomy under general anesthesia without surgery adjuncts for supratentorial glioblastoma in eloquent areas: a retrospective matched case-control study', *Acta Neurochirurgica*, 161(2), pp. 307–315. Available at: https://doi.org/10.1007/s00701-018-03788-y.

Gerstner, E.R. *et al.* (2010) 'Infiltrative patterns of glioblastoma spread detected via diffusion MRI after treatment with cediranib', *Neuro-Oncology*, 12(5), pp. 466–472. Available at: https://doi.org/10.1093/neuonc/nop051.

González-Darder, J.M. *et al.* (2010) 'Multimodal navigation in the functional microsurgical resection of intrinsic brain tumors located in eloquent motor areas: role of tractography', *Neurosurgical Focus*, 28(2), p. E5. Available at: https://doi.org/10.3171/2009.11.FOCUS09234.

Grant, G.A., Farrell, D. and Silbergeld, D.L. (2002) 'Continuous somatosensory evoked potential monitoring during brain tumor resection: Report of four cases and review of the literature', *Journal of Neurosurgery*, 97(3), pp. 709–713. Available at: https://doi.org/10.3171/jns.2002.97.3.0709.

Grossauer, S., Parpaley, Y. and Koeck, K. (2017) 'Motor Evoked Potentials in Supratentorial Glioma Surgery', *Event-Related Potentials and Evoked Potentials* [Preprint]. Available at: https://doi.org/10.5772/intechopen.70040.

Hadjipanayis, C.G., Widhalm, G. and Stummer, W. (2015) 'What is the Surgical Benefit of Utilizing 5-ALA for Fluorescence-Guided Surgery of Malignant Gliomas?', *Neurosurgery*, 77(5), pp. 663–673. Available at: https://doi.org/10.1227/NEU.0000000000000929.

Haglund, M.M. *et al.* (1994) 'Cortical Localization of Temporal Lobe Language Sites in Patients with Gliomas', *Neurosurgery*, 34(4), pp. 567–576. Available at: https://doi.org/10.1097/00006123-199404000-00001.

Hanif, F. *et al.* (2017) 'Glioblastoma Multiforme: A Review of its Epidemiology and Pathogenesis through Clinical Presentation and Treatment', *Asian Pacific Journal of Cancer Prevention : APJCP*, 18(1), pp. 3–9. Available at: https://doi.org/10.22034/APJCP.2017.18.1.3.

Hans, P. *et al.* (2000) 'Target-controlled infusion of propofol and remifentanil combined with bispectral index monitoring for awake craniotomy', *Anaesthesia*, 55(3), pp. 255–259. Available at: https://doi.org/10.1046/j.1365-2044.2000.01277.x.

Hegi, M.E. *et al.* (2005) 'MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma', *New England Journal of Medicine*, 352(10), pp. 997–1003. Available at: https://doi.org/10.1056/NEJMoa043331.

Herrlinger, U. *et al.* (2019) 'Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA–09): a randomised, open-label, phase 3 trial', *The Lancet*, 393(10172), pp. 678–688. Available at: https://doi.org/10.1016/S0140-6736(18)31791-4.

Hervey-Jumper, S.L. *et al.* (2015) 'Awake craniotomy to maximize glioma resection: methods and technical nuances over a 27-year period', *Journal of Neurosurgery*, 123(2), pp. 325–339. Available at: https://doi.org/10.3171/2014.10.JNS141520.

Hsu, F.J. *et al.* (1996) 'Vaccination of patients with B-cell lymphoma using autologous antigen-pulsed dendritic cells', *Nature Medicine*, 2(1), pp. 52–58. Available at: https://doi.org/10.1038/nm0196-52.

Huang, J. *et al.* (2019) 'Isocitrate Dehydrogenase Mutations in Glioma: From Basic Discovery to Therapeutics Development', *Frontiers in Oncology*, 9. Available at: https://doi.org/10.3389/fonc.2019.00506.

Huang, L.E. (2022) 'Impact of CDKN2A/B Homozygous Deletion on the Prognosis and Biology of IDH-Mutant Glioma', *Biomedicines*, 10(2), p. 246. Available at: https://doi.org/10.3390/biomedicines10020246.

Jp, T. *et al.* (2014) *Epidemiologic and molecular prognostic review of glioblastoma*, *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. Cancer Epidemiol Biomarkers Prev. Available at: https://doi.org/10.1158/1055-9965.EPI-14-0275.

Kahn, E., Lane, M. and Sagher, O. (2017) 'Eloquent: history of a word's adoption into the neurosurgical lexicon', *Journal of Neurosurgery*, 127(6), pp. 1461–1466. Available at: https://doi.org/10.3171/2017.3.JNS17659.

Kim, S.-M. *et al.* (2013) 'Intraoperative Neurophysiologic Monitoring: Basic Principles and Recent Update', *Journal of Korean Medical Science*, 28(9), p. 1261. Available at: https://doi.org/10.3346/jkms.2013.28.9.1261.

Kothari, R.U. *et al.* (1996) 'The ABCs of measuring intracerebral hemorrhage volumes', *Stroke*, 27(8), pp. 1304–1305. Available at: https://doi.org/10.1161/01.str.27.8.1304.

Krieg, S.M. *et al.* (2012) 'Predictive Value and Safety of Intraoperative Neurophysiological Monitoring With Motor Evoked Potentials in Glioma Surgery', *Neurosurgery*, 70(5), pp. 1060–1071. Available at: https://doi.org/10.1227/NEU.0b013e31823f5ade.

Kurimoto, M. *et al.* (2006) 'Safe Removal of Glioblastoma Near the Angular Gyrus by Awake Surgery Preserving Calculation Ability-Case Report-: —Case Report—', *Neurologia medico-chirurgica*, 46(1), pp. 46–50. Available at: https://doi.org/10.2176/nmc.46.46.

Kwak, R., Kadoya, S. and Suzuki, T. (1983) 'Factors affecting the prognosis in thalamic hemorrhage.', *Stroke*, 14(4), pp. 493–500. Available at: https://doi.org/10.1161/01.STR.14.4.493.

Lc, H. *et al.* (2006) *Recurrent glioblastoma multiforme: a review of natural history and management options*, *Neurosurgical focus*. Neurosurg Focus. Available at: https://doi.org/10.3171/foc.2006.20.4.2.

Louis, D.N. *et al.* (2007) 'The 2007 WHO Classification of Tumours of the Central Nervous System', *Acta Neuropathologica*, 114(2), pp. 97–109. Available at: https://doi.org/10.1007/s00401-007-0243-4.

Louis, D.N. *et al.* (2016) 'The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary', *Acta Neuropathologica*, 131(6), pp. 803–820. Available at: https://doi.org/10.1007/s00401-016-1545-1.

Lu, V.M. *et al.* (2018) 'The Survival Effect of Repeat Surgery at Glioblastoma Recurrence and its Trend: A Systematic Review and Meta-Analysis', *World Neurosurgery*, 115, pp. 453-459.e3. Available at: https://doi.org/10.1016/j.wneu.2018.04.016.

Lyden, P.D. *et al.* (2001) 'A Modified National Institutes of Health Stroke Scale for Use in Stroke Clinical Trials: Preliminary Reliability and Validity', *Stroke*, 32(6), pp. 1310–1317. Available at: https://doi.org/10.1161/01.STR.32.6.1310.

Macdonald, D.R. *et al.* (1990) 'Response criteria for phase II studies of supratentorial malignant glioma', *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, 8(7), pp. 1277–1280. Available at: https://doi.org/10.1200/JCO.1990.8.7.1277.

Mansouri, A. *et al.* (2019) 'MGMT promoter methylation status testing to guide therapy for glioblastoma: refining the approach based on emerging evidence and current challenges', *Neuro-Oncology*, 21(2), pp. 167–178. Available at: https://doi.org/10.1093/neuonc/noy132.

Minniti, G., Lombardi, G. and Paolini, S. (2019) 'Glioblastoma in Elderly Patients: Current Management and Future Perspectives', *Cancers*, 11(3). Available at: https://doi.org/10.3390/cancers11030336.

Molinaro, A.M. *et al.* (2020) 'Association of Maximal Extent of Resection of Contrast-Enhanced and Non–Contrast-Enhanced Tumor With Survival Within Molecular Subgroups of Patients With Newly Diagnosed Glioblastoma', *JAMA Oncology*, 6(4), p. 495. Available at: https://doi.org/10.1001/jamaoncol.2019.6143.

Nobusawa, S. *et al.* (2009) 'IDH1 Mutations as Molecular Signature and Predictive Factor of Secondary Glioblastomas', *Clinical Cancer Research*, 15(19), pp. 6002–6007. Available at: https://doi.org/10.1158/1078-0432.CCR-09-0715.

Opalak, C.F. *et al.* (2019) 'Comparison of ABC/2 estimation and a volumetric computerized method for measurement of meningiomas using magnetic resonance imaging', *Journal of Neuro-Oncology*, 144(2), pp. 275–282. Available at: https://doi.org/10.1007/s11060-019-03205-z.

Pamir, M.N., Black, P.M. and Fahlbusch, R. (eds) (2010) *Meningiomas: a comprehensive text*. Philadelphia, Pa: Saunders/Elsevier.

Penfield, W. (1954) 'Combined regional and general anesthesia for craniotomy and cortical exploration. I. Neurosurgical considerations', *Current Researches in Anesthesia & Analgesia*, 33(3), pp. 145–155.

Péus, D., Newcomb, N. and Hofer, S. (2013) 'Appraisal of the Karnofsky Performance Status and proposal of a simple algorithmic system for its evaluation', *BMC Medical Informatics and Decision Making*, 13, p. 72. Available at: https://doi.org/10.1186/1472-6947-13-72.

Qt, O. *et al.* (2015) *CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2008-2012*, *Neuro-oncology*. Neuro Oncol. Available at: https://doi.org/10.1093/neuonc/nov189.

Rapp, M. *et al.* (2013) 'Diagnostic Performance of 18F-FET PET in Newly Diagnosed Cerebral Lesions Suggestive of Glioma', *Journal of Nuclear Medicine*, 54(2), pp. 229–235. Available at: https://doi.org/10.2967/jnumed.112.109603.

Rapp, M. *et al.* (2018) 'A randomized controlled phase II trial of vaccination with lysate-loaded, mature dendritic cells integrated into standard radiochemotherapy of newly diagnosed glioblastoma (GlioVax): study protocol for a randomized controlled trial', *Trials*, 19(1), p. 293. Available at: https://doi.org/10.1186/s13063-018-2659-7.

Saito, T. *et al.* (2018) 'Neurophysiological Monitoring and Awake Craniotomy for Resection of Intracranial Gliomas', in M.F. Chernov et al. (eds) *Progress in Neurological Surgery*. S. Karger AG, pp. 117–158. Available at: https://doi.org/10.1159/000464387.

Sawaya, R. *et al.* (1998) 'Neurosurgical outcomes in a modern series of 400 craniotomies for treatment of parenchymal tumors', *Neurosurgery*, 42(5), pp. 1044–1055; discussion 1055-1056. Available at: https://doi.org/10.1097/00006123-199805000-00054.

Shinoura, N. *et al.* (2011) 'Advantages and disadvantages of awake surgery for brain tumours in the primary motor cortex: institutional experience and review of literature', *British Journal of Neurosurgery*, 25(2), pp. 218–224. Available at: https://doi.org/10.3109/02688697.2010.505671.

Shukla, G. *et al.* (2017) 'Advanced magnetic resonance imaging in glioblastoma: a review', *Chinese Clinical Oncology*, 6(4), p. 7. Available at: https://doi.org/10.21037/cco.v0i0.15820.

Skjøth-Rasmussen, J., Engelmann, C.M. and Brennum, J. (2017) 'SURG-26. AWAKE CRANIOTOMY WITH 5-ALA IN HIGH GRADE GLIOMAS GIVES SIMULTANEOUS GUIDANCE OF TUMOR AND FUNCTIONAL BORDER', *Neuro-Oncology*, 19(suppl_6), pp. vi240–vi241. Available at: https://doi.org/10.1093/neuonc/nox168.981.

Sreenivasan, S.A. *et al.* (2016) 'Measuring glioma volumes: A comparison of linear measurement based formulae with the manual image segmentation technique', *Journal of Cancer Research and Therapeutics*, 12(1), pp. 161–168. Available at: https://doi.org/10.4103/0973-1482.153999.

Stummer, W. *et al.* (1998) 'Intraoperative detection of malignant gliomas by 5-aminolevulinic acid-induced porphyrin fluorescence', *Neurosurgery*, 42(3), pp. 518–525; discussion 525-526. Available at: https://doi.org/10.1097/00006123-199803000-00017.

Stupp, R. *et al.* (2005) 'Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma', *New England Journal of Medicine*, 352(10), pp. 987–996. Available at: https://doi.org/10.1056/NEJMoa043330.

Stupp, R. *et al.* (2012) 'NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality', *European Journal of Cancer (Oxford, England: 1990)*, 48(14), pp. 2192–2202. Available at: https://doi.org/10.1016/j.ejca.2012.04.011.

Szelényi, A. *et al.* (2010) 'Intraoperative electrical stimulation in awake craniotomy: methodological aspects of current practice', *Neurosurgical Focus*, 28(2), p. E7. Available at: https://doi.org/10.3171/2009.12.FOCUS09237.

Talabaev, M. *et al.* (2020) 'Result of awake surgery for pediatric eloquent brain area tumors: single-center experience', *Child's Nervous System*, 36(11), pp. 2667–2673. Available at: https://doi.org/10.1007/s00381-020-04666-8.

'Tissue Plasminogen Activator for Acute Ischemic Stroke' (1995) *New England Journal of Medicine*, 333(24), pp. 1581–1588. Available at: https://doi.org/10.1056/NEJM199512143332401.

Topfer, L.-A. and Farrah, K. (2016) 'Alternating Electric Fields ("Tumour-Treating Fields") for the Treatment of Glioblastoma', in *CADTH Issues in Emerging Health Technologies*. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health. Available at: http://www.ncbi.nlm.nih.gov/books/NBK513128/ (Accessed: 6 February 2021).

Trinh, V.T. *et al.* (2013) 'Subcortical Injury Is an Independent Predictor of Worsening Neurological Deficits Following Awake Craniotomy Procedures', *Neurosurgery*, 72(2), pp. 160–169. Available at: https://doi.org/10.1227/NEU.0b013e31827b9a11.

Verger, A. and Langen, K.-J. (2017) 'PET Imaging in Glioblastoma: Use in Clinical Practice', in S. De Vleeschouwer (ed.) *Glioblastoma*. Brisbane (AU): Codon Publications. Available at: http://www.ncbi.nlm.nih.gov/books/NBK469986/ (Accessed: 25 September 2020).

Wang, L. *et al.* (2019) 'What is the advance of extent of resection in glioblastoma surgical treatment—a systematic review', *Chinese Neurosurgical Journal*, 5(1), p. 2. Available at: https://doi.org/10.1186/s41016-018-0150-7.

Weller, M. *et al.* (2021) 'EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood', *Nature Reviews Clinical Oncology*, 18(3), pp. 170–186. Available at: https://doi.org/10.1038/s41571-020-00447-z.

Wen, P.Y. *et al.* (2010) 'Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group', *Journal of Clinical Oncology*, 28(11), pp. 1963–1972. Available at: https://doi.org/10.1200/JCO.2009.26.3541.

Wick, W. *et al.* (2010) 'Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma', *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, 28(7), pp. 1168–1174. Available at: https://doi.org/10.1200/JCO.2009.23.2595.

Wick, W. *et al.* (2014) 'MGMT testing—the challenges for biomarker-based glioma treatment', *Nature Reviews Neurology*, 10(7), pp. 372–385. Available at: https://doi.org/10.1038/nrneurol.2014.100.

Wick, W. *et al.* (2017) 'Lomustine and Bevacizumab in Progressive Glioblastoma', *The New England Journal of Medicine*, 377(20), pp. 1954–1963. Available at: https://doi.org/10.1056/NEJMoa1707358.

Zhang, J.J.Y. *et al.* (2020) 'Awake craniotomy for resection of supratentorial glioblastoma: a systematic review and meta-analysis', *Neuro-Oncology Advances*, 2(1), p. vdaa111. Available at: https://doi.org/10.1093/noajnl/vdaa111.

Zikou, A. *et al.* (2018) *Radiation Necrosis, Pseudoprogression, Pseudoresponse, and Tumor Recurrence: Imaging Challenges for the Evaluation of Treated Gliomas*, *Contrast Media & Molecular Imaging*. Hindawi. Available at: https://doi.org/10.1155/2018/6828396.

Acknowledgments

First and foremost, I would like to thank my patients who entrust their lives into our hands. I am humbled by their trust. This dissertation would have not been possible without them.

I would like to thank Prof. Dr. med. Hänggi, Chairman of the department of neurosurgery at the university hospital of Duesseldorf, for giving me the opportunity to complete this dissertation in his department.

A sincere thanks to my thesis supervisor Prof. Sabel for his constant support and inputs during my thesis. I am grateful for all the moments of teaching and the constant belief he has had in me. I thank him for helping me to be the neurosurgeon I am now for which I will ever be grateful.

I thank my parents and my sister and my extended family for all their support and prayers.

Words cannot express how much I am grateful to my beloved wife Sarah for constantly believing and supporting me and never giving up on me and my dream. She has always been a strong hold in my life, and I am grateful for her trust in walking this journey beside me.

Lastly, I would like to thank God for giving me the wisdom and knowledge for completing this dissertation.