Aus der
Klinik für Neurochirurgie
Kommissarischer Direktor: Prof. Dr. J. F. Cornelius
Und dem Zentrum für Neuroonkologie
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INTRAOPERATIVE NEUROPHYSIOLOGICAL MONITORING AND CORTICAL/SUBCORTICAL MAPPING PROCEDURES IN AWAKE AND ASLEEP SUPRATENTORIAL INFILTRATING BRAIN TUMOUR SURGERY

- STRENGTHS, PITFALLS AND SPECIAL INDICATIONS -

Habilitationsschrift

zur Erlangung der Venia Legendi
für das Fach Neurochirurgie
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Heinrich-Heine-Universität Düsseldorf

Vorgelegt von
Dr. med. Franziska Staub-Bartelt

Düsseldorf im Mai 2024

“Nowadays, the so-called silent areas of the brain are eloquent to those who know how to listen.”

Macdonald Critchley

(1900- 1997)

This cumulative thesis is based on the following publications

I. Does positive MGMT methylation outbalance the limitation of subtotal resection in glioblastoma IDH-wildtype patients? Müller Mareike*, Staub-Bartelt Franziska*, Ehrmann Julia, Hänggi Daniel, Sabel Michael, Felsberg Jörg, Rapp Marion, *equal contribution
Journal of Neuro-Oncology (2021) 153:537–545

II. Establishment of different intraoperative monitoring and mapping techniques and their impact on survival, extent of resection and clinical outcome in patients with high-grade gliomas- a series of 631 patients in 14 years
Franziska Staub-Bartelt, Marian Preetham Suresh Babu, Andrea Szelényi, Marion Rapp, Michael Sabel
Cancers 2024, 16, 926. doi.org/10.3390/cancers16050926

III. Feasibility of intraoperative neuromonitoring and cortical/subcortical mapping in patients with cerebral lesions of highly functional localizations—pathway to case adapted monitoring and mapping procedures
Franziska Staub-Bartelt, Marion Rapp, Michael Sabel
Front. Oncol. 2023, 13:1235212. Doi: 10.3389/fonc.2023.1235212

IV. Resection of Eloquent Located Brain Tumors by Mapping Only—A Feasibility Study
Franziska Staub-Bartelt, Marion Rapp, Michael Sabel
Brain Sci. 2023, 13, 1366. doi.org/ 10.3390/brainsci13101366

V. Direct Cortical Stimulation in Neurosurgical Emergencies: Single-Centre Experience in 2 Patients
Franziska Staub-Bartelt, Björn B. Hofmann, Marion Rapp, Daniel Hänggi, Marcel Alexander Kamp, Michael Sabel
World Neurosurg. (2021) 150:147-152.https://doi.org/10.1016/j.wneu.2021.03.118

VI. Impact of Anticipated Awake Surgery on Psychooncological Distress in Brain Tumor Patients

Franziska Staub-Bartelt, Oliver Radtke, Daniel Hänggi, Michael Sabel, Marion Rapp

Front. Oncol. 11:795247. Doi: 10.3389/fonc.2021.795247

Abstract

In recent decades, brain tumour surgery has increasingly benefited from technological innovations. Through detailed surgical planning involving various imaging modalities and functional localization via navigated magnetic field stimulations, the tumour can be accurately localized both spatially and functionally within its surroundings. Intraoperatively, various tools have also been implemented to visualize the tumour and its boundaries, contributing to improved resectability, which, in turn, translates to a better patient outcome. However, when tumours are located in areas known to have significant functional importance, even thorough planning does not suffice for resection. In such cases, intraoperative monitoring and cortical and subcortical mapping techniques become crucial, providing real-time information about the tumour's relationship to the specific motor and- in the context of awake surgeries- sometimes linguistic and cognitive functions. These techniques help determine whether resection with functional preservation is feasible and, if so, whether maximal resection can be achieved. Over the years, intraoperative neurophysiological testing techniques have evolved, with various nuances tailored to individual cases. This study delves into the benefits and weaknesses of these intraoperative techniques, highlighting technical differences and their implications on surgical outcomes and patient outcomes. Additionally, the emergency indication, as a special case for cortical and subcortical mapping, was examined. Finally, the relatively overlooked aspect of psychooncological distress associated with the performance of awake surgeries, which have become a standard form of intraoperative functional monitoring in many centres, was thoroughly explored. The results underscore the importance of intraoperative functional monitoring through the application of various monitoring and mapping techniques, as well as the significance of awake surgery. The study introduces new perspectives on these techniques and aims to encourage colleagues to integrate them into their daily practice.

ZUSAMMENFASSUNG

Die Hirntumorchirurgie hat in den vergangenen Jahrzehnten mehr und mehr von technischen Innovationen profitiert. Aufgrund einer sehr detaillierten operativen Planung mit unterschiedlichster Bildgebung sowie Funktionslokalisation über eine navigierte Magnetfeldstimulationen kann der Tumor in seiner Umgebung detailgetreu sowohl räumlich lokalisiert als auch funktionell diagnostiziert werden. Intraoperativ wurden ebenfalls mehr und mehr Hilfsmittel zur Darstellung von Tumor und Tumorgrenzen implementiert. Diese Hilfsmittel dienen einer verbesserten Resektabilität, die wiederum ein besseres Outcome für die Patienten bedeutet. Wenn nun die Tumore jedoch an Stellen gelegen sind, von denen wir wissen, dass sie eine funktionell hohe Bedeutung haben, hilft eine noch so gründliche Planung nicht bei der Resektion. Hier sind das intraoperative Monitoring sowie die kortikalen und subkortikalen Mapping Techniken von großer Bedeutung, da sie, wenn sie richtig angewendet werden, eine Echtzeitinformation über die Lagebeziehung des Tumors zu einer gewissen motorischen und im Rahmen von Wachoperationen auch sprachlichen, manchmal kognitiven Funktion liefern. Diese Techniken geben Auskunft darüber, ob eine Resektion unter Funktionserhalt überhaupt möglich ist und, wenn ja, ob eine maximale Resektion erreicht werden kann. Über die Jahre haben sich die Techniken der intraoperativen neurophysiologischen Testung weiterentwickelt. Es gibt diverse Einzelheiten, die für den jeweiligen Einzelfall berücksichtigt werden können und müssen. Im Rahmen der vorliegenden Arbeit, wurde der Nutzen und die Schwächen dieser intraoperativen Techniken aufgearbeitet und entscheidende Nuancen in den technischen Unterschieden und Ihre Implikationen auf die Operationsergebnisse und den Patienten herausgearbeitet. Des weiteren wurde die Notfallindikation als Spezialfall einer Indikation für das kortikale und subkortikale Mapping untersucht. Letztlich wurde dann der bislang wenig im Fokus stehende Aspekte der psychonkologischen Belastung in Anbetracht der Durchführung von Wachoperationen, die heute als Maximalvariante einer Möglichkeit der intraoperativen Funktionsüberwachung standardmäßig in vielen Zentren durchgeführt wird, eingehend aufgearbeitet. Die Ergebnisse dieser Arbeit unterstreichen die Wichtigkeit der intraoperativen Funktionskontrolle durch die Anwendung verschiedener Monitoring- und mapping Techniken sowie die der Wachoperation, zeigen neue Aspekte dieser auf und sollen Kollegen ermutigen, sich diese zu eigen zu machen.

Abbreviations

ATRX	alpha thalassemia/mental retardation X-linked syndrome mutation
CDKN2A/B	cyclin-dependent kinase inhibitor 2A/B
CST	cortico-spinal-tract
CT	computed tomography
cMAP	compound muscle action potential
DT	distress thermometer
EGFR	epidermal growth factor receptor
fMRI	functional magnetic resonance imaging
GTR	gross total resection
GBM	IDH-Wildtype Glioblastoma, WHO Grade 4
HADS	Hospital Anxiety and Depression Scale
IONM	intraoperative neuromonitoring
IDH	isocitrate dehydrogenase
iMRI	intraoperative magnetic resonance imaging
iU	intraoperative ultrasound
KPS	Karnofsky Performance Status
MGMT	O-6-Methylguanin-DNA-Methyltransferase
NIHSS	National Institutes of Health Stroke Scale
OS	overall survival
PD-L1	programmed cell death ligand-1
PFS	progression-free survival
QoL	quality of life
RTV	residual tumour volume
TERT	telomerase reverse transcriptase
VEGF	vascular endothelial growth factor

INDEX

I INTRODUCTION AND BACKGROUND

1. Overview of malignant primary and secondary brain tumours and non-surgical therapies

Primary brain tumours

Primary brain tumours are tumours that originate from cells native to the brain. They occur with varying frequencies, but the majority of primary brain tumours are known as gliomas. Gliomas in adults (> 18 years) will be the main subgroup of interest and discussion here, as the majority of patients with primary brain tumours included in the later described studies at our department were diagnosed with glioma.

The classification of gliomas is primarily based on histological criteria, but molecular criteria have increasingly become part of the classification through intensive investigations on cell lines [1]. The majority of gliomas comprise IDH-mutated astrocytoma, IDH-wildtype glioblastoma and oligodendroglioma, in this group the glioblastoma, WHO grade 4 (GBM) is the most aggressive and most common malignant brain tumour in adults [2].

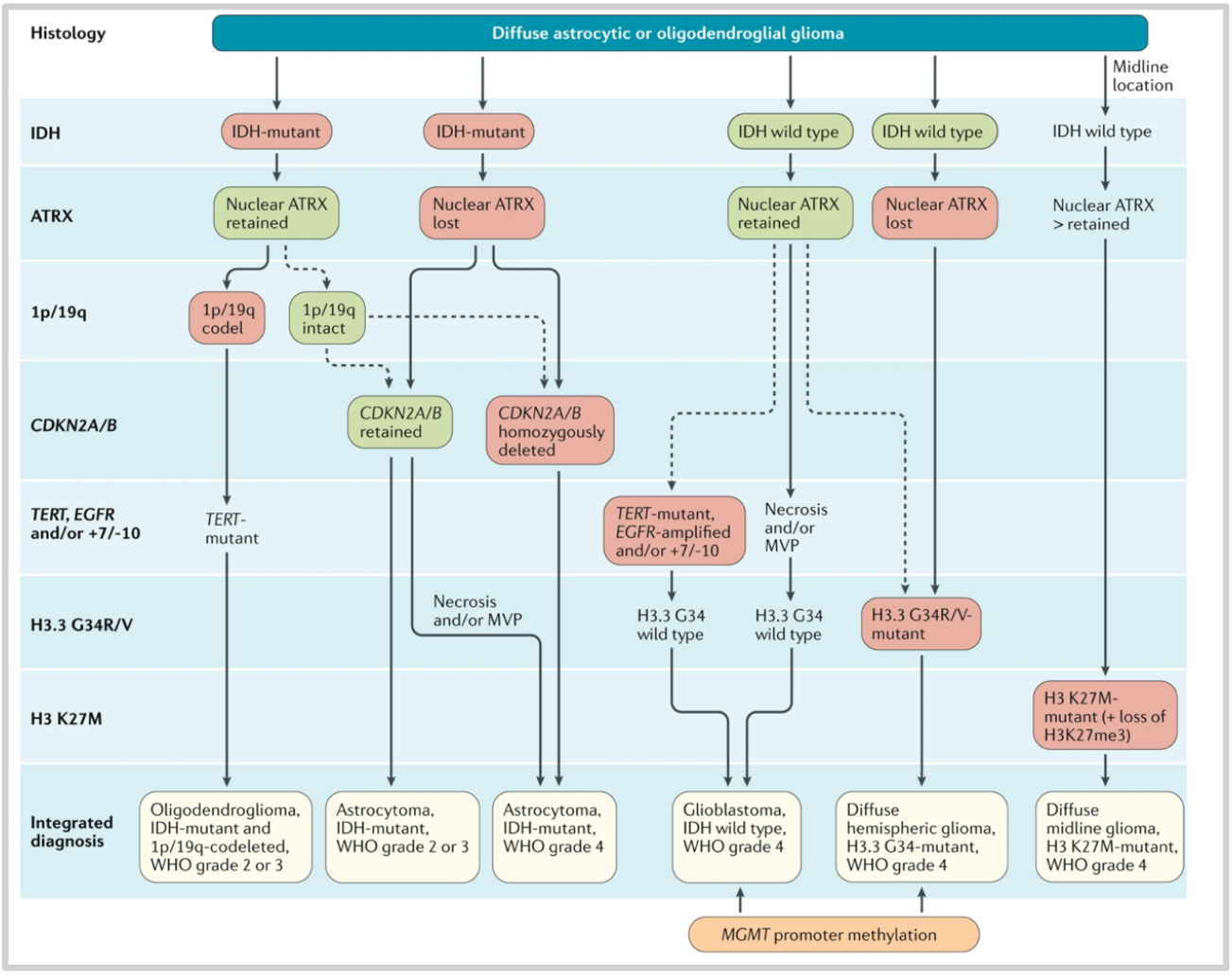

Figure 1: Integrated classification of the majority of diffuse gliomas in adults (from EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood [3], used under Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.).

Due to their infiltrative growth, high-grade gliomas are not curable by surgery alone. Adjuvant radiation and chemotherapy [3] play a crucial role here. Significant milestones include the work of Stupp, who demonstrated that adding alkylating chemotherapy with Temozolomide to a standard radiation protocol significantly extended the median overall survival (OS) in patients with GBM [4, 5] in 2005. In 2019, the benefit of additional chemotherapy with Lomustine was shown for the subgroup of GBM with molecular markers indicating methylation of the O-6-methylguanine-DNA-methyltransferase (MGMT) promoter [6]. The “Stupp”- and “Herrlinger”-protocols currently serve as standard protocols for first-line therapy in the group of high-grade gliomas, respectively GBM. For low-grade tumours, there might be the possibility of a watch-

and-wait approach depending on the location and clinical symptoms, although there is great evidence for resection [7, 8]. If resection is performed, either a watch-and-wait procedure or an adjuvant therapeutic concept follows depending on risk stratification. Radiation and chemotherapy using Temozolomide are employed in patients with 1p/19q non-co-deleted astrocytoma grade 3 (referred to as anaplastic glioma before an update of WHO classification in 2021 was published) and grade 4 tumours [9]. Patients with 1p/19q co-deleted tumours mostly receive chemotherapy using the "PCV - regimen" comprising chemotherapy with Procarbazine, Lomustine and Vincristine [10-12].

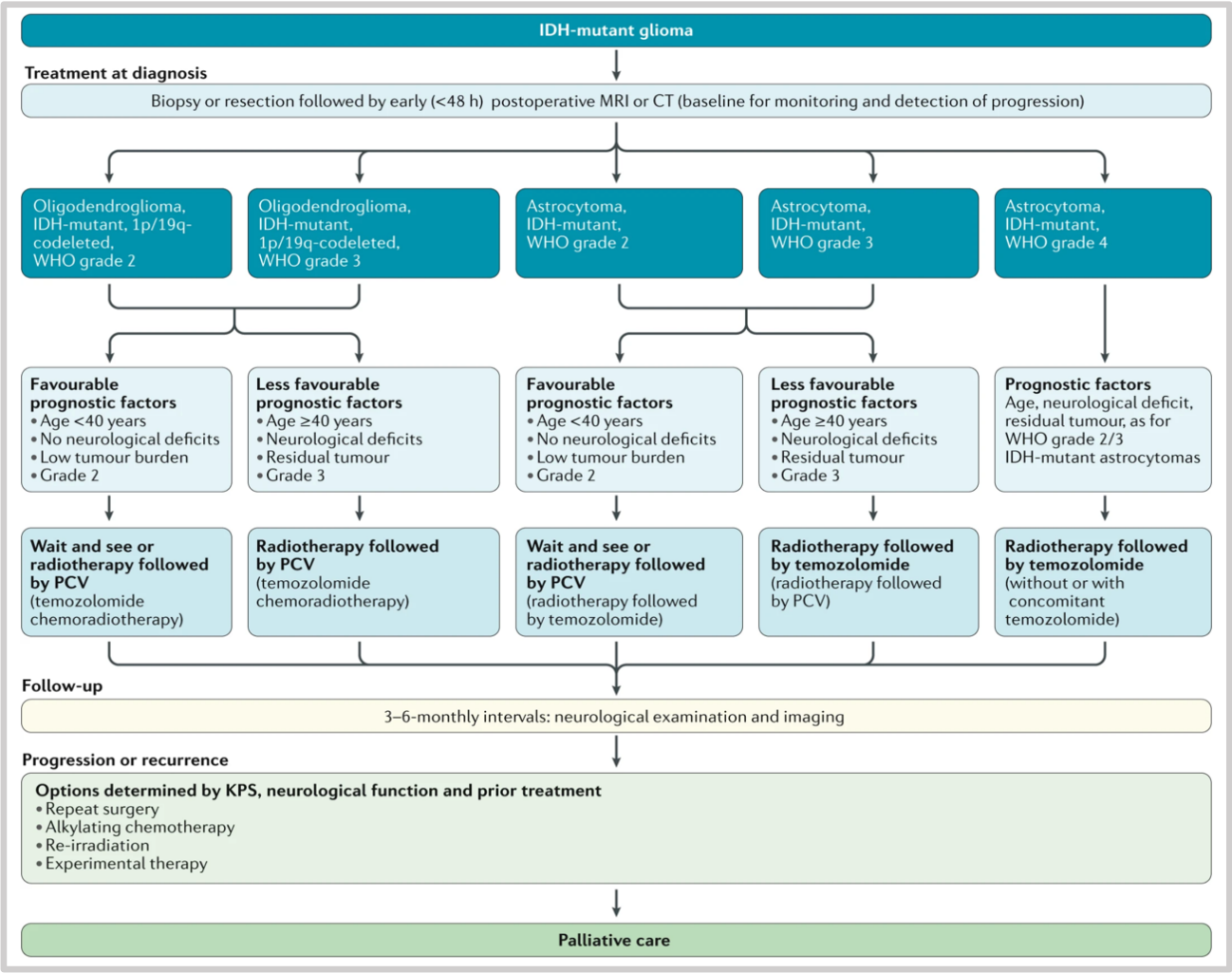

Figure 2: Diagnostic and therapeutical pathway on patients with IDH-mutant glioma (from EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood [3], used under Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.).

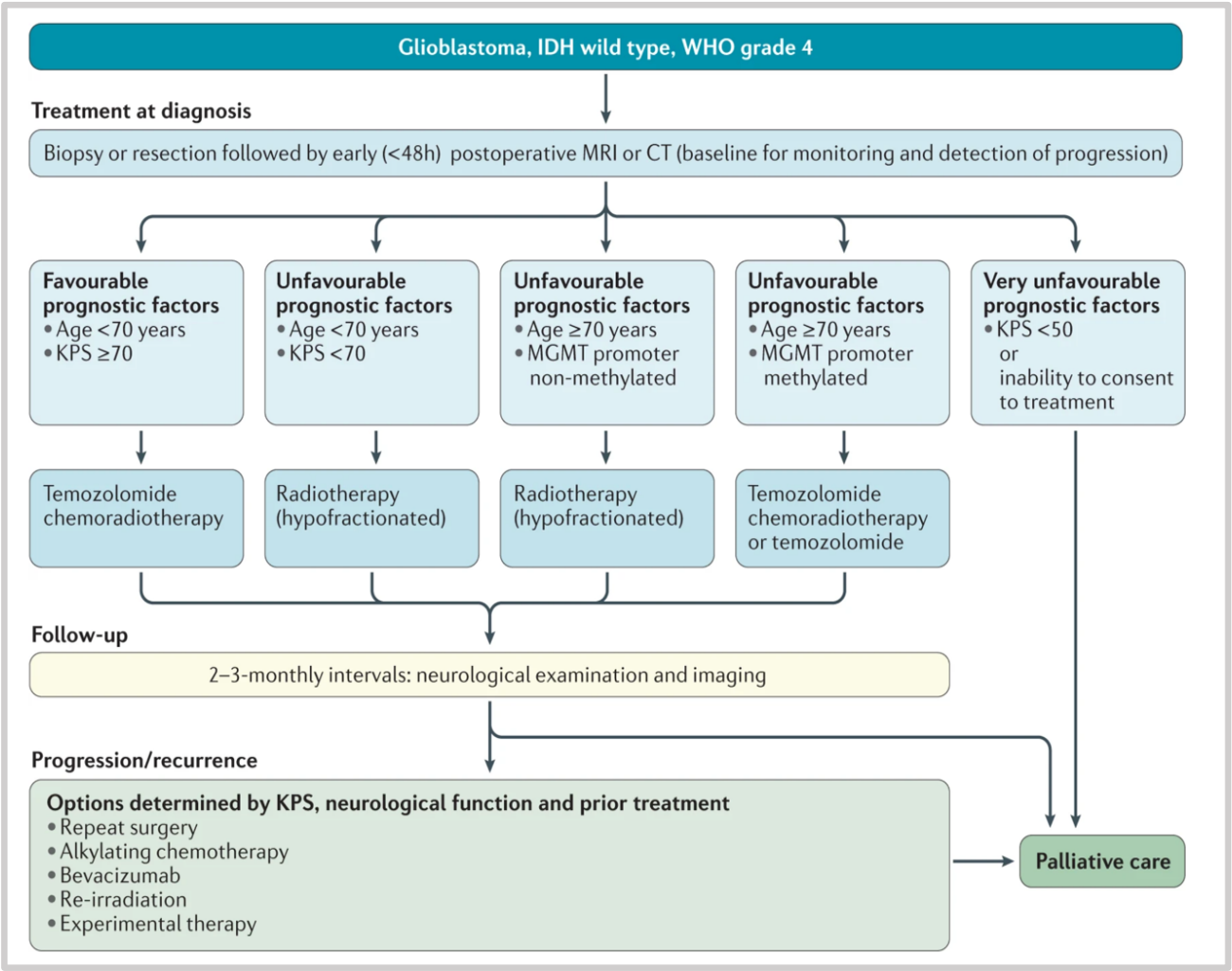

Figure 3: Diagnostic and therapeutical pathway on patients diagnosed with GBM (from EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood [3], used under Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.).

Besides all efforts made, patients with high-grade glioma, particularly GBM, experience a very limited life expectancy. Therefore, additional or alternative therapies are subject to various studies. In the past years, an additional therapy with Tumour-treating fields (TTF) found its way into clinical practice. TTF refers to wearable scalp transducers that administer localized, low-intensity, intermediate-frequency alternating electrical fields. These fields exert an anti-mitotic effect and operate in synergy with concurrent chemotherapies. Studies showed improved progression-free survival (PFS) and OS in patients who underwent TTF treatment [13].

Further experimental therapy research focuses on targeted therapies [14, 15], immunotherapy [16] either adjuvant or neoadjuvant [17] or vaccination studies with, among others, dendritic cell vaccines [18]. However, a breakthrough in treatment has not yet been achieved.

In case of recurrence, there is the option of re-irradiation with various re-treatment regimens or continuation of chemotherapy with temozolomide. Furthermore, there are several studies on bevacizumab, a humanized monoclonal antibody that binds to the vascular endothelial growth factor (VEGF), inhibiting its interaction with its receptors. As a result, there is a reduction in tumour vascularization and, consequently, tumour growth. Bevacizumab first received accelerated approval from the FDA in the USA for recurrent therapy in 2009, followed by full approval in 2019. The results of the studies leading to approval consistently demonstrated an advantage in PFS in the bevacizumab groups, although OS did not show a significant improvement [19-21] so did a recently published multi-centre prospective randomized study by Tsien et al., [22]. Data for non-GBM recurrences also did not reveal significant benefits in OS, although PFS was extended [23]. Thus, this therapy remains outside of a standardized treatment protocol. Other therapeutic strategies, like in the case of initial diagnosis, are reserved for experimental studies. Patients should be offered the opportunity to participate in studies early on, whenever possible. Similarly, supportive assistance from psycho-oncologists or a palliative care team should be provided as early as possible.

Secondary brain *tumours*

Secondary brain tumours are tumours whose cells originate from other organs and are known as brain metastases. Tumour cells from the primary tumour can spread hematogenous through the bloodstream or lymphogenic through the lymphatic pathways in the body. The most common tumours causing brain metastases are bronchial carcinomas, breast carcinomas, and malignant melanomas and their adjuvant therapies are determined by the primary tumour [24]. In the past, it was believed that cerebral metastases were delineated. Today, it is understood that brain metastases also exhibit an infiltrative growth pattern similar to that seen in intrinsic brain tumours [25] , the approach of treating brain metastases has changed over the past years. The significance of surgical resection will be discussed in the next chapter.

Other treatment options comprise whole-brain radiation and stereotactic single-dose radiation. Given diverse side effect profiles and discussed efficacy, the choice of specific radiation- as first-line therapy- depends on factors such as patient age, overall health, and the number and location of metastases [26, 27] .

Concerning an adjuvant treatment situation, typically, radiotherapy is performed, as studies have shown that adjuvant radiation significantly reduces the recurrence rate [28, 29] although OS remains unaffected. If possible, stereotactic radiotherapy should be considered [30] but this decision is as discussed earlier, individualized and based on a number of metastases, symptoms and the patient's condition. Regarding the optimal timing of adjuvant radiation, there is current evidence suggesting that the period of 3-4 weeks postoperatively proves to be the most favourable [31].

2. Resection as a foundation of therapy for high- and low-grade glioma and metastases

For years, gross total resection (GTR) has been the defined surgical goal in the context of brain tumour operations, particularly for high-grade intrinsic brain tumours. Therefore, evaluation of the extent of resection (EOR) and more recently the residual tumour volume (RTV) in the postoperative MRI became a standard procedure in patients with glioma [32]. Postoperative imaging is primarily assessed based on contrast enhancement in the T1-weighted sequence (with and without contrast for comparison) and changes in the T2- or Fluid-Attenuated Inversion Recovery (FLAIR) sequence, which played a significant role in low-grade glioma resection [33] but has also become important in high-grade glioma over the past few years.

To date, maximal safe resection is declared as the primary surgical objective in all leading treatment guidelines that refer to high-grade glioma [34, 35], based on various crucial resection studies. For example, in 2001 Lacroix et al., described that an EOR of more than 98% was significantly associated with a survival advantage [36]. Stummer et al., found significant results regarding OS for the patient group without residual tumour volume, measured as remaining contrast-enhanced tissue, compared to those with remaining tumour volume in the postoperative MRI [37] in patients with GBM. Additional studies have demonstrated that

patients with an EOR > 78% had a significant survival advantage, which further increased when considering subgroups with an EOR between 95-100% [38]. Over the years, the term "supratotal resection" was introduced, and studies were conducted to assess the impact on patient survival not only for resection of the T1 contrast-enhancing lesion but also for the surrounding T2/FLAIR - changes [39].

Recently, the Response Assessment in Neuro-Oncology (RANO) resect group proposed a classification for different subgroups of extent of resection and residual volume in GBM patients based on contrast-enhancing tissue and the surrounding T2/FLAIR changes in the postoperative MRI. The study revealed a significantly higher OS for patients with maximum EOR or minimal residual volume, meaning maximum resection not only of contrast-enhanced tissue but also T2/FLAIR changes [40].

Also, in case of low-grade glioma, studies have revealed that the amount of remaining tumour volume and the EOR can be indicative for PFS and the duration until malignant transformation as seen in radiological imaging [41, 42].

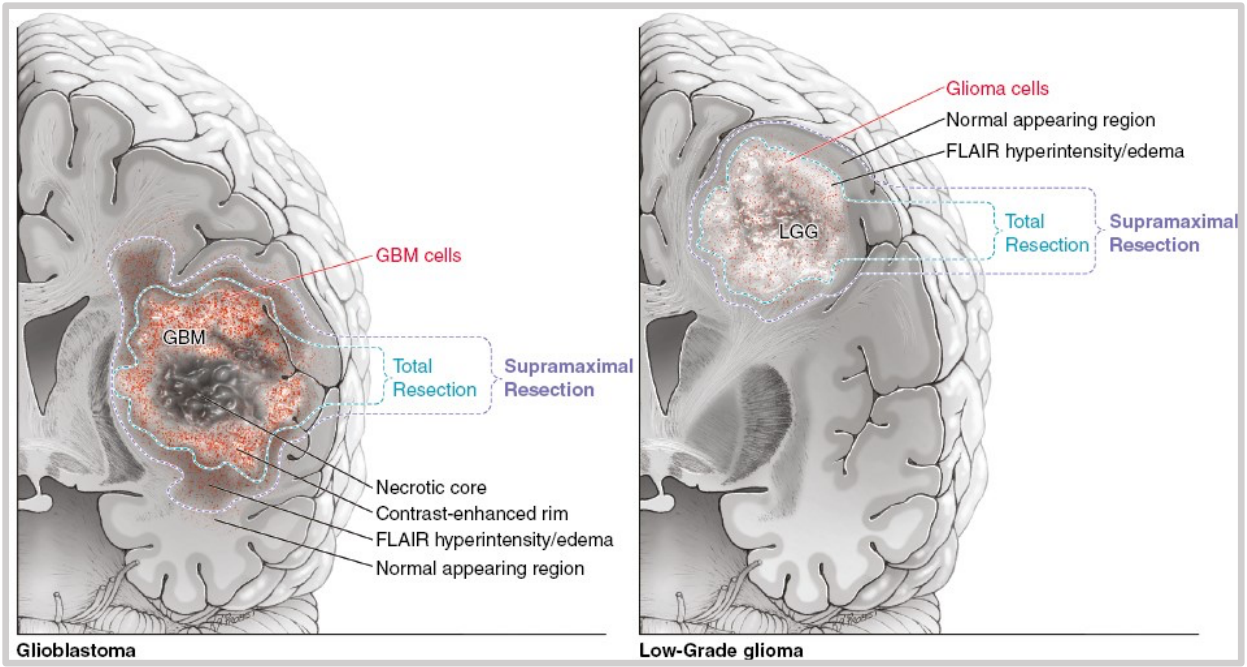

Figure 4 Schematic visualisation of total vs. supramarginal/supratotal resection in GBM (A) and low-grade Glioma (B) (from The surgical management of diffuse gliomas: Current state of neurosurgical management and future directions, Jacob S Young, Ramin A Morshed, Shawn L Hervey-Jumper, Mitchel S Berger, Neuro-Oncology, *Volume 25, Issue 12, December 2023, Pages 2117–2133 [43], image use with permission of Oxford University Press)*

Furthermore, not only in primary brain tumours evidence was proven that resection is a profound step in treatment. However, resection of brain metastases has been subject of much controversy for a long time and was seldom performed in earlier times. But, due to numerous studies comparing a surgical approach combined with radiation therapy or radiation therapy alone, surgical resection emerged as a crucial factor associated with prolonged survival and maintenance of functional status. It was shown that patients who underwent surgery before receiving radiation, irrespective of the radiation type (whole-brain or stereotactic radiosurgery), exhibited significantly longer survival and higher Karnofsky Performance Scale Scores (KPS) [44-46].

In summary, evidence supporting resection in patients with primary and secondary brain tumours is undeniable. Nevertheless, surgery can be highly challenging due to the location of the lesion. The primary objective is to achieve maximum resection without causing new neurological deficits, as we understand that new postoperative deficits can delay or even prevent adjuvant therapies and can lead to lower survival rates [47] at least in GBM. Furthermore, it diminishes the quality of life for patients who are already significantly affected by the diagnosis [48].

To achieve the defined surgical goal, a successful resection is preceded by precise surgical preparation. Various preoperative assessments can facilitate surgical planning. Imaging through MRI with T1 and T2/FLAIR sequences is considered standard [49]. Additionally, functional MRI and Diffusion Tensor Imaging (DTI) sequences can aid in depicting fibre pathways in the MRI and visualizing the tumour's position in relation to eloquent areas [50]. Preoperative mapping techniques, such as navigated transcranial magnetic stimulation [51], can precisely locate crucial brain functions on a map with millimetre accuracy. Intraoperatively, it is possible to easily locate the tumour using a radiological navigation system [52].

Also intraoperatively, some techniques have simplified the surgical approach, especially concerning achieving a significant EOR. Fluorescence-guided surgery, especially in the field of GBM surgery, has led to a significant increase in EOR [53, 54]. Intraoperative assessment of the lesion and resection outcome is possible through intraoperative ultrasound (iU) or intraoperative MRI (iMRI). IU can, among other things, contribute to the precise localization of the tumour, identification of vessels and anatomical structures, and especially real-time

resection control [55]. Real-time determination of the EOR can also be achieved through iMRI, potentially influencing decisions such as continuing the operation to achieve a more favourable EOR [56].

However, while these techniques are established and essential, they contribute to meticulous planning, nevertheless, they do not work as a control mechanism for the preservation of a patient's motor or language function in eloquent brain tumours intraoperatively. For this purpose, the techniques of intraoperative monitoring (IONM) and mapping as well as awake surgery, described in the next chapter, have evolved, forming the basis for the research conducted in this work.

3. Intraoperative neurophysiological monitoring (IONM) and mapping techniques for preservation of functionality during tumour resection in highly eloquent localizations

When discussing surgery for eloquently located brain tumours, it is crucial to clarify the term "eloquent" in the context of the brain. For decades, “eloquent” referred to areas that "contain identifiable neurologic function and, if injured, would result in a disabling neurologic deficit" [57]. The strategy was clear: preserving “eloquent” regions responsible for core brain functions, such as movement and speech, over “non-eloquent” regions that do not have an obvious function. Due to the ongoing progress in connectome research, we now understand that "non-eloquent" areas also play a crucial role in higher-order brain networks. Due to the extensive data, details on this cannot be addressed at this point. However, it is important to note that the term "eloquent" has evolved over the years and will continue to change with advancing research. Therefore, efforts regarding the intraoperative testing of these networks have been driving force behind this work and must be ongoing in the future.

Historical background of modern IONM and mapping procedures

The inception of IONM dates back to the 1930s when Walter Penfield used direct cortical stimulation (DCS) during epilepsy surgeries to localize the motor and sensory cortex. Alongside electroencephalogram (EEG) measurement derived directly from the cortex, areas exhibiting EEG abnormalities could now be resected [58, 59]. From the 1970s, the technique of IONM underwent rapid advancements. Firstly, monitoring spinal procedures via epidural monitoring was achieved [60]. A pivotal new technique involved deriving the first somatosensory potentials (SSEPs) during spinal surgeries [61, 62]. In their initial stages, SSEPs were prone to interference, leading to several technical modifications, particularly in the filter domain. Ultimately, by the mid-1980s, a technical setup was reported, serving as the foundation for modern SSEP monitoring [63]. Additional motor-evoked potential (MEP) monitoring through transcranial electric stimulation emerged as a technique in the 1990s [64].

Besides SSEP, MEP and EEG monitoring there are additional direct cortical and subcortical stimulation techniques under usage of different stimulation probes. Bipolar stimulation as mentioned at the beginning was introduced by Penfield and ever since has been referred to as a low-frequency stimulation with long stimulation duration. In the early 90s, Taniguchi et al. published a modification of direct cortical stimulation by using a monopolar stimulation probe using high-frequency stimulation parameters with shorter stimulation duration [65]. The techniques will be described in detail in the following.

IONM with motor-evoked potentials

IONM comprises different technical approaches. It is a passive way of patient monitoring, meaning that the patient can be monitored under general anaesthesia. If IONM using evoked potentials is planned, it is essential to administer total intravenous anaesthesia. Inhalation anaesthesia can adversely affect the derived potentials. This applies to both MEP and SSEP [66, 67]. MEP monitoring usually serves as monitoring of motor pathway integrity whereas SSEP monitors the function of sensory pathways.

MEP monitoring

The technique of MEP monitoring can be performed by either transcranial electric stimulation (TES) or direct cortical stimulation (DCS). Short-train, mostly “train-of-five”, high-frequency (250- 500 Hz) pulses are applied to elicit MEPs. MEPs are recorded compound muscle action potentials (cMAP) that can be registered via electromyogram (EMG).

Corkscrew electrodes are the preferred choice for TES due to their lower impedances compared to needle electrodes which might be used alternatively and are placed on the scalp analogue to the 10-20 system [68]. For upper limb monitoring, electrodes can be placed either at C1/C2 or C3/C4, whereas C1/C2 electrodes are preferable due to less biting movements. Lower limb montages can vary even more, however also C1/C2 or C3/C4 can be used like in upper limb monitoring. The advantage of C1/C2 or C3/C4 montages is that both the upper and lower extremities can be monitored simultaneously. Various stimulation setups should be explored, and the most effective montage can be chosen for each patient as ideal electrode configuration for stimulation may differ among patients and surgical scenarios [69].

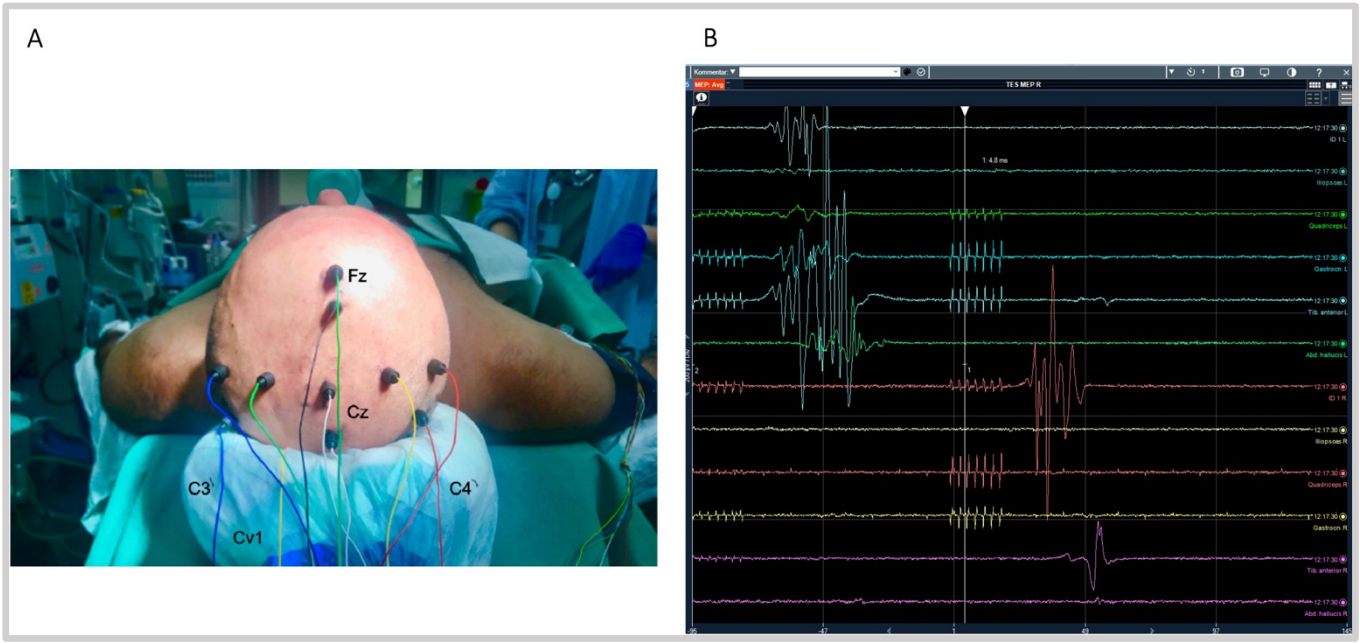

Figure 5: A) TES corkscrew placement for MEP monitoring; B) TES MEP recordings via EMG. Activity in nearly all derived muscles, copyright by University Hospital Düsseldorf, Department of Neurosurgery, image use with permission of Prof. Dr. Sabel, Video Atlas of Neurophysiological Monitoring in Surgery of Infiltrating Brain tumours, Thieme 2022

If continuous monitoring of MEPs is necessary, it is advisable to use DCS monitoring with a so-called strip electrode containing 4-8 contacts. This electrode is placed on the exposed precentral gyrus (M1, motor cortex) after opening the dura, allowing for continuous, directly cortical-triggered MEP monitoring.

As described EMG recording serves as tool for visualisation and registration of the triggered MEP respectively cMAP. In addition to scalp electrodes, paired needle electrodes are placed in the predefined muscles of the contralateral side and sometimes ipsilateral – which serves as control mechanism - for EMG recording. Furthermore, recommendations about number of monitored muscles are at least three contralateral hand and arm as well as two leg muscles and two face muscles. Before choosing monitored muscles, neurological examination of the patients has to take place, as presurgical neurological impairment influences chosen muscles and stimulation intensity. Therefore, number and location of monitored muscles can be adjusted due to various reasons [70].

Baseline recordings, that are performed before skin incision are needed in order to register MEP deviations during surgery. Stimulation intensity at about 20% above MEP thresholds, which is the lowest stimulation intensity obtaining motor feedback in the EMG, is considered as approximate optimal benchmark. Different warning signs are mentioned in the literature. While loss of MEP is usually seen as major warning sign, a reduction in amplitude of over 50% or threshold increases for triggering MEPs are also regarded as warning signs during MEP monitoring [71].

SSEP monitoring

As mentioned SSEP monitor function of sensory pathways, in this regard one of the main utilities of SSEP monitoring lies in its ability to discern ischemic events impacting the somatosensory cortex. There is a well-known correlation between critical cortical perfusion in brain parenchyma and a reduction in SSEP amplitudes, as indicated by Astrup [72].

SSEP recording is done by measuring latency and amplitude of signals between two determined points: stimulation of peripheral nerves and recording of the transmitted signal peripheral or centrally from the cortex. In the context of brain tumour surgeries, these procedures typically involve the stimulation of the N. medianus for the upper extremity (0.2 ms at 20 mA, 4.7 Hz) and the N. tibialis for the lower extremity (0.5 ms at 20 mA, 4.7 Hz). Normative latencies, denoting the duration from stimulus emission to registration at corresponding electrodes are established for both locations. While stimuli can be discerned at various anatomical levels, the focus during brain tumour surgery is on cortical-level signals. Analysis of the signal encompasses evaluation of latency (time taken from stimulus generation to detection) and the morphology/size of the signal (amplitude). It is crucial to emphasize that the assessment involves not only a single signal but also the averaging of numerous repetitively emitted signals (approximately 200-500). This averaging process, however, constitutes a drawback in SSEP measurement, as it extends over several seconds to minutes, consequently leading to a delayed identification of latency or amplitude alterations.

Deterioration of SSEP, characterized by the prolongation of latency and reduction in amplitude, is regarded as indicative of warning signs [67].

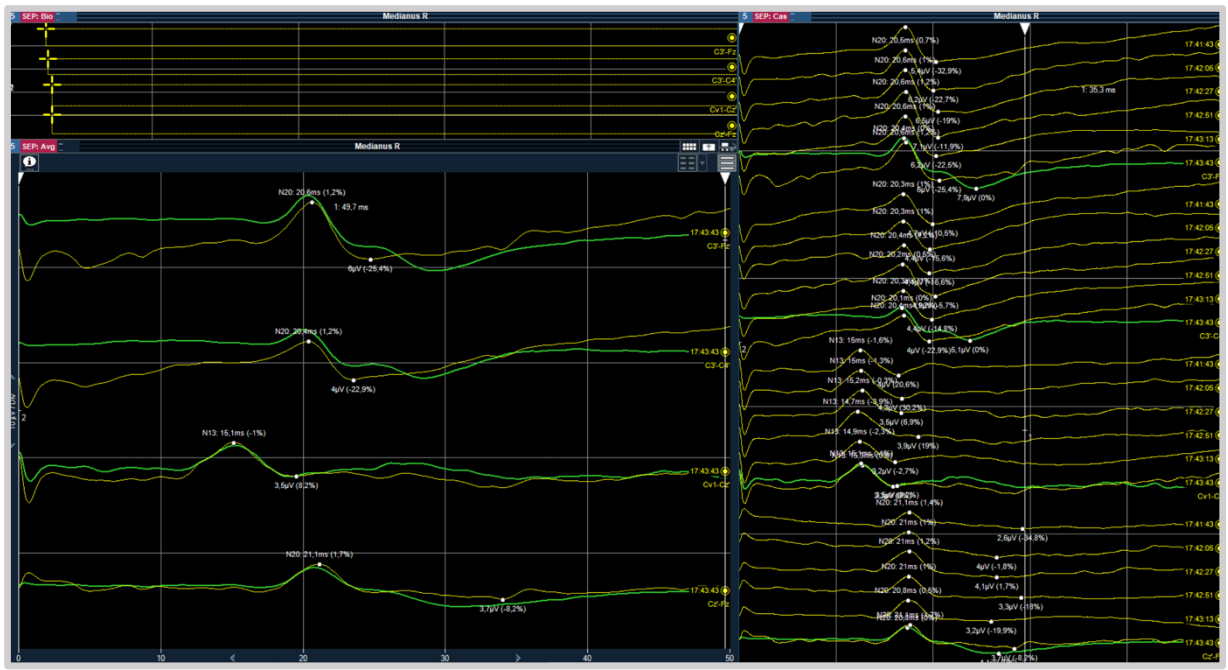

Figure 6: Example of intraoperative N. medianus SSEP monitoring. The green line indicates the baseline which is used for evaluation of intraoperative obtained SSEP average. The yellow line indicates the actual, averaged SSEPs. Own figure, image copyright by University Hospital Düsseldorf, Department of Neurosurgery.

A special technique in SSEP monitoring involves SSEP phase reversal. This involves recording the inversion of median nerve cortical SSEP polarity between the postcentral and precentral gyri to ascertain the location of the central sulcus, which can be helpful if motor mapping does not clearly reveal the M1 motor-cortex [73].

Cortical, subcortical mapping and language testing

Cortical and subcortical mapping of motor and language function can be performed by either high-frequency – monopolar- or low-frequency – bipolar – mapping techniques.

High-frequency stimulation is applied by a monopolar probe with a reference electrode, typically situated at the scalp in FZ position. During monopolar stimulation there is a substantial electrical field extending from the stimulation site (monopolar probe) to the reference electrode. In monopolar stimulation, either the tip of the stimulator or the reference electrode can function as anode or cathode, allowing for anodal-cathodal or cathodal-anodal stimulation configurations. Cortical mapping is applied in order to locate the M1, primary motor cortex in order to evaluate distance to tumour localization and safety of surgical approach and resection. Subcortical motor mapping is employed to locate the corticospinal tract (CST) and is applied under resection in order to obtain information on motor function during resection nearby the CST. Either way an EMG is established as visualization tool for cMAP just like with the TES technique described earlier. Monopolar mapping is the preferred technique for intraoperative monitoring of motor function. On one hand, it enables the assessment during resection to determine if the tumour is in close proximity to motorically functional areas. On the other hand, it provides a means of monitoring the preservation of motor activity [74, 75].

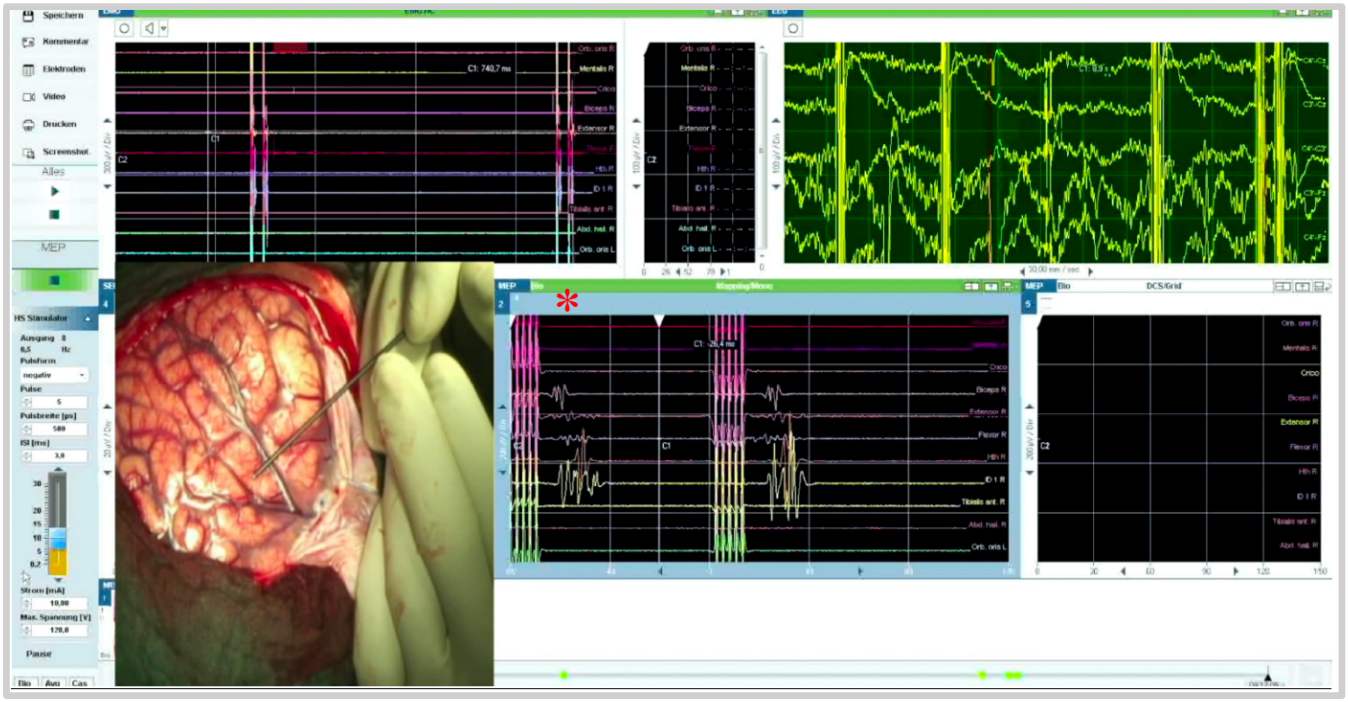

*Figure 7: Intraoperative example of monopolar mapping techniques. The probe is placed on the cortex. The technician choses amplitude of stimulation at the device. In this patient we obtained cortical and subcortical MEPs with 10 mA (red * = MEP BOX, MEPS for upper and lower extremities). Own figure, image copyright by University Hospital Düsseldorf, Department of Neurosurgery.*

Low-frequency bipolar stimulation (50 or 60 Hz) involves a bipolar stimulation probe which consists of 2 ball tips with typically 5-10 mm distance representing the cathode and anode. In contrast to monopolar stimulation/mapping the electrical field is concentrated only between those tips, creating an almost homogeneous and localized electrical field. Consequently, the bipolar technique yields a higher-resolution map of the cortex. Low-frequency stimulation also has the potential to elicit MEPs but the required stimulation intensity is significantly higher and thereby elevates the patient's risk for seizure. Therefore, it is not a standard procedure for motor control but primarily applied in awake surgery during language testing [76-78]. Bipolar stimulation is applied during testing and leads to “block of function”, the most pronounced form is “speech arrest”, wherein the patient completely ceases speaking. Between the extremes of “normal” language function and speech arrest, there are gradations depending on the testing procedure, nevertheless intraoperative language testing requires a compliant patient and

detailed and focused examination to elucidate intraoperative details of language and its impairment.

Intraoperative language testing presents two prominent challenges. Firstly, the conceptualization of localization of language function in the brain has undergone a significant shift in recent decades. Today, it is understood that functional language is organized at multiple locations, and DTI tractography studies have identified dorsal and ventral subcortical tracts crucial for language processing. Important subcortical tracts in language processing include the superior longitudinal fasciculus (SLF), the inferior fronto-occipital fasciculus (IFOF), the arcuate fasciculus (AF), and the uncinate fasciculus (UF). Various language deficits can be observed with damage to specific tracts, to cite just a limited number of examples, speech arrest and dysarthria can be triggered by disturbance of SLF and syntactical errors in case of affection of AF, IFOF or UF [79]. Secondly, language encompasses numerous dimensions, necessitating test batteries comprehensive but feasible for intraoperative application, for syntax, semantics, and phonology [80].

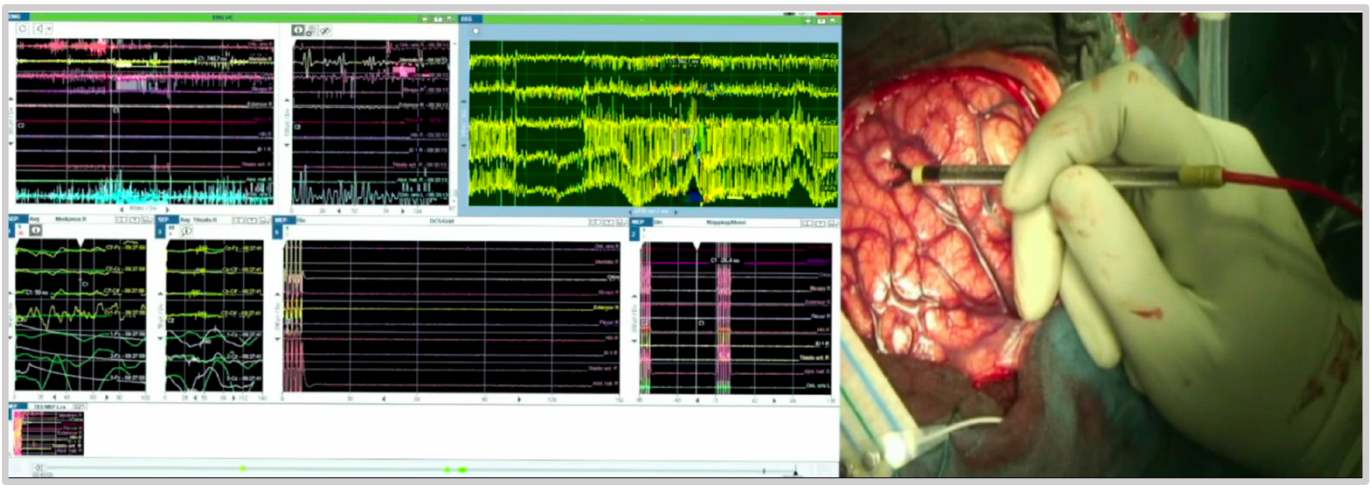

Figure 8: Intraoperative example of bipolar cortical mapping techniques. The probe is placed on the cortex. At the same time, the patient has to fulfil different language tasks. The monitor shows strong muscle potential due to the awake and speaking patient. Own figure, image copyright by University Hospital Düsseldorf, Department of Neurosurgery.

Awake surgery

In the planning of brain tumour resection, a decision must be made regarding the potential necessity of the patient's wakefulness during surgery. This may be required, for example, when the tumour's location necessitates language mapping, a procedure feasible only in an awake patient. Intraoperative language mapping is currently the standard indication for awake surgery in brain tumour patients. However, motor aspects can also be examined during awake surgery. The primary indication for motor awake monitoring arises when monitoring MEPs as an expression of overall function alone is not sufficiently informative. This particularly emphasizes the monitoring of fine motor skills or sensory aspects, such as the dependence of professional musicians like violinists, guitarists, etc., on their fine motor and sensory abilities.

Awake craniotomy also allows control over another domain that has been neglected for many decades but is crucial for the preservation of quality of life — neurocognition. In recent years, there has been an increasing focus on preserving non-motor or language-dependent abilities[81]. Intraoperative neurocognitive testing remains a subject of intense investigation, as test batteries are sometimes elaborate, and strategies for quickly and easily applying tests intraoperatively are still under development [82, 83].

When considering the indication for awake craniotomy, the necessity of intraoperative functionality monitoring must be balanced against the individual and specifically assessable compliance of the patient, as well as any pre-existing neurological deficits. For example, pre-existing sensory aphasia may be an exclusion criterion for awake surgery, as meaningful intraoperative testing is not possible with an existing deficit. Previously applied exclusion criteria, such as patient age, now play a subordinate role, as publications demonstrate the feasibility of awake craniotomies in both children and the elderly [84-87].

Various protocols exist for the technical execution of awake surgery, wherein patients may either be initially under general anaesthesia and awakened partially for intraoperative testing or may be awake during the whole surgery. In the “awake-asleep-awake” setting patients are under anaesthesia during craniotomy and awakened for testing afterwards. When testing is completed, patients can be either sedated or reintubated. In contrast, a patient may be awake

from the beginning of the operation in an "awake-awake-awake" setting. The decision on the approach is made by the surgeon. An essential factor for the success of awake craniotomy is a skilled and experienced anaesthesia team, along with trained personnel capable of conducting tests on the patient during surgery. Patients are prepared for the tests preoperatively, and baseline examinations are conducted to establish preoperative individual norm values for each patient.

II OBJECTIVES

This comprehensive thesis aims to address several key objectives to enhance the understanding of intraoperative monitoring and mapping techniques in eloquent brain tumour surgery, as these techniques built an important foundation of save and maximum resection in patients with brain tumours of several origins.

Our primary objectives were as follows:

1. Illustration of the importance of resection in a dedicated cohort of patients with high-grade tumours.

With the first study described in this thesis we aimed to build a foundation for understanding the significance of resection for patients, and the resulting necessity to maximize resection through the utilization of intraoperative monitoring and mapping techniques, specifically in a selected subgroup of brain tumour patients, those with high-grade tumours. For this purpose, a favourable molecular genetic factor was juxtaposed against the resection outcome concerning overall and progression-free survival.

2. Assessment of technical setup and personnel resources in IONM and mapping procedures

The aim was to reveal whether the same comprehensive technical setup and personnel resources are necessary for every patient to achieve the surgical goal. This involves evaluating the variability in requirements based on individual patient characteristics.

3. Evaluation of monitoring/mapping for an individual approach

We aimed to determine if the preoperatively chosen monitoring/mapping technique, based on defined criteria, remains the technique of choice postoperatively. We will explore potential influencing factors in the evaluation, considering the individual adaptability and efficacy of the chosen technique.

4. A mapping-only device in eloquent brain tumour surgery

The study investigated the feasibility of using a mapping-only device for tumours in eloquent locations without additional intraoperative monitoring. We aim to assess whether this approach can provide comparable safety to standard technical approaches.

5. Motor mapping emergency resection and its outcome

We explored the ease of performing motor mapping in emergencies, specifically when operating on decompensated brain tumours and evaluated whether complications arise during this process. Another aim of the study was to analyse the outcomes following motor mapping in emergencies, focusing on the effectiveness and safety of this technique in critical scenarios.

6. Impact of monitoring and mapping techniques on PFS and OS in GBM

We will investigate whether specific monitoring or mapping techniques have a significant impact on progression-free survival (PFS) or overall survival (OS) in the subgroup of highly malignant GBM.

7. Awake surgery and its impact on psychooncological outcome in patients with a malignant brain tumour

With this study, we examined whether awake craniotomy, representing a maximal variant of intraoperative monitoring of motor and language functions, negatively influences factors on the psychooncological outcome of brain tumour patients.

By addressing these objectives, we aimed to contribute valuable insights to the optimization of intraoperative techniques and enhance patient outcomes in the context of brain tumour surgeries.

III RESULTS

1. Can a favourable molecular genetic marker balance the lack of achieved complete resection concerning the OS of glioblastoma patients?

In the introduction, the importance of resection for various tumour entities is profoundly discussed. The first study in this comprehensive work serves as a basis for understanding why complete resection is crucial, focusing on a subgroup, the Glioblastoma patients. Here, we investigated whether the positive MGMT-status- considered a significant positive factor for OS in glioblastoma patients - can compensate for an incomplete resection in terms of OS. Understanding the significance of resection in brain tumour patients simultaneously emphasizes the importance of intraoperative techniques for maximizing safe resection. The original work can be found in the Appendix (1).

Does positive MGMT methylation outbalance the limitation of subtotal resection in glioblastoma IDH-wildtype patients? Müller Mareike, Staub-Bartelt Franziska*, Ehrmann Julia, Hänggi Daniel, Sabel Michael, Felsberg Jörg, Rapp Marion, *equal contribution*

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Introduction

Malignant gliomas, the most common adult brain tumours, have an incidence of 5–6 per 100,000 people annually, with GBM comprising over 50% of cases. Molecular-genetic markers play a crucial role in diagnosis, prognosis, and treatment decisions. In particular, isocitrate dehydrogenase (IDH) mutation status and O-6-methylguanine-DNA methyltransferase (MGMT) methylation are significant. IDH-mutation positively influences OS (31 vs. 15 months: IDH-mutated vs. IDH-wildtype [88, 89]), while MGMT promoter methylation enhances treatment response to standard chemotherapy and thereby has also proven to positively influence OS (median OS 21.7 vs. 12.7 months: “MGMT-positive” vs. “MGMT-negative” [5, 90]. Complete resection of contrast-enhancing tumour tissue is the primary goal to improve survival, albeit

challenging due to potential neurological deficits. Postoperative residual tumour correlates with decreased OS, emphasizing the importance of aggressive resection [37, 91]. Adjuvant therapies, including radio-chemotherapy and additional Lomustine administration in patients with methylated MGMT promoter, significantly enhance OS [6]. Intraoperative techniques such as neuromonitoring and fluorescence-guided surgery aid in achieving maximal resection while minimizing neurological damage. However, balancing the risk of deficits against tumour removal remains a complex decision, especially in eloquent areas.

The impact of molecular tumour status on surgical aggressiveness, particularly in MGMT-positive methylated tumours, raises questions regarding treatment strategies. In this study, we investigated whether MGMT promoter methylation could offset the negative effects of residual tumour tissue on tumour progression, PFS, OS, and clinical outcomes in IDH-wildtype GBM patients, correlating data with postoperative MRI findings of no residual tumour tissue. Understanding the interplay between molecular markers and surgical outcomes is vital for optimizing glioma management strategies, ensuring maximal tumour removal while preserving neurological function and improving patient outcomes.

Methods

The study was conducted as a retrospective single-centre study, exploring the influence of MGMT-status on the survival of GBM patients with postoperative residual tumours. The study received approval from the local ethical committee. Inclusion criteria encompassed patients diagnosed with IDH-wildtype GBM between January 2010 and December 2018, who underwent surgery at the neurosurgical department of the University Hospital Duesseldorf, with available pre- and postoperative MRI scans taken within 72 hours post-operation, exhibiting residual tumour tissue in the early postoperative MRI. MGMT promoter analysis has been standard practice since 2005 at the Institute of Neuropathology at the University Hospital Duesseldorf, employing methylation-specific PCR for determining MGMT promoter methylation status and immunohistochemistry for IDHR132H and DNA pyrosequencing for IDH mutation status. All

diagnoses predating the WHO 2016 classification were reclassified accordingly by the Institute of Neuropathology[1].

The KPS was assessed pre-and post-operatively to gauge patient clinical status, with clinical deterioration defined as a ≥10% decrease in KPS.

Initial and residual tumour volumes were calculated using MRI data. Subsequent analyses differentiated between residual tumour volumes smaller or larger than 1.5 cm^3. Follow-up MRIs were conducted every three months post-completion of concomitant radiotherapy and chemotherapy, with treatment response evaluated based on RANO criteria. Tumour recurrence was diagnosed using follow-up MRI showing the smallest measurable residual tumour volume, or evidence of increased contrast-enhancement tissue, metabolic activity in 18F-FET-PET examination, or histopathological diagnosis from re-resection.

Results

The study enclosed 81 patients with IDH-wildtype glioblastoma and residual tumour volume in the post-op MRI treated at a neurosurgical department from January 2010 to December 2018, who passed the inclusion criteria. The median age at diagnosis was 63 years, with a median observation period of 13 months. The median PFS was 7 months. Most patients had died by the time of data evaluation. 64% had unmethylated MGMT promoters, while 36% had positive MGMT-status.

Preoperatively, 66.7% had a median KPS > 90%, which did not change postoperatively. Upon local tumour progression, patients experienced either no change or a minor decline of 10% in KPS (n=37, 81.1%). 9 patients showed KPS decrease between 20-30% and two patients experienced a major decrease by 50%. Tumours were evenly distributed between hemispheres, with the frontal lobe being the most common location (35.0%). 92.6% of tumours were located in eloquent areas, necessitating awake brain surgery in 57.3% and intraoperative monitoring in 92.6% of cases. The median preoperative tumour volume was 36.85cm^3, with methylated MGMT promoter tumours showing a higher median volume compared to unmethylated ones.

[1] Histopathological classification for diffuse glioma has evolved over the years. For this paper, the terminologies of the WHO Classification 4 for Central Nervous System tumours were utilized. The data collected during times of older classification were adjusted according to the WHO 4 classification as described.

Concerning survival data, a significant increase in OS as well as PFS was observed in patients with MGMT-methylated tumours (p = 0.009, p = 0.003, respectively). Patients with MGMT hypermethylated residual tumours had a median OS of 16 months (95% CI, 13.00–19.01) and a median PFS of 13 months (95% CI, 5.94–20.06). In contrast, patients with MGMT-negative tumours exhibited a median OS of 12 months (95% CI, 9.92–14.08) and a median PFS of 5 months (95% CI: 2.92–7.08).

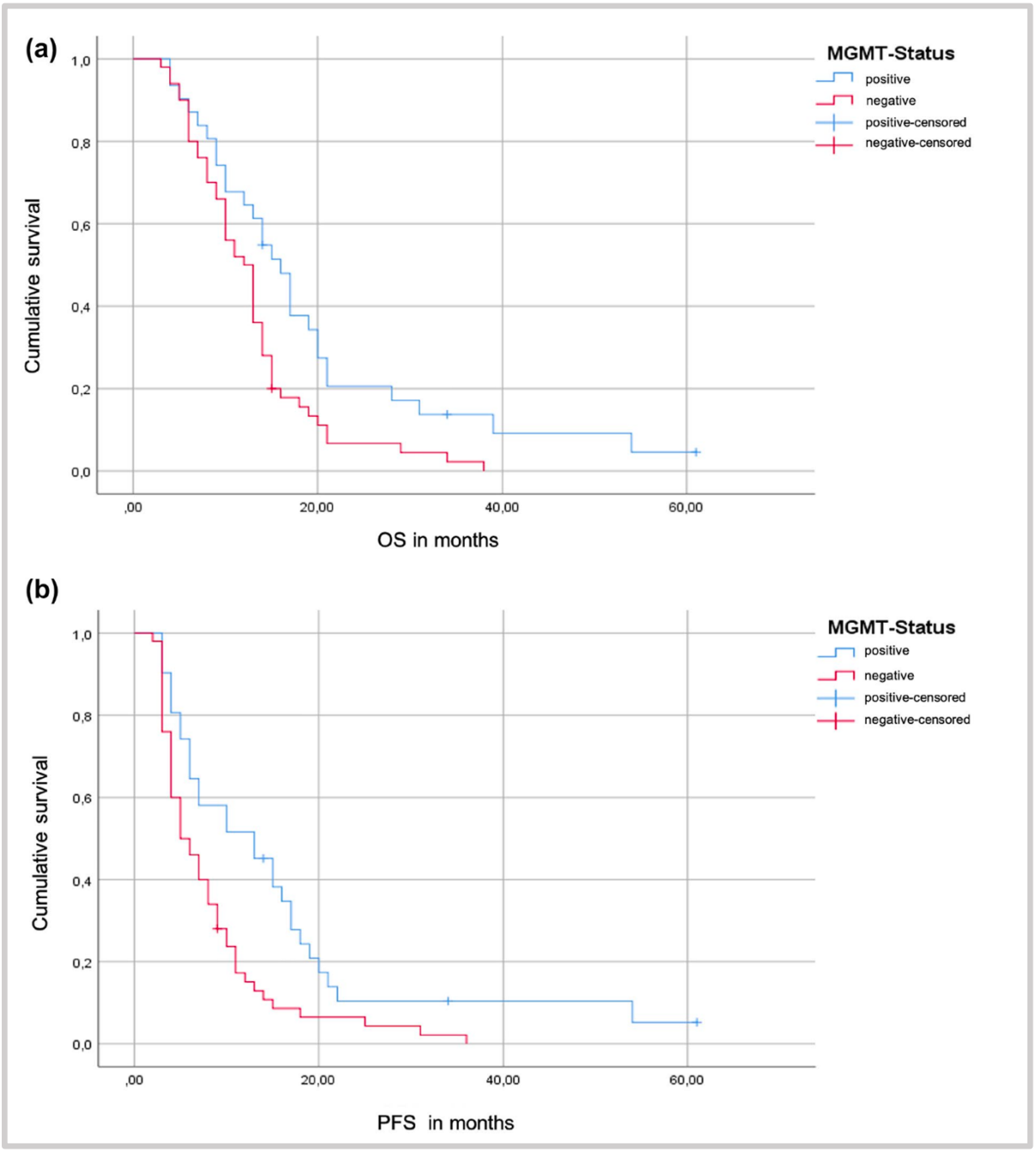


Figure 9: Kaplan-Meier Curve on OS (A) and PFS (B) for both groups (MGMT-methylated vs. MGMT unmethylated),figure cited from own publication [92], used under Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.).

Survival data were compared to a cohort of patients who underwent gross total resection at the same department. It was found that tumours were predominantly located in eloquent areas in both groups (67% vs. 92.6%). Complete resected tumours were more commonly found in the left hemisphere (58.8%), while incomplete resected tumours were more prevalent in the right hemisphere (48.2%). Incomplete resected patients had a larger preoperative tumour volume (median 36.85 cm3 vs. 23 cm3) and were associated with a higher age at diagnosis (median 63 years). Patients with a positive MGMT-methylation status demonstrated increased OS (median OS: 21.0 vs. 19.0 months) compared to those without. However, the median PFS was similar in both groups (9.0 months). Age over 60 years and a residual tumour volume greater than 1.5 cm3 were associated with decreased OS and PFS, although these findings were not statistically significant. Pre- and postoperative KPS did not significantly influence OS or PFS in the cohort.

Discussion

In this study, we aimed to investigate whether a methylated MGMT promoter could mitigate the negative impact of incomplete resection in IDH-wildtype glioblastoma patients, as the presence of a methylated MGMT promoter has been associated with improved response to adjuvant chemoradiotherapy and subsequently better OS.

Our findings support the commonly published observations, as patients with a hypermethylated MGMT promoter exhibited increased median OS (16 months) and median PFS (13 months), compared to those with unmethylated MGMT promoter residual tumours (median OS of 12 months and median PFS of 5 months, $p = 0.009$; $p = 0.003$).

Furthermore, MGMT tumour methylation was positively associated with increased treatment response (51.6% vs. 14.0%), consistent with findings in the literature [93, 94]. Nevertheless, when compared to patient cohorts undergoing complete resection, our study population exhibited decreased survival times. Therefore, our data do not support the notion that favourable MGMT methylation status could fully compensate for the survival detriment resulting from incomplete resection.

Besides molecular patterns, other variables are considered to influence the disease trajectory, accounting for similar survival patterns in the initial months of follow-up and the presence of long-term survivors with MGMT-negative glioblastoma. These variables typically include age at

diagnosis, overall health status, tumour location, and pre-and post-operative tumour volume. In our study, older patients and those with greater residual tumour volume tended to exhibit poorer outcomes, although these associations did not reach statistical significance. Postoperatively, patients maintained a median KPS of 90%, indicating no discernible difference between preoperative and postoperative functional status. Surgical interventions, often conducted under neuromonitoring and awake surgery settings to minimize new neurological deficits, likely contributed to both favourable outcomes and residual tumour volume, as functional constraints were addressed during surgery. Comparable studies have reported similar median postoperative KPS values of 90% in patients undergoing complete resection [95] with however lower amount of eloquently located lesions.

Conclusion

The findings of this paper emphasize the significance of the MGMT promoter methylation status in the treatment response of IDH-wildtype glioblastoma as patients with hypermethylated MGMT tumours exhibited increased OS and PFS compared to MGMT-negative patients. However, the detriment of incomplete resection could not be counteracted by a favourable MGMT-status. Therefore, maximized but safe resection should continue to be regarded as the gold standard in the treatment. In the era of personalized medicine, where optimizing quality of life is a primary objective in oncology, neuro-oncologists must comprehensively inform patients and their caregivers about the advantages and disadvantages of residual tumour volume versus potential neurological deficits associated with complete resection, especially in eloquent tumour locations and ensure the best possible intraoperative functional monitoring for achieving the surgical goal of "maximal" or "supramaximal" resection.

2. Strengths, pitfalls and optimization of intraoperative monitoring and mapping procedures – does everyone need everything?-

In this study, we examined various approaches of IOMN and mapping procedures in patients with highly eloquent brain tumours, focusing on the "utility-to-effort ratio". The idea behind the study was to investigate whether a technically and personnel-intensive monitoring/mapping setup is mandatory in all patients or if it could be replaced by a customized technical setup tailored to the patient and their brain tumour, mainly depending on localisation, with both, safety and resource efficiency, assured. The original work can be found in the Appendix (2).

Feasibility of intraoperative neuromonitoring and cortical/subcortical mapping in patients with cerebral lesions of highly functional localizations—pathway to case adapted monitoring and mapping procedures

Franziska Staub-Bartelt, Marion Rapp, Michael Sabel, Front. Oncol. 13:1235212. doi: 10.3389/fonc.2023.1235212

Introduction

IONM and mapping techniques have become standard in the care of patients with eloquently located brain tumours [74, 77, 96]. The technical execution cannot be carried out by the surgeon alone, as external devices are used for recording and analysis, and which cannot be handled simultaneously by the surgeon during surgery. Specifically trained personnel are required for the preoperative setup, operation of the technical devices, and the analysis of the collected data [97]. As described earlier in the introduction, various techniques can be applied intraoperatively. In our clinic, all monitoring procedures (MEP, SSEP, TES, DCS) and mapping procedures (monopolar and bipolar cortical/subcortical mapping) as well as awake craniotomies are performed. In 2019, we initiated a systematic prospective data collection aiming to provide a comprehensive overview of patients, diagnoses, intraoperatively applied techniques, and associated outcomes. Additionally, specific postoperative surveys were conducted among surgeons regarding the intraoperative usability of the preoperatively selected technique to achieve the surgical goal. The primary question addressed in this study was

identifying which patients or tumour locations necessitate a specific technical setting, and whether a highly differentiated selection of techniques could offer an individualized monitoring/mapping program for each patient. As the ultimate goal is to achieve maximal resection outcomes without inducing new neurological deficits, we also investigated whether a deliberate omission of certain techniques has consequences for clinical outcomes or resection results. Furthermore, the general strengths and weaknesses of each technique in daily clinical practice were to be elucidated.

Methods

From January 2019 to January 2023, monitoring and mapping data were collected for all patients in whom these techniques were preoperatively planned, along with information on the surgical mode of awake craniotomy, if performed. These data were supplemented with sociodemographic information, neuropathological results, and details of medical/surgical history where applicable. Additionally, clinical data on the neurological status were collected preoperatively, postoperatively, and during follow-up. Another focus of the study was the EOR, involving the determination of RTV, as well as matching the intraoperative evaluation of the surgeons (complete resection yes/no) with postoperative MRI data. Furthermore, surgeons were interviewed postoperatively to assess whether the preoperatively chosen monitoring or mapping technique also proved to be the most suitable technique intraoperatively.

Results

In total, data from 437 procedures involving 400 patients within the defined time frame were included in the study. The majority of operations were conducted for left-hemispheric lesions (54%) and in patients diagnosed with high-grade gliomas[2]. Overall, 53% of the interventions were performed as awake surgeries, primarily due to language mapping. However, there was a notable number of awake craniotomies (n=61) for right-hemispheric tumours, driven by specific

[2]. For this paper, the actual terminologies of the current WHO Classification 5 for diffuse gliomas were utilized. The data collected during the times of the old classification were adjusted according to the new terminology.

clinical questions. Interestingly, under these specific conditions, the awake phases for right-hemispheric cases significantly exceeded the duration of left-hemispheric cases.

SSEP and MEP monitoring were employed in about half of the procedures, indicating that in a substantial number of cases, monitoring was waived in favour of pure mapping. In 79.6% of the surgeries, one of the two mapping techniques (monopolar vs. bipolar) was used. When both mapping techniques were employed, it occurred in 91% of cases during awake craniotomies.

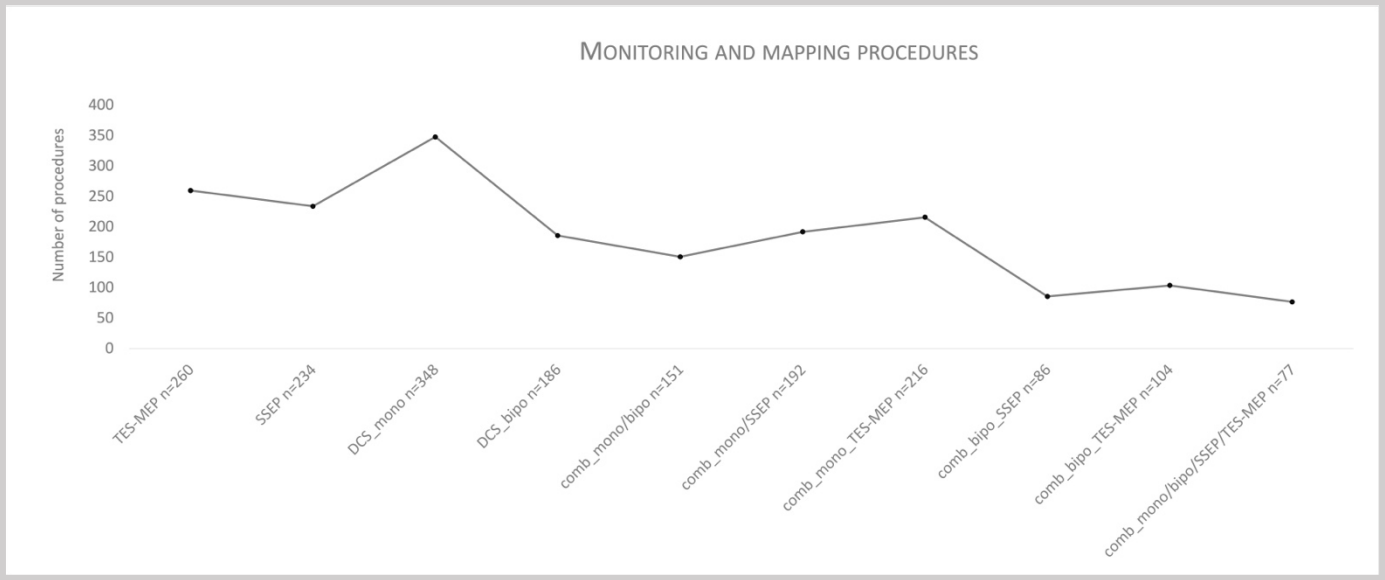


Figure 10: Number of procedures for different monitoring/mapping modes that were used intraoperatively. Mostly monopolar stimulation was used. The combination ("comb") of monopolar and bipolar mapping plus monitoring was the least combination that was used intraoperatively. Figure cited from own publication [98], used under Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.).

The choice of localization had a significant impact only on bipolar mapping, which was expectedly more frequently used for left-hemispheric tumours. The increased application of mapping procedures was evident in the postoperative survey of surgeons. In most cases, it was reported that either a mapping technique or the combination of both techniques was obligatory to achieve the surgical goal. It is noteworthy that only in 10 procedures, the combination of all available monitoring and mapping techniques was deemed obligatory. Three surgeries were ultimately conducted without any application of these techniques, suggesting a preoperative misjudgement of eloquence. SSEP and MEP monitoring were considered obligatory in only 16% of cases, particularly in right-hemispheric lesions in combination with monopolar mapping. The

correlation between tumour location and the postoperatively deemed obligatory monitoring/mapping mode was statistically significant ($p < 0.001$).

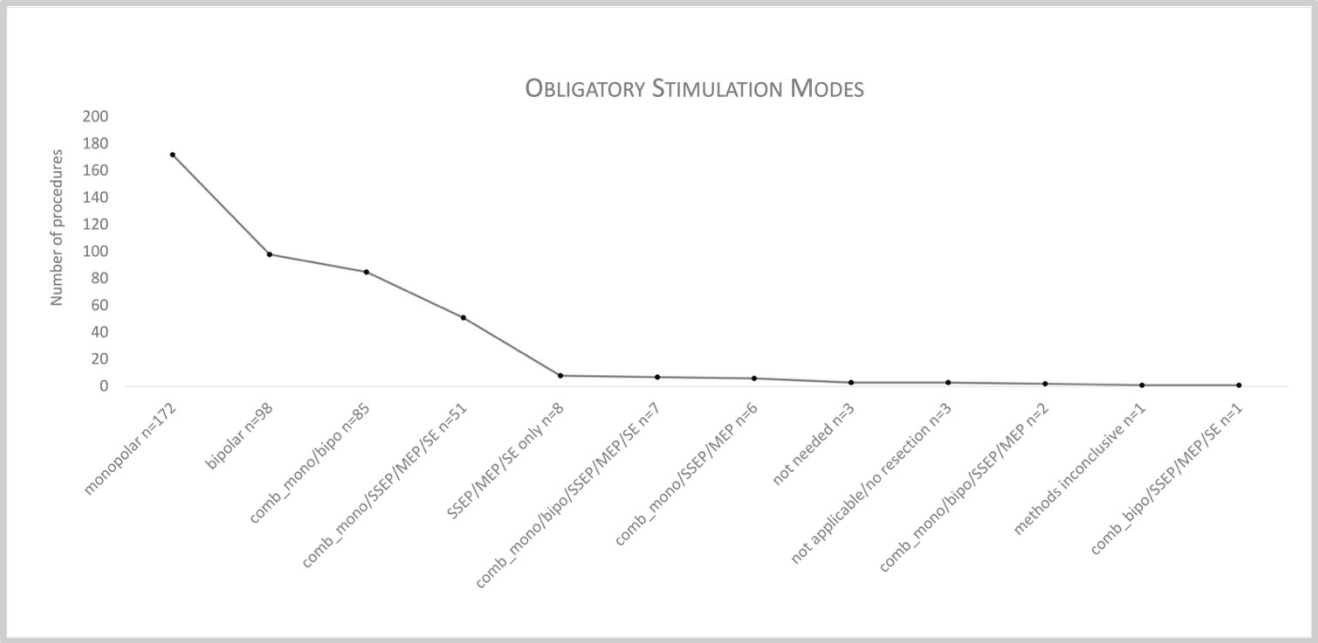


Figure 11: Postoperative evaluation of obligatory mapping or monitoring modes by the operating surgeon. Monopolar, bipolar, and a combination of both mapping procedures were mostly stated as "obligatory" for the preceding surgery. Full technical equipment with a combination of mapping and monitoring was less frequently recalled as obligatory. Figure cited from own publication [98] used under Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.).

Regarding neurological outcomes, a direct postoperative deficit was observed in 13% of patients, but it persisted as a permanent deficit in only 2% of patients after 6 months. The majority of permanent deficits were newly acquired language-associated disorders. The technique deemed obligatory did not correlate significantly with a new neurological deficit.

Concerning resection results, it was interesting to note that in one-third of procedures, a functional limit was reached due to mapping/monitoring, emphasizing the highly functional cohort that was operated on, in those cases a RTV was intentionally left. 50% of procedures achieved the expected complete resection. In procedures where an unexpected RTV was identified, an average of 0.41 ml RTV was recorded, which, according to various studies would correspond to a GTR and should not have a negative effect on overall survival in high-grade glioma according to the literature [36, 91, 99, 100], however we did not obtain data on OS in this study.

Discussion

The study predominantly utilized monopolar stimulation in the majority of procedures. Motor pathway mapping, involving both cortical and subcortical monopolar stimulation, demonstrated no significant differences between lesions in either hemisphere. Bipolar motoric mapping was selectively employed in our clinic, typically in conjunction with monopolar cortical mapping, especially when monopolar mapping revealed MEP responses in multiple gyri or displayed inconsistencies when defining M1. Bipolar mapping was more frequently applied for left hemispheric lesions during language mapping procedures, consistent with standard practices in the literature. However, for language mapping, patients needed to be awake during surgery. The majority of procedures in our cohort were performed with the patient in an awake state, and most lesions were located on the left hemisphere. SSEP monitoring was also more prevalent in left hemispheric lesions, likely influenced by the higher occurrence of lesions in this hemisphere (at least 54% of procedures). 31% of right hemispheric lesions were also operated on with the patient in an awake state. Our group primarily employed monopolar stimulation for right hemispheric lesions during awake surgeries, due to monitoring fine motor skills or complex motor tasks during the procedure.

Regarding resection outcome measured by RTV, our study showed comparable results to other major studies. The same applies to the neurological outcome consistent with the literature, featuring a new neurological permanent deficit in only 2 % of the patients. The postoperative control by investigating the surgeons' view on the feasibility of the chosen monitoring/mapping technique showed that in 73 % of the procedures, the preoperatively defined method matched as obligatory intraoperatively.

The tumour localization was found to correlate with the postoperative surgeons' evaluations, indicating that monopolar obligatory mapping was more frequently deemed essential for right hemispheric lesions, while bipolar mapping and combined monopolar/bipolar mapping were more frequently considered essential for tumours in the left hemisphere. Notably, the necessity for SSEP and MEP monitoring, either alone or in combination with mapping procedures, was seen as obligatory in only 16 % of cases. This percentage increased after the engagement of new monitoring staff, rising from 11 procedures initially evaluated as obligatory to 25 procedures per year. The authors discussed the observed increase, suggesting a potential bias due to the availability of more monitoring staff or an escalation in procedural complexity

involving high-risk vascular involvement. However, despite the rise in obligatory evaluations, there was no observed correlation between the stated obligatory stimulation mode and postoperative neurological outcomes. Interestingly, more incongruence between the evaluated obligatory method and the actual technique used was noted with bipolar mapping. This discrepancy may be attributed to situations where patients with left hemispheric lesions, requiring bipolar mapping due to the tumour's localization, were unable to undergo mapping or adequate testing due to noncompliance with the awake situation or experiencing seizures at the beginning of the procedure.

Conclusion

We concluded that not every patient necessitates the full spectrum of available technical capabilities to achieve favourable resection results under the preservation of neurological function. A meticulous surgical planning, conducted by experienced surgeons, allows for the omission of a standardized comprehensive monitoring concept without drawbacks for the patients. Instead, monitoring and mapping should be individually tailored for each patient.

3. Mapping-only procedures in eloquent brain tumour surgery

Since the beginning of 2019, we have been able to perform solely monopolar (and bipolar) mapping without the need for additional personnel other than the surgeon due to the implementation of a technological advancement. This marked a significant step towards a more personalized approach to intraoperative functional monitoring of patients. Independent of technical or personnel resources, cortical and subcortical mapping could now be conducted autonomously by the surgeon with the omission of bigger technical setups providing IONM. The study results are summarized below, and the original work can be found in Appendix (3).

Resection of Eloquent Located Brain Tumors by Mapping Only—A Feasibility Study

Franziska Staub-Bartelt, Marion Rapp, Michael Sabel, Brain Sci. 2023, 13, 1366. doi.org/10.3390/brainsci13101366

Introduction

As evident from the introduction and the first paper described above, intraoperatively cortical and subcortical mapping of motor and language functions is crucial for ensuring the functional preservation of patients. Bipolar mapping can be performed independently from the described techniques using a so-called Ojemann Stimulator. This is a bipolar stimulator developed according to the specifications of Dr. George Ojemann from the University of Washington in Seattle [101]. The stimulator can be used and adjusted intraoperatively by the surgeon, allowing for autonomous language mapping without the need for external personnel to set up and operate the technical applications. Until the beginning of 2019, there was no equivalent for monopolar mapping. At that time, the C2 Xtend was introduced by the company Inomed (Inomed Medizintechnik GmbH in Emmendingen, Germany). It is a mobile device that allows for cortical and subcortical mapping with monopolar and bipolar stimulation probes. Monopolar mapping is monitored similarly to the large standard devices using an EMG with up to 8 muscles being recorded intraoperatively. The needles used are in accordance with the standard equipment for IONM devices. Eight subdermal needles are attached for EMG, along with a reference electrode in the FZ position and a grounding electrode. All device settings are customizable and can be changed at any time. For bipolar stimulation, only one probe needs to be attached, and the stimulation intensity is then individually determined on the device. It is possible to perform both mapping techniques on a patient without changing the whole technical setup. The setup and intraoperative handling are carried out by the surgeon. The device provides acoustic feedback upon detection, and continuous EMG serves for visual control of MEPs. Our clinic was one of the early adopters, and we commenced data collection in early 2019 to evaluate a pure mapping approach for supratentorial eloquently located tumours.

Methods

The analysis included patients who underwent surgery between 2019 and 2023 using the C2 Xtend and its successor model, the C2 Xplore. The surgical team and neurophysiologists defined standard settings for both mapping techniques which were set on the device. Furthermore, the 8 muscles were defined for motor mapping. Here, standard recommendations were followed, which are also applicable in more elaborate technical setups [70]. The standard set up included monitoring of two face muscles (M. orbicularis oris and M. mentalis), three muscles in the upper extremity (M. biceps brachii, M. abductor pollicis brevis and the hypothenar muscle group) as well as three muscles in the lower extremity (M. quadriceps femoris, M. tibialis anterior and the M. abductor hallucis). For the general cohort description, we collected sociodemographic data and the histopathological diagnosis [3]. Regarding the utilized device, we examined the type of mapping (monopolar/bipolar) and the corresponding stimulation parameters and we additionally collected data on awake surgery. Postoperative MRIs were scrutinized to evaluate surgical success in terms of RTV. Additionally, preoperative, postoperative, and follow-up neurological examinations were incorporated into the study. At the conclusion of each operation, surgeons were asked to assess the applicability of the device. If an inadequate technical setting was postoperatively identified in a case, the reasons for this were documented too. Patients with lesions showing a clear vascular conflict on preoperative MRI were excluded to avoid the need to forgo SSEP monitoring.

[3] For this paper data concerning histopathological classification were also adjusted according to the new WHO 5 classification of diffuse glioma.

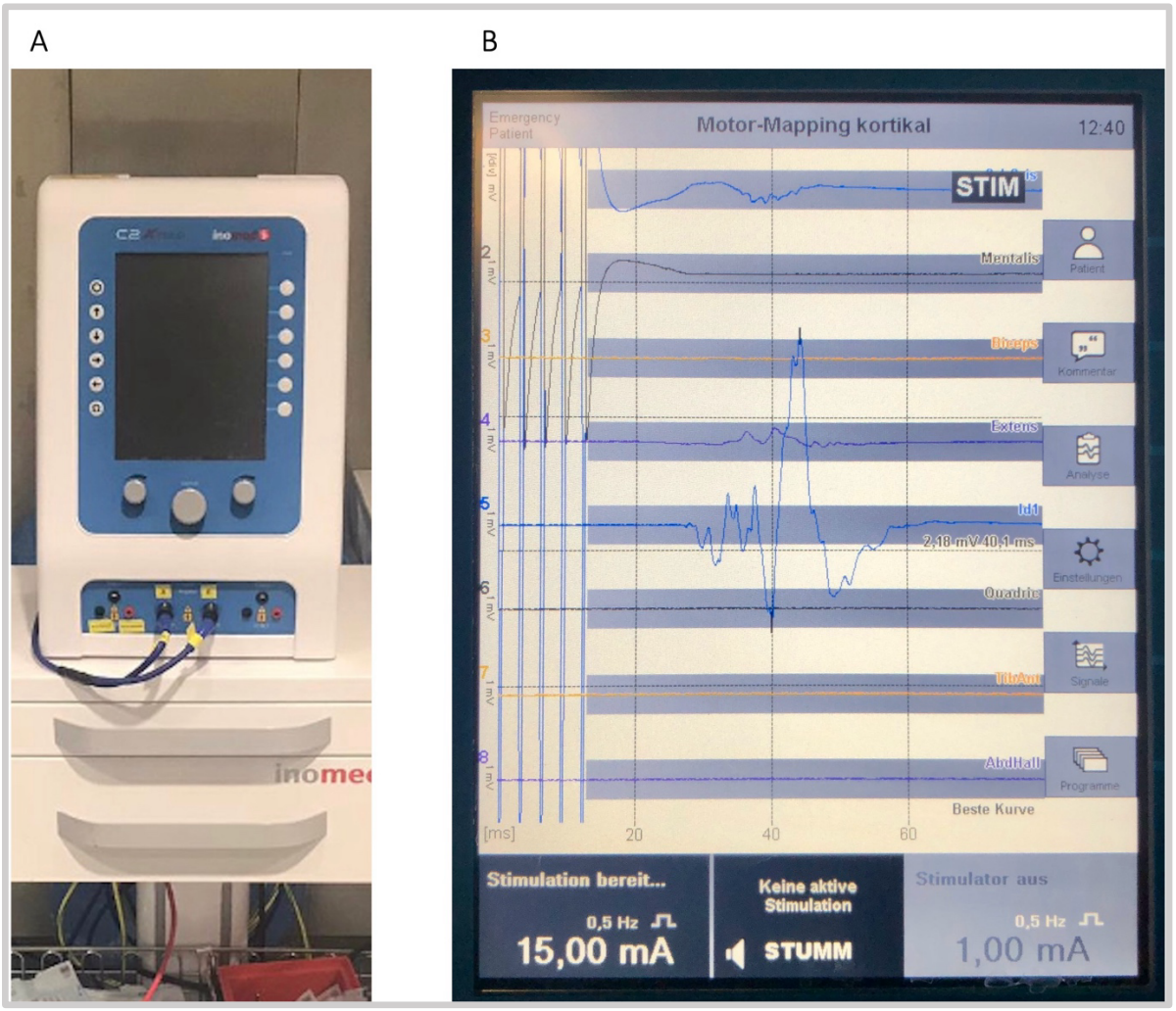


Figure 12:: First generation of mapping device (C2Xtend), B: Screenshot of the intraoperative display under usage of monopolar mapping. Cortical mapping was applied and with 15 mA there were EMG recordings of cMAP of face and hand muscles. Figure cited from own publication [102], used under Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.).

Results

In total, data from 131 patients who underwent 136 surgeries were included in the study. Patients with metastases and high-grade gliomas were equally represented in this cohort. Awake craniotomies were conducted in 53% of the procedures. As expected, lesions located in the left hemisphere were significantly more often operated on under awake conditions. Two cases were intraoperatively evaluated as non-eloquent lesions as there was no positive control in the near area around the localisation. All other cases showed highly functional involvement.

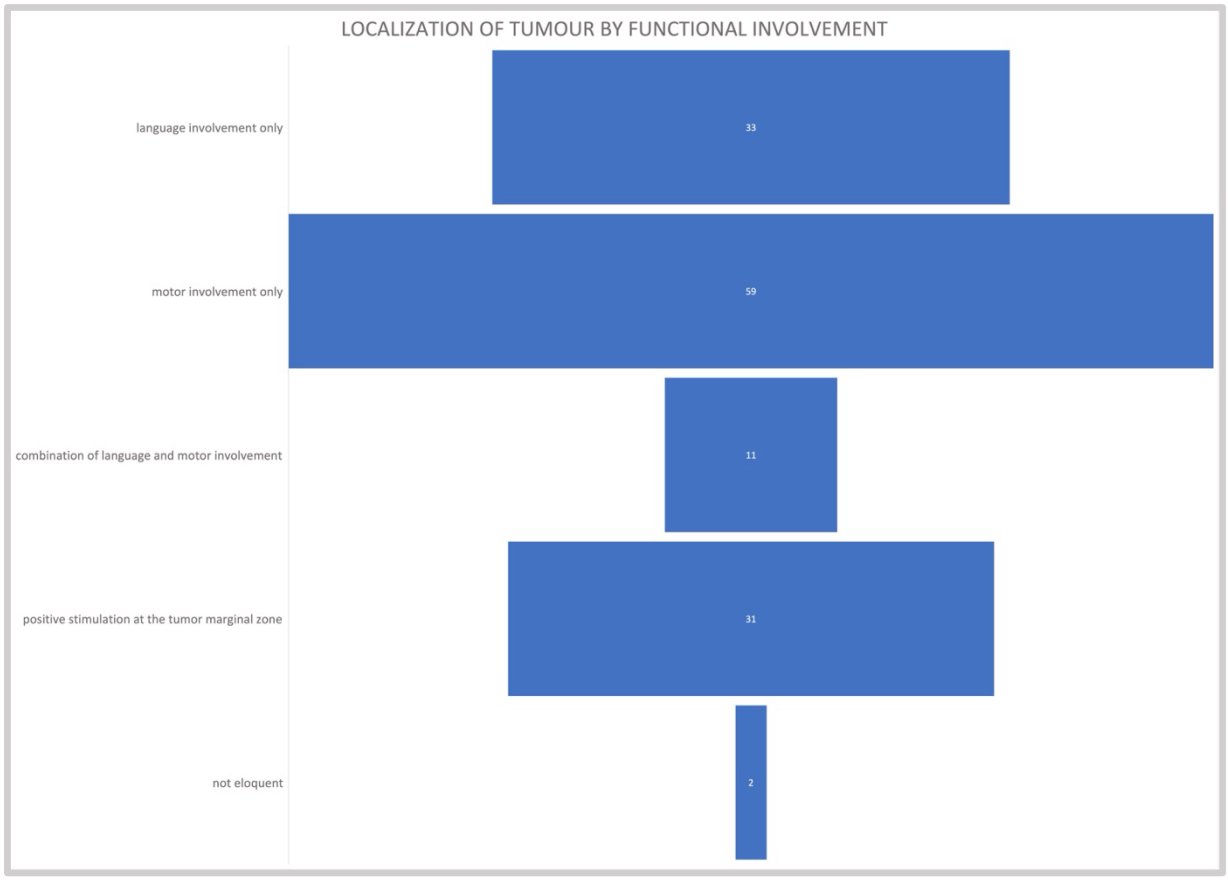


Figure 13: Details of tumour localization concerning the functional involvement, 99% of the lesions that were surgically approached by mapping-only strategy were functionally located. Figure cited from own publication [102], used under Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.).

The technical setup required for the surgery could be independently established by the surgeon in an average time of less than 6 minutes. In over 80% of patients, monopolar mapping was performed, primarily as this was the mapping technique of particular interest for the study. Bipolar mapping was conducted in 42% of cases, and a combined approach was used in approximately 30% of cases. The "mapping-only" strategy was deemed sufficient in 95% of the procedures. A permanent new neurological deficit occurred in 2.2% of the patients. Regarding the resection results, a GTR was achieved in 60% of cases, while in a quarter of patients, a residual lesion had to be left in situ due to the functional limit defined by mapping. This residual volume was estimated as minimal, with 0.47 ml and a maximum finding of 2.8 ml. The chosen mapping procedure did not influence the RTV. Overall, in 95% of the procedures, the mapping-only technique was evaluated as sufficient, which was emphasized by the outcome results of interest- neurological impairment and RTV.

Discussion

Before the introduction of the mapping-only device, the essential monitoring of neurological functionality in patients with eloquent brain tumours could only be achieved intraoperatively through extensive technical setups and external, highly trained personnel responsible for setup, handling, and result interpretation [97]. In the present study, we aimed to examine whether

cortical/subcortical mapping during brain tumour surgeries at functionally eloquent locations is sufficient using a new mapping-only device. According to our data, the device could replace standard technical settings 1:1 in 95% of all procedures. A bias that might have occurred due to non-eloquent lesions that were approached was disclosed by the evaluation of functional localization through mapping results.

The assessment's critical aspect lies in the outcome concerning the EOR respectively RTV and neurological deficits. Regarding EOR and RTV, the mapping-only technique yielded comparable results to other technical settings. While the discussion around the pure GTR rate must be approached carefully, our studies applied a stringent limit of 0.1 ml RTV for GTR. If we were to define the boundaries for GTR based on survival benefits as indicated in other publications,

excluding the subtotal resections due to functional limits, we would have also achieved a GTR rate close to 100%. Hence, we do not perceive a significant disadvantage with the mapping-only technique.

Furthermore, in terms of neurological outcomes, we did not observe adverse results for our patients. Similar studies conducted with combinations of monitoring and mapping have generated comparable outcomes [103, 104].

Conclusion

The combination of monitoring and mapping techniques is widely acknowledged for enhancing safety in brain tumour surgeries. However, our study demonstrates that deviating from the established combined setup by using a mapping-only device can yield comparable results in terms of postoperative deficits and resection outcomes. We've shown that the mapping-only technique is both safe (2% deficit) and efficient, offering a viable alternative for treating eloquently located tumours. Considering its simplicity and affordability, we advocate for the wider availability of mapping-only devices in neurosurgical units, particularly in emergency care or healthcare systems with limited resources for patients with eloquent brain tumours. This could significantly benefit brain tumour patients and improve outcomes, particularly in challenging situations.

4. Special indications of monopolar mapping– emergency resection of eloquent brain tumours

With the newly introduced mapping-only device the surgeon could perform mapping independently from other trained personnel. Thus, new ideas for application in a non-elective setting emerged. The operating surgeons and senior assistants responsible for routine procedures underwent training for the device, leading to the exploration of monopolar autonomous mapping in emergencies for certain patients. Detailed data were collected for two patients experiencing acute tumour decompensation, and these findings were summarized in a publication described below. The original work is included in the Appendix (4) to this study.

Direct Cortical Stimulation in Neurosurgical Emergencies: Single-Center Experience in 2 Patients

Franziska Staub-Bartelt, Björn B. Hofmann, Marion Rapp, Daniel Hänggi, Marcel Alexander Kamp, Michael Sabel

World Neurosurg. (2021) 150:147-152.https://doi.org/10.1016/j.wneu.2021.03.118

Introduction

The significance of intraoperative monitoring and mapping for successful tumour resection in lesions located in highly functional areas has already been emphasized in the preceding pages. However, logistical challenges and the need for a dedicated technician often limit the application of complete IONM and mapping techniques to elective cases. These methods may not be readily accessible in emergencies or neurosurgical departments with limited resources. Nevertheless, identifying eloquent cortical and subcortical structures during emergencies can enhance patient safety and outcomes.

In our clinic, there also is no IONM/mapping on-call service, creating a deficit in resources to perform functional monitoring urgently for patients with conditions affecting the motor system, such as intracerebral haemorrhages or decompensated tumours with a spatial relationship to M1 or CST. During the data collection for the mapping-only device, which was introduced in our

clinic in 2019, non-elective indications were also discussed as the device can be handled by the surgeon alone without any significant delay in patient care. Thus, all responsible surgeons involved in emergency services were trained in handling the device. Subsequently, a few patients presenting urgently with intracerebral haemorrhage or clinically evident decompensated tumour progression were operated on using the mapping device. Data from two tumour patients initially planned for elective resection using IONM and mapping techniques but rapidly deteriorating clinically, were analysed in detail to assess the device's applicability in emergencies.

Methods

The data of patients initially planned for elective IONM/mapping procedures but subsequently operated on in an emergency setting were subjected to a detailed retrospective analysis. The medical history and the course of treatment in the general ward were traced, and existing imaging and neurological findings were scrutinized for abnormalities. Additionally, an evaluation of the intraoperative mapping data was conducted. Due to the emergency nature of the situations, only monopolar mapping data were available, as language monitoring would not be feasible in acutely neurologically deteriorated patients due to the absence of the awake phase. The technical setup was solely managed by the operating surgeon.

Results

Two illustrative cases could be obtained from the data. Both cases showed decompensated GBM patients.

The first patient presented with a history of personality changes, aphasia and latent hemiparesis of the right side. A computed tomography (CT) scan revealed a massive bifrontal oedema and an urgently performed skull MRI confirmed the suspicion of a left hemisphere brain tumour. Due to the tumour’s size, there was compression of normal brain structures, causing a midline shift of more than 2 cm. Urgent tumour resection was discussed, and it was deemed mandatory to include monitoring and mapping due to the anticipated proximity of the lesion to motor pathways in the dorsal area. Awake surgery was obsolete due to the pre-existing aphasia. Later in the evening of admission, the patient exhibited a deterioration in vigilance requiring

intubation. An urgent indication for tumour decompression was established, and conducted with the assistance of the mapping device. Subcortical monopolar stimulation was applied up to 0.3 ms at the dorsal resection margins, confirming the tumour's immediate proximity to the Corticospinal tract (CST). The postoperative MRI revealed a minimal RTV at the dorsal resection margin, measuring < 2 ml. Neurologically, the patient was able to mobilize independently in the short term, with the aphasia not completely regressing, yet basic communication became possible.

In the case of the second patient, an initial diagnosis revealed a large right hemispheric mass with a massive oedema. Primary symptoms included left-sided hemiparesis and sensory disturbances. During the perioperative period, the patient presented with an acute decrease in vigilance. An immediate CT scan showed bleeding into the tumour with a progressive mass effect. Initially, the surgery addressed bleeding relief, followed by cortical and subcortical mapping (up to 2 mA). Tumour tissue here also demonstrated immediate proximity to the CST. Given the preservation of function, a complete resection was not possible. The postoperative MRI confirmed the expected residual volume (4.2 ml). Neurologically, the patient fully recovered, with, at most, a discreet residual limitation of the left leg at discharge.

Discussion

We here outlined a setup designed for eloquent tumour resection under monopolar mapping in emergency scenarios, particularly when the assistance of a clinical neurophysiologist is unavailable. Our approach involved the application of monopolar motor mapping in two patients with eloquently located pathologies to enhance resection safety regarding postoperative neurological deficits under emergency conditions. Notably, both patients experienced no new neurological deficits postoperatively. While the benefits of IONM are well-established, its use in emergencies is not standard in most neuro-oncological departments, primarily due to the need for specialized training, external staff and time-consuming setup associated with standard IONM devices. Our setup, in contrast, empowers surgeons to autonomously leverage direct brain mapping advantages, facilitating the use of direct cortical and subcortical stimulation beyond conventional surgery settings. Monopolar stimulation setup takes minutes and the mapping procedure can be conducted without third-party involvement.

Conclusion

In the light of emergency tumour resection, there is a notable lack of comparable literature. Our findings demonstrate that the resection of highly eloquently located tumours in acute emergencies, utilizing a mapping-only device, can be carried out without inducing new neurological deficits in the patients. Consequently, we have inferred that in emergencies, wherein standard IONM/-mapping may not be feasible, compact mapping-only devices can serve as valuable tools for monopolar motor mapping. This approach facilitates a safe and controlled resection, even in emergencies where standard IONM may not be practically applicable.

5. Impact of different intraoperative monitoring and mapping procedures on PFS and OS on patients diagnosed with high-grade glioma

When discussing the use of technical tools for resection, then as previously described, they are primarily employed to enhance safety and the outcome of the resection. Associated with resection as a therapeutic target, there is always the question of a survival advantage for patients. In the following study, data from 14 years of operative occupation in our clinic were analysed, incorporating over 600 patient records. As we gradually introduced various monitoring and mapping techniques throughout this period, we were able to examine the impact of each technique on the PFS and OS of GBM patients. The original work is included as an appendix to this manuscript (5).

Establishment of different intraoperative monitoring and mapping techniques and their impact on survival, extent of resection and clinical outcome in patients with high-grade gliomas - a series of 631 patients in 14 years

Franziska Staub-Bartelt, Marian Preetham Suresh Babu, Andrea Szelényi, Marion Rapp, Michael Sabel, Cancers 2024, 16, 926. doi.org/10.3390/cancers16050926

Introduction

GBM is the most aggressive form of glioma and is associated with the worst prognosis amongst glioma tumour entities. As described in the introduction at the beginning ongoing research seeks novel treatment strategies to extend the OS period and enhance the QoL for patients. However, despite maximum treatment efforts, GBM recurrence following surgical resection is nearly inevitable, and its management is often case-dependent. The standard of care was described in detail at the beginning, in summary, resection followed by radiation and chemotherapy still are the standard approaches. Surgical excision is challenging due to the infiltrating nature of GBM, but maximizing tumour resection is crucial for prognosis. The demand for intraoperative techniques preserving neurological integrity under maximization of resection results has led to the establishment of procedures like IONM and mapping procedures either with or without an awake approach during brain tumour resection.

As our department has implemented these techniques one by one over some years, a dataset of 1010 patients could be retrospectively screened as part of a doctoral thesis for in- and exclusion criteria. We excluded patients under 18 years old and patients who underwent primary surgery in an external hospital. Furthermore, if we could not obtain any clinical data, patients were also excluded, additionally, at least one follow-up had to be documented for inclusion. Lastly, retrospective analysis was conducted on data from 631 patients, who underwent surgery between 2004 and 2018 at our department. We focussed on analysing implemented monitoring techniques at different time points, that may influence the preservation of neurological functionality and assess whether intraoperative neurophysiological monitoring or mapping techniques significantly contributed to improving PFS and/or OS in patients with GBM or IDH-mutated astrocytoma WHO grade 4 [4].

Methods

A systematic analysis was conducted on data from patients who underwent primary surgery at the Neurosurgery Department of University Hospital Düsseldorf between January 1, 2004, and December 31, 2018. A subset of patients with diagnoses of GBM and IDH-mutated astrocytoma

[4] Again, for this publication, histopathological diagnosis was adjusted according to the new WHO 5 classification of diffuse glioma.

WHO grade 4 was selected as the target cohort, resulting in a cohort of 1010 patients. After applying the exclusion criteria, a cohort of 631 eligible patients for statistical analysis remained. Then the cohort was divided into two subgroups, one group comprised patients undergoing biopsy (n= 150) and the second group included patients who underwent resection (n= 481). To evaluate the influence of each monitoring/mapping technique the resection cohort was further divided into subgroups according to the technique used (table 1).

Monitoring/mapping technique	Description	Implemented since	N =
SP-O	surgical procedure only with no added monitoring and/or mapping modalities	n.a.	160
AWAKE-bipolar	awake craniotomy for 60-Hz bipolar stimulation (language monitoring)	2007	71
IONM-monopolar	surgery under general anaesthesia under usage of SSEP, MEP and EEG monitoring and additionally monopolar mapping	2010	145
AWAKE-IONM-mapping	this method incorporated all techniques- awake craniotomies with monitoring of SSEP and MEP as well as mapping procedures via bipolar and monopolar stimulation with focus on bipolar mapping for speech and language assessment and monopolar mapping for motor control	2010	105

Figure 14: Description of resection subgroups according to the specific monitoring/mapping technique that was used. *Figure cited from own publication [105], used under Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.).*

To evaluate the impact of those techniques on PFS and OS, PFS was determined by evaluation of RANO criteria for high-grade glioma in the post-operative and follow-up MRIs [106][5]. The

[5] The RANO criteria have been updated recently to consolidate the advancing knowledge of recent years, and are now summarized in a comprehensive new guideline. (Wen et al., RANO 2.0: Update to the Response Assessment in Neuro-Oncology Criteria for High- and Low-Grade Gliomas in Adults, J Clin Oncol. 2023 Nov 20;41(33):5187-5199. Doi: 10.1200/JCO.23.01059. Epub 2023 Sep 29.) However, during data collection the cited version was used for assessment.

date of the MRI was set as a diagnosis of progress if applicable. OS was calculated from the individual death data of the patients. Verification of the date of death was carried out through screening the local patient data management system, registering queries, or communicating with patients' families, adhering to local ethics approval. Furthermore, we collected data on clinical outcomes measured by the National Institutes of Health Stroke Scale (NIHSS) and KPS and resection results for the different groups. The impact of adjuvant therapies was also investigated as a confounding factor for PFS and OS within each group.

Results

A year-wise analysis of technical settings was conducted to understand the changes in surgical approaches over time. Awake surgeries with 60-Hz stimulation were introduced in 2007 and steadily increased until 2011. The combination of IONM with monopolar stimulation and awake surgeries with IONM and mapping procedures became the institutional standard after 2010. Towards 2011 SP-O as surgical approach decreased considerably (figure 10). The chi-square test indicated a significant decrease in biopsies and a simultaneous increase in AWAKE-bipolar, IONM-monopolar, and AWAKE-IONM-mapping surgical settings after 2010 ($p < 0.001$).

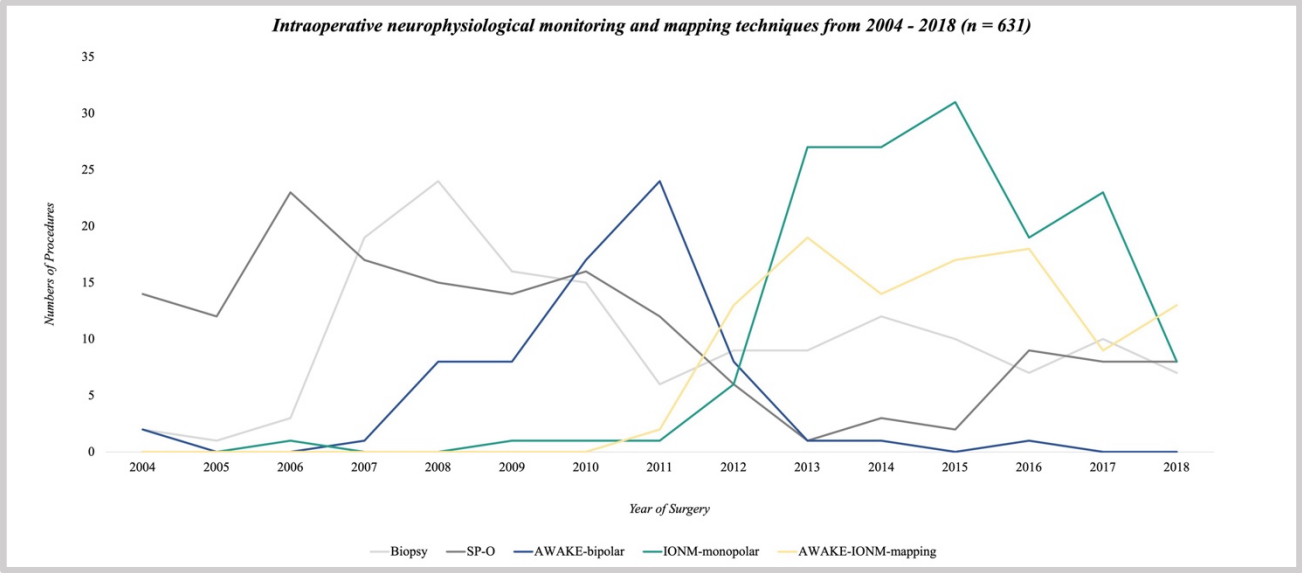


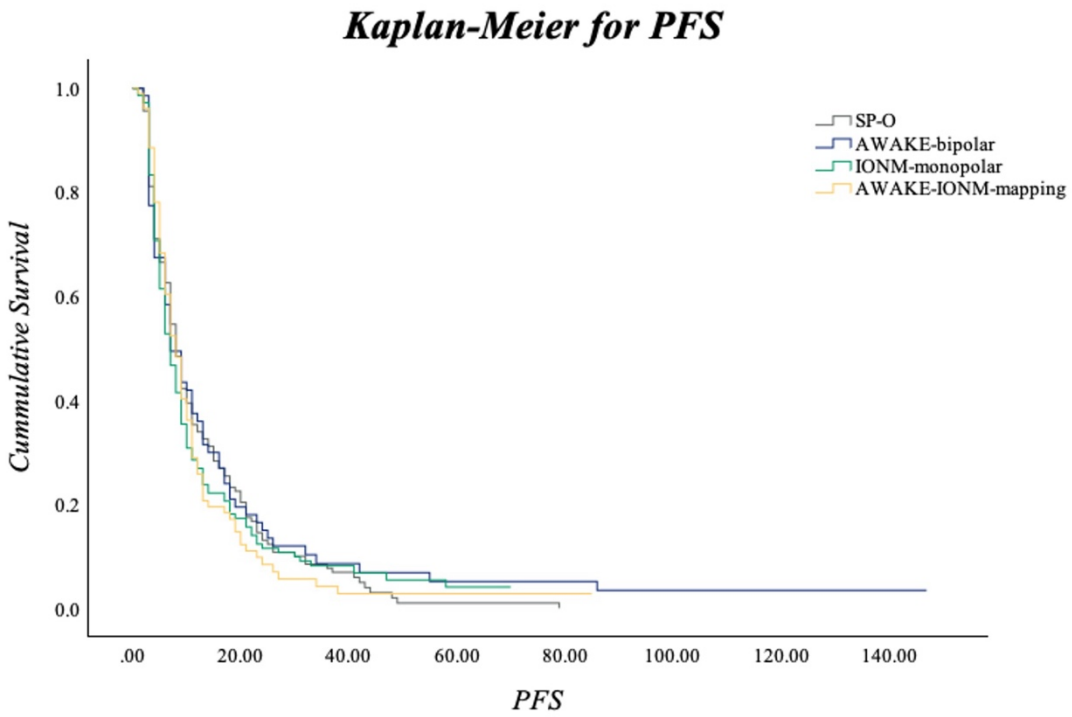
Figure 15: Line graph of patients enclosed in the analysis (n = 631) divided by technical settings from 2004–2018. Figure cited from own publication [105], used under Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.).

The proportion of eloquent surgeries increased to the total number of operations over the observed period (before and after 2010). SP-O group was the only subgroup with non-eloquent tumours. All other groups only included lesions located eloquently (eloquent tumours before 2010 64.7 % & 90.4 % after 2010).

The mean EOR of the cohort was 96% and it did not show a significant difference when analysed separately for the years before (2004-2009) and after (2010-2018) the introduction of all IONM and mapping techniques (mean EOR before 95%, mean EOR after 96%). Additionally, the mean RTV in the cohort was calculated (1.38 ml [± 4.16 SD]). The RTV measured in the postoperative MRI was lowest in the AWAKE-IONM-mapping group (0.9 [±4.2]) and highest in the SP-O group (1.93 ml [5.0]). However, the comparison of both techniques did not reach statistical significance.

Concerning short-term neurological outcome parameters measured by NIHSS and KPS, we saw no difference in the median values for NIHSS and KPS for the whole cohort. However, when comparing subgroups of monitoring/mapping techniques with the SP-O group, we found a significantly higher NIHSS in the AWAKE-bipolar group postoperatively and at 3 months follow-up and a significantly lower KPS at both time points postoperatively and at three months. Also, in the monitoring/mapping intergroup comparison, the AWAKE-bipolar group showed significantly higher NIHSS. KPS at three months follow-up was increased in patients operated by IONM-monopolar and AWAKE-IONM-mapping conditions compared to the SP-O group.

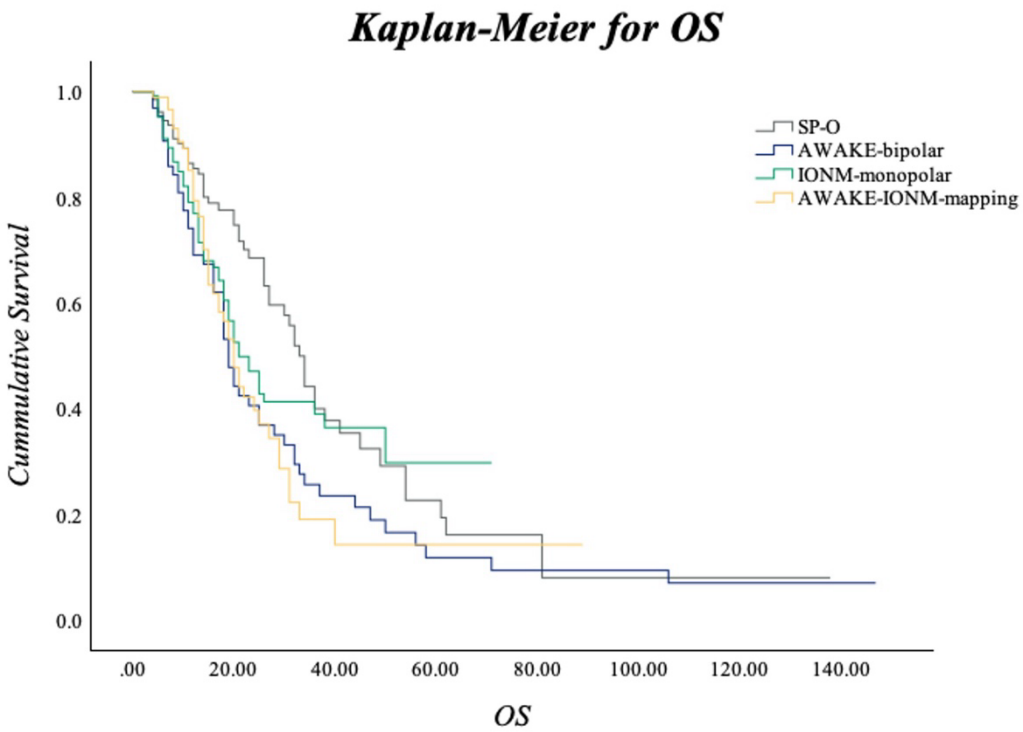
The long-term outcome parameters PFS and OS were evaluated by calculating Kaplan-Meier survival curves. They were plotted for different operative settings, showing no significant difference in PFS but a significantly increased OS for patients in the SP-O group. The single monitoring or mapping procedures did not influence the OS significantly.



Intraoperative technical setting	Median		95% Confidence Interval	
	Estimate	Std. error	Lower Bound	Upper Bound
SPO-O	8.0	.595	6.834	9.166
AWAKE-bipolar	7.0	1.210	4.629	9.371
IONM-monopolar	7.0	.635	5.755	8.245
AWAKE-IONM-mapping	8.0	.739	6.552	9.448
Overall	8.0	.374	7.266	8.734

Intraoperative technical setting	Total N	N of Events	Censored	
			N	%
SPO-O	160	145	15	9.4
AWAKE-bipolar	71	65	6	8.5
IONM-monopolar	145	127	18	12.4
AWAKE-IONM-mapping	105	94	11	10.5
Overall	481	431	50	10.4

Figure 16: Kaplan-Meier curve for PFS for the cohort with median PFS for all subgroups, number of events and number censored in the footnotes. There was no significant difference concerning intraoperative mapping or monitoring techniques in PFS (p = 0.749). Figure cited from own publication [105], used under Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.).



Intraoperative technical setting	Median		95% Confidence Interval	
	Estimate	Std. error	Lower Bound	Upper Bound
SPO-O	33.0	1.988	29.104	36.896
AWAKE-bipolar	19.9	1.385	16.285	21.715
IONM-monopolar	21.0	2.143	16.801	25.199
AWAKE-IONM-mapping	20.0	1.560	16.942	23.058
Overall	23.0	1.565	19.933	26.067

Intraoperative technical setting	Total N	N of Events	Censored	
			N	%
SPO-O	160	66	94	58.8
AWAKE-bipolar	71	55	16	22.5
IONM-monopolar	145	63	82	56.6
AWAKE-IONM-mapping	105	50	55	52.4
Overall	481	234	247	51.4

Figure 17: Kaplan-Meier curve for OS for the cohort with median OS for all subgroups, number of events and number censored in the footnotes. There was an increased OS in patients that underwent surgery in SP-O technique (p = 0.034). Figure cited from own publication [105], used under Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.).

Discussion

The standards for surgical treatment of GBM have undergone substantial evolution, particularly in intraoperative monitoring and mapping techniques, as observed in our study spanning from 2004 to 2018. Three distinct phases were identified: at first there was no monitoring until 2007, then the introduction of awake craniotomies with bipolar stimulation followed in 2008, and at last, there was the incorporation of IONM and mapping as a combined procedure in 2010, subsequently utilizing all techniques as a combined approach. The study aimed to assess the impact of these monitoring and mapping methods on both immediate neurological outcomes and long-term prognosis in patients with eloquently located GBM. Awake craniotomies with bipolar mapping were initially introduced for functional monitoring in eloquent tumour resection to preserve neurological function, particularly for language control. As discussed before, various studies have demonstrated improved outcomes highlighting the significance in preserving, particularly language functions, by awake surgery with combined mapping. In our study interestingly the AWAKE-bipolar group exhibited contrary results with an increased NIHSS and reduced KPS postoperatively, particularly in lesions located in the parietal lobe. We assumed that the absence of monopolar mapping for potential motor eloquent areas over a long period was responsible for this phenomenon. As at the time point of implementation and involving both- IONM and mapping techniques, the AWAKE-IONM-mapping group did not show higher postoperative NIHSS.

The introduction of combined monitoring/mapping approaches at our department led to a significant decrease in biopsies and an increase in surgical excision of eloquent tumours. Despite these changes, no significant impact on PFS or OS was observed in our cohort for the monitoring/mapping subgroups compared to the SP-O group. Studies assessing awake craniotomy and mapping on OS have reported mixed results, and our findings align with the absence of significant differences in PFS and OS between different technical settings. The side analysis investigating EOR and residual tumour volume (RTV) did not show significant differences between technical settings, possibly due to the increased eloquence of tumours and subtotal resections due to functional limits that were seen when using monitoring/mapping techniques. This present retrospective study spanning 14 years has important limitations that need to be addressed for better contextualization. Major issues in data collection were changes in documentation forms and standards over time. Furthermore, the introduction of advanced

surgical technologies, fluorescence techniques and evolving surgical approaches may introduce a bias into the surgical, particularly resection data. Additionally, the study's limited sample size and imbalances between groups made comprehensive comparisons challenging.

Conclusion

Various publications have advocated for the utilization of IONM, mapping and awake craniotomies in patients with GBM, typically in smaller patient cohorts. However, our study represents a unique contribution as, to our knowledge, no analysis of comparable cohort sizes has explored the influence of different intraoperative monitoring and mapping techniques on PFS and OS. We found that the incorporation of awake surgeries, IONM, and mapping techniques coincided with a significant reduction in the number of biopsies and a significant increase in eloquent localization of resected lesions. This substantial decrease in biopsies suggests a notable enhancement in the operability of eloquent tumours following the implementation of those intraoperative techniques. Consequently, we emphasize employing these methodologies, that facilitate the safe resection of eloquent GBM with an acceptable level of post-operative morbidity, even though our study did not reveal a significant impact of these various surgical monitoring and mapping techniques on PFS and OS within our large cohort.

6. Awake craniotomy as an indispensable monitoring setting in patients with (language-) eloquent tumours and its influence on the psychooncological burden of brain tumour patients

When considering the indication for an awake surgery, which generates the maximum functional monitoring level during an operation, it should be critically discussed on a highly individual basis for each patient. Various factors, as previously mentioned, should be taken into account and it's not just about intraoperative compliance. The potential effects in the realm of distress, anxiety, and depression resulting from such intraoperative procedures have not been systematically studied for a long time. As in our department, about 50% of the procedures that require monitoring/or mapping during resection are performed as awake craniotomy, we aimed to gain insights beyond a surgical outcome. Therefore, we compared psycho-oncological screening data from patients undergoing awake surgery with data from patients undergoing surgery under general anaesthesia to scale the burden such an awake procedure might have on these already "burdened-by diagnosis" patients. The original work is also available in the appendix (6).

Impact of Anticipated Awake Surgery on Psychooncological Distress in Brain Tumor Patients

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Front. Oncol. 11:795247. Doi: 10.3389/fonc.2021.795247

Introduction

The study addresses the heightened risk of distress, anxiety, and depression in cancer patients, particularly in neurooncological cases, where distress prevalence ranges from 38% to 52% [107]. Approximately one-fourth of cancer patients experience depression or depressive symptoms, with a reported prevalence of 21% in brain tumour patients, assumed to be higher than other cancers. Increased distress, anxiety, and depression correlate with a reduced quality of life (QoL) and decreased OS. Psychological distress is associated with higher cancer mortality, particularly in patients with high-grade gliomas. Longitudinal analyses indicate heightened

distress, especially perioperatively during hospitalization for neurooncological patients. Thus, perioperative screening is crucial for timely psychooncological support.

The primary surgical goal in neurooncological patients is, as described before, the maximal aggressive tumour resection without causing permanent neurological deficits. Advances in surgical techniques, such as neuronavigation, fluorescence-guided surgery and IONM/mapping technique have improved outcomes. Awake surgery in patients with eloquent lesions is known to maximize resection extent, improving outcomes while reducing risks for postoperative deficits [108, 109]. However, it is unclear if this anticipated technique causes additional distress for neurooncological patients. The study aimed to determine whether the anticipation of awake surgery negatively impacts distress, anxiety, depression and QoL compared to patients undergoing surgery under general anesthesia.

Methods

The inclusion criteria for this analysis involved patients aged >18 years diagnosed with a brain tumour, electively admitted for tumour surgery at the neurooncological department. Included patients had to have completed a preoperative dataset for distress and QoL assessment. Due to the retrospective study design, questionnaire completion varied, leading to heterogeneity and partial missing data. To ensure uniformity and reliable analyses, only patients with a complete psychooncological screening assessment were included. The analysis further categorized patients based on resection modality (awake vs. general anaesthesia) and explored the impact of primary or recurrent surgery. Screening assessments were conducted through tablet-based self-assessment, administered 1–2 days preoperatively during hospitalization, following brief instruction by medical staff. The used screening assessments were the National Comprehensive Cancer Network (NCCN) distress thermometer (DT) with a cut-off score of 5 and above as indicator for distress [110]. Furthermore, the Hospital Anxiety and Depression Scale (HADS) was administered. The 14-item self-report questionnaire is designed to assess anxiety and depression. It comprises seven items targeting anxiety (HADS-A) and seven for depression (HADS-D). A cut-off score of >8 is considered optimal for sensitivity and specificity in identifying anxiety disorders in patients [111]. In addition, we assessed QoL by using a disease-specific questionnaire for brain tumour patients, designed by The European Organisation for Research and Treatment of Cancer (EORTC).

Results

A total of 54 patients could be enclosed in the study. 35 patients underwent awake surgery and 19 patients were operated in GA. In the awake patient cohort 62.86% of the patients indicated to experience subjective increased distress, compared to 52.63% in the general anaesthesia (GA) cohort. Additionally, anxiety was reported by 17.14% of awake patients and 31.58% of GA patients, and depression by 14.29% of awake patients and 15.79% of GA patients. Prevalence of distress (p=0.465), anxiety (p = 0.223) and depression (p = 0.882) between both groups did not differ significantly.

The questionnaires revealed a mean score of 5.69 for DT in the awake surgery group and 6.26 for GA surgery, with no significant difference between the two groups (p = 0.668). The mean HADS-A and HADS-D scores did also not significantly differ between awake and GA groups (anxiety p = 0.682; depression p = 0.630).

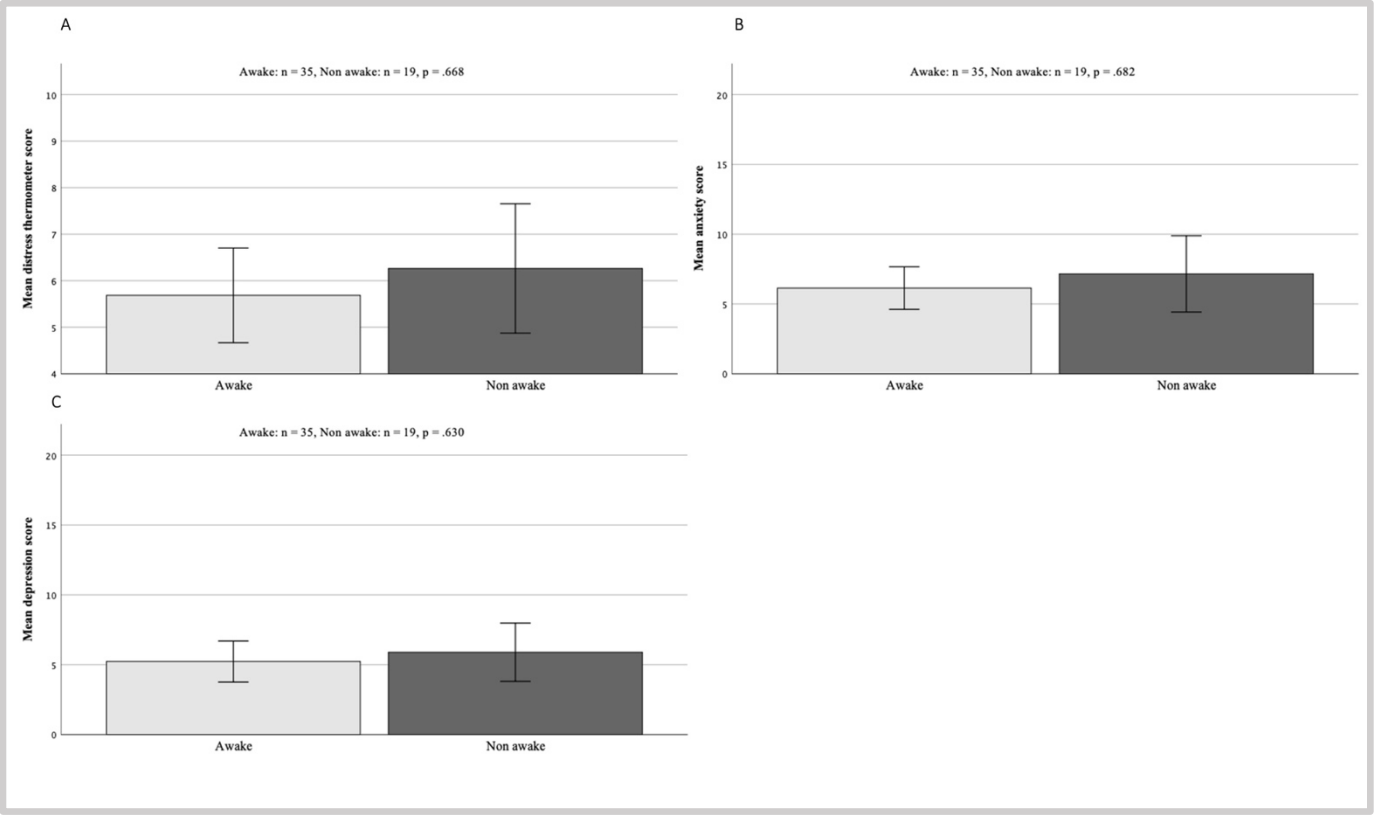

Figure 18: Mean cohort scores for DT (A), HADS-A (B) and HADS-D (C) divided into subgroups of awake and non-awake surgery. Results showed no significant differences in both subgroups (A, p = 0.668, B, p = 0.682, C, p = 0.630).Figure cited from own publication [112], used under Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.).

Recurrent surgery tended to show increased distress more often (76.47% vs. 51.35%) and demonstrated higher scores for both anxiety and depression. Analyses of global health status and future uncertainty from the EORTC QoL questionnaire did not show significant differences between awake and GA surgery (future uncertainty p = 0.436; global health status p = 0.943).

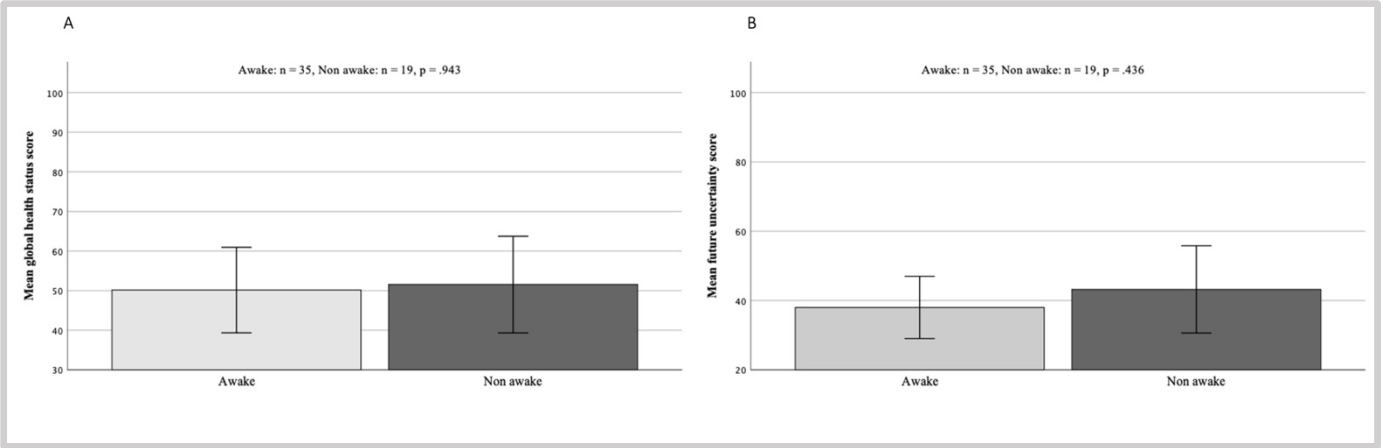

Figure 19: Mean cohort scores for global health (A) and future uncertainty (B) again divided into subgroups of awake and non-awake surgery. Again, results showed no significant differences in both subgroups (A, p = 0.943, B, p = 0.463). Figure cited from own publication [113], used under Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.).

In this case, recurrent surgery had no significant impact on these parameters, however an overall decreased global health status was observed in the recurrent surgery patient cohort.

Regarding need for psychooncological support, 27.78% of patients accepted additional support, with no significant differences observed between awake and GA surgery or recurrent and primary surgery groups.

Discussion

In the context of awake surgery being a major opportunity for safe resection eloquently located tumours, concerns arise about potential negative psychological impacts on neurooncological patients already at risk for distress, anxiety, and depression. This study aimed to comprehensively assess the preoperative psychological status of patients undergoing awake surgery compared to those under GA. The data indicate that patients undergoing awake surgery for cerebral lesions do not exhibit higher distress, anxiety, or depression preoperatively than those undergoing surgery under GA. Recurrent surgery, however, showed an additional impact on increased distress. While only limited data exist on the psychooncological impact of anticipated awake surgery, this study, with its detailed preoperative preparation and screening, demonstrates no significant negative influence on patients. Contrary to preoperative screening results, postoperative screening outcomes also reveal no major negative impact of awake surgery on patients.

Despite the positive outcomes, the study acknowledges the major limitation is, that only a small cohort could be enclosed. This was due to restrictive inclusion criteria and the exclusion of approximately 75% of screened patients because of missing single questionnaire items. However, this analysis stands as the first comprehensive psychooncological screening in patients undergoing brain tumour surgery under awake or non-awake conditions. The study emphasizes the importance of awake surgery, offering intraoperative monitoring benefits and underscores that, with thoughtful preparation and monitoring, awake surgery does not negatively impact patients. The positive effects, such as an increased EOR and OS, outweigh potential concerns. However, the indication for awake surgery should be carefully considered for each patient, taking into account the detailed preparation and close monitoring to ensure a positive experience without harm.

Conclusion

The study findings indicate that the anticipation of awake surgery does not significantly increase distress, anxiety, or depression in patients before brain tumour surgery. Thus, surgeons can anticipate their patients undergoing awake surgery without causing additional psychooncological distress. The recommendation for awake surgery is emphasized when the expected localization of the cerebral lesion involves eloquent areas, as it enhances patient

safety. Although the observed results regarding patients undergoing recurrent surgery were not statistically significant, there is a tendency for increased distress in this specific situation. In such cases, early contact with professional psychooncologists is recommended to address potential psychological challenges associated with recurrent surgery.

IV Discussion

1. Illustration of the importance of resection in a dedicated cohort of patients with high-grade tumours

The findings of the incorporated study concerning the potential compensation of residual tumour volume by a molecular genetic factor positively evaluated in the literature underscores the importance of achieving maximal resection outcomes in patients with high-grade intracranial tumours. We have demonstrated that even under optimal molecular genetic conditions for therapy response, subtotal resection remains an irreconcilable disadvantage. Understanding this is crucial when further investigating the works listed as the basis of the thesis and exploring strategies to maximize resectability in predominantly high eloquent location tumours

2. Assessment of technical setup and personnel resources &

3. Evaluation of monitoring/mapping for an individual approach

With our studies, we were able to demonstrate in a standard setup that this may not be necessary for every patient. The technical availability does not necessarily dictate a corresponding indication. In a large cohort of 437 procedures on highly functionally located tumours, mapping techniques were seen as relevant for achieving the surgical goal in the majority of procedures, with monitoring considered obligatory in only a fraction of surgeries. Of course, the importance of monitoring techniques should not be negated; they particularly contribute to additional assurance in cases of neurovascular conflicts and should be generously indicated in such cases. However, if neurovascular conflicts can be excluded through preoperative planning, the personnel and technically demanding monitoring can be omitted, provided that the technical capabilities for mapping-only procedures are present. According to our data, this can be done without compromising resection outcomes or resulting in poorer neurological outcomes compared to the literature. This is crucial, especially since IONM requires highly trained personnel in addition to the surgeon for setup, intraoperative operation

and ultimately, evaluation. The effectiveness of IONM is contingent on the competence of the technical operator, applying equally to preparation, execution, and analysis. These factors should be considered in the decision-making process. An individualized monitoring/mapping concept, conceptualized preoperatively for each patient based on preoperative assessments, should be the goal for high-output clinics that can also benefit from more efficient utilization.

4. A mapping-only device in eloquent brain tumour surgery &
5. Motor mapping emergency resection and its outcome

Starting in the spring of 2019, we were able to examine the hypothesis that, with proper indication, IONM could be omitted without compromising resection outcomes and neurological outcomes Introducing a mapping-only device allowed us to investigate the practical technical applicability by the surgeon during surgery and assess outcome parameters related to resection results and neurological outcomes in a subcohort of patients with eloquently located tumours. We observed that, with appropriate indication, a mapping-only device is comparable to larger technical setups, considering that IONM is not possible with this device. The practicability and adequacy were confirmed by the surgeon in 95% of the operations.

Regarding the EOR respectively RTV and neurological outcomes, we achieved comparable results to other cohorts with combined approaches. These positive initial findings after the introduction of the mapping-only device led us further to explore the specific indication for emergency mapping. Here, we obtained significantly positive results in patients presenting with either intracerebral bleeding or decompensated tumour events. This is particularly encouraging as active monitoring, such as awake surgery, is not feasible in neurologically compromised patients, and most clinics lack specially trained personnel on-call to operate monitoring devices during emergency procedures. Additionally, the setup of the mapping-only device is significantly faster and more compact compared to larger setups.

Overall, our studies summarized in this thesis, demonstrated the utility of the mapping-only approach for both elective and non-elective indications, specifically for highly functionally located tumours, without compromising quality for the patient.

6. Impact of monitoring and mapping techniques on PFS and OS in GBM

GBM is the most common brain tumour in adults and is considered inadequately treatable. Despite diverse efforts in exploring new therapeutic approaches, life expectancy remains significantly compromised. The literature consistently indicates a clear correlation between the EOR or RTV and the survival of GBM patients. Intraoperative monitoring - and mapping techniques aim to maximize the EOR, particularly in patients with highly functionally located lesions. Therefore, a subset of this study focused on examining the impact of various intraoperative neuromonitoring- and mapping techniques on PFS and OS in GBM patients. Conducting a subgroup comparison over a 14-year period during which these techniques were gradually introduced, no significant survival advantage was observed in groups employing monitoring or mapping techniques. While the EOR showed a minimal increase with the application of these techniques, statistical significance was not achieved. However, a significantly higher number of eloquently located lesions were operated on, potentially influencing the obtained results, as in some cases only subtotal resection could be achieved due to functional limits. Additional factors are extensively discussed in the summary. Nonetheless, the overarching conclusion, as demonstrated by other studies described in this thesis, is that the benefits of IONM and mapping for patients at risk of new neurological deficits due to surgery are substantial. In many cases, the introduction of these techniques has been crucial for achieving resectability, even though a direct significant impact on OS could not be demonstrated in this context in our cohort.

7. Awake surgery and its impact on psychoncological outcome in patients with malignant brain tumour

Awake surgery presents a unique situation for both the patient and the neuro-oncological surgeon. Much has been investigated regarding indications, inclusion and exclusion criteria and the possibilities arising from intraoperative testing during awake surgery. Awake surgery, as the maximal variant of patient monitoring, is now an integral part of everyday neurosurgical practice, especially in the context of language and the increasingly explored neurocognitive monitoring. In our clinic, awake surgery is a standard procedure and is performed in over 50% of patients with an indication for intraoperative monitoring- or mapping procedures. As we perform awake surgery weekly, the particular question arose whether patients, already known to be psychologically burdened, would experience further deterioration in an objective psycho-oncological screening due to awake surgery. This is of high relevance, as we know that increased stress in cancer patients, especially in neuro-oncological patients, can lead to decreased therapy responses and an overall worse outcome.

In the context of our subgroup investigation, we compared patients who underwent psycho-oncological screenings and awake surgery with a group of patients who underwent surgery under general anaesthesia. We demonstrated that the impending awake surgery had no significant impact on the screening results. From this, it can be concluded that with proper patient care, awake surgery, regardless of objective inclusion and exclusion criteria, is a very valid option for maximal monitoring. Early involvement in psycho-oncology can help mitigate the additional stress that may arise, especially in the context of disease recurrence that we saw in our data.

V Concluding Summary

The resectability of eloquently located brain tumours has immensely increased with the introduction of intraoperative neuromonitoring and cortical/subcortical stimulation techniques. This has resulted in significantly positive outcomes for affected patients. Naturally, the preparation for such surgeries, which involve various procedures for example MRI, DTI or transcranial mapping, needs to be thorough. However, the only intraoperative control factor remains the application of the various described monitoring and mapping techniques and the awake surgery setting. With a growing realization of the importance of supratotal resections, intraoperative monitoring of motor and language functions must also be increasingly emphasized. Additionally, strategies for the control of cognitive function during brain surgery are under reconsideration in research groups worldwide. The selection of the most suitable technique for the individual patient is of paramount importance and enables the performance of complex operations without causing long-term neurological damage to the patient and therefore contributes to a better outcome for patients with partially very limited survival due to their diagnosis.

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VII APPENDIX

The following 6 original peer-reviewed and published articles contributing to this habilitation thesis are published here under the Creative Commons Attribution 4.0 International License, http://creativecommons.org/licenses/by/4.0/.).

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CLINICAL STUDY

Does positive MGMT methylation outbalance the limitation of subtotal resection in glioblastoma IDH-wildtype patients?

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Abstract

Background The impact on survival of complete resection (CR) in patients with malignant glioma and MGMT promoter methylation on adjuvant therapy strategies has been proven in the past. However, it is not known whether a MGMT promoter methylation can compensate a subtotal resection. Therefore, we analyzed the progress of postoperative residual tumor tissue depending on the molecular tumor status.

Methods We included all glioblastoma, IDH-wildtype (WHO grade IV) patients with postoperative residual tumor tissue, who were treated at our neurooncological department between 2010 and 2018. Correlation of molecular patterns with clinical data and survival times was performed. The results were compared to patients following CR.

Results 267 patients with glioblastoma, IDH-wildtype (WHO grade IV) received surgery of whom 81 patients with residual tumor were included in the analysis. MGMT promoter was methylated in 31 patients (38.27%). Median OS and PFS were significantly increased in patients with methylated MGMT promoter (mOS: 16 M vs. 13 M, p = 0.009; mPFS: 13 M vs. 5 M, p = 0.003). In comparison to survival of patients following CR, OS was decreased in patients with residual tumor regardless MGMT methylation.

Conclusion Our data confirm impact of MGMT promoter methylation in patients with glioblastoma, IDH-wildtype on OS and PFS. However, in comparison to patients after CR, a methylated MGMT promoter cannot compensate the disadvantage due to residual tumor volume. In terms of personalized medicine and quality of life as major goal in oncology, neuro-oncologists have to thoroughly discuss advantages and disadvantages of residual tumor volume versus possible neurological deficits in CR.

Keywords Glioblastoma · Neurooncology · MGMT · Extend of resection · Subtotal resection

Introduction

Malignant gliomas are heterogeneous, infiltrative growing tumors and represent the most frequent diagnosed brain tumors in adults with an incidence of 5–6 per 100,000 inhabitants per year. The most common subgroup of malignant glioma is glioblastoma multiforme (GBM) mounting up to more than 50% of the malignant gliomas [1, 2]. Besides histomorphological aspects, impact of molecular-genetic tumor markers regarding diagnosis, prognosis and therapy decisions have been demonstrated [3, 4]. The use of "integrated" phenotypic and genotypic parameters for CNS tumor classification has led to the fact that glioblastomas are divided in the 2016 CNS WHO into glioblastoma, IDH-wildtype (about 90% of cases), which corresponds most frequently with the clinically defined primary or de novo

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glioblastoma and predominates in patients over 55 years of age [5].

As predominant markers isocitrate dehydrogenase (IDH) mutation status and O-6-methylguanine-DNA methyltransferase (MGMT) methylation have been discussed in multiple studies. IDH1/2 mutation has a positive prognostic influence on overall survival (OS) (31 months vs. 15 months) [6, 7]. Furthermore, MGMT promoter methylation was implemented in diagnostic and therapeutical considerations as studies have proven that a methylated MGMT promoter (i.e. a hypermethylation of MGMT) results in a significantly better treatment response to the standard alkylating chemotherapy with Temozolomid (TMZ). The median OS was 21.7 months in comparison to 12.7 months in patients without MGMT promoter methylation [8, 9].

Despite improvement of therapy regimes, tumor recurrence cannot be prevented. With a mean progression free survival (PFS) of 6.9 months mainly local tumor recurrence is inevitable [10].

Therefore, the actual primary gold standard to increase survival is a complete resection (CR) of the contrast enhancing tumor tissue. Even beyond whenever possible [11], respecting location, functional restrictions due to possible risks of permanent neurological deficits [12] as well as general health condition [13]. Vice versa it has been shown, that postoperative residual tumor tissue results in a decreased OS with an inverse correlation of tumor volume and survival [14, 15]. Additionally, adjuvant therapies with concomitant radio-chemotherapy according to the EORTC/NCIC 26,981–22,981 study [16] as well as additional administration of Lomustin in patients with methylated MGMT promoter, have proved to significantly increase OS [17].

To improve surgical outcome, intraoperative neuromonitoring, awake surgery or fluorescence guided surgery have become widely used standard tools in glioma surgery. Although CR or even supramarginal resection has been proven to be the gold standard for primary therapy, this is not always achievable. Neurosurgeons have to identify intraoperative limits in order to prevent permanent neurological deficits especially in eloquent located tumors. One of the most difficult and also ethical decisions is to outbalance the risk of permanent neurologic deficits, which may result in decreased health related quality of life versus leaving active tumor tissue behind, which inevitably results in decreased survival. But it is not known, if a favorable molecular tumor status may outbalance postoperative residual tumor tissue. Do we, as neurosurgeons, have to be as aggressive in MGMT positive methylated than in negative methylated tumors?

Therefore, to facilitate the decision process of "how far can you go" vs "how far must we go", we analyzed whether a methylated MGMT promoter is able to balance the disadvantage of post-op residual tumor regarding tumor progression, PFS, OS as well as clinical outcome in IDH-wildtype glioblastoma patients. In a second step, we correlated our data with patients with no residual tumor tissue in the postoperative MRI.

Patients and methods

In this retrospective single-center analysis we investigated the impact of MGMT status on survival of GBM patients with postoperative residual tumor. The study was approved by the local ethical committee (study number: 5632 and 3005). Reporting of this study was according to the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines for observational studies (supplementary material).

Patients

Inclusion criteria were: (1) initial diagnosis of IDH-wildtype glioblastoma between January 2010 and December 2018, (2) surgery at the neurosurgical department, University Hospital Duesseldorf, (3) availability of pre- and postoperative (< 72 h post-op) MRI scans, (4) residual tumor tissue in the early postoperative MRI, (5) neuropathological diagnosis according to the 2016 guideline, (6) availability of molecular-genetic testing of MGMT status, (7) adjuvant therapy with concomitant radio-chemotherapy followed by intermittent TMZ according to the EORTC/NCIC CTG 26,981–22,981 study.

Molecular analyses

Since 2005 MGMT promoter analysis is conducted standardly in regards to glioma diagnostic at the Institute of Neuropathology at the University Hospital Duesseldorf. MGMT promoter methylationstatus was determined by methylation-specific PCR (MSP) and IDH mutation status was determined by immunohistochemistry for IDHR132H and DNA pyrosequencing as reported before [18].

If histopathological and molecular genetic diagnosis were provided before introduction of WHO 2016 classification, all diagnoses were reclassified according to WHO 2016 classification by the Institute of Neuropathology prior to our analysis.

Clinical status

The Karnofsky performance status scale (KPS) was determined pre- and post-operatively in order to evaluate the clinical status of the patients during the course of disease. It was also evaluated when a recurrent or progressing tumor was diagnosed. We defined clinical deterioration as a decrease in the Karnofsky performance status scale of at least 10%.

A decrease in the KPS postoperatively can be caused by a new neurologic deficit as e.g. a hemiplegia but also by other factors such as side-effects from anesthesia, thrombosis, or infection.

Calculation of tumor volume and treatment response

Initial tumor volume was calculated at baseline (preoperative MRI) and at T0 (> 72 h postoperatively) by defining the largest diameter of contrast-enhancing tissue in three spatial dimensions and then subsequently using the simplified formula for ellipsoids (A × B × C/2) for calculating the volume [19]. When second look surgery was performed, the MRI after second look was used for calculation.

Residual tumor volume was defined as minimum tumor volume greater than or equal to 0.175 cm^3. In further analyses we differentiated between residual tumor volume smaller or greater than 1.5 cm^3. Follow-Up MRIs were performed every three months starting 6 weeks after completion of concomitant radio chemotherapy (T1, T2 …).

Treatment response was assessed regarding RANO criteria [20]. For evaluation of complete (CR) or partial remission (PR) current MRIs were compared to baseline MRIs. If current MRI demonstrated either CR or PR, an additional MRI after 4 weeks was performed to verify treatment response. If there was no further MRI stable disease (SD) only was defined.

According to Wen and colleagues [20] follow-up MRI with the smallest measurable residual tumor volume was used for diagnosing tumor recurrence.

Furthermore, tumor progression was defined in case of:

(1) > 25% increase of contrast-enhancement tissue in T1 + contrast with stable or increasing need for corticosteroids according to RANO criteria
(2) evidence of an increasing metabolic activity of tumor tissue in the ^{18}F-FET-PET examination (delimitation of progression vs. pseudoprogression)
(3) re-resection with histopathological diagnosis of recurrent tumor

Statistical analysis

Testing for normal distribution of the data was performed by using the Shapiro–Wilk test, variance homogeneity and sphericity were tested by Levene and Mauchly test. Nonparametric testing for independent samples was conducted using the Mann–Whitney *U* test and Kruskal–Wallis test. For significance testing of two categorical variables Fisher's exact test was used.

Survival was calculated by means of the Kaplan–Meier method. In case of multivariable analysis Cox regression was used.

All statistical analysis was performed by using IBM SPSS Statistics Version 26 (IBM Corporation, USA).

OS in month was defined by the period from histopathological diagnosis to the time of death. In case of missing date of death, the last follow-up was defined as time of death. The period from diagnosis until occurrence of de novo tumor growth corresponded to PFS.

The cohorts' survival data (median OS, median PFS) were additionally compared to data from cohorts reported with complete resection [21–23].

Results

Patients

Six hundred and sixty five patients with IDH-wildtype glioblastoma were treated at the neurosurgical department at the University Hospital in Duesseldorf from January 2010 until December 2018. 267 (40.15%) patients received a complete resection, in 256 (53.53%) patients, residual tumor on the early post-op MRI was diagnosed. Due to the retrospective study design and chosen inclusion criteria, finally 81 patients (male: n = 50, 61.7%) were included in the following analysis. Figure 1 illustrates the patient recruitment.

The median age at diagnosis was 63 years (range 30–86 years). The median observation period was 13 months (95% CI, 11.75–14.26). The median PFS was 7 months (95% CI, 4.97–9.04). At time of data evaluation, 77 patients (95.1%) had died. An unmethylated MGMT promoter was diagnosed in 49 (64%), a positive MGMT status in 28 (36%) tumors.

Pre-op, the KPS was > 90% in two thirds of the patients (66.7%) with a median of 90%. The median KPS did not change post-op. At the event of a local tumor progression, 37 patients (81.1%) had no change or a decline of 10% in their KPS, whereas nine patients (15.5%) had a KPS decrease from 20–30%, and two patients (3.4%) from 50%.

The tumors were located in both hemispheres equally (left n = 37, 45.7%; right n = 39, 48.2%; both n = 4, 4.9%; cerebellar n = 1, 1.2%). The most common location was the frontal lobe (35.0%), followed by the temporal lobe (22.5%). The location was considered eloquent in 92.6% leading to awake brain surgery in 43 patients (57.3%) and the application of intraoperative monitoring in 75 patients (92.6%). Incomplete resection was due to eloquent tumor location or vascular conflicts.

The median pre-op tumor volume was 36.85 cm^3 (range 3.34–127.05cm^3). The group of MGMT promoter methylated tumors had shown a higher median pre-op volume

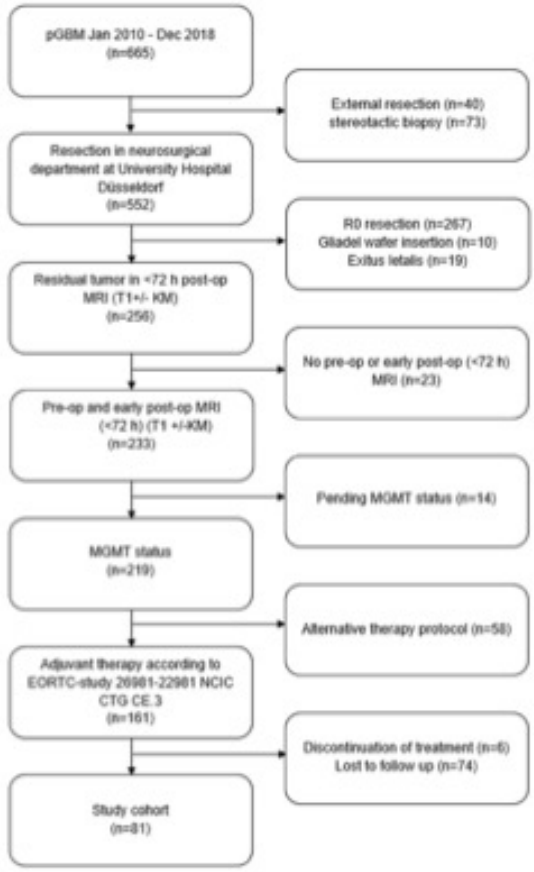

Fig. 1 Patients' inclusion and exclusion procedure illustrated as flow chart

(43.5cm^3) compared to the group of MGMT promoter unmethylated tumors (32.16cm^3). Patient characteristics are illustrated in Table 1.

Treatment response

At the time of data evaluation, PD was diagnosed in 58 patients. 23 patients showed a treatment response (TR). There was a significant correlation between methylated MGMT promoter and therapy response (p = 0.001). Tumors with methylated MGMT promoter demonstrated a significant higher TR (51.6%) compared to the tumors with unmethylated MGMT promoter (14.0%) (Table 2).

PD was diagnosed via RANO criteria in 24, via ^{18}F-FET-PET in 9, and via surgery in 25 patients. In case of recurrent tumor surgery, MGMT methylation status could be verified in all patients and was identical in 100% to the MGMT status of the tissue resected in the primary surgery.

Survival data

In patients with MGMT methylated tumors a significant increased OS as well as PFS were observed (p = 0.009, p = 0.003, respectively). OS and PFS (Fig. 2A, B) in patients with MGMT hypermethylated residual tumors were 16 months (95% CI, 13.00–19.01) and 13 months (95% CI, 5.94–20.06). In MGMT negative tumors mOS was 12 months (95% CI, 9.92–14.08) and mPFS 5 months (95% CI: 2.92–7.08).

Survival data were additionally correlated to a patient cohort who received a gross total resection at the same department [22]. Comparing available data of both groups tumors mostly were located eloquently (67% vs. 92.6%). While complete resected tumors were mainly localized on the left hemisphere (58.8%), incomplete resected tumors occurred mainly on the right hemisphere (48.2%). With a median preoperative tumor volume of 36.85 cm^3 incomplete resected patients showed a larger preoperative tumor volume (36.85 vs. 23 cm^3). The median preoperative KPS was 90% in both populations. Median age of patients with total resection was 58 years. An incomplete resection was associated with a higher age at time of diagnosis (median 63 years).

In this analysis, patients with a positive MGMT methylation status also demonstrated an increased OS (mOS: 21.0 vs. 19.0 months). The mPFS was 9.0 months in both groups. Compared to our data, following incomplete resection there is a similar mPFS, but increased mOS.

Tumor progression

Independent from molecular analysis, median residual tumor volume of all patients was 0.94 cm^3 (range: 0.18–11.50 cm^3, Table 3). There was no significant difference regarding residual tumor tissue and MGMT methylation status (Mann–Whitney U test: p = 0.392). Due to the significant difference of OS and PFS in patients with MGMT positive and negative methylated tumors, tumor volume was calculated at 3, 6, and 9 months post-op (Table 4).

Impact of age, residual tumor volume and KPS on survival

Our data demonstrate a negative impact of age and residual tumor volume on survival. In patients older than 60 years median OS (95% CI: 6.19–13.85) and median PFS (95% CI: 5.19–8.81) was decreased compared to younger patients (95% CI: 12.66–15.34 and 3.47–12.53). Patients with a residual tumor volume greater than 1.5 cm^3 had a shorter median OS (95% CI: 9.00–11.00) and median PFS (95%

Table 1 Patient characteristics

Parameter	Value	Whole population n = 81	MGMT positive n = 31	MGMT negative n = 50
At data evaluation	Alive	4 (4.9%)	3 (9.7%)	1 (2.0%)
	Dead	77 (95.1%)	28 (90.3%)	49 (98.0%)
Sex	Male	50 (61.7%)	18 (58.1%)	32 (64.0%)
	Female	31 (38.3%)	13 (41.9%)	18 (36.0%)
Age at initial diagnosis (in years)	≤ 60	38 (46.9%)	13 (41.9%)	25 (50.0%)
	> 60	43 (53.1%)	18 (58.1%)	25 (50.0%)
	Median (range)	63 (30–86)	64 (46–86)	61 (30–82)
	Mean (SD)	61.74 (11.53)	63.94 (9.93)	60.38 (12.32)
KPS at initial diagnosis	60	1 (1.2%)	1 (3.2%)	0 (0%)
	70	4 (4.9%)	3 (9.7%)	1 (2.0%)
	80	9 (11.2%)	2 (6.5%)	7 (14.0%)
	90	54 (66.7%)	19 (61.2%)	35 (70.0%)
	100	13 (16.0%)	6 (19.4%)	7 (14.0%)
	Median (range)	90 (60–100)	90 (60–100)	90 (70–100)
KPS post-op	60	0 (0%)	0 (0%)	0 (0%)
	70	4 (4.9%)	2 (6.5%)	2 (4.0%)
	80	8 (9.9%)	2 (6.5%)	6 (12.0%)
	90	45 (55.6%)	15 (48.4%)	30 (60.0%)
	100	24 (29.6%)	12 (38.6%)	12 (24.0%)
	Meadian (range)	90 (70–100)	90 (70–100)	90 (70–100)

The table shows the patient characteristics of the whole population and depending on the MGMT status

Table 2 Course of disease

	Cohort n = 81 (%)	MGMT positive n = 31 (%)	MGMT negative n = 50 (%)
Treatment response (TR) n = 23			
Complete remission (CR)	2 (8.7)	2 (12.5)	0 (0)
Partial remission (PR)	2 (8.7)	1 (6.3)	1 (14.3)
Stable disease (SD)	19 (82.6)	13 (81.2)	6 (85.7)
Progressive disease (PD) n = 58			
RANO-criteria	24 (41.4)	5 (33.3)	19 (44.2)
^{18}F-FET-PET	9 (15.5)	9 (6.7)	8 (18.6)
Surgery	25 (43.1)	25 (43.1)	16 (37.2)

Treatment response dependent from MGMT methylation status, and diagnosis of progressive disease

CI: 3.09–6.91) than patients with a smaller residual tumor volume (95% CI: 3.92–10.08 and 11.89–14.11). However, these findings were not statistically significant. The pre- and postoperative analysis of the KPS could not show any significant influence on OS or PFS in our cohort.

Discussion

In this study, we intended to analyze whether a methylated MGMT promoter could outweigh the burden of incomplete resection in IDH-wildtype glioblastoma patients. During the last years, the identification of molecular markers has been of high importance in the treatment of malignant gliomas [5, 24]. The methylated MGMT promoter is attributed to a better therapy response to adjuvant chemoradiotherapy, and hence to a better OS [3, 25, 26].

Our data support these findings, since patients with a hypermethylated MGMT promoter demonstrated an increased mOS (16 months with a mPFS of 13 months) compared to patients with unmethylated MGMT promoter residual tumors (mOS of 12 months with a mPFS of 5 mothns ($p = 0.009$; $p = 0.003$)). On average, tumor progression in MGMT promoter methylated residual tumors was

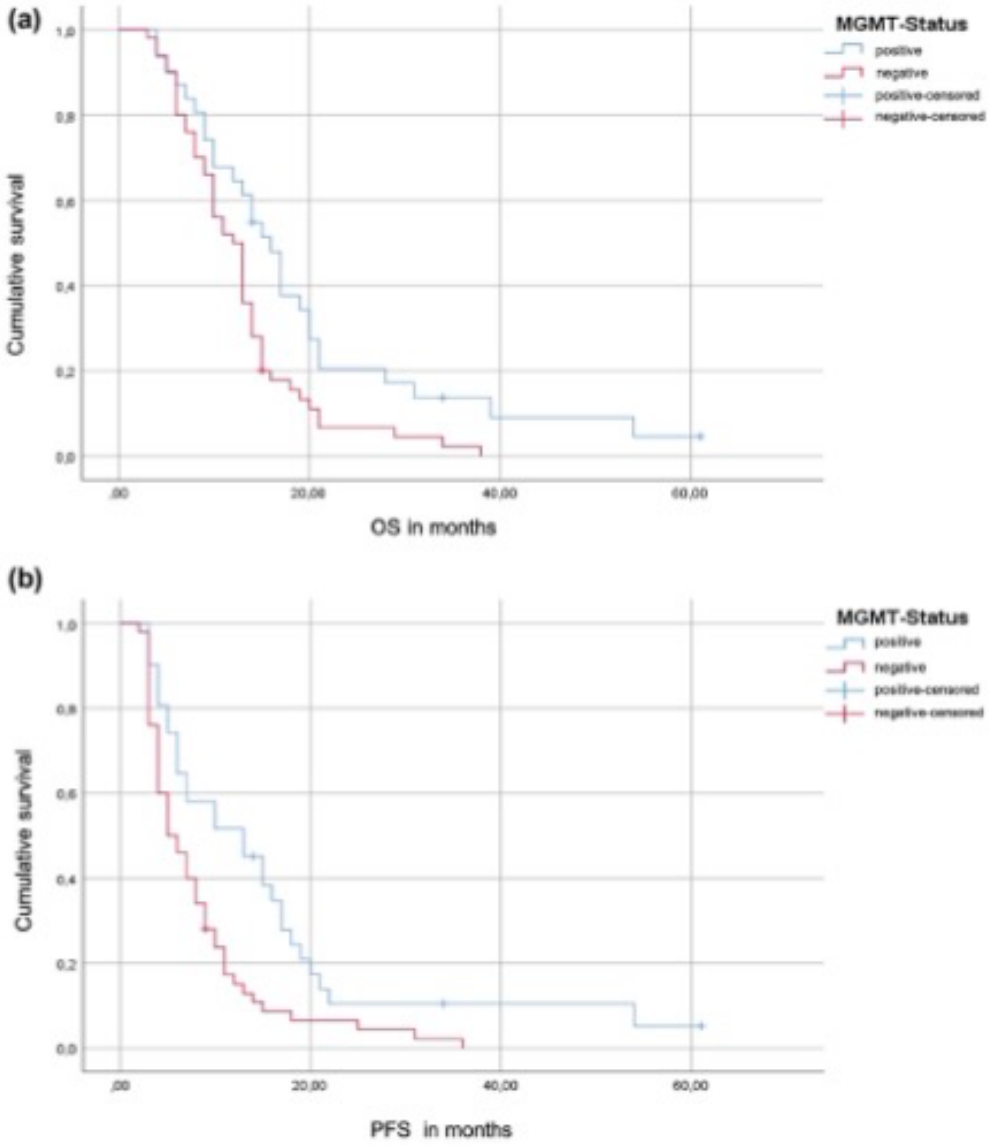

Fig. 2 Kaplan–Meier Curve overall survival (**A**) and progression free survival (**B**)

Table 3 Post-OP residual tumor volume

Value	Cohort n = 81	MGMT positive n = 31	MGMT negative n = 50
V_{Rest} in cm^3			
$\leq 1.5\ cm^3$ (%)	54 (66.7)	20 (64.5)	34 (68.0)
$> 1.5\ cm^3$ (%)	27 (33.3)	11 (35.5)	16 (32.0)
Median (Range)	0.94 (0.18–11.50)	0.94 (0.18–8.92)	0.94 (0.18–11.50)
Mean (SD)	1.63 (2.02)	1.68 (1.88)	1.61 (2.12)

The table shows the post-op residual tumor volume (at T0 = post-op) assorted by the MGMT status

Table 4 Residual tumor tissue at different timepoints

Value	T0	T3	T6	T9
V_{Rest} MGMT positive in cm^3				
n	31	26	20	13
Median (Range)	0.94 (0.18–8.92)	0.98 (0.17–10.4)	1.23 (0.21–10.75)	0.41 (0.18–5.60)
Mean (SD)	1.68 (1.88)	3.93 (10.4)	2.04 (2.58)	1.29 (1.6)
V_{Rest} MGMT negative in cm^3				
n	49	34	12	13
Median (Range)	0.94 (0.18–11.50)	1.43 (0.2–19.36)	1.75 (0.34–30.45)	1.23 (0.2–53.7)
Mean (SD)	1.61 (2.12)	3.95 (4.99)	4.4 (8.33)	6.38 (14.87)

The table shows the course of the residual tumor tissue in patients with a MGMT positive and MGMT negative GBM at different time points: T0 = post-op, after 3 (T3), 6 (T6), and 9 (T9) months post-op

diagnosed 0.41 months later than patients with an unmethylated MGMT promoter. A possible reason for this short time difference might be the gray zone of glioblastoma with borderline methylation of the promoter region and the selection of the cut-off to which category the tumors are classified [27].

MGMT tumor methylation was also positively correlated to increased treatment response (51.6% vs. 14.0%), which is in line with the recent literature [23, 25, 26, 28, 29].

However, compared to patient cohorts following CR, our study population showed decreased survival times. Thus, our data cannot support that a preferable MGMT methylation could compensate the loss in survival times from incomplete resection.

Surgical treatment strategies

The extent of resection is considered crucial for the further course of the disease in IDH-wildtype glioblastoma. Recently, Molinaro et al. discussed, that IDH -wild-type and IDH -mutant glioblastoma patients benefit from a maximized percentage of resection of contrast- and non-contrast enhancing tumor regardless the MGMT status [30]. Since residual tumor tissue is attributed to a reduced OS, aggressive gross total resection of at least all contrast-enhancing tumor on MRI or even beyond is the gold standard [13, 31–35]. Several surgical adjuncts can help to optimize the extent of resection without causing permanent post-op neurological deficits. They include intraoperative neuromonitoring with cortical and subcortical mapping, awake brain surgery, fluorescent-guided resection with 5-aminolevulinic acid, and intraoperative imaging techniques such as ultrasound or MRI [36]. In case of eloquent located tumors, complete resection without causing a new permanent neurological deficit is not always feasible and residual tumor tissue can be left in situ as risk–benefit analysis [22, 28, 31, 37].

This risk–benefit analysis should always include a thoroughly information of the patient and his relatives. Possible increased survival times that can be achieved through an extreme aggressive resection in which permanent new neurological deficits are hazarded need to be traded off for the quality of life. Surgeons carefully need to discuss possible postoperatively affection of quality of life with patients and relatives: what does quality of life mean for the particular patient? Is there an adequate home care infrastructure and what kind of professional support will be needed? This decision-making process requires well-trained neurooncological surgeons and neurooncologists as well as a considerable information of patients and relatives. Additionally, apart from personal preferences and environment that might be willing to accept new neurological deficits post-op, one also needs to consider and clarify the impact from neurological deficits on survival [38]. Postoperative new neurological deficits can affect survival to the extent of abolishment of the benefit caused from complete resection.

Impact factors on survival

Besides the molecular pattern, further variables are discussed to influence the course of the disease, explaining similar survival curves in the first months of follow up [8], and the existence of longtime survivors with MGMT negative GBM [39]. These variables are expected to be age at diagnosis, general condition, tumor location and pre- and post-op tumor volume [21, 40]. In accordance with that, in our study older patients and those with more residual tumor volume had a worse outcome. However, these findings were not statistically significant. With a postoperative median KPS of 90% patients of our study showed no difference between preoperative and postoperative scale. Patients were mostly operated under neuromonitoring and often awake surgery settings aiming to prevent new neurological deficits. We assume that operative procedure added to a favorable outcome but also to residual tumor voluminal as functional limits were achieved under surgery. The median post-op KPS in a comparable study, in which patients had a complete resection, was 90% as well [22]. In this study patients with mainly less frequent eloquent located lesions

were enclosed which might have contributed to a comparable KPS under total resection.

General limitations

Based on the strict inclusion criteria we analyzed data of a very homogenous group, which might also cause a selection bias. Due to the retrospective and monocentric study design, results may be less conclusive caused by small patient numbers especially in the subgroup analysis. However, here we present an analysis of residual tumor tissue throughout the whole course of disease, all patients were treated at the same neurosurgical department with the same adjuvant therapy scheme. Survival data of the other cohorts used for comparison between CR and residual tumor were extracted from literature. In one study, data was collected at the same hospital with comparable inclusion criteria, however data were not collected for this present study, particularly. Compared to other studies, a different cut-off to categorize MGMT promoter methylated and unmethylated glioblastomas might also have an impact [29]. Concerning evaluation of the clinical status measured by KPS in most of studies used for comparison, only little reference was made to the post-op KPS [21, 23]. Therefore, a comparison concerning the KPS as postoperative outcome score in patients with complete vs. incomplete resection between these study populations and the present reported data could not be made. In general, the KPS is only a restricted outcome measure as subtle cognitive impairment can hardly be measured with the KPS as it only measures the physical status but omits other parts that contribute to quality of life (e.g. spirituality). Therefore, additional neurocognitive and psychooncological assessments are crucial in neurooncological patients. Nevertheless, the KPS is an easily accessible and quickly performable tool and still important as a correlation of physical functioning deficits and significantly decreased quality of life has been reported. The KPS can assess the evolution of the clinical status of a glioblastoma patient and is therefore widely used in neurooncology.

At last, all histopathological diagnoses were re-classified according to the 2016 WHO guidelines, which lead to a loss of patients in which re-classification was not feasible. The risk of over- or underestimation of the manual tumor volume calculation was minimized since the same person calculated it in all cases.

Conclusion

Our data underline the impact of the MGMT promoter methylation status in the treatment response of IDH-wildtype glioblastoma. Even after incomplete resection, patients with MGMT hypermethylated tumor demonstrated increased OS and PFS. However, our data revealed that the disadvantage of an incomplete resection cannot be outweighed by a favorable MGMT status in contrast to. Therefore, gross total resection of IDH-wildtype glioblastoma should remain the gold standard. Still, more studies about the behavior and treatment of residual tumor tissue are required. In times of personalized medicine and quality of life representing a major goal in oncology, neuro-oncologists need to inform the patients and their caregivers thoroughly about advantages and disadvantages of residual tumor volume versus possible neurological deficits in gross total resection especially in an eloquent tumor location.

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Declarations

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Feasibility of intraoperative neuromonitoring and cortical/subcortical mapping in patients with cerebral lesions of highly functional localizations—pathway to case adapted monitoring and mapping procedures

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Background: Intraoperative neuromonitoring (IONM) and mapping procedures *via* direct cortical stimulation (DCS) are required for resection of eloquently located cerebral lesions. In our neurooncological department, mapping and monitoring are used either combined or separately for surgery of functional lesions. The study aims to provide a practical insight into strengths and pitfalls of intraoperative neuromonitoring and mapping in supratentorial functionally located infiltrating lesions.

Methods: IONM and mapping techniques performed in eloquent located brain tumors were analyzed with a focus on neurological outcome and resection results obtained *via* MRI. Additionally, the surgeons' view on obligatory techniques was explored retrospectively immediately after surgery. To evaluate the impact of the described items, we correlated intraoperative techniques in various issues.

Results: Majority of the 437 procedures were performed as awake surgery (53%). Monopolar stimulation was used in 348 procedures and correlated with a postoperative temporary neurological deficit. Bipolar stimulation was performed in 127 procedures, particularly on tumors in the left hemisphere for language mapping. Overall permanent deficit was seen in 2% of the patients; neither different mapping or monitoring modes nor stimulation intensity, localization, or histopathological findings correlated significantly with permanent deficits. Evaluation of post-OP MRI revealed total resection (TR) in 209 out of 417 cases. Marginal residual volume in cases where total resection was assumed but MRI failed to proof TR was found (0.4 ml). Surgeons' post-OP evaluation of obligatory techniques matched in 73% with the techniques actually used.

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Conclusion: We report 437 surgical procedures on highly functional located brain lesions. Resection without permanent deficit was adequately achievable in 98% of the procedures. Chosen mapping or monitoring techniques mostly depended on localization and vascular conflicts but also in some procedures on availability of resources, which was emphasized by the post-OP surgeons' evaluation. With the present study, we aimed to pave the way to à la carte choice of monitoring and or mapping techniques, reflecting the possibilities of even supratotal resection in eloquent brain tumor lesions and the herewith increased need for monitoring and limiting resources.

KEYWORDS

intraoperative monitoring, brain mapping, brain tumor, eloquent location, supratentorial brain tumor

Introduction

Surgical gross total resection represents the gold standard according to therapeutical approaches of infiltrating brain tumors. The aim of the surgical intervention is an achievement of complete removal of the tumor as seen on the MRI scan and described as gross total resection in the literature in order to extend survival of the patients as this is directly linked to an extended overall survival in high-grade glioma patients (1–3). For low-grade glioma, it is well known that a residual tumor volume and extent of resection can predict the progression-free survival and time to malignant transformation (4, 5) as well as overall survival. Surgical resection in brain metastasis has also been the object of partly critical investigation. For this brain tumor entity too, surgical resection was found to be a significant factor for longer survival and preservation of functional status in many studies comparing the surgical approach and radiation therapy or radiation therapy alone. Patients that underwent surgery before radiation, regardless of the type of radiation (whole-brain or stereotactic radiosurgery), showed a significant longer patient survival and higher Karnofsky Performance Scale Scores (6, 7).

Thus, surgical therapy represents a main step in therapeutical concepts for cerebral lesions of different etiologies.

The most common highly functional supratentorial cerebral lesions comprise areas of motor and speech function. An important feature of gliomas and to some extent metastasis is the infiltrating zone. Here, functional tissue is infiltrated by malignant cells. Surgical intervention in this zone would inherently result in neurological/neurocognitive deficits, a non-resection in potential earlier recurrence. Thus, a possible definition of "eloquent" localization could be the ability to correlate a defined neurological/neurocognitive deficit with the destruction of this tissue by progression of the tumor or resection.

Maximum but safe resection is the superior aim in brain tumor surgery. In order to achieve the aimed resection but also to preserve functional status, as well as to provide the patient with optimal conditions for adjuvant therapies, intraoperative neuromonitoring and mapping using direct cortical and subcortical stimulation techniques have been well-established procedures in resection of tumors relating to motor pathways or speech areas and fiber tracts (8–12). In addition to motor and speech function, neurocognitive integrity has more and more become a target for intraoperative testing over the last few years (13–15).

There are different methods used for intraoperative monitoring (IOM) of neurological function. Transcranial electric stimulation (TES) can be used for motor-evoked potentials (TES-MEP) for monitoring of motor pathway integrity. Additionally, somatosensory-evoked potential (SSEP) monitoring to watch over sensory function can be performed. MEP monitoring can also be performed *via* direct cortical stimulation (DCS) by placing a strip electrode (SE) on the precentral gyrus allowing a continuous control of neurological motor function in asleep patients. DCS is also carried out by the usage of handheld monopolar or bipolar stimulation probes (16, 17), which enables the surgeon to map the functionality of the tissue. Bipolar stimulation is commonly used for awake mapping procedures, whereas monopolar mapping is particularly used for motor mapping for tumors located near or around motor pathways even though speech mapping is also performed at least on a research basis *via* monopolar mapping stimulation (18, 19). In summary, to date there are several options for mapping and monitoring procedures available, from which the surgeon can choose for special indications.

Over the past two decades, we have implemented the mentioned technical methods as well as awake and asleep resection protocols at our department. Instead of choosing one method over the other, we preoperatively determine what we think is the most suitable technique for preservation of neurological function. For reevaluation of the decisions, the present study was conceived in which we analyzed clinical and intraoperative data of 437 procedures in 400 patients that underwent surgery of eloquent brain lesions during a period of 4 years and complemented these data with subjective evaluations of the decisions made preoperatively by the surgeons that had performed surgery. All patients underwent surgery using either a single or combination of different mentioned intraoperative neuromonitoring and mapping

methods. Additionally, we combined asleep and awake procedures. With this study, we aim to provide a deeper insight into strengths and pitfalls of intraoperative neuromonitoring and mapping in supratentorial eloquent brain tumors, especially gliomas and the hereby used methods at our institution.

Patients and methods

In this single-center analysis (screening period 01/2019–01/23), we performed evaluation of intraoperatively collected data of neuromonitoring and mapping procedures in patients undergoing surgery for eloquently located supratentorial brain lesions. We complemented these data with sociodemographic data, clinical findings of preoperative and postoperative neurological status up to 6 months postoperative, and MRI studies for residual volume evaluation and neuropathological diagnosis. The study was approved by the local ethical committee (Study Number 2022-2242). Reporting of this study was according to the strengthening of the reporting of observational studies in epidemiology (STROBE) guidelines for observational studies (Supplementary Material).

Patients

Inclusion criteria for the present analysis were (1) surgical intervention in patients >18 years between January 2019 and January 2023. (2) Intraoperative monitoring and/or mapping devices were used. (3) The addressed lesion was located supratentorial. Procedures for posterior fossa or spine surgery were excluded. Availability of IONM or mapping data was also taken into consideration as to some extent some data were missing in some of the cases. However, missing of few data of individuals did not lead to exclusion. The number of procedures is given for all single analyses.

Data collection

General data

Sociodemographic data, neuropathological results, and information on medical/surgical history, if applicable, were taken from the local patient administration system. Surgical history was divided into four categories: (1) primary surgery, (2) recurrent surgery with neuropathological confirmation of recurrent disease, (3) recurrent surgery without neuropathological confirmation of recurrent disease, (4) 2nd-look surgery.

Neuropathological results if obtained before introduction of WHO 5 Classifications of Central Nervous System Tumors 2021 (20) were adapted according to the new classification.

Neurological outcome

Patients underwent initial neurological examination at timepoint of admission; this was defined as timepoint "pre-operative". Postsurgery patients underwent multiple examination, especially in case of any new neurological deficit. For the present analyses, we consistently used the examination at timepoint of dismission for definition of timepoint "postoperative". Furthermore, patients with new neurological deficit in the postoperative state were followed up at around 3 months ("3-month FU") and 6 months (6-month FU). Neurological examination was performed by different specially trained team members who also carried out awake procedure preparation and awake procedure testing intraoperatively. Our protocol includes a detailed questionnaire about general condition and health-related problems as well as a detailed neurological examination of cranial nerves, motoric and sensory testing, and, if applicable, speech testing as described further on.

Monitoring and mapping data

Monitoring and mapping data were obtained using the following technical devices with a described standard setup for different monitoring/mapping techniques.

ISIS Xpert and C2 Xplore (inomed Medizintechnik GmbH, Emmendingen, Germany, NeuroExplorer Software Version 6).

monitoring
- SSEP (ISIS only)
- TES-MEP (ISIS only)
- DCS MEP (ISIS only, four to six contact subdural strips).

mapping
- Cortical and subcortical with monopolar probe
- cortical and subcortical with bipolar probe

In cases where the C2 Xplore device was used, amperage of bipolar stimulation is given in the numbers of ISIS Xpert device as there are other technical nuances between those devices leading to different settings. For better comparison, we standardized the data obtained.

Ojemann Cortical Stimulator (Integra LifeSciences)

mapping
- Cortical and subcortical with bipolar probe

Awake status

Additionally, surgical protocols were screened for stimulation details and information on awake status and time of awake condition if applicable. Awake status was divided into following subcategories: "awake," "not adequately awake," "not awake". In cases where awake surgery was planned but not conducted due to non-compliance of patients or other reasons ("not adequately awake"), the procedure was categorized in awake surgery status for statistical analyses.

More detailed technical data such as monitoring/mapping devices and technical setups are reported in the Supplementary Information.

Choice of adequate mapping/monitoring or speech testing

At patients' presentation and when indication for surgery is set due to radiological and or clinical findings, we take a deep look into MRI scans and decide as a team of the leading surgeon and assistant surgeon as well as monitoring staff which technique to use in this special case. There has to be careful consideration of clinical and technical examination results in order to choose the right methods for the particular cases. The day before surgery, team members of the neurooncological team will talk to the patient through the procedure and perform neurological examination of the patient with evaluation of cranial nerves, motor and sensibility deficits, and general symptoms as headaches and perform a quick screening of speech disturbances. If there are any conspicuousness about speech deficits in the screening, the whole testing battery that we defined at our department is useful for efficient speech testing is performed. Details about the speech testing are described below.

Language testing

When language testing was performed, different tests were conducted with some items taken from Aachen Aphasia Test (21). Baseline testing was performed the day before surgery in order to have comparable data for intraoperative testing. Furthermore, all patients underwent postoperative testing at least at one time point in the postoperative state until they were discharged.

The following dimensions of language skills were tested pre-intra- and postoperatively in order to evaluate patients' speech affection:

Spontaneous speech

Patients are motivated to talk about a topic of their choice. This is done to test semantic aspects of the patients' speech, articulation, phonology, and syntax in general.

Token test

Testing language comprehension by showing and matching geometrical shapes of different sizes and colors.

Free reading

By reading the written language comprehension is tested.

Picture naming

Analysis of the designation of images of colors, objects, or actions.

Pyramids and palm trees test

Test for semantic memory used to detect language impairment. The test uses iconic images to determine the degree to which a subject can access meaning from pictures and words.

Surgeons' postoperative evaluation

In order to compare chosen methods with a postoperative reevaluation, we retrospectively performed inquiries of surgeons concerning assessment of obligatory monitoring/mapping in the present case. Obligatory modes were divided into the following 13 categories: monopolar stimulation, bipolar stimulation, combination monopolar/SSEP/MEP, combination monopolar SSEP/MEP/SE, combination monopolar/bipolar, combination monopolar/bipolar/SSEP/MEP, combination monopolar/bipolar/SSEP/MEP/SE, combination bipolar SSEP/MEP/SE, SSEP/MEP/SE only, monitoring/mapping (m/m) not needed, m/m not applicable/no resection, used methods inconclusive.

The chosen method for each specific case served as preoperative evaluation and was not documented separately.

Procedures were led by three senior surgeons with each more than 10–25 years of experience in the field of brain tumor surgery and intraoperative monitoring/mapping procedures. Senior surgeons were accompanied by residents with different experiences in brain tumor surgery.

Residual volume (MRI)

For evaluation of residual tumor volume, results of postoperative conducted MRIs were screened. All MRIs were carried out within 72 h postsurgery. We defined four groups for result description:

(1) intraoperatively defined macroscopic total resection and total resection in postoperative MRI, (2) intraoperatively defined macroscopic total resection and residual tumor volume in postoperative MRI, (3) intraoperatively defined macroscopic residual tumor volume and residual tumor volume in postoperative MRI, and (4) no MRI. Residual volume was either calculated by the reporting radiologist or if missing by the study team under usage of a volumetry tool in the local radiology information system (SECTRA Workstation 101, IDS7, Version 24.1, Sectra AB, Sweden, 2022). Results of residual tumor volume are stated in milliliters. Residual volumes less than 0.1 ml were defined as total resection.

Statistical analyses

All statistical analyses were conducted using IBM SPSS Statistics Version 26 (IBM Corporation, USA). Obtained results were statistically analyzed by using chi-square test for nominal variables. Group comparison was performed by univariate analyses of variance by (ANOVA), and *post-hoc* tests were adjusted using Bonferroni correction. Additionally, we carried out correlation calculation under usage of Pearson correlation. Statistical cutoff stated as p-value for all results was set at 0.05.

Results

General data

Overall, we included 437 surgical procedures in 400 patients (47% women, n = 188; 53% men, n = 212) over a period of 48 months in the present analyses. There were 27 patients who underwent surgery twice and five patients who had triple surgery during the observation period.

The mean age of patients at surgery was 56.6 years [± SD 14.9, range 20–90 years]. If patients underwent more than one surgical procedure, age at first recorded surgery was enclosed in the reported data.

68% of surgeries were primary cases (n = 296). One-third were recurrent surgeries with neuropathological confirmation of recurrent disease (n = 121). In 3% (n=12), recurrent surgery revealed no recurrent disease but showed other diagnoses, for example radio necrosis or reactive tissue changes. Eight (2%) procedures were labeled as second-look surgery in patients with significant residual tumor volume in postoperative MRIs due to different reasons.

One patient underwent primary surgery without mapping/monitoring and showed residual volume in the postoperative MRI; therefore, second-look surgery was advised. Four patients showed different impairments under subcortical stimulation (one patient anomia with 2 mA bipolar subcortical stimulation, one patient >70% deterioration in the picture naming test as well as under subcortical bipolar stimulation, one patient who underwent monopolar subcortical mapping with a 2-mA resection limit achieved, and one patient who showed a significant increase in SSEP latencies and therefore resection had to be stopped).

In two patients, primary surgery was finished under expectance of total resection with no link to functional limits. One patient underwent primary surgery under expectance of debulking as resection could only be achieved under speech monitoring, but speech testing preoperatively showed too much effect for reliable intraoperative testing. After recovery from primary surgery, awake surgery was evaluated as soon as possible; therefore, a second-look surgery with indented total resection was performed.

A total of 235 procedures were performed on lesions in the left hemisphere (54%), 196 were right-hemispheric tumors (45%), and 6 were located elsewhere (1%, rostrum, splenium, bifrontal).

Majority of neuropathological diagnoses were high-grade glioma (glioblastoma, IDH-wild type, MGMT methylation positive or negative) with 191 procedures (43.7%). IDH-mutant astrocytoma (WHO 1–4) and cerebral metastases were each diagnosed in 86 procedures (19.7%). Oligodendroglioma, IDH-mutant 1p/19q co-deletion (WHO 2 + 3), was diagnosed in 38 procedures (8.7%).

For a summary of cohorts' complete general data results, please refer to Table 1.

TABLE 1 Summary of cohorts' general data.

AGE (y)	
Mean	56.6 [SD ± 14.9]
Range	20–90
	n = 400
SEX	
Female	188
Male	212
DIAGNOSIS	
Astrocytoma IDH-mutant (2-3)	80
Astrocytoma IDH-mutant (4)	6
Glioblastoma, IDH-wild type (4) MGMT −	105
Glioblastoma, IDH-wild type (4) MGMT +	86
Oligodendroglioma (2-3)	38
Diffuse hemispheric glioma	1
Cerebral metastasis	86
Aggressive NHL	7
Meningioma	1
Atypical meningioma	4
High-grade neuroepithelial tumor	1
Low-grade neuroepithelial tumor	3
Dysembrioplastic neuroepithelial tumor	1
Ganglioglioma	2
Radiation necrosis	2
Reactive tissue changes	10
Chronic inflammatory tissue changes	1
Florid inflammatory demyelinating	
CNS lesion	1
Cerebral toxoplasmosis	2
SURGICAL HISTORY	
Primary surgery	296
Recurrent surgery with diagnosis of	121
recurrent disease	
Recurrent surgery without diagnosis of	12
recurrent disease	
Second look	8
LOCALIZATION	
Left hemisphere	235
Right hemisphere	196
Other	6

Awake status

Overall, 53% (n = 233) of procedures were conducted as awake surgery or were at least planned as awake surgery. Out of 233 planned awake procedures, 36 were categorized as "not awake adequately" (15%). Most frequent localizations for awake surgery in left hemispheric tumors were frontal, temporal, fronto-temporal, and parietal lesions, in the right hemisphere most commonly right parietal tumors followed by temporal and frontal lesions. Patients that underwent planned awake surgery were significantly younger

compared with the non-awake patients with a mean age of 52.3 years in the awake group *vs.* 60.2 years in the non-awake group ($p < 0.001$, Figure 1A).

Awake status and duration of awake status differed significantly according to the hemisphere. While lesions located in the left hemisphere were more frequently planned and conducted as awake procedure ($p < 0.001$, Figure 1B), the duration of the awake phase was significantly longer when performed on lesions in the right hemisphere (left = 69.6 min [± SD 25.2] vs. right = 80.8 min [± SD 27.1], $p = 0.023$, Figure 1C).

Intraoperative monitoring/stimulation data

TES-MEP and SSEP monitoring

SSEP monitoring was conducted in 234 and TES-MEP in 260 procedures. The range of stimulation for the present cohort for left and right medianus SSEP monitoring was 0.8–20 mA and for tibilias SSEP on the right side 0.5–30 mA and for the left side 1.7–30 mA. For MEP monitoring, maximum stimulation of 220 mA at a band-pass filter between 250 and 500 Hz or a maximum of 100 mA at 500 Hz was used. For upper extremities, the range of stimulation was 40 to 80 mA and for lower extremities 60–110 mA in the present cohort.

SSEP and MEP monitoring *via* SE was conducted in 172 cases (Figure 2). SSEP monitoring was significantly more frequently used in left hemispheric lesions (n = 136 vs. 94, $p = 0.007$), whereas usage of TES-MEP did not significantly differ concerning localization (Figure 3). SSEP monitoring was significantly more often used in asleep surgery status ($p < 0.001$ SSEP, Figure 4).

Furthermore, we analyzed EEG documentation for intraoperative seizures; EEG data were available for 260 patients. Seizures were observed in 22 patients either *via* EEG only or by EEG and clinical determination (8%). There were 13 patients with seizure occurrence (59%) who underwent an awake procedure. Preoperative seizure did not increase the risk for intraoperative seizures ($p = 0.854$), but bipolar stimulation significantly correlated with occurrence of intraoperative seizures ($p = 0.008$) whereas monopolar stimulation did not.

Monopolar/bipolar mapping

Monopolar mapping was conducted in 348 procedures (Figure 2). Stimulation ranged from 0.5 to 20 mA. Epidural stimulation in 127 cases (36%) was conducted with a mean current of 10.6 mA [± SD 4.2]. In the vast majority of surgeries, a cortical stimulation was performed with 329 cases (96%) and a mean current of 7.6 mA [± SD 4.4]; subcortical stimulation was

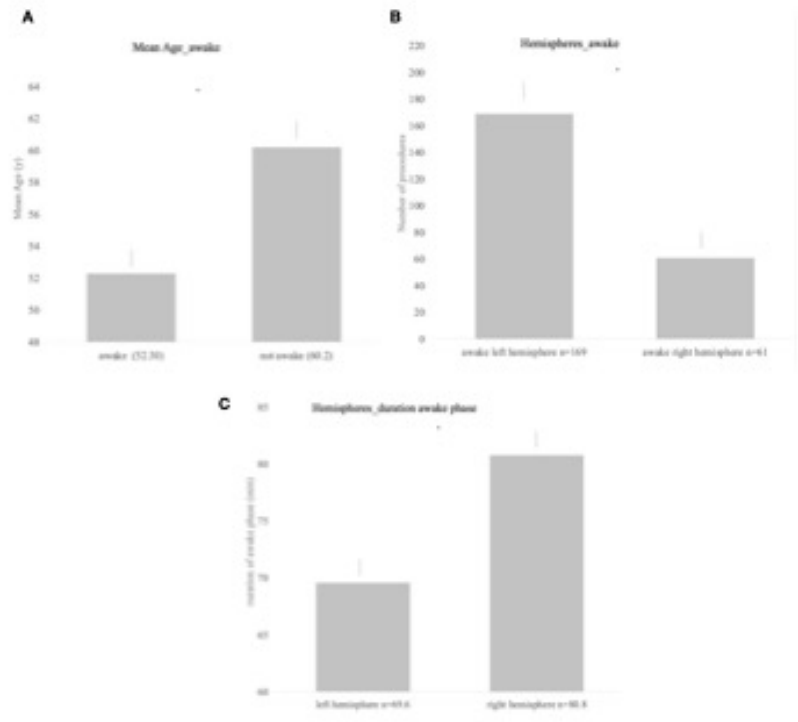

FIGURE 1
(A) Significant difference in the mean age and awake status ($p < 0.001$). **(B)** Awake status for procedures of both hemispheres; left hemispheric lesions were significantly more often operated under awake settings ($p < 0.001$). **(C)** Duration of the awake phase for both hemispheres showing significantly longer awake duration in right hemispheric lesions ($p = 0.0023$).

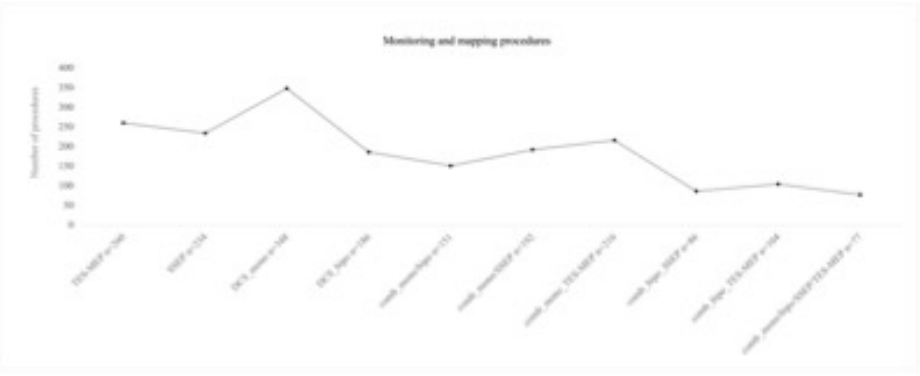

FIGURE 2
Number of procedures for different monitoring/mapping modes that were used intraoperatively. Mostly monopolar stimulation was used. The combination ("comb") of monopolar and bipolar mapping plus monitoring was the least combination that was used intraoperatively.

found in 302 surgeries (87%) with a mean current of 3.4 mA [± SD 3.2], ranging from 0.2 to 20 mA.

The proportion of awake procedures in monopolar mapping procedures was 52% with 181 cases (Figure 4).

There were 186 procedures conducted under usage of bipolar stimulation (Figure 2). Bipolar cortical mapping was found in 91% (n = 169) with a mean current of 2.2 mA [± SD 1.4, range 1–3 mA] and subcortical stimulation in 73% (n = 136) with a mean current of 2.1 mA [± SD 1.0, range 0.8–3 mA]. In the awake setting, 169 patients underwent bipolar stimulation (91%, Figure 4). If clinical evaluation, in case of awake surgery, or MEP/SSEP monitoring allowed so, resection was stopped at a minimum of 1 mA when performing subcortical mapping.

In 151 cases, both monopolar and bipolar stimulation were performed, thereof a total of 91% (n = 136) proceeded in an awake setting (Figure 2).

During both mapping procedures, awake surgery status was more frequently planned than asleep procedures (monopolar stimulation $p = 0.026$, bipolar stimulation $p \leq 0.001$, Figure 4).

Localization did not correlate significantly with use of monopolar mapping; however, bipolar mapping was used more frequently for left hemispheric tumors ($p \leq 0.001$, Figure 3).

Surgeons' evaluation of obligatory stimulation mode

Most frequently monopolar mapping (n= 172), bipolar mapping (n= 98), and combination of monopolar/bipolar mapping (n= 85) were designated as obligatory stimulation modes. In only 10 procedures, combination of all mapping and monitoring techniques was seen as obligatory (four lesions left frontal, temporal and fronto-temporal, six lesions right fronto-parietal, parietal and fronto-temporal); however, SSEP/MEP monitoring was seen obligatory in around 16% of all procedures, independently from mapping procedures that were performed, but most commonly in right hemispheric lesions with monopolar stimulation combined with SSEP/MEP monitoring.

FIGURE 3
Different monitoring and mapping procedures separated according to localization. Monopolar stimulation was mostly used on left hemispheric lesions followed by monopolar stimulation on right hemispheric procedures. The least used method was bipolar stimulation for right hemispheric lesions. * = significant results.

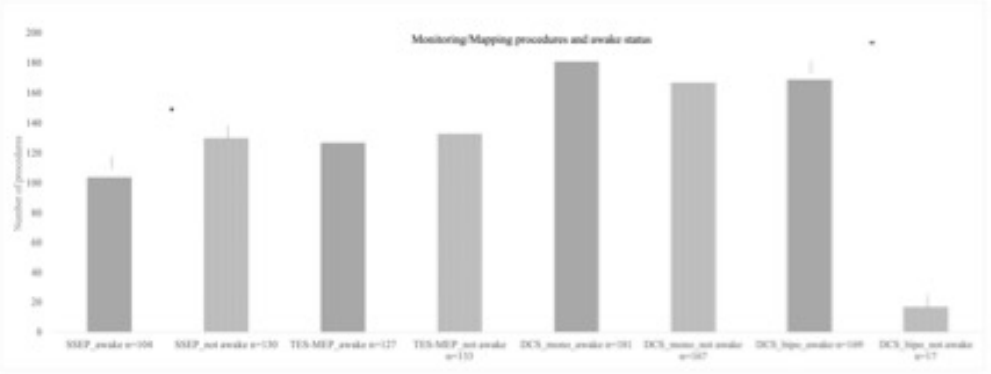

FIGURE 4
Different monitoring and mapping procedures here parted in accordance by awake status. Here, also monopolar mapping was most commonly used either awake or asleep with no significant difference in number of procedures. Bipolar stimulation in the asleep status was used least in the cohort. * = significant results.

In eight cases, SSEP/MEP monitoring only was evaluated as required without any mapping procedure. Three procedures were performed without any requirement of monitoring or mapping due to intraoperative non-functional localization (0.7%). Two surgeries were terminated without any intervention. In one procedure, all methods used were rated as inconclusive with no benefit for safe resection (Figure 5).

A significant correlation between localization of tumor and postoperative stated obligatory stimulation modus was found ($p = < 0.001$).

Monopolar obligatory mapping was found to be essential in right hemispheric tumors more often than left hemispheric ones; on the contrary, bipolar mapping and combination of monopolar/bipolar mapping were evaluated as essential more often on left hemispheric lesions.

Incongruency of the obligatory method according to surgeons' evaluation and the intraoperatively used method was more often seen with obligatory bipolar mapping (23% bipolar mapping, 10% for monopolar mapping).

Clinical outcome

In 279 cases, preoperative deficits were noticed (64%), mostly motor deficits (n = 70), speech disorders (n = 58), affection of vision and or cranial nerves (n = 28), and behavioral changes (n = 28). Additionally, preoperative seizures were observed in 49 cases (11%).

A new postoperative neurological impairment was seen in 57 patients (13%, Figure 6); seven patients died shortly after resection. However, deaths were not directly related to surgical complications. Majority of neurological deficits (61%) were seen after procedures on left hemispheric tumors, and right hemispheric surgeries led to postoperative new deficits in 35% of the cases. 4% occurred in other locations.

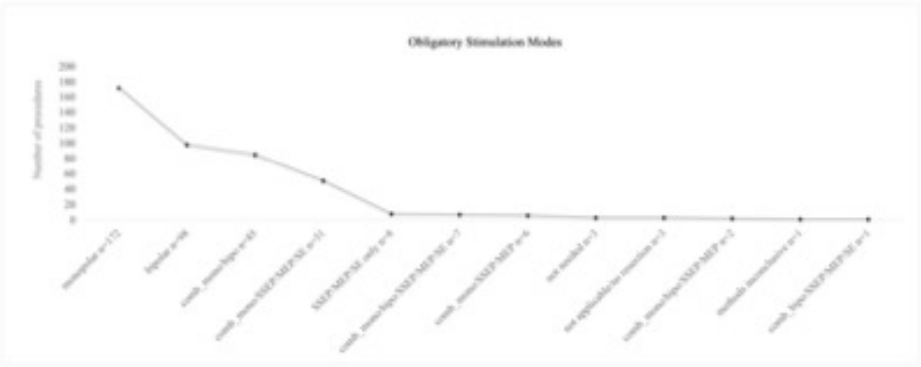

FIGURE 5
Postoperative evaluation of obligatory mapping or monitoring modes by the operating surgeon. Monopolar, bipolar, and a combination of both mapping procedures were mostly stated as "obligatory" for the preceding surgery. Full technical equipment with a combination of mapping and monitoring was less frequently recalled as obligatory.

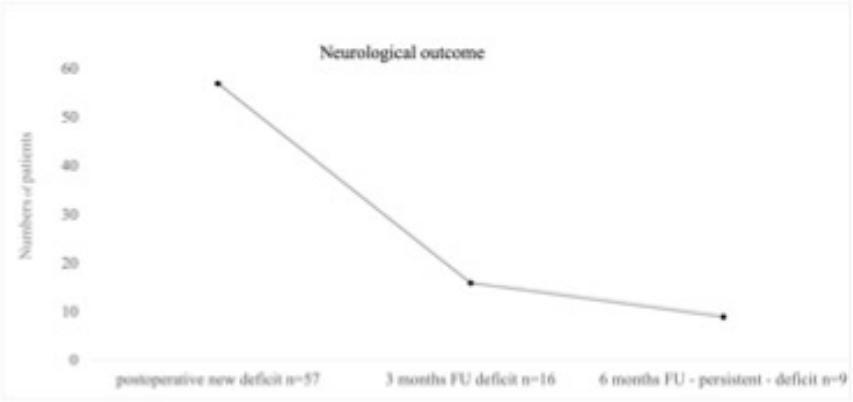

FIGURE 6
Illustrating cases with postoperative and persistent new neurological deficits. We defined "persistent deficit" as neurological impairment after 6 months postoperative. Nine patients suffered from persistent deficits after surgical intervention; mostly permanent speech disorders were seen.

A total of 24 patients suffered from high-grade hemiparesis, one patient showed sensory deficits as new and leading symptoms, 22 patients presented a new speech disorder affecting either sensory or motoric aspects of speech, and global aphasia as the combination of both was seen in one patient. Three patients presented new impairment in facial motoric or vision. Six patients had a combined deficit of speech and motor function.

At first follow-up after 3 months postoperative, persistent neurological deficits in 16 cases out of 56 were reported (4%, n = 411, Figure 6). At 6 months of follow-up, neurological deficits were still seen after nine procedures, an overall of 2% concerning all procedures, and were defined as permanent deficit by that time (n= 406, Figure 6) with five patients with persistent motor impairment and four speech disturbances. Overall, 13 patients had died within 6 months postsurgery (2%).

Permanent deficits occurred independently from diagnosis ($p = 0.958$) or localization ($p = 0.271$). Significantly increased risk of death was seen in cases with preoperative neurological deficit ($p = 0.030$). Surgical status "awake" significantly correlated with direct postoperative speech deficits not motor deficits ($p = 0.003$). Overall evaluation of persistent deficit after 6 months however revealed no significant influence by awake or asleep status ($p = 0.593$).

Correlation of stimulation/monitoring modes and postoperative neurological deficit revealed no significant results for SSEP monitoring ($p = 0.341$), TES-MEP ($p = 0.659$), and bipolar stimulation ($p = 0.061$), but monopolar stimulation with $p = 0.007$. Permanent deficit at 6 months did also only significantly correlate with usage of monopolar stimulation ($p = 0.012$). At last, neurological impairment and obligatory stimulation mode turned out to be not significantly related ($p = 0.109$).

We examined postoperative MRI scans of patients who experienced new neurological impairments after surgery. In our analysis, we identified indications of infarction or postoperative bleeding in 21 MRI scans (comprising 17 cases of infarction and 4 cases of bleeding). Notably, most infarctions were very and relatively small (n = 15) and are not assumed to be a potential reason for neurological impairment. In two patients, the infarction may have contributed to their postoperative and later permanent deficits. In a specific case, a patient exhibited a basal ganglia infarction and subsequently experienced postoperative motor deficits. Additionally, in the second patient, a relatively extensive territorial infarction occurred, leading to motor deficits as well.

Resection results

For evaluation of resection results, 417 MRIs were available. In 20 cases, postoperative MRI was renounced due to biopsy-only procedures or postoperative bleeding with no reasonable MRI results expected. In 50% of the procedures, a total resection was achieved (n = 209); in 149 (36%) procedures, an already intraoperatively expected residual volume was proven by postoperative MRI, mostly in left fronto-temporal and straight left temporal lesions. In 14% of the cases, intraoperative evaluation of total resection failed proof by postoperative MRI. Overall, 268 surgeries were evaluated as total resection procedures by the surgeons; however, in 59 cases, postoperative MRI revealed residual tumor volume in those cases with a mean residual volume of 0.41 ml [± SD 0.73, range 0.1–4.8 ml] (Figure 7).

Discussion

The present study summarizes neurological outcome and resection results of 437 procedures as well as risk factors for neurological impairment after surgical procedures in eloquent brain areas when combining all modalities of monitoring and mapping procedures for tumor resection of infiltrating lesions.

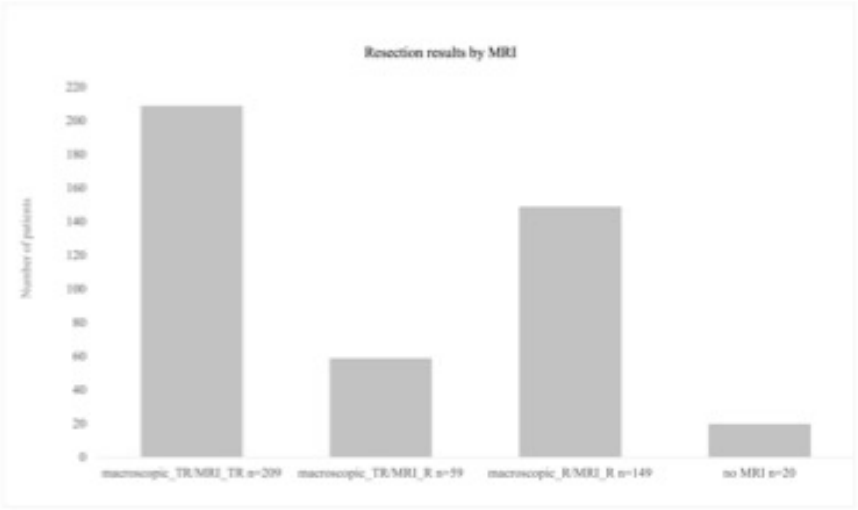

FIGURE 7
Resection results as obtained by postoperative MRI scans. A total of 209 procedures were finished with total resection. In 59 cases, surgeons' evaluation was total resection intraoperatively but nevertheless post-OP MRI revealed residual volume (mean 0.4 ml). A total of 20 procedures were biopsies only where no MRI postoperatively was conducted.

Stimulation procedures and neurological outcome

Monopolar stimulation was conducted in the vast majority of procedures. Motor pathway mapping with cortical and subcortical monopolar stimulation was performed on lesions in both hemispheres with no significant difference. This technique is widely used for intraoperative mapping of the motor cortex (M1) and cortico-spinal tract (22, 23). Mapping of motor functions can also be carried out using bipolar stimulation (12, 24); however, it is by far not as reliable as monopolar-induced MEPs or TES-MEP.

In our clinic, bipolar stimulation for motor mapping was only performed additionally to monopolar cortical mapping in cases when monopolar mapping revealed MEP answers in more than one gyrus or if obtained MEPs showed some inconsistences. Bipolar mapping was significantly more often used on left hemispheric lesions for language mapping procedures, which is also described as standard procedure in the literature (11, 25); however, for language mapping, patients need to be awake during surgery. In our cohort, the majority of procedures were performed in the awake status and hereof the majority of lesions were located on the left hemisphere. SSEP monitoring was also used more often in left hemispheric lesions, which the authors think is a result of the majority of lesions located left hemispheric; at least 54% of the procedures were performed on lesions located in the left hemisphere. 31% of the right hemispheric lesions were also operated on in the awake status. Our group mainly addressed right hemispheric lesions under monopolar stimulation in the awake status when fine motor skills or complex motor tasks had to be monitored during surgery.

Major focus when choosing individual mapping and or monitoring modes lies in the neurological outcome. Maximum resection results shall be achieved under maximum safe circumstances concerning motor and speech integrity of the patient. New neurological deficits after brain surgery negatively affect quality of life in glioma patients, which has been discussed more frequently in the past years to be defined as an important prognostic factor (26), and can contribute to a shorter overall survival at least in patients with glioblastoma (27). Furthermore, a delay in adjuvant therapies due new postoperative motor impairment contributes to a decrease in life expectancy. Thus, there is consensus about focusing on preservation of functional integrity during surgical therapy of brain tumors especially high-grade gliomas, as they cannot be cured by surgery (28).

In our study with a large number of procedures, we only found permanent new neurological deficits in 2% of the procedures. Viagano et al. published similar results with new permanent deficits in 1.9% of patients when combining TES and DCS high-frequency stimulation in asleep procedures for tumors affecting motor pathways (29). Rossi et al. studied outcomes in 102 patients with tumors affecting the motor cortex when using different stimulation paradigms for high-frequency stimulation. In the standard approach group, using the same paradigm for monopolar stimulation as we did in our study, also 2% of the patients suffered from permanent neurological impairment (30). A meta-analysis including 90 publications with over 8,000 glioma patients revealed slightly more permanent neurological deficits with 3.4% of surgeries under mapping procedures in eloquent procedures (31). The same result with 3.4% new deficits were achieved in a study by Gogos et al. (16), comprising 58 patients with diagnosed glioma and lesions located near motor pathways.

In patients with direct postoperative neurological impairment, we found two patients in which intraoperatively an increase of SSEP

latencies was seen. In three patients, speech testing showed difficulties due to lack of patients' compliance resolving in a new deficit in the postoperative phase. In the other cases, there were no warning signs such as loss of SSEP or MEP signals, but majority of patients that underwent surgery in the awake status showed fine impairment during intraoperative testing; therefore, resection was stopped under careful consideration of the clinical findings.

None of the patients with permanent deficits underwent surgery with special intraoperative monitoring or mapping events. Five patients suffered from speech disorders, and four patients suffered from new high-grade hemiparesis. Two patients showed minor territorial infarcts in the postoperative MRI; it must be assumed that these were causal for the new and then in the follow-up also permanent neurological deficit (hemiparesis).

There are two questions to be raised in the light of the certainly very low persistent deficits in our cohort. On the one hand, the question is whether the cohorts' localizations really were as functional as assumed from the MRI. We found that only in 0.7% of the procedures, there were only negative mapping results or there was no MEP or SSEP signal to be obtained during the surgical procedure. The authors concluded that in these cases, the tumor was not functionally located. However, this is a very small number given more than 99% of the surgeries with positive feedback and useful monitoring/mapping procedures as evaluated postoperatively by the surgeons. On the other hand, heterogeneity of our cohort might have contributed to the slightly better result as there are different growth and therefore infiltration patterns between tumor entities resulting in different complexities of functional preservation during resection. Infiltrating tumors might be relevantly of higher risk for postoperative deficits due to difficulties in resection limits. In our cohort, the infiltrating tumors were the majority, but there were a not insignificant number of patients with tumor entities that are known for not infiltrating but extruding growth patterns, which is different to the meta-analysis of de Witt et al. as they only enclosed glioma patients with infiltrating growth patterns. In order to evaluate the significance of neuropathological diagnoses, we correlated diagnoses with neurological outcome and found no significant correlation. Thus, for our cohort, we did not see a link from diagnoses to infiltration patterns, resection, and permanent deficits.

When searching for determinants that contributed to the patients' outcome, we found that surgical procedures on left hemispheric lesions were more often noticed to cause postoperative neurological deficits than right hemispheric procedures. Nevertheless, this did not result in permanent new neurological deficits at 6 months FU. However, nine patients suffered from permanent deficit after 6 months post-op, four had recurrent surgery, and five underwent primary surgery. 67% were left hemispheric lesions with five patients suffering from speech disorder and one patient suffering from motor impairment in a left-parietal lesion. Interestingly, we found a strong correlation of preoperative neurological deficit and death within the first 6 months postsurgery.

In our study, majority of left hemispheric lesions were operated in the awake status. Awake procedures are discussed to improve safety of resection (24, 32). Although we found that there was a significant correlation between awake surgical status and direct postoperative speech deficit, which was not seen for motor impairment, in our cohort and this correlation was seen independently from the localization of the lesion, the overall 6-month evaluation of persistent deficits was not significantly influenced by the surgical status. Early postoperative overall neurological deterioration was only seen when using monopolar stimulation; all other monitoring or mapping techniques did not significantly influence the neurological outcome. However, again this finding was not verifiable at the 6-month FU and might have been influenced by the circumstance that monopolar stimulation has been used in nearly 80% of the procedures compared with only 38% bipolar stimulation; we think that the wider exposure of monopolar stimulation might have increased the probability of postoperative effect. Other statistically significant cofounders were not found.

Intraoperative seizures

Intraoperative seizures induced by DCS are commonly seen and discussed complications in the literature. Studies provide a wide range of stimulation-induced seizures with reported rates in the low single-digit up to more than 50%, leading to an increase of neurological postoperative impairment (33–35). Part of the discussion are predictors for intraoperative seizures. Preoperative seizures tend to be risk factors for stimulation-induced intraoperative seizures (24, 33, 36). In our cohort, we recorded seizures in 8% of the procedures, with none of the patients suffering from preoperative seizures. All patients were therapy-naïve concerning anticonvulsants. We were not able to reproduce findings of correlation between preoperative and intraoperative seizures; however, in our cohort bipolar stimulation expectedly correlated with incidence of stimulation-induced seizures, whereas stimulation intensity did not significantly influence the incidence of intraoperative seizures.

Evaluation of surgeons

One of the major aims of this study was to correlate preoperatively chosen monitoring or mapping techniques with postoperative evaluation of the techniques used by the surgeon. We found that in 73% procedures, the postoperative evaluation of obligatory stimulation mode matched the preoperatively defined methods to be used intraoperatively. The localization of the tumor correlated with postoperative surgeons' evaluation, and as expected, monopolar obligatory mapping was found to be essential more often in right hemispheric lesions, whereas bipolar mapping and combined monopolar/bipolar mapping were more often evaluated as essential for tumors in the left hemisphere. Interestingly, SSEP/MEP monitoring only or in combination with DCS was only seen obligatory in 15% with a rising number of obligatory evaluations after engagement of new monitoring staff from 11 procedures that were evaluated as obligatory monitored by SSEP/MEP to 25 procedures (per year). The authors discussed that and found that

there either must be a bias due to availability of more monitoring staff or procedures became more demanding with high-risk vascular involvement. Nevertheless, there was no correlation between stated obligatory stimulation mode and postoperative neurological outcome. Interestingly, more incongruence between the evaluated obligatory method and actual technique used was seen with bipolar mapping. This might be a result of non-adequate awake patients with left hemispheric lesions that needed to undergo bipolar mapping due to localization, but mapping or adequate testing was not able to be performed due to noncompliance to awake situation or seizures at the beginning.

Resection result

The extent of resection and its impact on overall survival (OS) in patients suffering from glioma are widely discussed. Different thresholds for impact on OS were published ranging from 60% to 98% (37–40). Also, in oligodendroglioma and metastasis, the extent of resection seems to have a significant impact on survival (41, 42).

Total resection, meaning no detectable contrast enhancement in the post-OP MRI, was achieved in 50% of the procedures. There were 20 procedures performed as biopsy without post-OP MRI. In 149 (36%) procedures, the functional limit was achieved intraoperatively, as defined by monitoring and or mapping results. In 59 (14%) procedures, surgeons assumed total resection but post-OP MRI showed residual tumor volume with a very low mean residual volume of 0.41 ml and a maximum residual volume of 4.8 ml in one case. In our cohort, total resection was achieved in arguably fewer cases than in comparable publications (31), but there are some points that led to this result. Firstly, functional limits were achieved intraoperatively, in more than one-third of procedures. Achievement of total resection would have meant neurological deterioration for the patient, something that has to be avoided in the light of survival benefits. Secondly, using intraoperative tools for functional preservation and then deciding intraoperatively to maximize resection regardless of the mapping results would fail the surgical aim. Thirdly, in the procedures that were evaluated as total resection but nonetheless showed residual volume in the post-OP MRI, residual volume was marginal with a mean of 0.4 ml. Concerning comparable publications, a residual tumor volume up to 8 cm^3 could be acceptable for an effect on survival that can still be achieved at least for gliomas (40). Furthermore, with this study, we searched for impacts on resection results but found that there was no significant correlation either between monitoring/mapping results or between the resection result and neurological outcome. However, we did not analyze survival data of the present cohort. Nevertheless, in consideration of already published literature, we assume that the very much marginal residual volume did not have any negative impact on patients' OS.

Limitation

The lacking survival data might be a limitation to the study in order to comprehend the given resection results. Nonetheless, as this was not the focus of the present analysis, the authors renounced this fractional analysis. Additionally in some cases, information on stimulation modes or thresholds could not be obtained from all sources that were available to the authors. However, as there were only minor missing data, we do not think that this would have affected the results significantly.

In the context of determining and evaluating the extent of resection in patients with glioblastoma, another limitation might be the lack of an assessment of the influence of 5-ALA on the resection. However, a meaningful statistical analysis in the reported cohort was not feasible because all patients with suspected or confirmed brain tumors, and at least at the beginning of the observation period, patients suspected of cerebral metastasis, received 5-ALA. Therefore, group comparisons regarding the extent of resection for this cohort were not applicable. We clearly assume that, as reported in the literature, resection under 5-ALA had a positive impact on conduction of resection. However, it is important to consider that the current cohort consists of highly functionally located tumors. Even though resection was performed under fluorescence guidance, and residual fluorescence may have been visible, functional assessment was more decisive for the extent of resection.

Conclusion

In the light of the important role of surgical procedures in the therapy process for brain tumor lesions and the superior aim to preserve functionality of the patients, adequate planning of intraoperative required monitoring or mapping techniques is of highest priority. Deciding which intraoperative mapping and or monitoring procedure is best for the patient is highly individual. The choice of a certain technique mainly depends on localization and experience of the surgeon. With the present study, we demonstrate operability of highly functional infiltrating brain lesions of various localizations without major neurological impairment under usage of IONM and mapping techniques. We were able to give an overview of pitfalls and strengths of the different technical procedures and if, respectively, how they correlate with postoperative neurological outcome and resection results. Furthermore, we retrospectively included the surgeons' view and evaluated the impact of a possibly existing mismatch between preoperative and postoperative assessment of individual technical considerations for each procedure. With this evaluation, we were able to show that certain techniques might not be useful for every case and in the light of optimalization of resources not required for safe resections in every cases. These results shall contribute to a practical but high-quality decision-making process for every surgeon addressing eloquent brain lesions.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethikkommission Düsseldorf, Heinrich-Heine Universität. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because Local laws permit usage of clinical data that was obtained during routine procedures without informed consent.

Author contributions

FS-B contributed to the design and implementation of the research, performed data collection and designed statistical analysis of the results and wrote the manuscript. MR contributed to the design of the research and data collection and to the writing of the manuscript. MS designed and directed the project and contributed to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1235212/full#supplementary-material

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Resection of Eloquent Located Brain Tumors by Mapping Only—A Feasibility Study

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Abstract: Background: Patients with eloquently located cerebral lesions require surgery that usually employs mapping and monitoring techniques for the preservation of motor and language function. However, in many cases, mapping only might be sufficient, reducing the need for technical and personnel logistics. Here, we report our experiences using a device that can be operated by the surgeon independently, providing mapping techniques but omitting monitoring techniques. Methods: For monopolar and bipolar cortical/subcortical stimulation, pre-set programs were available and intraoperatively used—two enabling EMG real-time tracking of eight muscles for monopolar (cortical/subcortical) mapping, and two programs for 60 Hz stimulation, one with EMG and one without. Motor mapping was performed under continuous observation of the screened EMG signal and acoustic feedback by the surgeon. For the 60 Hz stimulation, a standard bipolar stimulation probe was connected through a second port. The preoperative application of the subdermal EMG needles, as well as the intraoperative handling of the device, were performed by the surgeons independently. Postoperatively, an evaluation of the autonomous handling and feasibility of the device for the chosen test parameters was conducted. Results: From 04/19–09/21, 136 procedures in patients with eloquently located cerebral lesions were performed by using the "mapping-only" device. Mapping was performed in 82% of the monopolar cases and in 42% of the bipolar cases. Regarding the setup and sufficiency for the cortical/subcortical mapping, the device was evaluated as independently usable for motor and language mapping in 129 procedures (95%). Gross total resection was achieved, or functional limit throughout resection was reached, in 79% of the patients. 13 patients postoperatively suffered from a new neurological deficit. At the 3–6-month follow-up, three patients showed persistent deficit (2%). All of them had language disturbances. The setup time for the device was less than 7 min. Conclusions: The device was evaluated as sufficient in over 90% of cases concerning monopolar and bipolar mapping, and the setup and handling was sufficient in all patients. With the present data we show that in well-selected cases, a very simple system providing mapping only is sufficient to achieve gross total resection with the preservation of functionality.

Keywords: brain mapping; monopolar stimulation; bipolar stimulation; eloquent brain tumor surgery

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1. Introduction

Maximum resection is crucial for favorable outcomes in patients with intrinsic brain tumors [1–3], but is also found to be important in patients with other histopathological entities [4–7]. In the past decades, numerous technical innovations have been introduced to facilitate the function-preserving resection of different brain tumor entities. Intraoperative neuromonitoring (IONM-o) and mapping (IONM-a) procedures of the cortex and subcortical structures, for example, have been complemented by fluorescence-guided procedures [8,9] and intraoperative MRI techniques [9]. Also, preoperative planning with mapping techniques via transcranial mapping [10–12] and diffusion weight imaging [13,14] has become more complex in order to increase safe maximum resection.

Particularly, intraoperative techniques like IONM-o and IONM-a by direct cortical and subcortical mapping techniques have been established widely in neurooncological surgery

for the resection of tumors relating to cortical and subcortical functional areas [12,15–18], as they provide real-time monitoring of the patient's motor and language functional integrity. IONM-o is applied for the monitoring of motor and sensory function. Motor evoked potentials (MEP) are employed for the monitoring of motor integrity. These evoked muscle responses are captured and analyzed, providing insights into the functional status of the motor pathways in patients who are asleep [19–22]. Sensory pathway integrity is monitored by somatosensory evoked potentials (SSEP), measuring the latency and amplitude of two signals between defined points. The underlying principle of SSEP monitoring involves the generation and recording of electrical signals that reflect the transmission of sensory information along neural pathways [15,23]. Thus, these technically and logistically demanding techniques play a crucial role in complex brain surgery where the risk of functional tissue damage is high, and where avoiding such damage while achieving the maximum extent of resection is the main goal in brain tumor surgery [24–26].

Besides these monitoring techniques, there is the possibility of intraoperative brain mapping. This can be done with a high-frequency stimulation technique using a monopolar stimulation probe as well as a low-frequency stimulation technique using a bipolar stimulation probe. Today, monopolar stimulation is the standard for monitoring motor functionality [27,28]. Language mapping is standardly performed by bipolar low-frequency stimulation due to its longer stimulus duration.

For IONM-o with MEP and SSEP monitoring, specially trained personnel are needed to operate technical devices, evaluate the collected measured values, and pass them on to the surgeons. These data serve the surgeon as the basis for further decisions regarding the surgical procedure. The use of bipolar stimulation requires a simple stimulation device (e.g., Ojeman stimulator) and a person who coordinates and evaluates the language test performance. Monopolar stimulation requires the monopolar stimulation device, a reference electrode, and the EMG recording. This technique is usually provided by IONM-o machines, which also provide SSEP, MEP, and ECOG options.

Due to the introduction of a small new device which allows both monopolar and bipolar mapping by the surgeon, a pilot project was started in our clinic. In this study, we report on the indications of "mapping only" without monitoring devices, the neurological outcomes, and the postoperative evaluation of whether the "mapping only" strategy that was determined preoperatively was also confirmed intraoperatively as sufficiently safe by the surgeons.

2. Patients and Methods

The present analysis was conducted between January 2019 and January 2023 at the Department of Neurosurgery at University Hospital Düsseldorf, with approval from the local ethical committee (Study Number 2022–2242). The study focused on evaluating intraoperatively collected data from cortical and subcortical mapping procedures performed on patients with eloquently located supratentorial brain lesions. We also conducted analyses on neurological outcomes, postoperative MRIs, and epidemiological data.

During all surgeries, we utilized the C2 Xtend, and later, the C2 Xplore devices (inomed Medizintechnik GmbH in Emending, Germany). These devices, particularly the C2 Xplore, were a novel addition at the beginning of this study, offering a wide range of functions, concerning brain mapping procedures. We have enclosed a figure illustrating the C2 Xtend device (Figure S1A) and an intraoperative screenshot under monopolar stimulation (Figure S1B). Consequently, the primary objective of our analysis was to determine whether these advanced devices could effectively replace the standard equipment typically used for mapping and monitoring procedures in cases involving eloquently located brain lesions.

2.1. Patients

Inclusion criteria for the present analysis were as follows: (1) supratentorial brain tumor surgery in patients >18 years between January 2019 and January 2023, and (2) the use of the C2 Xtend or C2 Xplore device during the surgery.

All patients that underwent surgery using the mapping-only device in the reported period were included, notwithstanding the assumed neuropathological diagnosis and surgery mode (resection vs. open biopsy). If an open rather than stereotactical biopsy was planned for lesions involving assumed high eloquent localizations, the mapping device was used for the definition of the biopsy limits. This is particularly important in patients with assumed high-grade intrinsic tumors, as the extent of resection is directly linked to the outcome of patients. If the preoperative MRI screening revealed a clear vascular conflict of the tumor, e.g., a tumor involving the Sylvian fissure, patients underwent the surgical procedure using the established IONM-o processes, including MEP and SSEP monitoring, and therefore were not included in the analysis.

2.2. Methods

2.2.1. Mapping Data

In the present cohort, two devices were used for intraoperative brain mapping procedures: firstly, the C2 Xtend, and later, the successor model C2 Xplore (inomed Medizintechnik GmbH, Emmending, Germany, Neuro Explorer Software Version 6). Both devices enable cortical and subcortical brain mapping. The setup and intraoperative handling of the device is conducted by the surgeon alone without the need of additional external staff.

2.2.2. Setup and Implementation

We implemented a standardized configuration and provided training to all neuro-oncology surgeons to ensure consistency in our procedures. This technical setup involved the preoperative placement of subdermal needles for an 8-channel electromyography (EMG) system. Individual customization is possible for the muscles to be monitored. At our clinic, during intraoperative monitoring via EMG, we focused on assessing the muscles located on the contralateral side of the lesion, which are listed below.

2.2.3. Face: *M. orbicularis* Oris, *M. mentalis*

Upper extremity: *M. biceps brachii*, *M. abductor pollicis breves*, and hypothenar muscle group.

Lower extremity: *M. quadriceps femurs*, *M. tibialis anterior*, and *M. abductor hallucis*.

In addition, a neutral electrode was placed in the deltoid muscle and a reference electrode was placed in the FC position according to the 10–20 system. If there was a conflict with the chosen skin incision, the reference electrode was positioned accordingly. After insertion of the needles, they were connected to an adapter box.

All presurgical preparations, including the EMG setup, were performed by the operating surgeon. The setup time for the device and needles was measured randomly.

2.2.4. Stimulation Settings

We stored various programs with the corresponding standard settings on the device. These can also be individually set and configured. At our department, we chose the same parameters as used in our IONM-o systems.

The monopolar cortical stimulation was performed either cortically or subcortically with a monopolar probe. In both operational modes, we employed continuous stimulation utilizing a repetition rate of 0.5 ms. Stimulation was administered in the form of a stimulus train, consisting of five individual pulses, commonly referred to as a "train of five". The interval between successive pulses within this train was set at 4 ms, while each individual pulse had a width of 500 µs. During the monopolar stimulation, the EMG was continuously transmitted to a large display for the visual control of the triggered muscles; in addition, acoustic feedback was triggered via an EMG signal. There were two different programs available: one for cortical and one for subcortical stimulation.

Bipolar stimulation was performed either cortically or subcortically as well. For stimulation, a range of 0.5 to 4 mA with a pulse width of 0.8 mA was used. Each stimulation

cycle consisted of a single pulse, delivered at a frequency of 60 Hertz. The stimulation duration was set at 4 s for each cycle.

During the resection and stimulation, language testing was performed using a standardized protocol with various types of test tools, covering different aspects of language. A more detailed description of this very specific test battery is beyond the scope of this paper.

For the monopolar mapping, the stimulation of the motor cortex standardly began at 10 mA (with the upper limit capped at 20 mA). Once the cortical thresholds for positive responses in the EMG were determined, we proceeded to test the cortical region encompassing the underlying lesion. If there was positive testing in the area of the surgical approach, a new threshold for this specific area was established. Depending on these results, the corticotomy and subcortical preparation could be initiated. The subcortical testing phase takes place during the resection procedure.

The specific program is chosen pre-surgically by the surgeon at the monitor. Programs could be changed throughout surgery.

Parameters related to the stimulation intensity, repetition rates, the quantity of stimuli, interpulse stimulation intervals, and pulse widths were all adjustable to accommodate the preferences and experience of the user. These adjustments could be made at any point during the procedure according to specific requirements.

If the device was under a sterile drape, it could be operated by the surgeon only during the surgery.

2.3. *Awake Surgery*

Awake surgery is a standard procedure in our department for patients with tumors located in the left frontal or temporal lobe, in order to be able to test for language disturbances during resection. We also indicated awake surgery for patients that had to undergo fine-motor skill testing during surgery or for vision control.

2.4. *Evaluation of Sufficiency*

Surgeons were interviewed directly in the postoperative phase if the applied technique was sufficient in their view. Comments were collected and grouped into an evaluation of "sufficient" or "non-sufficient" procedures.

2.5. *Evaluation of Neurological Outcome*

Upon admission, patients underwent an initial neurological examination in order to maintain comparability. Following surgery, patients were subject to multiple evaluations, particularly if any new neurological deficits arose. For the current analysis, we consistently utilized the examination conducted at the point of discharge to define the postoperative assessment. Furthermore, patients who developed new neurological deficits in the postoperative period were subsequently monitored at approximately 3 months and 6 months following surgery. Permanent deficit was defined by a persistent deficit at the 6-month follow-up.

2.6. *Residual Volume (MRI)*

To evaluate the remaining tumor volume, we conducted a review of the postoperative MRI scans. All MRIs were conducted within a 72-h window following surgery. Our classification system included four distinct groups for describing the results: (1) the macroscopic total resection and total resection in the postoperative MRI, (2) the macroscopic total resection and residual tumor volume in the postoperative MRI, (3) the macroscopic residual tumor volume and residual tumor volume in the postoperative MRI, and (4) no MRI.

The residual volume was calculated by one member of the study team by usage of a volumetry tool within the local radiology information system (SECTRA Workstation 101, IDS7, Version 24.1, Sectra AB, Sweden, 2022). The results of the residual tumor volume were expressed in mL, with volumes less than 0.1 mL defined as indicative of gross total resection.

Sociodemographic information, along with the neuropathological diagnosis and any pertinent medical/surgical histories, were extracted from the local patient administration system. Neuropathological findings predating the introduction of the WHO 5 Classifications of Central Nervous System Tumors in 2021 [29] were modified to conform to the revised classification criteria.

2.7. Statistical Analysis

A statistical analysis was performed using IBM SPSS Statistics Version 26 (IBM Corporation, Armonk, NY, USA).

Data were tested using the Shapiro–Wilk Test for normal distribution. Cohort data were not normally distributed; therefore, non-parametric testing with Pearson's chi-squared test for nominal variables, and the independent samples *t*-test, were performed. Statistical significance stated as a *p*-value for all results was set at 0.05.

3. Results

During the specified screening period from January 2019 to January 2023, the mapping devices were employed in 136 procedures. These procedures were carried out on 131 patients, with a mean age of 56 with a standard deviation of ±16 years at the time of their initial recorded surgery. The age range spanned from 22 to 86 years. Of the patients, 62 (47%) were female, while 69 (53%) were male.

Predominant neuropathological diagnoses were metastasis (35%, n = 34), with an equal distribution of Glioblastoma WHO grade 4. In terms of lesion location, 75 procedures were performed on lesions within the left hemisphere (55%), while 59 procedures were directed at right hemisphere tumors (43%). Moreover, two procedures involved surgery at the splenium (2%). Unexpectedly, intraoperative vascular conflicts were encountered in two patients. An overview of the cohort is presented in Table 1.

Table 1. A brief description of demographic, histopathological, localization and functional tumor involvement data of the cohort.

Age (Year) (n = 131)		
	mean	56 [SD ± 16]
	range	22–86
Sex (n = 131)		
	female	62
	male	69
Diagnosis (n = 136)		
	Astrocytoma IDH-mutant (2–3)	16
	Astrocytoma IDH-mutant (4)	2
	Glioblastoma, IDH-Wildtype (4) MGMT −	29
	Glioblastoma, IDH-Wildtype (4) MGMT +	28
	Oligodendroglioma (2–3)	15
	Cerebral metastasis	34
	Aggressive NHL	4
	Atypical Meningeoma	3
	Dysembrioplastic neuroepithelial tumor	1
	Ganglioglioma	1
	Reactive tissue changes	1
	Florid inflammatory demyelinating	1

Table 1. *Cont.*

Localisation (n = 136)	
Left hemisphere	75
Right hemisphere	59
Other	2
Functional Tumour Involvement (n = 136)	
Language only	33
Motor only	59
Combination of language and motor	11
Positive stimulation at tumour margin	31
Not eloquent	2

Figure 1A–D visualizes different neuropathological details and details about the localization of the lesions that were included in the study, as well as the functional involvement of the tumors that were surgically treated. Tumor localization was grouped into four functional involvements: "language involvement only", "motoric involvement only", "combination of language and motor involvement", as well as "positive mapping only at the tumor margin". The last group defined tumors, that might only have been partly functionally located, as we only received positive mapping/stimulation results at the tumor margins, sometimes with high current thresholds.

53% (n = 72) of all procedures in the cohort were performed as awake procedures, independent from localization or mapping techniques. Left-hemispheric lesions more often triggered awake status, with 56 procedures conducted in the awake setting in lesions located in the left-hemisphere, versus 16 procedures in right hemisphere lesions (78% vs. 22%; $p < 0.01$). All procedures (n = 2) with lesions located at the splenium were performed as awake surgeries. Patients with tumor-vascular conflicts in the preoperative MRI were excluded, adhering to the defined exclusion criteria. Nevertheless, in two patients, there was an unexpected vascular conflict due to a tumor extension to the vascular level of the Sylvian fissure, which was not seen in the preoperative MRI scan. The mean setup time (n = 48) was 5 min 48 s.

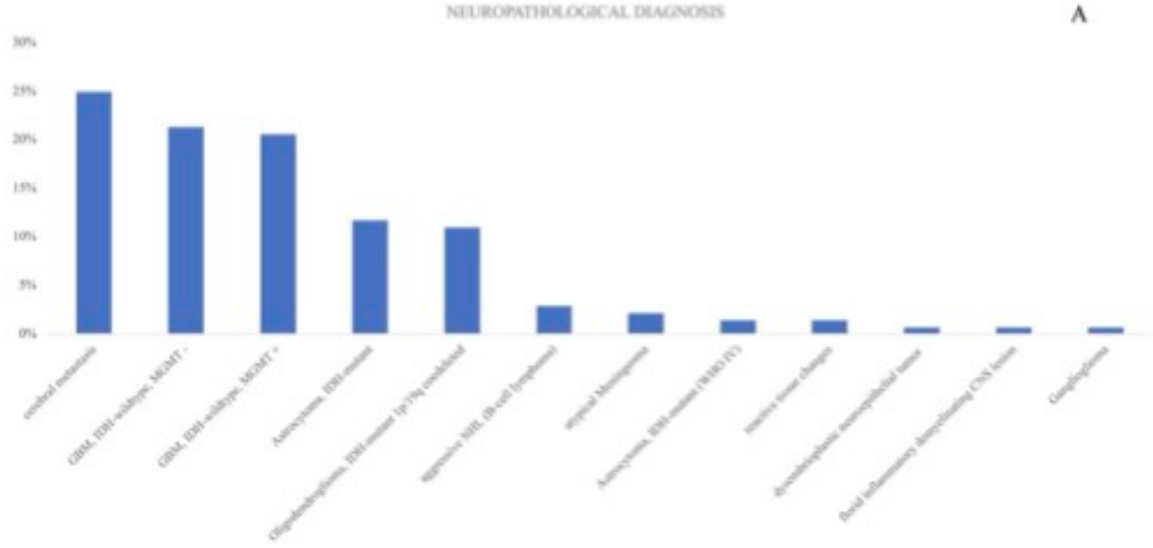

Figure 1. *Cont.*

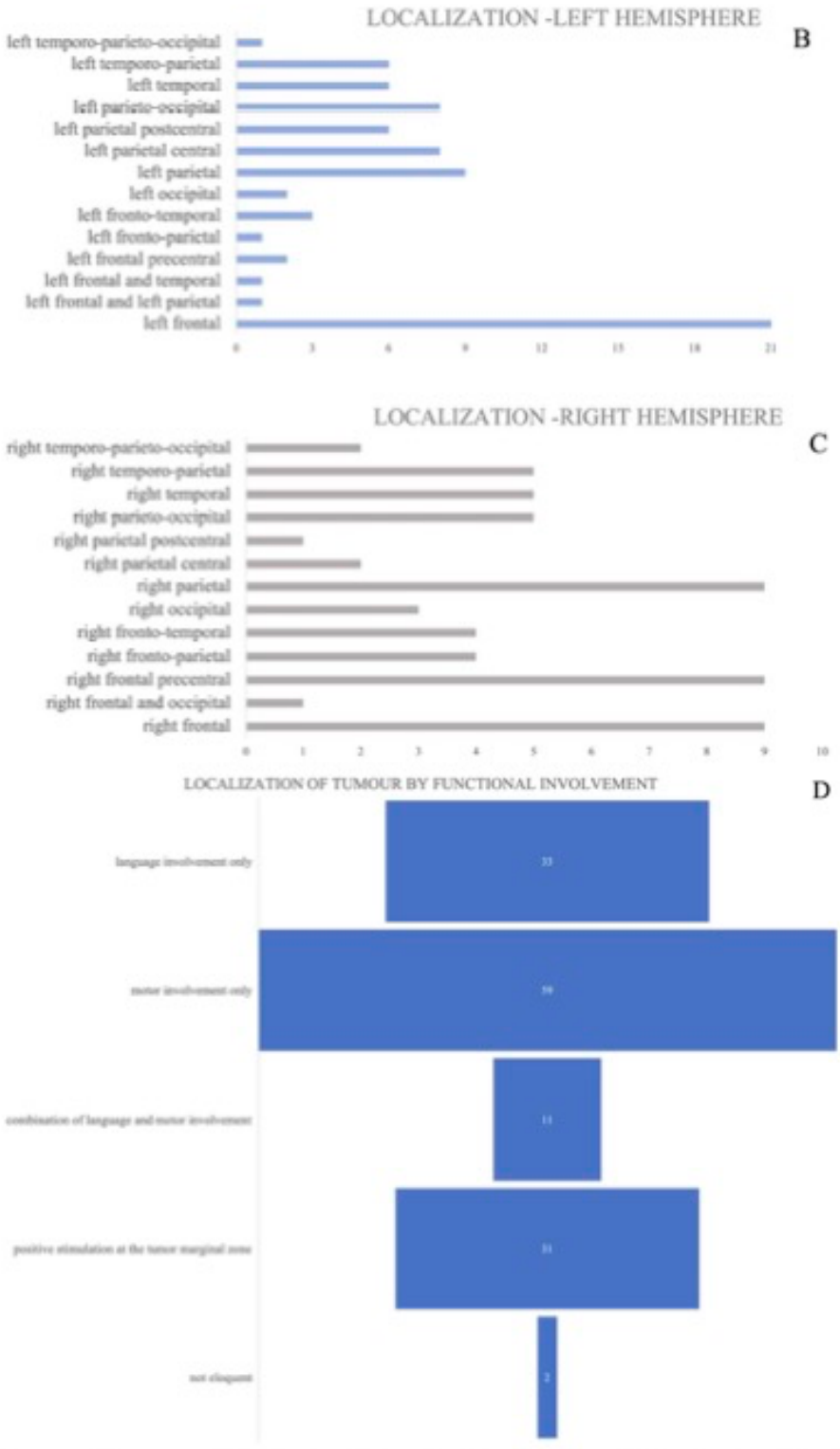

Figure 1. (**A**) percentage distribution of diagnosis within the cohort, (**B**) visualization of detailed tumor location in the left hemisphere, (**C**) details for tumor localization for right hemispheric tumors. (**D**) Details of tumor localization concerning the functional involvement.

3.1. Mapping Data of Monopolar Stimulation

In 111 procedures (82%), monopolar mapping was conducted by the surgeons. 24 procedures (18%) were performed without planned monopolar mapping. In one surgical case, there was partly missing documentation regarding the use of the monopolar mapping technique (information on cortical stimulation was present but information on subcortical stimulation was missing). Cortical monopolar mapping was performed in 111 procedures (82%), of which 87% (97) could define the cortical motor threshold. In the seven remaining cases, the cortical monopolar stimulation up to 20 mA remained negative regarding the EMG responses.

Subcortical monopolar stimulation was carried out in 101 surgical cases (74%). In 10 procedures, no tracking of the corticospinal tract defined as a positive EMG response was achieved, with a stimulation intensity of up to 15 mA (Figure 2).

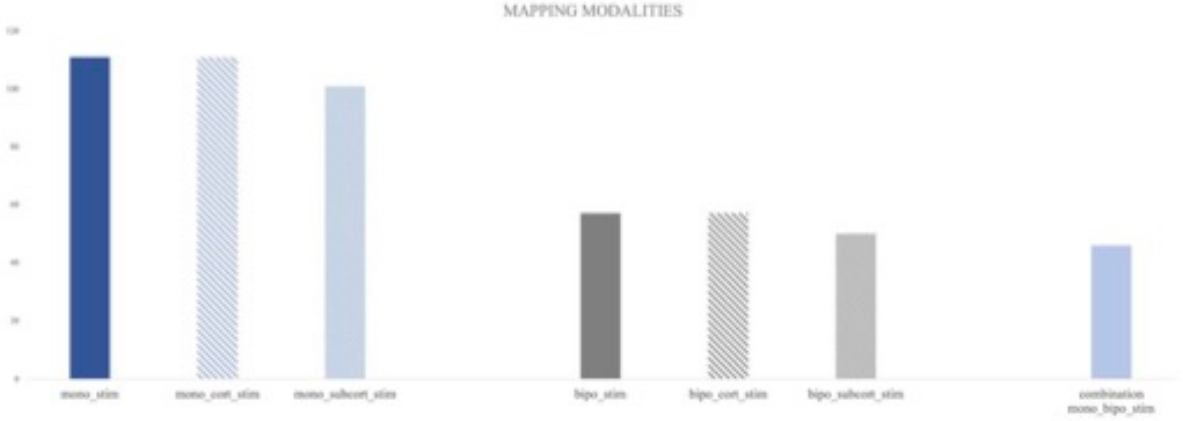

Figure 2. Overview of mapping modalities used in the cohort: mono_stim = monopolar stimulation, mono_cort_stim = monopolar cortical stimulation, mono_subcort_stim = monopolar subcortical stimulation, same abbreviations were used for bipolar stimulation).

The mean cortical stimulation intensity for the cohort was 7.7 mA [±4.3 SD], with a range of 1.5–20 mA, and the subcortical stimulation intensity was 4.4 mA [±3.6 SD] ranging from 0.3–15 mA.

3.2. Mapping Data of Bipolar Stimulation

Overall, 57 procedures were conducted with bipolar stimulation (42%). Bipolar cortical stimulation was employed in 42% of the cases (n = 57); however, in eight cases, there was no stimulation-induced effect on the control area (14%). Furthermore, 29% of the procedures used subcortical bipolar stimulation (n= 50), of which, in 15 cases, only negative stimulation results (no speech arrest or other disturbances in speech testing) were achieved (Figure 2).

The mean cortical bipolar stimulation intensity was 1.3 mA [±0.6 SD], ranging from 0.5 to 3 mA, and the subcortical bipolar stimulation intensity was 1.2 mA [±0.4 SD], with an observed range from 0.8 to 2 mA. At this point, it is important to notice that, due to technical differences in comparison to standard bipolar stimulation devices, including the Ojeman stimulator and monitoring devices with separate mapping boxes that measure the peak current, the device used measured the peak-to-peak current, leading to a displayed output stimulation intensity twice as high as those of standard devices (e.g., if the peak current is displayed as 0.5 mA, the peak-to-peak current is displayed with 1 mA). For the present analyses, the stimulation intensity results were recalculated as the peak current for better comparability to other IONM-o/IONM-a devices.

Bipolar stimulation was used significantly more often in left-hemisphere tumors than right-hemisphere lesions ($p = 0.011$).

A combination of both mapping modalities was used in 46 (34%) surgical procedures.

In regard to the preoperatively defined required mapping or monitoring techniques, in 95% (n = 129) of the procedures the choice of the "mapping-only" procedure was evaluated as sufficient by the performing surgeon. In this sub-cohort, in three cases additional monitoring via strip electrode was evaluated as "would have been helpful" but did neither influence the surgical outcome regarding the extent of resection nor the neurological outcome of the patients. In five cases, the "mapping-only" procedure was evaluated as "not sufficient". In two of the cases, there were technical issues leading to technically no stimulation. In three cases, MEP/SSEP monitoring was intraoperatively evaluated as obligatory. In two of those cases, a marginal residual tumor volume (0.1 mL) was revealed in the postoperative MRI. In two further cases, all applied mapping techniques remained negative; thus, the tumour localization appeared as not functional during surgery and mapping was evaluated as "not needed". An evaluation of the sufficiency of the "mapping-only" procedure did not significantly depend on localization ($p = 0.255$), but in cases when awake surgery was planned but patients were not adequately awake, the "mapping-only" procedure was significantly more often evaluated as "insufficient" ($p = 0.042$).

3.3. *Neurological Outcome*

3.3.1. Postoperative Neurological State

Neurological deterioration, defined as a new neurological deficit in the postoperative phase, was seen in 10% of the procedures (n = 13). Two patients died in the postoperative course; however, death was not directly associated to surgical intervention (Figure 3A). Localization did not significantly influence a direct postoperative deficit, however a trend for left-hemispheric lesions was seen ($p = 0.099$), whereas bipolar stimulation triggered new postoperative deficits more often ($p = 0.008$).

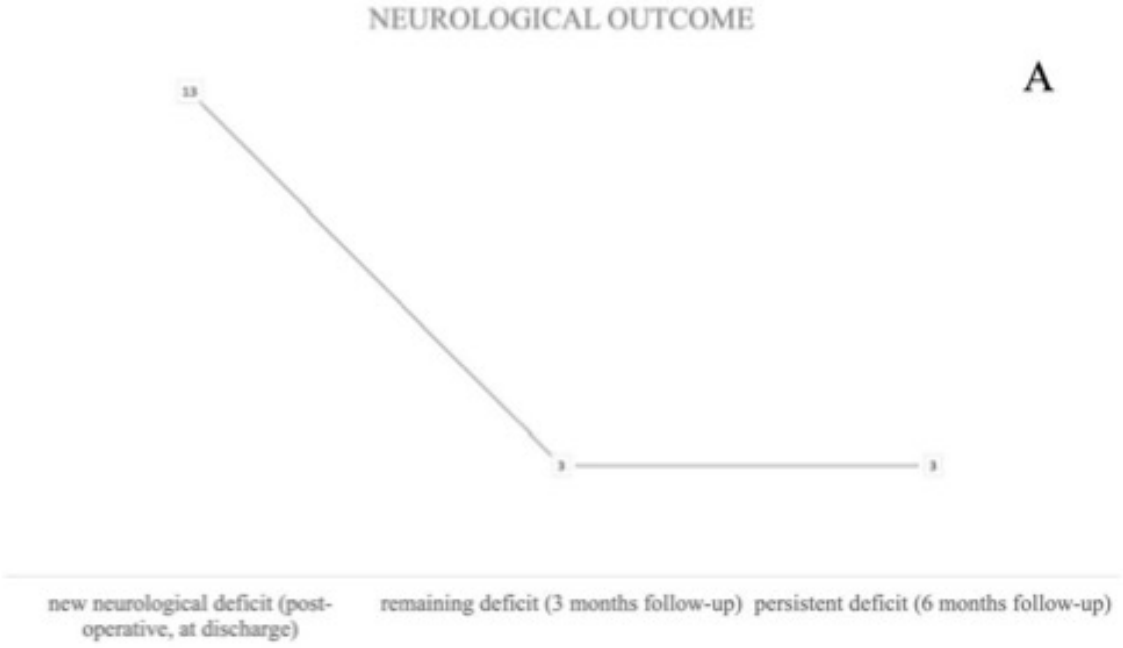

Figure 3. *Cont.*

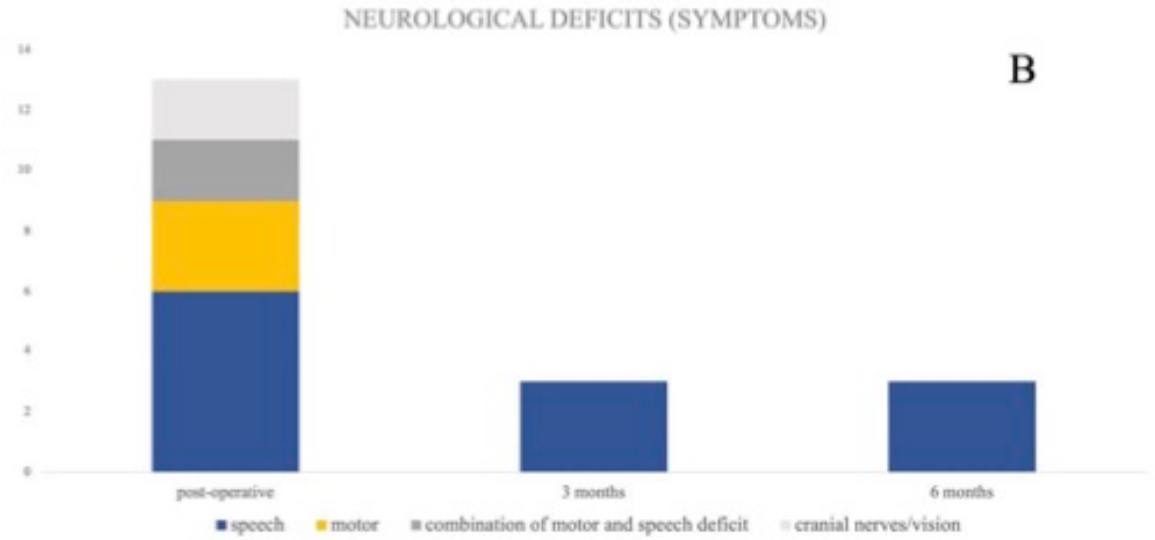

Figure 3. Number of new neurological deficits related to surgical intervention at three time points ("postoperative", "three-month", and "six-month follow-up") (**A**) and their corresponding symptoms at the corresponding time point (**B**).

The majority of patients suffered from new speech disturbances (46%, n = 6). Motoric impairment was seen in three patients (23%). A combination of new motor and speech deficits was seen in two patients (Figure 3B).

3.3.2. 3 Month FU

After three months, three (2.2%) patients still suffered from a neurological deficit, one more patient had died, and two patients did not show up to follow-up appointments and were therefore categorized as loss of follow-up (Figure 3A). A persistent, respectively permanent deficit at the 6-month follow-up was still recorded in those three patients (2.2%). All of them suffered from a persistent speech disturbance. There was no permanent motor deficit in this cohort (Figure 3A,B) under mapping-only conditions.

3.3.3. Permanent Deficit

Permanent deficits were not caused by any vascular complications such as infarction or bleeding. In all three patients with permanent deficit, a combination of monopolar and bipolar stimulation was used. There was a trend for a higher risk of postoperative deficits in patients who underwent awake surgery and in cases where awake surgery was planned but the patients did not wake up adequately ($p = 0.53$).

3.4. Resection Results as Evaluated by Postoperative MRI

In 127 procedures, a postoperative MRI was obtained (93%). Nine procedures were conducted as open biopsies and an MRI scan was not planned and therefore also not conducted in the postoperative course.

Concerning the whole cohort, 59% (n = 75) of the postoperative MRI scans showed no contrast enhancement (threshold defined as <0.1 mL), and an intraoperative evaluation of the gross total resection was confirmed. However, in 25% (n = 32) of all procedures, there was an expected residual tumour volume, as throughout the mapping process functional limits were defined and the resection had to be stopped at some point. In the remaining 16% (n = 20) of procedures, postoperative MRI scans revealed an unexpected residual volume with a mean residual volume of 0.47 mL [±0.7 SD] ranging from 0.1 to 2.8 mL. The mapping modality did not significantly correlate with the resection result (monopolar stimulation

$p = 0.303$, bipolar stimulation $p = 0.309$). Additionally, there was no significant correlation between the resection result and the sufficiency of the mapping procedure ($p = 0.114$). Figure 4A,B illustrates resection results of the cohort, as well as the resection results divided into groups of functional involvement. A total of 51% of the tumors involving motor pathways showed a postoperative total resection (as defined by contrast enhancement <0.1 mL in the postoperative MRI), as did 61% of the tumors involving language, and 36% of the tumors combining motor and language functionality. Surgery was stopped according to functional restrictions obtained by the mapping procedure due to motor impairment in 25% of the procedures, language affection in 21% of the procedures, and a combination of both motor impairment and language affection in 36% of the procedures (Figure 4B). Figure 4B illustrates the resection results grouped by the functional involvement of tumors.

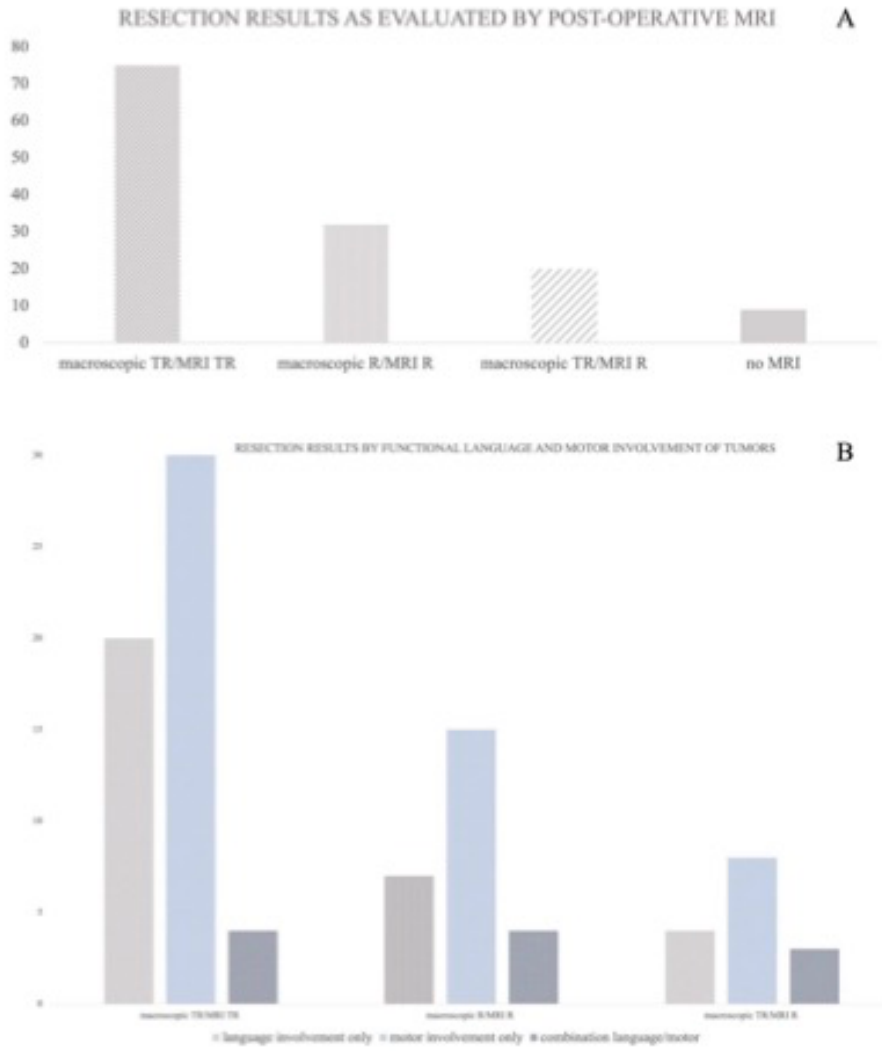

Figure 4. (**A**,**B**) A: Resection results evaluated by 72 h postoperative MRI scans. 127 MRIs were available for this analysis. In the majority of patients either gross total resection or expected residual volume was confirmed (79% macroscopic TR/MRI TR and macroscopic R/MRI R). In 20 procedures an unexpected residual volume was revealed with a mean volume of 0.47 mL (macroscopic TR/MRI R).

4. Discussion

In the present study, mapping-only surgical approaches that were performed with a device independently handled by the surgeon, are described for the resection of eloquently located supratentorial lesions, including the neurological outcomes and extent of resection in 136 procedures.

During the resection of brain lesions in critical brain regions that control motor and language functions, surgical neuro-oncology units commonly employ motor and language mapping. This practice aims to preserve the patient's neurological functioning. To carry out this mapping, specifically trained personnel like neurophysiologists or technicians are essential. They are responsible for the preoperative setup, operation of devices, and crucially, the real-time evaluation of data during surgery [30]. However, it is worth noting that these resources may not always be readily available, especially during night-time procedures or in regions with limited medical infrastructure. Therefore, in our study, we utilized a device that the surgeon can operate independently, which had previously been proven to be effective in emergency situations during the resection of Glioblastoma in two patients facing life-threatening neurological deterioration [31]. Thus, monopolar and bipolar brain mapping can be performed without any further need for external expert staff but by the surgeon alone.

In the present study, we assessed the effectiveness of using the mapping-only device in elective surgical procedures for patients with brain lesions located in critical areas. Our findings indicate that, in 95% of the procedures where we used the mapping-only device without additional monitoring, it was deemed sufficient. Our analysis primarily focused on two key aspects: the success of the lesion resection and the neurological outcomes of the patients.

Monopolar motor mapping was performed in 82% of all procedures and was of particular interest as it could be conducted with relatively straightforward effort. Motor mapping is indicated in order to improve the extent of resection and patients' outcome [32–34]. This approach is commonly employed in surgeries where there is a risk to the motor cortex or corticospinal tract and is often conducted with patients under general anesthesia. Bipolar stimulation is frequently used in patients who are required to undergo language testing during awake surgery, which is a practice commonly described as the standard procedure in the existing literature [16,18,35]. In our cohort, bipolar mapping was also mainly employed for language mapping procedures. For effective language mapping, patients must remain awake during surgery. In our patient group, the majority of procedures were conducted with patients in an awake state (53%). During procedures where bipolar stimulation was applied, a significant proportion of those lesions were found to be located within the left hemisphere, as described in Duffau et al.'s early mapping studies [36,37].

The neurological outcomes in our cohort showed a 2.2% occurrence of permanent neurological deficits, which is a result that is consistent with findings in other, sometimes larger, studies focusing on mapping procedures. In 2008, Sanai et al. described permanent speech deficits in 1.6% of patients in a cohort study of 250 Glioma patients [38]. In our cohort, we observed a tendency toward a higher risk of neurological impairment in patients scheduled for awake surgery but who did not adequately achieve an awake state. This emphasizes the critical importance of thorough awake testing in patients with lesions that potentially affect pathways related to phonological and semantic processing [39].

Motor impairments in our patients occurred only temporarily in a direct postoperative state, and there were no permanent motor deficits; thus we discussed that it is possible to dispense with monitoring procedures in selected cases without posing an additional risk to the patient. In studies where monitoring and mapping techniques were combined, comparable quotas of neurological impairment were seen. Viganò et al. reported 1.9% of permanent deficits using transcranial electric stimulation (TES) motor evoked potential monitoring and direct cortical stimulation [12]. Interestingly, in this study they saw a higher number of false positive results in TES monitoring in patients, depending on tumor localization and patient positioning during surgery. In 2020, Gogos et al. also reported a

combined study of "triple motor mapping" with TES, bipolar, and monopolar controls in patients with lesions located near motor pathways. Here, these authors found that, overall, two patients (3.4%) suffered from a new neurological permanent deficit at 6 months, although only one of them showed MEP worsening during resection [28].

As the extent of resection, particularly in high-grade glioma [40,41] but also low-grade glioma [42,43] and even metastasis [44], plays an important role for the overall survival of the patients, a major aim in the treatment of brain tumour patients is to maximize the extent of resection. In cases involving language or motor pathways, this shall be achieved under the preservation of functionability.

In our cohort, gross total resection, defined as residual volume < 0.1 mL (non-measurable) in the postoperative MRI, was achieved in 75 procedures; however, due to mapping results, surgeons were forced to stop the resection in order to preserve the functionability of the patients in 32 cases (25%). In only 20 procedures, an unexpected residual contrast enhancement was seen, with a mean volume of 0.47 mL and a maximum of 2.8 mL in one case. In the literature, there are various limits reported concerning the significant influence of residual tumor volume on overall survival, particularly in glioblastoma patients, ranging from 2 to 5 mL [45–47]. The arguably low rate of gross total resection is due to the strictly defined limit of 0.1 mL. If thresholds are applied on our cohorts, which are in line with other reported rates providing advantage for overall survival, we were able to achieve 100% gross total resection, excluding those patients that underwent subtotal resection due to functional limits in the mapping procedures. Therefore, we did not see disadvantages for our patients' cohort due to waiving additional monitoring.

There are certain limitations in our study that need to be considered. First, it is important to acknowledge that the favorable outcomes observed in our study may be influenced by the exclusion of patients with vascular conflicts. In these cases, MEP and SSEP monitoring is essential for safety reasons. However, it is worth noting that our cohort primarily consisted of patients with highly functional localizations. Second, due to the relatively small sample sizes in some specific subgroups we examined during our data analysis, statistical testing was not feasible and, consequently, was not conducted.

5. Conclusions

There is an indisputable increase in safety achieved through the combination of monitoring and mapping techniques. If they are easily and quickly available, these techniques should be aimed for in brain tumour surgeries as described in this paper as a standard procedure. However, we have showed that, deviating from the established combined technical setup of monitoring and mapping possibilities, using a mapping-only device, can achieve comparable results in terms of postoperative deficits and resection outcomes. We have demonstrated that a mapping only technique is safe (2% deficit) and efficient. Brain tumour surgery is performed in many countries around the world. With the help of a mapping-only technique, eloquently located tumors can be treated with great safety and very good resection results. This is a prerequisite for improved outcomes after therapy for aggressive diseases, not least in the case of high-grade infiltrative tumors. Given the simple logistics needed and the affordable price of the technology, we hope that our report promotes the supply and availability of mapping only devices in neurosurgical units under careful consideration of special indications. We think that this could be an absolute gain for brain tumour patients, especially in the field of emergency care, or in health care systems where there might be limited financial—and therefore personnel and technical—access to functional monitoring resources for patients with eloquent brain tumors.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/brainsci13101366/s1, Figure S1: C2 Xtend device and screenshot of intraoperative display of monopolar stimulation.

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Data Availability Statement: Data are available on request by the correspondent author, subject to ethical and legal restrictions.

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Conflicts of Interest: The authors declare no conflict of interest.

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(4)

Direct Cortical Stimulation in Neurosurgical Emergencies: Single-Center Experience in 2 Patients

Franziska Staub-Bartelt[1], Björn Bastian Hofmann[1], Marion Rapp[1,2], Daniel Hänggi[1], Marcel Alexander Kamp[1,3], Michael Sabel[1,2]

BACKGROUND: **Intraoperative neuromonitoring (IONM) is widely used for elective resection of eloquently located brain tumors to increase safety and extent of resection. Owing to the need for specially trained personnel for IONM and the sophisticated, time-consuming technical setup, standard IONM is usually not suitable for emergency situations. We report the use of a device that can be operated by the neurosurgeon autonomously for monopolar brain mapping in 2 emergency cases.**

METHODS: **Both patients were initially scheduled for elective neurosurgery under IONM. Acute neurological deterioration in both cases led to emergency surgery. For monopolar cortical/subcortical stimulation, a standard monopolar probe was connected to a new device enabling electromyography real-time tracking of 8 muscles. Preoperative application of subdermal electromyography needles and intraoperative handling of the device were performed by the neurosurgeons independently.**

RESULTS: **Cortical mapping of the motor cortex was performed in both patients with a threshold of 4 mA in case 1 and 14 mA in case 2. Gross total resection with residual tumor volume of <2 mL in case 1 and subtotal resection with residual tumor volume of 4.2 mL in case 2 were achieved under use of the new device without any new neurological deficit. Grade IV glioblastoma was diagnosed in both patients.**

CONCLUSIONS: **We demonstrate the feasibility of monopolar stimulation in 2 patients undergoing emergency neurosurgery using a device autonomously operated by the surgeon. Owing to fast setup and nondemanding handling, monopolar stimulation could be used during emergency neurosurgery to extend resection with preservation of neurological function in both cases.**

INTRODUCTION

Intraoperative neuromonitoring (IONM) including direct cortical and subcortical stimulation is the gold standard method for elective resection of eloquently located brain tumors. In high-grade glioma surgery, it has been shown that besides the extent of resection, preservation of motoric and speech function is crucial for survival of patients.[1,2] Motor and speech mapping is considered to increase the extent of resection and improve neurological outcome of patients by preventing perioperative neurological deterioration.[3] Basically, IONM for supratentorial lesions comprises transcranial electric stimulation monitoring of somatosensory evoked potentials (SSEPs) and motor evoked potentials (MEPs) and direct cortical stimulation by monopolar and/or bipolar stimulation probes or a grid electrode. Direct cortical stimulation by monopolar stimulation is a high-frequency stimulation establishing a large electric field between the stimulation probe and a reference electrode, resulting in electrical activity in the skeletal muscles. The triggered activity in terms of MEPs can be detected by electromyography (EMG). Motor mapping via direct cortical stimulation or MEP monitoring via transcranial electric stimulation is mainly used in the asleep state for motor testing only but can also be used in patients in the awake surgery setting for fine motor skill testing.[4]

Key words
- Brain tumor
- Direct cortical stimulation
- Glioblastoma
- Intracerebral haemorrhage
- Intraoperative neurophysiological monitoring

Abbreviations and Acronyms
EMG: Electromyography
IONM: Intraoperative neuromonitoring
MEP: Motor evoked potential
MRI: Magnetic resonance imaging
SSEP: Somatosensory evoked potential

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Anodal-cathodal (cortically) and cathodal-anodal (subcortically) monopolar stimulation can be performed. In contrast, bipolar stimulation is a low-frequency stimulation causing an electrical field between the 2 tips of the probe. Bipolar stimulation blocks neuronal activity and thus is used for speech mapping in the awake surgery state.[5] Motoric testing with bipolar stimulation probes is also possible, but the risk for intraoperative seizures is increased owing to a required higher amperage for motor response compared with monopolar stimulation.

Stimulation modes can be performed, but owing to logistic challenges of IONM in terms of sophisticated technical setup and the need for a dedicated technician for intraoperative evaluation of IONM results, full IONM techniques are usually applicable only in elective cases and might not be accessible in emergency situations or in elective settings in neurosurgical departments with limited resources. In emergency situations, identification of eloquent cortical and subcortical structures may enhance patients' safety as well. In this article, we describe a setup that enables direct cortical and subcortical mapping with monopolar and/or bipolar stimulation that can easily be performed by neurosurgeons without support by a clinical neurophysiologist.

MATERIALS AND METHODS

The C2 Xtend (inomed Medizintechnik GmbH, Emmendingen, Germany) is a device for intraoperative neurophysiological monitoring that uses EMG recordings of 8 muscles and monopolar or bipolar cortical and subcortical stimulation. The setup of the device can be performed by a trained neurosurgeon without additional support. We issued a standard operating procedure for our department and trained all surgical neurooncologists.

Intraoperative Neurophysiological Stimulation

Setup. Real-time EMG of 8 muscles is displayed on the monitor of the device (Figure 1) or a tablet screen. The handling of stimulation settings can be conducted only at the device itself. For EMG tracking, subdermal paired needle electrodes are applied preoperatively to predefined muscles. EMG of the following muscles/muscle groups is performed according to a standardized procedure: orbicularis oris, mentalis, biceps brachii, abductor pollicis brevis, hypothenar muscle group, quadriceps femoris, tibialis anterior, abductor hallucis. Additionally, a grounding single-needle electrode is placed at the deltoideus and a single corkscrew electrode is placed at FZ position (according to 10-20 system[6]) adjusted to the planned skin incision for reference of monopolar stimulation. EMG needles are placed to the muscles contralateral to the lesion. After connecting the needle electrodes with the device via an EMG adapter box, the monopolar mapping program with predefined stimulation settings is chosen. Regardless of the surgery setup, setup of the

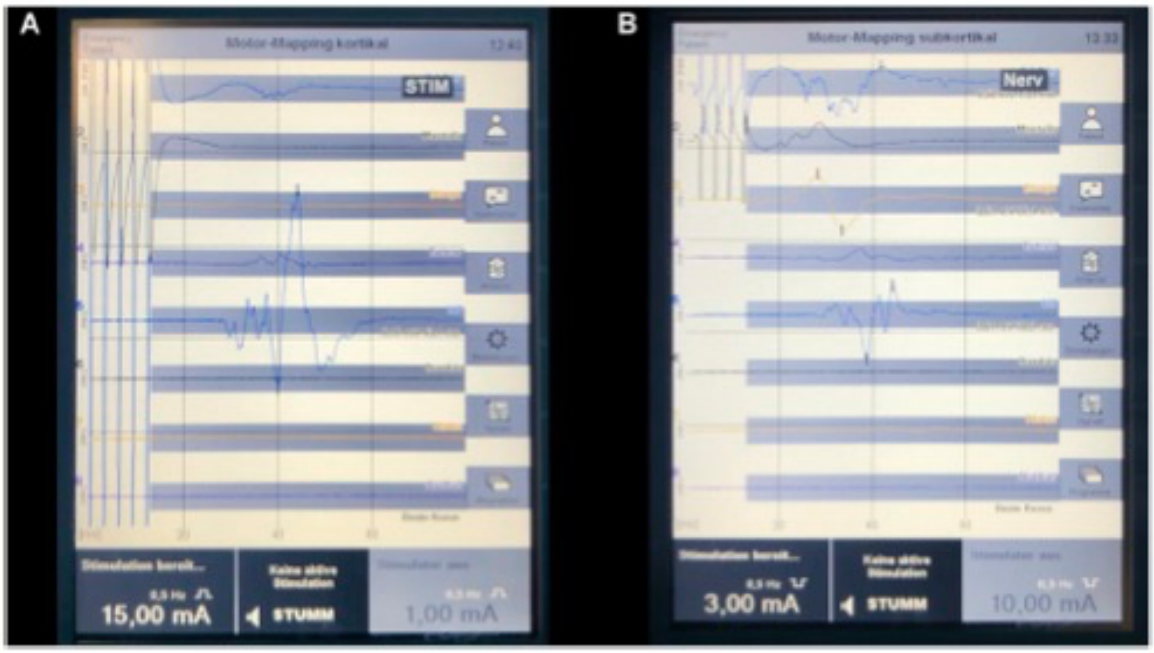

Figure 1. Screenshot of real-time electromyography tracking during (**A**) cortical and (**B**) subcortical monopolar stimulation. Electromyography tracking of 8 predefined muscles is shown on the device monitor. Visual and acoustic feedback is obtained under stimulation.

device can be performed in <10 minutes in parallel to the anesthetic procedures. Immediately before starting the surgical procedure, a sterile covering is placed over the device and the monopolar stimulation probe is connected to the device.

Standard Stimulation Settings. For cortical motor mapping, anodal-cathodal stimulation is performed; for subcortical stimulation, cathodal-anodal stimulation is used. In both modes, we use continuous stimulation mode with a repetition rate of 0.5 ms (2 Hz). Stimulation is conducted as a train of stimuli with 5 pulses (train of 5) with an interpulse stimulation interval of 4 ms and a pulse width of 500 μs. Cortical stimulation starting with 10 mA (up to a maximum of 20 mA) is conducted for defining the motor cortex. After determination of cortical thresholds for positive control, the cortical area with underlying lesion is tested and again a threshold is defined. After corticotomy and subcortical preparation, subcortical testing is conducted during resection. Repetition rates and number of stimuli as well as the interpulse stimulation interval and pulse width can be changed according to user requirements and experience at any time.

Illustrative Cases. *Case 1: Acute Decompensation of Glioblastoma.* A 30-year-old woman was brought to an emergency department at another hospital because of progressive behavioral changes in the past several weeks. The patient had a history of a constitutional mismatch repair deficiency syndrome with multiple cancer-related surgeries and had mental retardation. The initial computed tomography scan revealed huge bifrontal edema, and the patient was transferred to our neurosurgical ward. On examination, the patient presented with signs of frontal lobe malfunction as well as mutism, aphasia, and a low-grade paresis on the right side. We ordered emergency magnetic resonance imaging (MRI), which showed a massive contrast-enhancing cerebral lesion in the left frontal lobe crossing the midline and causing midline shifting of 2.1 cm and displacement of the ventricular system (Figure 2A). Additionally, a parafalcine extra-axial lesion was detected. The patient was scheduled for planned tumor resection under IONM. In the evening hours of admission day, the patient's condition deteriorated to a Glasgow Coma Scale score of 9 because of reduced vigilance, and emergency tumor decompression with monopolar stimulation was performed. Setup of the cortical mapping system was performed by the surgeon within 5 minutes in parallel to anesthetic preparations.

The motor cortex was identified by cortical monopolar mapping at a threshold of 4 mA with motor response in all tracked muscles. Subcortical monopolar stimulation was performed during removal of tumor masses in the frontal lobe pole. Subcortically, thresholds of 0.3 mA at the dorsal parts of the resection cavity were obtained. Intraoperatively, there were no macroscopic signs of remaining tumor tissue. Neuropathological results revealed a World Health

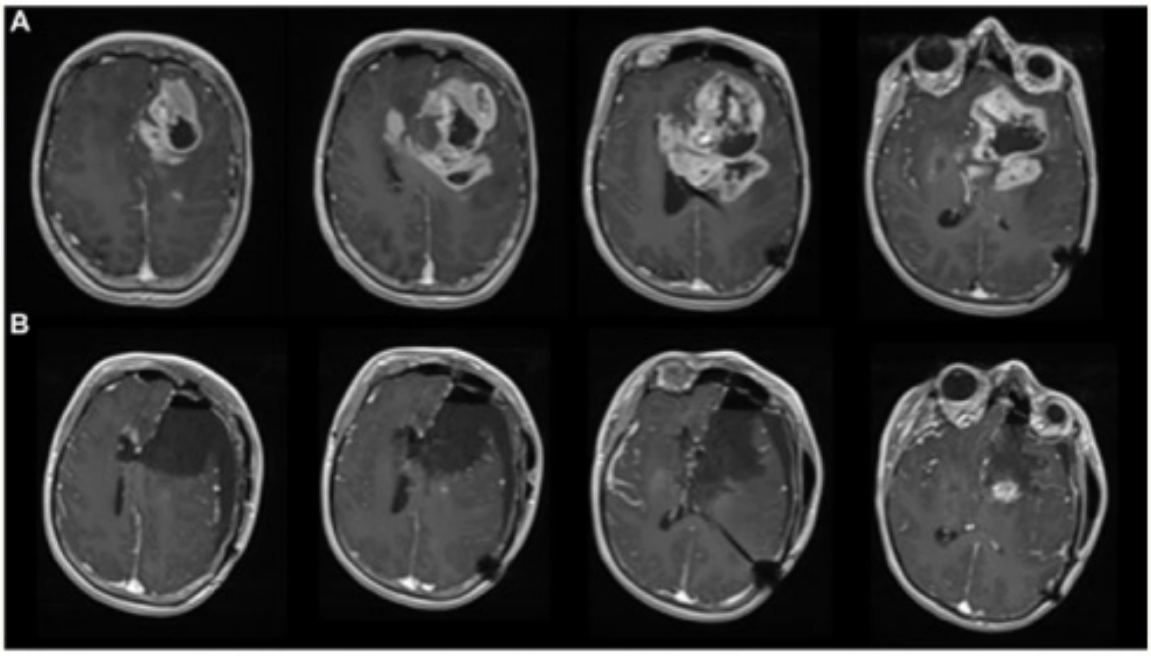

Figure 2. Acute decompensation of glioblastoma. (**A**) Preoperative magnetic resonance imaging showing left frontal contrast enhancement with midline crossing. (**B**) Postoperative magnetic resonance imaging showing extent of resection. Resection was stopped at 0.3 mA at the dorsal borders of the resection cavity.

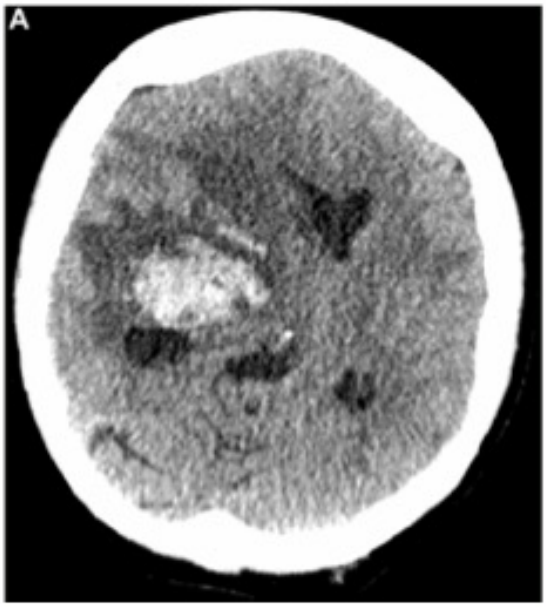

Figure 3. (**A**) Axial emergency computed tomography scan of glioblastoma in case 2 showing hyperdensity in the area of suspected neoplasia as a sign of acute bleeding. (**B**) Preoperative magnetic resonance imaging showing a contrast-enhancing structure infiltrating the right parietal and temporal lobes. (**C**) Postoperative magnetic resonance imaging showing residual contrast enhancement especially at the superior and temporal borders of the resection cavity. Owing to proximity to the corticospinal tract, resection was stopped intraoperatively at 2 mA, and residual tumor was left intentionally to preserve motor function.

(Continues)

Organization grade IV glioblastoma, IDH wild-type, and a World Health Organization grade I meningioma.

Postoperative MRI demonstrated regular postoperative tissue changes and a gross total resection with minimal (residual volume <2 mL) contrast-enhancing tissue (Figure 2B) with the maximum at the functional limit border. Postoperatively, the patient recovered without any additional neurological deficit. The patient's aphasia remained, but she was keenly responsive, adequate in nonverbal contact, and after physical therapy independently mobile on the ward.

Case 2: Glioblastoma and Acute Hemorrhage. A 65-year-old woman was referred to our hospital owing to a newly diagnosed cranial lesion with massive perifocal edema seen on computed tomography scan at another hospital. Initial symptoms were hyposensitivity and hemiparesis on the left side of the body mainly affecting the leg as well as recurring headaches. Furthermore, physical examination revealed homonymous hemianopsia and hemineglect. Preoperative MRI demonstrated a contrast-enhancing cerebral lesion in the right temporal and parietal lobes affecting the ventricular system and beginning of the midline shift to the left (Figure 3B). In the course of surgery preplanning, the patient presented with an acute reduction of vigilance with a Glasgow Coma Scale score 9 and progressive left hemiparesis. An emergency computed tomography scan was ordered, which showed massive bleeding into the tissue of the suspected tumor with progressive midline shifting and consecutive hydrocephalus (Figure 3A). The patient was immediately transferred to the operating room. Setup of monopolar stimulation was performed by the surgeon in 6 minutes. Craniotomy was performed, and the dura appeared to be under extreme tension; therefore, navigation-assisted decompression of the bleeding was performed initially. Following decompression, cortical and subcortical mapping was conducted with thresholds of 14 mA and 2 mA, respectively. Stimulation revealed localization of the corticospinal tract in direct relationship to the tumor and bleeding; hence resection was performed. Full macroscopic resection could not be achieved under preservation of the corticospinal tract.

Postoperative MRI demonstrated regular postoperative tissue changes and expected subtotal resection (residual volume 4.2 mL) (Figure 3C). Neuropathological results revealed a World Health Organization grade IV glioblastoma, IDH wild-type. The patient made a full recovery with a Glasgow Coma Scale score of 15 without any new neurological deficits.

DISCUSSION

In this article, we describe a setup that is suitable for intraoperative neurophysiological monitoring in emergency situations when support by a clinical neurophysiologist is not available. We chose to apply monopolar motor mapping in 2 patients with eloquently located pathologies to increase the safety of resection regarding postoperative neurological deficits under emergency conditions. As reported, our 2 patients did not experience any new neurological deficit in the postoperative course. We did not use bipolar stimulation, as in decompensated patients this method of standard mapping in awake patients is not applicable.

The advantages of IONM have been frequently described in recent decades[7-10]; however, use of IONM in emergencies is neither standard nor available in most neuro-oncological departments, and publications about usage in emergency situations are lacking. This could be due to a need for specially trained neurosurgeons and external staff for handling of the devices and neurophysiological assessment of the results obtained intraoperatively as well as the time-consuming setup. Besides the need for personal expertise, standard IONM devices might not be comprehensively available in all neurosurgical departments.

In contrast to a standard IONM setup, our setup enables the surgeon to use the advantages of direct brain mapping autonomously, allowing usage of direct cortical and subcortical stimulation beyond standard surgery settings. Monopolar stimulation can be set up within minutes, and the mapping procedure can be conducted without any third-party participation.

A general limitation of the present report is that we have limited data on only 2 patients. In general, the number of patients with decompensated tumors in eloquent locations that need to be resected in an emergency setting is limited. As we consider IONM techniques highly relevant for patients with eloquently located lesions not only in elective but also in emergency settings, further investigations are ongoing in this specific patient cohort. Furthermore, only direct monopolar or bipolar stimulation is possible, as the device does not allow constant transcranial

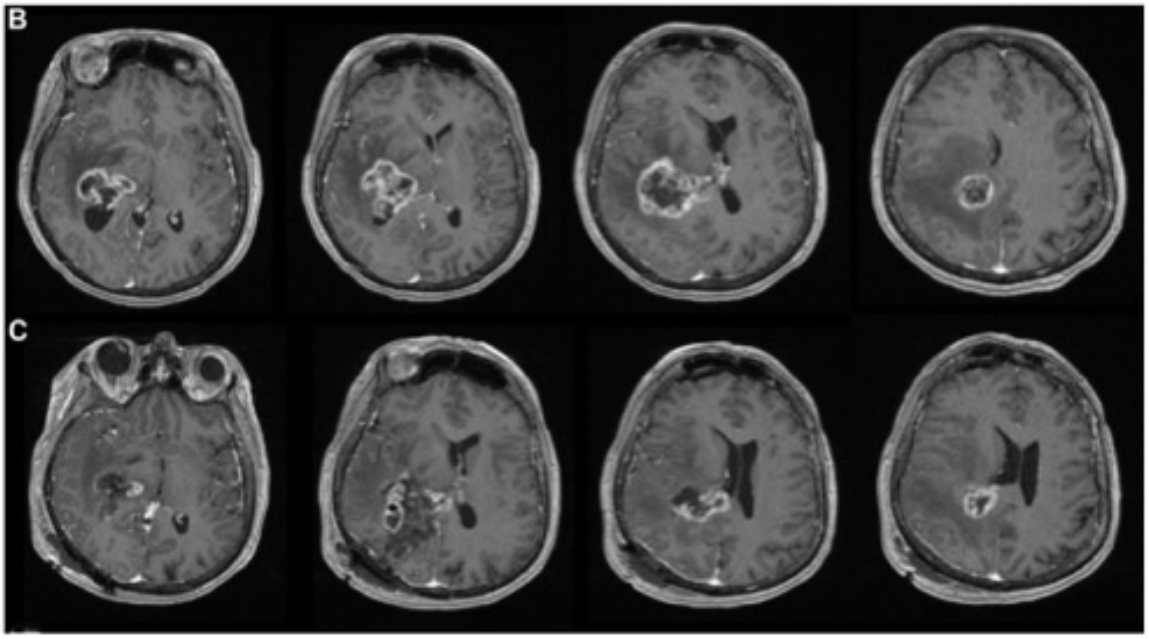

Figure 3. (Continued).

electrical SSEP or MEP monitoring, but SSEP and MEP monitoring still is essential at least in some localizations, especially in lesions with neurovascular conflicts.[7,11,12] In case 1, neurovascular conflict was assumed to be the localization of the tumor, and SSEP monitoring would have been indicated in elective surgery but was not available in the emergency setting at night; therefore, monopolar stimulation with the new device to obtain motoric control was chosen rather than not using any monitoring. Setup of SSEP and standard MEP monitoring by means of transcranial and direct cortical stimulation requires time and trained external personal.[13] Those requirements therefore might be a knockout criterion for the use of IONM in emergency surgeries such as the cases described here as well as in planned resections in neurosurgery departments with limited resources.

CONCLUSIONS

In emergency situations, which usually do not allow standard IONM monitoring, the C2 Xtend device could be a useful tool for monopolar motor mapping, leading to a safe and controlled resection. However, future studies of emergency use in larger patient cohorts as well as use for other indications are required.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Franziska Staub-Bartelt: Investigation, Resources, Writing - original draft, Writing - review & editing, Project administration. **Björn Bastian Hofmann:** Writing - original draft, Writing - review & editing. **Marion Rapp:** Writing - review & editing, Supervision, Methodology. **Daniel Hänggi:** Supervision, Writing - review & editing. **Marcel Alexander Kamp:** Methodology, Writing - review & editing. **Michael Sabel:** Conceptualization, Methodology, Writing - review & editing.

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Article

Establishment of Different Intraoperative Monitoring and Mapping Techniques and Their Impact on Survival, Extent of Resection, and Clinical Outcome in Patients with High-Grade Gliomas—A Series of 631 Patients in 14 Years

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Simple Summary: Glioblastoma is the most prevalent intracranial tumor in adults, and simultaneously the most aggressive. Surgical resection constitutes the initial step in the therapeutic approach, and is also highly significant, as studies have demonstrated that overall survival is markedly influenced by the extent of resection or residual tumor volume. Over the past few decades, various techniques for preoperative planning and intraoperative functional monitoring have been introduced to enhance the extent of resection, particularly in the case of functionally eloquent tumors. In this study, we conducted a monocentric investigation into the impact of various intraoperative surgical techniques within the realm of neurophysiological monitoring and mapping, introduced sequentially, on the overall survival of glioblastoma patients. In our cohort of 631 patients, each technique described did not exhibit a significant influence on overall survival.

Abstract: BACKGROUND: The resection of brain tumors can be critical concerning localization, but is a key point in treating gliomas. Intraoperative neuromonitoring (IONM), awake craniotomy, and mapping procedures have been incorporated over the years. Using these intraoperative techniques, the resection of eloquent-area tumors without increasing postoperative morbidity became possible. This study aims to analyze short-term and particularly long-term outcomes in patients diagnosed with high-grade glioma, who underwent surgical resection under various technical intraoperative settings over 14 years. METHODS: A total of 1010 patients with high-grade glioma that underwent resection between 2004 and 2018 under different monitoring or mapping procedures were screened; 631 were considered eligible for further analyses. We analyzed the type of surgery (resection vs. biopsy) and type of IONM or mapping procedures that were performed. Furthermore, the impact on short-term (The National Institute of Health Stroke Scale, NIHSS; Karnofsky Performance Scale, KPS) and long-term (progression-free survival, PFS; overall survival, OS) outcomes was analyzed. Additionally, the localization, extent of resection (EOR), residual tumor volume (RTV), IDH status, and adjuvant therapy were approached. RESULTS: In 481 patients, surgery, and in 150, biopsies were performed. The number of biopsies decreased significantly with the incorporation of awake surgeries with bipolar stimulation, IONM, and/or monopolar mapping ($p < 0.001$). PFS and OS were not significantly influenced by any intraoperative technical setting. EOR and RTV achieved under different operative techniques showed no statistical significance ($p = 0.404$ EOR, $p = 0.186$ RTV). CONCLUSION: Based on the present analysis using data from 14 years and more than 600 patients, we observed that through the implementation of various monitoring and mapping techniques, a significant decrease in biopsies and an increase in the resection of eloquent tumors was achieved. With that, the operability of eloquent tumors without a negative influence on neurological outcomes

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is suggested by our data. However, a statistical effect of monitoring and mapping procedures on long-term outcomes such as PFS and OS could not be shown.

Keywords: intraoperative neuromonitoring; brain mapping; supratentorial brain tumor; eloquent brain tumor; surgical approach; infiltrating tumor

1. Introduction

IDH-wildtype Glioblastoma (GBM) is the most aggressive form of glioma and the most common primary malignant brain tumor, accounting for 16% of primary brain and central nervous system (CNS) neoplasms [1]. The worldwide incidence varies [2], with an average age-adjusted incidence of GBM of 3.2 per 100,000 population in the USA [3]. 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 tumors reported among patients 0–19 years old [4].

Constant research is performed to identify novel treatment strategies that increase the OS period of patients while ameliorating their quality of life, as the prognosis still is very limited. Despite maximum treatment, the recurrence of GBM following surgical resection is nearly inevitable, and its management is typically not standardized, but rather case-dependent [5,6].

Currently, the standard of care for patients with GBM comprises surgical resection followed by radio and chemotherapy [7–9], with emphasis on the importance of the surgical approach. Since GBM is an infiltrating tumor, surgical excision is often challenging. However, maximizing the resection of the tumor plays an important role in the prognosis of the disease [10–12]. The extent of resection threshold >80% was shown to be beneficial in primary and recurrent high-grade gliomas [13,14]. Over the years, advances in "supratotal" resection, meaning resection beyond contrast-enhancing tumor margin, have also been commonly discussed in both low-grade and high-grade glioma surgery. In glioblastoma patients, evidence was found that supratotal resection increased survival benefit [11,15,16].

Hence, with the manifesting importance of surgical approaches, more techniques have evolved to push the limits of gross total resection. The introduction of 5-Aminolevulinic acid (5-ALA) as an intraoperative tool for the visualization of the tumor increased progression-free survival and results of tumor resection [17]. However, there is a significant demand for intraoperative techniques that enable the preservation of neurological integrity in the patients as postoperative new neurological deficits are well known to decrease survival benefits [18]. For the control of motor and sensory functionality, intraoperative neuromonitoring (IONM) and monopolar mapping procedures are well-established procedures during brain tumor resection [19–22]. Monitoring techniques with transcranial electric stimulation of motor-evoked potentials (MEP) as well as monopolar direct cortical stimulation are used for the control of motor function [23–25], whereas 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. The inception of awake craniotomy in glioma surgery additionally enables speech monitoring via bipolar mapping during surgery [26,27].

As we—one by one—have implemented different monitoring and mapping techniques as well as awake surgery in our surgical procedures over the past few years, we aimed to investigate the relevance and impacts of different technical approaches on the survival and outcome of GBM patients. For the present study, we retrospectively screened data from 1010 patients who underwent surgery at our department between 2004 and 2018. In total, 631 patients were included in a detailed study, analyzing the operative techniques that might have increased or decreased the preservation of neurological functionality and whether these intraoperative neurophysiological techniques played a significant role in

improving the PFS and OS of patients with GBM or IDH-mutated astrocytoma WHO grade 4.

2. Patients and Methods

The present study received approval from the local ethics committee of the University Hospital of Duesseldorf (Study-Nr. 2018-79-RetroDEuA) and was performed as a retrospective patient analysis. All patients enclosed in this study gave written informed consent on data processing within the neurosurgical working group for different scientific issues. The local ethics committee approved the informed consent document and procedure as appropriate for this study.

The authors want to emphasize that the used terms for histopathological diagnosis were adapted to the latest WHO classification published in 2021 [28], even though the observation time ended in 2018. Patients formerly classified as IDH-mutated glioblastoma and IDH-wildtype glioblastoma were included in the study. In the following, the authors will use the term "IDH-mutated astrocytoma WHO grade 4" for all patients in the cohort who were formerly diagnosed with IDH-mutated glioblastoma. IDH-wildtype glioblastoma patients remained the same and are referred to as "GBM".

The systematic data screening of patients who underwent primary surgery at the Department of Neurosurgery at University Hospital Düsseldorf from 1 January 2004 to 31 December 2018 was performed. Patient recruitment was conducted through "Medico", the local patient data management system (CompuGroupMedical, CGM Clinical Europe GmbH, Koblenz, Germany). 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 IDH-wildtype glioblastoma and IDH-mutated astrocytoma WHO grade 4 were selected (formerly IDH-mutated glioblastoma), resulting in 1010 patients. The verification of the date of death was performed by either screening the local patient data management system, registering queries, or contacting the patients' families. This procedure was in line with the obtained local ethics approval.

Then, we defined further exclusion criteria for the analysis to obtain comparable data:

1. Patients under 18 years at time of diagnosis;
2. Primary surgery at external hospital;
3. Loss of follow-up < 3 months;
4. Incomplete clinical data (NIHSS, KPS, MRI).

After applying the exclusion criteria, a cohort of 631 eligible patients remained (Figure 1).

2.1. Surgical Procedure—Resection vs. Biopsy and Categories of Surgical Monitoring and Mapping Approaches

Eligible patients were divided into two major subgroups according to the surgical procedure: "surgical resection" and "biopsy". The biopsy group was excluded from further statistical analysis as the major focuses of the study were PFS and OS. The comparison of biopsy-only patients to patients who underwent surgery in the context of PFS and OS would have been extremely biased. However, we included patients with biopsies for a description of their distribution from 2004 to 2018 to compare their frequencies in correlation with the implementation of different operative settings over the years.

Patients from the resection group additionally were analyzed according to the type of technical surgical approach.

The types of intraoperative neurophysiological mapping and monitoring techniques were categorized as follows:

SP-O—Surgical procedure only, with no added monitoring and/or mapping modalities;

AWAKE-bipolar—Awake craniotomy with 60 Hz bipolar stimulation;

IONM-monopolar—Surgery under general anaesthesia under usage of SSEP, MEP, and EEG monitoring, and additionally monopolar mapping;

AWAKE-IONM-mapping—This method incorporated all techniques, such as awake craniotomies with monitoring of SSEP and MEP as well as mapping procedures via bipolar

and monopolar stimulation, with a focus on bipolar mapping for speech and language assessment and monopolar mapping for motor control

The determination of the chosen surgical setting was given following the consideration of the lead surgeon(s). During the observation period, the same three surgeons were mainly leading the surgeries (two senior physicians, and one resident who later on also practiced as a senior physician). All of them received specialized training in tumor surgery. Localization of the lesion, evaluation of MRI scans, and neurological status as well as compliance of the patients were evaluated pre-surgery.

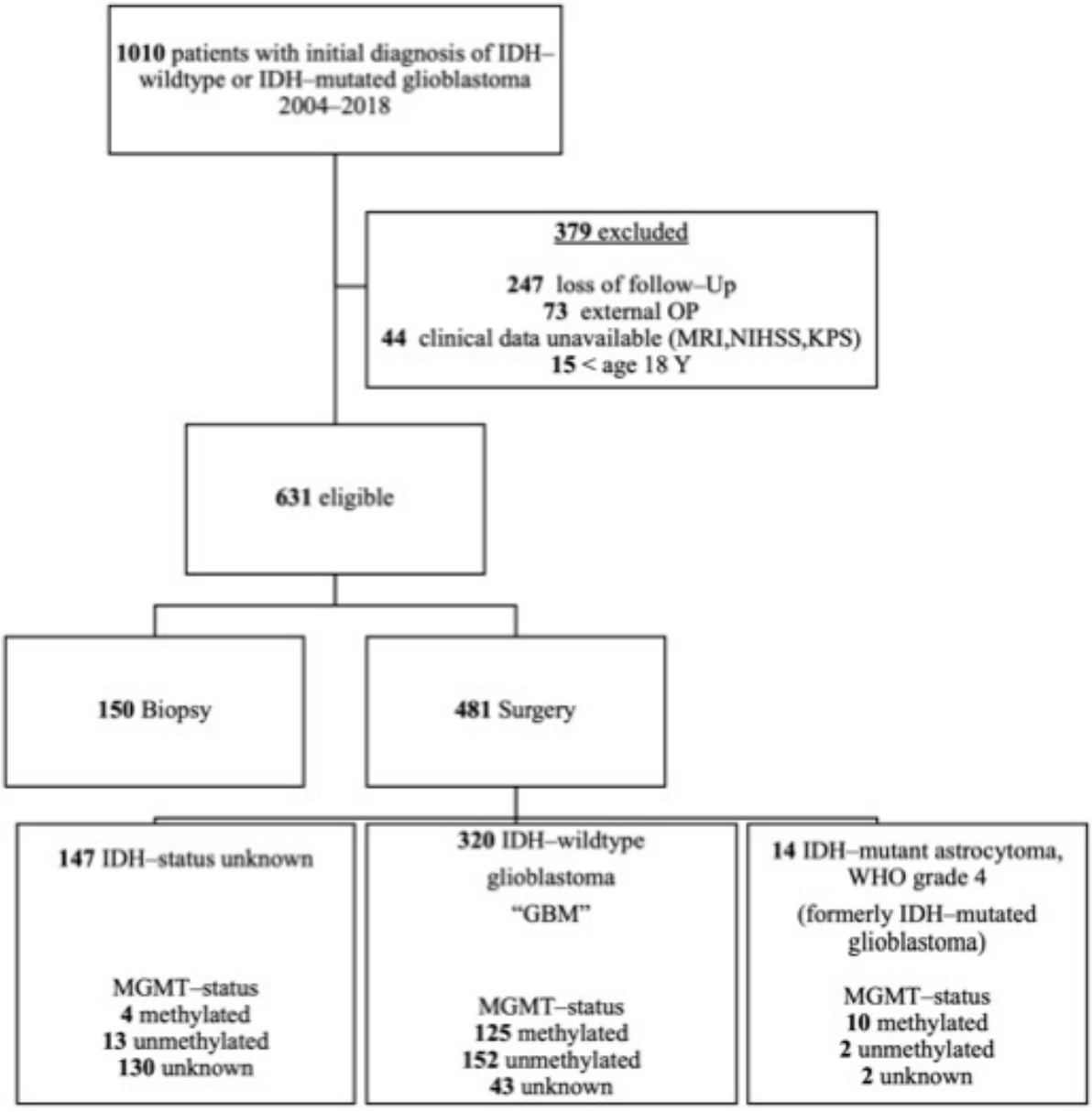


Figure 1. Flowchart of patient selection for analysis with numbers of drop outs at each stage.

2.2. PFS and OS

Progression-free survival was determined by an evaluation of RANO criteria for high-grade glioma [29] in the post-operative and follow-up MRIs. The date of MRI was set for the diagnosis of progress if applicable. OS was calculated from the individual death data of the patients. PFS and OS were calculated for the resection cohort regardless of adjuvant treatment, and PFS and OS were compared between the different surgical approaches. In a further subgroup analysis, patients from the resection group that were treated with the STUPP scheme in an adjuvant setting were separately analyzed concerning PFS and OS; here also surgical approach subgroups were compared to each other.

2.3. Further Variables of Data Collection

2.3.1. IDH Status and Adjuvant Therapy of Resection Group

For descriptive analysis, patients from the resection group were also divided into three sub-groups based on their IDH statuses. Group one included IDH-mutated patients, now referred to as IDH-mutated astrocytoma WHO grade 4; group two were IDH-wildtype glioblastoma patients, and group three were patients without a known IDH status. Within these subgroups, sub-classification related to MGMT status was performed, resulting in three additional subgroups: MGMT-methylated, MGMT-unmethylated, and MGMT-unknown. Additionally, adjuvant therapy was performed.

2.3.2. Eloquence of Tumor Localization

Although to some extent, the entire brain can be considered eloquent, for this study, the authors defined brain areas as eloquent if they suffered a predictable detectable loss of language, motor, or sensory function when affected by tumor growth or surgical approach. These included the right and left pre- and post-central cortex, the basal ganglia, the calcarine cortex, Wernicke's area, and areas of language function. The terms eloquent and functional tissue are used interchangeably.

2.3.3. Extent of Resection and Residual Tumor Volume

For the definition of EOR and residual tumor volume (RTV), contrast enhancement in the pre-operative T1-weighted MRI was compared to residual contrast enhancement in the post-operative T1-weighted MRI. Tumor volumetry was performed using either computer software (Brainlab, Elements, Smartbrush, Munich, Germany) or by measuring using the ABC/2 formula [30] if the Brainlab Software was not available. The EOR and RTV were consistently assessed by a single team member within the neuro-oncology team to avoid bias among various evaluators. An EOR, measured as a percentage reduction of tumor volume, of 95% or greater in the post-operative MRI was defined as near total contrast enhancement (CE) resection. Subtotal CE resection was achieved in cases with >80%–95% of CE resection + <5 mL residual tumor volume [31]. Percentage values of the mean, median, and range were calculated for the EOR. RTV was measured as residual contrast enhancement in the post-operative MRI and calculated in milliliters. EOR measured by RTV was categorized, according to Karschnia et al., into class 2 maximal CE resection and class 3 submaximal CE resection, while classes 1 and 4 EOR measured by RTV were not part of the cohort [11]. "Supratotal" resection, meaning the resection of contrast enhancement surrounding tissues with conspicuous findings in the MRI T2 or FLAIR sequence, was not the target of analysis, as this surgical approach was introduced relatively late in terms of the present data collection, and in earlier years of our cohorts' data, this concept was not standardized.

2.3.4. Neurological Outcome

To evaluate neurological outcomes in patients, we applied the National Institutes of Health Stroke Scale (NIHSS) pre-surgery, post-surgery at time of discharge, and 3 months after surgery. Additionally, we used the Karnofsky Performance Scale (KPS) to assess the functionality of all patients at the above-mentioned time points. NIHSS data were grouped

into score values of <5, 5–10, and >10 for the easier illustration of results. The KPS was divided for group analysis into <60%, then segmented in 10-point increments up to 100%. KPS and NIHSS were calculated with median values and their respective interquartile ranges for all included time points.

2.4. Statistical Analyses

Descriptive statistics with the mean, and medians with interquartile ranges and standard deviations, 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 (IBM Corp. Released 2019, IBM SPSS Statistics for Windows, Version 26.0., Armonk, NY, USA, IBM Corp.) was used. A Pearson chi-square test was used to determine whether the frequencies of different intraoperative techniques were statistically significant when compared to others. 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 relationships of the means between the independent groups, as repeated-measure ANOVA is a mode of analysis of dependencies. To analyze the distribution of survival, a Kaplan–Meier survival curve was used to determine the distribution of PFS and OS. Statistical significance was set at $p < 0.05$.

3. Results

Out of 1010 screened patients, 631 were considered eligible for the study. Of these, 150 were biopsied, and the remaining 481 patients underwent primary surgical resection. Up to the last individual observation time, 165 patients underwent recurrent surgery, 60 patients had a second recurrent surgery, 19 patients had a third surgery, 4 patients received a fourth surgery and 1 patient had five surgeries. The results are presented for the primary resection only. In total, 303 of the 481 patients were male (63%) and 178 were female (37%). The median age at diagnosis for the resection group was 61 years (IQR 52.8–70.0); 94% of the patients underwent surgery using 5-ALA fluorescence. For a summarized description of the resection cohort and its surgical subgroups, please refer to Table 1.

Table 1. Summary of resection cohorts' descriptive data (surgical subgroups and overall cohort).

Characteristic		SP–O n = 160	AWAKE–Bipolar n = 71	IONM–Monopolar n = 145	AWAKE–IONM–Mapping n = 105	Overall Resection Cohort n = 481
Sex						
	male	97	50	88	68	303 (63%)
	female	63	21	57	37	178 (37%)
Age at diagnosis, y						
($p = 0.281$)	Median (IQR)	62.1 (17.4)	60 (17.7)	60 (19.0)	64 (15.0)	61.0 (52.8-70)
	range	23.0–89	24–80	24–85	29–86	23–89
ALA						
($p = 0.281$)	Administered	142	70	136	104	452 (94%)
	Not administered	18	1	9	1	29 (6%)
IDH-Status						
($p < 0.001$)	Wildtype	50	36	134	100	320 (66.5%)
	Mutant	3	2	6	3	14 (2.9%)
	Unknown	107	33	5	2	147 (30.6%)

Table 1. *Cont.*

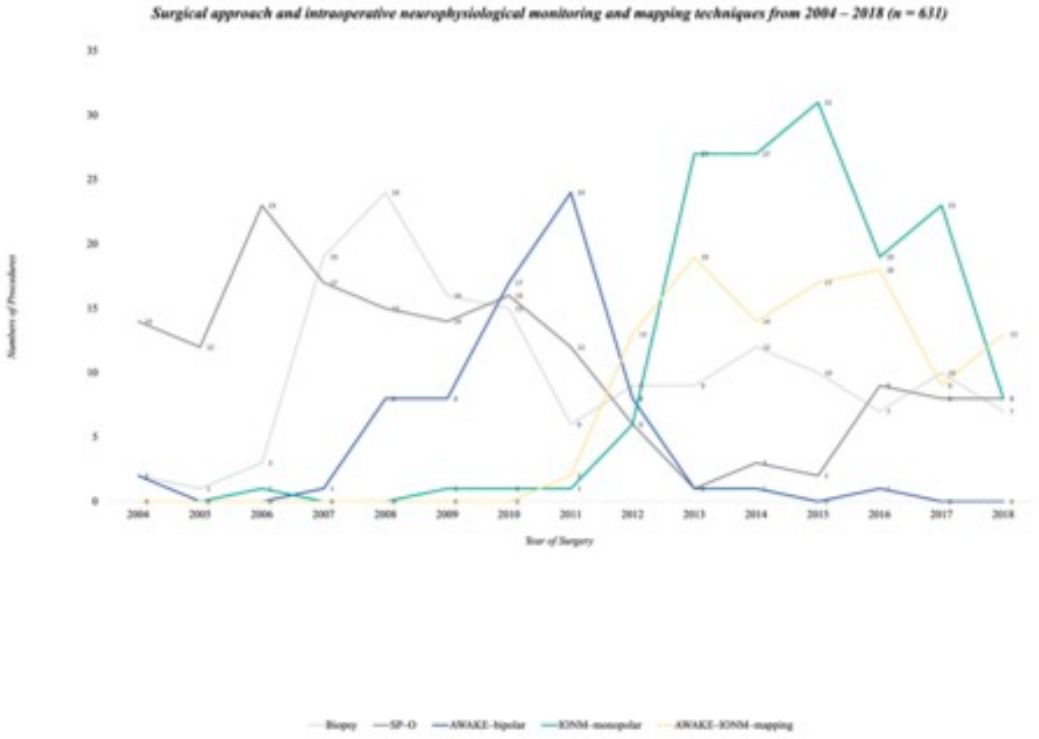
Characteristic		SP–O	AWAKE–Bipolar	IONM–Monopolar	AWAKE–IONM–Mapping	Overall Resection Cohort
		n = 160	n = 71	n = 145	n = 105	n = 481
MGMT-Status ($p < 0.001$)	MGMT +	22	7	60	50	139 (28.9%)
	MGMT -	30	15	75	46	166 (34.5%
	Unknown	107	49	10	9	176 (36.6%
KPS (mean)						
	preoperative	82	87	89	90	86.78 (±12.34)
	postoperative	85	77 ($p < 0.001$)	90	91	86.78 (±11.08)
	3 months	82	77 ($p = 0.012$)	88 ($p = 0.004$)	88 ($p = 0.021$)	84.57 (±13.22)
NIHSS (mean)						
	preoperative	1.9	1.6	1.4	1	1.4
	postoperative	1.6	2.5 ($p = 0.005$)	1.2	1	1.3
	3 months	1.6	2.3 ($p = 0.044$)	1.3	1.4	1.6
Pre- OP Tumour volume (mL) ($p = 0.288$)	Mean (SD)	37.99 (±28.14)	36.83 (±43.32)	35.97 (±33.21)	29.09 (±24.64)	35.2 (±31.8)
Extent of resection, % by volume ($p = 4.04$)	Mean	96%	97%	95%	96%	96.1 (8.6%)
	Median	100%	100%	100%	100%	
	Range	51–100%	76–100%	38–100%	55–100%	38.2–226
Residual volume (mL) ($p = 0.186$)	Mean (±SD)	1.95 mL (±5.1)	1.36 mL (±6.58)	1.11 mL (±2.26)	0.91 mL (±2.06)	1.37 (±4.16)
	Range	0–37 mL	0–54.91 mL	0–14.64 mL	0–15.83 mL	0–54.91
Tumour location by hemisphere ($p = 0.001$)	Bilateral	4	0	4	1	15 (3.1%)
	Left	60	42	40	82	223 (46.4%)
	Right	96	29	96	21	243 (50.5%)
Eloquence ($p < 0.001$)	Eloquent	84	71	145	105	405 (84.2%)
	Not eloquent	76	0	0	0	76 (15.8%)
Before 2010						
	Eloquent					75 (64.7%)
	Not eloquent					41 (35.3%)
After 2010						
	Eloquent					330 (90.4%)
	Not eloquent					35 (9.6%)

3.1. Surgical Characteristics and their Changes from 2004 to 2018

Out of 631 patients, 150 underwent biopsy only (24%) and 481 (76%) underwent primary resection. In the resection group, SP-O was performed in the majority of patients (n = 160, 33%) compared to surgery with intraoperative monitoring and monopolar mapping (IONM-monopolar), which was seen in 145 out of 481 patients (30%). Surgery under usage of all available methods (AWAKE-IONM-mapping) was seen in 22% of the patients (n = 105). AWAKE-bipolar surgery was performed in 71 patients (15%).

A year-wise extrapolation of the technical settings was performed for a better understanding of the changes in surgical settings over time. Towards the end of 2011, the number of SP-O decreased. In 2007, awake surgeries were implemented with 60 Hz stimulation, and their numbers steadily increased until 2011. IONM-monopolar and the combination of AWAKE-IONM-mapping were implemented in 2010, and over time, this became the

institutional standard of surgical care for patients. As IONM-monopolar increased, SP-O decreased considerably. As seen in the graphical representation, the period from 2010 to 2012 marked a pivotal change in defining the standard of care for surgery for patients with GBM (Figure 2). The chi-square test showed that the performance of biopsies decreased significantly after 2010, along with a statistically significant increase in AWAKE-bipolar, IONM-monopolar and AWAKE-IONM-mapping surgical settings after 2010 ($p < 0.001$).



total cases per year (n=)	18	13	27	37	47	39	49	45	42	57	57	60	54	50	36
loss to follow-up per year (n=)	20	16	23	30	48	29	36	25	31	38	30	40	27	32	25

Figure 2. Line graph of patients enclosed in the analysis (n = 631) divided by technical settings from 2004 to 2018. Extra information is given in the footnotes concerning the total number of cases and the cases that were lost to follow-up per year.

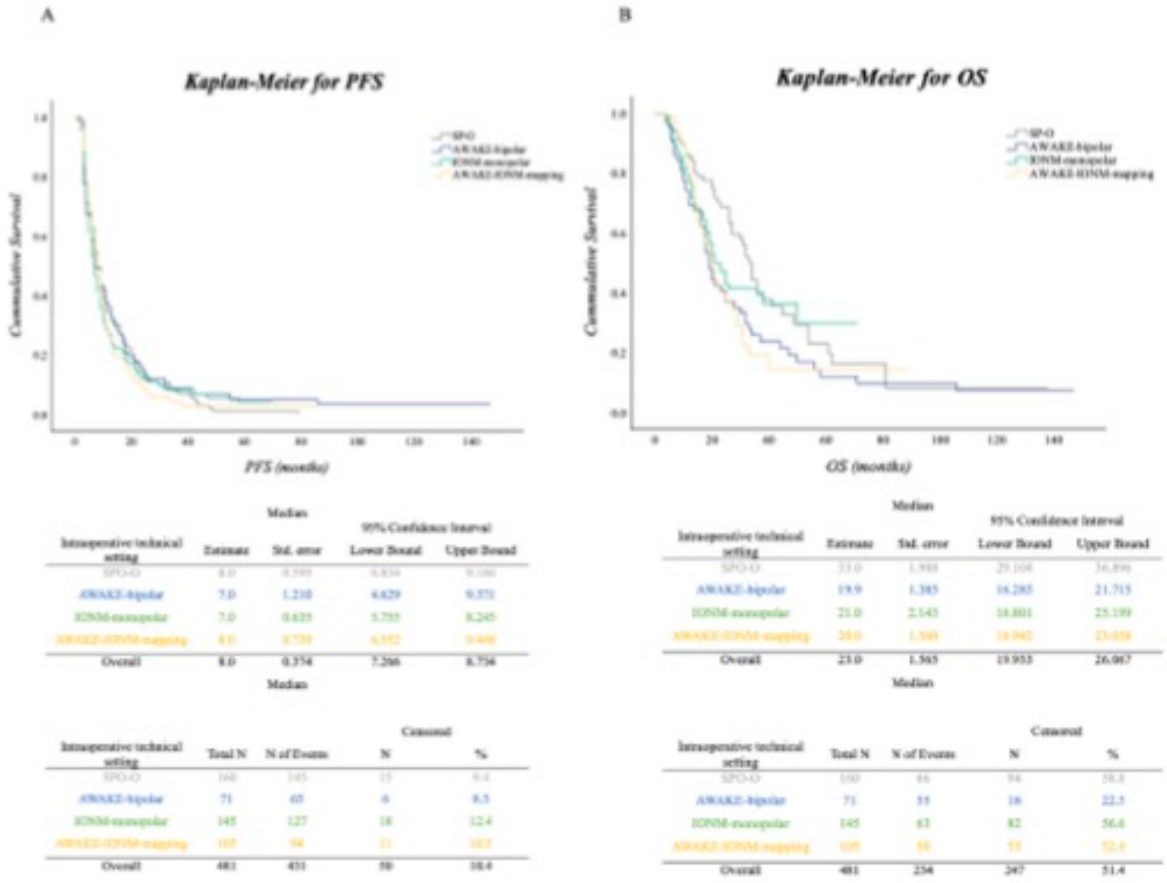
3.2. PFS and OS in the Surgical Cohort

To calculate the PFS and OS, Kaplan–Meier survival curves were plotted for the different operative settings. The median follow-up of the cohort was 14 months. The median PFS was 8 months (IQR 4–15). There was no significant difference in the PFS under the various surgical settings in the log-rank (Mantel-Cox) test ($p = 0.749$). The median OS for the resection cohort was 23 months (IQR 14–50). There was a significantly increased OS associated with SP-O surgical approach compared to the other surgical approaches/techniques ($p = 0.034$). Figure 3A,B illustrate Kaplan–Meier curves for PFS and OS for the entire cohort, with median survival, number of events and number censored for the cohort and all surgical subgroups.

Impact of Adjuvant Therapy in Surgical Approaches concerning PFS and OS

From the surgical cohort, 427 patients underwent adjuvant treatment. Out of 320 IDH-wildtype patients, 296 underwent at least one circle of treatment from the STUPP-protocol, and out of the 14 patients with mutated IDH statuses, 12 were treated with at least one circle of STUPP-scheme. More detailed findings on adjuvant therapies for all patients according to their surgical approaches are made available in Table 2.

We performed a subgroup analysis for the STUPP cohort of 427 patients to reveal a possible influence of adjuvant therapy on PFS and OS. There was no significant increase in PFS for any of the surgical approach subgroups (median PFS for all subgroups in months = 8; SP-O—9, AWAKE-bipolar—7, IONM-monopolar—7, AWAKE-IONM-mapping—9; $p = 0.923$). Regarding OS, we found statistically significantly increased OS in patients associated with the SP-O group for patients receiving adjuvant STUPP compared to the other surgical approaches (median OS for all subgroups in months = 25; SP-O—34, AWAKE-bipolar—19, IONM-monopolar—21, AWAKE-IONM-mapping—20; $p = 0.034$). The details of this subgroup analysis can be found in Figure 3C,D.



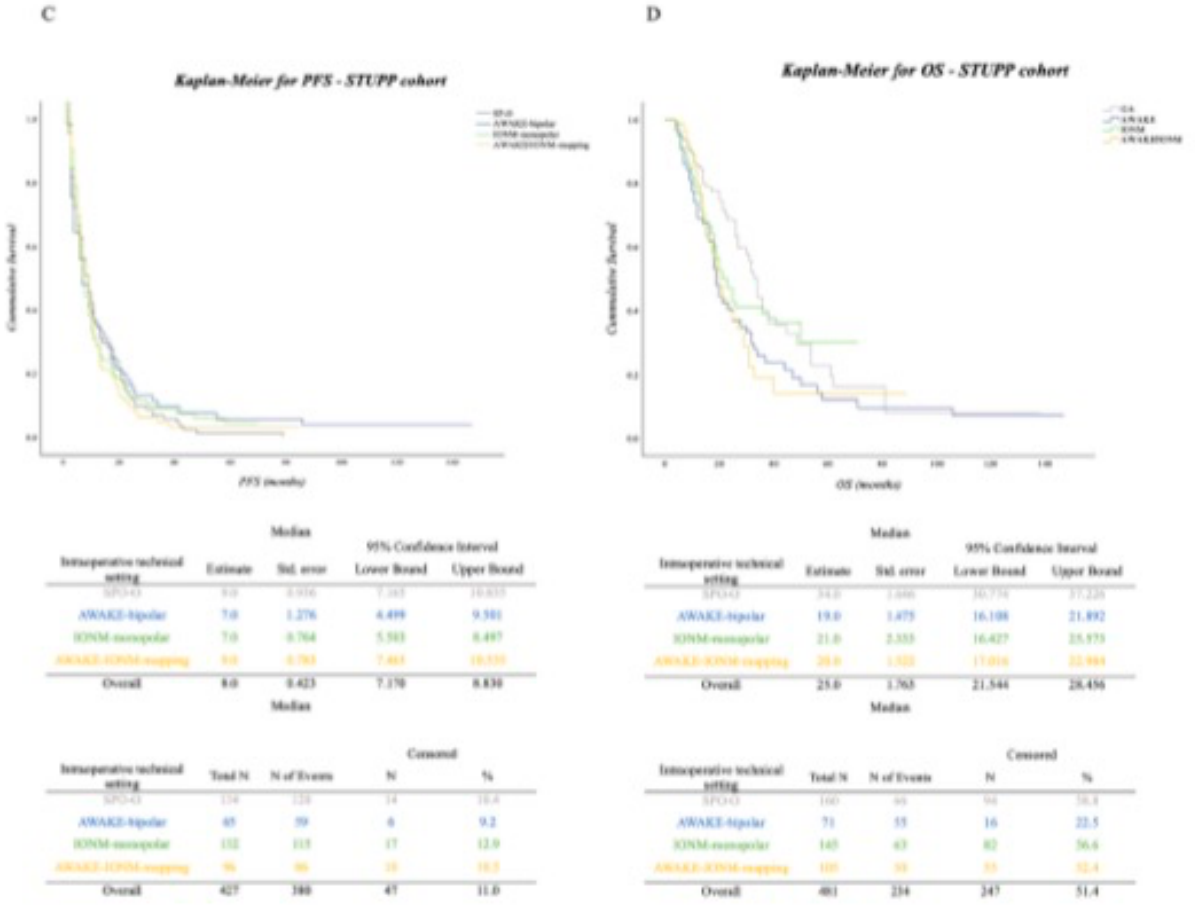
Intraoperative technical setting	Median Estimate	Median Std. error	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
SP-O	9.0	0.599	7.826	10.174
AWAKE-bipolar	7.0	1.210	4.629	9.371
IONM-monopolar	7.0	0.635	5.755	8.245
AWAKE-IONM-mapping	9.0	0.719	6.592	9.408
Overall	8.0	0.374	7.266	8.734

Intraoperative technical setting	Median Estimate	Median Std. error	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
SP-O	33.0	1.988	29.104	36.896
AWAKE-bipolar	19.9	1.385	16.285	21.715
IONM-monopolar	21.0	2.143	16.801	25.199
AWAKE-IONM-mapping	20.0	1.569	16.942	23.058
Overall	23.0	1.365	19.953	26.047

Intraoperative technical setting	Total N	N of Events	Censored N	Censored %
SP-O	166	145	21	12.7
AWAKE-bipolar	71	65	6	8.5
IONM-monopolar	145	127	18	12.4
AWAKE-IONM-mapping	105	94	11	10.5
Overall	481	431	50	10.4

Intraoperative technical setting	Total N	N of Events	Censored N	Censored %
SP-O	166	145	21	12.7
AWAKE-bipolar	71	65	6	8.5
IONM-monopolar	145	127	18	12.4
AWAKE-IONM-mapping	105	94	11	10.5
Overall	481	431	50	10.4

Figure 3. *Cont.*



Intraoperative technical setting	Median Estimate	Median Std. error	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
SP-O	8.0	0.916	7.205	10.855
AWAKE-bipolar	7.0	1.276	4.499	9.501
IOMN-monopolar	7.0	0.764	5.503	8.497
AWAKE-IOMN-mapping	9.0	0.783	7.465	10.535
Overall	8.0	0.423	7.170	8.830

Intraoperative technical setting	Median Estimate	Median Std. error	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
SP-O	34.0	1.646	30.774	37.226
AWAKE-bipolar	19.0	1.475	16.108	21.892
IOMN-monopolar	21.0	2.355	16.427	25.573
AWAKE-IOMN-mapping	28.0	1.522	17.016	22.984
Overall	25.0	1.763	21.544	28.456

Intraoperative technical setting	Total N	N of Events	Censored N	Censored %
SP-O	134	120	14	10.4
AWAKE-bipolar	65	59	6	9.2
IOMN-monopolar	132	115	17	12.9
AWAKE-IOMN-mapping	96	86	10	10.5
Overall	427	380	47	11.0

Intraoperative technical setting	Total N	N of Events	Censored N	Censored %
SP-O	160	66	94	58.8
AWAKE-bipolar	71	55	16	22.5
IOMN-monopolar	145	63	82	56.6
AWAKE-IOMN-mapping	105	53	53	52.4
Overall	481	234	247	51.4

Figure 3. (**A**,**B**): Kaplan–Meier curves for PFS (**A**) and OS (**B**) for the cohort with median OS for all surgical technique subgroups, along with number of events and number censored as well as 95% CI in the footnotes. There was no significant difference concerning intraoperative mapping or monitoring techniques in PFS ($p = 0.749$). Kaplan–Meier curve for OS (**B**) for the cohort with median OS for all subgroups, number of events and number censored as well as 95% CI in the footnotes. There was an increased OS in patients who underwent surgery via SP-O technique compared to the other surgical techniques ($p = 0.034$). (**C**,**D**): Kaplan–Meier curves for PFS (**C**) and OS (**D**) for the STUPP-subcohort with median OS for all surgical technique subgroups, number of events and number censored as well as 95% CI in the footnotes. There was an increased OS in patients who underwent surgery via the SP-O technique compared to the other surgical techniques ($p = 0.034$).

3.3. Tumor Localization and Eloquence

A total of 405 patients had eloquently located tumors. In order to compare the functional locations between different surgical methods, we chose to extrapolate the distribution of eloquently located tumors by years comprising the whole screening period. Statistical analysis showed that since the implementation of the AWAKE-bipolar and/or IOMN-monopolar settings after 2010, the total number of surgeries of eloquence increased significantly from 75 procedures between 2004 and 2009 to 330 procedures between 2010 and 2018 ($p < 0.001$). Furthermore, the proportion of surgeries comprising resection of functional tissue increased in relation to the total number of operations over the observed period (2004–2009, 116 procedures in total, 64.7% of those being eloquent, 35.3% not eloquent; 2010–2018, 365 procedures in total, of those 90.4% being eloquent and 9.6% not eloquent). The SP-O group was the only subgroup with non-functional tumors. All other groups only

included lesions located in functional areas. A summary of location and eloquence is illustrated in Table 1. Concerning the dependence of monitoring or mapping procedures, we analyzed all procedures performed after 2010, when all surgical techniques were available at our department. In line with a previous publication from another cohort that was treated at our department [22], we found that, consistent with the widespread use of mapping and monitoring, 82% of left hemisphere lesions were operated in an awake surgery setting, while in 64%, mapping procedures were performed. Intraoperative neuromonitoring (IONM) using monopolar stimulation was performed, manly for right hemispheric lesions (96%), particularly in frontoparietal and multilocular cases. Table 1 presents a summary of tumor location and eloquence by years and technical setting.

Table 2. Details on adjuvant therapy, if available, sub-grouped according to the surgical approaches/intraoperative techniques, TMZ = Temodal. Information regarding the initiation of adjuvant therapy in the form of combined radiochemotherapy was derived from the analyzed data from 427 patients. Details about the extent of this therapy were extracted from the data for a total of 321 patients. Subsequently, these patients were categorized into subgroups based on the surgical technique employed.

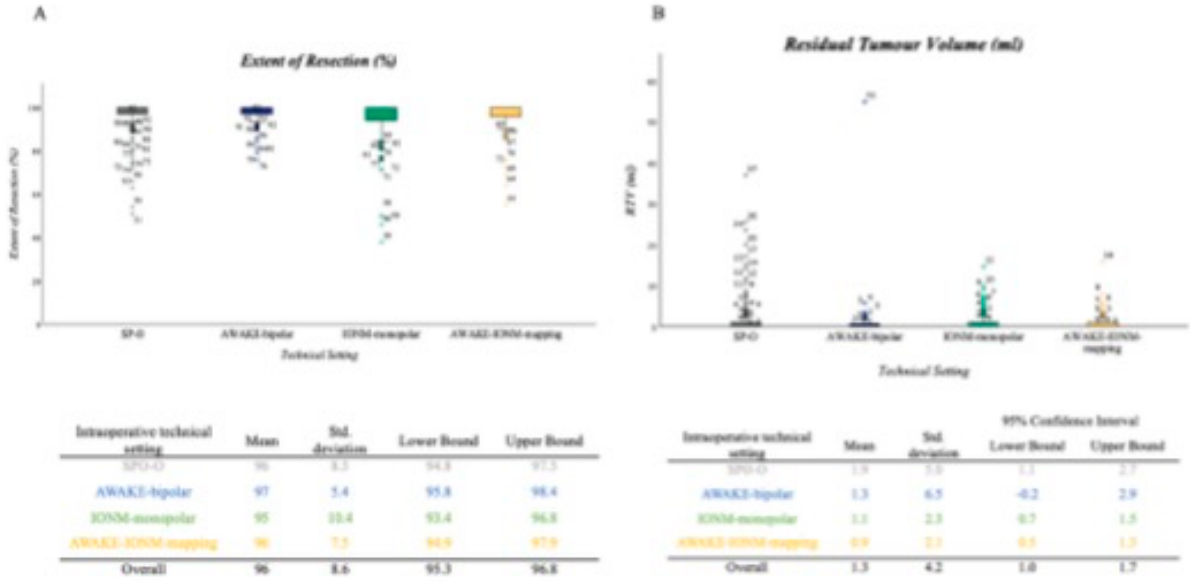
Adjuvant Therapy (n = 427)	**SP–O**	**AWAKE–BIPOLAR**	**IONM–Monopolar**	**AWAKE–IONM-Mapping**
Total Number	**n = 134**	**n = 65**	**n = 132**	**n = 96**
Details Concerning Adjuvant Therapy Available from	**n = 75**	**n = 52**	**n = 113**	**n = 81**
Stupp complete (60 Gy radiation + concomitant TMZ + adjuvant 6 cycles Temodal	22	14	16	14
Radiation + concomitant Chemotherapy applied, adjuvant TMZ cancelled after initiation	23	15	52	35
Radiation + concomitant Chemotherapy finalised, adjuvant TMZ not initiated	18	22	33	25
Radiation + concomitant Chemotherapy cancelled, adjuvant TMZ not initiated	3	0	2	2
Radiation + concomitant Chemotherapy cancelled, adjuvant TMZ finalised (at least 6 cycles)	1	0	2	0
Herrlinger scheme	8	1	7	5
Radiation only	0	0	1	0

3.4. Extent of Resection and RTV

In total, 479 patients received pre- and post-operative MRI to assess the EOR and RTV; 2 patients in the SP-O group did not receive post-op MRI. Mean tumor volume in the preoperative MRI was 35.2 mL ((SD ± 31.8), range 0.3–226.8 mL) for the cohort. Preoperative tumor volume did not differ significantly between the surgical subgroups ($p = 0.169$).

The mean EOR calculated as a percentage reduction of tumor volume was 96% ((±9 SD) for the entire cohort, range 38–100%); 373 patients (76%) had near-total CE resection, while the remaining 108 (22%) had subtotal CE resection. Of the patients who were operated on via SP-O, 129 showed near-total CE resection and 29 showed subtotal CE resection. In the AWAKE-bipolar setting, 56 patients showed near-total CE resection and 15 subtotal CE resection, and in the IONM-monopolar group, 108 patients had near-total CE resection, and 37 subtotal CE resection. Finally, in those operated on via the AWAKE-IONM-mapping setting, 82 had near-total CE resection and 23 had a subtotal CE resection. The EOR (%) did not show a significant difference when analyzed separately for the years before (2004–2009)

and after (2010–2018) the introduction of all IONM and mapping techniques (mean EOR before 95%, mean EOR after 96%). In line with that, no statistical significance ($p = 0.404$) was found regarding the EOR and different surgical settings for the whole period (Figure 4A).



Intraoperative technical setting	Mean	Std. deviation	Lower Bound	Upper Bound
SP-O	96	8.3	94.8	97.3
AWAKE-bipolar	97	5.4	95.8	98.4
IONM-monopolar	95	10.4	93.4	96.8
AWAKE-IONM-mapping	96	7.5	94.9	97.9
Overall	96	8.6	95.3	96.8

Intraoperative technical setting	Mean	Std. deviation	95% Confidence Interval	
			Lower Bound	Upper Bound
SP-O	1.9	5.8	1.1	2.7
AWAKE-bipolar	1.3	6.5	-0.2	2.9
IONM-monopolar	1.1	2.3	0.7	1.5
AWAKE-IONM-mapping	0.9	2.1	0.5	1.3
Overall	1.3	4.2	1.0	1.7

Figure 4. (**A**,**B**) Boxplots. (**A**) EOR (%) compared within the different surgical technique subgroups, showing intraoperative neurophysiological techniques of all cohort patients, and with one-way ANOVA revealing no statistically significant difference ($p = 0.404$, mean EOR in SP-O group was 96%, in AWAKE-bipolar subgroup it was 97%, in the IONM-monopolar cohort it was 95% and in the IONM-AWAKE-mapping subgroup it was 96%). (**B**) RTV (mL) compared with different intraoperative neurophysiological techniques for all cohort patients, and with one-way ANOVA revealing no statistically significant difference ($p = 0.188$). For illustrative purposes, the representation of two statistical outliers has been omitted. The values were group SP-O n = 1 with 37.00 mL residual volume and group AWAKE-bipolar n = 1 with 54.91 mL residual volume.

The extent of resection was also assessed as RTV in the postoperative MRI. The mean RTV in the cohort was 1.38 mL (±4.16 SD). The mean RTV measured in the postoperative MRI was the lowest in the AWAKE-IONM-mapping group (0.9 mL (±4.2)) and highest in the SP-O group (1.93 mL (5.0)). No statistical significance ($p = 0.186$) was found regarding the RTV and different surgical settings for the whole period; according to the mean values, all subgroups reached class 3 A (subtotal) resection (Figure 4B, mean RTV for SP-O = 1.93 mL, AWAKE-bipolar = 1.35 mL, IONM-monopolar = 1.1 mL and AWAKE-IONM-mapping = 0.9 mL). Of the patients who were operated on via SP-O, 118 showed class 2 B resection (near-total CE resection), 22 showed class 3 A resection and 18 showed class 3 B resection. In the AWAKE-bipolar setting, 57 patients showed class 2 B resection, and 12 showed 3 A, while 2 patients showed 3 B resection. In the IONM-monopolar group, 106 patients showed class 2 B, and 27 showed class 3 A resection, while 12 patients showed class 3 B resection. Finally, in those operated on via the AWAKE-IONM-mapping setting, 78 had class 2 B resection and 23 had class 3 A resection, while 4 patients showed class 3 B resection.

The RTV also did not show a significant difference when analyzed separately for the years before (2004–2009) and after (2010–2018) the introduction of all IONM and mapping techniques.

3.5. Neurological Outcome in Resection Group: NIHSS and KPS

3.5.1. NIHSS

Median NIHSS for the entire cohort pre-surgery was 1 (IQR 0–2) and remained the same at all other analyzed time points (Figure 5A). When comparing the subgroups of individual monitoring or mapping techniques, patients in the SP-O group served as the baseline without any monitoring, and were compared to other groups with monitoring and/or mapping techniques. In a post-hoc analysis, it was observed that at the time of postoperative assessment, patients in the "AWAKE-bipolar" group had a significantly higher NIHSS compared to non-monitored patients in the SP-O group ($p = 0.005$). This effect was also evident at the three-month follow-up ($p = 0.044$). In the intergroup comparison, when only the monitoring/mapping groups were considered, the AWAKE-bipolar group also exhibited a significantly higher NIHSS postoperatively and at the three-month follow-up.

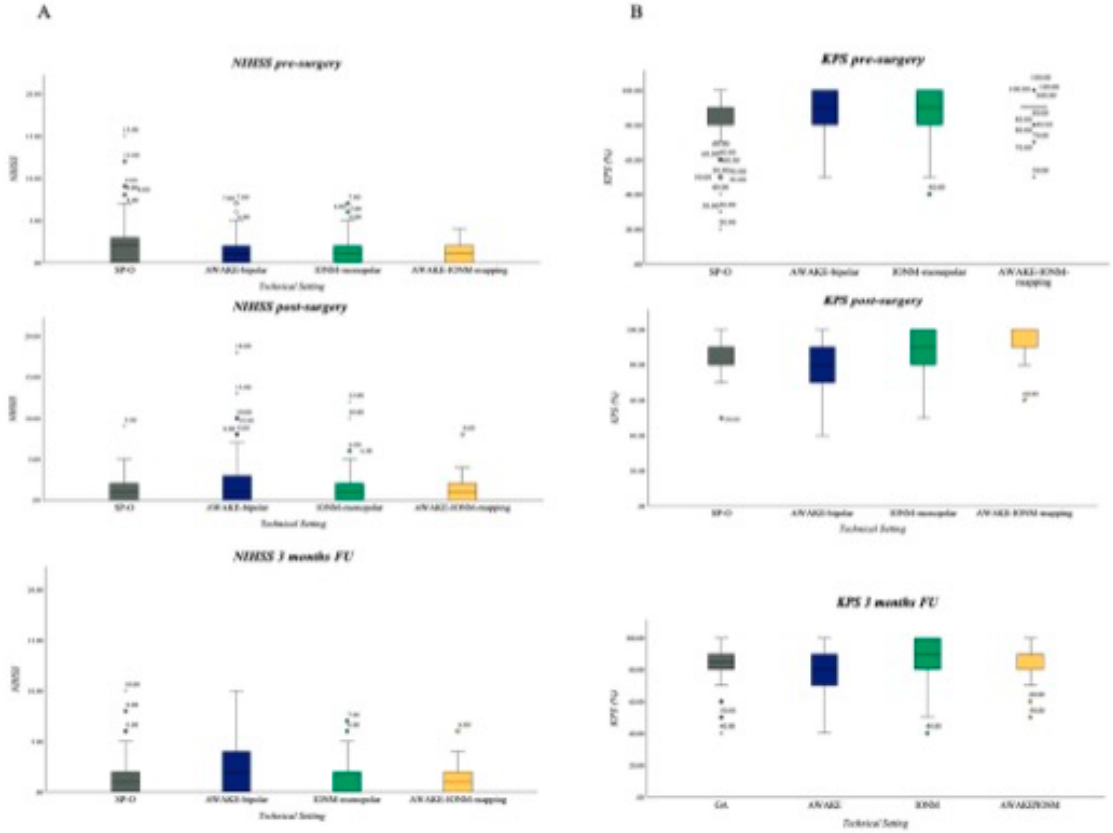


Figure 5. (**A**) Boxplot NIHSS: NIHSS pre- and post-surgery as well as at three-month follow-up for all patients. The median NIHSS scores for the surgical subgroups at different time points were (pre-surgery/post-surgery and at three-months follow-up): SP-O 2/1/1, AWAKE-bipolar 1/1/2, IONM-monopolar 1/1/0, AWAKE-IONM-mapping 1/1/1. (**B**) Boxplot, KPS pre- and post-surgery as well as at three-months follow-up for all patients. The median KPS scores for the surgical subgroups for different time points were (pre-surgery/post-surgery and at three-months follow-up): SP-O 80/80/85, AWAKE-bipolar 90/80/80, IONM-monopolar 90/90/90, AWAKE-IONM-mapping 90/90/90.

3.5.2. KPS

Median KPS pre-surgery for the whole cohort was 90 (IQR 80–100) and remained the same at post-surgical assessment and three-month follow-up. Post-operative analysis showed that the patients operated on under SP-O, IONM-monopolar and AWAKE-IONM-mapping settings experienced no deterioration in terms of their KPS score. However, a significant decrease in the KPS score was observed in patients who were operated on under the AWAKE-bipolar setting, while the KPS score for those who were operated on via SP-O increased (Figure 5B, $p < 0.001$).

The three-month follow-up revealed significantly higher KPS values for the IONM-monopolar ($p = 0.004$) and AWAKE-IONM-mapping ($p = 0.021$) groups compared to those under the SP-O surgical setting, and again, the AWAKE-bipolar group showed a significantly lower KPS score compared to SP-O, as calculated using the Bonferroni method ($p = 0.012$).

4. Discussion

The standards for the surgical treatment of GBM have evolved considerably. In our study, we found significant changes in the intraoperative monitoring techniques used since 2004. We observed three main phases: (1) no monitoring until 2007, (2) the introduction of awake craniotomies with bipolar stimulation as the only monitoring/mapping technique in 2008 and (3) the introduction of IONM and mapping as a combined procedure in 2010. From there on, whenever required, all techniques were used as combined techniques.

In the present study, which spanned 2004–2018, we aimed to quantify the influence of elaborate intraoperative monitoring and mapping methods on the immediate effects measured in neurological outcomes and the long-term prognosis of patients with eloquently located GBM.

Implementation of Different Surgical Monitoring and Mapping Techniques and Their Impacts on Short-Time and Long-Time Outcomes

In our department, awake surgery with bipolar mapping was the first technique used for the functional monitoring of patients with eloquent tumors, introduced to preserve functionality in patients with eloquent tumors. Awake craniotomies with 60 Hz bipolar stimulation as one technique for eloquent GBM resection provide functional control on the cortical and subcortical levels of a wide array of neurological functions, particularly language functions. Thus, the importance of awake craniotomies has been recognized in the surgical management of eloquently located gliomas in the past, and the implications of this technique for eloquently located GBM have been discussed widely in the literature. In 2008, Sanai et al. reported data on 250 patients who underwent resection under intraoperative language mapping. Further, they reported a worsening of language function in 8.4% of the patients during the postoperative phase. However, after 6 months, only 1.6% of the patients were reported with permanent worsening [32]. Recently, Gerritsen et al. published data from a multicenter study comprising 536 GBM patients with eloquently located lesions; 134 of the patients underwent awake surgery. Overall, patients in the awake subgroup compared to the non-awake group had significantly fewer neurological deficits at three and six months [33]. Comparable results were obtained in a meta-analysis published by Sattari, revealing a significantly greater EOR, longer PFS and OS, as well as higher KPS scores at three months in 2032 eloquent gliomas [34]. In our cohort, we found a median PFS of 8 months. PFS as calculated by Kaplan–Meier curve showed no significant superiority of the technical settings that were used. For OS, a median survival of 14 months was observed for the entire cohort, and here, the Kaplan–Meier curve revealed significant results in the SP-O group. However, the authors want to interpret these results judicially. First and foremost, the SP-O group was the largest, with 160 patients compared to the other subgroups. Several cases might have biased outcomes regarding PFS and OS. Furthermore, SP-O 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 on via

SP-O in our cohort comprised mostly unknown IDH statuses. Amongst these patients, statistical outliers had an OS of more than the expected normal average life expectancy. The authors can only speculate that a majority of patients in this cohort may have an IDH-mutated status with a known beneficial overall survival (OS), although this cannot be conclusively demonstrated. It should also be noted that the groups were highly imbalanced (14 IDH-mutated vs. 320 IDH-wildtype patients), allowing for trends but not statistically robust conclusions.

The AWAKE-bipolar group in our study exhibited a significantly increased NIHSS and reduced KPS in the postoperative phase compared to the other groups. To further evaluate this phenomenon, we examined factors that could have had some influence on these unexpected results. The eloquence of the operated lesions was not a contributing factor. However, upon investigating the locations, it was found that a quarter of the lesions were located in the parietal lobe. Since, in comparison to the AWAKE-bipolar group, the AWAKE-IONM-mapping group that implemented additional IONM and both mapping techniques did not show a higher postoperative NIHSS, the possible absence of monopolar mapping when addressing motor eloquent areas in the parietal lobe may explain this outcome. However, as the nature of the deficit—motor or language—was not able to be obtained from the raw data, and therefore not further evaluated, the authors can only make conjectures in this regard.

As there is a distinctive dependence on the patient's compliance, not all patients can undergo awake surgery. If patients are identified as not suitable for awake craniotomy or in cases where the control of motor function is prioritized over language testing due to localization or clinical findings, IONM and monopolar mapping are profoundly effective techniques for monitoring somatosensory and motor functions in the asleep setting, providing the active monitoring (monopolar stimulation) of cortical or subcortical motor functions.

Combined monitoring/mapping approaches for surgical resection were implemented in our department, starting at the end of 2009. When using IONM with monopolar mapping only or awake surgery combined with those techniques, we did not see any significant increases in NIHSS or decreases in KPS as parameters for new neurological deficits, which is in line with multiple studies reporting save resection under usage of these techniques [20,35–37]. After the implementation of these combined techniques, the ratio of biopsies compared to surgeries decreased significantly, and the incorporation of IONM-monopolar and AWAKE-IONM-mapping procedures drastically increased in our cohort. The surgical excision of eloquently located tumors also significantly increased from there on. Nevertheless, as reported in our data, those techniques did not have any influence on PFS or OS in our cohort. Our findings are in line with a study by Fukui et al., which focussed on the impact of awake craniotomy and mapping on OS in a cohort of 335 patients and found no significant results for OS when patients were operated on in the awake setting compared to under general anaesthesia [38]. Additionally, Pan et al. found no statistically significant differences between "IONM" and "no-IONM" groups concerning PFS and OS [39].

Lastly, in a side analysis, we aimed to access possible significant differences in EOR and RTV within technical settings to determine a possible influence on PFS and OS in our cohort, as EOR and RTV are known to be significant factors for prolonged PFS and OS. Maximizing EOR is a well-established concept applied to prolong overall survival (OS). Many studies have proven the significant influence of this approach in the past, e.g., Sanai et al. [13,40] and Lacroix et al. [41]. In a recent study, the RANO Resect Group demonstrated that resections beyond the contrast-enhancing part even more notably impact OS [11]. In our cohort, a mean EOR measured as a percentage reduction of 96% was observed throughout the entire period, regardless of the technical setting employed. The average EOR before the incorporation of IONM or mapping techniques or awake surgery was 95%; after that, we saw an average of 96%. Furthermore, we evaluated the residual tumor volume, which did also not differ significantly between technical settings; however, the lowest RTV was seen in the AWAKE-IONM-mapping group in which all IONM and mapping techniques

were incorporated. With the implementation of IONM and or mapping techniques, the authors would have expected more different results favouring IONM and or mapping techniques regarding resection results. However, in our cohort, no significant difference was observed compared to the period without the use of IONM or mapping techniques. An important factor to consider here is that with the introduction of these techniques, the eloquence of tumors significantly increased. Comparing EOR or RTV in patients without eloquently located tumors is challenging when compared to those with motor or language-relevant tumors. For non-eloquently located tumors, resection can be guided radiologically/anatomically. But, with eloquent tumors, the aim is to avoid functional deficits, necessitating the acceptance of functional resection boundaries. This could have contributed to the very similar outcomes between the SP-O and various AWAKE and IONM-mapping groups.

Overall, the equally distributed EOR and RTV may have resulted in a non-significant impact of the monitoring/mapping techniques on PFS and OS, as it is known that the extent of resection highly impacts survival in high-grade patients. Since there were no differences in the cohort regarding the extent of resection, the influence on OS of the respective monitoring/mapping techniques could probably not be shown.

5. Limitations

This study has certain limitations that the authors want to point out. The retrospective study is based on data spanning 14 years, with some data acquisition dating back significantly into the past. Meanwhile, changes in documentation forms and standards have occurred, posing challenges to comprehensive data collection and meaningful analysis. For example, the chosen intraoperative technical setting was naturally dependent on the standard technology available at the time of data collection. This factor influenced patient allocation to different technical groups until the introduction of all mapping and monitoring techniques after 2010. Notably, out of over 1000 screened patients, only just over 600 were included in the study. Additionally, since the first patient's surgery, intraoperative techniques, excluding the monitoring and mapping approaches under investigation in this study, have evolved. The introduction and routine use of fluorescence techniques like 5-ALA, or increasingly advanced microscopes, intraoperative imaging, and preoperative planning over the years, have shifted the boundaries of surgeries, likely introducing a certain bias into the data. Moreover, the group sizes of the surgical approaches have varied significantly, making comparisons challenging in some instances. A prospective setting of data acquisition and analysis would have certainly resulted in significantly less data loss, thereby allowing for a substantial increase in both the total number of patients and the data available for analysis. Additionally, the matching of patients would have been simplified, helping to minimize the numbers and impacts of confounders.

6. Conclusions

Several publications have advocated for the utilization of intraoperative neuromonitoring (IONM), mapping, and awake craniotomies in the resection of glioblastoma in smaller patient cohorts. However, to our knowledge, there has been no analysis of comparable cohort sizes in the current study that examines the influence of different intraoperative monitoring and mapping techniques on PFS and OS. We observed a significant decrease in the number of biopsies following the incorporation of awake surgeries, intraoperative IONM, and mapping. This decrease suggests a considerable increase in the operability of eloquent tumors since the adoption of awake craniotomies and IONM or mapping techniques.

Therefore, employing these techniques facilitates the safe resection of eloquent GBM with acceptable post-operative morbidity. Nevertheless, our cohort did not demonstrate a significant impact of one of these various surgical monitoring and mapping techniques alone on PFS and OS. Although specific individual techniques did not show a significant impact, our study highlights the importance of intraoperative monitoring and mapping

techniques in enhancing overall resectability in GBM, which now provides an opportunity for surgery to some patients who previously would not have been candidates for surgery.

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Institutional Review Board Statement: The study was conducted following the Declaration of Helsinki, and approved by the Institutional Ethics Committee of Heinrich-Heine University, medical faculty, Düsseldorf, Germany (study number 2018-79 RetroDEuA, two amendments number 2018-79_1; 2018-79_2).

Informed Consent Statement: All patients whose data were enclosed in this study gave written informed consent for data processing within the neurosurgical working group. The local ethics committee approved the informed consent document and procedure as appropriate for this study.

Data Availability Statement: Data are available on request due to privacy restrictions.

Conflicts of Interest: The authors declare no conflict of interest.

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Impact of Anticipated Awake Surgery on Psychooncological Distress in Brain Tumor Patients

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Background: Brain tumor patients present high rates of distress, anxiety, and depression, in particular perioperatively. For resection of eloquent located cerebral lesions, awake surgery is the gold standard surgical method for the preservation of speech and motor function, which might be accompanied by increased psychological distress. The aim of the present study was to analyze if patients who are undergoing awake craniotomy suffer from increased prevalence or higher scores in distress, anxiety, or depression.

Methods: Patients, who were electively admitted for brain tumor surgery at our neurooncological department, were perioperatively screened regarding distress, anxiety, and quality of life using three established self-assessment instruments (Hospital Anxiety and Depression Scale, distress thermometer, and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30-BN20). Screening results were correlated regarding operation technique (awake vs. general anesthesia). Retrospective statistical analyses for nominal variables were conducted using chi-square test. Metric variables were analyzed using the Kruskal–Wallis test, the Mann–Whitney U-test, and independent-samples t-tests.

Results: Data from 54 patients (26 male and 28 female) aged 29 to 82 years were available for statistical analyses. A total of 37 patients received primary resection and 17 recurrent tumor resection. Awake surgery was performed in 35 patients. There was no significant difference in awake versus non-awake surgery patients regarding prevalence (of distress ($p = 0.465$), anxiety ($p = 0.223$), or depression ($p = 0.882$). Furthermore, awake surgery had no significant influence on distress thermometer score ($p = 0.668$), anxiety score ($p = 0.682$), or depression score ($p = 0.630$) as well as future uncertainty ($p = 0.436$) or global health status ($p = 0.943$). Additionally, analyses revealed that primary or recurrent surgery also did not have any significant influence on the prevalence or scoring of the evaluated items.

Conclusion: Analyses of our cohort's data suggest that planned awake surgery might not have a negative impact on patients concerning the prevalence and severity of manifestation of distress, anxiety, or depression in psychooncological screening. Patients undergoing recurrent surgery tend to demonstrate increased distress, although results were not significant.

Keywords: awake surgery, psychooncological distress, glioblastoma, brain tumor, HADS, EORT C QLQ-C30

INTRODUCTION

Cancer patients are at high risk of suffering increased levels of distress, anxiety, and depression. A study regarding the prevalence of distress in patients with different types of cancer reported an overall prevalence of distress of about 35% (1). When focusing on neurooncological patients, prevalence of distress is reported to be even higher with ranges of between 38% and 52% (2, 3). According to previous studies, approximately one-fourth of cancer patients also suffer from depression or depressive symptoms (4). In brain tumor patients, the prevalence of depression is reported to be approximately 21% and generally assumed to be higher than in patients with different cancers (4, 5). Further analyses underlined that in correlation to increased levels of distress, anxiety, and depression, brain tumor patients additionally show a reduction of quality of life (QoL) (6, 7), finally resulting in decreased overall survival. Studies reported that psychological distress is associated with increased cancer mortality (8) and significantly worse outcomes in cancer patients with brain tumors, especially in patients with high-grade glioma (9–12). Longitudinal analyses regarding distress in neurooncological patients underlined increased distress especially perioperatively during hospitalization (13). Therefore, in particular, perioperative screening to facilitate a timely additional psychooncological support seems to be crucial.

The aim of surgery in neurooncological patients is a maximal aggressive tumor resection without causing permanent neurological deficits. In order to achieve this goal, the operation techniques were significantly improved by using neuronavigation, fluorescence-guided surgery, and intraoperative neuromonitoring during the last decade. Especially awake surgery in patients with eloquent located lesions has been proven to maximize the extent of resection leading to an improved outcome while decreasing risks for new postoperative neurological deficits (14–16). But less is known if this anticipated operation technique causes additional distress for neurooncological patients.

Therefore, the present study aimed to answer the question of whether the anticipation of awake surgery has an additional negative impact on distress, anxiety, depression, and QoL status in neurooncological patients in the preoperative phase as compared with patients undergoing surgery under general anesthesia (GA).

PATIENTS AND METHODS

In this retrospective single-center analysis (screening period January 2019 to September 2020), we investigated the perioperative impact of anticipation of awake surgery regarding psychooncological distress of brain tumor patients. The study was approved by the local ethics committee (Study Number 4087). Reporting of this study was according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies (**Supplementary Material**).

Patients

Inclusion criteria for the present analysis were 1) patients age >18 years with the diagnosis of a brain tumor 2) who were electively admitted for tumor surgery at our neurooncological department with 3) a complete preoperative data set of distress and QoL assessment. Due to the retrospective study design, assessment questionnaires were filled out quite heterogeneously with partially missing data. In order to avoid interference of analyses by an indifferent amount of data for each single screening parameter, we defined that only patients with a complete psychooncological screening assessment were eligible for inclusion. Patients with missing data in any of the below-described screening items were excluded, finally leading to exclusion of 74.65% of the patients. Screening assessment comprising all screening items will be described further below.

For further analysis, patients were divided regarding their resection modality (awake vs. GA) (**Figure 1**). Secondly, analyses concerning the impact of primary or recurrent surgery were performed.

Detailed epidemiological information including clinical data of both groups is summarized in **Table 1**.

Screening Assessments

Screening was performed as tablet-based self-assessment after short instruction by our medical staff. All patients were screened 1–2 days preoperatively during hospitalization with the following instruments.

National Comprehensive Cancer Network, Distress Thermometer

As a routine screening instrument for distress in cancer patients, the distress thermometer (DT) was firstly published in 1999 by the National Comprehensive Cancer Network (NCCN). The DT is now part of the NCCN guidelines and an easy-to-administer self-reporting tool with a rating scale ranging from 0 (no distress) to 10 (extreme distress). According to the NCCN guidelines, we defined a DT score of 5 or above as indicating distress. The DT also contains a list of 40 symptoms representing practical, family,

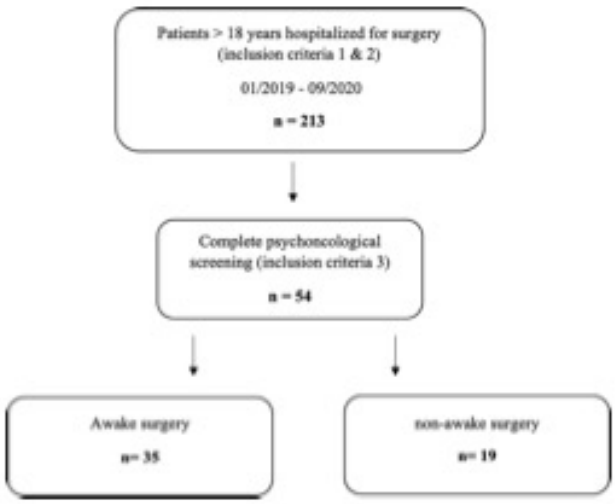

FIGURE 1 | Flowchart describing patient selection.

emotional, spiritual–religious, and physical concerns. In our setting, we only used the visual scale, and the symptom list was excluded.

Hospital Anxiety and Depression Scale

Firstly published in 1983, the Hospital Anxiety and Depression Scale (HADS) was originally designed to assess the psychological state of physically ill patients. Meanwhile, it has been established as an effective screening tool for the assessment of anxiety and depression.

TABLE 1 | Descriptive epidemiologic data of patient cohort.

	Awake (n = 35)	Non-awake (GA) (n = 19)
Age (years)		
Mean	55 [SEM ± 2.9]	59 [SEM ± 2.8]
Range	29–81	40–83
Gender		
Female	21	7
Male	14	12
Diagnosis		
Glioblastoma (WHO IV)	18	13
Anaplastic oligodendroglioma (WHO III)	2	0
Anaplastic astrocytoma (WHO III)	3	1
Diffuse glioma (WHO II)	2	0
Astrocytoma IDH mutant (WHO II)	5	0
Cerebral metastases	4	2
Cerebral lymphoma	0	3
Ganglioglioma (WHO I)	1	
ECOG pre-op		
Mean	0.8 [SEM ± 0.1]	1.0 [SEM ± 0.2]
ECOG post-op		
Mean	0.9 [SEM ± 0.2]	1.2 [SEM ± 0.2]
Primary surgery	25	12
Recurrent surgery	10	7

GA, general anesthesia; ECOG, Eastern Cooperative Oncology Group.

The 14-item self-report questionnaire consists of 7 items used to identify anxiety (HADS-A) and 7 items for depression (HADS-D), with each item having a 4-point (0–3) Likert-type scale. The maximum score on each subscale is 21 points. A cutoff score of >8 is assumed to be optimal concerning sensitivity and specificity in defining anxiety disorders in patients (17, 18).

Health-Related Quality of Life Assessment

The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30-BN20 is a disease-specific questionnaire developed by the EORTC to assess the QoL of cancer patients. The EORTC QLQ-C30 consists of a 4-point scale containing four function scales, three symptom scales, and six single-item scales as well as two 7-point scales: the global health status and the QoL. The QLQ-BN20 is an additional module for brain tumor patients, consisting of 20 questions specifically assessing brain tumor-related symptoms. Distress screening results were correlated with the following items: global health status, QoL, and future uncertainty (7, 19). The threshold for the global health and QoL score was ≤4 and for emotional function, cognitive function, and future uncertainty ≥2.75, scored according to the recommended scoring manual of the EORTC.

Indication for Awake Surgery and Preparation Protocol

For eloquent (cortically and/or subcortically) located tumors (evaluated in preoperative MRI scans), awake surgery with intraoperative monitoring was planned to preserve functionality. In patients with suspected language affecting lesions or for specific motoric testing, awake surgery was indicated in order to perform adequate intraoperative monitoring of function (14, 20). Speech monitoring was performed using 60-Hz stimulation,

and motor stimulation was performed using high-frequency monopolar stimulation.

Independently from localization, patients with severe preoperative speech disorders were excluded from the awake surgery group.

All patients in the awake group underwent baseline testing 1 day prior to surgery, with the same tests used intraoperatively. Additionally, the intraoperative setting of awake surgery was practiced with the patients in order to prepare patients for the upcoming procedure.

In patients with a suspected malignant brain tumor, 5-aminolevulinic acid (5-ALA) was administered orally 3–4 h prior to surgery. 5-ALA leads to the accumulation of fluorescent porphyrins in malignant cells and helps intraoperatively with the identification of tumor tissue leading to the increased extent of resection and increased progression-free survival in patients with malignant glioma (21, 22).

Statistical Analyses

Obtained results were statistically analyzed by using the chi-square test for nominal variables. Metric variables were analyzed using the Kruskal–Wallis test, the Mann–Whitney U-test, and independent-samples t-tests. Statistical analyses were conducted using IBM SPSS Statistics Version 26 (IBM Corporation, USA). Statistical cutoff stated as p-value was set at 0.05.

RESULTS

Fifty-four out of 213 patients were eligible for inclusion in the final analysis (**Figure 1**). Of the patients, 26 were male and 28 female, with mean age of 56.04 [± 2.1 SEM]. A total of 37 patients (68.52%) received first tumor resection, and 17 (31.48%) were hospitalized due to recurrent surgery. Out of 54, 35 patients were undergoing awake surgery (64.81%), as intraoperative speech and motoric testing were required for enabling safe resection due to eloquent localization of the lesion. In the recurrent patient group, there was one case where surgical procedures had changed (primary surgery, non-awake; recurrent surgery, awake surgery). Sixteen patients underwent recurrent surgery following the same surgical strategy compared with primary surgery. The subgroups' mean time between primary and recurrent surgery was 2.9 years [± 0.54 SEM].

Preoperative mean Eastern Cooperative Oncology Group (ECOG) Performance Status was 0.9 [± 0.1 SEM] and postoperative 1 [± 0.1 SEM]. Neither of the included patients reported a psychiatric diagnosis in medical history.

Screening Results

Independent from the screening instruments, in the awake patient cohort, 22 patients were indicated to suffer from increased distress (62.86%). In comparison, 10 out of 19 patients who were undergoing surgery under GA complained about distress (52.63%). The prevalence of distress ($p = 0.465$) did not significantly differ between both cohorts. Furthermore, six patients of the awake patient cohort indicated increased anxiety (17.14%) and five depression (14.29%). Also, six patients (31.58%) in the GA cohort (n = 10/19) reported anxiety and three depression (15.79%). Therefore, again, the prevalence of anxiety ($p = 0.223$) and depression ($p = 0.882$) did not differ significantly between patients who were undergoing awake surgery and patients undergoing surgery under GA.

The main results are presented regarding the different screening instruments.

Distress Thermometer

Regarding results of the DT assessment, the mean score in the awake surgery patient cohort was 5.69 [± 0.50 SEM], compared with 6.26 [± 0.66 SEM] for patients undergoing surgery under GA. Statistical analyses revealed no significant difference in the scoring of DT in both cohorts ($p = 0.668$, **Figure 2A**).

Regarding the impact of recurrent surgery, there was no significant influence, although patients undergoing recurrent surgery tended to demonstrate increased distress more often (recurrent 76.47% vs. primary 51.35%, **Figure 2B**).

Hospital Anxiety and Depression Scale

Scoring of anxiety and depression items showed a mean score of 6.14 [± 0.75 SEM] for anxiety and 5.23 [± 0.72 SEM] for depression score in the awake group. In comparison, the mean score in the GA group was 7.16 [± 1.29 SEM] for anxiety and 5.89 [± 0.99 SEM] for depression. Neither of both results reached significance (anxiety awake vs. GA $p = 0.682$; depression $p = 0.630$, **Figures 3A, B**).

Comparable with the DT results, although recurrent surgery had no significant influence on the prevalence or scoring of both parameters, patients with recurrent surgery tend to demonstrate higher scores for anxiety and depression.

Quality of Life

Concerning analyses of global health status and future uncertainty from the EORTC brain module, awake surgery did not have any significant influence on scores of future uncertainty ($p = 0.436$) or global health status ($p = 0.943$, **Figures 4A, B**).

Again, there was no significant impact on those parameters concerning recurrent surgery; however, a decreased global health status was observed in the recurrent surgery patient cohort.

Psychooncological Support

At hospitalization, all patients were asked if they wish to get psychooncological support perioperatively. Fifteen patients (27.78%) accepted additional support. Regarding different patient groups awake vs. GA and recurrent vs. primary surgery, there was no difference ($p > 0.05$).

DISCUSSION

For eloquent located tumors, awake surgery is the gold standard treatment option to obtain maximal safe resection. But less is known about the potential negative impact that this additional pressure may have on neurooncological patients who are already at high risk for increased distress, anxiety, and depression.

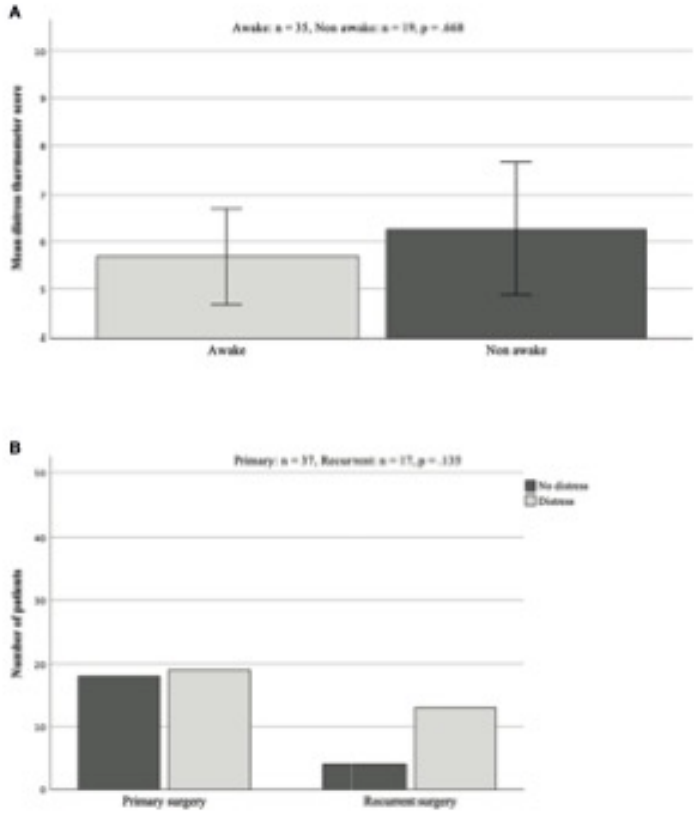

FIGURE 2 | **(A, B)** Mean scoring in DT in group comparison. There were no significant differences seen between both patient groups (**A**; p = 0.668). Concerning comparison of reported distress in either primary or recurrent surgery, although not statistically significant, patients undergoing recurrent surgery reported distress more often **(B)**. DT, distress thermometer.

We aimed to include various essential psychooncological testing parameters in order to obtain a comprehensive overview of the preoperative psychological status of patients when undergoing awake surgery compared with undergoing surgery under GA. Our data reflect that patients undergoing awake surgery for cerebral lesions do not demonstrate distress, anxiety, or depression more often than patients who are undergoing surgery under GA in the preoperative phase. Furthermore, our analysis also clearly underlines the additional impact of recurrent surgery regarding increased distress.

There are only a few data regarding the psychooncological impact of anticipated awake surgery. Ruis et al. analyzed 70 patients using the HADS, and they reported a mean anxiety scale of 6.1 points, comparable with our data. In this analysis, particularly younger patients and women were identified with higher anxiety scores (23). However, they did not compare results with patients undergoing surgery under GA. Our 2013 research group performed a postoperative survey of brain tumor patients who received awake surgery. Most patients stated that they would undergo awake surgery at any time again. A thoroughly pre-op preparation was the most important to support the patients in this situation (24). Different studies underlined that detailed preparation of a well-selected patient cohort is essential to prevent stress disorders and negative psychological aftereffects (25, 26). In this context, Santini and colleagues firstly reported psychological profiling for candidates of awake surgery under the use of psychological questionnaires, neuropsychological testing of language, neurocognition, and intraoperative interviews (27).

At our department, patients undergo a preoperative psychooncological screening as described before; furthermore, a simulation of the awake situation 1 day before scheduled surgery is performed, and all intraoperative performance tasks are explained and practiced with the patient.

Besides careful patient selection and preparation, participation in the decision making and anticipated active role throughout surgery and therefore active role in a positive surgery outcome might contribute to the fact that awake surgery does not have a negative influence on the patients (28). Additionally, contrary to our preoperative screening results, published reports

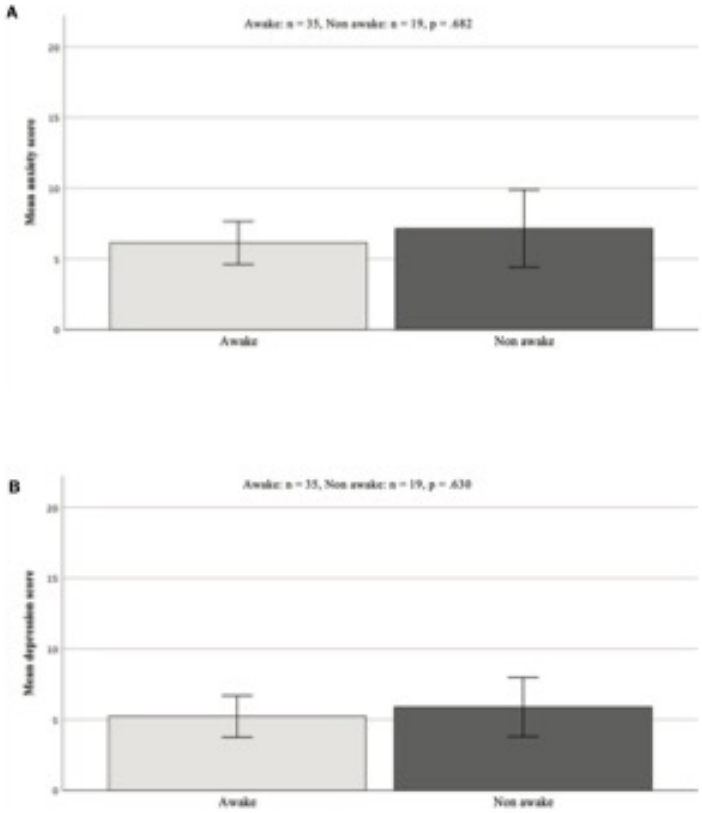

FIGURE 3 | **(A, B)** Group comparison of scores in HADS screening. Results did not differ significantly [awake vs. GA anxiety scores p = 0.682 **(A)**; depression scores p = 0.630 **(B)**]. HADS, Hospital Anxiety and Depression Scale; GA, general anesthesia.

of postoperative screening results of patients undergoing awake craniotomy also revealed no major negative impact of awake surgery on patients. Goebel et al. described pre- and postoperative HADS anxiety and depression scores of 25 patients undergoing awake surgery combined with intraoperative MRI, and only 1 patient showed negative reaction to surgery protocol postoperatively (29). In line with that, Danks et al. reported no major consequences like post-traumatic stress disorders after awake surgery (29, 30).

Although not significant, independent from the assessment instrument, here, patients undergoing recurrent surgery presented increased scores for distress, anxiety, and depression. In the literature, there are some data about distress in the course of neurooncological diseases. There seem to be specific time points, where increased distress was observed, especially during hospitalization as well as at the time point of tumor recurrence (31). This might be due to various general apprehensions when being diagnosed with recurrent cancer. In our cohort additionally, a worse subjective global health status at recurrence was revealed, and that might have also contributed to the increase of psychooncological screening scores.

However, along with positive results from our study, we also have to state major limitations of our data analyses with an arguable small cohort due to our restrictive inclusion criteria. We only included patients with full data sets during preoperative psychooncological testing in order to generate comparability in all analyzed categories. That led to exclusion of approximately 75% of the screened patients. Furthermore, the size of both patient groups quite differed in numbers and might have led to some bias in the analysis.

Nevertheless, to our knowledge, this is the first analysis of a comprehensive psychooncological screening in patients undergoing brain tumor surgery under either awake or non-awake surgery. Hence, our data are of high importance, as awake surgery offers a full range of intraoperative monitoring of speech and motor function for the surgeon, which is essential in patients with brain tumors of some locations. According to previous research perioperative psychooncological distress, anxiety and depression can have a negative influence on the outcome and the patients'

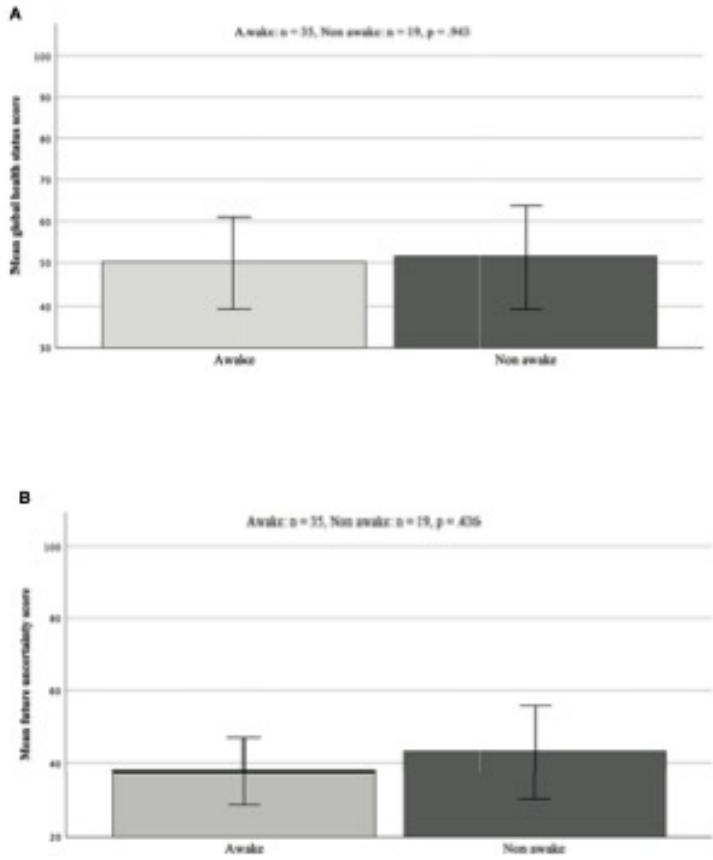

FIGURE 4 | **(A, B)** Analysis of differences in future uncertainty and global health status taken from *EORTC QLQ-BN20* quality of life questionnaire. There was no significant difference in mean scores in both analysed items [global health status p = 0.943 **(A)** future uncertainty p = 0.436 **(B)**]. EORTC, European Organisation for Research and Treatment of Cancer.

subjective perception of global health care status, which is quite the opposite of the treatment intention. Therefore, an indication for awake surgery has to be questioned for every single patient. But our data show that with detailed preparation and close monitoring of the patients, awake surgery does not have any negative influence on patients, and we can expect our patients to go through this procedure without harming them. On the contrary, the positive effects of a possible increased extent of resection and that accompanying increased overall survival predominate.

CONCLUSION

Our data demonstrate that anticipation of awake surgery represents no significant impact for increased distress, anxiety, or depression preoperatively. Surgeons can expect their patients to undergo awake surgery without increasing psychooncological distress. If expected localization of cerebral lesion includes eloquent areas, awake surgery is recommended in order to increase the safety of the patient.

Even if the results were not significant, our data clearly illustrate that patients undergoing recurrent surgery tend to demonstrate increased distress; in this special situation, early contact with professional psychooncologists is recommended.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the correspondent author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the medical faculty of the

University of Düsseldorf (Study Number 4087). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MR designed and directed the project. FS-B analyzed the data and wrote the paper. OR analyzed the data. DH and MS provided critical feedback and helped shape the research and manuscript. All authors discussed the results and commented on the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2021.795247/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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VIII Publication list

12) Establishment of different intraoperative monitoring and mapping techniques and their impact on survival, extent of resection and clinical outcome in patients with high-grade gliomas - a series of 631 patients in 14 years

Franziska Staub-Bartelt, Marian Preetham Suresh Babu, Andrea Szelényi, Marion Rapp, Michael Sabel

Cancers 2024, 16, 926. doi.org/10.3390/cancers16050926

11) Functional outcome and overall survival in patients with primary or secondary CNS lymphoma after surgical resection vs. biopsy

Franziska Staub-Bartelt, Jos Rittenauer, Michael Sabel, Marion Rapp

Cancers 2023, 15(21):5266. doi.org/10.3390/cancers15215266

10) Feasibility of intraoperative neuromonitoring and cortical/subcortical mapping in patients with cerebral lesions of highly functional localizations—pathway to case adapted monitoring and mapping procedures

Franziska Staub-Bartelt, Marion Rapp, Michael Sabel

Front. Oncol. 2023, 13:1235212. doi: 10.3389/fonc.2023.1235212

9) Resection of Eloquent Located Brain Tumors by Mapping Only—A Feasibility Study

Franziska Staub-Bartelt, Marion Rapp, Michael Sabel

Brain Sci. 2023, 13, 1366. doi.org/ 10.3390/brainsci13101366

8) Impact of COVID-19 Epidemic on Psycho-Oncological Distress in Neuro-Oncological Patients

Franziska Staub-Bartelt, Julia Steinmann, Oliver Radtke, Daniel Hänggi, Michael Sabel, Marion Rapp

Curr. Oncol. 2023, 30, 358 – 369 doi.org/10.3390/curroncol30010029

7) Does positive MGMT methylation outbalance the limitation of subtotal resection in glioblastoma IDH-wildtype patients?

Mareike Müller*, Franziska Staub-Bartelt*, Ehrmann Julia, Hänggi Daniel, Sabel Michael, Felsberg Jörg, Rapp Marion *equal contribution

Journal of Neuro-Oncology (2021) 153:537–545

6) Direct Cortical Stimulation in Neurosurgical Emergencies: Single-Centre Experience in 2 Patients

Franziska Staub-Bartelt, Björn B. Hofmann, Marion Rapp, Daniel Hänggi, Marcel Alexander Kamp, Michael Sabel

World Neurosurg. (2021) 150:147-152.https://doi.org/10.1016/j.wneu.2021.03.118

5) Impact of Anticipated Awake Surgery on Psychooncological Distress in Brain Tumor Patients

Franziska Staub-Bartelt, Oliver Radtke, Daniel Hänggi, Michael Sabel, Marion Rapp

Front. Oncol. 11:795247. doi: 10.3389/fonc.2021.795247

4) The impact of preoperative MRI-based apparent diffusion coefficients on local recurrence and outcome in patients with cerebral metastases

Julia Steinmann, Marion Rapp, Hosai Sadat, Franziska Staub-Bartelt, Bernd Turowski, Hans-Jakob-Steiger, Daniel Hänggi, Michael Sabel, Marcel A Kamp

Br J Neurosury 2020 Sep 29;1-8. doi: 10.1080/02688697.2020.1817856

3) Evaluation of volumetric change of intracerebral hemorrhage in patients treated with thrombolysis for intraventricular hemorrhage

Staub-Bartelt F, van Lieshout J, Beez Th, Kram R, Hänggi D, Beseoglu K

Neurocrit Care. 2020 Jul 31. doi: 10.1007/s12028-020-01054-7. Online ahead of print.PMID: 32737761

2) SURGICAL MANAGEMENT OF SPINAL MENINGIOMAS: FOCUS ON UNILATERAL POSTERIOR APPROACH AND ANTERIOR LOCALIZATION.

Onken J, Obermüller K, Staub-Bartelt F, Meyer B, Vajkoczy P, Wostrack M

J Neurosurg Spine. 2018 Dec 7;30(3):308-313. doi: 10.3171/2018.8.SPINE18198

1) ACCEPTANCE AND COMPLIANCE OF TTFIELDS TREATMENT AMONG HIGH GRADE GLIOMA PATIENTS.

Onken J, Staub-Bartelt F, Vajkoczy P, Misch M

J Neurooncol. 2018 Aug;139(1):177-184. doi: 10.1007/s11060-018-2858-9. Epub 2018 Apr 11

The following 3 papers present findings derived from my doctoral thesis. They have been included here to ensure the comprehensiveness of my published works and are not considered to contribute to my habilitation credentials.

3) Long-term correlation of subthalamic beta-band activity with motor impairment in patients with Parkinson's disease

Wolf-Julian Neumann*, Franziska Staub-Bartelt*, et al. *equal contribution

Clin Neurophysiol. 2017 Nov;128(11):2286-2291. doi: 10.1016/j.clinph.2017.08.028. Epub 2017 Sep 20

2) Subthalamic beta dynamics mirror parkinsonian bradykinesia months after neurostimulator implantation

Leon Amadeus Steiner, Wolf-Julian Neumann, Franziska Staub-Bartelt et al.

Mov Disord. 2017 Aug;32(8):1183-1190. doi: 10.1002/mds.27068. Epub 2017 Jun 22.

1)Deep Brain Recordings Using an Implanted Pulse Generator in Parkinson's

Disease

Neumann, W.J., F. Staub et al.

Neuromodulation. 2016 Jan;19(1):20-24. doi: 10.1111/ner.12348. Epub 2015 Sep 21.

Declaration

Die vorliegende kumulative Habilitationsschrift vereint von der Verfasserin publizierte Originalarbeiten, deren inneren wissenschaftlichen Zusammenhang der Themenkomplex des intraoperativen Neuromonitorings und des kortikalen/subkortikalen Mappings bei Hirntumoroperationen umfasst. Die vorliegende Arbeit ist in Übereinstimmung mit der geltenden Habilitationsordnung der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf vom 24.11.2022 verfasst worden.

Ich versichere an Eides Statt durch meine Unterschrift, dass ich die vorliegende schriftliche Habilitationsleistung als eigenständige wissenschaftliche Leistung selbständig und ohne unzulässige fremde Hilfe angefertigt habe.

Bei den wissenschaftlichen Untersuchungen, die Gegenstand der schriftlichen Habilitationsleistung sind, wurden ethische Grundsätze und die Grundsätze und Empfehlungen zur Sicherung guter wissenschaftlicher Praxis beachtet.

Ich versichere, dass keine anderen eingeleiteten oder erfolglos beendeten Habilitationsverfahren bestehen.

Düsseldorf, Mai 2024

Dr. med. Franziska Staub-Bartelt

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